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Clínica Alemana - Universidad del Desarrollo

Novel strategies to assess the clinical outcome of patients affected by long COVID or stroke, considering its impact on quality of life

By: CARLOS OSVALDO DELFINO

Thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Science in Science and Innovation in Medicine from Faculty of Medicine, Clínica Alemana de Santiago, Universidad del Desarrollo.

Supervisor: **PAULA MUÑOZ VENTURELLI**

Co-supervisor**: CRAIG ANDERSON**

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Acknowledgments

I would like to use this space to express my gratitude to those who have been part of this process. To organise what I feel, I thought I would divide it by countries.

In Argentina are my roots: a family that holds and supports me. Thank you to my parents and my sisters for being my foundation and for standing by me in every life decision; it is thanks to you that this has been possible. There are also my friends: the family I chose and carry with me. Thank you, Juan Manuel, Victoria, Anabel, and Virginia, for a friendship that sustains us through the deepest love and endures despite the distance.

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Abbreviations

A1-A7	Rey Auditory Verbal Learning Test learning trials 1–7
aOR	Adjusted odds ratio
AQoL	Assessment of Quality of Life (instrument)
AUC	Area under the curve
BMI	Body mass index
C19-YRS	Covid-19 Yorkshire rehabilitation scale
CI	Confidence interval
CoV-2	Coronavirus 2
COVID-19	Coronavirus disease 2019
CWIT	Color-word interference test
D-KEFS	Delis–kaplan executive function system
DALY	Disability-adjusted life year
EEG	Electroencephalography
EOS	End of study
EQ-5D	EuroQol 5-Dimension questionnaire
EQ-5D-3L	EQ-5D three-level version
EQ-5D-5L	EQ-5D five-level version
EQ-5D-Y	EQ-5D Youth version
EQ-VAS	EQ visual analogue scale
ESOC	European Stroke Organisation conference
GAD-7	Generalized Anxiety Disorder-7 questionnaire
GBD	Global Burden of Disease

HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HRQoL	Health-related quality of life
HUI	Health utilities index
ICH	Intracerebral haemorrhage
INTERACT-3	The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial
IQR	Interquartile range
IS	Ischaemic Stroke
LMICs	Low- and middle-income countries
LOCF	Last observation carried forward
MDC	Minimal detectable change
MIC	Minimal important change
MIDs	Minimally important differences
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
NIDO	Neuroimaging, Inflammation, and Brain Doppler (long COVID-19 cohort)
NIHSS	National Institutes of Health Stroke Scale
NVU	Neurovascular unit
OLS	Ordinary least squares
OR	Odds ratio
OTMT	Oral trail making test
OTMT-A/B	Oral Trail Making Test parts A and B
PCC	Post-COVID-19 condition (long COVID)

PCO	Patient-centred outcomes
PCORI	Patient-centered outcomes research institute
PHQ-9	Patient health questionnaire 9 item
PROMIS	Patient-reported outcomes measurement information system
PROMIS-29	PROMIS 29-item profile
PROMS	Patient-reported outcome measures
PROs	Patient-reported outcomes
PSQI	Pittsburgh sleep quality index
QALYs	Quality-adjusted life years
QoL	Quality of life
RAVLT	Rey auditory verbal learning test
RCTs	Randomised controlled trials
SAH	Subarachnoid haemorrhage
SD	Standard deviation
SDMT	Symbol digit modalities test
SEM	Standard error of measurement
SF	Semantic fluency
SG	Standard gamble
smRS	Simplified modified Rankin scale
STRONGER	Statin treatment for COVID-19 to Optimise neurological recovery
TRIDENT	Triple-pill antihypertensive strategy for secondary prevention after ICH
TTO	Time trade-off
UK	United Kingdom

US	United States
UW	Utility-weighted / utility weights
UW-mRS	Utility-weighted modified Rankin Scale
VAS	Visual analogue scale
WHO	World Health Organization

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List of publications arising from the thesis

- Patient Centered Outcomes in Stroke: Utility-Weighted Modified Rankin Scale 1 results in a community-based study. Carlos Delfino, G Cavada, L Hoffmeister, Pablo Lavados, Paula Muñoz Venturelli. Frontiers in Neurology. Doi: doi.org/10.3389/fneur.2025.1539107.

- Post-COVID-19 condition: a sex-based analysis of clinical and laboratory trends. Carlos Delfino; M. Cecilia Poli; Cecilia Vial; Pablo A. Vial; Gonzalo Martínez; Amy Riviotta; Catalina Arbat; Nicole Mac-Guire; Josefina Hoppe; Cristóbal Carvajal et al. Frontiers in Medicine, 2024. DOI: doi.org/10.3389/fmed.2024.1376030.

- STatin TReatment for COVID-19 to Optimise NeuroloGical recovERy (STRONGER): study protocol for a randomised, open label clinical trial in patients with persistent neurological symptoms after COVID-19 infection. Delfino Carlos, Carcel Cheryl, Muñoz Paula, et al. BMJopen, Doi:10.1136/bmjopen-2024-089382.

List of other publications during PhD candidature

- Stroke in Latin America: systematic review of incidence, prevalence, and case-fatality in 1997–2021. Carlos Delfino, Marilaura Nuñez, Claudia Asenjo-Lobos, Francisca Gonzalez, Amy Riviotta, Francisca Urrutia, Pablo Lavados, Craig Anderson, Paula Muñoz Venturelli. Int J Stroke, 2022 Nov 25;. doi: 10.1177/17474930221143323

- Disparities in stroke incidence over time by sex and age in Latin America and the Caribbean region: a systematic review and meta-analysis 2023-02-23 | . Marilaura Nuñez; Carlos Delfino; Claudia Asenjo-Lobos; Andrea Schilling; Pablo Lavados; Craig S. Anderson; Paula Muñoz Venturelli. Preprint DOI: 10.1161/JAHA.123.029800

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- Intracerebral haemorrhage management practices and adherence to the INTERACT3 care bundle in Latin America: Results from an international survey,

Julieta Rosales MD, Leonardo Augusto Carbonera MD, MSc, Ana Cláudia de Souza MD, PhD, Eva Rocha MD, PhD, Vanessa Cano-Nigenda MD, MSc, Karen D. Orjuela MD, MSc, MBA, Rodrigo Guerrero MD, Carlos Delfino MD, PhD(c), Marilaura Nuñez MD, PhD(c), Paula Muñoz Venturelli MD, PhD, Alejandro Gonzalez-Aquines MD, MPH, Journal of Stroke and Cerebrovascular diseasee, 2025 doi: 10.1016/j.jstrokecerebrovasdis.2025.108419

- Statistical analysis plan for the STatin TReatment for COVID-19 to Optimise NeuroloGical recovERy (STRONGER) study: a randomised, open label, controlled trial in subjects with persistent neurological symptoms after COVID-19 infection Xiaolei Lin, Carlos Delfino, Cheryl Carcel, Paula MuñozVenturelli, Sharon Naismith, Mark Woodward, Ruth Peters, Nirupama Wijesuriya, Meng Law, IanH. Harding, Xia Wang, Karin Leder, Owen Hutchings, Marina Skiba, Ximena Stecher, Ella Zomer, Sophia Zoungas, Craig S. Anderson, doi: 10.1136/bmjopen-2024-089382

- A triple Low-Dose Antihypertensive Pill after Intracerebral Hemorrhage, C Anderson et al, Submitted to the New England Journal of Medicine, Jan 2025. Article in press.

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- C Delfino, C Asenjo-Lobos, F Gonzalez, A Riviotta, F Urrutia, P Lavados, C Anderson, P Muñoz Venturelli, Stroke in Latin America: systematic review of incidence, prevalence, and case-fatality in 1997–2021, Poster presentation, 31st Annual Scientific Meeting of the Stroke Society of Australasia 2022, Christchurch, New Zealand.

- C Delfino, C Poli, C Vial, P Vial, C Arbat, J Hoppe, N Mac-Guire, Muñoz Venturelli Increased risk of long-term post-COVID neurologic symptoms in women, World Congress of Neurology, Montreal Canada, 2023.

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- C Delfino, Patient Centered Outcomes in Stroke: Utility-Weighted Modified Rankin Scale results in a community-based study. DCIM 2025 Scientific exhibition, March 2025, Clínica Alemana de Santiago, Chile, poster format

- C Delfino, M Ouyang, P Muñoz Venturelli, C Anderson, Oral presentation: Determinants of Quality of Functional Outcome in Intracerebral Hemorrhage (ICH). The INTERACT3 trial World ICH conference (WICH), Australia 2025.

Author's contributions

Chapter I provides the theoretical and methodological foundations of the thesis, establishing the preference-based framework that is applied operationally in the subsequent empirical chapters. Specifically, it sets out how patient-centred outcomes are quantified using utilities obtained directly or indirectly through mapping approaches, including the derivation and interpretation of the utility-weighted modified Rankin Scale (UW-mRS), and it outlines key methodological considerations that informed my analytic decisions across the thesis. As such, this chapter functions as a unifying methodological basis and is not linked to a standalone published or submitted article.

In Chapter II, I led the secondary analysis of the ÑANDU stroke cohort, a prospective community-based study in the Ñuble region, Chile, which identified and followed hospitalised, ambulatory, and deceased stroke cases using multiple overlapping sources. Using these data, I applied the UW-mRS at six months and evaluated demographic and clinical determinants of utility-weighted outcomes to characterise patient-experienced health in a non-interventional, real-world setting. This work resulted in the first peer-reviewed article arising from this doctoral thesis.

In Chapter III, I pursued two distinct lines of work within international clinical trials in intracerebral haemorrhage. First, I led a secondary analysis of INTERACT3; the parent trial is a pragmatic stepped-wedge cluster randomised study testing an acute ICH care bundle. Within this dataset, I assessed determinants of patient-reported health-related quality of life and disseminated these findings through an oral

presentation at the 2025 World Congress on Intracerebral Hemorrhage (WICH) in Sydney.

Second, within the TRIDENT trial, an international, multicentre, double-blind, placebo-controlled, parallel-group randomised trial evaluating a fixed-dose low-dose triple antihypertensive strategy versus placebo for secondary prevention after ICH, I developed the dementia adjudication operations manual and contributed to outcome ascertainment by serving as a blinded adjudicator for participants with suspected cognitive impairment/dementia during my internship in Australia. In addition, I contributed to the main TRIDENT results manuscript accepted in the New England Journal of Medicine (in press; included in the Appendix), and a thesis-derived secondary analysis from this programme of work was accepted for presentation at the European Stroke Organisation Conference (ESOC) 2026.

In Chapter IV, I led the analysis of the Chilean NIDO prospective cohort (Neuroimaging, Inflammation, and Brain Doppler in patients with prolonged COVID-19), which was designed to characterise post-COVID-19 condition using a multidimensional approach integrating clinical and neurocognitive assessment with neuroimaging, inflammatory and haemodynamic profiling, alongside patient-centred outcomes. I conducted the statistical evaluation of its associations with cognition, functioning, and health-related quality of life, which resulted in the second peer-reviewed article arising from this doctoral thesis. In addition to the analytic work, I completed hands-on laboratory training to learn how patient biospecimens were processed and analysed, strengthening my understanding of the biological data underpinning the cohort.

For the STRONGER clinical trial—Statin Treatment For COVID-19 To Optimise Neurological Recovery, which evaluated whether atorvastatin can mitigate cognitive decline by targeting neuroinflammation assessed through MRI changes and blood biomarkers—I contributed as a co-investigator, undertaking on-site activities in Chile that included participant recruitment and follow-up. I also led the publication of the STRONGER trial protocol, which constitutes the third peer-reviewed article derived from this doctoral thesis.

Regarding Chapter V, I worked closely with the Australian STRONGER team during my doctoral internship to analyse trial data. I contributed to the preliminary cross-sectional analysis of baseline (pre-randomisation) assessments, quantifying preference-based HRQoL using the EQ-5D-5L and examining its associations with symptom impact, mental health, sleep quality, and cognitive performance. These baseline results provide a benchmark for interpreting longitudinal change, while the prespecified primary trial analyses remain ongoing.

ABSTRACT

Introduction

Brain disorders such as stroke and post-COVID-19 condition (PCC) can compromise Brain health through different pathways, yet both produce long-term sequelae that are often incompletely captured by traditional clinician-rated endpoints. The aim of this thesis is to apply novel assessment strategies for people with highly prevalent neurological conditions, incorporating the impact on their daily lives, and compare these results to conventional clinical outcomes using clinical trials databases.

Methods

This thesis combined a conceptual and an applied programme of work to evaluate PCO assessment across established and emerging conditions affecting brain health. First, in the Chilean prospective stroke cohort, HRQoL was measured using the EQ-5D-3L and integrated with functional status (mRS) to derive UW-mRS. In INTERACT3, an international intracerebral haemorrhage (ICH) trial, UW-mRS was derived from EQ-5D-3L and mRS data and used to assess clinical and socioeconomic determinants of poorer patient-centred outcomes. In TRIDENT, an international double-blind ICH trial with longitudinal follow-up, repeated EQ-5D-3L, cognitive screening (Montreal Cognitive Assessment, MoCA), and disability assessments were analysed using longitudinal modelling to characterise recovery trajectories, evaluate time-dependent differences in UW-mRS, and quantify the association between cognition and HRQoL. Finally, in STRONGER, an international trial in adults with persistent neurological symptoms following COVID-19, a cross-sectional baseline analysis quantified EQ-5D-5L utility and examined its associations

with symptom burden, mental health, sleep quality, and cognitive performance within a trial-ready framework for long COVID management.

Results

Preference-based PCO consistently revealed health losses not fully captured by conventional endpoints across conditions affecting brain health. In the Chilean community-based stroke cohort, EQ-5D utilities declined sharply across mRS categories and problems were common across all dimensions, particularly pain/discomfort (67%); notably, participants with mRS 0–1 still reported HRQoL impairment, indicating residual burden despite “favourable” disability. In INTERACT3, 6-month patient-perceived burden was substantial and poorer HRQoL was largely explained by acute severity and baseline vulnerability, while variation by context (country and living situation) showed that similar disability did not equate to comparable lived health across settings. In TRIDENT, PCO improved from baseline and were largely maintained, with no clear treatment-by-time differences; cognition remained a consistent correlate of HRQoL, supporting a model where utilities add patient-valued meaning to traditional assessments. In STRONGER, baseline analyses showed marked HRQoL impairment alongside a heterogeneous cognitive profile, suggesting that lived health in PCC is strongly shaped by multidomain symptom impact—especially fatigue, affective symptoms, and sleep disturbance—beyond what standard cognitive tests capture at a single timepoint.

Conclusion

This thesis advanced patient-centred assessment of brain health by applying preference-based PCO across stroke, intracerebral haemorrhage, and post-COVID-19 condition. It shows that disability scales and cognitive tests remain indispensable, yet they do not fully capture what matters to patients—how health is experienced, valued, and lived in daily life. Preference-based utilities provide a common metric to summarise multidimensional burden across diseases and study designs, but require contextual interpretation because valuation choices, setting, assessment timing, and capacity for self-report can influence what is measured. By making otherwise under-recognised burden visible and comparable, PCO strengthen outcome interpretation, help identify high-burden subgroups, and support more targeted prevention, follow-up, and rehabilitation strategies that address the domains driving lived morbidity.

SECTION 1: BACKGROUND

1 INTRODUCTION

In recent years, the concept of brain health has garnered increasing attention, particularly within the context of aging populations and the rising prevalence of neurological disorders. Brain health refers to the state of brain functioning across cognitive, sensory, social-emotional, behavioural, and motor domains, allowing a person to realize their full potential over the life course, irrespective of the presence or absence of disorders.[1] This could be assessed in terms of competencies across the domains of “thinking, moving, and feeling,” encompassing, for example, the abilities pay attention, perceive, and recognize sensory input; to learn and remember; to communicate; to problem solve and make decisions; to have mobility; and to regulate emotional status. These domains are largely attributable to the functions of the brain, can be operationally defined and measured; are affected by environment, behaviours, and disease; and are potentially modifiable if changes are detected early enough.[2,3]

To maintain optimal brain function, the brain depends on adequate cerebral perfusion and a well-functioning neurovascular unit (NVU)—a dynamic interface of vascular and brain cells responsible for preserving neuronal homeostasis.[4] Vascular risk factors, such as hypertension, diabetes mellitus and dyslipidaemia, have deleterious effects on the structure and function of the NVU, leading to vascular remodelling and stiffness, impaired cerebral blood flow autoregulation, endothelial dysfunction, impaired neurovascular coupling and failure of clearance systems, resulting in neurovascular dysfunction and suboptimal brain health.[5]

The determinants of optimal brain health are multifactorial, including genetic predispositions, environmental influences, and behavioural choices. Vascular risk factors exacerbate brain damage through cardiovascular and cerebrovascular

pathways, leading to cognitive decline and neurological impairment.[2] (Figure 0-1). Epidemiological evidence has further reinforced the importance of addressing these risks: approximately 90% of all strokes are attributable to a small number of potentially modifiable factors, underscoring the critical role of primary prevention in reducing stroke burden.[6] Likewise, it is estimated that up to 40% of dementia cases may be prevented or delayed by targeting modifiable cardiovascular and lifestyle factors.[7]

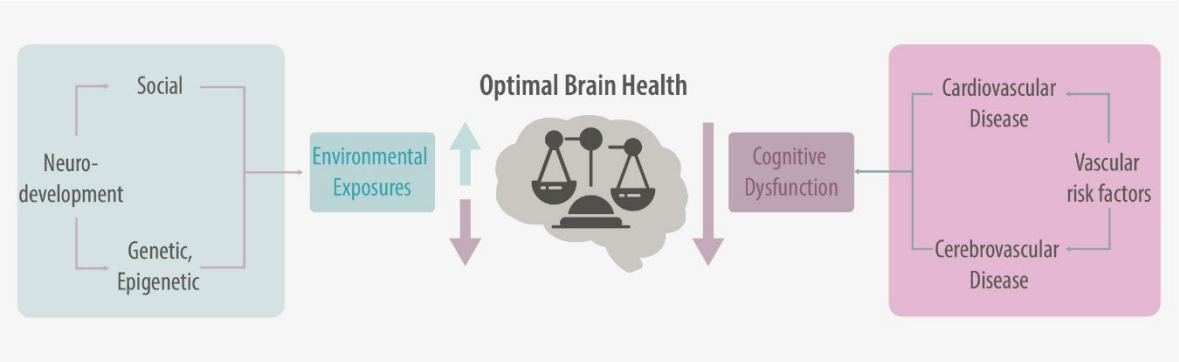

Figure 0-1. Major determinants of optimal Brain health.
Adapted from Gorelick et al 2017

With the global increase in life expectancy, the burden of diseases affecting brain health—such as stroke, cognitive impairment, and dementia—is rising steadily. For instance, the age-standardised incidence and prevalence of Alzheimer's disease and other dementias are projected to reach 145 and 822 cases per 100,000 people, respectively, by 2040.[8] As vascular and metabolic risk factors accumulate throughout the life course, the ageing brain becomes increasingly vulnerable to both acute events and progressive deterioration. Many of these conditions share modifiable risk factors, particularly vascular and metabolic ones such as hypertension, diabetes, and dyslipidemia.[9,10] As these risks accumulate over a lifetime, the ageing brain

becomes increasingly vulnerable to both acute and progressive neurological damage. These findings emphasise that brain health is not only clinically significant but also a realistic and urgent target for public health action.

Despite its intuitive appeal, the construct of brain health remains complex and lacks a universally accepted operational definition or standardized measurement approach.[11] This lack of consensus presents a significant challenge for research and clinical practice, particularly in designing and evaluating interventions targeting neurological outcomes. The problem is further compounded by the heterogeneity of neurological conditions, which vary widely in etiology, clinical presentation, and long-term consequences. Traditional neurologic outcome measures—such as mortality, lesion size, or clinician-rated disability scales—often fail to capture the full spectrum of impairment, especially subtle yet disabling symptoms like fatigue, executive dysfunction, and emotional disturbances, which significantly affect quality of life (QoL).[12] This disconnect hampers the comprehensive evaluation of disease burden and recovery.

Furthermore, many existing tools rely on ordinal scales that lack sensitivity and do not incorporate patients' preferences. The modified Rankin Scale (mRS), the most widely used outcome in stroke trials, exemplifies these limitations.[13,14] This 7-level scale (ranging from 0 = no symptoms to 6 = death) offers a broad assessment of disability; however, by its ordinal nature, it does not represent equal intervals of patient-perceived health between categories and cannot differentiate the relative value patients assign to different functional states.

This issue extends beyond stroke to other neurological conditions such as dementia,[15] Parkinson's disease,[16] and emerging post-viral syndromes like Long COVID.[17] Patients with Long COVID, for example, frequently report persistent cognitive "fog," fatigue, and emotional dysregulation long after the acute infection, symptoms that are difficult to quantify but profoundly impact daily life.[18] Similarly, survivors of intracerebral hemorrhage experience a complex interplay of physical, cognitive, and psychological sequelae that often remain underrepresented in clinical assessments.[19]

In recent years, other fields, such as oncology, have made significant advances by integrating patient-reported outcomes (PROs) into routine evaluation—assessing fatigue, pain, and well-being—thus capturing aspects of health that matter most to patients.[20,21] Incorporating similar approaches into neurology could enhance our understanding of how brain disorders affect individuals' lives and inform the development of more patient-centered interventions.

One of the most commonly used approaches to estimate utility values is through standardized instruments that capture patients' health-related quality of life (HRQoL). Among these, the EQ-5D is one of the most widely adopted.[22,23] It assesses HRQoL across five key domains—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—through patient self-report.[24] Each combination of responses is assigned a corresponding index value based on societal preferences, generating what is known as a *utility weight*. These values range from 0 (equivalent to death) to 1 (perfect health), with the possibility of negative scores for health states perceived as worse than death.[25,26]

These utility values offer several advantages. First, they enable comparisons across diverse conditions and interventions, providing a common metric to assess and prioritise health outcomes. Second, they serve as the foundation for calculating quality-adjusted life years (QALYs), a composite measure that incorporates both the quantity and quality of life lived. QALYs are widely used in health economics and policy-making to inform decisions about cost-effectiveness, resource allocation, and clinical guideline development. [25] Beyond their use in health economics, utility values represent a shift toward person-centred and preference-sensitive assessment frameworks. In stroke research, they have been incorporated into outcome measures through the development of the utility-weighted modified Rankin Scale (UW-mRS), which assigns each mRS category a corresponding utility score based on EQ-5D-derived preferences. [27,28] This approach transforms an ordinal functional score into a continuous, patient-informed outcome that is better aligned with real-world priorities.

These measures represent a shift toward more person-centred and preference-sensitive frameworks in health assessment—particularly relevant in complex and heterogeneous fields like neurology. Despite their strengths, these tools remain underused in neurology, especially in contexts marked by complex, long-term sequelae.

The focus of this thesis on two distinct populations—patients with Stroke and those affected by Long COVID—derives from their shared relevance as models of impaired brain health despite contrasting aetiologies. Stroke, and particularly ICH, represents the archetype of a vascular insult leading to abrupt neurological injury, while Long COVID illustrates an emerging infectious–inflammatory pathway to persistent

neurocognitive dysfunction.[18] Although the initiating mechanisms differ, both conditions converge on common pathophysiological processes such as neuroinflammation, endothelial dysfunction, and disruption of the neurovascular unit, ultimately compromising neuronal homeostasis and resilience. [29] Studying these two populations within the same framework therefore allows the evaluation of patient-centred outcomes across heterogeneous but complementary scenarios, testing the validity and generalisability of novel assessment strategies while capturing the multidimensional impact of neurological disease beyond conventional clinical endpoints.

This project seeks to address that gap by placing PCO at the centre of brain health assessment. By applying validated tools such as the EQ-5D and UW-mRS across diverse datasets—including prospective cohorts and clinical trials, the project will evaluate how cognitive performance, clinical characteristics, and self-reported health status intersect to define outcomes in people affected by post COVID-19 condition, and stroke. By focusing on what patients themselves report about their health, this research will contribute to a more comprehensive and person-centered model of outcome evaluation in neurology.

Ultimately, the aim is to support a paradigm shift: from a model of care and research grounded in biomedical endpoints, to one that values the individual experience of disease. By highlighting the importance of integrating PCO in the evaluation of brain health, this work will help fill a critical gap in the current landscape of neurological research and contribute to the development of more relevant, equitable, and human-centered healthcare strategies.

2 GENERAL AND SPECIFIC OBJECTIVES

2.1 General Objective

To apply novel assessment strategies for people with highly prevalent neurological conditions (long COVID or stroke), incorporating the impact on their daily lives, and compare these results to conventional clinical outcomes using clinical trials databases.

2.2 Specific Objectives

1. **Patient-centered assessment strategies: Conceptual Foundation**

   - To review and critically explain the existing patient-centered assessment strategies currently available in the literature.

2. **Application to Established Conditions**

   - To describe stroke burden and treatment strategies.
   - To apply and analyze patient-centered assessment strategies in the context of stroke.
   - To apply and analyze patient-centered assessment strategies in the context of the most devasting stroke that is ICH.

3. **Application to Emerging Conditions**

   - To provide a comprehensive description of long COVID.
   - To propose innovative therapeutic strategies for long COVID management, including the exploration of novel protocols such as STRONGER.
   - To apply and adapt patient-centered assessment strategies to Post COVID-19 condition

3.1 CHAPTER I: PATIENT-CENTERED ASSESSMENT STRATEGIES: CONCEPTUAL FOUNDATIONS

3.1.1 Chapter overview

This chapter provides the conceptual foundations for the use of PCOs in neurological research. It begins by reflecting on the limitations of traditional physician-centered measures and highlights the shift towards approaches that value patients' perspectives on their health and quality of life. In this context, utility-based methods are introduced as a way to translate patients' experiences into measurable outcomes that can be compared across different conditions. By outlining these principles, the chapter establishes the methodological basis upon which the subsequent analyses of this thesis are built.

3.1.2 Introduction

In the evolving landscape of clinical research and healthcare delivery, the integration of patient-centered outcomes (PCO) has become increasingly important. PCO are defined as outcomes that reflect the patient's own perspective on their health status, including the impact of illness and treatment on physical function, emotional well-being, social participation, and overall quality of life.[30] Unlike conventional clinical endpoints, which are typically clinician-reported or based on physiological measurements, these measures go beyond traditional clinician-reported endpoints, aiming to quantify aspects of health that patients themselves consider most important.

PCO can be classified into patient-reported outcomes (PROs), which provide detailed self-reported information about symptoms or functional limitations, and preference-based measures, which additionally assign a numerical value—known as a utility weight (UW)—to each health state. Utility weights are expressed on a continuous scale anchored by two reference points: 0, representing death, and 1, representing perfect health. Importantly, some health states may be valued as worse than death, resulting in negative utility values (Figure 1-1).

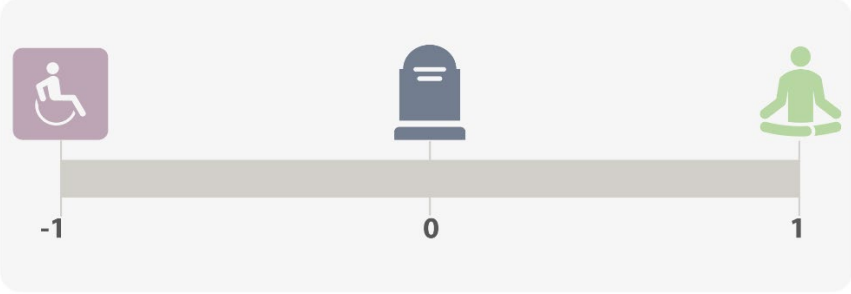

Figure 1-1 Utility weights scale

To generate preference-based measures that incorporate patient and societal values, PCO can be estimated through two main approaches: direct measurement and indirect estimation. The direct approach involves administering standardized instruments designed to produce a utility score, while the indirect approach relies on mapping scores from clinical outcome scales to pre-established utility values.

3.1.3 Direct Method

In the direct method, patients self-report their health status using standardized instruments, such as the European Quality of Life Scale (EQ-5D-3L),[13] the Health Utilities Index (HUI),[31] and the Assessment of Quality of Life (AQoL).[32] These tools describe health across multiple domains and levels of severity, producing a health profile.

These instruments rely on various elicitation methods to assign preference values to health states, the most common being the Standard Gamble (SG), Time Trade-Off (TTO), and Visual Analogue Scale (VAS).[33–35] The choice of instrument and elicitation method depends on factors such as the research question, the characteristics of the study population, and the intended application of results. It is important to distinguish between two components:

- Descriptive system: the self-reported health state profile provided by the respondent.
- Index value: the preference-based UW assigned to that profile, which varies depending on the country-specific value set.

3.1.4 Indirect Method

When direct utility data are unavailable, the indirect method is used to estimate UWs by linking clinical scale scores to previously obtained utility values. This is done through mapping algorithms developed in independent datasets.[36] In neurology, a common example is the derivation of utilities from the mRS, the most widely used measure of global disability after stroke.

In the present project, the indirect method is applied using the EQ-5D-3L as the reference instrument and mapping mRS scores to utility values to create the UW-mRS. This approach harmonizes outcome reporting across studies and facilitates cost-utility analysis in datasets where only mRS scores are available.

3.1.4.1 EQ-5D

The EQ-5D is a concise, generic measure of self-reported health that measures health in a way that can be compared across different sorts of patients, disease areas, and treatments. Since its development nearly three decades ago, it has become the most widely used Patient Reported Outcomes Measures (PROMS) questionnaire internationally, used in population health surveys, clinical studies and in routine outcomes measurement in healthcare systems.[37]

The EQ-5D instruments includes the original three-level version (EQ-5D-3L), a five-level version (EQ-5D-5L), and a youth version (EQ-5D-Y). While originally developed for use in economic evaluations, its brevity, validity, and versatility have led to its adoption in a variety of contexts, including large-scale PROMS programs aimed at healthcare quality improvement.[38]

The EQ-5D asks patients to indicate whether they have no, some, or extreme problems on each of five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the EQ-5D-3L (Table 1-1) three level problems are described in each dimension, representing no, moderate, or extreme problems. This structure yields 3^5=243 possible health states.

Each EQ-5D health state can be summarised as a five-digit code, with the digit in each position representing the level reported for the corresponding dimension (e.g., 11111 = no problems in any dimension; 22331 = some problems with mobility and self-care, extreme pain/discomfort, and some anxiety/depression). These codes form the ***descriptive system*** of the EQ-5D, and they are categories, not numbers, and do not even have ordinal properties. They do have a limited logical ordering, and in some cases can be used to compare profiles. For example, profile 11111 is better than profile 11112 (it logically dominates it) and 11112 is better than 11122. But we cannot say anything about *how much* better 11111 is compared to 11112. To compare health profiles, and to measure the magnitude of the difference between any profiles requires a scoring system that assigns weights to each profile***. EQ-5D value sets*** achieve that.[38 39]

Dimension	Level 1	Level 2	Level 3
Mobility	No problems walking about	Some problems walking about	Confined to bed
Self-care	No problems with self-care	Some problems washing or dressing	Unable to wash or dress
Usual activities	No problems performing usual activities	Some problems performing usual activities	Unable to perform usual activities
Pain / Discomfort	No pain or discomfort	Moderate pain or discomfort	Extreme pain or discomfort
Anxiety / Depression	Not anxious or depressed	Moderately anxious or depressed	Extremely anxious or depressed

Table 1-1 EQ-5D-3L descriptive system.

An ***EQ-5D value set*** is a complete list of the values assigned to every one of the 243 possible profile. These numbers are derived from population-based valuation studies, in which members of the general public are asked to express their preferences for different health states using techniques such as the Time Trade-Off (TTO), Standard Gamble (SG), or Visual Analogue Scale (VAS). Algorithms then assign scores to each level in each dimension—sometimes adjusting for interactions between dimensions—to produce the full set of values. Value sets are country-specific, reflecting cultural and societal differences in how health states are valued, and are sometimes referred to as tariffs.

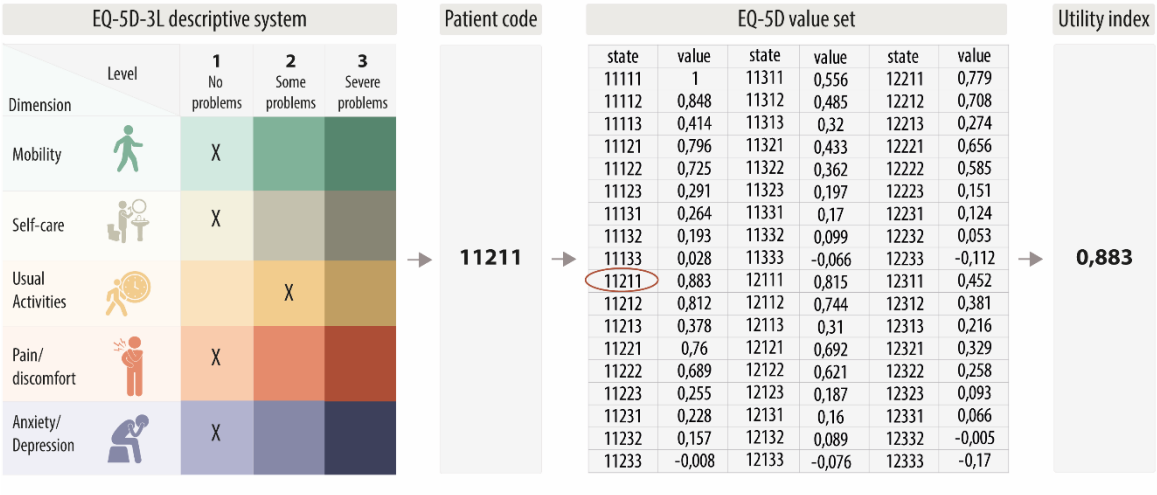

Figure 1-2. Calculation of the Utility Index from the EQ-5D-3L questionnaire.

Once the patient completes the questionnaire, a five-digit code is generated, which is then compared with the population value set to estimate the utility index.

3.1.4.2 From profile to utility index

To compare health states quantitatively, *value set* must be converted into a utility index. They can be obtained by matching their reported EQ-5D profile to the corresponding value in that set. This utility index ranges from 1 (full health) to 0 (dead), with negative values representing health states considered worse than death.[38] It allows comparisons across diseases and interventions, supports the calculation of quality-adjusted life years (QALYs), and provides a metric that incorporates patient- and society-based preferences into health outcome measurement (Figure 1-2).

3.1.4.3 Summarizing EQ-5D profiles

It is important to note that using the value sets to generate EQ-5D values data introduces a source of exogenous variance into the analysis of profile data which can bias statistical inference.[40] Each value set places a different weight on the various levels and dimensions of the profile data, reflecting underlying differences in

preferences, the methods used to elicit them, or both. This means that whether there are statistically significant differences in the EQ-5D values between, for example, two arms of a clinical trial, or between two regions in a national health survey, may depend on which value set is used, and the relative importance it puts on the different types of health problems and improvements in them. More generally, there is no neutral way to summarise the data from the EQ-5D profile into a single number.

Finally, an important consideration is that attaching values to descriptive data introduces an exogenous source of variance, which can bias statistical inference.[40,41] This is a special problem for applications where people's preferences are not directly relevant and is a key reason why it should not be assumed that values provide a suitable index for non-economics applications. Conclusions about whether there are statistically significant differences in, for example, the health of 2 regions, or health over time, or between 2 arms of a clinical trial, may be influenced by which value set is used.

An obvious advantage of using a summary value to represent a health profile is that it simplifies statistical analysis. But since all value sets embody preferences about the relative importance of each level of each dimension, it is not possible to offer generalised guidance about which value set to use if the objective is to summarise profiles for descriptive or inferential statistical analysis.

3.1.4.4 From mRS to UW-mRS using the indirect method

The mRS is the most widely used global disability outcome in stroke research, ranging from 0 (no symptoms) to 6 (death) (Figure 1-3). While clinically intuitive and easy to administer, the mRS is ordinal in nature: the difference in health status

between adjacent categories is not necessarily proportional to patient-perceived changes in quality of life. For example, moving from mRS 4 to 3 (regaining some independence) may be valued much more by patients than moving from mRS 2 to 1 (minor residual symptoms), even though both represent a one-point change on the scale. These nuances are often lost in conventional analyses, which tend to overlook individual patient perspectives.[42,43]

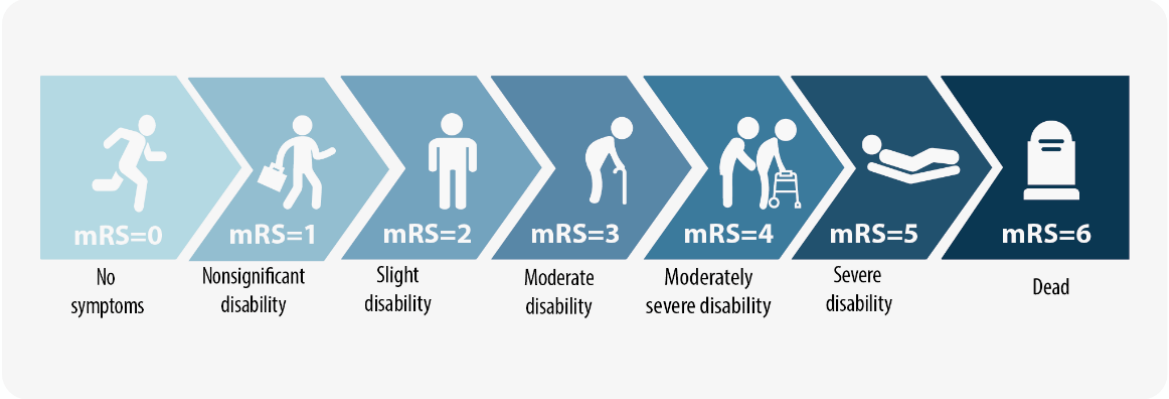

Figure 1-3 modified Rankin Scale

The UW-mRS addresses this limitation by transforming the ordinal mRS into a continuous, preference-based measure. This is achieved by assigning utility weights to each mRS category based on valuations of HRQoL obtained from instruments such as the EQ-5D.[27,44] The resulting scale integrates both survival and functional status into a single metric.

3.1.4.4.1 Methodological approach

The derivation of UW-mRS values involves three key components:

a. Selection of the reference HRQoL instrument and value set

A validated preference-based instrument—most commonly the EQ-5D—is chosen as the reference for utility estimation. The EQ-5D descriptive profiles are converted

into a utility index using a country-specific value set (or tariff) derived from population-based valuation studies. The value set reflects societal preferences for different health states and determines the mapping between mRS categories and utility values.

b. Mapping mRS scores to utility values

A mapping function or look-up table is developed in a dataset containing paired measurements of mRS and EQ-5D (or another reference instrument). In most cases, ordinary least squares (OLS) regression is used, with the EQ-5D utility index as the dependent variable and mRS score as the independent variable. Covariates may be included to improve precision, but in its simplest form, the model yields an average utility weight for each mRS category.[27,44]

c. Assigning utilities to mRS categories in the study dataset

Once the mapping is established, each patient's mRS score is replaced by the corresponding utility weight. Death (mRS = 6) is generally assigned a utility of 0, although some algorithms allow for states worse than death (negative utilities) if the reference value set supports this. This produces a continuous outcome variable that can be averaged, compared between groups, and used to calculate quality-adjusted life years (QALYs) over time.

3.1.4.4.2 Procedure

First, for each participant, the EQ-5D-3L responses across its five dimensions are converted into a utility index using a country-specific value set. In this case, the Chilean EQ-5D-3L tariff, derived using the time trade-off (TTO) method in the Chilean population,[45] was applied to local datasets, while the UK value set was used for the

INTERACT-3 and TRIDENT trials.[46] This tariff assigns a numerical weight to each level within each dimension, with potential adjustments for combinations of severe problems, producing a utility value for each of the 243 possible EQ-5D-3L health states.

$$U_{\{EQ5D\}} = 1 - \sum_{\{i=1\}_{i(l_i)}}^{\{5\}w} wi\,(li) - N3 \times w_{\{N3\}}$$

Where:

- l_i = level reported in dimension *i*
- $w_i(l_i)$ = weight assigned to level *l* in dimension *i*
- N3 = indicator variable (1 if any dimension is at level 3; otherwise, 0)
- w_{N3} = additional weight for severe problems (level 3)

Next, the relationship between mRS categories and EQ-5D-derived utilities is estimated using ordinary least squares regression, with the EQ-5D utility as the dependent variable and mRS categories as independent variables. mRS 0 is used as the reference category, and dummy variables are included for mRS 1 to 5, while mRS 6 (death) is assigned a utility value of 0 by definition. The predicted mean utility from the regression model for each mRS category represents the utility weight for that level. These category-specific weights form the UW-mRS look-up table.

$$\overline{U}_{\text{mRS}=k} = \frac{1}{n_k}\sum_{j=1}^{n_k} U_{\text{EQ5D},j}$$

Where n_k = number of participants with mRS = *k*.

Finally, this table is applied to any dataset containing mRS scores to generate the corresponding UW-mRS values. Each mRS score is replaced by its assigned utility weight, yielding a continuous outcome measure that incorporates both the quantity and quality of life. This transformation allows for more sensitive comparisons between groups, facilitates the estimation of QALYs through integration over time, and ensures that outcome assessment reflects patient and societal preferences.

3.1.4.4.3 UW Interpretation

The interpretation of the UW presents several conceptual and methodological challenges. While UWs provide a more patient-centered representation of outcomes than traditional clinical scales, their meaning depends on how score changes are defined, valued, and contextualized.

One important issue is distinguishing between statistical significance and clinical relevance. Small changes in UW may be statistically detectable but clinically trivial, whereas larger differences may reflect meaningful shifts in patients' quality of life. To clarify this, two related concepts are essential. The *minimally detectable change* (MDC) refers to the smallest change beyond measurement error, while *minimally important change* (MIC) corresponds to the smallest change perceived as important by patients or clinicians.[47] Importantly, MIC thresholds are not universal; they vary depending on the instrument, the descriptive system, and the population under study. In stroke cohorts, anchor-based studies using EQ-5D have estimated MIDs of approximately 0.08–0.12, values often used as benchmarks when interpreting changes in utility.[48] Establishing MIC values for the UW-mRS remains a key methodological priority, as they help determine when an intervention truly improves or worsens a patient's condition.

When applied to the modified Rankin Scale, the UW-mRS translates ordinal disability categories into utilities to approximate interval-level meaning. However, score differences are not uniformly interpretable across the continuum: a one-point change may represent a profound shift in independence at severe levels, but only a marginal improvement at the mild end of the scale. Moreover, utilities derived from different instruments (e.g., EQ-5D vs AQoL) or national value sets may yield substantially different results, and patients within the same mRS category can present wide variability in utility values.[49] Therefore, UW-mRS differences should be interpreted with caution. In the absence of specific MIC/MID thresholds, a practical approach is to (i) anchor changes to external criteria (e.g., mRS categories or EQ-5D shifts) and compare them with known utility MIDs (≈0.08–0.12 for EQ-5D in stroke), (ii) confirm changes exceed the MDC (derived from the SEM of mapped utilities), and (iii) consider directionality, since larger declines are often needed for patients to perceive worsening than for improvement. [47,48]

In summary, while the UW-mRS advances the field by integrating patient utilities into stroke and neurological outcomes, its interpretation requires caution. Defining thresholds for meaningful change, accounting for measurement error, and recognizing the unequal impact of score differences across the scale are essential to avoid misrepresentation of patients' experiences and to ensure robust conclusions in clinical trials.

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SECTION 2: STROKE

3.2 CHAPTER II: STROKE BURDEN AND TREATMENT STRATEGIES

3.2.1 Chapter overview

This chapter summarises the burden of stroke as a leading cause of death and disability worldwide, highlighting regional disparities and evidence gaps in Latin America and the Caribbean. It then outlines key treatment strategies across the stroke spectrum, distinguishing time-critical reperfusion and secondary prevention in IS from bundled acute care and blood-pressure–centred prevention in intracerebral haemorrhage.

By framing stroke as both a major public health challenge and a condition with evolving, system-dependent care pathways, the chapter provides the clinical and epidemiological context for the subsequent thesis investigations.

3.2.2 Stroke as a global health priority

Stroke is a clinical syndrome of acute neurological dysfunction caused by focal disturbance of cerebral circulation, resulting from either vessel occlusion (ischaemic stroke [IS]) or vessel rupture, the latter encompassing both intracerebral haemorrhage (ICH) and subarachnoid haemorrhage.[1] While IS accounts for most incident events globally ICH contributes disproportionately to early mortality and severe disability in many settings, reinforcing the need to distinguish stroke subtypes when describing burden and when framing care pathways.[2]

The most recent Global Burden of Disease (GBD) 2021 analysis shows that, despite declines in age-standardised rates in many countries, the absolute numbers of incident strokes, stroke deaths, and disability-adjusted life years (DALYs) have risen from 1990 to 2021.[3] This pattern reflects population growth and ageing, compounded by trends in key risk factors—most notably elevated systolic blood pressure, obesity, diabetes, and other cardiometabolic exposures.[3,4] From a health-system perspective, these trends translate into sustained demand for hyperacute care, inpatient management, rehabilitation, and long-term follow-up services.[5]

3.2.3 Disparities in stroke

This burden is not uniform across regions, and contemporary evidence highlights important gaps in epidemiological surveillance in Latin America and the Caribbean (LAC). A recent systematic review emphasised that few robust population-based data are available for LAC and that existing estimates are highly heterogeneous, underscoring the need for comparable designs and standardised methods for case ascertainment, data collection, and reporting.[6] Across the included studies, the

pooled crude annual incidence of first-ever stroke in LAC was 119.0 per 100,000, with wide variability between settings, and the pooled 1-month case-fatality after first stroke was 21.1%. Notably, ICH contributed disproportionately to early mortality: in subgroup analyses from the same review, 1-month case-fatality was substantially higher for ICH (38.0%) than for IS (13.3%), reinforcing ICH as a high-severity stroke phenotype and a priority for targeted improvements in acute care and prevention.

This excess early mortality is consistent with global evidence that ICH represents a particularly severe and resource-intensive stroke subtype. ICH accounts for approximately 28.8% of incident strokes, with an age-standardised incidence of around 40.8 per 100,000 population and roughly 3.44 million new cases worldwide in 2021. Although age-standardised rates have declined over recent decades, the absolute burden remains high, with mortality and disability rates disproportionately elevated in lower Socio-demographic Index settings. [7,8] Globally, ICH resulted in 3.31 million deaths and 79.46 million disability-adjusted life years (DALYs), with age-standardized mortality and DALY rates still significantly elevated in settings with lower Socio-demographic Index.[9]

3.2.4 Consequences beyond survival

Improvements in acute care have increased survival, but this has also expanded the number of people living with long-term post-stroke sequelae.[10] Post-stroke disability encompasses a wide range of impairments, including motor deficits, language disorders, sensory loss, and cognitive impairment, as well as psychological and emotional disturbances such as depression, anxiety, and post-stroke fatigue.[11] These consequences can persist for months or years after the event, significantly limiting independence and quality of life.[12,13] In ICH specifically, recovery is often

protracted and incomplete, and discordance between clinician-rated disability and patient-perceived health status is common, reinforcing the need to measure outcomes that reflect lived experience rather than impairment alone.[14]

From a societal perspective, stroke—including IS and ICH— generates high healthcare utilisation, prolonged rehabilitation needs, productivity losses, and extensive informal caregiving, with particularly severe consequences in LMICs where access to specialised post-acute services and community-based supports is frequently constrained. A comprehensive analysis across Europe estimated that in 2017, the total annual cost of stroke—including medical care, social services, productivity losses, and informal care—reached approximately €60 billion, of which informal caregiving alone accounted for €16 billion and productivity losses for €12 billion.[15] The magnitude of this impact is particularly evident in low- and middle-income countries (LMICs), where access to specialised rehabilitation services is limited, and community-based support structures are often underdeveloped.[16]

Recent regional evidence reinforces these global patterns. A comprehensive analysis of stroke trends across 38 countries and territories of the Americas from 1990 to 2021 demonstrated that, although age-standardised mortality rates have declined in most settings, the absolute number of stroke cases, deaths, and DALYs continues to increase, driven primarily by demographic ageing and persistent exposure to vascular risk factors. The study further revealed striking disparities: while North America has seen consistent reductions in both incidence and disability burden, Latin America and the Caribbean continue to carry disproportionately higher rates of stroke-related morbidity and mortality.[17]

3.2.5 Treatment strategies across the stroke pathway

For IS, acute reperfusion therapies (intravenous thrombolysis and mechanical thrombectomy in eligible patients) can substantially improve outcomes when delivered rapidly, and are complemented by secondary prevention focused on vascular risk reduction.[18] In practice, the effectiveness of these strategies is highly dependent on pre-hospital systems, rapid recognition, organised stroke pathways, and equitable access to imaging and specialist care—factors that vary substantially across regions and strongly shape real-world impact.

In contrast, acute ICH management has historically relied on timely physiological optimisation and complication prevention.[19] Recently, INTERACT3 trial operationalised this concept through a pragmatic, goal-directed care bundle for acute spontaneous ICH, anchored in early intensive blood pressure lowering (target systolic blood pressure <140 mm Hg) combined with structured management algorithms for hyperglycaemia, pyrexia, and abnormal coagulation. This bundle was shown to be safe and to improve functional outcomes at 6 months, with favourable effects on survival and HRQoL, supporting the implementation of bundled, time-sensitive acute ICH care across diverse health systems.[20]

3.2.6 Long-term prevention after stroke: sustained risk-factor control

Long-term prevention is central to reducing recurrent events and cumulative disability after both IS and ICH. For ICH survivors in particular, blood pressure control remains a cornerstone modifiable target. However, achieving sustained control is frequently limited by adherence barriers and therapeutic complexity in real-world settings. In this context, the TRIDENT trial evaluated a fixed low-dose single-pill

“triple pill” strategy (telmisartan, amlodipine, and indapamide) added to standard care to intensify and simplify blood pressure lowering after ICH, aiming to reduce recurrent stroke and other vascular outcomes while addressing barriers that commonly limit effectiveness in routine practice. [21]

The epidemiology of stroke and the evolution of its treatments establish stroke as a major source of potentially preventable brain health loss. However, the benefits of acute and preventive strategies are not uniform and depend on timely delivery, health-system capacity, and continuity of care—factors that vary substantially across settings, including Latin America and the Caribbean. This context is essential for this thesis because it motivates the need to quantify outcomes beyond survival and crude disability, capturing the patient-experienced consequences of stroke across recovery. The next chapter therefore introduces patient-centred outcomes in stroke and the rationale for preference-based measures as a complementary lens to describe and compare lived brain health compromise across populations and study designs.

3.3 CHAPTER III: PATIENT-CENTERED OUTCOMES IN STROKE

3.3.1 Chapter overview

Building on the preceding chapter's description of stroke burden and treatment strategies, this chapter introduces PCO in stroke and argues that preference-based metrics can complement conventional endpoints by incorporating HRQoL valuations. Using the UW-mRS at 180 days in a Chilean population-based cohort, the chapter shows that utilities decrease consistently with increasing disability and that severe post-stroke dependence is associated with substantial health utility loss when valued using a local EQ-5D-3L tariff.

The analyses further indicate that patient-centered outcomes after stroke are shaped by baseline vulnerability and initial stroke severity, as measured by the National Institutes of Health Stroke Scale (NIHSS). Older age, pre-stroke disability, and greater neurological impairment at admission emerged as key determinants of worse UW-mRS, alongside sex- and subtype-specific patterns after multivariable adjustment. Overall, the chapter positions UW-mRS as a feasible and informative endpoint for real-world stroke research in Chile and establishes the methodological foundation for subsequent thesis chapters applying preference-based outcomes across the stroke spectrum.

3.3.2 Introduction

Despite the therapeutic advances, traditional endpoints in stroke research (mortality, imaging markers, or clinician-rated disability scales such as the mRS) may fail to capture the full spectrum of consequences experienced by survivors, particularly “invisible” cognitive and psychosocial limitations that strongly influence daily functioning and well-being.[22] For example, subtle but disabling symptoms, such as executive dysfunction or reduced participation in daily activities, are often overlooked despite their substantial influence on patient well-being.[11] This gap underscores the importance of incorporating PCO into both research and practice.

PCO enable a more holistic evaluation of recovery, integrating the patient’s own perspective on their health status and daily functioning. This approach aligns outcome measurement with what matters most to patients—such as autonomy, cognitive clarity, and social participation—rather than solely focusing on biomedical parameters. In this context, preference-based measures like the UW-mRS offer an important bridge between traditional disability scales and HRQoL assessment, facilitating both clinical interpretation and health-economic evaluation.[23,24]

Within this thesis, applying UW-mRS to population-based stroke outcomes in Chile provides context-specific evidence on the patient-experienced impact of stroke and clarifies which baseline and acute factors drive utility-weighted recovery. This framing sets up the next chapters, where preference-based outcomes are extended to other stroke phenotypes and study designs, including analyses focused on ICH.

3.3.3 Article

Patient centered outcomes in stroke: utility-weighted modified Rankin Scale results in a community-based study

Doi: 10.3389/fneur.2025.1539107

3.3.3.1 Introduction

According to the most recent Global Burden of Disease (GBD) study, stroke remains one of the leading cause of death and disability combined worldwide.[23] Between 1990 to 2019, the global burden of stroke, in terms of absolute number of cases, increased substantially, with the majority (86.0% of deaths and 89.0% of disability-adjusted life years, DALYs) residing in low- and lower-middle-income countries (LMICs).[2] Given the wide range of functional disability among stroke survivors, it is crucial to accurately measure and classify these impairments.

Several scales have been developed to categorize stroke patients. The mRS, a seven-level scale of global impairment and disability is widely used as a functional outcome measure in both clinical research and practice.[24] While the mRS provides valuable insights into functional status, it does not reflect the broader impact on quality of life.[21] Moreover, its power is limited when analysed dichotomously and its indication of effect size is difficult to interpret when analysed ordinally.[25] Therefore, the development of a UW-mRS, which incorporates a health utility scale as PCO, is recommended and has been used in several recent clinical trials.[26,27] Health utility weights represent the preference for a specific health outcome, allowing comparison of quality of life across different clinical settings.[28] They range from perfect health (a score of 1) to outcomes worse than death (where death is scored as 0 and negative

values indicate worse-than-death states). The utility approach offers several advantages: it aligns with the principles of economic evaluation, enables broad comparisons, and provides a detailed view of patients' experiences, highlighting both improvements and declines in health status.[28] Despite these benefits, the application of UW-mRS outside the clinical setting remains limited.[29]

The aim of this study was to incorporate the quality-of-life perspective into functional scales and analyze its determinants, by developing the UW-mRS as an outcome measure for patients 180 days after suffering a stroke, using data from the Ñuble population between 2015 and 2017.

3.3.3.2 Material and methods

Individual participant data were pooled from the ÑANDU study, a large prospective community-based study in Chile, whose methodology and results have been previously published.[32] At 180 days after the event, trained personnel conducted telephone interviews to evaluate the patients. Information was collected on recovery, dependency, and health-related quality of life.

Instruments

The mRS is a widely used tool for assessing health outcomes in stroke patients (11). The mRS evaluates the level of disability by considering activity limitations and lifestyle changes. The scale has 7 grades, from 0 to 6: 0 means no symptoms, 5 means severe disability, and 6 indicates death.[24]

The EuroQol EQ-5D-3L is a questionnaire designed to measure a patient's health status preferences (12). It consists of 5 dimensions: mobility, self-care, usual activities, pain, and anxiety. Each dimension has 3 levels: no problems, some

problems, and extreme problems, coded from 1 to 3.[31] The EQ-5D-3L health states are represented by a sequence of 5 numbers that describe each level within each dimension. For example, 11111 indicates perfect health, while 33333 represents the worst possible health state. The system defines 243 possible health states, each of which can be supplemented using a scoring or weighting system to convert profile data into a single numerical value: the EQ-5D-3L values.[32] These scoring systems are typically preference-based, meaning that the problems in each dimension are weighted to reflect public perception of their severity. The EQ-5D-3L index values are constructed on a scale anchored at 1, representing full health, and 0, representing death.[32]

The EQ-5D-3L value set was selected from a previous study conducted in Chile, which evaluated the health status of the general population using the Time Trade-Off technique.[33] Patients who died during follow-up (mRS = 6) were assigned an EQ-5D-3L value of 0 (zero).

Statistical analyses

Quantitative variables were reported as means (SD) or medians (IQR) depending on normality (using K-S test) and were compared according normal/ non-normal distribution using the T test or Mann–Whitney U test. Qualitative variables were reported as absolute and percentage prevalence and were compared using the $\chi 2$ test or Fisher's exact test, as appropriate.

UW-mRS scores were calculated only for patients alive during follow-up using an ordinary least squares regression model, with mRS scores as discrete ordinal dummy variables and EQ-5D scores as the continuous response variable, adhering

to the methodology established by prior studies.[34] UW-mRS scores were obtained and validated separately for acute IS, intracerebral hemorrhage, and by sex. A simple linear regression analysis was performed to identify variables associated with UW-mRS scores. Multivariable linear regression models were subsequently used to evaluate factors influencing UW-mRS, including both variables significantly correlated in the simple analysis and those considered clinically relevant. This included sex, age over 70, low socioeconomic status, urban residence, prior disability (mRS 3–5), stroke type, and an NIHSS score above 5 at admission. An alfa level of 5% ($p < 0.05$) was considered significant, and 95% confidence intervals were used. Data were processed using STATA software (version 18.5).

3.3.3.3 Results

Of the 1,103 patients who experienced a stroke between 2015 and 2016, 890 were a first-ever stroke. At 180 days post the acute event, 773 patients were evaluated, with a 13% loss to follow-up. Baseline characteristics are summarized in Table 3-1. The cohort consisted of 398 (51%) females, with a mean age of 70.6 years (14.1). Nearly half of the patients (386, 49.9%) had less than 12 years of formal education, and 533 (82%) were classified as having low socioeconomic status based on their public health insurance classification.[35] 536 (65%) patients experienced an AIS, had a median NIHSS score of 5 (IQR 3–11), and a median hospital stay of 9 days (IQR 4–15).

Demographics (n,%)	
Age, mean SD	70.6 (14.10)
Female	398 (51)
<12 years of formal education	386 (49.93)
Occupation	
- Homemaker	166 (21)
- Dependent work	63 (8)
- Self-employment	97 (13.5)
- Pensioner	96 (12.5)
- Unknown	347 (45)
Urban resident[a]	248 (32)
Low socioeconomic status[b]	533 (82)
Premorbid modified Rankin Scale (n, %)	
0-2	171 (32)
3-5	47 (8)
Unknown	374 (60)
Risk factors, (n, %)	
Hypertension	498/619 (80)
Atrial Fibrillation	58/617 (9)
Diabetes Mellitus	221/618 (36)
Acute coronary syndrome	44/616 (7)
Hypercholesterolemia	56/617 (9)
Stroke subtype, (n, %)	
Acute ischaemic stroke	536 (69)
Intracerebral haemorrhage	106 (14)
Subarachnoid haemorrhage	44 (5)
Cerebral venous thrombosis	4 (1)
Undetermined	83 (11)
Stroke severity (median, IQR)	
NIHSS at admission (n= 494)	5 (3-11)
Glasgow coma scale (n= 274)	15 (14-15)
Median time of hospitalization in days (IQR)	9 (4-15)
Modified Rankin Scale (mRS)	
0-2	341(44)

3-5	165 (21)
6	267(35)
Any change in EQ-5D-3L (level 1 or 2)[c]	
Mobility (n=506)	279 (53)
Self-Care (n= 505)	181 (36)
Usual activities (n= 504)	257 (53)
Pain/Discomfort(n=502)	336 (67)
Anxiety/Depression(n=499)	263 (53)
[a] Based on the sociodemographic characterization of the patient's municipality of residence at the time of the 2017 census. [b] Among those with National Healthcare insurance; NIHSS, National Institutes of Healt Stroke Scale; c Dead patients or patients with no information were excluded.	

Table 3-1 Baseline characteristics of th 1Table 3-1 Baseline characteristics of the 773 patients with first ever stroke (FES) followed at 180 days.

At 180 days post-acute event, 41% of patients had an mRS score of 0–2, 21% had a score of 3–5, and 35% had died (Table 3-1; Figure 3-1). Among patients with hemorrhagic stroke, 62% died, compared to 21% of those with an AIS ($p < 0.001$). No significant differences were observed in the distribution of mRS scores by sex (Supplementary Material).

In the EQ-5D-3L assessment, the most affected dimension was pain/ discomfort (67%), followed by mobility and anxiety/depression (53%). Figure 3-2 shows the distribution of the EQ-5D-3L for each mRS category. There was a strong negative association between mRS and EQ-5D-3L index values overall ($r = -0.82$; $p < 0.001$; Supplementary Material).

The UW-mRS values, calculated from the mean EQ-5D-3L utility scores from the Chilean population,[33] across mRS categories 0–6 at 180 days, were: 0.913, 0.694, 0.425, 0.249, −0.102, −0.347 and 0, respectively (Table 3-2). When disaggregated by sex, females tended to have slightly lower UW-mRS values compared to males,

though this difference was not statistically significant (p = 0.194, Figure 2-3). In terms of stroke type, IS survivors had lower UW-mRS scores than those with hemorrhagic stroke at 180 days post-acute event (Figure 3-3).

A linear regression analysis was conducted to explore the relationship between UW-mRS scores and key variables. In the simple regression, significant associations were found between age > 70 years (Coefficient β [β] −0.007 [Standard error SE] 0.001, p < 0.001), lower socioeconomic status (β −0.075 [SE 0.040], p < 0.001), previous mRS score of 3–5 (β −0.607 [SE 0.018], p < 0.001), IS subtype (β −0.025 [SE 0.041], p < 0.001), and NIHSS >5 at admission (β−0.273 [SE 0.028], p < 0.001) with worse outcome (Table 3-3). In the multivariable model, age > 70 years (β −0.038 [SE 0.018], p = 0.032), previous mRS score of 3–5 (β −0.556 [SE 0.197], p < 0.001), IS (β −0.066 [SE 0.025] p = 0.010), and NIHSS >5 at admission (β −0.015 [SE 0.002], p < 0.001) remained significant predictors of lower UW-mRS scores, with an R2 of 70%. When the multivariable model was disaggregated by sex to assess potential differences, the previous mRS score of 3–5 and NIHSS >5 at admission were associated to worse UW-mRS in both sexes (Supplementary Material). Distinctly, age > 70 years was significant for males (β −0.069 [SE 0.024], p = 0.006) and having an AIS was significant for females (β −0.087 [SE 0.033], p = 0.010) (Figure 3-4; Supplementary Material). The model explained a similar proportion of variance in both groups, with an R2 of 69% for females and 72% for males (Supplementary Material).

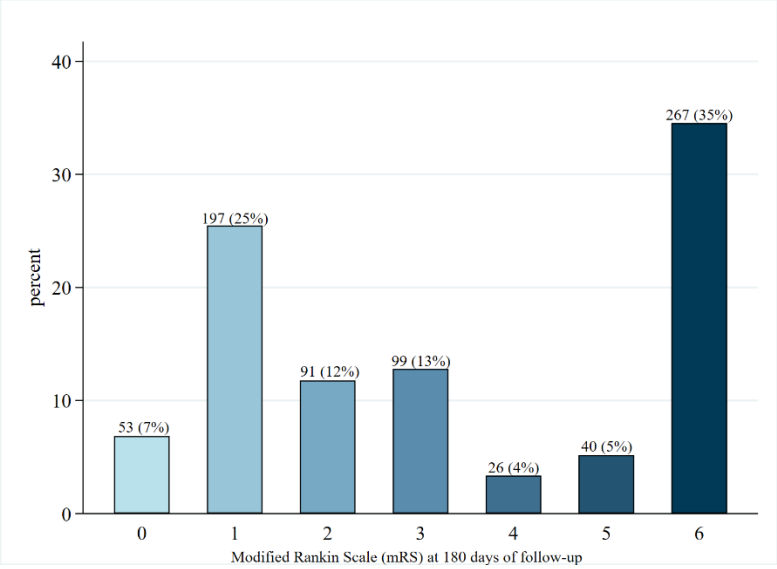


Figure 3-1 Modified Rankin Scale (mRS) at 180 days after the acute event.

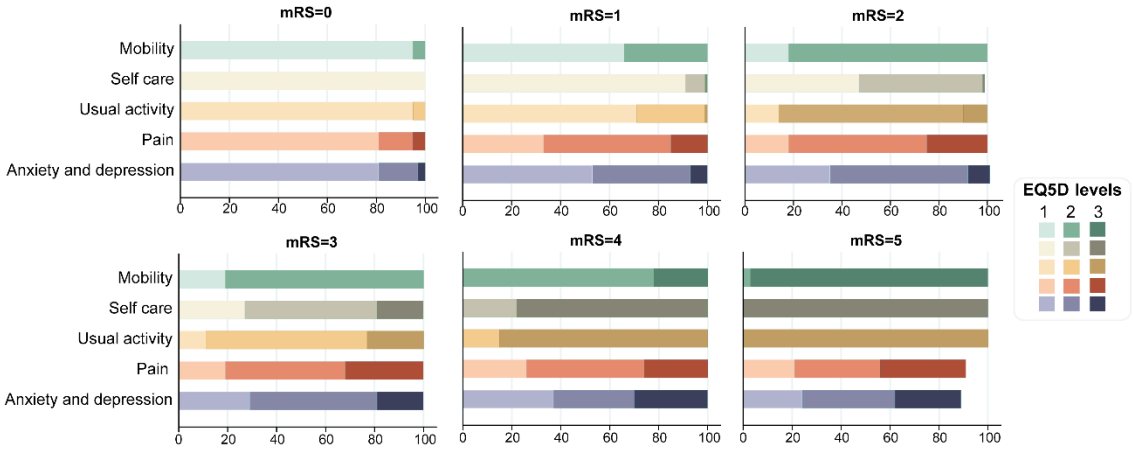


Figure 3-2 European quality of life 5-dimensional questionnaire utility scores by modified Rankin Scale scores at 180 days of follow up.

mRS	UW-mRS	SD
0	0.913	0.157
1	0.694	0.234
2	0.425	0.425
3	0.249	0.294
4	-0.102	-0.102
5	-0.347	-0.347
6	0	0

mRS: modified Rankin Scale, UW-mRS: utility-weighted modified Rankin Scale, SD: standard deviation.

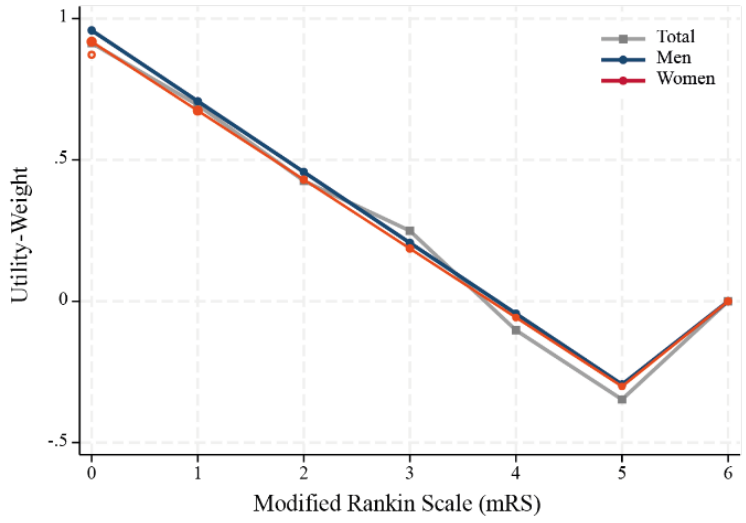
Table 3-2 UW-mRS values derived for each category of the modified Rankin scale

	Simple			Multivariable Model		
	Coefficient β	**Standard error**	**P value**	**Coefficient β**	**Standard error**	**P value**
Sex	0.059	0.030	0.052	-0.006	0.171	0.710
Age >70 years old	-0.007	0.001	**<0.001**	**-0.038**	**0.018**	**0.032**
<12 years of formal education	-0.029	0.030	0.347	-0.010	0.017	0.546
Low socioeconomic status [a]	-0.075	0.040	0.063	0.006	0.022	0.781
Urban resident	-0.007	0.032	0.812	0.009	0.017	0.613
Previous mRS 3-5	-0.607	0.018	**<0.001**	**-0.556**	**0.197**	**<0.001**
Acute IS	-0.025	0.041	0.529	**-0.066**	**0.025**	**0.010**
NIHSS at admission >5	-0.273	0.028	**<0.001**	**-0.015**	**0.002**	**<0.001**
Constant	**-**	**-**	**-**	**0.775**	**0.034**	**<0.001**
$R^{2:}$ 70%						

[a] Among those with National Healthcare insurance; NIHSS, National Institutes of Health Stroke Scale.

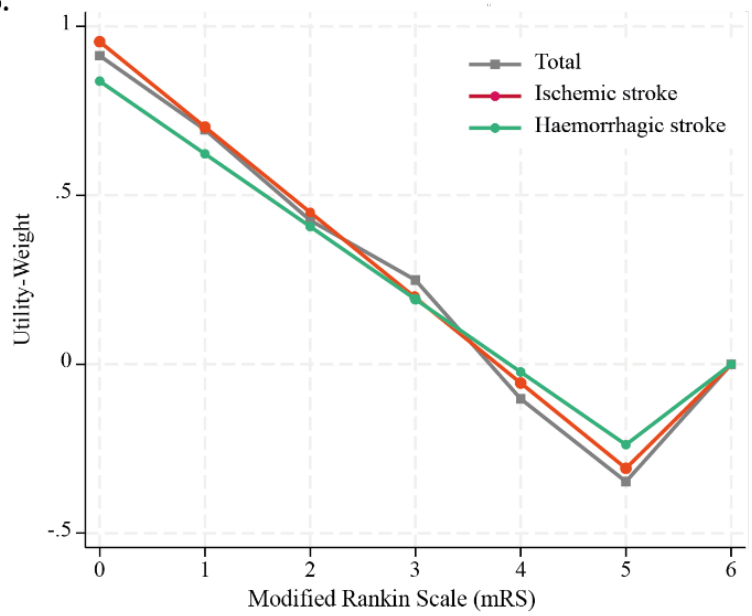
Table 3-3 Results of Simple and Multivariable Linear Regression Models Analysing Factors Associated with UW-mRS Scores

a.



mRS	UW-mRS Men (n=375)	UW-mRS Women (n=398)
0	0.958	0.918
1	0.707	0.674
2	0.457	0.430
3	0.206	0.186
4	-0.048	-0.057
5	-0.294	-0.301
6	0	0

b.



mRS	UW-mRS Ischemic (n=375)	UW-mRS Haemorrhagic (n=398)
0	0.954	0.918
1	0.702	0.674
2	0.449	0.430
3	0.197	0.186
4	-0.055	-0.057
5	-0.308	-0.301
6	0	0

Figure 3-3 UW-mRS score derived from the regression model by sex, and stroke subtype

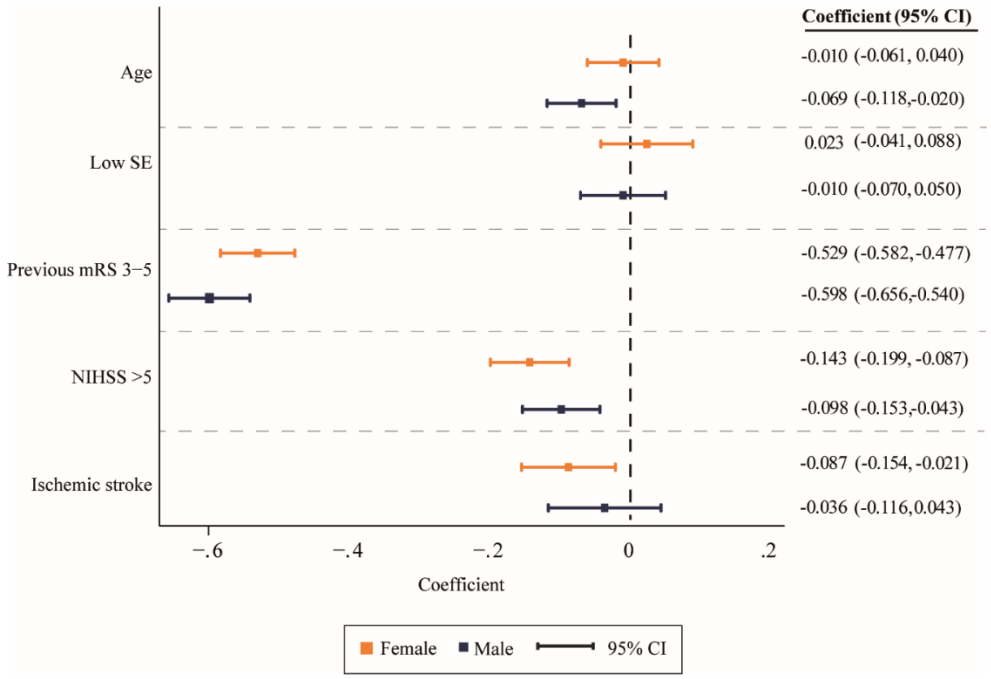


Figure 3-4 Multivariable model coefficients assessing risk factors by sex with 95% confidence intervals.

3.3.3.4 Discussion

The present study examined the distribution of health outcomes in a Chilean population-based cohort of patients who suffered an acute stroke. To our knowledge, this study is the first to derive a quality-of-life scale, like the EQ-5D-3L, using the UW-mRS in a community-based study, incorporating the patient perspective outside of controlled clinical settings. At 180 days post-stroke, 35% of patients had died, and among the survivors, the most affected dimension of the EQ-5D-3L were pain/discomfort, followed by mobility and anxiety/depression. These results align with studies comparing healthy populations in other countries within the region[36] and in countries like China. [37]

The UW-mRS values demonstrated a gradual decline in utility as mRS scores increased, reflecting the expected deterioration in health-related quality of life as

disability worsened. These findings corroborate those of Wang et al., who applied similar methodologies based on cohorts from clinical trials. [34] Their reported utility values for mRS scores 0-6 were 0.96, 0.88, 0.74, 0.56, 0.25, -0.11, and 0, respectively. Notably, the utility values for mRS 4 and 5 were significantly lower in the Chilean population, resulting in negative values, which suggest a more severe perception of quality of life at the same mRS level compared to Wang et al.'s cohort. This variation may be attributed to cultural differences in health perception, disparities in access to healthcare, or other socioeconomic factors [32,38] as well as the methodological differences between studies that derived the EQ-5D-3L value sets. [36,39] These findings underscore the importance of using population-specific utility values when calculating UW-mRS scores, as the choice of value set can significantly influence results and their interpretation, with important implications for clinical practice and research.

When analysing the UW-mRS scores by sex, females were found to report worse health status than males for the same level of motor disability, though the differences were not statistically significant. Previous studies indicate that, on average, females score 0.03 points lower than males.[40] These discrepancies may be explained by the influence of distinct cultural and social factors that shape how females perceive and report their health status,[41] as well as to higher levels of anxiety or depression, pain, and discomfort compared to males.[42] Interestingly, age emerged as a significant predictor of worse UW-mRS scores in males, which may be explained by the fact that, at the time of stroke, females were significantly older than males (mean age 72.17 vs. 68.94 years, $p < 0.001$). Additionally, IS was a significant predictor of poorer outcomes in females. Although the proportion of IS was similar between sexes, a

higher percentage of females who suffered IS (30%) had mRS scores between 3 and 5 compared to males (21%), and the higher UW-mRS weights for IS further accentuated the impact on females.

When comparing UW-mRS scores by stroke type, we found that the values for IS were lower than those for ICH, and this impact was more relevant in women. The difference may be attributed to the greater severity typically associated with ICH and the higher early mortality rate among ICH patients during follow-up.

This study has strengths and limitations that must be acknowledged. Among its strengths, we identified key predictors of UW-mRS scores in stroke survivors, including age, prior mRS score, and NIHSS at admission, which aligns with previous findings.[43] Notably, age over 70 years emerged as a significant predictor only in males, while acute IS had a greater impact on females. These sex-specific insights are crucial for tailoring personalized treatment and rehabilitation strategies. The use of a population-based cohort from a low-income setting adds to the relevance of the findings, providing valuable reference data for understanding stroke recovery in real-world conditions and informing future healthcare policies.

However, there are also important limitations. The data come from a single population-based cohort in Chile, which may limit the generalizability of the findings. Despite this, the results are representative of a low-income population with high stroke risk factors and could serve as a reference for future population-based studies. The follow-up was conducted by telephone, though studies have validated this method's effectiveness,[44] and it was carried out by trained personnel. Additionally, we lacked consistent information on access to rehabilitation or post-

stroke care, which may have influenced the reported quality of life perceptions. Lastly, using the ordinary least squares regression model to derive UW-mRS scores may not fully capture the complexity of outcomes across stroke subtypes and demographics. Future research should explore alternative models and validate the UW-mRS in diverse populations.

The integration of patient-centered outcomes into a population-based cohort offers significant implications for both clinical practice and health policy. For clinicians, UW-mRS scores provide a more nuanced understanding of recovery trajectories, complementing traditional ordinal scales. For policymakers, they highlight the importance of incorporating patient valuations into outcome assessment, particularly when designing interventions and allocating resources in settings with limited access to specialised rehabilitation services.

Overall, the findings demonstrate that the UW-mRS is a feasible and informative tool for evaluating stroke outcomes in Chile, and its application may contribute to harmonising stroke research in the region with international standards while ensuring alignment with outcomes that matter most to patients. Future studies should explore its use in prospective cohorts and clinical trials to further validate its applicability across diverse populations.

3.3.3.5 Conclusion

These results present UW-mRS values derived from a population-based stroke study, further supporting UW-mRS as a reliable measure of PCO in post-stroke patients. Key determinants of health-related quality of life included age, prior disability, and stroke severity, with age over 70 years being a significant predictor for

males and AIS having a greater impact on females. Incorporating UW-mRS as a PCO in future stroke research and clinical practice may provide a more nuanced understanding of the impact of stroke on survivors, offering valuable insights for clinical decision-making and rehabilitation strategies across diverse healthcare settings.

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3.4 CHAPTER IV: PATIENT CENTERED OUTCOMES IN INTRACEREBRAL HEMORRHAGE

3.4.1. Chapter overview

This chapter examines the application of PCO in ICH, using two large international clinical trial datasets to characterise recovery beyond conventional endpoints. First, a secondary analysis of INTERACT3 evaluates HRQoL at six months using UW-mRS. In this cohort, more than half of survivors reported utility values below the cohort median. Unfavourable HRQoL was most strongly associated with older age and markers of clinical severity, including higher admission scores on the National Institutes of Health Stroke Scale (NIHSS), larger haematoma volume, and pre-stroke disability. Utility scores showed a strong inverse association with the mRS, and the resulting UW-mRS values provide a preference-based mapping of disability states in ICH.

Second, a prespecified secondary analysis of TRIDENT uses longitudinal follow-up to describe trajectories of utility-weighted disability, HRQoL, cognition, and functional status over time. This analysis evaluates whether UW-mRS trajectories differ according to randomised allocation, examines the relationship between cognitive performance and HRQoL, and identifies predictors of poorer utility-weighted outcomes at end of study.

Taken together, this chapter illustrates how preference-based measures can integrate survival, disability, and patient-reported health into a common metric, thereby complementing conventional clinical scales and providing a more comprehensive characterisation of recovery after ICH.

3.4.2 Determinants of Quality of Functional Outcome in ICH. The INTERACT3 trial

3.4.2.1 Introduction

The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3) was a pragmatic, international, multicentre, blinded endpoint, stepped wedge cluster randomised controlled trial at hospitals in nine low-income and middle-income countries (Brazil, China, India, Mexico, Nigeria, Pakistan, Peru, Sri Lanka, and Viet Nam) and one high-income country (Chile). It aimed to evaluate the effect of a multifaceted care bundle—comprising rapid intensive blood pressure lowering, glycaemic control, antipyretic, and reversal of anticoagulation—on outcomes after ICH. The trial demonstrated that implementation of this standardized bundle was associated with improved functional outcomes at six months, measured by the mRS, with a shift towards lower disability scores compared to usual care.[1] These findings provided robust evidence to guide acute ICH management worldwide, particularly in resource-limited contexts.

While mortality and functional status remain cornerstone outcomes, there is increasing recognition of the need to integrate patient-centered measures to capture the broader impact of ICH on survivors' lives. Building on this premise, the present analysis focused on the determinants of HRQoL in survivors of ICH within the INTERACT3 population. Specifically, the objective was to evaluate how UW outcomes varied according to demographic, socioeconomic, and clinical factors, thereby providing a more comprehensive picture of recovery.

3.4.2.2 Methods

For the present secondary analysis, functional outcomes were assessed using the mRS, while HRQoL was measured using the EQ-5D-3L instrument at six months

post-ICH. Patient-reported EQ-5D-3L profiles were converted into utility index values by applying country-specific tariffs. In this case, the Chinese EQ-5D-3L value set was used for participants from China, while the United Kingdom value set was applied to data from other countries to ensure comparability.

UW-mRS values were derived by mapping mean EQ-5D utilities to each mRS category, following established algorithms.[2,3] This transformation yielded a continuous, preference-based scale integrating both survival and disability.

To identify determinants of HRQoL, multivariable linear regression models were constructed. Independent variables included demographic factors (age, sex, occupation as a proxy for socioeconomic status), clinical characteristics (stroke severity by NIHSS at baseline, hematoma volume, comorbidities, and pre-stroke mRS), and trial-specific factors (care bundle allocation, calendar time). Hospital site was incorporated as a random effect to account for within-cluster correlation. Results are presented as regression coefficients (β) with 95% confidence intervals, with statistical significance set at $p<0.05$.

3.4.2.3 Results

A total of 7.036 patients were included in the analysis, with a mean age of 62 years, 64% were male. Baseline characteristics are summarized in Table 4-1. At six months post- ICH, 978 of 6.255 (15.6%) had died, and 3.908 patients (55.5%) reported unfavourable health-related quality of life (HRQoL), defined as EQ-5D utility scores <0.702. (Figure 4-1).

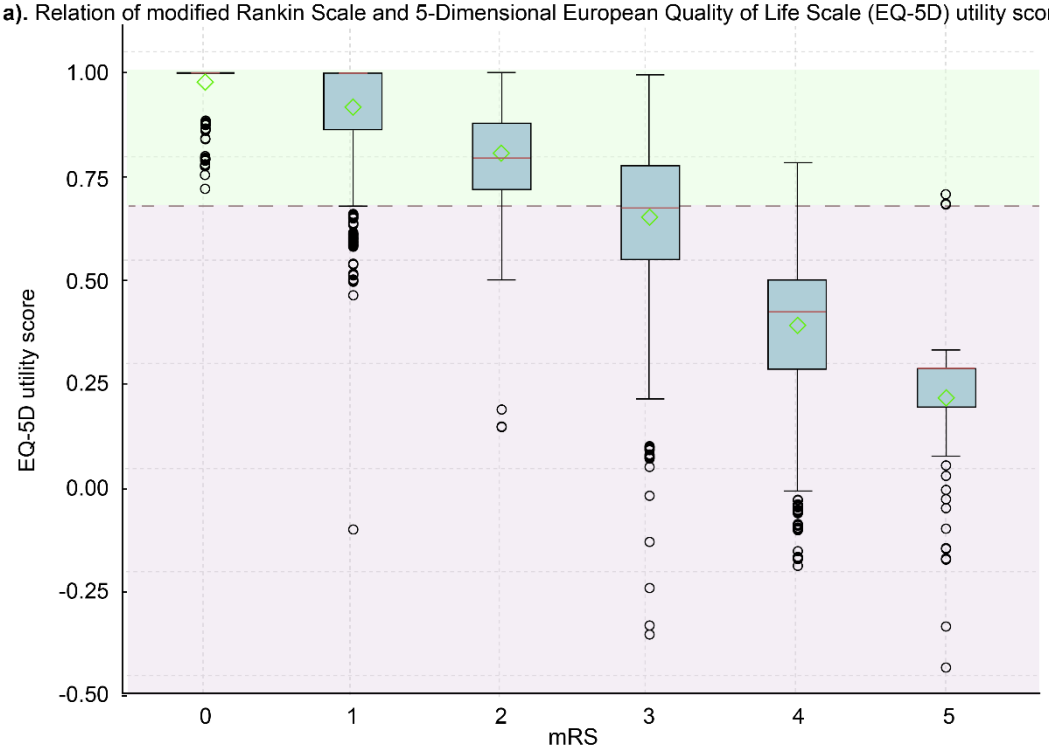
EQ-5D utility scores showed a strong negative correlation with mRS levels (Spearman R = –0.934, p<0.0001) The corresponding UW-mRS values ranged from 0.983 for mRS 0 to 0.221 for mRS 5. (Figure 4-1).

In the bivariate analysis, older age, female sex, higher NIHSS score, larger haematoma volume, and pre-stroke disability (mRS ≥1) were associated with unfavourable HRQoL (all p<0.01). Our bivariate analysis showed thar older patients, particularly those aged 65 and above, had significantly lower HRQoL compared to younger patients. While males initially appeared to have slightly better HRQoL than females, this difference disappeared after adjusting for clinical variables. More importantly, clinical factors played the most significant role in HRQoL outcomes. Stroke severity, as measured by NIHSS, haematoma volume, and pre-stroke disability (mRS ≥1), remained significantly associated with poor HRQoL after adjustment. Patients from China, as well as those who were living at home six months post-ICH, tended to report better HRQoL.

In the regression analyses (Table 4-2), older age was consistently associated with unfavourable HRQoL, with an adjusted odds ratio (aOR) of 1.43 per 10-year increase (95% CI 1.36–1.50, p<0.0001). Female sex was associated with higher odds of unfavourable HRQoL in the crude model (OR 1.15, 95% CI 1.03–1.28, p=0.0099), but this association was not significant after adjustment (aOR 1.06, 95% CI 0.94–1.19, p=0.37). Occupation showed differences in the crude analysis (p<0.0001), although these did not remain significant after adjustment (p=0.87). Clinical factors demonstrated the strongest associations: NIHSS scores greater than 4 at admission were associated with markedly higher odds of unfavourable HRQoL (aOR 3.48, 95% CI 2.91–4.17, p<0.0001), as were haematoma volumes greater than 10 mL (aOR

2.49, 95% CI 2.21–2.82, p<0.0001). Pre-stroke disability, defined as mRS ≥1, was also significantly associated with unfavourable HRQoL (aOR 1.56, 95% CI 1.34–1.81, p<0.0001).

a). Relation of modified Rankin Scale and 5-Dimensional European Quality of Life Scale (EQ-5D) utility scores



*Red dashed line indicates the mean EQ-5D utility score (0.702)

b). UW-mRS values derived for each category of the modified Rankin scale.

mRS	0	1	2	3	4	5
N (%)	589 (9.4)	1803 (28.8)	383 (6.1)	1120 (17.9)	784 (12.5)	598 (9.6)
Mean (SD)	0.98 (0.05)	0.92 (0.10)	0.81 (0.13)	0.66 (0.17)	0.40 (0.16)	0.22 (0.13)

Spearman correlation coefficient: R= -0.93408 (p<0.0001)

Multiple regression coefficient with adjusted for age and baseline NIHSS: R^2 =(p<0.0001)

Figure 4-1 Relationship between Functional Disability (mRS) and Health-Related Quality of Life (EQ-5D Utility): Distributions and UW-mRS Values by mRS Category

Baseline characteristics	Overall	Unfavourable <median (0.702)	Favourable ≥median (0.702)	P-value
Age in years, n / mean (SD)	7031 / 62.0 (12.6)	3906 / 63.9 (12.7)	3125 / 59.6 (12.1)	**<.0001**
Male, n (%)	4503 (64.0)	2471 (63.2)	2032 (65.0)	0.1325
Country, n(%)				
China	6356 (90.3)	3534 (90.4)	2822 (90.2)	0.0006
India/Parkistan/Sri Lanka/Vietnam	505 (7.2)	256 (6.6)	249 (8.0)	
Brazil/Peru/Chile/Mexico/Nigeria	175 (2.5)	118 (3.0)	57 (1.8)	
Education, n(%)				
Basic	6074 (86.6)	2801 (85.1)	2762 (88.5)	**<.0001**
Superior	354 (5.1)	182 (4.7)	172 (5.5)	
Never had education	585 (8.3)	399 (10.2)	186 (6.0)	
Occupation, n(%)				
Manual or fieldwork	3256 (46.3)	1467 (37.6)	1489 (47.7)	**0.0007**
Formal occupations	883 (12.6)	449 (11.5)	434 (13.9)	
Domestic duties and others	2888 (41.1)	1688 (43.2)	1200 (38.4)	
Clinical features				
SBP (mmHg), n /median (IQR)	7034 / 173.0 (155.0-192.0)	3907 / 176.0 (157.0-196.0)	3127 / 170.0 (153.0-189.0)	**<.0001**
NIHSS at admission, n / median (IQR)	6842 / 13.0	3803 / 17.0	3039 / 9.0	**<.0001**

	(7.0-22.0)	(10.0-27.0)	(4.0-16.0)	
GCS score, n / median (IQR)	7029 / 12.0 (9.0-14.0)	3905 / 11.0 (7.0-14.0)	3124 / 14.0 (12.0-15.0)	**<.0001**
Medical history, n (%)				
Hypertension	4888 (69.5)	2757 (70.5)	2131 (68.1)	**0.0299**
Current alcohol consumption	1394 (19.8)	738 (18.9)	656 (21.0)	**0.0289**
Current smoker	1359 (19.3)	723 (18.5)	636 (20.3)	0.0529
Previous stroke	1076 (15.3)	694 (17.8)	382 (12.2)	**<.0001**
Diabetes mellitus	729 (10.4)	442 (11.3)	287 (9.2)	0.0036
Coronary artery disease	193 (2.7)	134 (3.4)	59 (1.9)	**<.0001**
Hipercolesterolemia	207 (2.9)	125 (3.2)	82 (2.6)	0.1559
Atrial fibrillation	82 (1.2)	59 (1.5)	23 (0.7)	**0.0026**
mRS of >=1 before onset	1586 (22.8)	1007 (26.0)	579 (18.7)	**<.0001**
Medication at time of admission, n(%)				
Antihypertensive agents	3072 (43.7)	1755 (44.9)	1317 (42.1)	**0.0196**
Blood glucose lowering agents	513 (7.3)	314 (8.0)	199 (6.4)	**0.0074**
Aspirin or another antiplatelet agent	378 (5.4)	252 (6.4)	126 (4.0)	**<.0001**
Statin or another lipid lowering agent	222 (3.2)	138 (3.5)	84 (2.7)	**0.0440**
Anticoagulation agent	65 (0.9)	42 (1.1)	23 (0.7)	0.1395
Randomized group, n(%)				

Control	3815 (54.2)	2215 (56.7)	1600 (51.2)	**<.0001**
Intervention	3221 (45.8)	1693 (43.3)	1528 (48.8)	
Brain imaging features, n(%)				
Deep	5638 (82.3)	3196 (83.7)	2442 (80.6)	**0.0009**
Cortical	628 (9.2)	333 (8.7)	295 (9.7)	0.1477
Cerebellum	369 (5.4)	184 (4.8)	185 (6.1)	**0.0191**
Brainstem	351 (5.1)	209 (5.5)	142 (4.7)	0.1428
Left side hematoma	3403 (49.7)	1876 (49.1)	1527 (50.4)	0.2966
Midline hematoma	393 (5.7)	236 (6.2)	157 (5.2)	0.0776
Intraventricular hematoma	2093 (29.8)	1373 (35.2)	720 (23.0)	**<.0001**
Baseline haematoma volumen, n / median (IQR)	6652 / 15.0 (7.8, 30.0)	3703 / 20.0 (10.0, 36.3)	2949 / 10.0 (5.0, 20.0)	**<.0001**
Other management from day 2 to day 7, n(%)				
Decompressive surgery	1035 (55.6)	772 (57.1)	263 (51.8)	0.0027
Intensive care admission	351 (5.1)	209 (5.5)	142 (4.7)	0.1428
Residence at home at 6 months	3404 (64.5)	1299 (60.4)	2105 (67.3)	**<.0001**

Level of education: Basic (Primary, Junior, High School), superior (Undergraduate, Postgraduate.); SBP, Systolic Blood Pressure; mRS, Modified Rankin scale score;

Table 4-1. Participant baseline characteristics in INTERACT3 trial

Variable	Crude OR (95%IC)	p-value	Adjusted OR (95%IC	p-value
Age (per 10-year increase)	1.39 (1.33-1.45)	<0.0001	1.43 (1.36-1.50)	<0.0001
Sex (female vs male)	1.15 (1.03-1.28)	0.0099	1.06 (0.94-1.19)	0.3716
Occupation		<0.0001		0.8740
Manual/Fieldwork (Ref)	1.00		1.00	
Formal occupation	0.79 (0.67-0.93)		0.98 (0.82-1.18)	
Domestic/Other	1.17 (1.04-1.32)		1.03 (0.90-1.17)	
NIHSS at admission >4	4.34 (3.68-5.13)	<0.0001	3.48 (2.91-4.17)	<0.0001
Haematoma volume >10 mL	2.74 (2.45-3.07)	<0.0001	2.49 (2.21-2.82)	<0.0001
Pre-stroke mRS ≥ 1	1.84 (1.61-2.11)	<0.0001	1.56 (1.34-1.81)	<0.0001

Table 4-2 Determinants of poor HRQoL in patients with ICH in INTERACT3

3.4.2.4 Discussion

Strengths

This analysis leverages a large, international cohort of patients with ICH from the INTERACT3 trial, providing a robust and generalisable assessment of patient-reported HRQoL at 6 months. The use of EQ-5D utilities alongside the mRS allowed a clear examination of how preference-based HRQoL relates to conventional disability outcomes, supporting the relevance of utility-weighted metrics in this context. In addition, the availability of detailed baseline clinical variables enabled identification of predictors of poor HRQoL that are clinically interpretable and consistent with established prognostic determinants after ICH.

Limitations

Several limitations should be considered when interpreting these findings. HRQoL was assessed at a single follow-up time point and among survivors, which may introduce survivor bias and does not capture trajectories of recovery. EQ-5D is a generic instrument and may not fully reflect domains particularly relevant after ICH (e.g., cognition, communication, participation), and responses may be influenced by adaptation and cross-cultural differences in health perception. The predominance of recruitment in China may limit generalisability to other regions and may also attenuate the apparent influence of socioeconomic variables, particularly if clinical severity outweighs contextual gradients in this setting. Finally, residual confounding remains possible despite adjustment, especially for social and healthcare system factors that are difficult to measure comprehensively.

Summary

In this large, international cohort of patients with ICH from the INTERACT3 trial, more than half of survivors reported unfavorable HRQoL at 6 months, highlighting the substantial long-term burden of this condition beyond conventional clinical outcomes. Predictors of poor HRQoL were consistent with established determinants of worse prognosis after ICH, including older age, higher stroke severity at admission, larger hematoma volume, and pre-stroke disability. These findings align with previous studies that identified clinical severity and baseline functional status as key determinants of post-stroke quality of life.[4]

The strong correlation observed between EQ-5D utility scores, and the mRS reinforces the value of the UW-mRS as a preference-based outcome measure. The UW-mRS captures both survival and disability in a single metric, providing a more patient-centered representation of recovery compared with the conventional ordinal mRS. The derived UW-mRS values from this study (ranging from 0.98 for mRS 0 to 0.22 for mRS 5) are consistent with prior reports in ischaemic and haemorrhagic stroke populations, although scores for moderate disability (mRS3-5) were not as low, possibly reflecting more favourable health perceptions in this cohort. [3]

Consistent with prior research, age and stroke severity emerged as the most important determinants of post-ICH HRQoL.[5] Older age, higher NIHSS scores at admission, larger hematoma volume, and pre-stroke disability were all independently associated with unfavourable outcomes, underscoring the impact of both baseline vulnerability and acute clinical severity. Although previous reports have suggested worse HRQoL among women,[6] we did not observe an independent

association with sex after adjustment, indicating that differences may be explained by variations in clinical presentation or baseline characteristics rather than sex itself. With respect to socioeconomic status, manual workers initially appeared to have worse HRQoL, but this association did not persist after adjustment. Given that the vast majority of participants were recruited in China, clinical severity factors may have outweighed the influence of socioeconomic variables, and contextual characteristics of the study populations may partly explain differences from other reports.

A novel contribution of this analysis is the demonstration of geographical and social determinants of HRQoL, with patients from China and those living at home after ICH reporting higher utility values. These findings highlight the influence of contextual factors—such as healthcare systems, rehabilitation access, and cultural perceptions of health—on patient-reported outcomes. Incorporating these dimensions into future evaluations is essential for tailoring interventions and ensuring equity in post-stroke care.[6]

3.4.2.5 Conclusions

This study, derived from a large international clinical trial, identified key predictors of HRQoL and developed UW-mRS scores for patients with ICH. These findings enhance our understanding of the long-term impact of ICH and offer a robust framework for assessing interventions and outcomes in this population.

3.4.3 Longitudinal evaluation of Health-Related Quality of Life after Intracerebral Haemorrhage: A Secondary Analysis of the TRIDENT Trial

3.4.3.1 Introduction

TRIDENT (A Triple Low-dose Antihypertensive Pill after Intracerebral Hemorrhage) trial was an international, multicentre, double-blind, placebo-controlled, parallel-group randomised trial evaluating a fixed-dose, low-dose triple-pill antihypertensive strategy (telmisartan 20 mg, amlodipine 2.5 mg, and indapamide 1.25 mg) versus matching placebo, in addition to usual care, for secondary prevention after ICH (NCT02699645). Clinically stable participants with confirmed ICH and systolic blood pressure 130–160 mmHg were enrolled after a 2-week active run-in phase and randomly assigned (1:1) to continue triple-pill or placebo. Details of the study have been published elsewhere. [7,8] By targeting intensive blood pressure control, the trial aimed to reduce the risk of recurrent stroke and major vascular events in a high-risk population.

In addition to its primary clinical outcomes, TRIDENT incorporated systematic and longitudinal collection of PCO, including HRQoL, assessed with EQ-5D-3L, cognitive function (MoCA), and functional disability mRS. This comprehensive dataset offers a unique opportunity to characterise the long-term trajectories of recovery after ICH from a patient-centered perspective.

In this secondary analysis, we aimed to characterise longitudinal trajectories of HRQoL, cognition, and functional disability after ICH in TRIDENT; evaluate whether UW-mRS trajectories differed by randomised treatment allocation; examine the cognition–HRQoL association; and identify predictors of poorer UW-mRS at end of study.

3.4.3.2 Methods

This was a pre-specified secondary analysis of the TRIDENT trial. Participants were included if they had at least one post-baseline assessment of the patient-centred outcomes relevant to each analysis.

Procedures and assessments

Follow-up assessments were scheduled every 6 months up to 72 months after randomisation. Cognition, HRQoL, and functional status were assessed using the MoCA, the EQ-5D-3L, and the simplified mRS (smRS), respectively, at prespecified visits. Assessments were not fully aligned across instruments throughout follow-up (Figure 4-2). For participant-level summaries, end of study (EOS) was defined as the last attended scheduled follow-up visit (maximum follow-up 72 months), such that EOS could occur earlier than 72 months if a participant completed follow-up before the final scheduled visit.

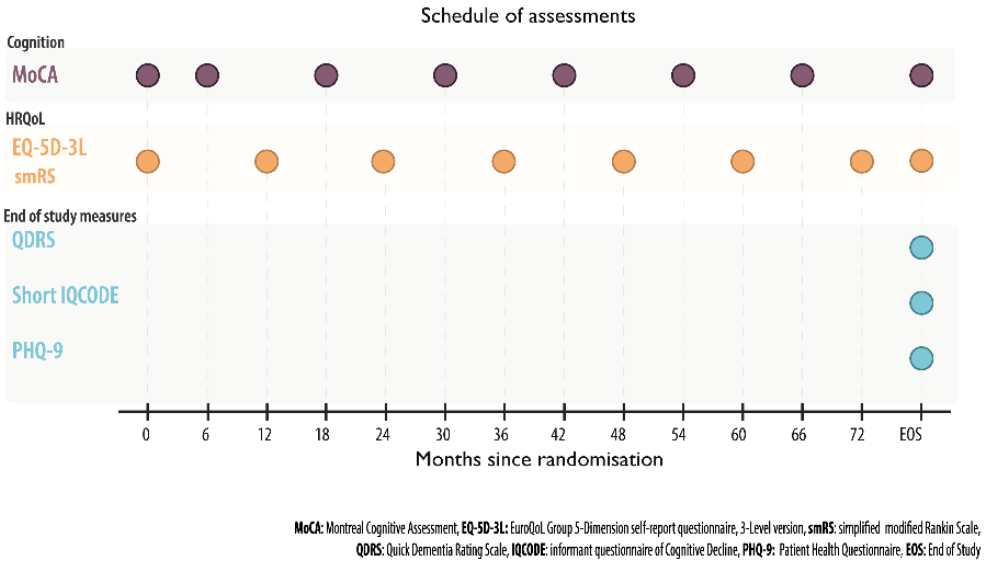


Figure 4-2 Schedule of assessments in TRIDENT clinical trial

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EQ-5D-3L index values were derived using country-specific value sets. The smRS was treated as an ordered categorical measure of disability, with lower scores indicating less disability.

Outcomes

Longitudinal profiles of MoCA, EQ-5D-3L index, and smRS over follow-up were described using observed summaries at each scheduled visit. Utility-weighted disability was additionally evaluated using the UW-mRS, calculated using an indirect utility-weighting approach as described in Chapter 1.

The association between cognition and HRQoL was assessed using EQ-5D-3L index as the outcome and MoCA as the primary predictor, focusing on paired assessment timepoints. Because MoCA and EQ-5D-3L were not scheduled at identical visits across follow-up, the primary analysis used paired baseline and EOS observations. In a prespecified sensitivity analysis, EQ-5D-3L assessments were aligned to the most recent prior MoCA score using last observation carried forward (LOCF).

Statistical analysis

Baseline characteristics were summarised using mean (SD) or median (IQR) as appropriate and counts and percentages for categorical variables. Longitudinal differences in UW-mRS between randomised treatment groups were assessed using marginal longitudinal models fitted as linear regression with robust standard errors clustered by participant. Models included visit indicators and a treatment-by-visit interaction; we reported the global test for the interaction and estimated treatment–control differences at each visit.

The cognition–HRQoL association was assessed using mixed-effects linear regression with EQ-5D-3L index as the outcome and MoCA as the main predictor, including a participant-level random intercept and robust standard errors. Models were adjusted for age, sex, education (<12 vs ≥12 years), randomised treatment allocation, and follow-up time/visit. To separate within-person from between-person associations, person-mean centring of MoCA (within–between/Mundlak decomposition) was used to estimate within-individual and between-individual effects.

Predictors of poorer UW-mRS at EOS were examined using multivariable logistic regression defining “poor” UW-mRS as below the cohort median. Models included age, sex, education, randomised treatment allocation, ethnicity, work status, haemorrhage location, haemorrhage side, and relevant vascular risk factors as covariates. A sensitivity analysis treated UW-mRS at EOS as a continuous outcome using multivariable linear regression with robust standard errors. All statistical tests were two-sided with $p<0.05$. Analyses were performed in Stata.

3.4.3.3 Results

A total of 1,670 participants with ICH were included in the analytic cohort (Figure 4-3, Table 4-3, Supplementary Table S1-2). Mean age was 57.8 years (SD 11.3), and 563 (33.7%) were female. Mean body index mass (BMI) was 24.5 kg/m² (SD 4.5). Most participants were Asian (68.9%), followed by White (12.6%), Black (11.7%), and other ethnic groups (6.8%). Countries that participated in the study are shown in Supplementary Figure S1. Fewer than 12 years of formal education was reported by 570 (34.1%). Regarding social characteristics, 57.1% were employed and 15.4%

were retired; approximately one-third worked in manual roles and a similar proportion in service roles.

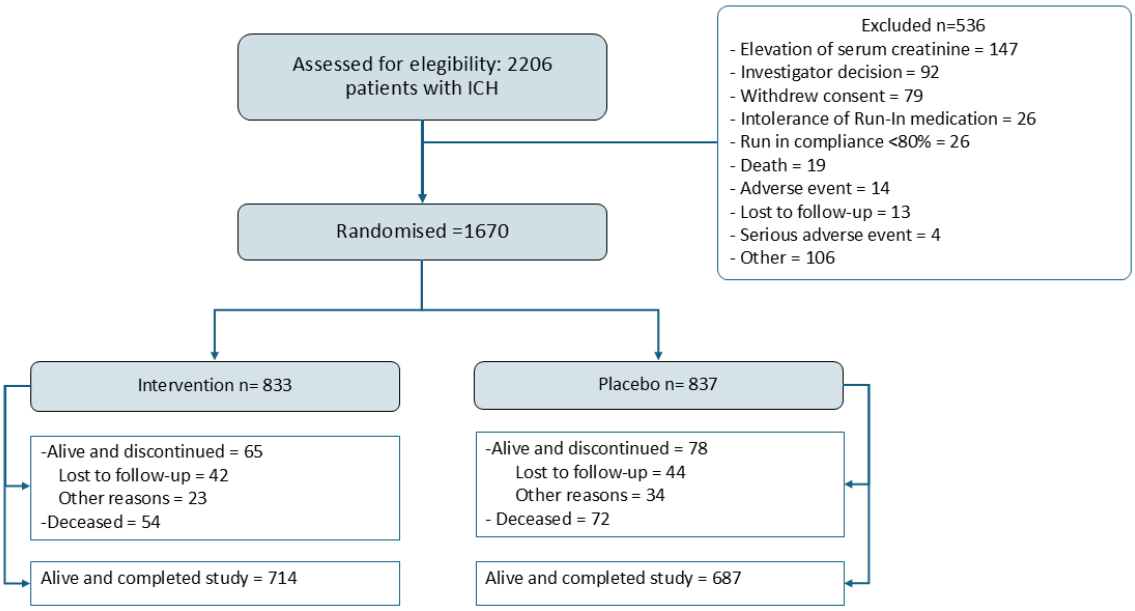

Figure 4-3 TRIDENT flowchart.

Pre-morbid vascular risk factors and comorbidities were common, with hypertension affecting 1,347 (80.7%) participants. Diabetes mellitus was reported in 369 (22.1%), and a prior ischaemic stroke or transient ischaemic attack in 82 (5.0%). Among participants with available measurements (n=392), haematoma volume had a mean of 27.6 mL (SD 67.6). Haemorrhages were most frequently deep (77.1%), typically lateralised (51.1% left only; 46.0% right only), with intraventricular blood present in 17.0% (285/1,669). Presumed etiology was predominantly hypertensive (93.7%).

Baseline Characteristics	Triple pill (N=833)	Placebo (N=837)	Total (n=1670)
Female sex, n (%)	275 (33.0)	288 (34.0)	563 (33.7)
Age – years, mean (SD)	57.5 (11.2)	58.0 (11.5)	57.8 (11.3)
BMI– kg/m2, mean (SD)	25.0 (4.51)	24.9 (4.57)	24.5 (4.5)
Race group, n (%)			
Asian	610 (73.2)	603 (72.0)	1213 (72.6)
White	102 (12.2)	109 (13.0)	211 (12.6)
Black	96 (11.5)	100 (11.9)	196 (11.7)
Other	25 (3.0)	25 (3.0)	50 (3.0)
Educational Level <12 years , n (%)	285 (34.2)	285 (34.1)	570 (34.1)
Employment, n (%)			
Employed (full-time /part-time paid work)	492 (59.0)	462 (55.2)	954 (57.1)
Home duties	139 (16.7)	137 (16.4)	276 (16.6)
Retired	119 (14.3)	138 (16.5)	257 (15.4)
Unemployed	43 (5.2)	55 (6.6)	98 (5.9)
Other	38 (4.6)	44 (5.3)	82 (4.9)
Medical history, n (%)			
N	833	836	1669
Hypertension	667 (80.1)	680 (81.3)	1347 (80.7)
Diabetes mellitus Type II	163(19.6)	166 (19.9)	329 (19.7)
ICH (i.e. prior to qualifying ICH)	56 (6.7)	56 (6.7)	112 (6.7)
Ischaemic heart disease / coronary artery disease	47 (5.6)	55 (6.6)	102 (6.1)
Ischaemic stroke	33 (4.0)	33 (3.9)	66 (4.0)
Migraine	22(2.6)	21 (2.5)	43 (2.6)
Myocardial infarction	21 (2.5)	21 (2.5)	42 (2.5)
Diabetes mellitus Type I	18 (2.2)	22 (2.6)	40 (2.4)

Depression requiring treatment	17 (2.0)	13 (1.6)	30 (1.8)
Chronic kidney disease	13 (1.6)	16 (1.9)	29 (1.7)
Coronary bypass grafting or coronary intervention	16 (1.9)	6 (0.7)	22 (1.3)
Atrial fibrillation	11 (1.3)	7 (0.8)	18 (1.1)
Transient ischaemic attack	11 (1.3)	5 (0.6)	16 (1.0)
Valvular heart disease	4 (0.5)	4 (0.5)	8 (0.5)
Peripheral arterial disease	3 (0.4)	3 (0.4)	6 (0.4)
Current smoker, n (%)	43 (5.2)	47 (5.6)	90 (5.4)
ICH characteristics, n (%)			
Hematoma volume			
N	192	200	392
Mean (SD)	31.2 (83.3)	24.0 (48.0)	27.6 (67.6)
Hematoma side			
N	832	836	1668
Left only	424 (50.9)	429 (51.3)	853 (51.1)
Right only	384 (46.1)	383 (45.8)	767 (46.0)
Midline	18 (2.2)	18 (2.2)	36 (2.2)
Mixed	6 (0.8)	5 (0.7)	12 (0.7)
Hematoma location			
Deep	653 (78.4)	635 (75.9)	1,288 (77.1)
Cortical (lobar)	125 (15.0)	127 (15.1)	252 (15.1)
Both/Other	55 (6.6)	75 (9.0)	130 (7.8)
Intraventricular blood (n=1669)	137 (16.4)	148 (17.7)	285 (17.04)
Presumed aetiologies of ICH, n (%)			
Hypertension	785 (94.2)	780 (93.2)	1565 (93.7)
Anticoagulation-related	1 (0.1)	4 (0.5)	5 (0.3)

Antiplatelet-related	1 (0.1)	1 (0.1)	2 (0.1)
Cerebral Amyloid Angiopathy related	3 (0.4)	6 (0.7)	9 (0.5)
Uncertain	25 (3.0)	21 (2.5)	46 (2.8)
Multiple/other	18 (2.2)	25 (3.0)	44 (2.6)

Table 4-3 Baseline characteristics of TRIDENT participants.

UW-mRS over follow-up

At baseline, mean UW-mRS was 0.637 (SD 0.135) in the placebo group (n=838) and 0.650 (SD 0.126) in the triple-pill group (n=833) (Table 4-4). UW-mRS increased over follow-up in both groups, reaching 0.724 (0.170) and 0.741 (0.148) at 12 months, and 0.754 (0.160) and 0.768 (0.143) at 24 months in the placebo and triple-pill groups, respectively. At EOS, mean (SD) UW-mRS was 0.741 (0.166) in the placebo group (n=678) and 0.751 (0.158) in the triple-pill group (n=701).

Longitudinal cognition, health-related quality of life, and functional status

Overall, cognition, HRQoL, and functional outcomes improved from baseline and were broadly maintained at later follow-up. Median MoCA increased from 22 (IQR 18–26) at baseline to 25 (IQR 20–28) at EOS (Supplementary Table S3, Figure 4-4).

	UW-mRS							
	N	**Global (SD)**	**mRS 0**	**mRS 1**	**mRS 2**	**mRS 3**	**mRS 4**	**mRS 5**
Month 0								
Placebo	838	0.637 (0.135)	0.839	0.744	0.648	0.552	0.457	0.361
Triple pill	833	0.650 (0.126)	0.846	0.754	0.662	0.570	0.478	0.386
Month 12								
Placebo	653	0.724 (0.170)	0.920	0.770	0.621	0.472	0.322	0.173
Triple pill	674	0.741 (0.148)	0.918	0.788	0.659	0.530	0.400	0.271
Month 24								
Placebo	437	0.754 (0.160)	0.931	0.791	0.650	0.510	0.370	0.229
Triple pill	443	0.768 (0.143)	0.930	0.806	0.682	0.558	0.434	0.310
Month 36								
Placebo	284	0.753 (0.156)	0.942	0.791	0.639	0.488	0.336	0.185
Triple pill	293	0.775 (0.139)	0.948	0.817	0.685	0.553	0.422	.
Month 48								
Placebo	190	0.780 (0.143)	0.950	0.814	0.678	0.542	0.406	.
Triple pill	207	0.769 (0.151)	0.952	0.801	0.651	0.500	0.349	0.198
Month 60								
Placebo	96	0.747 (0.196)	0.944	0.790	0.636	0.482	0.328	0.174
Triple pill	100	0.766 (0.154)	0.942	0.806	0.671	0.535	0.399	0.264

Month 72								
Placebo	49	0.796 (0.133)	0.948	0.810	0.672	0.533	0.395	.
Triple pill	42	0.815 (0.160)	1.002	0.845	0.688	0.531	.	.
EOS								
Placebo	678	0.741 (0.166)	0.931	0.798	0.665	0.532	0.399	0.266
Triple pill	701	0.751 (0.158)	0.926	0.792	0.659	0.525	0.392	0.258

Table 4-4 Utility-weighted modified Rankin Scale (UW-mRS) values over follow-up by treatment group and mRS category (mean [SD])

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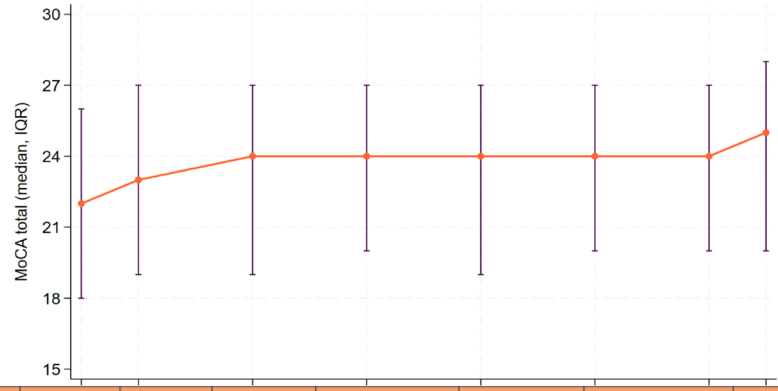
EQ-5D index increased from baseline (mean 0.643; 95% CI 0.630–0.656) to 12 months (0.733; 0.720–0.747; n=1,317) and 24 months (0.761; 0.746–0.777; n=873), with similar values at EOS (0.747; 0.733–0.760; n=1,374). The proportion of participants achieving mRS 0-2 increased from 59.7% at baseline to 82.8% at 12 months and remained high thereafter (83.9%–87.4% across 24–72 months). No differences were observed in these longitudinal patterns when analyses were stratified by randomised treatment group (Supplementary Figure S2).

In marginal longitudinal models including a treatment-by-visit interaction (linear regression with robust standard errors clustered by participant), UW-mRS values increased over follow-up in both groups (Table 4-4). There was no evidence of a baseline difference between treatment arms (difference at month 0: −0.003), and no clear evidence that trajectories differed between groups (p=0.154).

When exploring the association between cognition and HRQoL, using the primary mixed-effects model based on concurrent MoCA and EQ-5D assessments at baseline and end-of-study , higher MoCA scores were associated with higher EQ-5D index values (β=0.012 per 1-point MoCA; 95% CI 0.010–0.013; p<0.001, Supplementary Table S4). Older age was inversely associated with lower EQ-5D (p<0.001), and women had slightly lower EQ-5D than men (p=0.039), whereas level of education and randomised treatment arm were not associated with EQ-5D (p=0.905 and p=0.247, respectively). The association between EQ-5D and MoCA remained in the prespecified LOCF sensitivity analysis , adjusted for age, sex, education, treatment arm, and follow-up time (β=0.009; 95% CI 0.008–0.011; p<0.001). Finally, a within–between decomposition showed that the positive MoCA–EQ-5D index association was present both within individuals over time (within-

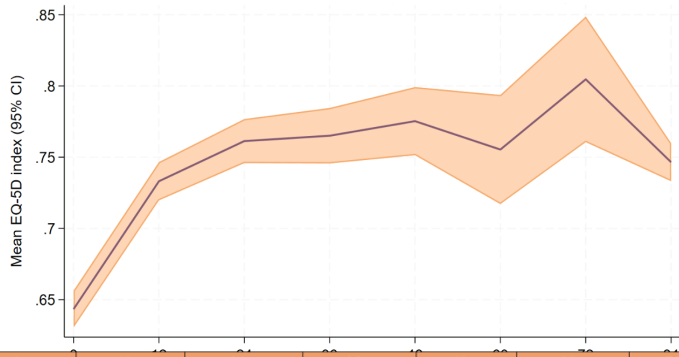
person β=0.0057, p<0.001) and between individuals (between-person β=0.0141, p<0.001), with a larger between-person component (Supplementary Table S5).

a.



Visit	0m	6 m	18 m	30 m	42 m	54 m	66 m	EoS
N	1651	1376	954	563	422	255	125	1249
Median (IQR)	22 (18–26)	23 (19–27)	24 (19–27)	24 (20–27)	24 (19–27)	24 (20–27)	24 (20–27)	25 (20–28)

b.



c.

Visit	0m	12m	24m	36m	48m	60m	72m	EoS
N	1,669	1,317	873	576	394	196	90	1,374
Mean	0.643	0.733	0.761	0.765	0.775	0.755	0.805	0.747
CI 95%	0.630 – 0.656	0.720 – 0.747	0.746 – 0.777	0.746 – 0.785	0.751 – 0.799	0.717 – 0.794	0.761 – 0.849	0.733 – 0.760

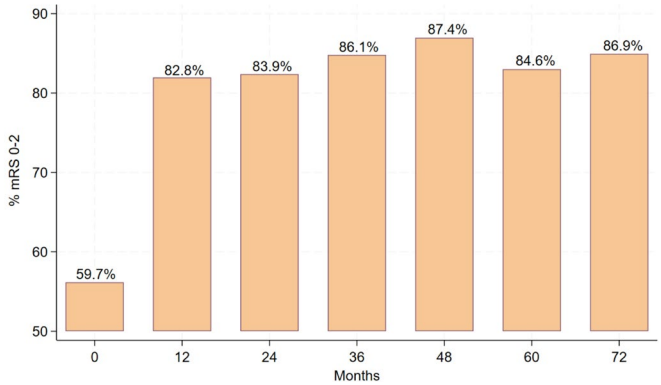


Figure 4-4 Cognitive function and health-related quality of life in the randomised cohort:
(a) MoCA total score (median, IQR) and **(b)** Mean EQ-5D index (mean, 95% CI) **(c)** Percentage of participants with mRS 0-2 across follow-up visits.

Predictors of poorer UW-mRS at the end of the study

In EOS analyses (n=1,364), a “poor” UW-mRS outcome (defined as UW-mRS below the cohort median) was observed in 472 participants (34.4%). In multivariable logistic regression, older age was associated with higher odds of poor UW-mRS (adjusted OR 1.036 per year, 95% CI 1.023–1.048; p<0.001), as was hypertension (aOR 1.782, 95% CI 1.291–2.462; p<0.001) (Table 4-5). Compared with White participants, Asian ethnicity was associated with lower odds of poor UW-mRS (aOR 0.669, 95% CI 0.463–0.966; p=0.032), whereas no clear associations were observed for Black ethnicity or other ethnic groups. Compared with employed participants, those reporting home duties had higher odds of poor UW-mRS (aOR 1.551, 95% CI 1.044–2.305; p=0.030), while retired, unemployed, or other work categories were not associated with the outcome. Compared with deep ICH, cortical (lobar) location was associated with lower odds of poor UW-mRS (aOR 0.577, 95% CI 0.408–0.816; p=0.002); no association was observed for other locations. No clear evidence of association was found for sex, ICH side, or diabetes (all p>0.05). Randomised treatment allocation showed a non-significant trend towards lower odds of poor UW-mRS in the active arm (aOR 0.820, 95% CI 0.650–1.035; p=0.096).

In sensitivity analyses treating UW-mRS at EOS as a continuous outcome, results were broadly consistent. Older age was associated with lower UW-mRS (β −0.003 per year, 95% CI −0.004 to −0.003; p<0.001) and hypertension was associated with lower UW-mRS (β −0.043, 95% CI −0.062 to −0.024; p<0.001). Cortical (lobar) location was associated with higher UW-mRS compared with deep ICH (β 0.034, 95% CI 0.014–0.054; p=0.001). Diabetes was associated with a small increase in

UW-mRS (β 0.022, 95% CI 0.001–0.043; p=0.043). No clear associations were observed for sex, ethnicity, work status, ICH side, or treatment allocation (all p>0.05)

Predictor	Odds ratio	SE	p	95% CI
Age (per year)	1.036	0.006	<0.001	1.023; 1.048
Female sex	0.902	0.141	0.508	0.664; 1.224
Ethnic group				
Black	0.721	0.185	0.203	0.437; 1.192
Other	1.382	0.551	0.416	0.633; 3.018
Asian	0.669	0.126	0.032	0.463; 0.966
Work situation				
Retired	1.174	0.216	0.384	0.819; 1.682
Unemployed	1.135	0.297	0.628	0.680; 1.896
Home duties	1.551	0.314	0.030	1.044; 2.305
Other	0.745	0.244	0.368	0.392; 1.414
Location				
Cortical (lobar)	0.577	0.102	0.002	0.408; 0.816
Other	0.887	0.236	0.652	0.526; 1.494
ICH side				
Right only	1.031	0.124	0.799	0.814; 1.305
Midline	0.600	0.298	0.304	0.227; 1.588
Mixed	1.211	0.906	0.798	0.280; 5.245
Hypertension	1.782	0.294	<0.001	1.291; 2.462
Diabetes	0.851	0.130	0.293	0.631; 1.149
Treatment arm	0.820	0.098	0.096	0.650; 1.035

SE: standard error, Reference categories were White ethnic group, employed work status, deep ICH location, left ICH side, absence of hypertension, absence of diabetes, and placebo treatment arm. Age was modelled per 1-year increase.

Table 4-5 Multivariable logistic regression for predictors of having a poor UW-mRS (below the median).

3.3.3.4 Discussion

Strengths

This secondary analysis of TRIDENT leverages repeated measures to characterise how patient-perceived health evolves after ICH, demonstrating that longitudinal HRQoL assessment adds clinically relevant information beyond functional disability alone. By jointly examining HRQoL, cognition (MoCA), disability (smRS), and an integrative preference-based endpoint (UW-mRS), the analysis provides a pragmatic framework to capture broader consequences of ICH beyond dependence alone. The within–between decomposition and the use of sensitivity analyses further strengthen the robustness of the observed cognition–HRQoL relationship.

Limitations

Longitudinal assessment of HRQoL after ICH is informative, yet longer-term trajectories remain less well characterised because most prior evidence focuses on early follow-up (~90 days).[5] In this cohort, no clear differences were detected between treatment groups in UW-mRS trajectories. Generic preference-based measures may also under-capture post-stroke sequelae and show limited discrimination at the healthier end of the scale, particularly in milder strokes; EQ-5D utilities can cluster near “full health,” potentially attenuating detectable change at later timepoints.[9] Accordingly, although UW-mRS pragmatically integrates disability and health utility in a multinational cohort, absolute values and between-group contrasts should be interpreted cautiously because utilities were derived from country-specific value sets; the null between-arm trajectory difference mainly argues against a large, consistent treatment effect on utility-weighted disability.[10]

MoCA also has limitations as a longitudinal measure (measurement error, practice effects, and uncertainty around the minimum detectable change), which should temper causal interpretation of small within-person changes. [12]

Analyses were complete case for each model, so denominators varied by outcome and timepoint, and differential missingness related to severity may have introduced survivorship/attrition bias; results therefore primarily reflect participants with observed long-term follow-up. In addition, MoCA and EQ-5D-3L were not fully aligned across follow-up; this was addressed using paired baseline–EOS analyses and a prespecified LOCF sensitivity analysis, but this does not fully substitute for concurrent repeated measurements throughout follow-up. Finally, the limited sensitivity of EQ-5D-3L to mild but clinically meaningful symptoms may have attenuated change, partially mitigated here by interpreting HRQoL alongside cognition (MoCA), disability (smRS), and UW-mRS as an integrative endpoint.

Summary

This secondary analysis of TRIDENT showed that longitudinal HRQoL assessment adds clinically relevant information beyond functional disability alone, and it quantified a consistent positive association between cognition and HRQoL, supporting cognition as an important correlate of patient-perceived health after ICH. In addition, UW-mRS provides a pragmatic, patient-centred integrative summary by weighting disability states with health-utility values, thereby linking functional status with perceived health and offering a framework for capturing broader consequences of ICH beyond dependence alone, despite no clear evidence that UW-mRS trajectories differed by randomised allocation.

As reported in other studies,[11] a strong association was observed between cognition and HRQoL, where each additional point on the MoCA score was associated with a higher EQ-5D-3L index (β = 0.012; 95% CI: 0.010–0.013; p < 0.001), and this relationship was maintained when sensitivity analyses were performed. The within-between decomposition further indicated that the association was present both within individuals over time (β-within=0.0057; p<0.001) and between individuals (β-between=0.0141; p<0.001), with a larger between-person component. The quantified effect size is likely to be clinically modest at the individual level but may be significant at the population level during long-term follow-up, where subtle cognitive differences can influence independence, participation, and perception of health. Overall, these findings support routine consideration of cognitive status when interpreting HRQoL after ICH and reinforce the value of integrating cognition into patient-centered outcome frameworks, rather than treating HRQoL as purely "functional."

When predictors of poorer UW-mRS at end of study were examined, lower scores were associated with older age, hypertension, and home duties (vs paid employment), whereas Asian ethnicity and cortical haemorrhage location were associated with lower odds of poor UW-mRS. Similar clinical correlates of HRQoL after ICH have been reported,[5,13] but these associations require cautious interpretation: employment status is an imperfect proxy for socioeconomic context, premorbid function, and caregiving demands; "ethnicity" in a multinational trial may partly reflect centre-level differences and differential valuation of identical health states when country-specific EQ-5D value sets are applied; and haemorrhage location is intertwined with severity, complications, and selective long-term follow-

up.[14] More broadly, utility-weighted endpoints such as UW-mRS are contingent on the choice of utility weights and valuation framework, and substantial between-study variability in mRS utility weighting has been documented—limiting causal attribution and comparability across cohorts.

3.3.3.5 Conclusion

Longitudinal HRQoL assessment complemented traditional functional outcomes by characterising patient-perceived recovery over time, supporting interpretation beyond a single end-point disability score. A consistent positive association between cognition and HRQoL was quantified, indicating that cognitive status is an important correlate of patient-reported health after ICH. At end of study, lower UW-mRS was associated with older age, hypertension, and not being in paid employment, while the inverse associations observed for lobar/cortical location and Asian ethnicity warrant cautious interpretation given the potential for residual confounding and cross-country differences in utility valuation.

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SECTION 3: POST COVID CONDITION

3.5 CHAPTER V: POST-COVID-19 CONDITION: CLINICAL CHARACTERISATION AND THERAPEUTIC STRATEGIES

3.5.1 Chapter overview

This chapter addresses post-COVID-19 condition (PCC) as an emerging threat to brain health, shifting from the vascular injury paradigm emphasised in earlier chapters toward an infectious–inflammatory pathway that can nonetheless result in persistent neurocognitive and functional limitations.

Using a Chilean prospective cohort, the chapter characterises the clinical profile of PCC and quantifies the persistence of symptoms after hospital discharge, highlighting a substantial and clinically meaningful burden at 6 and 12 months. A central finding is that recovery is frequently incomplete, with a disproportionate impact on women, who report a higher prevalence of cognitive and multisystem complaints and lower rates of return to usual activities. In parallel, the chapter shows that acute-phase predictors remain difficult to identify consistently, reinforcing the need for multidimensional phenotyping and patient-centred endpoints to capture the outcomes that matter most to patients.

Building on this evidence gap—high burden, sex-related disparities, and limited predictive tools—the chapter transitions from description to intervention by introducing the STRONGER trial framework, designed to test whether a biologically plausible, widely available therapy (atorvastatin) can improve cognitive, imaging, and patient-centred outcomes in individuals with persistent neurological symptoms after COVID-19. This structure therefore advances from observational characterisation and risk profiling to pragmatic interventional evaluation and sets the rationale for the subsequent chapter’s focus on PCO to quantify PCC burden and recovery.

3.5.2 Introduction

Since its emergence in late 2019, COVID-19 has affected hundreds of millions of people worldwide, leaving a considerable proportion of survivors with persistent symptoms extending beyond the acute phase of infection.[1] —commonly referred to as long COVID or post-COVID-19 condition (PCC)—encompasses a broad spectrum of manifestations, including fatigue, cognitive complaints, sleep disturbances, anxiety, and depression.[2] Prevalence estimates vary across settings and study designs, but may reach up to 40–45% in previously infected individuals, with neurological and cognitive symptoms being among the most disabling and impactful on daily functioning.[3]

From a brain health perspective, PCC represents a shift from the vascular injury paradigm addressed in earlier chapters toward an infectious–inflammatory pathway that can nonetheless produce sustained neurocognitive and functional limitations. Proposed mechanisms include persistent immune activation and dysregulation, endothelial and microvascular dysfunction, autonomic disturbance, and, in some individuals, potential direct or indirect effects on the central nervous system (Figure 4-1).[4–6] Neurocognitive sequelae such as impaired attention, memory problems, and executive dysfunction have been consistently reported, even in individuals with initially mild disease. cross cohorts, symptoms such as impaired attention, memory difficulties, slowed processing, and executive dysfunction have been reported even after initially mild acute disease, and may persist for months, raising concerns about their longer-term implications for brain health.[7]

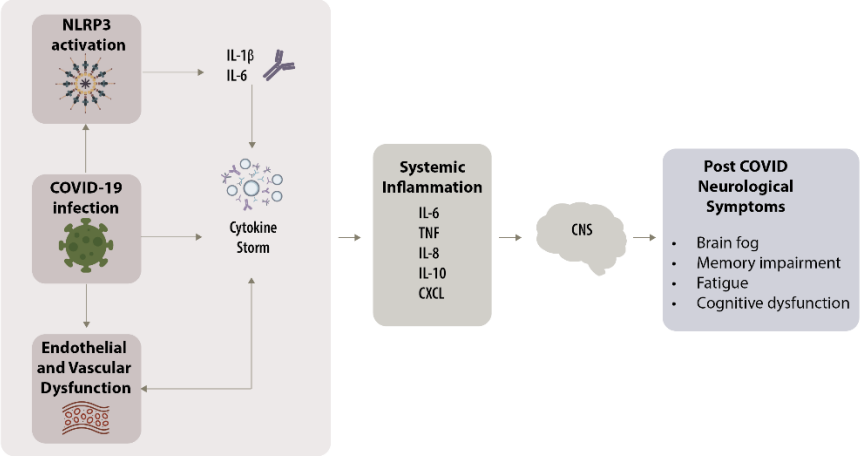

Figure 5-1 Pathophysiological Mechanisms Leading to PCC Neurological Symptoms

Despite growing recognition of PCC as a contributor to chronic morbidity, its evaluation and clinical characterisation remain challenging, particularly for neurocognitive sequelae. Conventional clinical and epidemiological endpoints often under-represent the patient experience and may not adequately quantify the outcomes patients identify as most disabling, constraining both the description of disease burden and the identification of clinically actionable predictors. To address this gap, several studies have applied targeted neuropsychological assessments and reported impairments across executive function, attention, and memory, motivating the search for biological correlates that can strengthen diagnosis, refine prognostication, and inform therapeutic development.[8]

Advanced neuroimaging and biomarker approaches provide complementary lenses through which to study the neurobiology of PCC. Brain free-water quantification derived from diffusion-weighted MRI has emerged as a sensitive marker linked to small vessel disease,[9] cognitive impairment,[10] and neurodegenerative processes.[11] Elevated free-water is thought to reflect extracellular microstructural change

associated with vasogenic oedema, neuroinflammatory gliosis, or axonal/myelin injury.[12] In parallel, blood-based markers of endothelial dysfunction, inflammatory activity (including cytokines, chemokines, and acute-phase proteins), and neuronal or glial injury (for example, neurofilament light chain and glial fibrillary acidic protein) have been proposed as candidate predictors of PCC and its neurological sequelae.[13] Collectively, these data reinforce the multifactorial nature of PCC-related neurocognitive impairment and underscore the need for integrated clinical, imaging, and biomarker phenotyping aligned with patient-centred outcomes.

Therapeutic strategies for PCC remain similarly limited. Current management is largely symptomatic, and no pharmacological intervention has yet demonstrated consistent efficacy in improving neurological recovery in PCC. This unmet need has fuelled interest in repurposing medications with pleiotropic actions on inflammatory and vascular pathways. Statins, widely used for cardiovascular disease prevention via inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase, also exert anti-inflammatory, antioxidant, endothelial function-enhancing, and neuroprotective effects.[14–17] Observational evidence has further suggested associations between statin use and reduced risk of all-cause dementia and Alzheimer's disease, with heterogeneity potentially influenced by statin type, dose, treatment duration, and the timing of initiation across the life course.[18–23] Importantly, atorvastatin crosses the blood–brain barrier due to its high lipophilicity,[24] strengthening the biological plausibility for evaluating its role in persistent neurological symptoms following COVID-19.[25]

Against this background, this thesis addresses the PCC evidence gap in two complementary steps that align with the overarching theme of patient-centred

outcomes. First, it presents evidence from the Chilean NIDO prospective cohort (Neuroimaging, Inflammation, and Brain Doppler in patients with prolonged COVID-19), designed to characterise PCC using a multidimensional approach that integrates clinical and neurocognitive assessment with neuroimaging, inflammatory and haemodynamic profiling, alongside patient-centred outcomes. Building on this framework, the chapter describes the rationale and methodological approach of NIDO and examines predictors of symptom burden, aiming to quantify PCC-related disability in a way that better aligns with what patients report as most impactful.

The chapter then introduces the STRONGER trial (STatin TReatment for COVID-19 to Optimise NeuroloGical recovERy), a pragmatic randomised framework developed to evaluate whether atorvastatin can improve cognitive, imaging, and patient-centred outcomes in individuals with persistent neurological symptoms after COVID-19. Taken together, this structure advances from observational characterisation and risk profiling to interventional evaluation within a pragmatic trial platform.

3.5.3 Article

Post-COVID-19 condition: a sex-based analysis of clinical and laboratory trends

Doi: 10.3389/fmed.2024.1376030

3.5.3.1 Introduction

Since the declaration of the COVID-19 pandemic in March 2020, approximately 760 million individuals worldwide have been diagnosed with SARS-CoV-2 infection.[1] Beyond the acute phase of the illness, some people experience ongoing symptoms, known as post-COVID-19 condition (PCC). PCC includes individuals with confirmed or probable COVID-19 who continue to have symptoms or develop new ones at least 3 months after the initial infection, lasting for at least 2 months.[2] Studies suggest that a staggering 31 to 67% of patients infected with SARS-COV-2 endure these post-acute sequelae.[3]

Among the published findings related to PCC, a stark disparity emerges, with women facing a significantly higher risk compared to men (63.2% vs. 36.8%).[26] It has also been proposed that the severity of the acute infection and BMI may increase the risk of developing PCC,[27] although this remains a topic of ongoing debate.[28] Both systemic inflammation and neuroinflammation, as well as microvascular injury and thrombosis are critical to COVID-19 pathobiology.[29,30] Among these, the NLRP3 inflammasome plays a prominent role, triggering the release of highly inflammatory cytokines (e.g., IL-1β and IL-18).[31] Activation by SARS-CoV-2 of this complex results in the downstream production of interleukin-6 and C-reactive protein (CRP)[32].

Additionally, the central nervous system can initiate an immune response through inflammasome activation.[33] Moreover, a common genetic polymorphism (NLRP3 rs10754555 variant) has been reported to enhance systemic inflammation and inflammasome activity in patients with atherosclerosis, with those with the C/G and G/G genotype being at higher risk.[34] This polymorphism may potentially influence the severity of COVID-19 and the neurological symptoms experienced by affected individuals. As of now, no biomarkers have emerged during acute COVID-19 that can predict the occurrence of PCC.[35]

Because of the described sex predisposition to PCC, in this study, we sought to describe clinical and immunological profiles of acute COVID-19 patients, focusing on sex-specific analysis and potential predictors of PCC including comprehensive acute inflammatory and immunological response.

3.5.3.2 Methods

Study design, patients, and endpoints definitions

These analyses are based on a prospective single-centre cohort study conducted at Clínica Alemana Santiago, Chile. Patients under 65 years of age who were admitted for COVID-19 between June 2020 and July 2021 (corresponding to the two first waves of the pandemic) were consecutively enrolled. During this initial phase of the pandemic, where clinical assessments were severely restricted and there was a risk of underreporting comorbidities, we made the decision to concentrate on a younger demographic. This approach aimed to mitigate potential comorbidities that could independently contribute to poorer outcomes. During this period, the predominant circulating variants were Gamma (51.7%), Lambda (22.8%), and Alpha (6%). [36] Only

patients who were discharged alive were included in the follow-up at 6 and 12 months. Detailed records of their previous medical history and acute clinical data upon admission were collected. Acute information regarding the patients was gathered during the initial 11 days of their hospitalization. The study protocol was approved by the local Ethics Committee (2022-33) and informed consent from all participants was obtained.

Baseline clinical-laboratory parameters including white blood cell count, ESR, CRP, ferritin and procalcitonin were measured at the time of acute hospital admission. In addition, acute phase samples were collected for comprehensive inflammatory response assessment including quantification of serum amyloid levels, inflammatory cytokines (IL-1β, IL-6, IL-8, IL-10, IL-12, IL-18, TNF) and chemokines (CCL2, CCL5, CCL8, CXCL9, CXCL10). Furthermore, samples were tested for the presence of the NLRP3 polymorphism (variant rs10754555), considering the C/G and G/G alleles as risk genotypes.[37]

Following discharge, assessments were conducted by telephone interviews at 6 and 12 months to identify the presence of PCC symptoms using a structured questionnaire. These assessments utilized a structured questionnaire encompassing cognitive, cardiovascular, and gastrointestinal symptoms, as well as fatigue levels and return to normal activities (Supplementary material 9.3.1). Questions were related to current symptoms, therefore only those patients who still had symptoms at the time of the call were considered in the PCC group.

Statistical analysis

Quantitative variables are reported as means ± SD or median (IQ range) depending on the normality (K-S test) and were compared using T Test or Mann-Whitney U test. Qualitative variables are reported as absolute and % prevalence and compared using the χ^2 test or Fisher's exact test. A multivariate logistic regression analysis was performed to explore variables associated with PCC. The variables were identified by univariate logistic regression analysis, including those that correlated significantly with the symptoms at follow-up and clinically significant variables were also included. In this analysis, we considered sex, age, BMI, data of acute care clinical setting, and comorbidities. Multivariable logistic regression was done to obtain an adjusted odds ratio with a 95% confidence interval. STATA version 18.0 was used to perform the analyses.

3.5.3.3 Results

During the study period, a total of 130 patients under 65 years were discharged alive (Figure 5-2). At six months, 104 patients completed the follow up assessment. Patients had a median age of 42 years (IQR 37-56) and 30% were women. Most of them had no comorbidities (64%), while a minority had been previously vaccinated against COVID-19 (19%), and only 11% required invasive mechanical ventilation (IMV). (Table 5-1). Regarding the acute laboratory findings and immune biomarkers obtained during acute hospitalization, it was noted

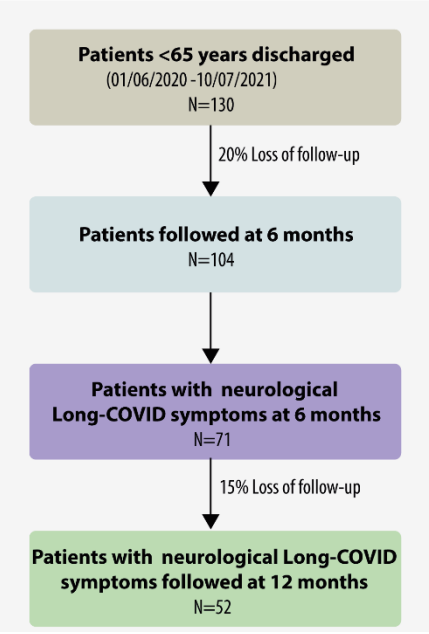

Figure 5-2 Study flowchart

that women had significantly lower ferritin values compared to men (465 vs 1,141 ng/ml p=0.004). No differences were found for inflammatory cytokines, chemokines or the presence of the NLRP risk variant (Supplementary material 9.3.1).

Seventy-one (68%) out of 104 patients fulfilled criteria for PCC at 6 months, more commonly in women (87 vs. 60%, p=0.007) and those requiring mechanical ventilation (p=0.017). (Table 5-2 and 5-3.). Significant differences were observed between sexes. Women reported higher presence of cognitive (52 vs 25% p=0.007), cardiovascular (26 vs 10% p=0.031), and gastrointestinal (32 vs 8% p=0.002) symptoms compared to men. The assessment of return to usual activities revealed a significant disparity: 97% of the non-PCC group successfully resumed their usual activities compared to 75% within the PCC group (p=0.006). Particularly notable was the marked sex contrast within the PCC group; only 61% of women managed to resume their usual activities, while a substantial 90% of men with PCC achieved the same (p<0.001).

	Total	Women	Men	p
N (%)	104	31 (30)	73 (70)	
Age, years*	42 (37-56)	44 (35 - 59)	41 (37 - 55)	0.741
BMI (kg/cm^2)* (n=89)	27.99 (25.81-30.83)	27.63 (25.39 - 31.82)	28.27 (26.29 - 30.39)	0.921
No comorbidity, (n, %)	67 (64)	20 (64.5)	47 (64.3)	0.990
Length of hospitalization in days*	5 (4-6)	4 (3.5- 6.5)	5 (4-6)	0.855
IMV requirement (n, %)	11 (11)	3 (9)	8 (11)	0.846
Vaccination before the 6-month call (n, %)	20 (19)	6 (19)	14 (19)	0.983
Blood exams during hospitalization*				
WBC, /mm3	7450(0.597-10200)	7100(4500 - 1020)	7800(6200 - 10200)	0.272
VHS (mm/h)	43 (27-58)	38 (24-56)	44 (29-60)	0.315
Highest value of CRP (mg/L)	2.64 (1.4-4.75)	3.08 (1.35 - 5.2)	2.63 (1.42 - 4.60)	0.762
Ferritin (ng/mL, n=77)	1010 (453-1722)	465 (236 -1261.55)	1141 (700 - 1805)	**0.004**
Procalcitonin (ng/mL, n=79)	0.06 (0.02-0.09)	0.07 (0.04 - 0.11)	0.09 (0.06 - 0.16)	0.109
Serum Amyloid (mg/L)	327.32 (116.39-954.25)	265.8 (74.92 - 265.8)	446.6 (131.5 - 973.4)	0.584
Inflammatory cytokines during hospitalization*				
IL-1b (pg/mL)	4.82 (4.19-5.30)	4.52 (4.21 - 5.15)	4.86 (4.17 - 5.46)	0.288
IL-6 (pg/mL)	9.12 (6.26-19.89)	13.18 (6.64 - 21.27)	8.23 (6.04 - 16.89)	0.198
IL-8 (pg/mL)	15.89 (11.49-25.76)	20.81 (12.43 - 26.36)	14.77 (11.35 - 24.30)	0.228
IL-10 (pg/mL)	4.29 (2.27-6.02)	4.07 (2.33 - 5.35)	4.36 (2.16 -6.39)	0.596
IL-12 (pg/mL)	0.82 (0.40-1.47)	0.83 (0.34 - 1.17)	0.83 (0.42 - 1.49)	0.283
IL-18 (pg/mL)	12.44 (9.18-16.62)	12.24 (7.21 - 15.94)	12.46 (9.45 - 18.06)	0.156
TNF (pg/mL)	0.12 (0-0.58)	0.26 (0 - 0.74)	0.09 (0 - 0.37)	0.136
Chemokines during hospitalization*				

CCL2 (pg/mL)	72.67 (42.89-119.68)	80.75 (51.57 - 122.49)	63.33 (37.77 - 119.59)	0.207
CCL5 (pg/mL)	17148.1 (11475.7-25592.5)	18016.2 (10798.1 - 25275.1)	16903.8 (11592.0 - 25909.9)	0.800
CXCL8 (pg/mL)	8.33 (5.30-19.27)	11.11(5.85- 19.88)	7.91 (5.08 -17.56)	0.346
CXCL9 (pg/mL)	173.18 (79.76-298.26)	170.34 (67.42 - 249.31)	192.18 (84.87- 308.11)	0.399
CXCL10 (pg/mL)	544.20 (322.43-1118.59)	589.43 (363.46 - 1208.57)	519.84 (292.96 - 954.78)	0.567
Risk NLRP3 genotype (n, %)**	**64 (62)**	**18 (58)**	**46 (63)**	**0.774**
*Values expressed as median and interquartile range (IQR), BMI: body mass index, IMV: Invasive mechanical ventilation; WBC: white blood cells, CRP: C reactive protein. **C/G and G/G alleles were considered risk genotypes.				

Table 5-1 Demographic, clinical characteristics and inflammatory parameters of study participants

	Women (n=31)	Men (n=73)	p	Total (n=104)
Any symptoms referred at 6 months (PCC), n (%)	27 (87)	44 (60)	**0.007**	71 (68)
Cognition	16 (52)	18 (25)	**0.007**	34 (32)
Fatigue	16 (52)	27 (37)	0.166	43 (41)
Cardiovascular	8 (26)	7 (10)	**0.031**	15(14)
Gastrointestinal	10 (32)	6 (8)	**0.022**	16 (15)
Return to daily duties at six months	19 (61)	66 (90)	**< 0.001**	66 (90)

Table 5-2 Sex-Based Differences in Symptom Profiles at 6 Months' Follow-Up.

	With PCC (n=71)				Without PCC (n=33)	p***
	Women (n=27)	Men (n=44)	p**	Total		
Age, years*	45 (36-59)	43 (37.5-55)	0.669	44 (37-56)	40 (37-56)	0.216
BMI (kg/cm2) (n=89)	27.06 (25.42-31.93)	28.40 (26.54-30.86)	0.744	28.19 (25.71-31.56)	27.98 (26.15-29.38)	0.364
No comorbidity (Charlson Index =0), (n, %)	17 (63)	28 (63)	0.955	45 (63)	22 (67)	0.745
Length of hospitalization in days	5 (4-7)	5 (4-7)	0.891	5 (4-7)	4 (4-6)	0.081
IMV requirement (n,%)	3 (11)	8 (18)	0.424	11 (15)	0	**0.017**
Vaccination before the 6-month call (n,%)	4 (14)	8 (18)	0.713	12 (17)	5 (15)	0.313
Blood exams during hospitalization*						
Ferritin (ng/mL)	470 (332-1190.8)	1695 (849.75-2279.55)	**0.001**	1062 (519-1805)	876.55 (340.35 1433)	0.178
Procalcitonin (ng/mL)	0.06 (0.05-0.12)	0.11 (0.08-0.18)	**0.021**	0.1 (0.06-0.16)	0 .08 (0.04-0.12)	0.082
Seric Amyloid (mg/L)	265.8 (74.92-990.6)	379.17 (123.14-987.65)	0.549	311.74 (114.8-988.6)	363.36 (117.99-890.67)	0.880
TNF (pg/mL)	0.26 (0-1.38)	0 (0 -0.312)	**0.042**	0 (0.10-0.59)	0.020 (0-0.62)	0.203

PCC: Post COVID Condition; BMI: body mass index; IMV: Invasive mechanical ventilation. *Values expressed as median and interquartile range (IQR). ** p-values reflect comparisons between men and women with PCC. *** p-values comparing total patients with and without PCC.

Table 5-3 Differential Analysis of Demographic and Laboratory Characteristics at 6 Months: Patients with and without PCC

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Among those with PCC at the 6-month follow-up (n=71), women presented lower levels of ferritin (470 vs 1695 ng/ml p=0.001) and procalcitonin (0.06 vs 0.11 p=0.021), yet higher TNF values (0.26 vs 0 p=0.042), compared to men in the acute phase (Figure 4-3, and Supplementary material 9.3.1). Furthermore, only 56% of women with PCC were able to return to their regular activities, in contrast to 86% of men (p=0.004). Being women was the only independent predictor factor for PCC at six months, as they were 7.60 times more likely to experience it compared to men (p=0.026, CI 1.27-45.18) (Supplementary material 7.3.1, Figure 7).

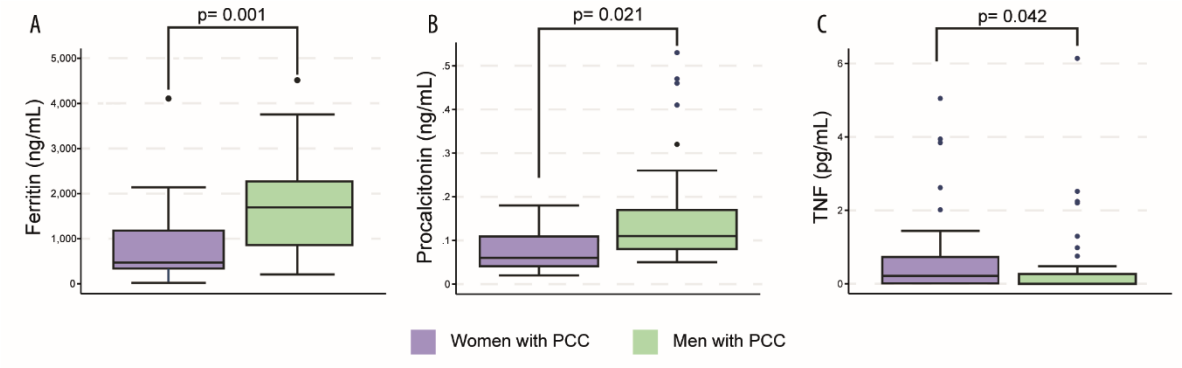

Figure 5-3 Acute phase biomarkers during hospitalisation according to sex in patients with PCC symptoms at 6 months.

* PCC: post COVID-19 condition. (A) Ferritin, (B) Procalcitonin, (C) TNF.

At 12 months, 87% of patients with previous PCC at 6 months still had symptoms but showed no evident clinical or laboratory differences by sex (Supplementary material 7.3.1). Importantly, in this subgroup, only 56% of women were able to return to their regular activities, as opposed to 86% of men (p=0.004).

3.5.3.4 Discussion

The results of our study provide valuable information on the lasting impact of COVID-19 among adults under the age of 65 with non-critical disease. Despite a higher initial admission rate of men for COVID-19, PCC affected predominantly women. Specifically, they reported a higher prevalence of cognitive, cardiovascular, and gastrointestinal compromise. This is in line with previous reports,[38–40] although it is noteworthy that these women did not have other concurrent comorbidities, as has been observed in other cohorts.[41]

Only female sex was found to be predictive of subsequent PCC. This finding is consistent with previous research, which highlights the notable association between the risk of PCC and specific socio-demographic factors, in particular female sex.[42] Although some studies have hinted at possible links with ethnicity or pre-existing conditions (such as poor mental and general health or asthma), there is a lack of consistent evidence across studies to designate these as reliable predictors of PCC.[43–45] Despite this, we observed clear acute differences in ferritin and procalcitonin levels between sexes, with lower levels in women than in men. Many studies have found a link between elevated ferritin levels and increased risk of death. However, the relationship is complex, and other factors can play a role.[42,43] It should be noted that, to our knowledge, no previous research has specifically examined sex disparities in ferritin values among patients with mild COVID-19. However, the lower ferritin values observed in women could be attributed to the fact that they experience a milder acute infectious course. In addition, women showed higher TNF values than men. This is consistent with recent studies that have indicated elevated TNF levels in patients with post-COVID symptoms, suggesting its potential role as a predictor

of PCC.[44] This finding could be related to variations in immune response, hormonal factors, or other underlying biological mechanisms. The absence of notable disparities in inflammatory cytokines, chemokines and the NLRP3 risk variant suggests a more nuanced interaction between sex and immune response in COVID-19. At 12-month follow-up, we observed that patients with PCC had no significant clinical or laboratory differences, suggesting a possible stabilisation or stagnation of symptoms in this subgroup, possibly influenced by different factors such as the initiation of COVID-19 vaccination.[43]

In terms of the return to daily activities, when comparing individuals with and without PCC, the PCC-affected group demonstrated greater difficulty resuming their usual routines (75% vs. 97%, p = 0.006). Within the PCC group, women showed significantly lower rates of resumption of usual activities compared to men, both at 6-and 12-months follow-up. This observation points to a possible impact on quality of life and highlights the specific obstacles that women may encounter during their recovery process. This may be associated with a higher prevalence of neuropsychiatric symptoms and the societal expectation that males often shoulder the primary role in household support.[46] It underlines the need for personalised care plans after COVID-19, especially adapted to female patients.

The results herein support the need to establish PCC assessment in all adults in the aftermath of COVID-19, particularly in women, as predictive factors in the acute setting remain elusive.

To the best of our knowledge, this represents the largest cohort of COVID-19 patients with a 12-month follow-up, coupled with a comprehensive evaluation of inflammatory

biomarkers. This is especially significant as obtaining blood samples during the early stages of the pandemic posed considerable challenges, given the limited availability of specific laboratory reagents and the associated costs of analysis. Notably, this cohort primarily comprised individuals affected during the two initials waves of the pandemic; therefore, effects of infection can be assessed independently of vaccination, which could be confounding.

Our study has remarked limitations that deserve to be acknowledged. First, it is a single-centre investigation conducted in a relatively uniform cohort of patients with moderate COVID-19 severity, because of challenges associated to consenting acute severe patients for the study or had died at follow up. In addition, participants were under 65 years old. Therefore, larger scale studies covering a broader spectrum of patients, including those who did not require hospitalisation and with more comorbidities, are essential to validate these findings. Second, our admission information was limited to 11 days, potentially leading to loss of relevant information from the acute phase. However, the comprehensive characterisation of acute patients, including assessment of inflammatory markers and evaluation of risk genotypes, lends strength to the study results. Finally, discharge follow-up was conducted by telephone and employing a concise questionnaire with broad questions regarding PCC symptoms, which could introduce bias in the results by restricting participation to those who could answer the call and incomplete information. Throughout the pandemic, numerous studies have employed similar methodologies, demonstrating their reliability.[45–47] Unlike other studies with high non-response rates or unreachable participants, our study had only a 20% dropout rate at 6 months and a 15% dropout rate at 12 months.[48] Nevertheless, it is likely that our

results are more representative of a younger, healthier population, whereas frail subjects are under-represented in our study.

3.5.3.5 Conclusion

In summary, our study emphasizes the significance of acknowledging and addressing sex-specific nuances among COVID-19 survivors. These findings support the need for a more individualized and comprehensive approach to post-COVID care, with particular attention to the distinct challenges encountered by female patients. Further research is essential to elucidate the underlying mechanisms contributing to these disparities and to enhance interventions for achieving the best possible recovery and rehabilitation outcomes.

3.5.3.6 Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://www.ncbi.nlm.nih.gov/clinvar/, SUB14168930.

3.5.3.7 Bibliography

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3.5.4 Article: Innovative therapeutic strategies for Post-COVID-19 condition management

STatin TReatment for COVID-19 to Optimise NeuroloGical recovery (STRONGER): study protocol for a randomised, open label clinical trial in patients with persistent neurological symptoms after COVID-19 infection

Doi: 10.1136/bmjopen-2024-089382

3.5.4.1 Introduction

The epidemiological pattern and clinical spectrum, pathogenesis, and complications in people infected with SARS-CoV-2 have been well-described.[1,2] However, it is increasingly recognised that many patients have persistent symptoms, in particular related to cardiorespiratory, mobility, cognitive and psychological function. [3–5] This phenomenon has been termed “long COVID” to describe symptoms that continue or develop after acute COVID-19, arbitrarily defined as either ongoing symptomatic COVID-19 (from 4 to 12 weeks) or post-COVID-19 syndrome (12 weeks or more).[6]

As many as three-quarters of patients have at least one ongoing symptom several months after onset of the infection.[7] About 5-10% of individuals experience neurological symptoms, including issues with higher-level cognitive functions such as sustained attention, cognitive flexibility, and memory, collectively termed ‘brain fog’, along with symptoms such as headaches, dizziness, anxiety, depression, insomnia, and fatigue.[8–11] Such manifestations may persist even among individuals with mild or absent respiratory symptoms.[12] These late neurocognitive problems following COVID-19 could be attributed to: (i) direct non-resolving low-grade

inflammation or immune reactions in the brain;[13] and (ii) indirect cerebral injury from hypotension, hypoxia, and metabolic dysfunction from effects on the heart, lungs and other organs.[4,14] Full neurocognitive recovery post-COVID-19 may take months,11 and akin to other forms of brain injury may have long-term impacts on brain health and neurodegenerative conditions such as Alzheimer's disease.[15]

Several studies have utilized specific tests to diagnose neurocognitive symptoms in long COVID patients, revealing impairments in executive functions, attention, and memory.[16] These findings could be elucidated through various modalities such as magnetic resonance imaging (MRI), and blood biomarkers. In particular, brain free water quantification using diffusion-weighted MRI is a sensitive marker of small vessel disease,[17] cognitive impairment (especially decision-making performance and working memory)[18] and neurodegenerative disease.[19] Increases in brain free water reflect an enlargement of extracellular space within the cellular matrix of the grey matter or axonal pathways of the white matter due to vasogenic oedema, neuroinflammatory gliosis, and/or loss of neuropil or myelin.[20] Blood markers of endothelial damage, immune function (cytokines/chemokines, acute phase proteins), and neuronal and glial health (e.g., neurofilament light chain, glial fibrillary acidic protein) in the acute phase of COVID-19 may function as predictors of long COVID.[21]

Statins, widely prescribed for cardiovascular disease prevention, inhibit cholesterol biosynthesis by targeting 3-hydroxy-3-methylglutaryl coenzyme A reductase. They also have anti-inflammatory, antioxidant, vascular endothelial function-enhancing, plaque-stabilising and platelet aggregation-inhibiting effects.[22–24] Statins may have neuroprotective effects beyond their cholesterol-lowering properties.[25]

Epidemiological associations show a reduced risk of all-cause dementia and Alzheimer's disease in individuals using statins,[15,26–29] with effects likely related to type, dose, duration, and onset timing over the life course.[30,31] Given the key role of the neurovascular unit in modifying the brain's susceptibility to injury, any benefit of statin therapy is more likely when initiated promptly after an acute inflammatory insult. As atorvastatin crosses the blood-brain barrier due to its high lipophilicity,[32] is shows promise as a treatment of neurological symptoms of prolonged COVID.[33]

Here, we outline the protocol for the STatin TReat-ment for COVID-19 to Optimise NeuroloGical recovERy (STRONGER) study, which aims to determine the efficacy of atorvastatin in primarily mitigating cognitive decline by reducing (or stabilising) neuroinflammation indicated by MRI changes and blood biomarkers.

3.5.4.2 Objectives

To determine the effects of a standard 40 mg dose of atorvastatin on improving neurological outcomes in adults experiencing persistent cognitive symptoms after acute infection with COVID-19. The primary outcome is cognitive processing speed, assessed by the symbol digit modalities test (SDMT); the key secondary outcome is total white matter free water on MRI. Additionally, the study will investigate other cognitive measures and health assessments and MRI markers, including white matter hyperintensity volume, perivascular space enlargement, grey matter cortical thickness, white matter microstructure, basal ganglia iron load and cerebral perfusion. A cost-effectiveness analysis will also be undertaken.

3.5.4.3 Methods and Analysis

Study design and setting

STRONGER is an international, investigator-initiated and conducted, multicentre, prospective, randomised, open label, blinded endpoint study, with a fixed time point for outcome assessments. Open label indicates that participants and researchers are aware of the treatment allocation. Participants are centrally randomised (1:1) to either the intervention group to receive 40 mg atorvastatin for 12 months on top of usual care or to the control group to receive usual care. Recruitment began on 5 May 2022 and ended in July 2024. The follow-up of participants is until July 2025, and the results are planned to be presented in October 2025. The study was approved for conduct at three medical clinic sites: the Brain and Mind Centre of the University of Sydney, Monash University in Australia (central ethics approval from Sydney Local Health District Royal Prince Alfred Hospital Ethics, numbers X21-0113 and 2021/ETH00777 10, date of first approval 19 May 2021) and at the Clínica Alemana Universidad del Desarrollo, Santiago, Chile (Comité ético científico: Facultad de Medicina, Clínica Alemana de Santiago, Universidad del Desarrollo, number 2021–75, date of first approval 20 August 2021; government approval: number EC1707587, date: 17 November 2021) as outlined in online supplemental file 1. All subjects provided written informed consent according to the forms shown in online supplemental file 2.

Eligibility of study participants

Eligible participants are aged ≥18 years, have a history of COVID-19 that is confirmed by a positive PCR test, a rapid antigen test or as per local guidelines for COVID-19 diagnosis at the time of screening and have ongoing neurological symptoms as a result of COVID-19. These symptoms included problems with memory, concentration, sleep disturbance and fatigue and were systematically

identified through administration of the Somatic and Psychological Health Report-34 item questionnaire[34] and of any reported loss of smell (anosmia). They must be able to participate in all procedures and provide written informed consent. Participants were excluded if they had any of the following: evidence of dementia and/or significant cognitive impairment on screening; a severe comorbid medical (e.g., renal failure) or psychiatric condition (i.e., drug or alcohol dependence and schizophrenia) that prevented participation; history of traumatic brain injury with loss of

consciousness (>30 min) within the last 2 years; ongoing long-term use or clear indication or contraindication for statin use; evidence of severe or significant liver disease; creatine kinase levels more than twice the upper limit of normal; being female of childbearing potential and unable or unwilling to use a reliable method of contraception, currently breastfeeding or planned pregnancy. For the subgroup of participants who agree to undergo MRI, they must have had no contraindication due to metallic body parts or claustrophobia. Finally, participants were excluded if their medical history might, in the opinion of their treating physicians, put them at significant risk if they were to participate in the trial.

Intervention

Participants who meet the eligibility criteria are randomised to receive standard care or atorvastatin 40 mg on top of standard care for a period of 12 months (Figure 5-4). The randomisation is stratified by country, time (<6 vs. ≥6 months since acute COVID-19 illness), age (<60 vs. ≥60 years), current anosmia (yes vs. no) that has occurred with temporal relation to COVID-19, and participation in the MRI/biomarker sub study. The study treatment is open label. The randomisation allocation is

blinded to researchers conducting cognitive assessments and endpoint adjudication; participants, physicians and other study team members are aware of the treatment allocation.

Visit Summary

The study will incorporate a blend of in-person visits and telephone interviews (Figure 5-4). Preliminary screening will occur via telephone or teleconference to obtain informed consent and review inclusion and exclusion criteria. In-person visits will encompass baseline assessments, a clinical evaluation at 6 months, and an end-of-study assessment at 12 months. During the baseline visit, various evaluations will be performed, including fasting blood tests, clinical assessment, cognitive tests, health questionnaires, and physical activity assessments. Randomisation will follow these assessments, with participants only being informed of their allocation after completion of all baseline evaluations to mitigate the risk of differential withdrawal between study arms. Furthermore, participants enrolled in the sub-study will undergo MRI scans and blood biomarker analyses. The 6-month visit focuses on clinical evaluation and adverse event assessment within the treatment group. Upon the 12-month follow-up, baseline assessments are repeated.

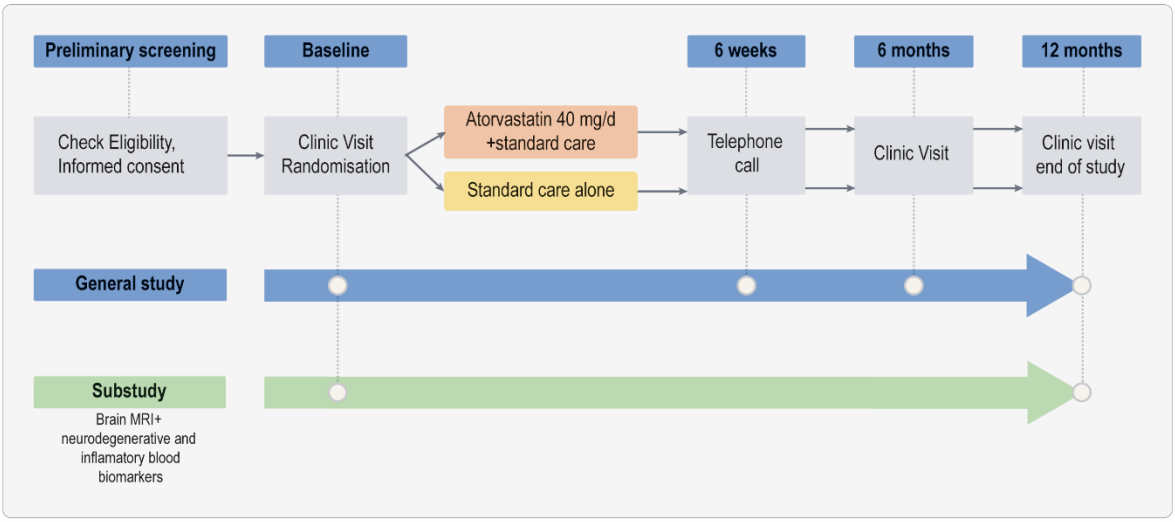

Figure 5-4 Flow chart of Stronger design

Telephone interviews complement in-person visits, particularly at the 6-week mark, to evaluate adverse events, medication adherence, and changes in concomitant medication. Every effort is to be made to conduct assessments remotely for participants unable to attend in-person visits.

Outcomes

Primary outcome is processing speed, assessed by the SDMT,[35,36] which evaluates frontal lobe executive processing. Participants match numbers to symbols based on a cue of 9 abstract symbols paired with numbers. Performance is measured by the number of correct symbols within 90 seconds.

Secondary outcomes include a comprehensive battery of assessments covering executive functions, memory, processing speed, and other domains, alongside evaluations of health status, MRI and blood biomarkers. Furthermore, a cost-effectiveness analysis, relative to standard care, will be executed. Table 5-4 provides a detailed overview of all evaluations.

Cognitive assessments are administered by trained research personnel specialised in cognitive measures. Importantly, the assessments could be conducted either in person or via video conference.

Safety Outcomes

This study document expected adverse reactions to the study medication of special interest (AESI), including myalgia, nausea, elevated blood glucose, elevated creatine kinase, abdominal pain, new-onset diabetes mellitus, and rhabdomyolysis. These AESIs are closely monitored at specific visits to assess participants' tolerability to study drugs, noting whether they are new or continuing from baseline, regardless of severity. Additionally, Serious Adverse Events (SAEs)[37] and adverse events (AEs) are reported. If treatment is discontinued as a result of any AE, serious or not, the site study team documents all events leading to the discontinuation of treatment.

Sample size

A sample of 410 patients will provide 80% power (α=0.05) to detect at least a 0.3 standard deviation (SD) effect size difference between groups, assuming equal group participation. These calculations assume a modest 5% non-compliance and 5% dropout over 12-months of follow-up. The SDMT age-adjusted mean score is estimated at 60 (SD = 13) at baseline (based on healthy control data)[35]. The effect is based on statin dementia prevention and multiple sclerosis trials, where achieved effect sizes of 0.3-0.4 are clinically meaningful and likely to confer public health benefits.[38]

For the sub-study of people undergoing MRI, a sample size of 220 (110 per group) is estimated to provide 80% power (α=0.05) to detect an effect size of relative difference of 5.0-6.5 (variance between groups/variance within groups) for the imaging endpoints, assuming a 20% drop out.

Data collection methods

All data entry is completed via a secure Web-based data management system (IBM Clinical Development) at The George Institute for Global Health. Data entry is performed at the participating sites by authorised site staff who have completed training and been given appropriate role-based access to the system. Data logic and consistency checks are programmed into the data entry forms so that data entry errors are captured in real-time and queries auto generated. Authorised electronic signatures are used to lock completed data entry forms once all data queries have been resolved within the system. Data entry and all subsequent changes or deletions are captured in an accessible audit trail. Coding of outcomes is centrally performed either automatically via the IBM coding module or manually by the Central Coordinating Centre (CCC). All coding is reviewed and verified by a Medical Monitor. Reporting within the system is used for regular data reviews and overall trial monitoring. Data is stored and backed up on the IBM cloud servers in the United States.

Statistical analysis plan

The study will follow the intention-to-treat principle for analysis. Baseline characteristics will be summarised by treatment group. Continuous baseline characteristics will be described by means (SD), if approximately normally

distributed, or by medians (IQR), if normality cannot be assumed. Categorical baseline characteristics will be presented by frequency per category. Statistical comparisons of baseline characteristics between treatment and control groups are not planned.

The primary endpoint, SDMT score, will be summarised by means (SD) if normally distributed, or by medians (IQR) if normality cannot be assumed. The primary analysis will be conducted using linear regression, with the dependent variable being SDMT and the independent variable being group allocation (treatment vs control) with adjustment for the covariates of age, sex and site. A sensitivity analysis will be undertaken with adjustment for any meaningful baseline imbalances and clinically confounders. Another sensitivity analysis will be conducted by dichotomising SDMT according to population norms (average scores of 54 in Australia and 53.2 in Chile for people aged 44 years) and use of logistic regression models with adjustment for age, sex and study site.

Continuous secondary endpoints will be analysed using linear regression, adjusting for age, sex, study site, unbalanced baseline characteristics and clinically meaningful confounders. Binary secondary endpoints will be analysed using binary logistic regression, adjusting for age, sex, study site, unbalanced baseline characteristics and clinically meaningful confounders. Ordinal secondary endpoints with more than two categories will be analysed using a cumulative logit model, adjusting for age, sex, study site, unbalanced baseline characteristics and clinically meaningful confounders and with testing of the proportional odds assumption.

Descriptive statistics will be provided for safety data, where SAEs and treatment discontinuation will be tabulated using standard terminology. Heterogeneity of the treatment on the primary endpoint will be assessed in the predefined subgroups of age (<60 vs ≥60 years), time since COVID-19 diagnosis (<6 vs ≥6 months), baseline C-reactive protein levels (0–9 vs ≥10 mg/L), ethnicity (white Caucasian vs other) and prior cardiovascular risk (no vs yes for any of a history of hypertension, hyperlipidaemia, current smoker and body mass index (height (cm)/weight (kg) ≥10).[2] The hypothesis is that there will be a larger relative treatment effect in younger people, in people with higher levels of inflammation by virtue of an earlier time from the acute COVID-19 infection, in people with raised inflammatory markers, in non-white individuals and those with elevated cardiovascular risk. A detailed outline of the statistical analyses will be specified a priori in a full statistical analysis plan prior to unblinding of the data. A modelled cost-utility analysis using trial data (health-related quality of life, captured by EuroQoL Group 5-Dimension 5-level self-report questionnaire; drug costs; health service utilisation costs, including AEs) will be conducted by comparing use of atorvastatin with standard of care. A 5-year time horizon will be undertaken, with analyses conducted in line with accepted Australian standards for use of economic evaluation in decision-making.

Data monitoring

Trial data are monitored, using central risk-based monitoring principles, to detect any unusual patterns of data that would require further investigation. During the study, representatives of the CCC monitor site performance and quality via remote methods, including via videoconference, to ensure that the study is conducted in accordance with the protocol, International Conference on Harmonisation guidelines

for Good Clinical Practice (ICH-GCP) guidelines and relevant ethical and regulatory requirements.

Areas of potential bias

As this is a clinical trial, a major source of bias is *selection*, so we plan to compare the characteristics of participants with those in published cohorts and between those who were screened. Being an open trial, another main source of bias relates to *differential drop-out*, for example, participants in the control 'no treatment' group failing to return to follow-up assessments or withdrawing from the study. We will try to reduce this by ensuring that all participants fully understand the importance of participation and follow-up, irrespective of ceasing the study medication, and in maintaining good communication and relationships with participants. A final source of bias is *behavioural*, where participants in either group may change their lifestyle and attitude simply due to participation or in response to factors outside of the trial. We will monitor this by asking questions about use of concomitant medications, diet, smoking and exercise and through use of actigraphy as a proxy measure of sleep and physical activity. There is a low likelihood that the control 'no treatment' group will receive atorvastatin (i.e., *treatment crossover*) as this can only be prescribed for people who are at high risk of cardiovascular disease.

Patient and public involvement

The STRONGER study protocol was presented to the Brain Health Consumer Panel of The George Institute for Global Health at meetings in March and November of 2021. This panel comprises a dozen people with lived experience of brain health conditions or their caregivers. Feedback was sought regarding the protocol and

patient-facing documents. Those with lived experience provided comments on the feasibility of the study, mode of recruitment, activities and information dissemination. This feedback was incorporated into the study where appropriate, and there was agreement to ensure that the findings of the study, along with a plain language summary, will be disseminated to participants of the trial after the study is published.

3.4.4.4 Ethics and dissemination

This study protocol was designed and shall be implemented and reported in accordance with the ICH-GCP, the National Health and Medical Research Council, the National Statement on Ethical Conduct in Human Research and with the ethical principles laid down in the World Medical Associations Declaration of Helsinki. Potentially eligible participants are provided with information about the study, and informed consent is obtained from all participants prior to screening assessments.

Writing committees, with oversight by the steering committee, will be formed from members of the various committees, statisticians, research fellows and investigators. Authors of publications must meet the International Committee of Medical Journal Editors guidelines for authorship.[39] The study has been approved by relevant ethics committees and regulatory bodies at country level and local sites in Australia and Chile. The current protocol is V.9.0, and all protocol updates have been approved by the Steering Committee and Ethics Committees and communicated with investigators and Data and Safety Monitoring Board members.

3.5.4.5 Conclusion

The study has been approved by relevant ethics committees and regulatory bodies at country level and local sites in Australia and Chile. The current protocol is version

9.0, and all protocol updates have been approved by the Steering Committee and Ethics Committees and communicated with investigators and Data and Safety Monitoring Board (DSMB) members.

	Name	Purpose	Assessment
a. Primary Outcome			
	Symbol Digit Modalities Test (SDMT)[35]	Assesses frontal lobe executive processing	Requires participants to match numbers to symbols according to a key, containing 9 abstract symbols each paired with a number. Performance is measured by the number of correct symbols within 90 seconds.
b. Secondary Outcomes			
Neuropsychological Assessments	Rey Auditory Verbal Learning test (RAVLT-D)[40]	Assesses memory and learning	Requires participants to learn a 15-item word list over 5 learning trials, followed by a distractor list, and short and long-delayed recall.
	Oral Trail Making Test (OTMT) A & B[41]	Summarizes visual search, scanning, speed of processing, mental flexibility, and executive functions	Has two parts: Part A – participant count from 1 to 25 as quickly as possible. In Part B – participant alternately count numbers up to 13 and recite letters of the alphabet up to L as quickly as possible. The primary performance metric is the time in seconds required to complete each of the two parts of the test.
	Delis-Kaplan Executive Functioning System "Stroop" Color-Word interference Test (D-KEF CWIT)[42]	Measure executive functions.	Has four parts: colour naming, word reading, inhibition, and inhibition/switching. Performance is measured by completion time for each trial. Composite score: colour naming and word reading times. Contrast scores: inhibition vs. colour naming, inhibition/switching vs. combined colour naming and word reading, and inhibition/switching vs. inhibition, assess disproportionate impairments in higher-level functions compared to component functions.
	Semantic Fluency (SF)[43,44]	Assesses language processing	Requires the generation of as many 'animal names' in 1-minute. Performance is measured by counting the number of correct unique semantic category items produced.

	Name	Purpose	Assessment
a. Primary Outcome			
Health Assessments	C19-YRS[45]	Evaluate the long-term impact of COVID- 19	It is administered by self-report or clinician. It will be used as a baseline measure and then at follow-up at 18 months as an assessment of response to therapy.
	Patient Health Questionnaire (PHQ-9)[46]	Measure the presence and severity of depression	Evaluates each of the nine DSM-V major depression criteria on a scale from '0' (not at all) to '3' (nearly every day). It aids in making a preliminary diagnosis of depression in at-risk populations (e.g., individuals with coronary heart disease or after stroke), with scores of ≥10 indicating probable clinically significant depression.
	General Anxiety Disorder (GAD-7)[47]	Measure the presence and severity of generalised anxiety	A score of ≥10 represents a reasonable cut point for identifying cases of generalised anxiety. Cut points of 5, 10, and 15 might be interpreted as representing mild, moderate, and severe levels of anxiety.
	Pittsburgh Sleep Quality Index (PSQI)[48]	Assesses overall sleep quality in clinical populations	Covers 19 self-reported items across seven sub-categories: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction; with five additional questions rated by the respondent's roommate or bed partner, if available. Scores >5 are generally indicative of poor sleep quality.
	EQ5D-5L[49]	Measures HRQoL	Across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each rated according to five levels, as well as providing an integrated utility score for calculating an overall score against population-based preference weights.

	Name	Purpose	Assessment
a. Primary Outcome			
	International Physical Activity Questionnaire-Long Form (IPAQ-LF)[50]	Physical Activity Assessment	A valid 27-item self-reported assessment to provide an estimate of physical activity and sedentary behaviour for adults aged 15-69 years. Participants reflect on activities over the previous 7 days across five domains: 1) occupational physical activity; 2) transportation physical activity; 3) housework, house maintenance and caring for family; 4) recreation, sport and leisure-time physical activity; and 5) time spent sitting. Physical activity scores can be calculated in either categorical score (high, medium, low) or MET minutes per week.
c. Sub study outcomes			
MRI	Total white matter free water (dMRI)		Using multi-shell diffusion spectral imaging with fibre orientation and compartment modelling.
	Others		MRI markers of white matter hyperintensity volume, enlarged peri-vascular space volume, total grey matter volume, white matter microstructure (fractional anisotropy), basal ganglia iron load and total cerebral perfusion,
Blood biomarkers	Neurodegenerative markers		Ptau-181, neurofilament light chain (NfL) and Aβ42/40, and DNA extraction for apolipoprotein E genotype.
	Peripheral markers		IL-6, IL-1β,NAD+, TNF-α, hsCRP

DSM-V denotes Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EQ-5D-5L EuroQoL Group 5-Dimension 5-level self-report questionnaire ; hs-CRP high-sensitivity C-reactive protein; MET metabolic equivalent (1 MET is the energy spent sitting at rest); NAD nicotinamide adenine dinucleotide; TNF tumour necrosis factor.

Table 5-4 Outcomes assessed in Stronger trial

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3.6 CHAPTER VI: PATIENT-CENTERED OUTCOMES IN POST-COVID-19 CONDITION

3.6.1 Chapter overview

Chapter IV first characterised the clinical and patient-reported profile of patients with PCC and then introduced the STRONGER trial protocol designed to evaluate a therapeutic strategy for persistent neurological symptoms after COVID-19. Building on that progression, this chapter presents a preliminary cross-sectional analysis of baseline (pre-randomisation) STRONGER data to quantify preference-based HRQoL using the EQ-5D-5L and to examine its associations with symptom impact, mental health, sleep quality, and cognitive performance. This baseline profiling complements the prior descriptive work in PCC and provides a benchmark for interpreting longitudinal change and treatment effects in subsequent STRONGER analyses.

3.6.2 Introduction

Chapter IV described PCC as a complex and heterogeneous syndrome with a significant patient-reported disease burden and subsequently introduced the STRONGER trial protocol as a pragmatic, randomized framework for evaluating a therapeutic strategy in adults with persistent neurological symptoms following COVID-19. Within the structure of this thesis, this progression—characterizing PCC and then describing the trial designed to address it—leads to an assessment focused on the baseline health status of the STRONGER trial participants before considering the effects of any intervention.

HRQoL is a key outcome in PCC, as it quantifies the patient-perceived consequences of persistent sequelae on daily functioning and well-being. It has been reported that patients with PCC are up to 4.7 times more likely to report a loss in quality of life compared to those who did not have PCC after infection.[1] In a structured review synthesising studies that reported EQ-5D-5L outcomes after COVID-19, mean EQ-5D-5L index values were consistently below full health and varied across settings, ranging from 0.612 in Iran to 0.714 in the United Kingdom (Belgium 0.620; Norway 0.690), suggesting substantial losses in health utility beyond the acute phase.[2] Moreover, impairment appears multidimensional: across three studies reporting EQ-5D-5L domain problems, 25.9% to 45.2% of participants reported difficulties in at least one domain, with a particularly high burden in pain/discomfort (up to 69.6% in one cohort) and anxiety/depression (up to 58.7% in another), underscoring the combined physical and psychosocial constraints associated with PCC.

Cognitive dysfunction is a clinically relevant contributor to this HRQoL burden, given its direct implications for work capacity, social roles, and independent living. Evidence showed that 85% of adults with PCC demonstrated impairment in at least one cognitive task, with attention and executive function tests showing the highest proportion of severe impairment.[3] These findings support the need to analyse HRQoL alongside cognitive assessments, because symptom persistence alone may not fully characterise the functional and participation-related consequences that drive perceived health status.

The need to quantify the patient-perceived health loss associated with PCC has accelerated the use of patient-reported outcome measures (PROMs) in this field. A COSMIN-based systematic review of PCC-specific PROMs identified substantial gaps in the evidence on measurement properties across instruments and highlighted content validity as a major limitation, underscoring the need for further validation and stronger involvement of both patients and healthcare professionals during instrument development and refinement.[1] In parallel, given the variable performance and limited comparability of disease-specific tools, the review also noted that an assessment of generic PROMs recommended the EQ-5D index for PCC, supporting the use of preference-based measures when cross-study comparability and interpretability on a common utility scale are priorities. This is particularly relevant when HRQoL estimates are intended to inform broader decision-making, including comparisons across health conditions and health-economic evaluation. Accordingly, this chapter applies patient-centred assessment strategies to PCC within STRONGER by operationalising preference-based HRQoL measurement. Baseline patterns in EQ-5D-derived utility are characterised among enrolled participants, and

individuals are classified into “mild” and “extreme” health-status groups based on EQ-5D index scores to identify those with the greatest patient-perceived health loss.

3.6.3 Methods

This chapter reports a cross-sectional analysis of baseline (pre-randomisation) data from STRONGER (ClinicalTrials.gov NCT04904536), an international, multicentre, prospective, randomised, open-label, blinded-endpoint trial evaluating atorvastatin 40 mg plus usual care versus usual care in adults with persistent neurological symptoms after confirmed COVID-19 infection. Baseline assessments were completed prior to randomisation, and participants were informed of allocation only after all baseline procedures had been finalised; therefore, treatment assignment was not relevant for the present analysis. The analysis population comprised all randomised participants with available baseline EQ-5D-5L data. Analyses used a complete-case approach for each model (with denominators reported where they differed), and no imputation was performed.

HRQoL was assessed at baseline using the EQ-5D-5L descriptive system.[4] Baseline patient-reported symptom and mental health measures included depressive symptoms (PHQ-9),[5] anxiety symptoms (GAD-7),[6] sleep quality (PSQI),[7] and PCC symptom impact (COVID-19 Yorkshire rehabilitation scale ,C19-YRS).[8] These questionnaires were administered as part of the baseline visit, alongside clinical and cognitive assessments, as specified in the STRONGER protocol mentioned in chapter IV.

Cognitive performance was evaluated using a neuropsychological battery comprising global cognition (Blind Montreal Cognitive Assessment, MoCA) as

screening,[9] with the subsequent neuropsychological battery: processing speed (Symbol Digit Modalities Test, SDMT),[10] verbal learning and memory (Rey Auditory Verbal Learning Test, RAVLT),[11] set-shifting/executive control (Oral Trail Making Test parts A and B, OTMT-A/B),[12] inhibitory control (Stroop/Delis–Kaplan Executive Function System Colour–Word Interference Test, D-KEFS CWIT),[13] and language/executive retrieval (semantic fluency)[14] Where published norms were available (RAVLT, SDMT, OTMT), scores were converted to norm-referenced z-scores using Australian normative references; this approach was prioritised given the small number of Chilean participants and the lack of validated Chilean norms for several tests. When external norms were not applicable, regression-based internal norms were derived within the cohort (adjusting for key demographic determinants such as age, sex, and education) and used to express performance on a standardised scale.

The primary outcome for this analysis was the EQ-5D-5L index (utility) score at baseline, derived by applying Australian and Chilean-based preference weights.[15,16] Baseline HRQoL severity was operationalised using the distribution of the EQ-5D index. Participants were categorised into tertiles (low, mid, high), and “extreme impairment” was defined a priori as belonging to the lowest tertile. The three-level variable was used to describe gradients in HRQoL and to visualise differences across EQ-5D domains, while the binary definition (lowest tertile vs the remaining two tertiles) was used for multivariable modelling.

Descriptive analyses summarised baseline EQ-5D index and EQ-5D domain profiles using means (SD) or medians (IQR), as appropriate, and proportions for categorical variables. For bivariate comparisons, participants with extreme versus non-extreme

HRQoL impairment were contrasted using Student's t-test or Mann–Whitney U test for continuous variables and chi-square tests for categorical variables, depending on distributional assumptions. Multivariable logistic regression was used to identify variables independently associated with extreme HRQoL impairment, with results reported as odds ratios (ORs) and 95% confidence intervals. Model diagnostics included the Hosmer–Lemeshow goodness-of-fit test, area under the receiver operating characteristic curve (AUC), classification statistics, and assessment of multicollinearity using variance inflation factors.

Exploratory analyses examined relationships among continuous health measures using correlation matrices (Pearson correlations; with Spearman correlations as a sensitivity analysis where distributions were non-normal). All analyses were conducted in Stata (v19), using two-sided tests with $\alpha=0.05$.

3.6.4 Results

A total of 190 participants were included in the STRONGER baseline analysis, with 82% recruited in Australia and 18% in Chile (Table 6-1). The mean age was 44.4 years (SD 10.5) and 78% were women. The mean time since acute infection was 13.6 months (SD 9.5), and participants had received a median of 3 COVID-19 vaccine doses (IQR 3–4). Global cognitive screening performance at trial screening (MoCA) averaged 20.5 (SD 1.6). At the baseline clinical assessment, mean BMI was 29.0 kg/m² (SD 7.0), with mean blood pressure 124/82 mmHg (SD 15/10). Laboratory results are provided in Supplementary Table S1.

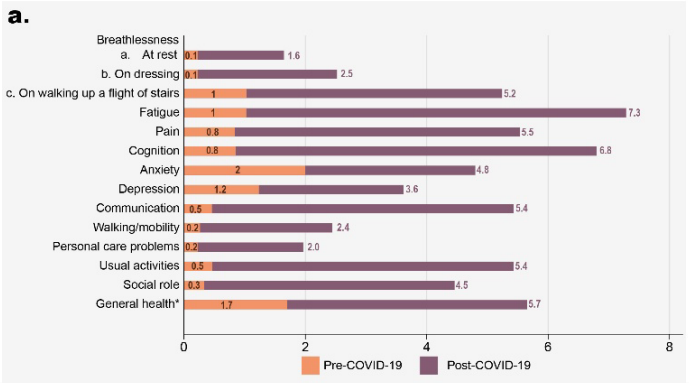
Self-reported symptom severity and functional impact were characterised with the C19-YRS by contrasting participants perceived pre-COVID-19 and post-COVID-19

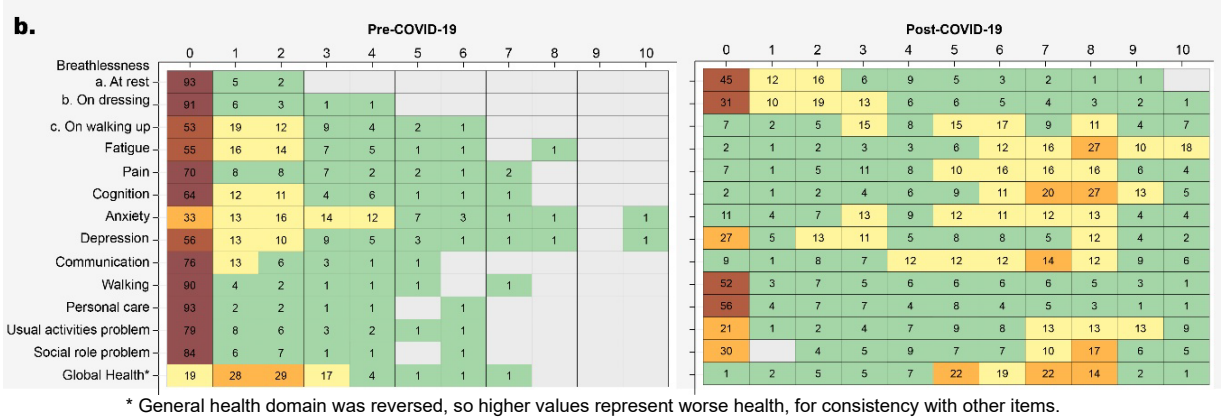
status (Figure 6-1a). Mean item scores increased across all domains, with the largest absolute increases observed for fatigue (1.0 to 7.3), cognition (0.8 to 6.8), pain (0.8 to 5.5), and communication (0.5 to 5.4). The accompanying heatmap (Figure 6-1b) shows that these changes were not limited to shifts in central tendency: responses moved from a pre-COVID pattern concentrated at low severity levels (predominantly 0–2) toward a broader and right-shifted post-COVID distribution, with substantial proportions reporting moderate-to-severe impact (commonly 6–10) across multiple domains. Full paired summaries for each C19-YRS item are presented in Supplementary Table S2.

Characteristic	**N (190)**
Country of origin, n (%)	
Australia	155 (82)
Chile	35 (18)
Age, years, mean (SD)	44.0 (10.5)
Female sex, n (%)	149 (78)
Ethnicity, n (%)	
Caucasian/European	134 (71)
Hispanic/Latino	33 (17)
Asian/Aboriginal/Other	23 (12)
Education level, n (%)	
Secondary	28 (15)
University (undergraduate or postgraduate)	136 (73)
Technical/vocational training or other	23 (12)
Partnered (married/de facto), n (%)	118 (65)
Time since acute infection (months), mean (SD)	13.6 (9.5)
COVID-19 vaccine doses, median (IQR)	3 (3-4)
Any comorbidity, n (%)	**170 (89)**
Cardiovascular	54 (33)

Mental / mood disorder	54 (33)
Neurological	51 (31)
Hormonal	42 (26)
Musculoskeletal	42 (26)
Respiratory	38 (24)
Gastrointestinal	31 (19)
Genitourinary	23 (14)
Alcohol intake, n=79, (%)	
< 5 standard drinks/week	60 (76)
≥ 5 standard drinks/week	19 (24)
Basal physical examination, mean (SD)	
Body Mass Index (kg/m²)	29.0 (7.0)
Systolic blood pressure (mmHg)	124.1 (15.3)
Diastolic blood pressure (mmHg)	82.3 (10.6)
Heart rate (bpm)	76.5 (12.3)
Cognitive performance (MoCA), mean (SD)	20.5 (1.6)

Table 6-1. Baseline Characteristics of Stronger participants.





* General health domain was reversed, so higher values represent worse health, for consistency with other items.

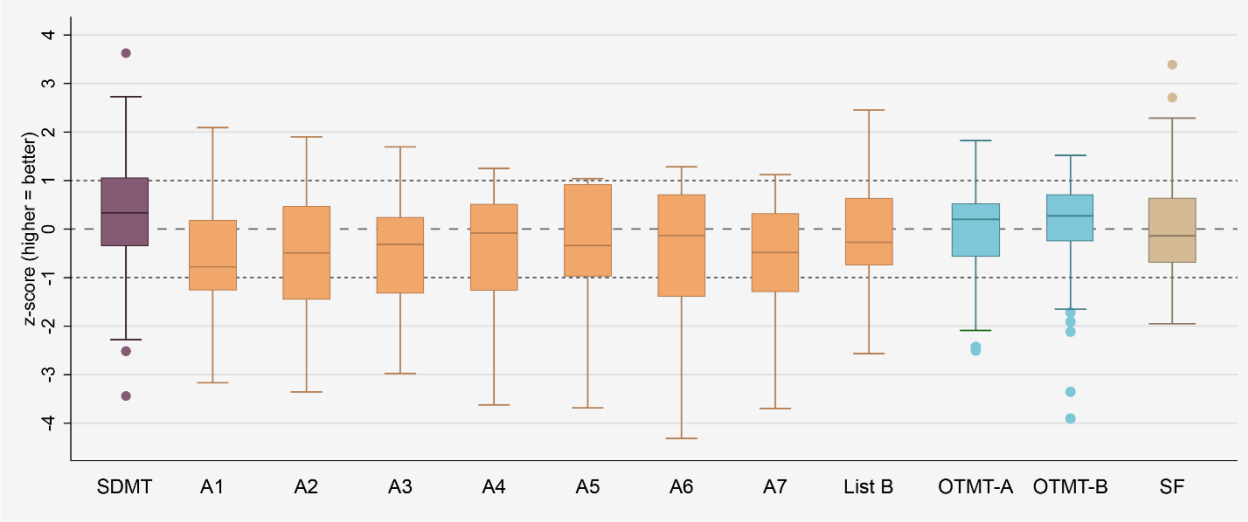
Figure 6-1. Mean C19-YRS scores: Pre- and Post-COVID-19 comparison.

Regarding cognitive performance using norm-referenced z-scores (Table 6-2, Figure 6-2), semantic fluency had a mean z-score of −0.67 (SD 1.14). On the RAVLT, mean z-scores across learning trials and recall indices ranged from −0.56 to −0.42 for learning (A1–A5), −0.48 for immediate recall (A6), and −0.52 for delayed recall (A7), indicating lower standardised performance in verbal learning and memory relative to norms. For the Oral Trail Making Test, mean z-scores were −0.46 (SD 2.39) for Trail A and 0.01 (SD 1.02) for Trail B. No relevant differences were found when analysing data by country (Supplementary Table S3).

	Raw score	**z-score**	**t-score**
SDMT	56.58 (10.56)	0.58 (1.27)	44.18 (12.69)
RAVLT			
A1 (trial 1)	6.36 (2.04)	-0.56 (0.97)	44.40 (9.70)
A2 (trial 2)	9.69 (2.38)	-0.56 (1.11)	44.40 (11.10)
A3 (trial 3)	11.34 (2.33)	-0.42 (0.98)	45.80 (9.80)
A4 (trial 4)	12.24 (2.23)	-0.50 (1.28)	45.00 (12.80)
A5 (trial 5)	12.74 (2.11)	-0.49 (1.30)	45.10 (13.00)
A7 (delayed recall)	10.79 (3.20)	-0.52 (1.23)	44.80 (12.30)
A6 (immediate recall)	11.11 (3.01)	-0.48 (1.23)	45.20 (12.30)
List B (B1)	6.18 (2.40)	-0.17 (1.09)	48.30 (10.90)
Oral Trail-Making Test			
Trail A (time)	12.13 (65.94)	-0.46 (2.39)	45.44 (23.86)
Trail B (time)	35.45 (67.46)	0.01 (1.02)	50.14 (10.18)
Semantic Fluency	24.69 (6.25)	-0.67 (1.14)	56.6 (11.39)

SDMT: Symbol Digit Modalities Test; RAVLT: Rey Auditory Verbal Learning Test.

Table 6-2. Cognitive Assessments at baseline in Stronger participants



Higher z-scores correspond to better performance relative to the normative reference. SDMT, Symbol Digit Modalities Test; A1-A7 and list b correspond to the Rey Auditory Verbal Learning Test; OTMT-A/B, Oral Trail-Making Test parts A and B; SF, semantic fluency.

Figure 6-2. Distribution of age- and education-adjusted z-scores for cognitive tests.

HRQoL measured with the EQ-5D-5L utility (n=188) showed a mean utility index of 0.71 (SD 0.22; median 0.78, IQR 0.56–0.89; Supplementary Table S3). Participants recruited in Australia reported lower mean EQ-5D utility than those recruited in Chile (0.68 [SD 0.22] vs 0.81 [SD 0.16]). Psychological tests indicated a substantial symptom burden, with mean PHQ-9 11.0 (SD 5.7), GAD-7 7.6 (SD 5.2), and PSQI 9.8 (SD 3.8).

Higher EQ-5D utility was associated with lower depressive symptoms (PHQ-9; Pearson r = −0.53, p < 0.001), lower anxiety (GAD-7; r = −0.25, p < 0.001), and better sleep quality (lower PSQI; r = −0.23, p = 0.0016). The correlation with processing speed (SDMT) was weaker but statistically significant (r = 0.17, p = 0.022).

To describe gradients in HRQoL, participants were subsequently classified into tertiles of baseline EQ-5D utility, with the lowest tertile defined a priori as “extreme impairment”. Overall, 33.5% (63/188) of the participants were classified in the

extreme impairment group (Supplementary Table S4). Participants from Chile were less likely to belong to the extreme impairment group than those enrolled in Australia (OR 0.35, 95% CI 0.14–0.89; p=0.023). Also, large differences were observed in patient-reported health measures. Mean EQ-VAS was 40.6 (SD 18.1) in the extreme impairment group versus 71.8 (SD 13.6) in the non-extreme group (mean difference 24.7, 95% CI 19.8–29.7; p<0.001). Depressive symptoms were higher in the extreme impairment group (PHQ-9 15.6 [SD 5.8] vs 10.0 [SD 4.7]; mean difference 5.60, 95% CI 4.03–7.16; p<0.001), as were anxiety symptoms (GAD-7 9.1 [SD 5.9] vs 6.8 [SD 4.6]; mean difference 2.34, 95% CI 0.80–3.87; p=0.003). PSQI scores were also higher in the group with worst HRQoL (10.4 [SD 3.6] vs 7.9 [SD 3.5], p <0.001).

Multivariable logistic regression models were fitted to identify independent correlates of extreme HRQoL impairment (lowest EQ-5D utility tertile). In the clinical–demographic model (Table 6-3), higher MoCA score was associated with lower odds of extreme impairment (OR 0.80 per point, 95% CI 0.65–0.98; p = 0.031). Participants recruited in Chile had substantially lower odds of extreme impairment compared with those recruited in Australia (OR 0.15, 95% CI 0.04–0.63; p = 0.010), and having received ≥3 COVID-19 vaccine doses was also associated with lower odds of extreme impairment (OR 0.32, 95% CI 0.12–0.81; p = 0.017). No other demographic or clinical predictors showed statistically significant associations in this model. Model discrimination was moderate (AUC 0.70, Hosmer–Lemeshow p= 0.99).

Predictor	Model 1: clinical demographic OR (95% CI)	p-value
Age (years)	0.99 (0.95–1.02)	0.379
BMI (kg/m²)	1.02 (0.98–1.07)	0.315
Time since acute COVID (months)	1.00 (0.96–1.04)	0.989
Medical comorbidities (count)	2.06 (0.68–6.23)	0.198
MoCA (per point)	0.80 (0.65–0.98)	0.031
Sex: male (vs female)	0.72 (0.31–1.67)	0.446
Ethnicity: non-Caucasian (vs Caucasian)	1.50 (0.55–4.13)	0.431
In a relationship (vs not)	0.94 (0.44–2.00)	0.864
Country: Chile (vs Australia)	0.15 (0.04–0.63)	0.010
Higher education (vs no higher education)	1.94 (0.83–4.55)	0.125
≥3 vaccine doses (vs <3)	0.32 (0.12–0.81)	0.017
Anosmia (yes vs no)	1.25 (0.50–3.16)	0.633
Current smoking (yes vs no)	1.35 (0.42–4.27)	0.613
Alcohol consumption (yes vs no)	0.69 (0.33–1.43)	0.316

Table 6-3 Multivariable associations with extreme HRQoL impairment in baseline STRONGER participants

3.6.5 Discussion

Strengths

This baseline analysis of the STRONGER clinical trial provides a well-characterised outpatient PCC cohort (n=190) assessed a mean of 13.6 months after acute infection, enabling a structured description of preference-based HRQoL alongside an objective cognitive test battery. The use of EQ-5D-5L utilities offers a common, interpretable metric to summarise multidimensional burden and to support comparisons across studies and conditions.[17] The analysis also benefits from concurrent measurement of symptom impact, mental health (PHQ-9, GAD-7), sleep quality (PSQI), and cognition (including MoCA and SDMT), allowing a clinically coherent profile of severe HRQoL impairment beyond a purely distribution-based categorisation. Although SDMT was prioritised as the trial's primary cognitive endpoint, the inclusion of memory and executive-function measures is particularly informative, as these domains may be more closely aligned with patient-centred outcomes and everyday functioning than processing speed alone.

Limitations

This chapter reports a preliminary, cross-sectional baseline analysis; therefore, observed associations between HRQoL and concurrent symptoms or cognitive measures are correlational and do not address treatment effects, which will be evaluated longitudinally. Defining "severe/extreme" impairment using internal EQ-5D tertiles supports within-cohort stratification but does not map to externally validated clinical thresholds; future work using anchor-based methods, clustering, and alternative cut-points would strengthen interpretability. Between-country

comparisons should be interpreted cautiously because differences may reflect recruitment pathways, time since infection, and case-mix rather than PCC burden alone; using a single EQ-5D-5L value set improves internal consistency but cannot fully account for cross-country differences in health-state valuation. Cognitive findings may also be influenced by cross-cultural/language factors, and SDMT-based eligibility may have truncated processing-speed variability, limiting generalisability to more severely affected PCC populations. Finally, multivariable models that include overlapping health domains risk collinearity and coefficient instability, supporting the use of a parsimonious primary model with extended analyses presented separately.

Summary

Participants reported a substantial HRQoL burden at baseline, with no clear corresponding deficit across the objective cognitive test battery. The mean EQ-5D-5L utility was 0.71, and one in three participants fell into the lowest tertile ("extreme impairment"), consistent with contemporary PCC cohorts showing meaningful HRQoL loss, although estimates vary by setting and assessment timing.[18] For context, an EQ-5D-5L utility of approximately 0.71 is comparable to values reported in symptomatic heart failure cohorts (mean EQ-5D-5L index ≈0.78), lower than Australian general population norms (mean EQ-5D-5L index ≈0.86) and in many post-stroke samples without transient ischaemic attack (mean EQ-5D-5L index ≈0.78), and higher than utilities commonly reported in major depressive disorder (mean EQ-5D-5L utilities ≈0.56). [16,19,20]

Between-country differences should be interpreted cautiously. Utilities were lower in Australia than Chile (0.68 vs 0.81), and this contrast may reflect differences in recruitment pathways, case-mix, timing since infection, and how health is self-rated across settings, rather than burden alone. [15,21]

Cognitive performance showed modest and heterogeneous decrements (notably in verbal learning/memory), with generally small differences across HRQoL strata. In contrast, HRQoL varied more clearly with psychological symptom burden (especially depressive symptoms) and, to a lesser extent, anxiety and sleep disturbance, consistent with evidence that perceived health in ambulatory PCC is often driven more by symptom burden than by deficits detectable on standard neuropsychological tests.[22–24]

In multivariable analyses, severe HRQoL impairment captured a broad phenotype characterised by higher psychological symptoms and sleep disturbance. Objective cognition contributed only modestly: SDMT associations were statistically significant but small, while higher MoCA scores were linked to lower odds of severe impairment. Greater vaccine dose exposure (≥3 doses) was also associated with lower odds of severe impairment, concordant with evidence that vaccination reduces PCC risk and may attenuate symptom burden.[25,26] However, findings should be interpreted cautiously given the cross-sectional design and moderate model discrimination (AUC 0.70).

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4 DISCUSSION

4.1 Key findings and integrative interpretation

This thesis brought PCO to the foreground of brain health assessment across conditions that differ in aetiology, clinical course, and research context. Across stroke, intracerebral haemorrhage (ICH), and post-COVID-19 condition (PCC), a consistent message emerged: conventional endpoints—including disability scales and cognitive tests—remain necessary for clinical and trial evaluation, but they are insufficient on their own to characterise outcomes that matter to patients, namely how health is experienced, valued, and lived in everyday life. Preference-based utilities offered a common metric to summarise multidimensional health and to support comparison of burden and recovery across populations. However, these analyses also highlight that utility-based outcomes are inherently context-dependent: valuation choices, cultural and health-system setting, assessment timing, and the capacity to self-report can materially influence what PCOs capture and how they should be interpreted.

Therefore, the choice of how to estimate preference-based PCOs was not a purely technical detail, but a substantive decision that shaped what could be learned across conditions. Using EQ-5D–derived utilities provided a broad, standardised summary of health that could be applied across clinically distinct contexts (e.g., cerebrovascular disease and PCC), while keeping the analytic focus on how brain health is experienced and valued in everyday life. In parallel, utility weighting also offered a way to enrich the interpretation of clinician-rated disability: by linking mRS categories to preference-based utility values, the UW-mRS expresses functional outcome on a scale that is directly interpretable in terms of health-state value, thereby integrating information from traditional neurological endpoints with a

preference-sensitive metric rather than treating “clinician” and “patient” perspectives as competing criteria.

In the community-based Chilean stroke cohort, utilities declined sharply across mRS categories and problems were frequent across EQ-5D dimensions, particularly pain/discomfort (67%). Importantly, the burden was not confined to those with severe disability: even participants classified as mRS 0–1 reported non-trivial problems across EQ-5D domains that a global disability scale is not designed to capture. Relative to trial-derived cohorts using similar approaches, utilities in this population-based sample appeared lower, particularly in higher disability strata (mRS 4–5).[1] This result is consequential because it reframes what “favourable outcome” means: functional independence does not necessarily equate to restoration of valued health, and preference-based outcomes make residual burden visible in patients who would often be considered recovered if interpretation relied on disability grades alone. At the same time, the between-cohort contrast reinforces that utilities are not merely a different scale; they are sensitive to contextual determinants of recovery (including rehabilitation access and broader socioeconomic factors), which conventional endpoints capture less directly.

The ICH analyses extended this integrative logic to an international trial context. In INTERACT3, patient-perceived burden at 6 months was substantial and determinants of poorer HRQoL were largely explained by markers of acute severity and baseline vulnerability, reinforcing that lived health after ICH is strongly shaped by the combined effects of pre-event reserve and acute injury. However, the utility framework also clarifies a second layer that disability grading alone cannot fully resolve: the close correlation between EQ-5D utilities and mRS confirms that

disability is a dominant driver of HRQoL, but variation by contextual factors such as country and living situation underscores that similar disability grades do not necessarily translate into comparable lived health across settings. This matters for interpretation and for translation: it indicates that “equivalent” neurological outcomes may still correspond to different lived outcomes depending on the environment in which recovery occurs.

TRIDENT then moved the thesis beyond cross-sectional burden by characterising longitudinal patterns of patient-centred recovery under controlled conditions. EQ-5D index values and functional status improved from baseline and were largely maintained, with no clear evidence of differential trajectories by treatment group. Two features of the trial context are relevant when integrating this finding: participants entered with relatively mild baseline disability (59.7% with mRS 0–2), which may have favoured recovery and reduced headroom for detectable between-group differences; and the structured follow-up typical of secondary prevention trials may have supported broader improvements in care and health behaviours in both groups, attenuating contrasts between intervention and placebo arms.[2] Crucially, even in the absence of clear treatment separation on utility-weighted trajectories, cognition remained a consistent correlate of HRQoL. In mixed-effects models with paired MoCA and EQ-5D assessments, higher MoCA scores were associated with higher EQ-5D index values both between individuals and within individuals over time. Taken together, the ICH findings support an integrative outcome model: preference-based outcomes do not replace traditional endpoints; rather, they provide a patient-valued frame that helps interpret why conventional impairments (including cognitive performance) matter in terms of lived health.

Finally, PCC provided a stringent test of the thesis framework because outcomes are less naturally anchored to a single traditional endpoint, and the relationship between patient-perceived impact and objective performance can be discordant. The PCC chapters emphasise that PCC is characterised by a multi-domain symptom burden, making preference-based PCO particularly relevant to quantify lived health loss even when clinician-assessed disability is non-existent, mild, or poorly discriminating. In STRONGER, preliminary baseline analyses highlighted an interpretive tension: substantial impairment in HRQoL coexisted with a more heterogeneous cognitive profile, supporting the interpretation that lived health in PCC may be shaped at least as much by fatigue, affective symptoms, sleep disturbance, and broader functional impact as by deficits detectable on standard cognitive tests at a single timepoint. Notably, sleep emerged as clinically relevant in STRONGER, yet sleep is not an explicit EQ-5D dimension; this reinforces the need to pair utilities with complementary PROMs when PCC burden is driven by domains that generic HRQoL instruments may not capture directly.[3] This pattern is consistent with growing evidence that subjective cognitive difficulties in PCC can be disproportionately driven by fatigue, anxiety/stress, and depressive symptoms, and may be only weakly related to objective cognitive performance.[4] In this setting, the added value of preference-based outcomes is particularly clear: they quantify clinically important health loss that conventional anchors may fail to capture or may capture ambiguously.

Viewed across conditions, the thesis therefore contributes more than parallel disease-specific summaries. It demonstrates a recurring mechanism by which preference-based PCOs improve inference: they reveal residual burden among

“favourable” disability outcomes, expose contextual determinants of lived recovery in multinational settings, and provide a coherent metric to quantify multidomain impact when traditional anchors are weak. At the same time, cross-dataset comparisons illustrate why utilities must be interpreted contextually. Similar point estimates across conditions should not be read as “equivalent burden” because they are anchored to different time points, populations, designs, and EQ-5D versions, and they remain sensitive to valuation choices and measurement properties.

4.2 Contrasts with the scientific literature and contribution of this thesis

The literature increasingly recognises the need to incorporate patient-valued outcomes into neurological research and practice, and utility-weighted disability has been proposed to improve interpretability of functional disability gradients. Early work positioned the UW-mRS as a patient-centred alternative to purely ordinal mRS analyses, and subsequent applications (including MR CLEAN–based evaluations) suggested potential gains in statistical efficiency relative to common mRS approaches.[5] This promise, however, has been accompanied by two enduring controversies that frame how preference-based outcomes should be used and interpreted.

The first controversy concerns what is gained—and what may be obscured—when a single preference weight is assigned to each mRS category.[6] Because UW-mRS assigns one value per category, it can mask within-category heterogeneity in symptoms, participation, and wellbeing that patients may experience despite similar disability grades. The ÑANDU findings empirically reinforce the relevance of this concern, particularly in mild disability states (mRS 0–1) where conventional scales are prone to ceiling effects and where “good outcome” can conceal persistent pain,

participation restriction, and reduced wellbeing. Rather than presenting this as a binary choice between disability scales and preference-based outcomes, the thesis advances a complementary position: disability grading remains a valid anchor for functional severity, but utilities and domain-level profiles add necessary information when the clinical question is lived recovery and residual burden.

The second controversy concerns comparability. Utility estimates are sensitive to modelling decisions and to the value sets used to translate EQ-5D profiles into utilities; consequently, UW-mRS and utility results may differ across studies and settings even when disability distributions appear comparable.[7] These concerns have been raised in methodological literature and correspondence and are supported by substantial between-study variability in published mRS utility weights. Within this context, pooled analyses using individual participant data have contributed by deriving and applying UW-mRS weights at scale while reinforcing the need for transparent reporting of weighting assumptions and context-aware interpretation.[8] In addition to valuation choice, cross-cultural relevance matters at the descriptive level: the salience and interpretation of EQ-5D domains (notably anxiety/depression and pain/discomfort) can vary across societies, and differences in reporting may reflect cultural norms as well as underlying health. Empirical work has shown links between national cultural characteristics and the relative valuation of EQ-5D dimensions, supporting the view that both valuation and reporting require explicit contextualisation in multinational cohorts such as TRIDENT (including large samples from Sri Lanka).[9] By applying a coherent preference-based framework across a community cohort, a multinational trial, and longitudinal trial analyses, the thesis strengthens a pragmatic conclusion emerging from this debate: utilities can

enable meaningful synthesis and comparison, but only when the interpretation remains explicitly method-aware and context-dependent rather than assuming direct equivalence across settings.

Measurement properties are also central to this debate. Although the EQ-5D index was designed to be brief and widely applicable, its discriminative capacity can be constrained in milder health states because of ceiling effects, potentially reducing sensitivity to subtle but meaningful differences;[10] this limitation is partially mitigated in the EQ-5D-5L, developed to improve sensitivity and reduce ceiling effects relative to the 3L. Likewise, utility-weighted disability metrics depend on the valuation framework used to generate the weights and cannot fully capture within-category heterogeneity that direct patient report may reveal.[11] The thesis advances the field by showing that these methodological issues are not abstract: they are directly linked to where utilities add value (mild disability states, multinational interpretation, multidomain syndromes such as PCC) and to how preference-based outcomes should be integrated with conventional endpoints rather than substituted for them.

Finally, in PCC the thesis aligns with a growing body of evidence describing imperfect alignment between subjective cognitive difficulties, objective cognitive performance, and HRQoL, with fatigue, affective symptoms, and sleep disturbance frequently contributing to perceived health loss.[4] The STRONGER baseline interpretation strengthens this literature by framing the mismatch in preference-based terms: the clinically relevant signal is not only whether objective cognition is impaired, but whether patients experience meaningful health loss and functional impact that warrants clinical attention and can be tracked over time.

4.3 Strengths and limitations

A key strength of this thesis is the coherent application of a preference-based framework across conditions and study designs, enabling integrated interpretation anchored on patient-valued health rather than condition-specific endpoints alone. The inclusion of both usual-care and trial contexts strengthens interpretability: the community cohort provides insight into lived recovery under routine conditions, while INTERACT3 and TRIDENT provide standardised assessment, multinational generalisability, and longitudinal inference. Another strength is the deliberate integration of traditional outcomes (disability and cognition) with utilities, supporting an outcomes model that remains clinically grounded.

Several limitations are inherent to preference-based measurement and constrain inference. First, EQ-5D indices may show ceiling effects in milder health states, potentially reducing sensitivity to subtle yet meaningful differences;[11] although the 5L improves discrimination, ceiling limitations remain relevant in populations with mild impairment. Relatedly, sensitivity limitations can also operate at the opposite end of severity. In advanced cognitive impairment, some measures may show floor effects or reduced responsiveness, and the feasibility and validity of self-report can diminish, increasing reliance on proxy reporting and potentially altering the construct being measured. This has been documented in dementia research using EQ-5D, where responsiveness evidence is mixed and self-completion becomes less feasible as disease progresses.[12] Second, utility-weighted disability metrics compress heterogeneity within mRS grades and may underrepresent symptom burden, participation restriction, or wellbeing differences that matter to patients.[13] Third, cross-setting and cross-condition comparisons are constrained by differences in

instrument versions, assessment timing, study design, and valuation choices; therefore, similarities in utility point estimates across datasets should not be interpreted as equivalent burden. These limitations do not invalidate the approach; they define the conditions under which preference-based outcomes are most informative and how they should be reported and interpreted.

4.4 Future directions

Future research should build on these findings to strengthen both the methodological rigour and clinical usefulness of preference-based PCO in brain health. Priorities include developing and validating tools that better identify when brain health is meaningfully affected from the patient perspective and ensuring that such measures remain applicable across different neurological conditions and care settings. This thesis supports a precision-medicine approach in which objective assessments are complemented by how individuals experience and value their health.

Beyond methodological refinement, the most direct implication of this thesis is for clinical follow-up pathways and trial design. In practice, preference-based PCOs can operationalise “what matters” by systematically revealing domains that are not reliably captured by clinician-rated disability or isolated cognitive tests, thereby supporting more targeted symptom management, rehabilitation referral, and psychosocial support. For trials, these findings reinforce the rationale for incorporating patient-centred endpoints more routinely—ideally as prespecified secondary outcomes and, in selected settings, as co-primary outcomes—particularly when biological effects do not clearly translate into patient-relevant benefit. This issue is exemplified by current debates around disease-modifying therapies in Alzheimer’s disease: biomarker changes such as amyloid removal do not, by

themselves, resolve questions about meaningful effects on daily functioning, quality of life, and caregiver burden, which remain central to decision-making.[14] In Australia, broader national initiatives such as the Australian Dementia Network (ADNeT) aim to strengthen trial readiness and the relevance of outcomes by linking research, clinical services, and people with lived experience, illustrating the direction of travel towards more patient-centred evaluation frameworks.[15]

Methodological work should move beyond reliance on a single index by routinely pairing utility estimates with domain-level profiles and complementary PROMs (for example, fatigue, sleep, mood, and participation). This is particularly important in mild disability states, where residual burden can be substantial yet easily overlooked by traditional endpoints. In parallel, greater emphasis is needed on feasibility and implementation: PCO must be translated into practical, clinically interpretable outputs that can be used efficiently by clinicians and understood by patients, leveraging current measurement platforms and emerging digital tools.

In the short term, an immediate extension of this thesis is to evaluate the main outcomes of the STRONGER clinical trial and integrate them with the preference-based approach proposed here. This will enable identification of determinants of improvement versus persistence and assessment of whether interventions meaningfully change lived health even when objective cognitive outcomes show limited change. Finally, implementation-oriented research is warranted to test whether routine incorporation of preference-based PCOs into follow-up pathways results in more targeted rehabilitation, symptom management, and psychosocial support. Over time, wider adoption of standardised PCO could also support health-

economic evaluation by quantifying the costs associated with impaired brain health and the value of interventions that improve patient-valued outcomes.

Finally, an important longer-term extension—beyond the scope of this thesis—is to link patient-centred outcomes to biological mechanisms, particularly neuroinflammatory and glial pathways implicated in both cerebrovascular disease and post-infectious syndromes. Emerging work suggests that biomarkers may index neuroglial activation and injury in COVID-related neurological phenotypes, and analogous pathways are increasingly relevant in vascular brain health research. Integrating such biomarkers with preference-based PCOs could help clarify when biological change translates into patient-valued benefit.[16]

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5 CONCLUSION

This thesis advanced patient-centred assessment of brain health by applying PCO in highly prevalent and disabling conditions: stroke and post-COVID-19. The work demonstrated that conventional assessment criteria, such as disability scales and cognitive tests, remain indispensable but do not fully capture what matters to patients: how they experience, value, and live their health in daily life. The utilities offered a common metric to summarize the multidimensional burden across different diseases and study designs, while requiring contextualized interpretation, given the influence of assessment decisions, the cultural and healthcare system environment, the timing of the assessment, and self-assessment capacity.

At the same time, this thesis highlights that improving measurement is only one part of improving outcomes. Preference-based PCO can make otherwise under-recognised burden visible and comparable, but they also sharpen the imperative to act—through better prevention, more personalised follow-up, and rehabilitation strategies that address the domains driving lived morbidity. This aligns with the broader evidence that a large proportion of cerebrovascular and cognitive morbidity is linked to modifiable factors and is therefore potentially preventable or delayable through coordinated approaches across the lifespan.

Overall, this thesis supports the integration of PCO as a routine complement to neuropsychological and clinician-assessed outcomes, both in research and care. This can improve the interpretation of recovery, identify high-burden subgroups that might be missed with traditional assessment criteria, and better align neurological assessment with the realities of individuals affected by common brain health disorders.

9 APPENDICES

9.1 Supplementary material of Chapter III

9.1.1 Patient centered outcomes in stroke: utility weighted modified Rankin Scale results in a community-based study.

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EDITED BY
Hrvoje Budincevic,
University Hospital Sveti Duh, Croatia

REVIEWED BY
Stela Rutovic,
Clinical Hospital Dubrava, Croatia
Hua Hu,
The First Hospital of Hunan University of Chinese Medicine, China

*CORRESPONDENCE
Paula Muñoz Venturelli
paumunoz@udd.cl

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Patient centered outcomes in stroke: utility-weighted modified Rankin Scale results in a community-based study

Carlos Delfino[1], Gabriel Cavada[2], Lorena Hoffmeister[1], Pablo Lavados[2,3] and Paula Muñoz Venturelli[1,3,4]*

[1]Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile, [2]Unidad de Investigación y Ensayos Clínicos, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile, [3]Servicio de Neurología, Departamento de Neurología y Psiquiatría, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile, [4]Faculty of Medicine, The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia

Background and aims: The transformation of modified Rankin Scale (mRS) scores based on the corresponding utilities of health-related quality of life questionnaires can facilitate the capture of Patient-Centered Outcomes (PCO) in stroke. We aimed to derive utility-weighted modified Rankin Scale (UW-mRS) values by mapping mRS functional status to EQ-5D-3L scores in a population-based cohort of stroke patients.

Methods: The UW-mRS was obtained by analyzing the EQ5-D-3 L and mRS scores at 180 days after any stroke in the ÑANDU study, a large prospective community-based study in Chile. The mRS prediction was estimated using a linear regression adjusted by the EQ-5D-3L value. Generalized linear and binary logistic regression models were constructed to determine influencing factors of the UW-mRS, using STATA software (version 18.0).

Results: We included 773 patients presenting with any stroke during 2015–2016: 48% were female, with a mean age of 71 years (SD 13.8), and 85% had an acute ischemic stroke (AIS). 82% of patients had a low socioeconomic status, 50% had less than 12 years of formal education, and only 32% lived in urban areas. UW-mRS values for mRS categories 0–6 at 180 days were 0.913, 0.694, 0.425, 0.249, −0.102, −0.347 and 0, respectively. Multivariable analysis identified age > 70 years (Coefficient β [β] -0.038 [Standard error SE 0.018], $p = 0.032$), prior mRS score 3–5 (β −0.556 [SE 0.197], $p < 0.001$), ischemic stroke (β −0.066 [SE 0.025], $p = 0.010$), and National Institutes of Health Stroke Scale (NIHSS) at admission>5 (β −0.015 [SE 0.002], $p < 0.001$) as significant predictors of worse UW-mRS scores ($R^2 = 70\%$) in the overall group. Sex-disaggregated analysis showed that age > 70 years was a significant predictor in males (β −0.069 [SE 0.024], $p = 0.006$), while presenting an AIS had a greater impact on female's worse UW-mRS score (β −0.087 [SE 0.033], $p = 0.010$).

Conclusion: These results present UW-mRS values derived from a population-based stroke study. Key determinants of health-related quality of life in post-stroke patients included age, prior disability, and stroke severity. Sex-disaggregated analysis revealed age being significant for males and AIS for females. Incorporating PCO as UW-mRS in stroke research can provide a more nuanced understanding of the impact of stroke on survivors, offering valuable insights for clinical decision-making and rehabilitation strategies across diverse healthcare contexts.

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KEYWORDS

patient-centered outcomes, stroke, utility-weighted, modified Rankin Scale, community-based study

Introduction

According to the most recent Global Burden of Disease (GBD) study, stroke remains one of the leading cause of death and disability combined worldwide (1). Between 1990 to 2019, the global burden of stroke, in terms of absolute number of cases, increased substantially, with the majority (86.0% of deaths and 89.0% of disability-adjusted life years, DALYs) residing in low- and lower-middle-income countries (LMICs) (2). Given the wide range of functional disability among stroke survivors, it is crucial to accurately measure and classify these impairments.

Several scales have been developed to categorize stroke patients. The modified Rankin Scale (mRS), a seven-level scale of global impairment and disability is widely used as a functional outcome measure in both clinical research and practice (3). While the mRS provides valuable insights into functional status, it does not reflect the broader impact on quality of life (4). Moreover, its power is limited when analyzed dichotomously and its indication of effect size is difficult to interpret when analyzed ordinally (5). Therefore, the development of a utility-weighted modified Rankin scale (UW-mRS), which incorporates a health utility scale as Patient Centered Outcome (PCO), is recommended and has been used in several recent clinical trials (6, 7).

Health utility weights represent the preference for a specific health outcome, allowing comparison of quality of life across different clinical settings (8). They range from perfect health (a score of 1) to outcomes worse than death (where death is scored as 0 and negative values indicate worse-than-death states). The utility approach offers several advantages: it aligns with the principles of economic evaluation, enables broad comparisons, and provides a detailed view of patients' experiences, highlighting both improvements and declines in health status (8). Despite these benefits, the application of UW-mRS outside the clinical setting remains limited (9).

The aim of this study was to incorporate the quality-of-life perspective into functional scales and analyze its determinants, by developing the UW-mRS as an outcome measure for patients 180 days after suffering a stroke, using data from the Ñuble population between 2015 and 2017.

Materials and methods

Individual participant data were pooled from the ÑANDU study, a large prospective community-based study in Chile, whose methodology and results have been previously published (10). At 180 days after the event, trained personnel conducted telephone interviews to evaluate the patients. Information was collected on recovery, dependency, and health-related quality of life.

Instruments

The mRS is a widely used tool for assessing health outcomes in stroke patients (11). The mRS evaluates the level of disability by considering activity limitations and lifestyle changes. The scale has 7 grades, from 0 to 6: 0 means no symptoms, 5 means severe disability, and 6 indicates death (3).

The EuroQol EQ-5D-3L is a questionnaire designed to measure a patient's health status preferences (12). It consists of 5 dimensions: mobility, self-care, usual activities, pain, and anxiety. Each dimension has 3 levels: no problems, some problems, and extreme problems, coded from 1 to 3 (13). The EQ-5D-3L health states are represented by a sequence of 5 numbers that describe each level within each dimension. For example, 11111 indicates perfect health, while 33333 represents the worst possible health state. The system defines 243 possible health states, each of which can be supplemented using a scoring or weighting system to convert profile data into a single numerical value: the EQ-5D-3L values (14). These scoring systems are typically preference-based, meaning that the problems in each dimension are weighted to reflect public perception of their severity. The EQ-5D-3L index values are constructed on a scale anchored at 1, representing full health, and 0, representing death (14).

The EQ-5D-3L value set was selected from a previous study conducted in Chile, which evaluated the health status of the general population using the Time Trade-Off technique (15). Patients who died during follow-up (mRS = 6) were assigned an EQ-5D-3L value of 0 (zero).

Statistical analyses

Quantitative variables were reported as means (SD) or medians (IQR) depending on normality (using K-S test) and were compared according normal/ non-normal distribution using the T test or Mann–Whitney U test. Qualitative variables were reported as absolute and percentage prevalence and were compared using the $\chi 2$ test or Fisher's exact test, as appropriate.

UW-mRS scores were calculated only for patients alive during follow-up using an ordinary least squares regression model, with mRS scores as discrete ordinal dummy variables and EQ-5D scores as the continuous response variable, adhering to the methodology established by prior studies (16). UW-mRS scores were obtained and validated separately for acute ischemic stroke, intracerebral hemorrhage, and by sex. A simple linear regression analysis was performed to identify variables associated with UW-mRS scores. Multivariable linear regression models were subsequently used to evaluate factors influencing UW-mRS, including both variables significantly correlated in the simple analysis and those considered clinically relevant. This included sex, age over 70, low socioeconomic status, urban residence, prior disability (mRS 3–5), stroke type, and an NIHSS score above 5 at admission. An alfa level of 5% ($p < 0.05$) was considered significant, and 95% confidence intervals were used. Data were processed using STATA software (version 18.5).

Results

Of the 1,103 patients who experienced a stroke between 2015 and 2016, 890 were a first-ever stroke. At 180 days post the acute event, 773

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patients were evaluated, with a 13% loss to follow-up. Baseline characteristics are summarized in Table 1. The cohort consisted of 398 (51%) females, with a mean age of 70.6 years (14.1). Nearly half of the patients (386, 49.9%) had less than 12 years of formal education, and 533 (82%) were classified as having low socioeconomic status based on their public health insurance classification (17). 536 (65%) patients experienced an AIS, had a median NIHSS score of 5 (IQR 3–11), and a median hospital stay of 9 days (IQR 4–15).

At 180 days post-acute event, 41% of patients had an mRS score of 0–2, 21% had a score of 3–5, and 35% had died (Table 1; Figure 1). Among patients with hemorrhagic stroke, 62% died, compared to 21% of those with an AIS ($p < 0.001$). No significant differences were observed in the distribution of mRS scores by sex (Supplementary Figures 1, 2).

In the EQ-5D-3L assessment, the most affected dimension was pain/discomfort (67%), followed by mobility and anxiety/depression (53%). Figure 2 shows the distribution of the EQ-5D-3L for each mRS category. There was a strong negative association between mRS and EQ-5D-3L index values overall ($r = -0.82$; $p < 0.001$; Supplementary Figure 3).

The UW-mRS values, calculated from the mean EQ-5D-3L utility scores from the Chilean population (15), across mRS categories 0–6 at 180 days, were: 0.913, 0.694, 0.425, 0.249, −0.102, −0.347 and 0, respectively (Table 2). When disaggregated by sex, females tended to have slightly lower UW-mRS values compared to males, though this difference was not statistically significant ($p = 0.194$, Figure 3a). In terms of stroke type, ischemic stroke survivors had lower UW-mRS scores than those with hemorrhagic stroke at 180 days post-acute event (Figure 3b).

A linear regression analysis was conducted to explore the relationship between UW-mRS scores and key variables. In the simple regression, significant associations were found between age > 70 years (Coefficient β [β] −0.007 [Standard error SE] 0.001, $p < 0.001$), lower socioeconomic status (β −0.075 [SE 0.040], $p < 0.001$), previous mRS score of 3–5 (β −0.607 [SE 0.018], $p < 0.001$), ischemic stroke subtype (β −0.025 [SE 0.041], $p < 0.001$), and NIHSS >5 at admission (β −0.273 [SE 0.028], $p < 0.001$) with worse outcome (Table 3). In the multivariable model, age > 70 years (β −0.038 [SE 0.018], $p = 0.032$), previous mRS score of 3–5 (β −0.556 [SE 0.197], $p < 0.001$), ischemic stroke (β −0.066 [SE 0.025] $p = 0.010$), and NIHSS >5 at admission (β −0.015 [SE 0.002], $p < 0.001$) remained significant predictors of lower UW-mRS scores, with an R^2 of 70%. When the multivariable model was disaggregated by sex to assess potential differences, the previous mRS score of 3–5 and NIHSS >5 at admission were associated to worse UW-mRS in both sexes (Supplementary Table 1). Distinctly, age > 70 years was significant for males (β −0.069 [SE 0.024], $p = 0.006$) and having an AIS was significant for females (β −0.087 [SE 0.033], $p = 0.010$) (Figure 4; Supplementary Table 1). The model explained a similar proportion of variance in both groups, with an R^2 of 69% for females and 72% for males (Supplementary Table 1).

TABLE 1 Baseline characteristics of the 773 patients with first ever stroke (FES) followed at 180 days.

Demographics (*n*, %)	
Age, mean SD	70.6 (14.10)
Female	398 (51)
<12 years of formal education	386 (49.93)
Occupation	
Homemaker	166 (21)
Dependent work	63 (8)
Self-employment	97 (13.5)
Pensioner	96 (12.5)
Unknown	347 (45)
Urban resident[a]	248 (32)
Low socioeconomic status[b]	533 (82)
Premorbid modified Rankin Scale (*n*, %)	
0–2	171 (32)
3–5	47 (8)
Unknown	374 (60)
Risk factors (*n*, %)	
Hypertension	498/619 (80)
Atrial fibrillation	58/617 (9)
Diabetes mellitus	221/618 (36)
Acute coronary syndrome	44/616 (7)
Hypercholesterolemia	56/617 (9)
Stroke subtype (*n*, %)	
Acute ischemic stroke	536 (69)
Intracerebral hemorrhage	106 (14)
Subarachnoid hemorrhage	44 (5)
Cerebral venous thrombosis	4 (1)
Undetermined	83 (11)
Stroke severity (median, IQR)	
NIHSS at admission ($n = 494$)	5 (3–11)
Glasgow coma scale ($n = 274$)	15 (14–15)
Median time of hospitalization in days (IQR)	**9 (4–15)**
Characteristics at 180 days (*n*, %)	
Modified Rankin Scale (mRS)	
0–2	341 (41)
3–5	165 (21)
6	267 (35)
Any change in EQ-5D-3L (level 1 or 2)[c]	
Mobility ($n = 506$)	279 (53)
Self-Care ($n = 505$)	181 (36)
Usual activities ($n = 504$)	257 (53)
Pain/Discomfort ($n = 502$)	336 (67)
Anxiety/Depression ($n = 499$)	263 (53)

[a]Based on the sociodemographic characterization of the patient's municipality of residence at the time of the 2017 census. [b]Among those with National Healthcare insurance; NIHSS, National Institutes of Health Stroke Scale; [c]Dead patients or patients with no information were excluded.

Discussion

The present study examined the distribution of health outcomes in a Chilean population-based cohort of patients who suffered an acute stroke. To our knowledge, this study is the first to derive a quality-of-life scale, like the EQ-5D-3L, using the UW-mRS in a community-based study, incorporating the patient perspective outside of controlled clinical settings. At 180 days post-stroke, 35% of patients had died, and

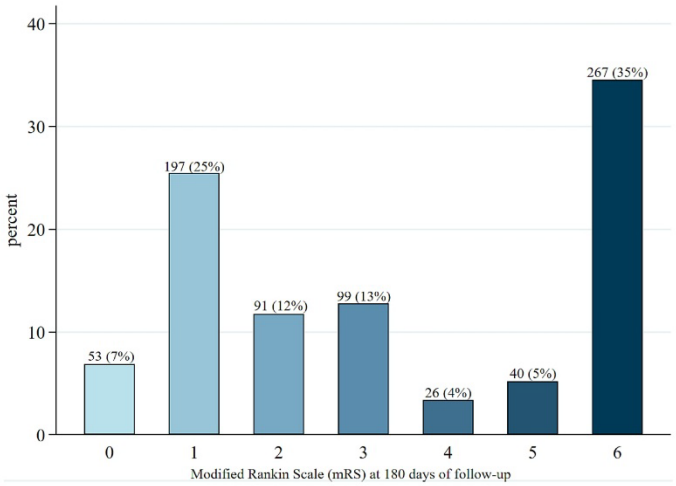


FIGURE 1
Modified Rankin Scale (mRS) at 180 days after the acute event in the 773 patients.

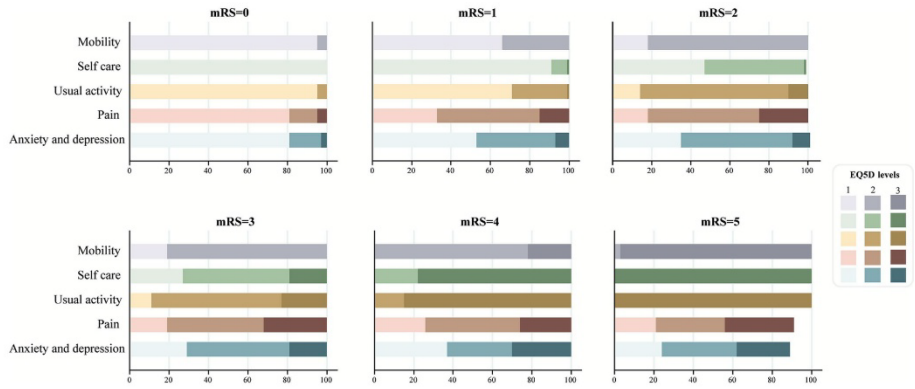
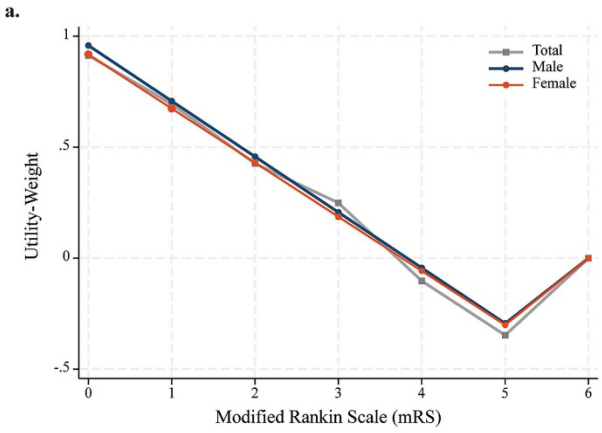


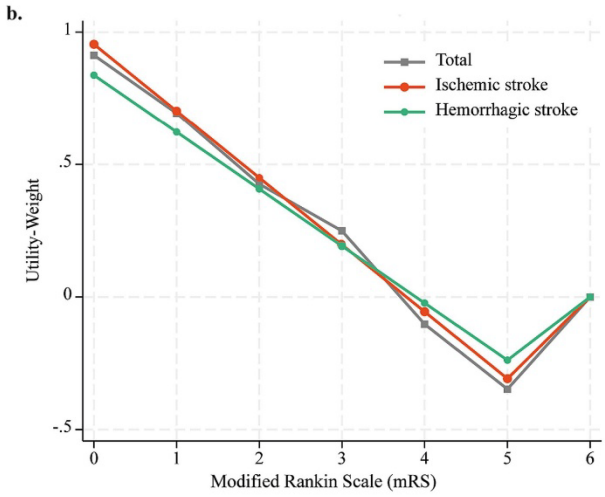
FIGURE 2
European quality of life 5-dimensional questionnaire utility scores by modified Rankin Scale scores at 180 days of follow up.

among the survivors, the most affected dimension of the EQ-5D-3L were pain/discomfort, followed by mobility and anxiety/depression. These results align with studies comparing healthy populations in other countries within the region (18) and in countries like China (19).

The UW-mRS values demonstrated a gradual decline in utility as mRS scores increased, reflecting the expected deterioration in health-related quality of life as disability worsened. These findings corroborate those of Wang et al., who applied similar methodologies based on cohorts from clinical trials (16). Their reported utility values for mRS scores 0–6 were 0.96, 0.88, 0.74, 0.56, 0.25, −0.11, and 0, respectively. Notably, the utility values for mRS 4 and 5 were significantly lower in the Chilean population, resulting in negative values, which suggest a more severe perception of quality of life at the same mRS level compared to Wang et al.'s cohort. This variation may be attributed to cultural differences in health perception, disparities in access to healthcare, or other socioeconomic factors (7, 14) as well as the methodological differences between studies that derived the EQ-5D-3L value sets (18, 20). These findings underscore the importance of using population-specific utility values when calculating UW-mRS scores, as the choice of value set can significantly influence results and their interpretation, with important implications for clinical practice and research.



mRS	UW-mRS Male (n=375)	UW-mRS Female (n=398)
0	0.958	0.918
1	0.707	0.674
2	0.457	0.430
3	0.206	0.186
4	-0.048	-0.057
5	-0.294	-0.301
6	0	0



mRS	UW-mRS Ischemic (n=536)	UW-mRS Hemorrhagic (n=106)
0	0.954	0.837
1	0.702	0.622
2	0.449	0.407
3	0.197	0.192
4	-0.055	-0.002
5	-0.308	-0.238
6	0	0

FIGURE 3
UW-mRS score derived from the regression model by sex **(a)**, and stroke subtype **(b)**.

When analyzing the UW-mRS scores by sex, females were found to report worse health status than males for the same level of motor disability, though the differences were not statistically significant. Previous studies indicate that, on average, females score 0.03 points lower than males (21). These discrepancies may be explained by the influence of distinct cultural and social factors that shape how females perceive and report their health status (22), as well as to higher levels of anxiety or depression, pain, and discomfort compared to males (23). Interestingly, age over 70 years emerged as a significant predictor of worse UW-mRS scores in males, which may be explained by the fact that, at the time of stroke, females were significantly older than males (mean age 72.17 vs. 68.94 years respectively). Additionally, ischemic stroke was a significant predictor of poorer outcomes in females. Although the proportion of ischemic stroke was similar between sexes, a higher percentage of females who suffered ischemic stroke (30%) had mRS scores between 3 and 5 compared to males (21%), and the higher UW-mRS weights for ischemic stroke may have further accentuated its impact on females.

When comparing UW-mRS scores by stroke type, we found that the values for ischemic stroke were lower than those for ICH, and this impact was more relevant in women. The difference may be attributed to the greater severity typically associated with ICH and the higher early mortality rate among ICH patients during follow-up.

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TABLE 2 UW-mRS values derived for each category of the modified Rankin scale.

mRS	UW-mRS	SD
0	0.913	0.157
1	0.694	0.234
2	0.425	0.213
3	0.249	0.294
4	−0.102	0.267
5	−0.347	0.127
6	0	0

mRS, modified Rankin Scale; UW-mRS, utility-weighted modified Rankin Scale; SD, standard deviation.

This study has strengths and limitations that must be acknowledged. Among its strengths, we identified key predictors of UW-mRS scores in stroke survivors, including age, prior mRS score, and NIHSS at admission, which aligns with previous findings (24). Notably, age over 70 years emerged as a significant predictor only in males, while acute ischemic stroke had a greater impact on females. These sex-specific insights are crucial for tailoring personalized treatment and rehabilitation strategies. The use of a population-based cohort from a low-income setting adds to the relevance of the findings, providing valuable reference data for understanding stroke recovery in real-world conditions and informing future healthcare policies.

TABLE 3 Results of simple and multivariable linear regression models analyzing factors associated with UW-mRS scores.

	Simple			Multivariable model		
	Coefficient β	Standard error	*p* value	Coefficient β	Standard error	*P* value
Sex	0.059	0.030	0.052	−0.006	0.171	0.710
Age > 70 years old	**−0.007**	**0.001**	**<0.001**	**−0.038**	**0.018**	**0.032**
<12 years of formal education	−0.029	0.030	0.347	−0.010	0.017	0.546
Low socioeconomic status[a]	**−0.075**	**0.040**	**<0.001**	0.006	0.022	0.781
Urban resident	−0.007	0.032	0.812	0.009	0.017	0.613
Previous mRS 3–5	**−0.607**	**0.018**	**<0.001**	**−0.556**	**0.197**	**<0.001**
Acute ischemic stroke	**−0.025**	**0.041**	**<0.001**	**−0.066**	**0.025**	**0.010**
NIHSS at admission >5	**−0.273**	**0.028**	**<0.001**	**−0.015**	**0.002**	**<0.001**
R^2: 70%						

[a]Among those with National Healthcare insurance; NIHSS, National Institutes of Health Stroke Scale.
Bold values indicate statistically significant *p*-values ($p < 0.05$).

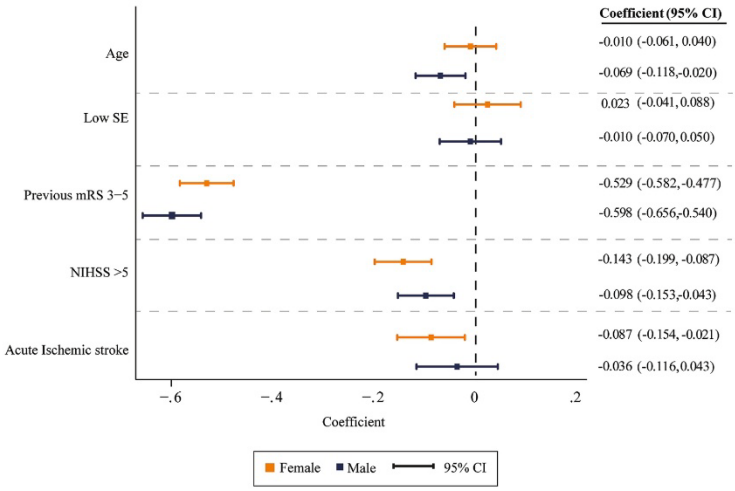

FIGURE 4
Multivariable model coefficients assessing risk factors by sex with 95% confidence intervals.

However, there are also important limitations. The data come from a single population-based cohort in Chile, which may limit the generalizability of the findings. Despite this, the results are representative of a low-income population with high stroke risk factors and could serve as a reference for future population-based studies. The follow-up was conducted by telephone, though studies have validated this method's effectiveness (25), and it was carried out by trained personnel. Additionally, we lacked consistent information on access to rehabilitation or post-stroke care, which may have influenced the reported quality of life perceptions. Lastly, using the ordinary least squares regression model to derive UW-mRS scores may not fully capture the complexity of outcomes across stroke subtypes and demographics. Future research should explore alternative models and validate the UW-mRS in diverse populations.

Conclusion

These results present UW-mRS values derived from a population-based stroke study, further supporting UW-mRS as a reliable measure of PCOs in post-stroke patients. Key determinants of health-related quality of life included age, prior disability, and stroke severity, with age over 70 years being a significant predictor for males and AIS having a greater impact on females. Incorporating UW-mRS as a PCO in future stroke research and clinical practice may provide a more nuanced understanding of the impact of stroke on survivors, offering valuable insights for clinical decision-making and rehabilitation strategies across diverse healthcare settings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by scientific ethics committee of the Universidad del Desarrollo, Clínica Alemana School of Medicine in Santiago. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CD: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. GC: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. LH: Methodology, Supervision, Validation, Writing – review & editing. PL: Conceptualization, Project administration, Supervision, Writing – review & editing. PM: Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The authors declare that no Gen AI was used in the creation of this manuscript.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1539107/full#supplementary-material

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9.1.2 Supplementary material

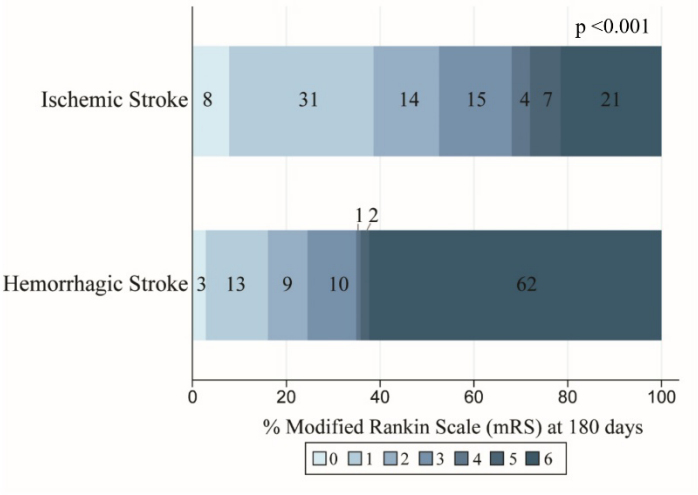
Supplementary Material

Stroke Outcomes using Utility-Weighted Modified Rankin Scale Scores: Results from a large community-based study in Chile

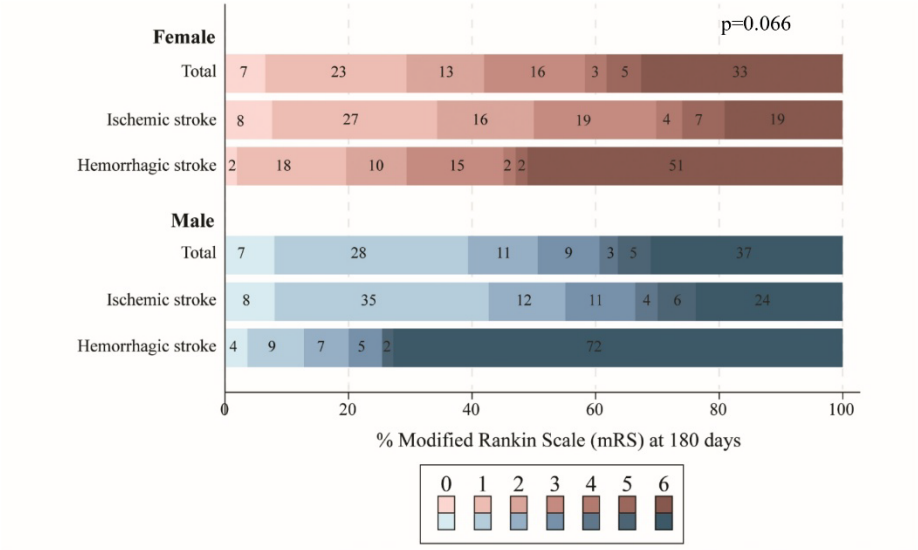
Carlos Delfino, Paula Muñoz Venturelli, Gabriel Cavada, Lorena Hoffmeister, Pablo Lavados

- Supplementary figures: 3
- Supplementary tables: 1

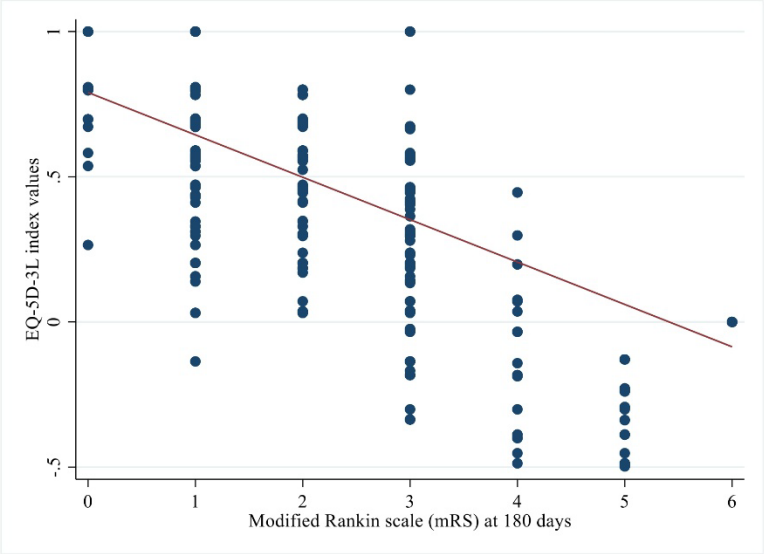
Supplementary Figure 1. 180-Day modified Rankin scale (mRS) scores across different stroke types



Supplementary Figure 2. Sex-specific percentage distribution of modified Rankin Scale (mRS) at 180 days of follow-up, stratified by stroke type.



Supplementary Figure 3. Distribution of EQ-5D-3L utility index values according to modified Rankin scale (mRS) at 180 days



note: Values of mRS 6 were arbitrarily assigned to a zero index value.

Supplementary table 1. Multivariate linear regression models in females and males to analyse factors associated with UW-mRS scores.

	Females			Males		
	Coefficient	Standard error	P value	Coefficient	Standard error	P value
Age >70 years old	-0.010	0.025	0.691	-0.069	0.024	**0.006**
Low socioeconomic status[a]	0.023	0.033	0.482	-0.010	0.030	0.734
Previous mRS 3-5	-0.529	0.026	**< 0.001**	-0.598	0.029	**< 0.001**
Acute ischemic stroke	-0.087	0.033	**0.010**	-0.036	0.040	0.370
NIHSS at admission >5	-0.143	0.028	**< 0.001**	-0.098	0.027	**0.001**
Constant	0.771	0.045	**< 0.001**	0.774	0.045	**< 0.001**
R^2	**69%**			**72%**		

[a] Among those with National Healthcare insurance; NIHSS, National Institutes of Healt Stroke Scale.

9.2 Supplementary material of Chapter IV

9.2.1 TRIDENT sub analysis

Supplementary Table 1. Modified Rankin Scale (mRS) by visit and treatment arm

Timepoint	smRS	All	Triple-pill	Placebo
Baseline				
	0	188/1670 (11,3%)	79/833 (9,5%)	109/837 (13,0%)
	1	484/1670 (29,0%)	261/833 (31,3%)	223/837 (26,6%)
	2	324/1670 (19,4%)	156/833 (18,7%)	168/837 (20,1%)
	3	351/1670 (21,0%)	174/833 (20,9%)	177/837 (21,1%)
	4	251/1670 (15,0%)	131/833 (15,7%)	120/837 (14,3%)
	5	72/1670 (4,3%)	32/833 (3,8%)	40/837 (4,8%)
	6	0/1670 (0,0%)	0/833 (0,0%)	0/837 (0,0%)
	missing	0/1670 (0,0%)	0/833 (0,0%)	0/837 (0,0%)
	Independent [smRS 0-2]	996/1670 (59,6%)	496/833 (59,5%)	500/837 (59,7%)
	Dependent [smRS 3-6]	674/1670 (40,4%)	337/833 (40,5%)	337/837 (40,3%)
12 Months				
	0	330/1476 (22,4%)	160/745 (21,5%)	170/731 (23,3%)
	1	611/1476 (41,4%)	314/745 (42,1%)	297/731 (40,6%)
	2	252/1476 (17,1%)	130/745 (17,4%)	122/731 (16,7%)
	3	192/1476 (13,0%)	98/745 (13,2%)	94/731 (12,9%)
	4	57/1476 (3,9%)	28/745 (3,8%)	29/731 (4,0%)
	5	19/1476 (1,3%)	10/745 (1,3%)	9/731 (1,2%)
	6	15/1476 (1,0%)	5/745 (0,7%)	10/731 (1,4%)
	missing	0/1476 (0,0%)	0/745 (0,0%)	0/731 (0,0%)
	Independent [smRS 0-2]	1193/1476 (80,8%)	604/745 (81,1%)	589/731 (80,6%)
	Dependent [smRS 3-6]	283/1476 (19,2%)	141/745 (18,9%)	142/731 (19,4%)
24 Months				

	0	334/1291 (25,9%)	176/652 (27,0%)	158/639 (24,7%)
	1	503/1291 (39,0%)	258/652 (39,6%)	245/639 (38,3%)
	2	207/1291 (16,0%)	97/652 (14,9%)	110/639 (17,2%)
	3	151/1291 (11,7%)	78/652 (12,0%)	73/639 (11,4%)
	4	43/1291 (3,3%)	18/652 (2,8%)	25/639 (3,9%)
	5	21/1291 (1,6%)	9/652 (1,4%)	12/639 (1,9%)
	6	32/1291 (2,5%)	16/652 (2,5%)	16/639 (2,5%)
	missing	0/1291 (0,0%)	0/652 (0,0%)	0/639 (0,0%)
	Independent [smRS 0-2]	1044/1291 (80,9%)	531/652 (81,4%)	513/639 (80,3%)
	Dependent [smRS 3-6]	247/1291 (19,1%)	121/652 (18,6%)	126/639 (19,7%)
36 Months				
	0	199/888 (22,4%)	96/453 (21,2%)	103/435 (23,7%)
	1	357/888 (40,2%)	184/453 (40,6%)	173/435 (39,8%)
	2	156/888 (17,6%)	76/453 (16,8%)	80/435 (18,4%)
	3	96/888 (10,8%)	56/453 (12,4%)	40/435 (9,2%)
	4	31/888 (3,5%)	18/453 (4,0%)	13/435 (3,0%)
	5	8/888 (0,9%)	3/453 (0,7%)	5/435 (1,1%)
	6	41/888 (4,6%)	20/453 (4,4%)	21/435 (4,8%)
	missing	0/888 (0,0%)	0/453 (0,0%)	0/435 (0,0%)
	Independent [smRS 0-2]	712/888 (80,2%)	356/453 (78,6%)	356/435 (81,8%)
	Dependent [smRS 3-6]	176/888 (19,8%)	97/453 (21,4%)	79/435 (18,2%)
48 Months				
	0	130/585 (22,2%)	65/304 (21,4%)	65/281 (23,1%)
	1	228/585 (39,0%)	124/304 (40,8%)	104/281 (37,0%)
	2	99/585 (16,9%)	47/304 (15,5%)	52/281 (18,5%)
	3	61/585 (10,4%)	33/304 (10,9%)	28/281 (10,0%)
	4	20/585 (3,4%)	10/304 (3,3%)	10/281 (3,6%)
	5	4/585 (0,7%)	3/304 (1,0%)	1/281 (0,4%)
	6	43/585 (7,4%)	22/304 (7,2%)	21/281 (7,5%)

	missing	0/585 (0,0%)	0/304 (0,0%)	0/281 (0,0%)
	Independent [smRS 0-2]	457/585 (78,1%)	236/304 (77,6%)	221/281 (78,6%)
	Dependent [smRS 3-6]	128/585 (21,9%)	68/304 (22,4%)	60/281 (21,4%)
60 Months				
	0	100/444 (22,5%)	54/226 (23,9%)	46/218 (21,1%)
	1	171/444 (38,5%)	85/226 (37,6%)	86/218 (39,4%)
	2	60/444 (13,5%)	34/226 (15,0%)	26/218 (11,9%)
	3	45/444 (10,1%)	20/226 (8,8%)	25/218 (11,5%)
	4	16/444 (3,6%)	8/226 (3,5%)	8/218 (3,7%)
	5	5/444 (1,1%)	2/226 (0,9%)	3/218 (1,4%)
	6	47/444 (10,6%)	23/226 (10,2%)	24/218 (11,0%)
	missing	0/444 (0,0%)	0/226 (0,0%)	0/218 (0,0%)
	Independent [smRS 0-2]	331/444 (74,5%)	173/226 (76,5%)	158/218 (72,5%)
	Dependent [smRS 3-6]	113/444 (25,5%)	53/226 (23,5%)	60/218 (27,5%)
72 Months				
	0	48/227 (21,1%)	26/115 (22,6%)	22/112 (19,6%)
	1	85/227 (37,4%)	42/115 (36,5%)	43/112 (38,4%)
	2	23/227 (10,1%)	11/115 (9,6%)	12/112 (10,7%)
	3	15/227 (6,6%)	11/115 (9,6%)	4/112 (3,6%)
	4	4/227 (1,8%)	1/115 (0,9%)	3/112 (2,7%)
	5	3/227 (1,3%)	1/115 (0,9%)	2/112 (1,8%)
	6	49/227 (21,6%)	23/115 (20,0%)	26/112 (23,2%)
	missing	0/227 (0,0%)	0/115 (0,0%)	0/112 (0,0%)
	Independent [smRS 0-2]	156/227 (68,7%)	79/115 (68,7%)	77/112 (68,8%)
	Dependent [smRS 3-6]	71/227 (31,3%)	36/115 (31,3%)	35/112 (31,3%)
End of Study				
	0	350/1378 (25,4%)	186/700 (26,6%)	164/678 (24,2%)
	1	553/1378 (40,1%)	288/700 (41,1%)	265/678 (39,1%)
	2	205/1378 (14,9%)	96/700 (13,7%)	109/678 (16,1%)

	3	179/1378 (13,0%)	91/700 (13,0%)	88/678 (13,0%)
	4	70/1378 (5,1%)	31/700 (4,4%)	39/678 (5,8%)
	5	21/1378 (1,5%)	8/700 (1,1%)	13/678 (1,9%)
	6	0/1378 (0,0%)	0/700 (0,0%)	0/678 (0,0%)
	missing	0/1378 (0,0%)	0/700 (0,0%)	0/678 (0,0%)
	Independent [smRS 0-2]	1108/1378 (80,4%)	570/700 (81,4%)	538/678 (79,4%)
	Dependent [smRS 3-6]	270/1378 (19,6%)	130/700 (18,6%)	140/678 (20,6%)

Supplementary table S2. EQ-5D-3L by dimension and treatment arm

Month	Arm	N	Mobility affected n (%)		Self-care affected n (%)		Usual activity affected n (%)		Pain/discomfort affected n (%)		Anxiety/depression affected n (%)	
			2,3	1	2,3	1	2,3	1	2,3	1	2,3	1
0	P	836	483/836 (57,8%)	353/836 (42,2%)	343/836 (41,0%)	493/836 (59,0%)	485/836 (58,0%)	351/836 (42,0%)	460/836 (55,0%)	376/836 (45,0%)	141/836 (16,9%)	695/836 (83,1%)
	T	833	481/833 (57,7%)	352/833 (42,3%)	346/833 (41,5%)	487/833 (58,5%)	486/833 (58,3%)	347/833 (41,7%)	434/833 (52,1%)	399/833 (47,9%)	132/833 (15,8%)	701/833 (84,2%)
12	P	649	288/649 (44,4%)	361/649 (55,6%)	149/649 (23,0%)	500/649 (77,0%)	250/649 (38,5%)	399/649 (61,5%)	300/649 (46,2%)	349/649 (53,8%)	81/649 (12,5%)	568/649 (87,5%)
	T	668	295/668 (44,2%)	373/668 (55,8%)	144/668 (21,6%)	524/668 (78,4%)	260/668 (38,9%)	408/668 (61,1%)	279/668 (41,8%)	389/668 (58,2%)	75/668 (11,2%)	593/668 (88,8%)
24	P	435	182/435 (41,8%)	253/435 (58,2%)	86/435 (19,8%)	349/435 (80,2%)	143/435 (32,9%)	292/435 (67,1%)	179/435 (41,1%)	256/435 (58,9%)	45/435 (10,3%)	390/435 (89,7%)
	T	438	176/438 (40,2%)	262/438 (59,8%)	84/438 (19,2%)	354/438 (80,8%)	145/438 (33,1%)	293/438 (66,9%)	177/438 (40,4%)	261/438 (59,6%)	29/438 (6,6%)	409/438 (93,4%)
36	P	283	110/283 (38,9%)	173/283 (61,1%)	53/283 (18,7%)	230/283 (81,3%)	100/283 (35,3%)	183/283 (64,7%)	127/283 (44,9%)	156/283 (55,1%)	32/283 (11,3%)	251/283 (88,7%)
	T	293	108/293 (36,9%)	185/293 (63,1%)	47/293 (16,0%)	246/293 (84,0%)	91/293 (31,1%)	202/293 (68,9%)	119/293 (40,6%)	174/293 (59,4%)	32/293 (10,9%)	261/293 (89,1%)

48	P	189	66/189 (34,9%)	123/189 (65,1%)	36/189 (19,0%)	153/189 (81,0%)	58/189 (30,7%)	131/189 (69,3%)	75/189 (39,7%)	114/189 (60,3%)	19/189 (10,1%)	170/189 (89,9%)
	T	205	78/205 (38,0%)	127/205 (62,0%)	30/205 (14,6%)	175/205 (85,4%)	58/205 (28,3%)	147/205 (71,7%)	85/205 (41,5%)	120/205 (58,5%)	13/205 (6,3%)	192/205 (93,7%)
60	P	96	40/96 (41,7%)	56/96 (58,3%)	16/96 (16,7%)	80/96 (83,3%)	30/96 (31,2%)	66/96 (68,8%)	44/96 (45,8%)	52/96 (54,2%)	5/96 (5,2%)	91/96 (94,8%)
	T	100	45/100 (45,0%)	55/100 (55,0%)	13/100 (13,0%)	87/100 (87,0%)	24/100 (24,0%)	76/100 (76,0%)	43/100 (43,0%)	57/100 (57,0%)	7/100 (7,0%)	93/100 (93,0%)
72	P	48	18/48 (37,5%)	30/48 (62,5%)	6/48 (12,5%)	42/48 (87,5%)	10/48 (20,8%)	38/48 (79,2%)	26/48 (54,2%)	22/48 (45,8%)	3/48 (6,2%)	45/48 (93,8%)
	T	42	17/42 (40,5%)	25/42 (59,5%)	4/42 (9,5%)	38/42 (90,5%)	5/42 (11,9%)	37/42 (88,1%)	15/42 (35,7%)	27/42 (64,3%)	2/42 (4,8%)	40/42 (95,2%)
EOS	P	676	309/676 (45,7%)	367/676 (54,3%)	164/676 (24,3%)	512/676 (75,7%)	252/676 (37,3%)	424/676 (62,7%)	275/676 (40,7%)	401/676 (59,3%)	63/676 (9,3%)	613/676 (90,7%)
	T	698	306/698 (43,8%)	392/698 (56,2%)	152/698 (21,8%)	546/698 (78,2%)	255/698 (36,5%)	443/698 (63,5%)	253/698 (36,2%)	445/698 (63,8%)	56/698 (8,0%)	642/698 (92,0%)

P: Placebo, T: treatment arm; 2,3: Some, moderate or severe problems; 1: No problems

Supplementary Table S3. Schedule of assessments and outcome summaries across follow-up visits.

Variable/visit (months)	0m	12m	24m	36m	48m	60m	72m	EOS
EQ-5D index , mean SD	0.643 (0.270)	0.733 (0.249)	0.761 (0.233)	0.765 (0.238)	0.775 (0.242)	0.755 (0.274)	0.805 (0.213)	0.747 (0.253)
EQ-5D domains, n(%)								
Mobility								
Some/moderate or severe problems	965/1672 (57.7%)	583/1317 (44.3%)	358/873 (41.0%)	218/576 (37.8%)	144/394 (36.5%)	85/196 (43.4%)	35/90 (38.9%)	615/1374 (44.8%)
No problems	707/1672 (42.3%)	734/1317 (55.7%)	515/873 (59.0%)	358/576 (62.2%)	250/394 (63.5%)	111/196 (56.6%)	55/90 (61.1%)	759/1374 (55.2%)
Self-care								
Some/moderate or severe problems	691/1672 (41.3%)	293/1317 (22.2%)	170/873 (19.5%)	100/576 (17.4%)	66/394 (16.8%)	29/196 (14.8%)	10/90 (11.1%)	316/1374 (23.0%)
No problems	981/1672 (58.7%)	1024/1317 (77.8%)	703/873 (80.5%)	476/576 (82.6%)	328/394 (83.2%)	167/196 (85.2%)	80/90 (88.9%)	1058/1374 (77.0%)
Usual activity								
Some/moderate or severe problems	973/1672 (58.2%)	510/1317 (38.7%)	288/873 (33.0%)	191/576 (33.2%)	116/394 (29.4%)	54/196 (27.6%)	15/90 (16.7%)	507/1374 (36.9%)
No problems	699/1672 (41.8%)	807/1317 (61.3%)	585/873 (67.0%)	385/576 (66.8%)	278/394 (70.6%)	142/196 (72.4%)	75/90 (83.3%)	867/1374 (63.1%)
Pain/discomfort								
Some/moderate or severe problems	896/1672 (53.6%)	579/1317 (44.0%)	356/873 (40.8%)	246/576 (42.7%)	160/394 (40.6%)	87/196 (44.4%)	41/90 (45.6%)	528/1374 (38.4%)
No problems	776/1672 (46.4%)	738/1317 (56.0%)	517/873 (59.2%)	330/576 (57.3%)	234/394 (59.4%)	109/196 (55.6%)	49/90 (54.4%)	846/1374 (61.6%)
Anxiety/depression								
Some/moderate or severe problems	273/1672 (16.3%)	156/1317 (11.8%)	74/873 (8.5%)	64/576 (11.1%)	32/394 (8.1%)	12/196 (6.1%)	5/90 (5.6%)	119/1374 (8.7%)
No problems	1399/1672 (83.7%)	1161/1317 (88.2%)	799/873 (91.5%)	512/576 (88.9%)	362/394 (91.9%)	184/196 (93.9%)	85/90 (94.4%)	1255/1374 (91.3%)

mRS, n (%)								
0	188/1670 (11.3%)	330/1476 (22.4%)	334/1291 (25.9%)	199/888 (22.4%)	130/585 (22.2%)	100/444 (22.5%)	48/227 (21.1%)	350/1378 (25.4%)
1	484/1670 (29.0%)	611/1476 (41.4%)	503/1291 (39.0%)	357/888 (40.2%)	228/585 (39.0%)	171/444 (38.5%)	85/227 (37.4%)	553/1378 (40.1%)
2	324/1670 (19.4%)	252/1476 (17.1%)	207/1291 (16.0%)	156/888 (17.6%)	99/585 (16.9%)	60/444 (13.5%)	23/227 (10.1%)	205/1378 (14.9%)
3	351/1670 (21.0%)	192/1476 (13.0%)	151/1291 (11.7%)	96/888 (10.8%)	61/585 (10.4%)	45/444 (10.1%)	15/227 (6.6%)	179/1378 (13.0%)
4	251/1670 (15.0%)	57/1476 (3.9%)	43/1291 (3.3%)	31/888 (3.5%)	20/585 (3.4%)	16/444 (3.6%)	4/227 (1.8%)	70/1378 (5.1%)
5	72/1670 (4.3%)	19/1476 (1.3%)	21/1291 (1.6%)	8/888 (0.9%)	4/585 (0.7%)	5/444 (1.1%)	3/227 (1.3%)	21/1378 (1.5%)
6	0/1670 (0.0%)	15/1476 (1.0%)	32/1291 (2.5%)	41/888 (4.6%)	43/585 (7.4%)	47/444 (10.6%)	49/227 (21.6%)	0/1378 (0.0%)
Independent [smRS 0-2]	996/1670 (59.6%)	1193/1476 (80.8%)	1044/1291 (80.9%)	712/888 (80.2%)	457/585 (78.1%)	331/444 (74.5%)	156/227 (68.7%)	1108/1378 (80.4%)
Dependent [smRS 3-6]	674/1670 (40.4%)	283/1476 (19.2%)	247/1291 (19.1%)	176/888 (19.8%)	128/585 (21.9%)	113/444 (25.5%)	71/227 (31.3%)	270/1378 (19.6%)

Variable/visit (months)	**0m**	**6m**	**18m**	**30m**	**42m**	**54m**	**66m**	**EOS**
MoCA, median IQR	22 (18–26)	23 (19–27)	24 (19–27)	24 (20–27)	24 (19–27)	24 (20–27)	24 (20–27)	25 (20–28)

Supplementary Table S4. Association between cognition (MoCA) and health-related quality of life (EQ-5D index) in mixed-effects models (primary, sensitivity, and time-varying analyses).

a. Primary analysis (concurrent observations; baseline and EOS)

Predictor	Coefficient	Std_err	p	95% CI
Time (84 months vs baseline)	0.026	0.008	0.001	0.011; 0.041
MoCA total (per 1-point increase)	0.006	0.001	<0.001	0.005; 0.008
smRS				
1	-0.097	0.012	<0.001	-0.120; -0.074
2	-0.183	0.014	<0.001	-0.210; -0.155
3	-0.278	0.015	<0.001	-0.307; -0.250
4	-0.362	0.017	<0.001	-0.395; -0.328
5	-0.447	0.026	<0.001	-0.498; -0.396
Age (per 1-year increase)	-0.001	0.000	<0.001	-0.002; -0.001
Sex (female vs male)	-0.012	0.009	0.221	-0.030; 0.007
Education ≤12 years (vs >12 years)	-0.005	0.010	0.586	-0.024; 0.014
Treatment arm (triple pill vs placebo)	0.005	0.008	0.540	-0.011; 0.023
Constant	0.796	0.034	<0.001	0.728; 0.863

b. Sensitivity analysis (LOCF-aligned dataset)

Predictor	β	SE	95% CI	p-value
12 months vs baseline	0.072	0.007	0.059; 0.085	<0.001
24 months vs baseline	0.098	0.007	0.082; 0.113	<0.001
36 months vs baseline	0.094	0.009	0.076; 0.112	<0.001
48 months vs baseline	0.103	0.103	0.082; 0.124	<0.001
60 months vs baseline	0.079	0.078	0.051; 0.107	<0.001
72 months vs baseline	0.107	0.107	0.067; 0.147	<0.001
EOS vs baseline	0.080	0.006	0.067; 0.093	<0.001
MoCA total (per-1 point)	0.009	<0.001	0.008; 0.010	<0.001
Age (per-1 year)	-0.003	<0.001	-0.003; -0.002	<0.001
Female sex (vs male)	-0.021	0.010	-0.041; -0.001	0.039
Education (<12 years old vs > 12 years old)	-0.001	0.010	-0.021; 0.019	0.905
Treatment arm (active vs placebo)	0.011	0.009	-0.007; 0.029	0.247
_cons	0.609	0.032	0.546; 0.672	<0.001

c. Time-varying association (MoCA×time interaction terms)

Predictor	Coefficient (95% CI)	p value
Time: baseline vs		
12 month	0.046 (−0.005;0.098)	0.080
24 month	0.039 (−0.021;0.100)	0.206
36 month	0.022 (−0.052; 0.096)	0.562
48 month	0.105 (0.022; 0.189)	0.014
60 month	−0.115 (−0.232; 0.001)	0.052
72 month	0.103 (−0.074; 0.281)	0.254
EOS	−0.018 (−0.069; 0.032)	0.480
MoCA score		
MoCA total (per 1-point increase)	0.007 (0.006; 0.009)	<0.001
MoCA × time: 12 months	0.001 (−0.001; 0.003)	0.289
MoCA × time: 24 months	0.002 (<0.001: 0.005)	0.049
MoCA × time: 36 months	0.003 (<0.001; 0.006)	0.047
MoCA × time: 48 months	−0.000 (−0.003; 0.003)	0.987
MoCA × time: 60 months	0.008 (0.004; 0.013)	0.001
MoCA × time: 72 months	0.000 (−0.007; 0.007)	0.939
MoCA × time: 84 months	0.004 (0.002; 0.006)	<0.001
Age (per 1-year increase)	−0.002 (−0.003; −0.009)	<0.001
Female sex (vs male)	−0.020 (−0.040; −0.000)	0.042
Education <12 years (vs ≥12)	−0.001 (−0.021; 0.019)	0.885
Treatment arm (triple pill vs placebo)	0.011 (−0.007; 0.029)	0.241
Constant	0.653 (0.585; 0.721)	<0.001

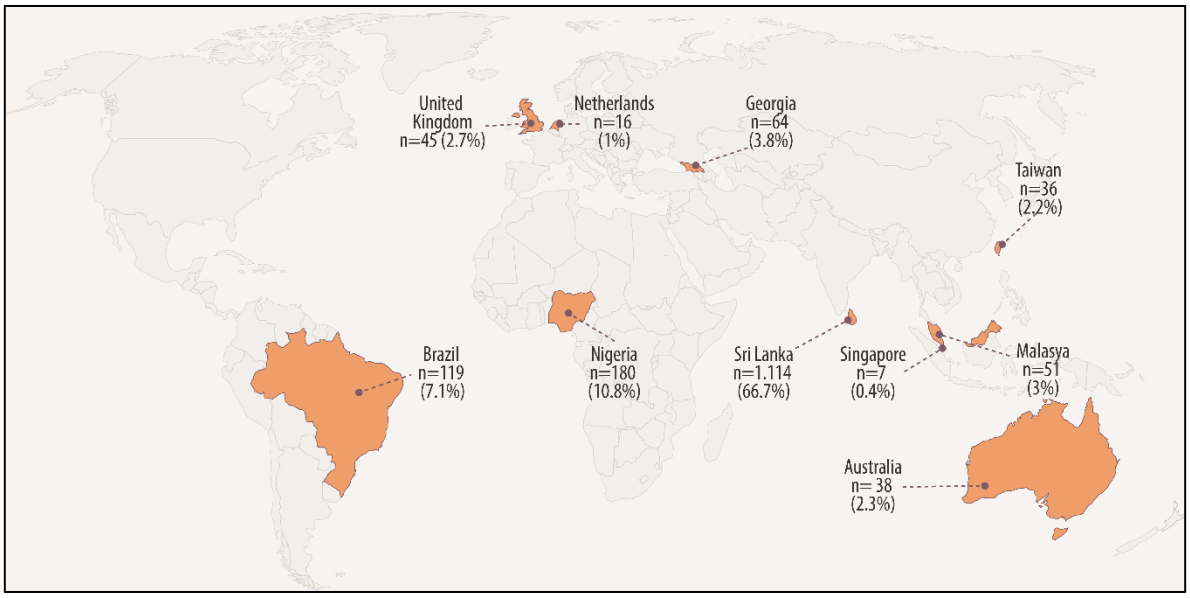
Notes: β coefficients are adjusted mean differences in EQ-5D index. Panel B N(obs)=6,442; N(subjects)=1,651. Panel C reports interaction terms indicating whether the MoCA–EQ-5D association differs from baseline at each follow-up time point.

Supplementary Table S5. Within–between decomposition of the association between cognition (MoCA) and HRQoL (EQ-5D index) in a mixed-effects linear model (concurrent observations only)

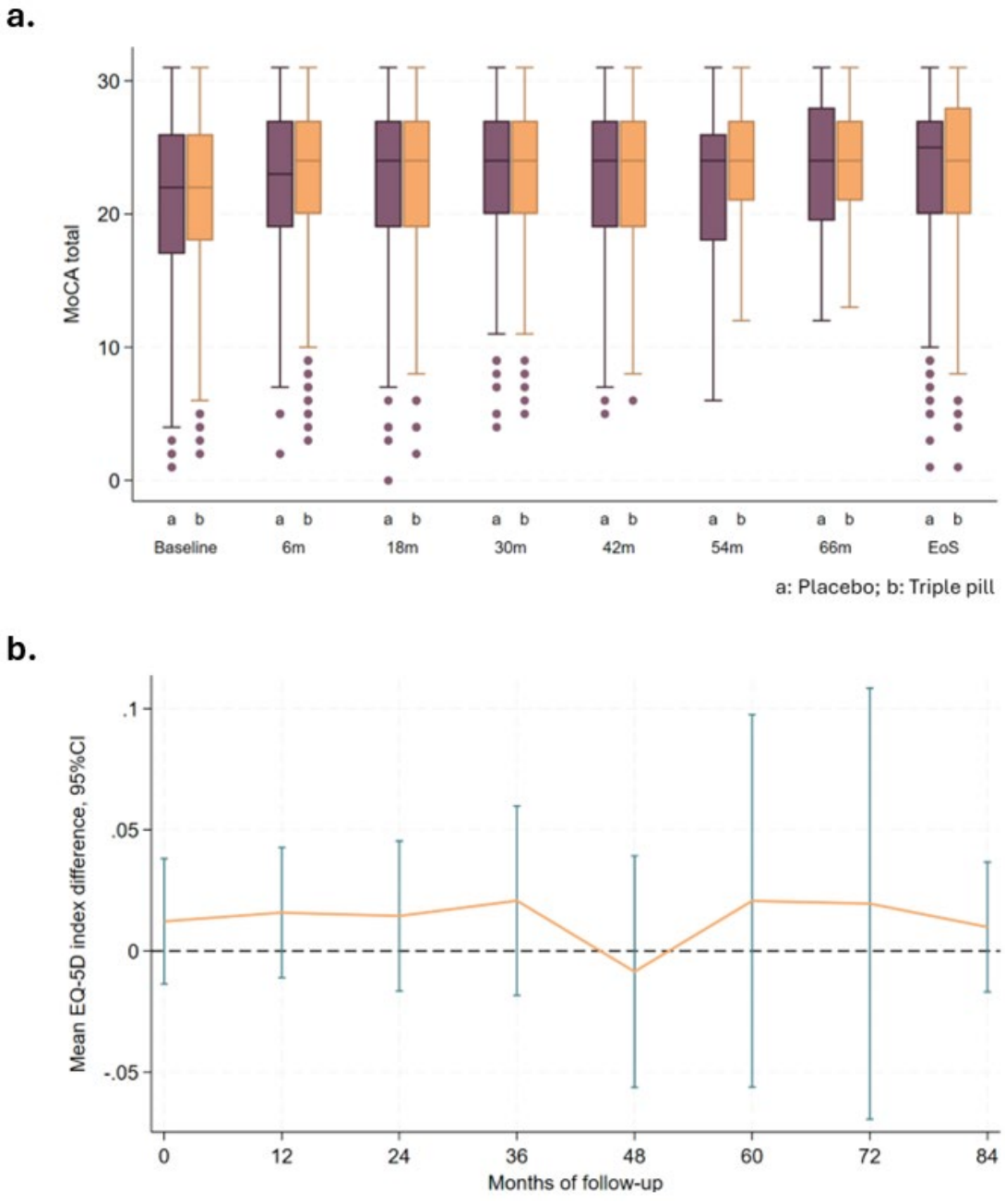
Predictor	**Coefficient**	**Std. err.**	**z**	p-value	**95% CI**	
EOS vs baseline	0.093	0.007	12.09	<0.001	0.078	0.109
MoCA within-person	0.005	0.001	3.66	<0.001	0.002	0.009
MoCA between-person	0.014	0.001	14.33	<0.001	0.012	0.016
Age (years)	-0.002	<0.001	-4.20	<0.001	-0.002	-0.001
Female (vs male)	-0.021	0.011	-1.96	0.050	-0.043	0.000
Education <12 years (vs ≥12)	-0.021	0.011	-1.83	0.067	-0.043	0.001
Treatment arm (triple pill vs placebo)	0.004	0.010	0.47	0.637	-0.015	0.025
_cons	0.474	0.039	11.87	<0.001	0.396	0.553

Log restricted-likelihood: 20.84587; Prob > chi2 0.0000

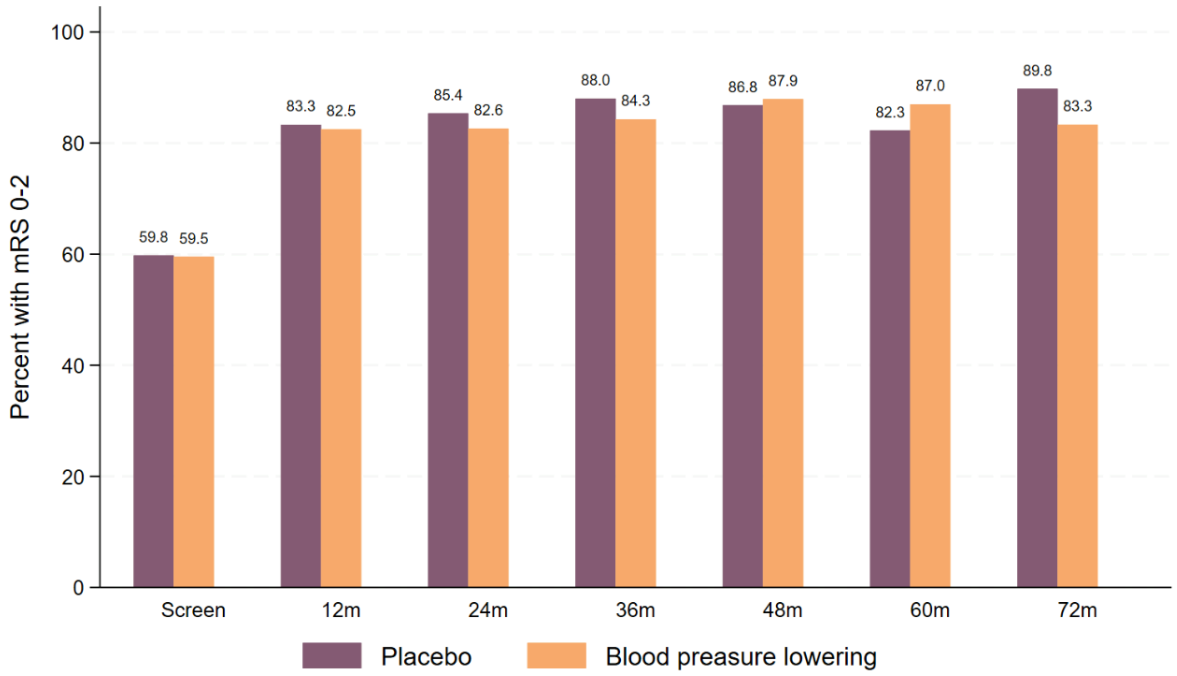
Supplementary Figure S1. Countries that participated in TRIDENT.



Supplementary Figure S2. Longitudinal trajectories of cognitive function and health-related quality of life by treatment arm: **(a)** MoCA total score (median, IQR); and **(b)** Mean EQ-5D index difference between treatment arms (mean, 95% CI) across follow-up visits. **(c)** Percentage with mRS 0-2 by treatment arm



c.


Percent with mRS 0-2
100
80
60
40
20
0
59.8
59.5
83.3
82.5
85.4
82.6
88.0
84.3
86.8
87.9
82.3
87.0
89.8
83.3
Screen
12m
24m
36m
48m
60m
72m
Placebo
Blood preasure lowering

9.2.2 Main Article of TRIDENT trial (in press)

Submitted to the New England Journal of Medicine

The NEW ENGLAND JOURNAL of MEDICINE

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A Triple Low-Dose Antihypertensive Pill after Intracerebral Hemorrhage

Journal:	*New England Journal of Medicine*
Manuscript ID	25-15043
Article Type:	Original Article
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Complete List of Authors:	Anderson, Craig; The George Institute for Global Health, Global Brain Health Chow, Clara; The University of Sydney Westmead Applied Research Centre, Faculty of Medicine and Health; Westmead Hospital, Department of Cardiology de Silva, Asita; University of Kelaniya Senanayake, Bimsara; National Hospital of Sri Lanka, Neurology Wahab, Kolawole; University of Ilorin Al-Shahi Salman, Rustam; University of Edinburgh, Centre for Clinical Brain Sciences Klijn, Catharina; Radboud Universiteit Nijmegen Martins, Sheila; Hospital de Clinicas de Porto Alegre, Neurology Espinosa, Natalie; The George Institute for Global Health Kuhles, Lauren; The George Institute for Global Health Billot, Laurent; The George Institute for Global Health, Arima, Hisatomi; Fukuoka University, Public Health Carcel, Cheryl; The George Institute for Global Health Wang, Xia; The George Institute for Global Health Li, Qiang; The George Institute for Global Health, Shan, Sana; The George Institute for Global Health Shanthakumar, Mathangi; The George Institute for Global Health Thang, Nguyen Huy ; People's 115 Hospital, Cerebrovascular Disease Palliyaguruge, Dilum; Teaching Hospital Kurunegala Peiris, Janaka; National Hospital Kandy, Neurology Ranawaka, Udaya; University of Kelaniya, Faculty of Medicine Bandusena, Senaka; Kalubowila (Colombo South) Teaching Hospital Rajendiran, Thambippillai; Kalubowila (Colombo South) Teaching hospital, Neurology Wijegunasinghe, Dharshana; University of Kelaniya, Medicine Gunasekara, Harsha ; Sri Jayewardenepura General Hospital Wijeweera, Indunil; National Hospital Kandy Dissanayake, Athula; Karapitiya Teaching Hospital, Neurology Keshavaraj, Ajantha; Jaffna Teaching Hospital, Department of Neurology Obiako, Reginald; Ahmadu Bello University, Medicine Akinyemi, Rufus; University of Ibadan College of Medicine, Neuroscience and Ageing Research Unit, Institute for Advanced Medical Research and Training Nasi, Luiz; Hospital das Clinicas de Porto Alegre, Neurology Bazan, Rodrigo; Unesp/ Botucatu,

	Moro, Carla; Clínica Neurológica e Neurocirurgica de Joinville Battaglini, Mariana; Hospital de Base São José do Rio Preto Zétola, Viviane; Hospital Santa Cruz, Neurology; Hospital de Clínicas - Federal University of Paraná (HC - UFPR), Neurology Law, Wan; Sarawak General Hospital, Neurology Chia, Yuen Kang; Hospital Queen Elizabeth, Neurology Unit, Department of Medicine Cordato, Dennis; Liverpool Hospital Grimley, Rohan; Sunshine Coast University Hospital, Neurosciences; Griffith University Faculty of Health, School of Medicine and Dentistry Dahanayaha, Anuradha; RemedianOne Contract Research Organization Liyanagamage, Sonali; RemedianOne Contract Research Organization Fernando, Nilukshi; Gampaha District General Hospital Rasheed, Nihara; Gampaha District Hospital, Neurology Kakabadze, Nodar; Urgent Neurological Clinic "Neurology" Beridze, Maia; Urgent Neurological Clinic "Neurology" Aravinthan, Mythily; National Hospital of Sri Lanka, Neurology Sahathevan, Vithoosan; National Hospital of Sri Lanka, Neurology Wijesundara , Devasmitha; National Hospital of Sri Lanka, Institute of Neurology Ruwanpathirana, Pramith; National Hospital of Sri Lanka, Wan Zaidi, Wan Asyraf; Hospital Universiti Kebangsaan Malaysia Kherkheulidze, Tinatin; Urgent Neurological Clinic Neurology Fischer, Urs; University Hospital Basel, Department of Neurology; Inselspital University Hospital Bern, Department of Neurology de Souza, Ana Claudia; Associação Hospital Moinhos de Vento, Department of Neurology Lee, Tsong-Hai; Linkou Chang Gung Memorial Hospital Chen, Christopher; Singapore General Hospital, Pontes-Neto, Octavio; Ribeirão Preto School of Medicine, University of Sao Paulo, Neuroscience and Behavioral Sciences Robinson, Thompson; University of Leicester, Cardiovascular Sciences Wang, Jiguang; Shanghai Municipal Institute of Hypertension Naismith , Sharon; University of Sydney CAR Barnett, Michael; The University of Sydney, Brain and Mind Centre; Royal Prince Alfred Hospital, The Department of Neurology Delfino, Carlos; Universidad del Desarrollo Facultad de Medicina Clínica Alemana You, Shoujiang; Second Affiliated Hospital of Soochow University, Neurology Liu, Feifeng; Shanghai East Hospital, Delcourt, Candice; The George Institute and Royal Prince Alfred Hospita, Neurological and Mental Health Division Moullaali, Tom J; University of Edinburgh Western General Hospital Wilkinson, Tim; University of Edinburgh Western General Hospital Watson, Neil; University of Edinburgh Western General Hospital Santo, Karla; Academic Research Organization, Hospital Israelita Albert Einstein Han, Qiao; The George Institute for Global Health Souza, Mariana Almudi; Associação Hospital Moinhos de Vento Jolink, Wilmar; Isala Zwolle Cristofari, Anderson; Universidade de Lisboa Zhou, Zien ; The George Institute for Global Health, UNSW Sydney; Department of Radiology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University Schreuder, Floris; Radboud University Donders Institute for Brain Cognition and Behaviour, Neurology Lindley, Richard; The George Institute and University of Sydney, Armenis, Manuela; The George Institute for Global Health Woodward, Mark; The George Institute for Global Health, Freed, Ruth; The George Institute for Global Health

	Song, Lili; Fudan University, Institute of Science and Technology for Brain-inspired Intelligence Chalmers, John; University of Sydney, The George Institute for Global Health Rodgers, Anthony; The George Institute for Global Health, ; The George Institute for Global Health
Abstract:	BACKGROUND Blood pressure (BP) control from a single pill containing three antihypertensive drugs at low-doses may improve recurrent stroke prevention after intracerebral hemorrhage (ICH). METHODS In this multinational, double-blind, randomized, placebo-controlled trial, we recruited ICH patients with systolic BP 130-160mmHg. After a 2-week, single-blind, active run-in phase, eligible patients were randomized to a triple-pill containing telmisartan 20mg, amlodipine 2.5mg, and indapamide 1.25mg or matching placebo, on top of usual care. The primary outcome was first occurrence of recurrent stroke. Secondary outcomes included major cardiovascular events, BP control, and safety. Analysis was according to the intention-to-treat principle. RESULTS A total of 1670 patients (mean age 58 years) underwent randomization at 57 sites in 10 countries. Baseline characteristics were balanced with mean age 58 years and 34% female. After the run-in phase, mean systolic BP was 127mmHg on a mean 1.2 classes of background antihypertensive drugs. A primary-outcome event occurred in 38 (4.6%) of 833 patients assigned to the triple-pill and 62 (7.4%) of 837 patients on placebo after a mean follow-up of 3 years (hazard ratio 0.61, 95%CI 0.41-0.92; P=0.017). Mean systolic BP during follow-up was 127mmHg in the triple-pill group and 138mmHg in the placebo group; mean adjusted difference 9mmHg (95%CI 7-10mmHg). The rate of major cardiovascular events was lower with the triple-pill. Serious adverse events were 23.8% with the triple-pill and 26.8% with placebo. CONCLUSIONS Among patients with ICH, intensive BP reduction with a pill containing a combination of three low-dose antihypertensive drugs reduced the incidence of recurrent stroke.
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
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A Triple Low-dose Antihypertensive Pill after Intracerebral Hemorrhage

Prof. Craig S Anderson MBBS PhD,[1,2,3] Prof. Clara K Chow MBBS PhD,[4] Prof. H Asita de Silva MBBS DPhil,[5] Bimsara Senanayake MD,[6] Prof. Kolawole Wahab MBBS MD,[7] Prof. Rustam Al-Shahi Salman PhD FMedSci,[8] Prof. Catharina JM Klijn MD PhD,[9] Prof. Sheila Ouriques Martins MD PhD,[10,11] Natalie Espinosa MSc,[2] Lauren Kuhles BN,[2] Prof. Laurent Billot MRes,[2,12] Prof. Hisatomi Arima MD PhD,[13] Cheryl Carcel MD PhD,[2] Xia Wang PhD,[2] Qiang Li MBiostat,[2] Sana Shan MBiostat,[2] Mathangi Shanthakumar MSc,[2] Prof. Nguyen Huy Thang MD,[14] Dilum Palliyaguruge MD,[15] Janaka Peiris MD,[16] Prof. Udaya K. Ranawaka MD,[17] Senaka Bandusena MD,[18] Thambipillai Rajendiran MD,[18] Darshana Wijegunasinghe MD,[17] Harsha Gunasekera MD,[19] Indunil Wijeweera MD,[16] Athula Dissanayake MD,[20] Ajantha Keshavaraj MD,[21] Prof. Reginald O. Obiako MD PhD,[22] Prof. Rufus Akinyemi MD PhD,[23] Prof. Luiz Nasi MD PhD,[24] Prof. Rodrigo Bazan MD PhD,[25] Carla Heloisa Cabral Moro MD,[26] Mariana Battaglini MD,[27] Viviane Zétola MD,[28] Wan Chung Law MD,[29] Yuen Kang Chia MD,[30] Prof. Dennis Cordato MBBS PhD,[31,32] Rohan Grimley MBBS PhD,[33,34] Anuradha Dahanayaka MSc,[35] Sonali Liyanagamage MSc,[35] Nilukshi Fernando MD,[36] Nihara Abdul Rasheed MD,[37] Prof. Nodar Kakabadze MD,[38] Prof. Maia Beridze MD PhD,[39] Mythily Aravinthan MD,[6] Vithoosan Sahathevan MD,[6] Devasmitha Wijesundara MD,[6] Pramith Ruwanpathirana MD,[6] Prof. Wan Asyraf Wan Zaidi MMed,[40] Tinatin Kherkheulidze MD,[38] Prof. Urs Fischer MD,[41] Ana Cláudia de Souza MD PhD,[11] Prof. Tsong-Hai Lee MD PhD,[42,43] Prof. Christopher Chen MD,[44] Prof.Octavio Pontes-Neto MD PhD[45] Prof. Thompson Robinson MBChB,[46] Prof. Jiguang Wang MD PhD,[47] Prof. Sharon L. Naismith DPsych,[48,49] Prof. Michael Barnett MBBS PhD,[3,48] Carlos Delfino MD,[2,50] Shoujiang You MD PhD,[51] Feifeng Liu MD PhD,[52] Candice Delcourt MD PhD,[2,53] Tom J. Moullaali MBBS PhD,[8] Tim Wilkinson MBChB PhD,[8] Neil Watson MBChB MD,[8] Karla Santo MD PhD,[54] Qiao Han MD PhD,[2] Mariana Almudi Souza MD,[24] Wilmar MT Jolink MD PhD,[55] Anderson Berni Cristofari MD,[56] Zien Zhou MD PhD,[2] Floris H Schreuder

MD PhD,[9] Prof. Richard I Lindley MBBS MD,[2,4] Manuela Armenis,[2] Prof. Mark Woodward PhD,[2,57] Ruth Freed MSc (Hons),[2] Prof. Lili Song MD PhD,[1,2] Prof. John Chalmers MBBS PhD,[2*] Prof. Anthony Rodgers MBChB PhD;[2,57*] for the TRIDENT Research Group.[†]

[*]Co-senior

[‡]Full list of members of the TRIDENT Research Group outlined in Supplementary Appendix

[1]Institute of Science and Technology for Brain-inspired Intelligence, Fudan University, Shanghai, China

[2]The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia

[3]Neurology Department, Royal Prince Alfred Hospital, Sydney, NSW, Australia

[4]Westmead Applied Research Centre, Faculty of Medicine and Health, University of Sydney, Westmead Hospital, Westmead, NSW, Australia

[5]Clinical Trials Unit, Department of Pharmacology, Faculty of Medicine, University of Kelaniya, Colombo, Sri Lanka

[6]Institute of Neurology, National Hospital of Sri Lanka, Colombo, Sri Lanka

[7]Department of Medicine, University of Ilorin, Ilorin, Nigeria

[8]Institute for Neuroscience and Cardiovascular Research, University of Edinburgh, Edinburgh, UK

[9]Department of Neurology, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

[10]Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

[11]Neurology Service Hospital Moinhos de Vento, Porto Alegre, Brazil

[12]School of Public Health, University of Bordeaux, Bordeaux, France

[13]Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

[14]Stroke Unit, 115 Hospital, Ho Chi Minh City, Vietnam

[15]Neurology Department, Teaching Hospital Kurunegala, Kurunegala, Sri Lanka

[16]Neurology Department, National Hospital, Kandy, Sri Lanka

[17]Department of Medicine, Faculty of Medicine, University of Kelaniya, Kelaniya, Sri Lanka

[18]Neurology Department, Kalubowila (Colombo South) Teaching Hospital, Dehiwala, Sri Lanka

[19]Neurology Department, Sri Jayewardenepura General Hospital, Nugegoda, Sri Lanka

[20]Neurology Department, Karapitiya Teaching Hospital, Galle, Sri Lanka

[21]Neurology Department, Jaffna Teaching Hospital, Jaffna, Sri Lanka

[22]Department of Medicine, Ahmadu Bello University Teaching Hospital, Zaria, Nigeria

[23]Neuroscience and Ageing Research Unit, Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, Ibadan, Nigeria

[24]Neurology Department, Hospital Moinhos de Vento, Porto Alegre, Brazil

[25]Department of Neuroscience and Mental Health, Botucatu School of Medicine, UNESP, Brazil

[26]Neurology Department, Clinica Neurológica e Neurocirurgica de Joinville, Joinville, Brazil

[27]Neurology Department, Hospital de Base São José do Rio Preto, São José do Rio Preto, Brazil

[28]Instituto Flumignano de Medicina, Curitiba, Brazil

[29]Neurology Department, Sarawak General Hospital, Jalan Hospital, Kuching, Sarawak, Malaysia

[30]Neurology Department, Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia

[31]Neurology Department, Liverpool Hospital, Liverpool, Sydney, NSW, Australia

[32]Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia

[33]Sunshine Coast University Hospital, Sunshine Coast, QLD, Australia

[34]School of Medicine and Dentistry, Griffith University, Birtinya, QLD, Australia

[35]RemediumOne Contract Research Organization, Colombo, Sr Lanka

[36]Peradeniya Teaching Hospital, Kandy, Sri Lanka

[37]Neurology Department, Gampaha District General Hospital, Gampaha, Sri Lanka

[38]Urgent Neurology Clinic "Neurology", Tbilisi State Medical University, Tbilisi, Georgia

[39]First University Clinic, Tbilisi State Medical University, Tbilisi, Georgia

[40]Department of Medicine, Faculty of Medicine Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

[41]Department of Neurology University Hospital Bern and University of Bern, Bern, Switzerland

[42]Stroke Center and Department of Neurology, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan

[43]College of Medicine, Chang Gung University, Taoyuan, Taiwan

[44]Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[45]Department of Neurosciences and Behavioural Sciences, Ribeirao Preto School of Medicine, University of Sao Paulo, Ribeirao Preto, Brazil

[46]College of Life Sciences and NIHR Biomedical Research Centre, University of Leicester, Leicester, UK

[47]Centre for Epidemiological Studies and Clinical Trials, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

[48]Brain and Mind Centre, University of Sydney, Camperdown, Sydney, NSW, Australia

[49]Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia

[50]Centro de Estudios Clínicos, Instituto de Ciencias e Innovación en Medicina (ICIM), Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile

[51]Department of Neurology and Clinical Research Center of Neurological Disease, The Second Affiliated Hospital of Soochow University, Suzhou, China

[52]Department of Neurology, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China

[53]Macquarie University, Department of Clinical Medicine, Faculty of Medicine, Health and Human Sciences, Sydney, NSW, Australia

[54]Academic Research Organization, Hospital Israelita Albert Einstein, São Paulo, Brazil

[55]Department of Neurology, Zwolle, The Netherlands.

[56]Universidade de Lisboa, Lisbon, Portugal

[57]The George Institute for Global Health, School of Public Health, Imperial College London, London, UK

Corresponding authors:
Professor Lili Song
Institute for Science and Technology for Brain-inspired Intelligence, Fudan University, Shanghai, 201203, China.
E: lili_song@fudan.edu.cn

Professor Craig Anderson
The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia
Postal: PO Box M213 Missenden Road, Camperdown NSW, Australia
E: canderson@georgeinstitute.org.au

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Table 1 Characteristics of Patients

Table 2 Efficacy and Safety Outcomes

Figure 1 Mean Systolic Blood Pressure over Time

Figure 2 Cumulative Incidence Event Curves for (A) Any Stroke, (B) Any Intracerebral Hemorrhage (C) Any Major Cardiovascular Event (Death from Cardiovascular Causes, Recurrent Myocardial Infarction, or Stroke), and (D) Death from Cardiovascular Causes

Figure 3 Primary Outcomes According to Prespecified Subgroups.

Supplementary Appendix - includes 27 additional Tables and 9 additional Figures.

References: 32

ABSTRACT

BACKGROUND

Blood pressure (BP) control from a single pill containing three antihypertensive drugs at low-doses may improve recurrent stroke prevention after intracerebral hemorrhage (ICH).

METHODS

In this multinational, double-blind, randomized, placebo-controlled trial, we recruited ICH patients with systolic BP 130-160mmHg. After a 2-week, single-blind, active run-in phase, eligible patients were randomized to a triple-pill containing telmisartan 20mg, amlodipine 2.5mg, and indapamide 1.25mg or matching placebo, on top of usual care. The primary outcome was first occurrence of recurrent stroke. Secondary outcomes included major cardiovascular events, BP control, and safety. Analysis was according to the intention-to-treat principle.

RESULTS

A total of 1670 patients (mean age 58 years) underwent randomization at 57 sites in 10 countries. Baseline characteristics were balanced with mean age 58 years and 34% female. After the run-in phase, mean systolic BP was 127mmHg on a mean 1.2 classes of background antihypertensive drugs. A primary-outcome event occurred in 38 (4.6%) of 833 patients assigned to the triple-pill and 62 (7.4%) of 837 patients on placebo after a mean follow-up of 3 years (hazard ratio 0.61, 95%CI 0.41-0.92; P=0.017). Mean systolic BP during follow-up was 127mmHg in the triple-pill group and 138mmHg in the placebo group; mean adjusted difference 9mmHg (95%CI 7-10mmHg). The rate of major cardiovascular events was lower with the triple-pill. Serious adverse events were 23.8% with the triple-pill and 26.8% with placebo.

CONCLUSIONS

Among patients with ICH, intensive BP reduction with a pill containing a combination of three low-dose antihypertensive drugs reduced the incidence of recurrent stroke.

Trial registration: The trial is registered at ClinicalTrials.gov (NCT02699645) and the Australian New Zealand Clinical Trial Registry (ACTRN12616000327482).

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Spontaneous intracerebral hemorrhage (ICH) is the most serious and least treatable form of stroke.[1] The only proven treatment to prevent incidence and recurrent ICH is effective blood pressure (BP) reduction.[2,3] However, the benefits of intensive BP-lowering and the optimal approach to treatment are uncertain.[2-5]

Although most survivors of stroke are discharged from hospital on BP-lowering therapy, long-term BP control is generally inadequate from poor adherence, insufficient up-titration of medicines, and therapeutic inertia.[6-11] Single pill combination antihypertensive therapy holds considerable promise as a strategy to improve BP control.[12-14]

We undertook the Triple therapy prevention of Recurrent Intracerebral Disease Events Trial (TRIDENT) to determine the effectiveness of more intensive long-term BP-lowering using a single combination antihypertensive 'triple-pill' on top of standard of care, on the time to recurrent stroke in patients with prior ICH.

METHODS

TRIAL DESIGN AND OVERSIGHT

We undertook an international, multicenter, double-blind, randomized, placebo-controlled controlled trial. Details of the rationale, design and analysis of the trial protocol and statistical analysis plan have been published[15,16] and are available at NEJM.org. Funding was through grants from the National Health and Medical Research Council of Australia and Ministry of Health, Brazil. The study was approved by a central ethics committee and at each participating hospital, and by relevant national/local regulatory bodies. All patients provided written informed consent. TRIDENT is registered at ClinicalTrials.gov (NCT02699645) and the Australian New Zealand Clinical Trials Registry (ACTRN12616000327482). The George Institute for Global Health coordinated the trial in accordance with the principles of the Declaration of Helsinki and guidelines for Good Clinical Practice and performed the analysis. There was an independent data

and safety monitoring committee. Dr Anderson wrote the first draft of the manuscript with input from Dr Rodgers. All authors commented on drafts of the manuscript, approved the final version, vouch for the fidelity to the study protocol, and the accuracy and completeness of the data.

ELIGIBILITY

Adult patients (≥18 years) with a history of primary ICH were eligible for the inclusion if they had resting seated clinic systolic BP 130-160mmHg while on any BP-lowering therapy as appropriate, and had no contraindication to any individual component of the triple-pill. Patients taking an angiotensin converting enzyme inhibitor that could not be switched to a suitable alternative or were unable to complete the study procedures or had abnormal renal and/or liver function tests, were ineligible.

Potentially eligible patients entered an active run-in phase with single-blind triple-pill containing the antihypertensive drugs telmisartan 20 mg, amlodipine 2.5 mg and indapamide 1.25 mg for 2-weeks, with an optional second 2-weeks if necessary. This was designed to ensure patients had ≥80% adherence and tolerance of the treatment and procedures and were free of any significant change in tests of renal function. The exclusion of patients whose serum creatinine at the end of the run-in and during follow-up was ≥20% higher than at screening/baseline was a regulatory requirement.

RANDOMIZATION AND PROCEDURES

Patients were central randomly assigned in a 1:1 ratio, stratified by country, age, and baseline systolic BP, to receive the triple-pill or matching placebo. The study medication first used was single pill encapsulation of the individual regulatory-approved drugs or three matching placebos, manufactured by PCI Pharma Services (previously Pharmaceutical Packaging Professionals) in Melbourne, Australia. In June 2022, the study medication was switched to a bespoke triple-pill called GMRx2, and single matching placebo, manufactured by Piramal Pharma Ltd India;

bottling, labelling and distribution was done by Eramol (previously RenaClinical), UK. Throughout the trial, the study medication had identical packaging, labelling and administration scheduling. The study protocol recommended local hypertension prescribing guidelines were adhered to and provided options to achieve this with additional concomitant medications.

Baseline data were collected on demographics, medical history, lifestyle factors, and medications. Follow-up data were collected at 6-weeks and 6-months post-randomization, and 6-monthly thereafter. Patients were assessed for any adverse events, medication adherence and measurements of resting clinic BP. Protocol-directed blood tests were done at 6-weeks and study end. Patients received 6-monthly supplies of study medication, with home delivery provided during the COVID-19 pandemic.

OUTCOMES

The primary-outcome was time to first recurrent stroke. Secondary outcomes were time to first occurrence of a composite of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke); time to cardiovascular death; and hypertension control, defined as systolic BP <130mmHg at 6-months.

Other cardiovascular endpoints were times to first recurrent ICH, ischemic stroke, stroke of any type, or non-fatal myocardial infarction; deaths related to stroke, cardiovascular causes, or any cause; and various other measures of BP control. Several cognitive, disability, and quality of life outcomes were defined; these results are not presented here. Medication adherence was defined according to missed doses and pill counts. Serious adverse events and adverse events of special interest were defined according to standard definitions.

STATISTICAL ANALYSIS

The study was initially designed to recruit 3782 patients (1891 per group) to achieve 230 recurrent stroke events, based on a 2.5% annual rate and hazard ratio (HR) of 0.65. In early 2020,

the sample size was reduced after challenges were experienced in recruitment and following publication of the Japanese Recurrent Stroke Prevention Clinical Outcome trial (RESPECT).[17] RESPECT showed a large effect of intensive BP lowering on ICH consistent with the large effect seen in the Perindopril Protection against Recurrent Stroke Study (PROGRESS).[18,19] The decision to change the sample size to 1500 patients, made without any knowledge of the evolving treatment effect in the study, was estimated to provide 90% power to detect a HR of 0.50 when 100 primary-endpoints would be accrued over a mean 3-years with 5% lost to follow-up and 10% crossover.

Efficacy analyses were conducted according to the intention-to-treat principle. The effect of the intervention on the primary outcome was estimated as a cause-specific HR and 95%CI in a Cox proportional hazard model, with randomization stratification factors included as fixed covariates. Sensitivity analyses included a Fine and Gray competing risk model[20] and an extended adjusted analysis.

Logistic regression was used for analysis of hypertension control.[21] All tests are two-sided with a nominal level set at 5%. For the 3 secondary efficacy outcomes, the family-wise error rate was controlled with a sequential Holm-Sidak correction.[22] No multiplicity adjustment was applied to the other outcomes which were to be considered exploratory. Heterogeneity of treatment on the primary outcome and SBP reduction was to be assessed across 10 pre-defined subgroups, but this was not possible for race and ethnicity due to small numbers. These statistical analyses were performed using SAS (version 8.3 or above) and R (version 4.0 or above).

RESULTS

PARTICIPANTS AND TRIAL COHORTS

From September 28, 2017, to November 30, 2024, 2206 patients with ICH were assessed for eligibility and entered the active run-in phase at 61 sites in 12 countries (Australia, Brazil,

Georgia, Malaysia, Netherlands, Nigeria, Singapore, Sri Lanka, Switzerland, Taiwan, UK, and Vietnam). Ultimately, 1670 patients underwent randomization, with 833 assigned to the triple-pill and 837 to placebo at 57 sites in 10 countries at a median of 54 days (27-127) after the index ICH (Table S1, and Figs. S1-2). The main reasons for 536 (24.6%) patients not being randomized were serum creatinine changes of ≥20% elevation, which affected 147 (24.3%) patients, and 68 (12.7%) had ≥30% elevations. Key other reasons were an investigator decision (17.2%), withdrawal of consent (14.7%), intolerance (5.9%), and poor adherence (5.9%) (Table S2).

Among the randomized patients, the mean age was 58±11 years, 563 (33.7%) were female, and 1213 (72.6%) were Asian of whom 1114 (66.7%) resided in Sri Lanka. Patient characteristics were balanced between the two trial groups, and representative of patients with ICH by age, sex, comorbidity and ethnicity (Tables S3-12). Mean systolic BP was 143±10mmHg and 127±16mmHg at the commencement and end of the run-in phase, respectively. At the time of randomization, patients used a mean 1.2±1.1 background BP-lowering drugs with 57.7% including ≥2 drugs with an angiotensin receptor blocker being the most common (43.6%) (Tables 1 and S13).

There were 1401 (83.9%) patients alive at completion of the study after a mean follow-up of 3 years (Tables S14-15). Of 267 (16.0%) patients who failed to complete the study, 86 (5.1%) were lost to follow-up (Table S16). Among 1524 patients where an assessment was possible, adherence to study medication was deemed acceptable in 1317 (86.4%) during follow-up (Table S17). Early withdrawal of treatment due to an adverse event occurred in 113 (13.5%) patients in the triple-pill group and 50 (6.0%) in the placebo group, mainly from a ≥20% increase in the serum creatinine from the baseline level (Table S18). Few protocol violations were mainly errors in dispensing of study medication (Table S19). Over the entire time of follow-up, the mean systolic BP was 127mmHg in the triple-pill group and 138mmHg in the placebo group; between-group mean systolic BP difference 9mmHg (95% CI, 7-10mmHg) (Table S20 and Fig. 1). Mean

diastolic BP during follow-up were 82mmHg in the triple-pill group and 86mmHg in the placebo group (Table S20 and Fig. S3). BP differences attenuated over time due to greater use of concomitant antihypertensive drugs in the placebo group (Table S13 and Fig. 1).

PRIMARY EFFICACY RESULTS

The primary-outcome event of any recurrent stroke was observed in 38 patients (4.6%) in the triple-pill group and in 62 patients (7.2%) in the placebo group (HR 0.61; 95% CI, 0.41-0.92; P=0.017) (Table 2 and Fig. 2A). The result was unchanged when death from any cause was treated as a competing risk and in a fully adjusted model (Table S21). The primary outcome was driven by effects on recurrent ICH, which occurred in 15 patients (1.8%) in the triple-pill group and 37 patients (4.4%) in the placebo group (HR, 0.40; 95%CI 0.22-0.73) (Fig. 2B). The number needed to treat estimate for the prevention of recurrent stroke was 27 (95% CI, 19-61). The effect was broadly consistent across 8 pre-specified subgroups; only baseline BP category showed a degree of heterogeneity (Fig. 3).

SECONDARY AND OTHER EFFICACY RESULTS

A composite outcome of major adverse cardiovascular events was observed for 55 patients (6.6%) in the triple-pill group and for 82 participants (9.8%) in the placebo group (HR, 0.67; 95% CI, 0.47-0.94]; Table 2 and Fig. 2C). The point estimate was similar for cardiovascular death, but the 95%CI was wide and crossed the line of unity (Fig. 2D). Hypertension control at 6-months was achieved in 416 patients (49.9%) in the triple-pill group and 221 patients (26.4%) in the placebo group (OR, 3.15; 95%CI, 2.53-3.93). All other measures of BP control were also improved in the triple-pill group (Tables S21-25). There were no clear treatment group differences in the other cardiovascular outcomes; however, power to detect differences was limited due to low numbers (Table S21). There were no clear differences in the effects on mean

systolic BP during follow-up between the two formulations of study medication nor in hypertension control across pre-specified subgroups (Tables S22-25 and Figs. S4-6).

SAFETY RESULTS

Serious adverse events occurred in 198 (23.8%) patients in the triple-pill group and 224 (26.8%) patients in the placebo group (Tables 2 and S26). Adverse events of special interest in the first 6-months of follow-up were low and comparable between groups, except for headaches which occurred less often in the triple-pill group. Injurious falls and biochemical abnormalities occurred in less than 0.2% of patients in both groups. In 1118 patients with both a baseline and end of study measure of estimated glomerular filtration rate (eGFR), this declined by ≥30% in 7.7% (43/558) in the triple-pill group and 4.3% (24/550) of the placebo group. There were no group differences in serum biochemistry or heart rate over time (Figs. S7-9 and Table S27).

DISCUSSION

Among patients with ICH, a single pill combination low-dose triple antihypertensive reduced the incidence of recurrent stroke and of major adverse cardiovascular outcomes over a mean treatment duration of 3 years, compared with placebo. The large treatment effect was driven by the prevention of recurrent ICH. Patients given the triple-pill had better BP control, with a mean systolic BP of 127mmHg being approximately 9mmHg lower than that in patients given the matching placebo pill. This was achieved despite background BP-lowering therapy being used in a high proportion of patients according to usual standard of care. Safety, tolerability and adherence to the study medication were good.

TRIDENT is the largest secondary prevention trial in ICH to date, and the first to specifically determine the effect of more intensive BP control with a triple-pill approach on hard clinical endpoints. The results are consistent with prior indirect evidence of the benefits of intensive BP-lowering in patients with ICH. Of most relevance, among the 660 patients with prior ICH who

participated in PROGRESS that compared active treatment (perindopril with/without indapamide) with placebo over a mean of 4-years, a 11/4mmHg BP reduction conferred a 49% (95%CI, 18-66%) lower stroke risk.[18,19] Among participants with prior ischemic stroke or ICH, open trials of more versus less intensive BP-lowering demonstrate large reductions in recurrent ICH.[17,23,24] Finally, cohort and Mendelian randomization studies show particularly strong associations between BP and ICH, with each 10mmHg lower SBP associated with approximately 40% lower ICH risk.[25,26]

In practice, there are considerable challenges to achieving effective BP control. Clinician therapeutic inertia is a key barrier to preventing patients achieving guideline-recommended BP targets due to various factors such as workflow and time constraints, concern over side-effects, insufficient knowledge over drug dosing adjustments, and uncertainty regarding the out-of-office BP of patients.[27] Another fundamental issue is cognitive bias influencing the perception that BP is well controlled from accepting levels within a certain range and ignoring all other readings. Low adherence to treatment is another major contributing factor to poor BP control. Single pill combination therapy has been shown to provide a well-tolerated and scalable therapeutic approach that has the potential to maintain BP control better than conventional strategies.[12,14] Triple-pill therapy has recently been included in US[4] and European[5] hypertension guidelines and in the WHO Essential Medicines List.[28]

Key strengths of this study were the broad inclusion criteria, double-blind placebo-controlled design and conduct across ethnically and socio-demographically diverse populations from different resource settings. However, there are some limitations. Most of the patients were from Sri Lanka, which may raise concern over the generalizability of the results. However, the BP reductions from treatment were consistent across different participating countries and demographic groups. Patients had an age, sex and disease profile that is similar to patients with ICH, worldwide.[29,30] In particular, the placebo group in this trial had a mean systolic BP of

approximately 140mmHg which was comparable to ICH patients after discharge from a large US tertiary care center.[9] As there is no treatment for stroke prevention after ICH other than BP-lowering, the likelihood of income-dependent disparities in the care in the study population is likely to have been small. The active run-in phase was designed to provide efficiency gains in a long-term prevention trial. This means the tolerability findings only apply to patients who tolerated an initial 2-weeks of therapy. We were required to exclude patients who had a ≥20% increase in creatinine levels during run-in and follow-up. However, evidence now suggests that this is predominantly a hemodynamic response not necessarily associated with long-term kidney disease progression, with a ≥30% increase in eGFR being a more reasonable threshold to trigger evaluation and consideration of dose reduction/cessation.[31,32] The triple-pill showed good tolerability, with a small excess of treatment withdrawal due to symptomatic adverse effects.

The beneficial effects of the triple-pill were manifest after 1-year of intensive BP-lowering treatment and continued to increase thereafter. This finding is consistent with results of a recent open trial of intensive BP control in patients with a history of stroke in China.[24] TRIDENT evaluated the triple-pill against placebo on top of any background use of BP-lowering drugs in the management of patients according to guideline-recommended standard of care. Use of this approach as open label treatment, including initial treatment after ICH or that of another type of combination of BP-lowering drugs, requires further research.

In conclusion, among patients with ICH, treatment with a single triple low-dose combination antihypertensive pill for a median of 2.5 years was safe and reduced the incidence of stroke from improved BP control.

Data sharing

Individual, de-identified participant data used in these analyses may be able to be shared on request from any qualified investigator following approval of a protocol and signed data access agreement via both the Trial Steering Committee and the Research Office of The George Institute for Global Health, Australia.

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Disclosures

CSA has received grants from the National Health and Medical Research Council (NHMRC) and Medical Research Futures Fund (MRFF) of Australia, the Medical Research Foundation (MRF) of the UK, and AstraZeneca Australia. He is a consultant to Auzone BioTech China, a Chair of the data and safety monitoring boards for several trials, President-elect of the World Stroke Organization, and the Editor-in-Chief of Cerebrovascular Diseases. George Health Enterprises,

the social enterprise arm of The George Institute for Global Health (TGI), has received investment to develop fixed-dose combination products containing aspirin, statin and BP-lowering drugs. George Health Enterprises has patents for low-dose BP combinations, on which Professor Rodgers is listed as one of the inventors. Professor Rodgers is seconded part-time to George Medicines Pty Ltd, which is partly owned by George Health Enterprises, and secured FDA approval for GMRx2 in 2025. No staff at TGI have a financial interest in this product. The other authors have no disclosures.

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Table 1: Baseline Characteristics of Patients*

Characteristic	Triple-pill (N=833)	Placebo (N=837)
Demographic characteristics		
Age – y	57.5±11.2	58.0±11.5
Female sex - no. (%)	275 (33.0)	288 (34.4)
Race or ethnic group - no. (%)†		
Asian	610 (73.2)	603 (72.0)
White	102 (12.2)	109 (13.0)
Black	96 (11.5)	100 (11.9)
Hispanic / Latino	11 (1.3)	16 (1.9)
Other	14 (1.7)	9 (1.1)
Level of education, 12 years or more - no. (%)	548 (65.8)	552 (65.9))
Medical history		
Hypertension - no. (%)	667 (80.1)	680 (81.3)
Previous ischemic stroke - no. (%)	33 (4.0)	33 (3.9)
Previous intracerebral hemorrhage before index event - no. (%)	56 (6.7)	56 (6.7)
Previous stroke of unknown type - no. (%)	6 (0.7)	5 (0.6)
Diabetes mellitus - no. (%)	181 (21.7)	188 (22.5)
Coronary artery disease - no. (%)	47 (5.6)	55 (6.6)
Atrial fibrillation - no. (%)	11 (1.3)	7 (0.8)
Chronic kidney disease - no. (%)	13 (1.6)	16 (1.9)
Current alcohol consumption - no. (%)‡	75 (9.0)	78 (9.3)
Current smoker - no. (%)	43 (5.2)	47 (5.6)
Clinical features		
Features of the index intracerebral hemorrhage event		
Median time from the onset of symptoms (IQR) - days	52 (27-129)	54 (28-126)
Median volume of the hematoma (IQR)§ - mL	12 (5-24)	11 (5-21)
Location - no. (%)¶		
Cortical	125 (15.0)	127 (15.2)
Deep	653 (78.4)	635 (75.9)
Both/other	55 (6.6)	75 (9.0)
Presumed main cause - no. (%)¶		
Hypertension	785 (94.2)	780 (93.2)

Anticoagulation-related	1 (0.1)	4 (0.5)
Antiplatelet-related	1 (0.1)	1 (0.1)
Cerebral amyloid angiopathy	3 (0.4)	6 (0.7)
Uncertain	25 (3.0)	21 (2.5)
Multiple/other	18 (2.2)	25 (3.0)
BMI - kg/m^2 - no. (%)	25.0±4.5	24.9±4.6
BP management		
Background treatment		
Nil - no. (%)	93 (11.2)	96 (11.5)
Single antihypertensive drug - no. (%)	252 (30.3)	261 (31.2)
Multiple antihypertensive drugs - no. (%)	487 (58.5)	476 (56.9)
Number of antihypertensive drugs per patient	1.2±1.1	1.2±1.1
BP parameters		
Systolic BP at beginning of run-in phase	143±10	143±10
Diastolic BP at beginning of run-in phase	88±10	88±10
Systolic BP at baseline after run-in phase**	127±16	127±16
Diastolic BP at baseline after run-in phase**	82±11	82±11
Level of control of systolic BP at randomization		
<140 mmHg - no. (%)	662 (79.5)	666 (79.5)
≥140 mmHg - no. (%)	171 (20.5)	171 (20.4)

*Plus-minus values are means±SD. Data are shown for the intention-to-treat population. BMI denotes body mass index, BP blood pressure, IQR interquartile range.

†Race or ethnic group was reported by the patients.

‡Defined as one standard drink or more per week reported by the patients.

§Data were available in only 192 patients in the triple-pill group and 200 patients in the placebo group reported by investigators (further details outlined in Table S3).

¶Reported by investigators in all patients.

**There were 85 patients in the triple-pill group and 76 patients in the placebo group who underwent a second run-in phase.

Table 2: Efficacy Outcomes and Safety*

Outcome	Triple-pill (N=833)	Placebo (N=837)	Measure of Effect (95%CI)
	Number (percentage)		
Primary outcome - recurrent stroke	38 (4.6)	62 (7.4)	Hazard ratio 0.61 (0.41-0.92)†
Secondary outcomes			
Major cardiovascular event	55 (6.6)	82 (9.8)	Hazard ratio 0.67 (0.47-0.94)†
Cardiovascular death	17 (2.0)	25 (3.0)	Hazard ratio 0.67 (0.36-1.25)
Hypertension control at 6-months	416 (49.9)	221 (26.4)	Odds ratio 3.15 (2.53-3.93)
Other cardiovascular outcomes‡			
Intracerebral hemorrhage	15 (1.8)	37 (4.4)	Hazard ratio 0.40 (0.22-0.73)
Ischemic stroke	25 (3.0)	28 (3.3)	Hazard ratio 0.90 (0.52-1.54)
Stroke of unknown type	0 (0.0)	2 (0.2)	-
Fatal stroke	3 (0.4)	12 (1.4)	Hazard ratio 0.25 (0.07-0.89)
Non-fatal stroke	35 (4.2)	51 (6.1)	Hazard ratio 0.68 (0.44-1.05)
Non-fatal myocardial infarction	5 (0.6)	7 (0.8)	Hazard ratio 0.69 (0.22-2.19)
Death of any cause	54 (6.5)	72 (8.6)	Hazard ratio 0.75 (0.53-1.07)
Safety			
Patients with an adverse event of special interest at 6 months¶	56 (6.7)	55 (6.6)	
Patients with a serious adverse event§	198 (23.8)	224 (26.8)	Odds ratio 0.89 (0.74-1.08)
Patients who withdrew from treatment due to an adverse event†	113 (13.6)	50 (6.0)	

*Data are shown for the intention-to-treat population.

†In sensitivity analysis, the effects were 0.61 (0.41-0.92) in a competing risk model and 0.62 (0.41 to 0.93) in a fully adjusted model that included age, sex, pre-morbid function, history of hypertension, cardiac disease, and diabetes mellitus, and level of education (<12 vs. ≥12 years).

‡A patient could have multiple specific outcomes.

¶Includes hypotension, syncope, headache, hyponatremia, hyperkalemia, injurious falls, and acute kidney injury.

§Serious adverse events were prespecified to include events that may or may not be considered to be related to the treatment and that were life-threatening or resulted in hospitalization or prolongation of existing hospitalization, persistent or clinically significant disability or incapacity, medical or surgical intervention to prevent permanent impairment to bodily structure or function, or death. A patient could have more than one event. In all there were 350 and 414 serious adverse events reported in the triple-pill and placebo groups, respectively.

**Binomial regression model.

††Includes 59 patients in the triple-pill group and 21 patients in the placebo groups who had ≥20% change in serum creatinine from the bseline value, which was a protocol requirementd.

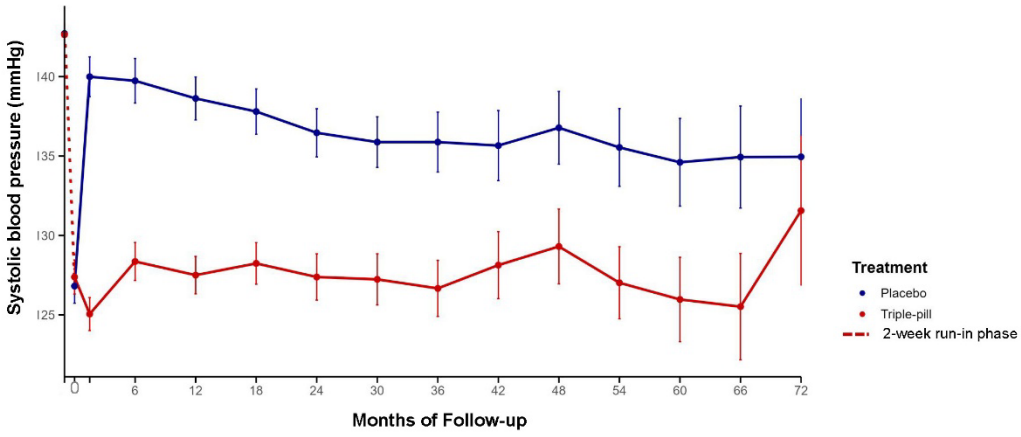
Figure 1. Mean systolic blood pressure over time

Figure 2. Cumulative Incidence Event Curves for (A) Any Stroke, (B) Any Intracerebral Hemorrhage (C) Any Major Cardiovascular Event (Death from Cardiovascular Causes, Recurrent Myocardial Infarction, or Stroke), and (D) Death from Cardiovascular Causes.

Footnote: The inset shows a magnified version of the graph.

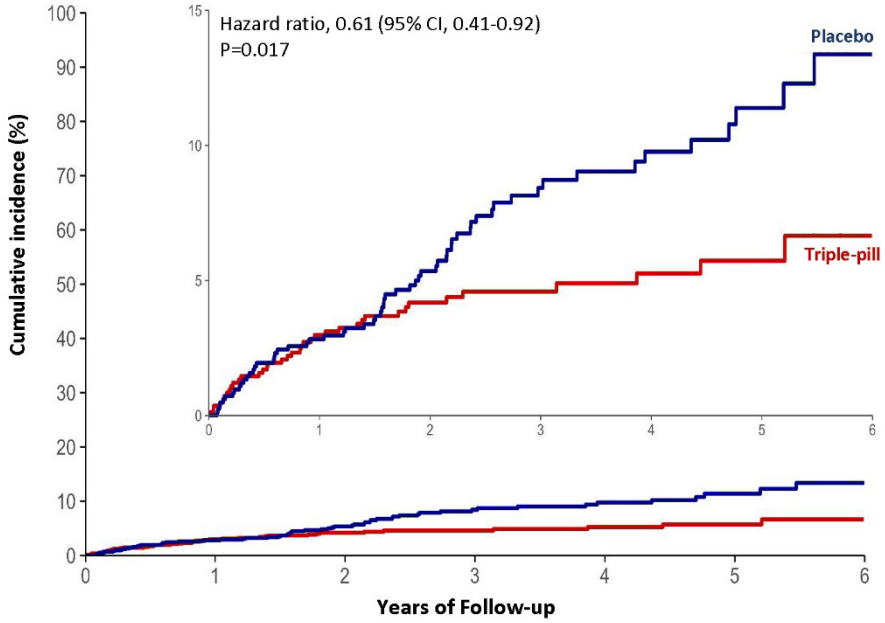
Figure 3. Primary Outcomes According to Prespecified Subgroups.

Figure 1. Mean systolic blood pressure over time



Mean No. of Background Antihypertensive Drugs per Patient													
Placeb	1.2	1.5	1.7	1.8	1.8	1.9	1.9	2.0	2.0	2.0	1.9	2.0	2.1
Triple-	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
No. at Ris													
Placebo	837	748	686	613	497	399	316	261	218	187	123	85	61
Triple-pill	833	746	695	623	504	412	323	265	230	189	136	82	63

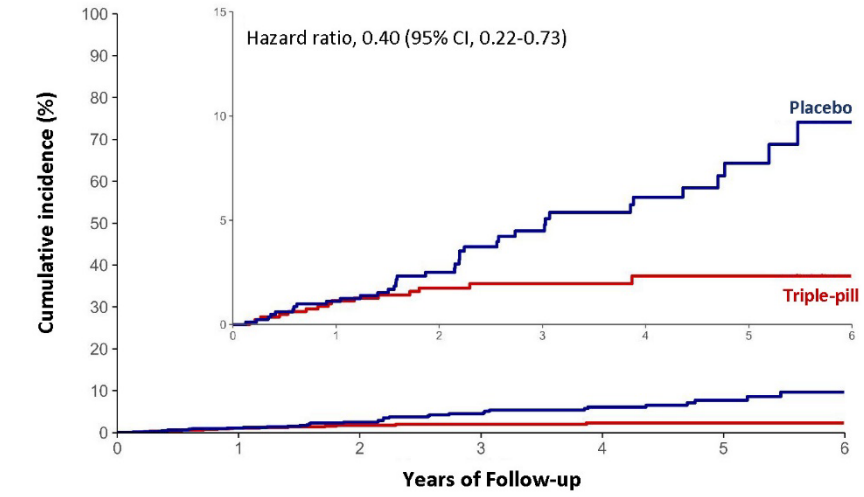
Figure 2A. Time to first occurrence of any stroke



No. at Risk

Triple-pill	833	734	518	330	250	120	52
Placebo	837	738	517	315	237	123	55

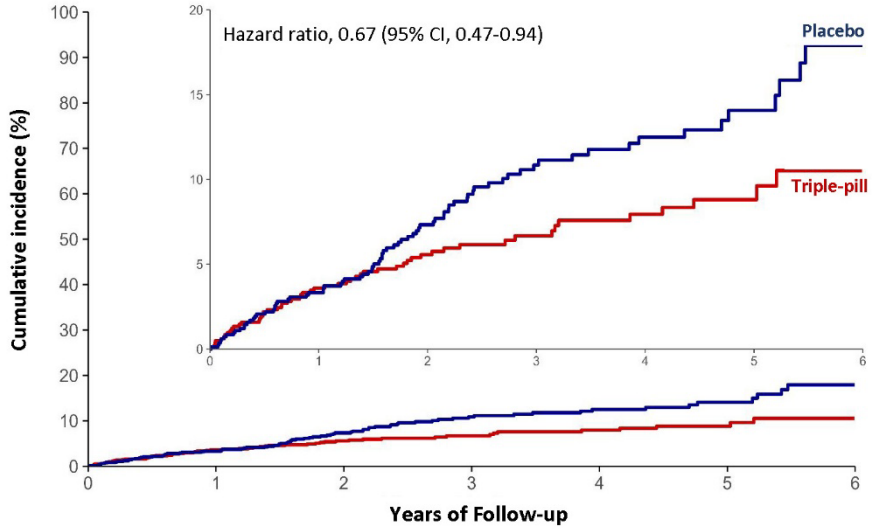
Figure 2B. Time to first occurrence of intracerebral hemorrhage



No. at Risk

Triple-pill	833	744	529	337	256	125	55
Placebo	837	748	529	326	245	128	58

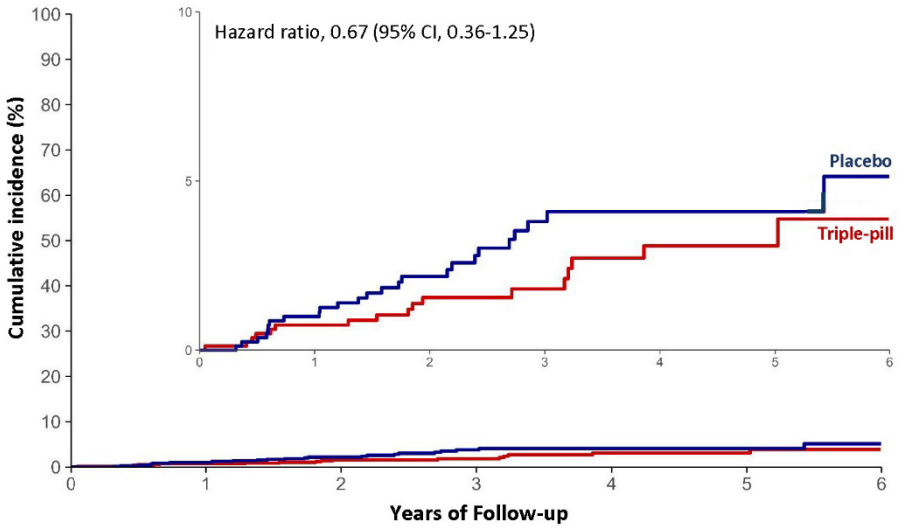
Figure 2C. Time to any major cardiovascular event



No. at Risk

Triple-pill	833	733	516	327	247	118	51
Placebo	837	737	513	313	234	122	54

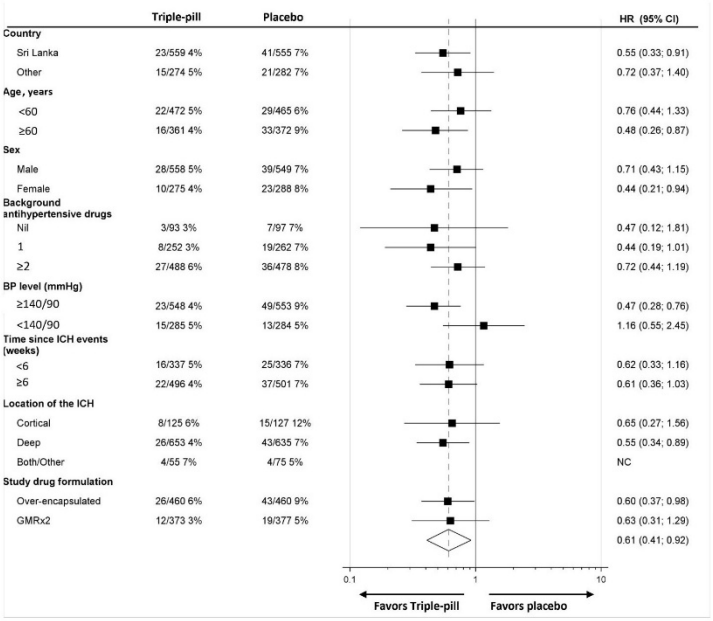
Figure 1D. Time to cardiovascular death



No. at Risk

Triple-pill	833	751	537	343	261	128	55
Placebo	837	753	538	332	251	133	60

Figure 3. Subgroup analysis



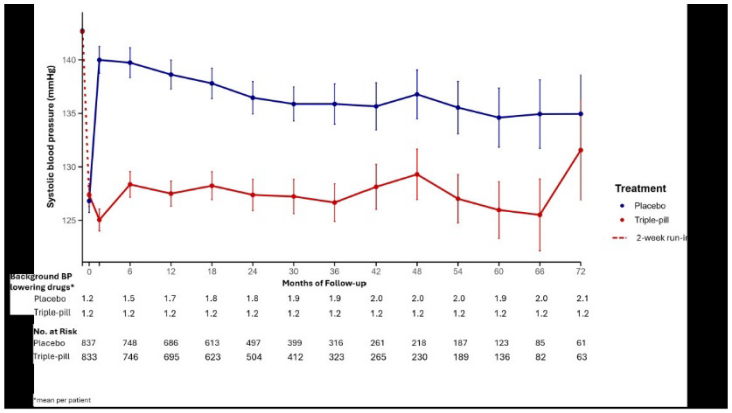


Figure 1

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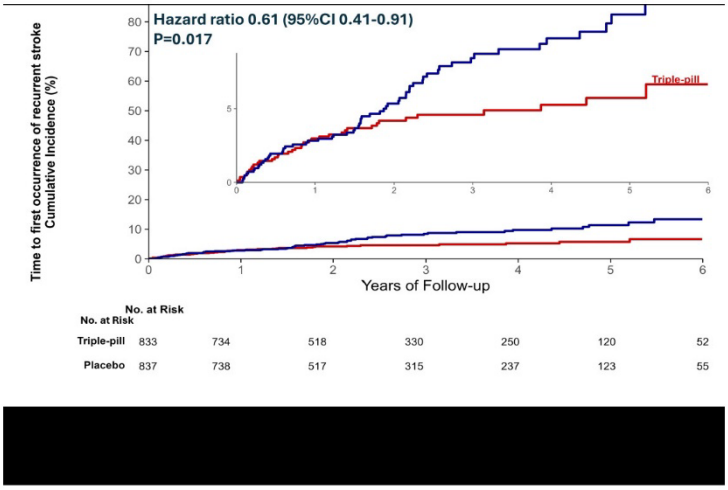

Figure 2

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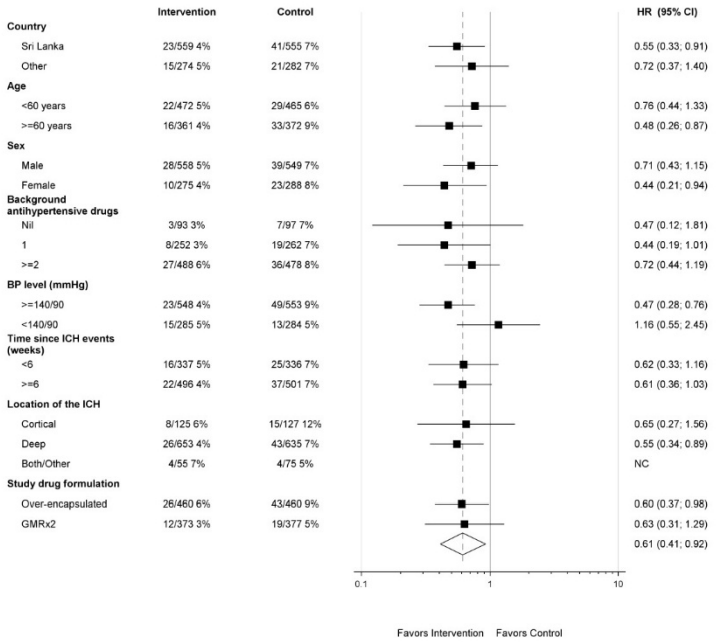

Figure 3

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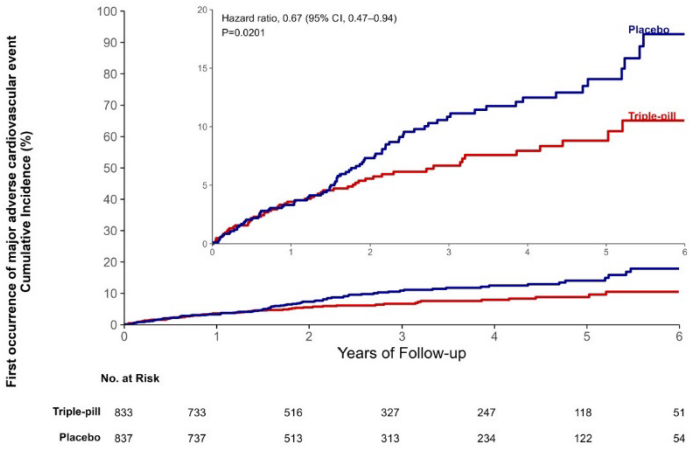

Figure 2c

228x152mm (300 x 300 DPI)

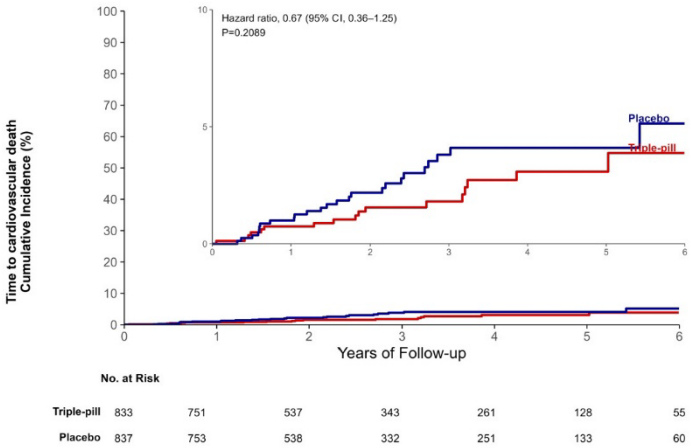

Figure 2D

228x152mm (300 x 300 DPI)

9.3 Supplementary material of Chapter V

9.3.1 Post-COVID-19 condition: a sex-based analysis of clinical and laboratory trends

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EDITED BY
César Fernández-de-las-Peñas,
Rey Juan Carlos University, Spain

REVIEWED BY
Martin Helán,
St. Anne's University Hospital, Czechia
Elham Jamshidi,
Johns Hopkins University, United States
Zaki A. Sherif,
Howard University, United States

*CORRESPONDENCE
Paula Muñoz Venturelli
paumunoz@udd.cl

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Post-COVID-19 condition: a sex-based analysis of clinical and laboratory trends

Carlos Delfino[1], M. Cecilia Poli[2,3,4], Cecilia Vial[2,5], Pablo A. Vial[2,5], Gonzalo Martínez[6], Amy Riviotta[1], Catalina Arbat[2], Nicole Mac-Guire[2], Josefina Hoppe[2], Cristóbal Carvajal[7] and Paula Muñoz Venturelli[1,8,9]*

[1]Centro de Estudios Clínicos, Instituto de Ciencias e Innovación en Medicina (ICIM), Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile, [2]Facultad de Medicina Clínica Alemana de Santiago, Universidad del Desarrollo, Santiago, Chile, [3]Programa de Inmunogenética e Inmunología Traslacional, Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina, Santiago, Chile, [4]Unidad de Inmunología y Reumatología, Hospital Roberto del Río, Santiago, Chile, [5]Programa de Hantavirus y Zoonosis, Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina, Santiago, Chile, [6]Departamento de Enfermedades Cardiovasculares, Pontificia Universidad Católica de Chile, Santiago, Chile, [7]Centro de Informática Biomédica, Instituto de Ciencias e Innovación en Medicina (ICIM), Facultad de Medicina Clínica Alemana—Universidad del Desarrollo, Santiago, Chile, [8]Servicio de Neurología, Departamento de Neurología y Psiquiatría, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana—Universidad del Desarrollo, Santiago, Chile, [9]The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia

Background and aim: Post-COVID-19 condition (PCC) encompasses long-lasting symptoms in individuals with COVID-19 and is estimated to affect between 31–67% of patients, with women being more commonly affected. No definitive biomarkers have emerged in the acute stage that can help predict the onset of PCC, therefore we aimed at describing sex-disaggregated data of PCC patients from a local cohort and explore potential acute predictors of PCC and neurologic PCC.

Methods: A local cohort of consecutive patients admitted with COVID-19 diagnosis between June 2020 and July 2021 were registered, and clinical and laboratory data were recorded. Only those <65 years, discharged alive and followed up at 6 and 12 months after admission were considered in these analyses. Multivariable logistic regression analysis was performed to explore variables associated with PCC (STATA v 18.0).

Results: From 130 patients in the cohort, 104 were contacted: 30% were women, median age of 42 years. At 6 months, 71 (68%) reported PCC symptoms. Women exhibited a higher prevalence of any PCC symptom (87 vs. 60%, $p = 0.007$), lower ferritin ($p = 0.001$) and procalcitonin ($p = 0.021$) and higher TNF levels ($p = 0.042$) in the acute phase compared to men. Being women was independently associated to 7.60 (95% CI 1.27–45.18, $p = 0.026$) higher risk for PCC. Moreover, women had lower return to normal activities 6 and 12 months.

Conclusion: Our findings highlight the lasting impact of COVID-19, particularly in young women, emphasising the need for tailored post-COVID care. The lower ferritin levels in women are an intriguing observation, warranting further research. The study argues for comprehensive strategies that address sex-specific challenges in recovery from COVID-19.

KEYWORDS

post COVID-19 condition, long COVID, COVID-19, sex-disaggregated, neurologic long-COVID-19

Background

Since the declaration of the COVID-19 pandemic in March 2020, approximately 760 million individuals worldwide have been diagnosed with SARS-CoV-2 infection (1). Beyond the acute phase of the illness, some people experience ongoing symptoms, known as post-COVID-19 condition (PCC). PCC includes individuals with confirmed or probable COVID-19 who continue to have symptoms or develop new ones at least 3 months after the initial infection, lasting for at least 2 months (2). Studies suggest that a staggering 31 to 67% of patients infected with SARS-COV-2 endure these post-acute sequelae (3).

Among the published findings related to PCC, a stark disparity emerges, with women facing a significantly higher risk compared to men (63.2% vs. 36.8%) (4). It has also been proposed that the severity of the acute infection and BMI (5) may increase the risk of developing PCC, although this remains a topic of ongoing debate (6). Both systemic inflammation and neuroinflammation, as well as microvascular injury and thrombosis are critical to COVID-19 pathobiology (7, 8). Among these, the NLRP3 inflammasome plays a prominent role, triggering the release of highly inflammatory cytokines (e.g., IL-1β and IL-18) (9). Activation by SARS-CoV-2 of this complex results in the downstream production of interleukin-6 and C-reactive protein (CRP) (10). Additionally, the central nervous system can initiate an immune response through inflammasome activation (11). Moreover, a common genetic polymorphism (NLRP3 rs10754555 variant) has been reported to enhance systemic inflammation and inflammasome activity in patients with atherosclerosis, with those with the C/G and G/G genotype being at higher risk (12). This polymorphism may potentially influence the severity of COVID-19 and the neurological symptoms experienced by affected individuals. As of now, no biomarkers have emerged during acute COVID-19 that can predict the occurrence of PCC (13).

Because of the described sex predisposition to PCC, in this study, we sought to describe clinical and immunological profiles of acute COVID-19 patients, focusing on sex-specific analysis and potential predictors of PCC including comprehensive acute inflammatory and immunological response.

Methods

Study design, patients, and endpoints definitions

These analyses are based on a prospective single-centre cohort study conducted at Clínica Alemana Santiago, Chile. Patients under 65 years of age who were admitted for COVID-19 between June 2020 and July 2021 (corresponding to the two first waves of the pandemic) were consecutively enrolled. During this initial phase of the pandemic, where clinical assessments were severely restricted and there was a risk of underreporting comorbidities, we made the decision to concentrate on a younger demographic. This approach aimed to mitigate potential comorbidities that could independently contribute to poorer outcomes. During this period, the predominant circulating variants were Gamma (51.7%), Lambda (22.8%), and Alpha (6%) (14). Only patients who were discharged alive were included in the follow-up at 6 and 12 months. Detailed records of their previous medical history and acute clinical data upon admission were collected. Acute information regarding the patients was gathered during the initial 11 days of their hospitalization. The study protocol was approved by the local Ethics Committee (2022–33) and informed consent from all participants was obtained.

Baseline clinical-laboratory parameters including white blood cell count, ESR, CRP, ferritin and procalcitonin were measured at the time of acute hospital admission. In addition, acute phase samples were collected for comprehensive inflammatory response assessment including quantification of serum amyloid levels, inflammatory cytokines (IL-1β, IL-6, IL-8, IL-10, IL-12, IL-18, TNF) and chemokines (CCL2, CCL5, CCL8, CXCL9, CXCL10). Furthermore, samples were tested for the presence of the NLRP3 polymorphism (variant rs10754555), considering the C/G and G/G alleles as risk genotypes (12).

Following discharge, assessments were conducted by telephone interviews at 6 and 12 months to identify the presence of PCC symptoms using a structured questionnaire. These assessments utilized a structured questionnaire encompassing cognitive, cardiovascular, and gastrointestinal symptoms, as well as fatigue levels and return to normal activities. (Supplementary Table S1). Questions were related to current symptoms, therefore only those patients who still had symptoms at the time of the call were considered in the PCC group.

Statistical analysis

Quantitative variables are reported as means ± SD or median (IQ range) depending on the normality (K-S test) and were compared using *T* Test or Mann–Whitney U test. Qualitative variables are reported as absolute and % prevalence and compared using the χ^2 test or Fisher's exact test. A multivariable logistic regression analysis was performed to explore variables associated with PCC. The variables were identified by univariate logistic regression analysis, including those that correlated significantly with the symptoms at follow-up and clinically significant variables were also included. In this analysis, we considered sex, age, BMI, data of acute care clinical setting, and comorbidities. Multivariable logistic regression was done to obtain an adjusted odds ratio with a 95% confidence interval. STATA version 18.0 was used to perform the analyses.

Results

During the study period, a total of 130 patients under 65 years were discharged alive (Figure 1). At 6 months, 104 patients completed the follow up assessment. Patients had a median age of 42 years (IQR 37–56) and 30% were women (Table 1). Most of them had no comorbidities (64%), while a minority had been previously vaccinated against COVID-19 (19%), and only 11% required invasive mechanical ventilation (IMV). Regarding the acute laboratory findings and immune biomarkers obtained during acute hospitalization, it was noted that women had significantly lower ferritin values compared to men (465 vs. 1,141 ng/mL $p = 0.004$). No differences were found for inflammatory cytokines, chemokines or the presence of the NLRP risk variant (Table 1 and Supplementary Figures S1–S3).

At 6 months, 71 out of 104 patients (68%) met the criteria for PCC, with a higher proportion of women (87 vs. 60%, $p = 0.007$) (Table 2). Of relevance, significant differences were observed between sexes. Women reported higher presence of cognitive (52 vs. 25% $p = 0.007$), cardiovascular (26 vs. 10% $p = 0.031$), and gastrointestinal (32 vs. 8% $p = 0.022$) symptoms compared to men. The evaluation of return to

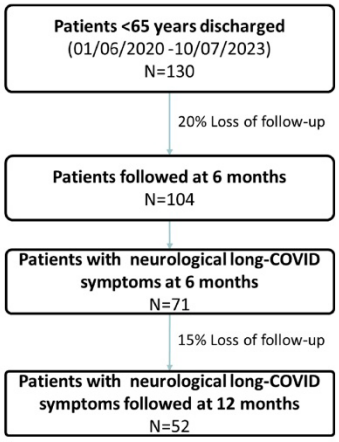

FIGURE 1
Study flowchart.

usual activities revealed a noteworthy gap: only 61% of women managed to resume their normal routines, whereas a substantial 90% of men with PCC achieved the same ($p < 0.001$). A comparison between those with and without PCC revealed a higher proportion of women in the former group (27 vs. 4, $p = 0.007$), as well as a greater requirement for IMV (11 vs. 0, $p = 0.017$) (Table 2). Nevertheless, no significant differences were observed in other clinical characteristics or blood test results (Table 2 and Supplementary Figures S4–S6). Moreover, 97% of individuals in the non-PCC group successfully resumed their usual activities compared to 75% within the PCC group ($p = 0.006$). In the group without PCC symptoms at 6 months, there were no significant differences between men (29/33) and women (4/33).

In the PCC group, there were differences regarding laboratory findings during hospitalisation between sexes: women exhibited lower levels of ferritin (470 vs. 1,695 ng/mL, $p = 0.001$) and procalcitonin (0.06 vs. 0.11, $p = 0.021$), but higher TNF values (0.26 vs. 0, $p = 0.042$) compared to men in the acute phase (Table 2; Figure 2; Supplementary Figures S4–S6). Being women was the only independent predictor factor for PCC at 6 months, as they were 7.60 times more likely to experience it compared to men ($p = 0.026$, CI 1.27–45.18, Supplementary Figure S7).

At 12 months, 87% of patients with previous PCC at 6 months still had symptoms but showed no evident clinical or laboratory differences by sex (Supplementary Table S2). Importantly, in this subgroup, only 56% of women were able to return to their regular activities, as opposed to 86% of men ($p = 0.004$).

Discussion

The results of our study provide valuable information on the lasting impact of COVID-19 among adults under the age of 65 with non-critical disease. Despite a higher initial admission rate of men for COVID-19, PCC affected predominantly women. Specifically, they reported a higher prevalence of cognitive, cardiovascular, and gastrointestinal compromise. This is in line with previous reports (15–17), although it is noteworthy that these women did not have other concurrent comorbidities, as has been observed in other cohorts (18).

Only female sex was found to be predictive of subsequent PCC. This finding is consistent with previous research, which highlights the notable association between the risk of PCC and specific socio-demographic factors, in particular female sex (19). Although some studies have hinted at possible links with ethnicity or pre-existing conditions (such as poor mental and general health or asthma), there is a lack of consistent evidence across studies to designate these as reliable predictors of PCC (20–22). Despite this, we observed clear acute differences in ferritin and procalcitonin levels between sexes, with lower levels in women than in men. Many studies have found a link between elevated ferritin levels and increased risk of death. However, the relationship is complex, and other factors can play a role (19, 20). It should be noted that, to our knowledge, no previous research has specifically examined sex disparities in ferritin values among patients with mild COVID-19. However, the lower ferritin values observed in women could be attributed to the fact that they experience a milder acute infectious course. In addition, women showed higher TNF values than men. This is consistent with recent studies that have indicated elevated TNF levels in patients with post-COVID symptoms, suggesting its potential role as a predictor of PCC (21). This finding could be related to variations in immune response, hormonal factors, or other underlying biological mechanisms. The absence of notable disparities in inflammatory cytokines, chemokines and the NLRP3 risk variant suggests a more nuanced interaction between sex and immune response in COVID-19. At 12-month follow-up, we observed that patients with PCC had no significant clinical or laboratory differences, suggesting a possible stabilisation or stagnation of symptoms in this subgroup, possibly influenced by different factors such as the initiation of COVID-19 vaccination (20).

In terms of the return to daily activities, when comparing individuals with and without PCC, the PCC-affected group demonstrated greater difficulty resuming their usual routines (75% vs. 97%, $p = 0.006$). Within the PCC group, women showed significantly lower rates of resumption of usual activities compared to men, both at 6-and 12-months follow-up. This observation points to a possible impact on quality of life and highlights the specific obstacles that women may encounter during their recovery process. This may be associated with a higher prevalence of neuropsychiatric symptoms (23) and the societal expectation that males often shoulder the primary role in household support. It underlines the need for personalised care plans after COVID-19, especially adapted to female patients.

The results herein support the need to establish PCC assessment in all adults in the aftermath of COVID-19, particularly in women, as predictive factors in the acute setting remain elusive.

To the best of our knowledge, this represents the largest cohort of COVID-19 patients with a 12-month follow-up, coupled with a comprehensive evaluation of inflammatory biomarkers. This is especially significant as obtaining blood samples during the early stages of the pandemic posed considerable challenges, given the limited availability of specific laboratory reagents and the associated costs of analysis. Notably, this cohort primarily comprised individuals affected during the two initials waves of the pandemic; therefore, effects of infection can be assessed independently of vaccination, which could be confounding.

TABLE 1 Demographic, clinical characteristics and inflammatory parameters of study participants.

	Total	Women	Men	*p*
N (%)	104	31 (30)	73 (70)	
Age, years*	42 (37–56)	44 (35–59)	41 (37–55)	0.741
BMI (kg/cm2)* (*n*=89)	27.99 (25.81–30.83)	27.63 (25.39–31.82)	28.27 (26.29–30.39)	0.921
Charlson Comorbidity Index=0 (no comorbidity), (*n*, %)	67 (64)	20 (64.5)	47 (64.3)	0.99
Length of hospitalization in days*	5 (4–6)	4 (3.5– 6.5)	5 (4–6)	0.855
IMV requirement (*n*, %)	11 (11)	3 (9)	8 (11)	0.846
Vaccination before the 6–month call (*n*, %)	20 (19)	6 (19)	14 (19)	0.983
Blood exams during hospitalization*				
WBC, /mm3	7450 (0.597–10200)	7100 (4500–1020)	7800 (6200–10200)	0.272
VHS (mm/h)	43 (27–58)	38 (24–56)	44 (29–60)	0.315
Highest value of CRP (mg/L)	2.64 (1.4–4.75)	3.08 (1.35–5.2)	2.63 (1.42–4.60)	0.762
Ferritin (ng/mL, *n*=77)	1010 (453–1722)	465 (236–1261.55)	1141 (700–1805)	0.004
Procalcitonin (ng/mL, *n*=79)	0.06 (0.02–0.09)	0.07 (0.04–0.11)	0.09 (0.06–0.16)	0.109
Serum Amiloide (mg/L)	327.32 (116.39–954.25)	265.8 (74.92–265.8)	446.6 (131.5–973.4)	0.584
Inflammatory cytokines during hospitalization*				
IL-1b (pg/mL)	4.82 (4.19–5.30)	4.52 (4.21–5.15)	4.86 (4.17–5.46)	0.288
IL-6 (pg/mL)	9.12 (6.26–19.89)	13.18 (6.64 –21.27)	8.23 (6.04–16.89)	0.198
IL-8 (pg/mL)	15.89 (11.49–25.76)	20.81 (12.43–26.36)	14.77 (11.35–24.30)	0.228
IL-10 (pg/mL)	4.29 (2.27–6.02)	4.07 (2.33–5.35)	4.36 (2.16–6.39)	0.596
IL-12 (pg/mL)	0.82 (0.40–1.47)	0.83 (0.34–1.17)	0.83 (0.42–1.49)	0.283
IL-18 (pM)	12.44 (9.18–16.62)	12.24 (7.21–15.94)	12.46 (9.45–18.06)	0.156
TNF (pg/mL)	0.12 (0–0.58)	0.26 (0–0.74)	0.09 (0–0.37)	0.136
Chemokines during hospitalization*				
CCL2 (pg/mL)	72.67 (42.89–119.68)	80.75 (51.57–122.49)	63.33 (37.77–119.59)	0.207
CCL5 (pg/mL)	17148.09	18016.27	16903.78	0.8
	(11475.71–25592.55)	(10798.15–25275.10)	(11592.01–25909.99)	
CXCL8 (pg/mL)	8.33 (5.30–19.27)	11.11(5.85–19.88)	7.91 (5.08–17.56)	0.346
CXCL9 (pg/mL)	173.18 (79.76–298.26)	170.34 (67.42–249.31)	192.18 (84.87–308.11)	0.399
CXCL10 (pg/mL)	544.20 (322.43–1118.59)	589.43 (363.46–1208.57)	519.84 (292.96–954.78)	0.567
Risk NLRP3 genotype** (*n*, %)	64 (62)	18 (58)	46 (63)	0.774

*Values expressed as median and interquartile range (IQR), BMI: body mass index, IMV: Invasive mechanical ventilation; WBC, white blood cells; CRP, C reactive protein. **C/G and G/G alleles were considered risk genotypes.

Our study has remarked limitations that deserve to be acknowledged. First, it is a single-centre investigation conducted in a relatively uniform cohort of patients with moderate COVID-19 severity, because of challenges associated to consenting acute severe patients for the study or had died at follow up. In addition, participants were under 65 years old. Therefore, larger scale studies covering a broader spectrum of patients, including those who did not require hospitalisation and with more comorbidities, are essential to validate these findings. Second, our admission information was limited to 11 days, potentially leading to loss of relevant information from the acute phase. However, the comprehensive characterisation of acute patients, including assessment of inflammatory markers and evaluation of risk genotypes, lends strength to the study results. Finally, discharge follow-up was conducted by telephone and employing a concise questionnaire with broad questions regarding PCC symptoms, which could introduce bias in the results by restricting participation to those who could answer the call and incomplete information. Throughout the pandemic, numerous studies have employed similar methodologies, demonstrating their reliability (22–24). Unlike other studies with high non-response rates or unreachable participants, our study had only a 20% dropout rate at 6 months and a 15% dropout rate at 12 months (25). Nevertheless, it is likely that our results are more representative of a younger, healthier population, whereas frail subjects are under-represented in our study.

Conclusion

In summary, our study emphasizes the significance of acknowledging and addressing sex-specific nuances among COVID-19 survivors. These

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TABLE 2 Relevant acute phase characteristics and reported symptoms at 6 months.

a. Sex-based differences in symptom profiles at 6 months' follow-up				
	Women (n = 31)	Men (n = 73)	p	Total (n = 104)
Any symptoms referred at 6 months (PCC), n (%)	27 (87)	44 (60)	0.007	71 (68)
Cognition	16 (52)	18 (25)	0.007	34 (32)
Fatigue	16 (52)	27 (37)	0.166	43 (41)
Cardiovascular	8 (26)	7 (10)	0.031	15(14)
Gastrointestinal	10 (32)	6 (8)	0.022	16 (15)
Return to daily duties at 6 months	19 (61)	66 (90)	< 0.001	66 (90)

b. Differential analysis of demographic and laboratory characteristics at 6 months: patients with and without PCC						
	With PCC (n = 71)				Without PCC (n = 33)	p***
	Women (n = 27)	Men (n = 44)	p**	Total		
Age, years*	45 (36–59)	43 (37.5–55)	0.669	44 (37–56)	40 (37–56)	0.216
BMI (kg/cm2) (n = 89)	27.06 (25.42–31.93)	28.40 (26.54–30.86)	0.744	28.19 (25.71–31.56)	27.98 (26.15–29.38)	0.364
Charlson Comorbidity Index = 0 (no comorbidity), (n, %)	17 (63)	28 (63)	0.955	45 (63)	22 (67)	0.745
Length of hospitalization in days	5 (4–7)	5 (4–7)	0.891	5 (4–7)	4 (4–6)	0.081
IMV requirement (n, %)	3 (11)	8 (18)	0.424	11 (15)	0	0.017
Vaccination before the 6-month call (n, %)	4 (14)	8 (18)	0.713	12 (17)	5 (15)	0.313
Blood exams during hospitalization*						
Ferritin (ng/mL)	470 (332–1190.8)	1,695 (849.75–2279.55)	0.001	1,062 (519–1805)	876.55 (340.351433)	0.178
Procalcitonin (ng/mL)	0.06 (0.05–0.12)	0.11 (0.08–0.18)	0.021	0.1 (0.06–0.16)	0 0.08 (0.04–0.12)	0.082
Seric Amiloide (mg/L)	265.8 (74.92–990.6)	379.17 (123.14–987.65)	0.549	311.74 (114.8–988.6)	363.36 (117.99–890.67)	0.880
TNF (pg/mL)	0.26 (0–1.38)	0 (0–0.312)	0.042	0 (0.10–0.59)	0.020 (0–0.62)	0.203

PCC: Post COVID Condition; BMI: body mass index; IMV: Invasive mechanical ventilation. *values expressed as median and interquartile range (IQR). ** p-values reflect comparisons between men and women with PCC. *** p-values comparing total patients with and without PCC.

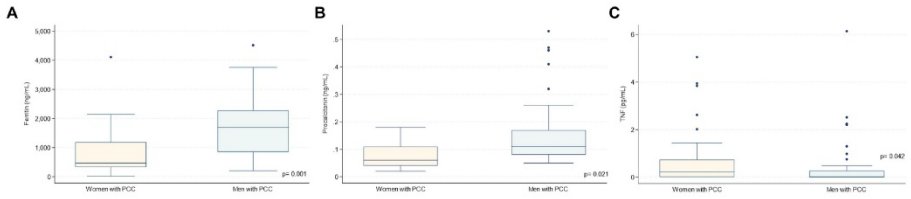

FIGURE 2
Acute phase biomarkers during hospitalisation according to sex in patients with PCC symtoms at 6 months. * PCC: post COVID-19 condition. **(A)** Ferritin, **(B)** Procalcitonin, **(C)** TNF.

findings support the need for a more individualized and comprehensive approach to post-COVID care, with particular attention to the distinct challenges encountered by female patients. Further research is essential to elucidate the underlying mechanisms contributing to these disparities and to enhance interventions for achieving the best possible recovery and rehabilitation outcomes.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://www.ncbi.nlm.nih.gov/clinvar/, SUB14168930.

Ethics statement

The studies involving humans were approved by Centro de bioética, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CD: Data curation, Formal analysis, Validation, Writing – original draft, Investigation. MCP: Investigation, Supervision, Writing – review & editing. CV: Investigation, Methodology, Writing – review & editing. PVi: Conceptualization, Supervision, Writing – review & editing. GM: Conceptualization, Supervision, Visualization, Writing – review & editing. AR: Data curation, Investigation, Project administration, Writing – review & editing. CA: Writing – review & editing, Investigation. NM-G: Writing – review & editing, Investigation. JH: Writing – review & editing, Investigation. CC: Software, Writing – review & editing. PMV: Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1376030/full#supplementary-material

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9.3.1.1 Supplementary material

Supplementary Material

Post-COVID-19 Condition: A Sex-Based Analysis of Clinical and Laboratory Trends

Carlos Delfino, Cecilia Poli, Cecilia Vial, Pablo Vial, Gonzalo Martínez, Amy Riviotta, Catalina Arbat, Nicole MacGuire, Josefina Hoppe, Cristóbal Carvajal, Paula Muñoz Venturelli

- Supplementary tables:2
- Supplementary figures: 7

Supplementary tables

Table S1. Structured questionnaire applied at 6 months.

	Yes	No	Comment
Cognitive			
Compared to your pre-COVID-19 state, do you feel that you have worse concentration or forget things easier?			
Fatigue			
Do you get more tired during physical activity than before COVID-19?			
Cardiovascular			
Have you experienced new or more tachycardia or palpitations when you are at rest compared to your pre-COVID state??			
Gastrointestinal			
Have you developed new food intolerances and/or recurrent diarrhoea and/or constipation compared to your pre-COVID state?			
Return to usual activities			
Have you been able to return to the usual activities you did before COVID-19?			

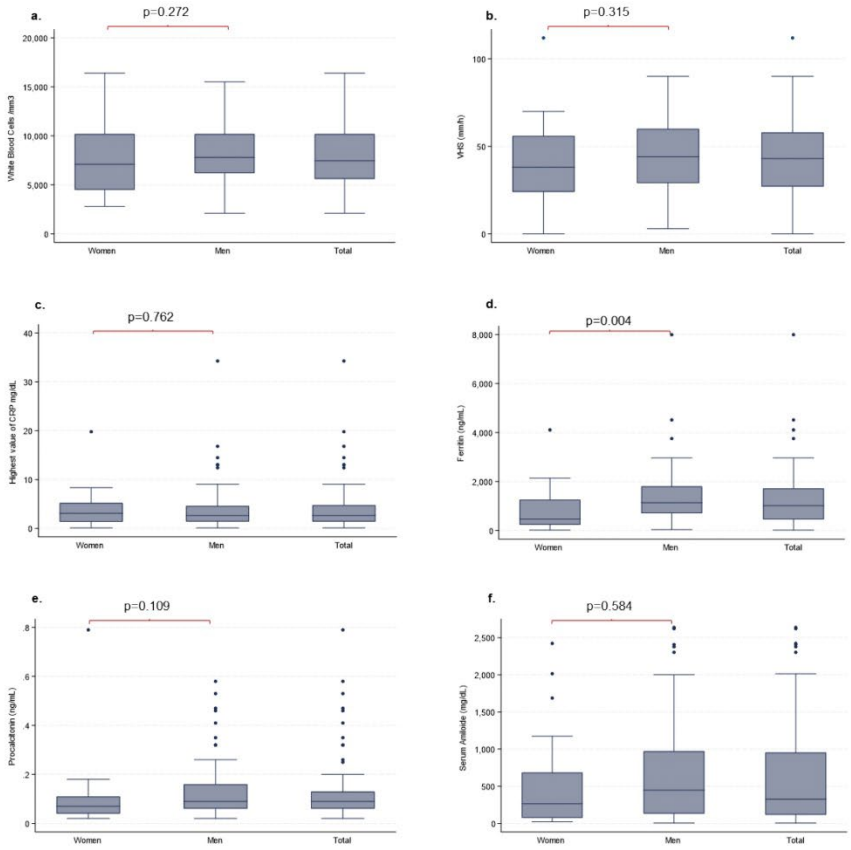
Supplementary Table 2. Post COVID-19 Condition (PCC) symptoms reported at 12 months

	Total	Women	Men	p
N (%)	52/60 (87)	23/24 (96)	29/36 (56)	0.088
Symptoms refered at 12 months, n (%)				
Cognition	30 (58)	16 (70)	14 (48)	0.123
Fatigue	33 (63)	14 (61)	19 (65)	0.730
Cardiovascular	12 (23)	7 (30)	5 (17)	0.262
Gastrointestinal	9 (17)	6 (26)	3 (10)	0.136
Return to daily duties	35 (67)	12 (52)	23 (79)	**0.038**

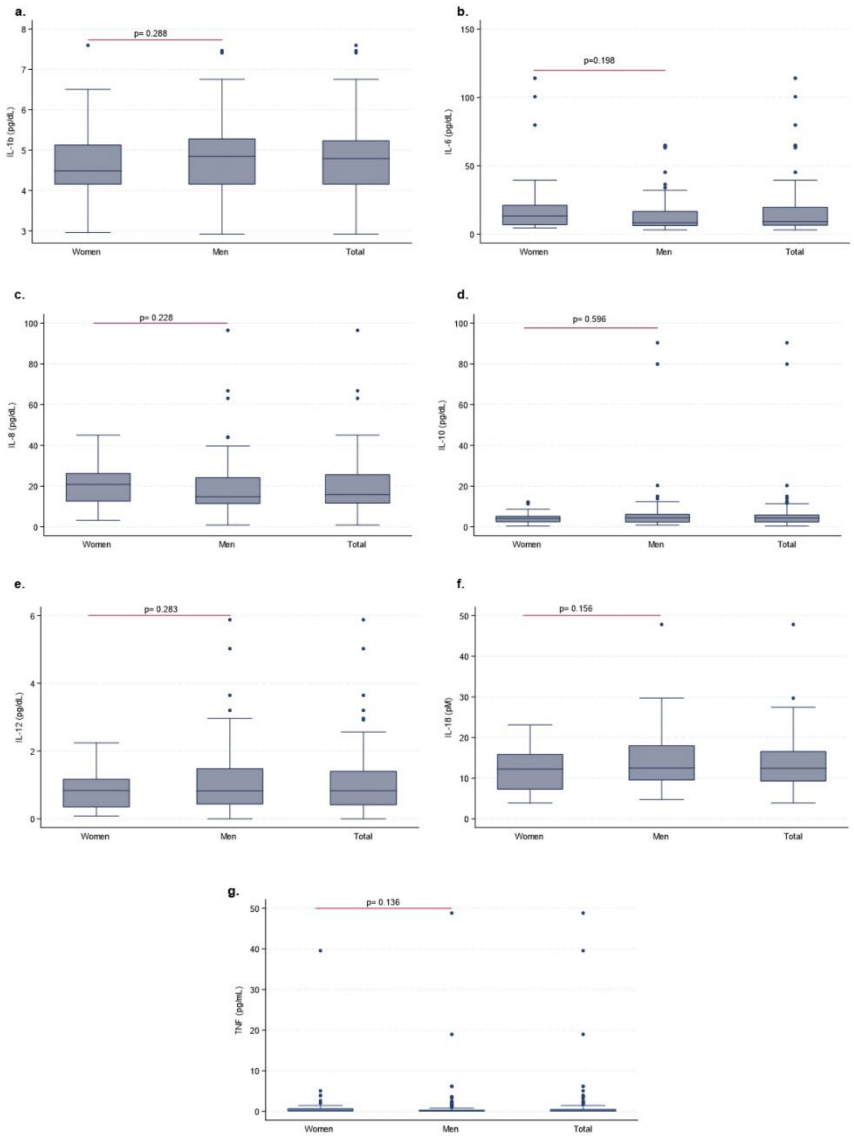
PCC: Post COVID-19 Condition

Supplementary Figures

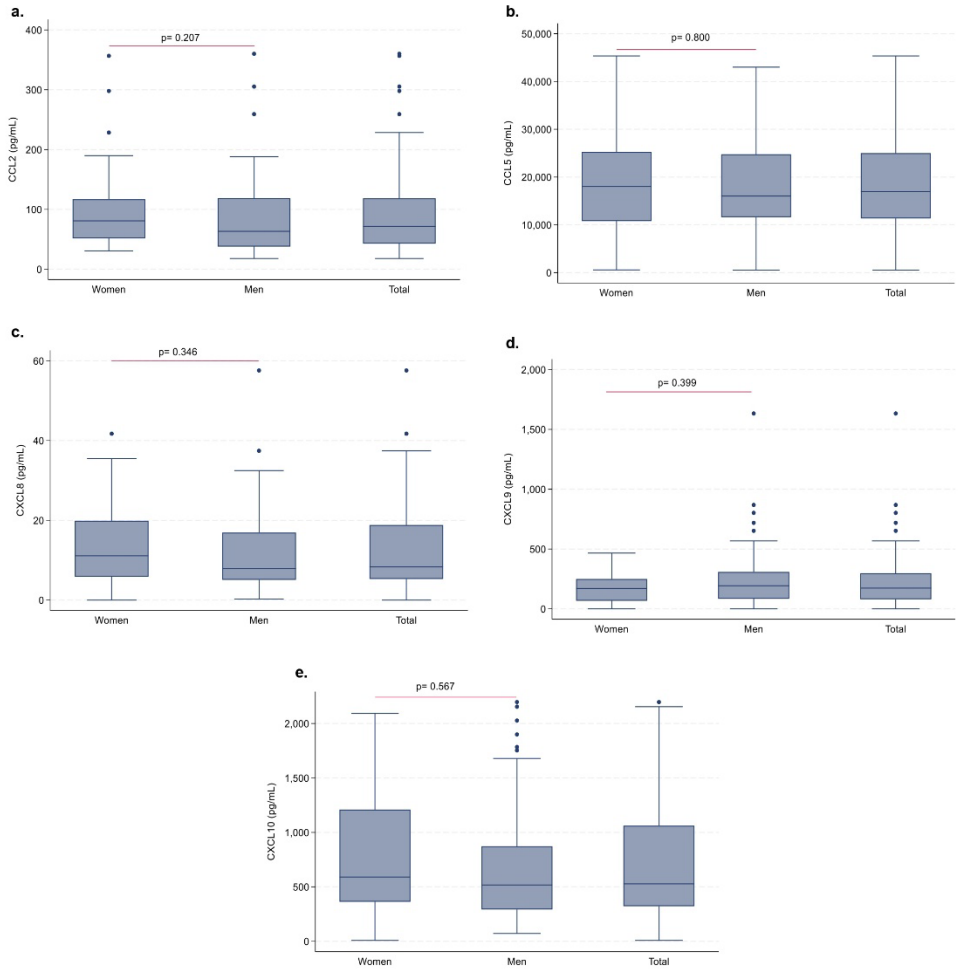
Supplementary Figure 1. Blood tests during hospitalisation of study participants (n=104)



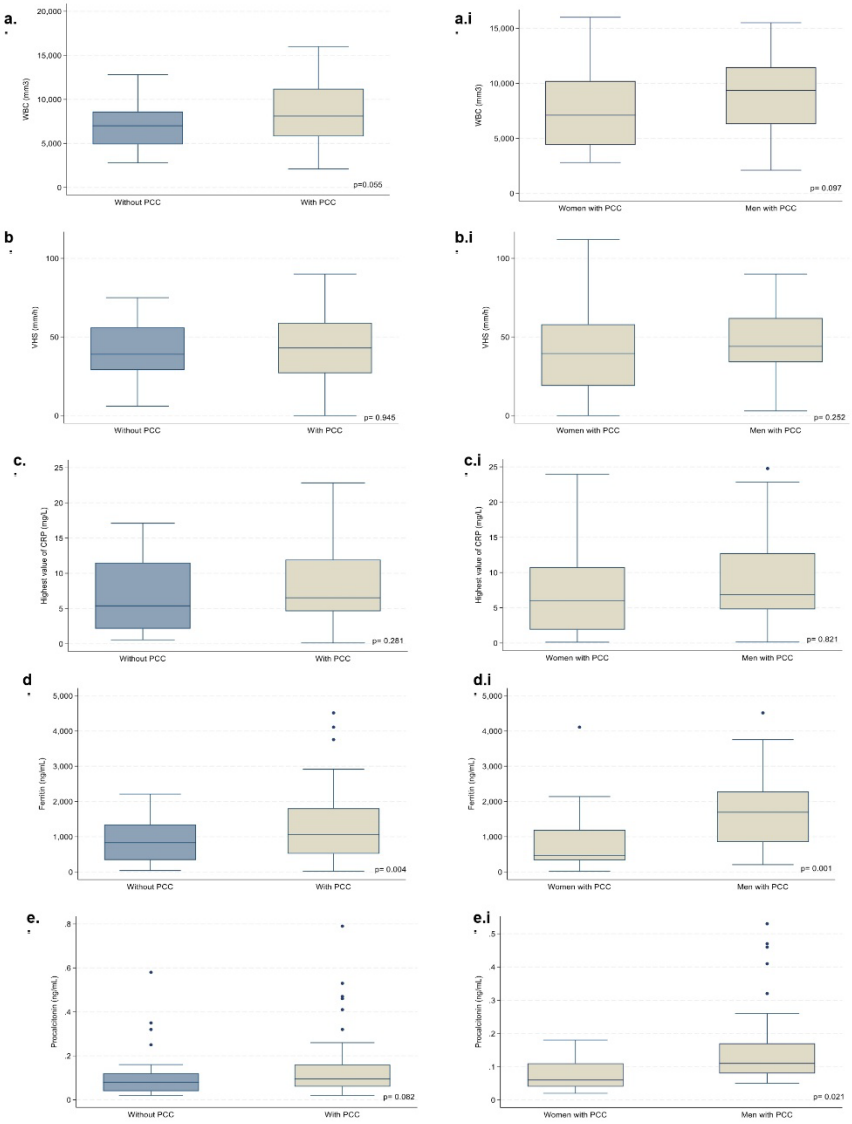
Supplementary Figure 2. Inflammatory cytokines during hospitalisation of study participants (n=104)



Supplementary Figure 3. Chemokines during hospitalisation of study participants (n=104)

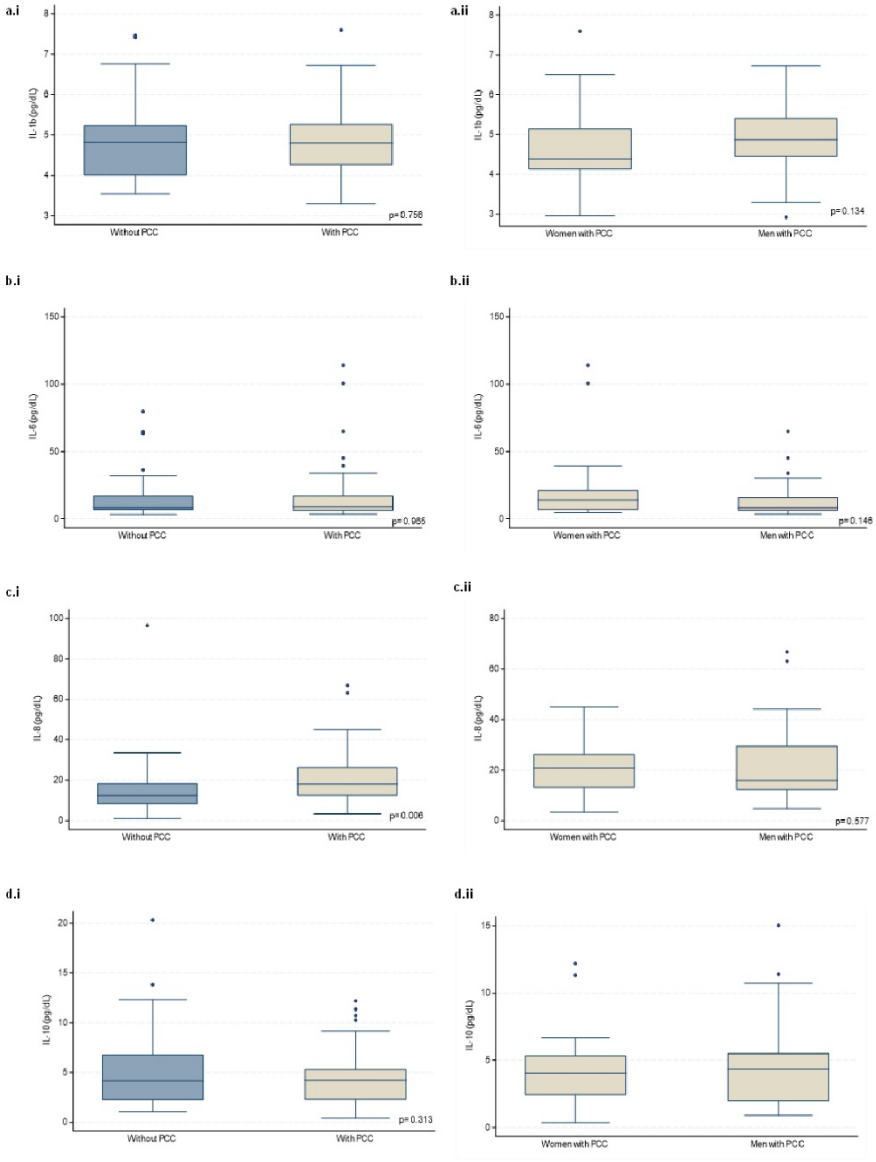


Supplementary Figure 4. Comparison of blood test results during hospitalisation: Participants with and without Post-COVID-19 condition, including sex breakdown in the affected group.

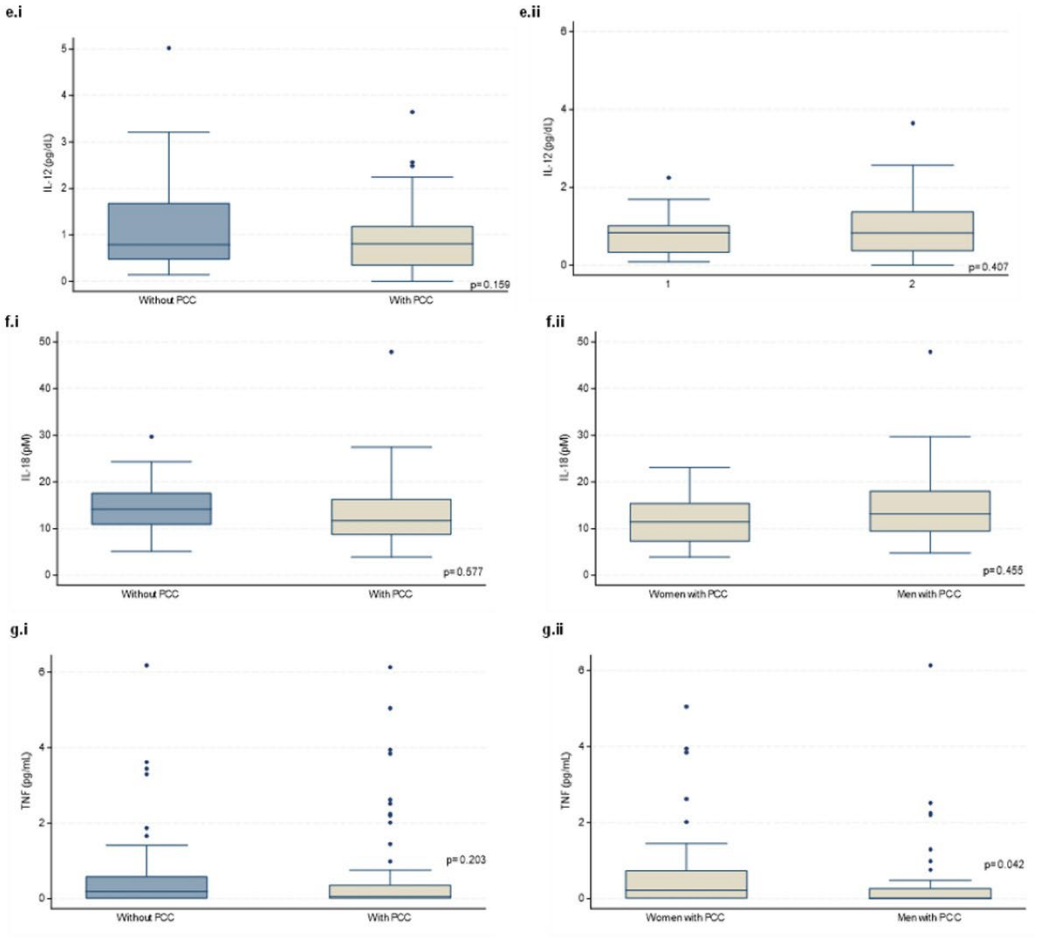


*Post-COVID-19 condition

Supplementary Figure 5. Comparison of inflammatory cytokines during hospitalisation: Participants with and without Post-COVID condition, including sex breakdown in the affected group.

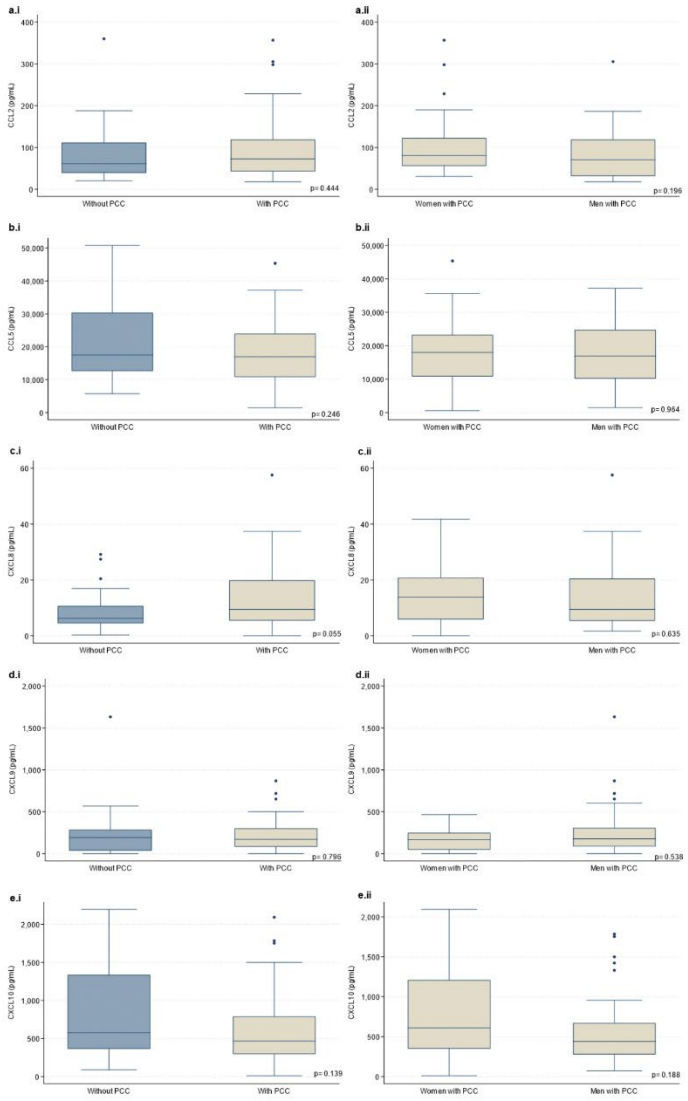


(Cont Fig 5)



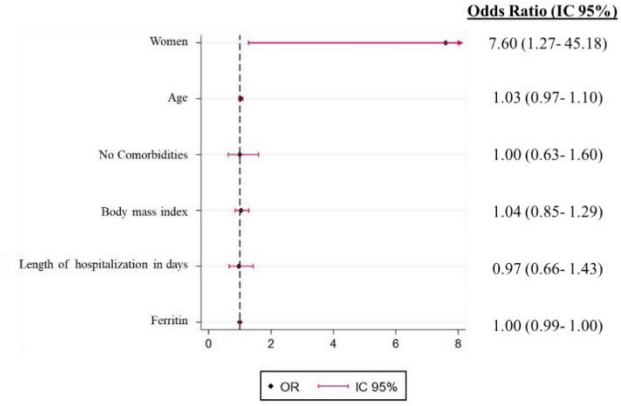
*Post-COVID-19 condition

Supplementary Figure 6. Comparison of inflammatory chemokines during hospitalisation: Participants with and without Post-COVID-19 condition, including sex breakdown in the affected group.



*Post-COVID-19 condition

Supplementary Figure 7. Predictors of Post COVID-19 condition (PCC) at 6 months



Open access Protocol

BMJ Open

STatin TReatment for COVID-19 to Optimise NeuroloGical recovERy (STRONGER): study protocol for a randomised, open label clinical trial in patients with persistent neurological symptoms after COVID-19 infection

Carlos Delfino ,[1] Cheryl Carcel ,[2] Xiaolei Lin,[3] Paula Muñoz-Venturelli ,[1,2] Sharon L Naismith,[4] Mark Woodward,[2,5] Ruth Peters,[2] Nirupama Wijesuriya,[2] Meng Law,[6] Ian H Harding,[6] Xia Wang,[2] Julian Elliott,[7] Karin Leder ,[7] Owen Hutchings,[8] Ximena Stecher ,[9] Sophia Zoungas ,[7] Craig S Anderson[2,8,10]

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For numbered affiliations see end of article.

Correspondence to
Professor Craig S Anderson; canderson@georgeinstitute.org.au

ABSTRACT

Introduction Increasing awareness of the high frequency, wide spectrum and disabling nature of symptoms that can persist following COVID-19 infection has prompted the investigation of management strategies. Our study aims to determine the effectiveness of atorvastatin on cognitive function, physical activity, mood, health-related quality of life and features of neurovascular impairment and neuroinflammation in adults with ongoing neurological symptoms after COVID-19 infection.

Methods and analysis The STatin TReatment for COVID-19 to Optimise NeuroloGical recovERy study is an ongoing international, investigator-initiated and conducted, multicentre, prospective, randomised, open label, blinded endpoint trial with fixed time points for outcome assessments. A total of 410 participants with long covid neurological symptoms were planned to be randomly assigned to either the intervention group to receive 40 mg atorvastatin for 12 months or to a control group of no treatment, on top of usual care.

Ethics and dissemination This study protocol was designed, implemented and reported, in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice, the National Health and Medical Research Council of Australia, the National Statement on Ethical Conduct in Human Research and with the ethical principles laid down in the World Medical Association Declaration of Helsinki. Central ethics committee approval was obtained from Sydney Local Health District Royal Prince Alfred Hospital Ethics (No: X21-0113 and 2021/ETH00777 10) in Australia. Site-specific ethics committee approvals were obtained elsewhere before any local study activities. All participants provided written informed consent.

Trial registration number The study protocol is registered at Clinicaltrials.gov (NCT04904536).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study was designed as a prospective, randomised, open label, blinded endpoint trial, comparing atorvastatin 40 mg to standard care for the treatment of neurological symptoms associated with long covid.
⇒ The study will be able to systematically and comprehensively characterise patients with neurological long COVID.
⇒ The study is open-label, but cross-over to the use of atorvastatin is unlikely, and the primary outcome measure is objective.

INTRODUCTION

The epidemiological pattern and clinical spectrum, pathogenesis and complications in people infected with SARS-CoV-2 have been well-described.[1 2] However, it is increasingly recognised that many patients have persistent symptoms, in particular, related to cardiorespiratory, mobility, cognitive and psychological function.[3–5] This phenomenon has been termed 'long COVID' to describe symptoms that continue or develop after acute COVID-19, arbitrarily defined as either ongoing symptomatic COVID-19 (from 4 weeks to 12 weeks) or post-COVID-19 syndrome (12 weeks or more).[6]

As many as three-quarters of patients have at least one ongoing symptom several months after onset of the infection.[7] About 5–10% of individuals experience neurological symptoms, including issues with higher level cognitive functions such as sustained

attention, cognitive flexibility and memory, collectively termed 'brain fog', along with symptoms such as headaches, dizziness, anxiety, depression, insomnia and fatigue.[8–11] Such manifestations may persist even among individuals with mild or absent respiratory symptoms.[12] These late neurocognitive problems following COVID-19 could be attributed to: (1) direct non-resolving low-grade inflammation or immune reactions in the brain[13] and (2) indirect cerebral injury from hypotension, hypoxia and metabolic dysfunction from effects on the heart, lungs and other organs.[4 14] Full neurocognitive recovery post-COVID-19 may take months,[11] and akin to other forms of brain injury, it may have long-term impacts on brain health and neurodegenerative conditions such as Alzheimer's disease.[15]

Several studies have used specific tests to diagnose neurocognitive symptoms in long covid patients, revealing impairments in executive functions, attention and memory.[16] These deficits manifest clinically as difficulties in planning, sustaining focus, recalling information and effectively processing new stimuli, which significantly impact daily functioning and quality of life. Such neurocognitive impairments may be linked to underlying neuropathological changes elucidated through advanced imaging modalities and biomarker analyses.

MRI findings in the brain, particularly of free water quantification using diffusion-weighted sequences, are a sensitive marker of small vessel disease,[17] cognitive impairment (especially decision-making performance and working memory)[18] and neurodegenerative disease.[19] Increases in brain free water reflect an enlargement of extracellular spaces within the cellular matrix of the grey matter or axonal pathways of the white matter due to vasogenic oedema, neuroinflammatory gliosis and/or loss of neuropil or myelin.[20] While these changes are traditionally evaluated through histopathological analyses, advanced MRI techniques provide a valuable non-invasive approach to approximating pathological processes.

Additionally, blood markers of endothelial damage, immune function (cytokines/chemokines and acute phase proteins) and neuronal and glial health (eg, neurofilament light chain and glial fibrillar acidic protein) in the acute phase of COVID-19 may function as predictors of long covid.[21] These insights underscore the multifactorial nature of neurocognitive symptoms in long covid and the importance of integrating clinical, imaging and biomarker data to better understand and manage this condition.

Statins, widely prescribed for cardiovascular disease prevention, inhibit cholesterol biosynthesis by targeting 3-hydroxy-3-methylglutaryl coenzyme A reductase. They also have anti-inflammatory, antioxidant, vascular endothelial function-enhancing, plaque-stabilising and platelet aggregation-inhibiting effects.[22–24] Statins may have neuroprotective effects beyond their cholesterol-lowering properties.[25] Epidemiological associations show a reduced risk of all-cause dementia and Alzheimer's disease in individuals using statins,[15 26–29] with effects likely related to type, dose, duration and onset timing over the life course.[30 31] Given the key role of the neurovascular unit in modifying the brain's susceptibility to injury, any benefit of statin therapy is more likely when initiated promptly after an acute inflammatory insult. As atorvastatin crosses the blood-brain barrier due to its high lipophilicity,[32] it shows promise as a treatment of neurological symptoms of prolonged COVID-19.[33]

Here, we outline the protocol for the STatin TReatment for COVID-19 to Optimise NeuroloGical recovERy (STRONGER) study, which aims to determine the efficacy of atorvastatin in primarily mitigating cognitive decline by reducing (or stabilising) neuroinflammation indicated by MRI changes and blood biomarkers.

Objectives

To determine the effects of a standard 40 mg dose of atorvastatin on improving neurological outcomes in adults experiencing persistent cognitive symptoms after acute infection with COVID-19. The primary outcome is cognitive processing speed, assessed by the symbol digit modalities test (SDMT); the key secondary outcome is total white matter free water on MRI. Additionally, the study will investigate other cognitive measures and health assessments and MRI markers, including white matter hyperintensity volume, perivascular space enlargement, grey matter cortical thickness, white matter microstructure, basal ganglia iron load and cerebral perfusion. A cost-effectiveness analysis will also be undertaken.

METHODS AND ANALYSIS

Study design and setting

STRONGER is an international, investigator-initiated and conducted, multicentre, prospective, randomised, open label, blinded endpoint study, with a fixed time point for outcome assessments. Open label indicates that participants and researchers are aware of the treatment allocation. Participants are centrally randomised (1:1) to either the intervention group to receive 40 mg atorvastatin for 12 months on top of usual care or to the control group to receive usual care. Recruitment began on 5 May 2022 and ended in July 2024. The follow-up of participants is until July 2025, and the results are planned to be presented in October 2025.

The study was approved for conduct at three medical clinic sites: the Brain and Mind Centre of the University of Sydney, Monash University in Australia (central ethics approval from Sydney Local Health District Royal Prince Alfred Hospital Ethics, numbers X21-0113 and 2021/ETH00777 10, date of first approval 19 May 2021) and at the Clínica Alemana Universidad del Desarrollo, Santiago, Chile (Comité ético científico: Facultad de Medicina, Clínica Alemana de Santiago, Universidad del Desarrollo, number 2021–75, date of first approval 20 August 2021; government approval: number EC1707587, date: 17 November 2021) as outlined in online supplemental

file 1. All subjects provided written informed consent according to the forms shown in online supplemental file 2.

Eligibility of study participants

Eligible participants are aged ≥18 years, have a history of COVID-19 that is confirmed by a positive PCR test, a rapid antigen test or as per local guidelines for COVID-19 diagnosis at the time of screening and have ongoing neurological symptoms as a result of COVID-19. These symptoms included problems with memory, concentration, sleep disturbance and fatigue and were systematically identified through administration of the Somatic and Psychological Health Report-34 item questionnaire[34] and of any reported loss of smell (anosmia). They must be able to participate in all procedures and provide written informed consent.

Participants were excluded if they had any of the following: evidence of dementia and/or significant cognitive impairment on screening; a severe comorbid medical (eg, renal failure) or psychiatric condition (ie, drug or alcohol dependence and schizophrenia) that prevented participation; history of traumatic brain injury with loss of consciousness (>30 min) within the last 2 years; ongoing long-term use or clear indication or contraindication for statin use; evidence of severe or significant liver disease; creatine kinase levels more than twice the upper limit of normal; being female of childbearing potential and unable or unwilling to use a reliable method of contraception, currently breastfeeding or planned pregnancy. For the subgroup of participants who agree to undergo MRI, they must have had no contraindication due to metallic body parts or claustrophobia. Finally, participants were excluded if their medical history might, in the opinion of their treating physician, put them at significant risk if they were to participate in the trial.

Intervention

Participants who meet the eligibility criteria were randomised to receive standard care or atorvastatin 40 mg on top of standard care for a period of 12 months (figure 1). The randomisation was stratified by country, time (<6 vs ≥6 months since acute COVID-19 illness), age (<60 vs ≥60 years), current anosmia (yes vs no) that has occurred with temporal relation to COVID-19 and participation in the MRI/biomarker substudy. The randomisation allocation was blinded to researchers conducting the cognitive assessments and endpoint adjudication, and participants, physicians and other study team members were aware of the treatment allocation.

Visit summary

The study incorporates a blend of inperson visits and telephone interviews (figure 1). Preliminary screening was via telephone or teleconference to obtain informed consent and for review of the inclusion and exclusion criteria. Inperson visits encompass baseline assessments, a clinical evaluation at 6 months and an end-of-study assessment at 12 months. During the baseline visit, various evaluations were performed, including fasting blood tests, clinical assessment, cognitive tests, health questionnaires and physical activity assessments (table 1). Randomisation was undertaken after these assessments were completed, with the participants only being informed of their allocation when all the baseline evaluations were finished, to mitigate the risk of differential withdrawal between the study arms. Furthermore, participants who were enrolled in the substudy are required to undergo MRI scans and blood biomarker analyses at baseline and the end of follow-up. The 6-month visit focused on clinical evaluation and adverse

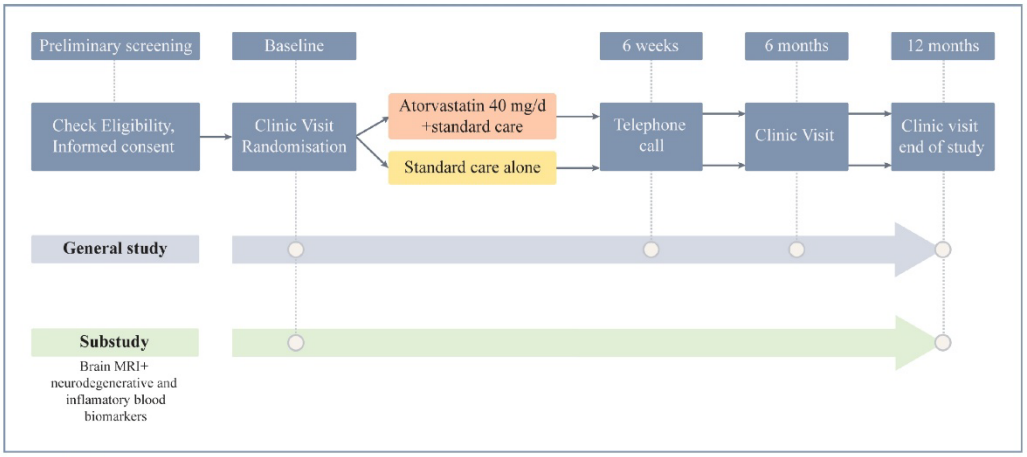

Figure 1 Flow chart of study design.

Table 1 Study outcomes

Name		Purpose	Assessment
Primary outcome			
	Symbol Digit Modalities Test[35]	Assesses frontal lobe executive processing	Requires participants to match numbers to symbols according to a key, containing nine abstract symbols, each paired with a number. Performance is measured by the number of correct symbols within 90 s.
Secondary outcomes			
Neuropsychological assessments	Rey Auditory Verbal Learning test[40]	Assesses memory and learning	Requires participants to learn a 15-item word list over five learning trials, followed by a distractor list and short and long-delayed recall.
	Oral Trail Making Test A and B[41]	Summarises visual search, scanning, speed of processing, mental flexibility and executive functions	Has two parts: part A—participants count from 1 to 25 as quickly as possible. In Part B—participants alternately count numbers up to 13 and recite letters of the alphabet up to L as quickly as possible. The primary performance metric is the time in seconds required to complete each of the two parts of the test.
	Delis-Kaplan Executive Functioning System 'Stroop' Colour-Word Interference Test[42]	Measure executive functions	Has four parts: colour naming, word reading, inhibition and inhibition/switching. Performance is measured by completion time for each trial. Composite score: colour naming and word reading times. Contrast scores: inhibition versus colour naming, inhibition/switching versus combined colour naming and word reading and inhibition/switching versus inhibition, assess disproportionate impairments in higher-level functions compared with component functions.
	Semantic Fluency[43 44]	Assesses language processing	Requires the generation of as many 'animal names' in 1 min. Performance is measured by counting the number of correct unique semantic category items produced.
Health assessments	COVID-19 Yorkshire Rehabilitation Scale[45]	Evaluate the long-term impact of COVID- 19	It is administered by self-report or clinician. It will be used as a baseline measure and then at follow-up at 18 months as an assessment of response to therapy.
	Patient Health Questionnaire[46]	Measure the presence and severity of depression	Evaluates each of the nine DSM-V major depression criteria on a scale from '0' (not at all) to '3' (nearly every day). It aids in making a preliminary diagnosis of depression in at-risk populations (eg, individuals with coronary heart disease or after stroke), with scores ≥10 indicating probable clinically significant depression.
	General Anxiety Disorder[47]	Measure the presence and severity of generalised anxiety	A score ≥10 represents a reasonable cut point for identifying cases of generalised anxiety. Cut points of 5, 10 and 15 might be interpreted as representing mild, moderate and severe levels of anxiety.
	Pittsburgh Sleep Quality Index[48]	Assesses overall sleep quality in clinical populations	Covers 19 self-reported items across seven subcategories: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction; with five additional questions rated by the respondent's roommate or bed partner, if available. Scores >5 are generally indicative of poor sleep quality.
	EQ-5D-5L[49]	Measures health-related quality of life	Across five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each rated according to five levels, as well as providing an integrated utility score for calculating an overall score against population-based preference weights.

Continued

Table 1 Continued

Name		Purpose	Assessment
	International Physical Activity Questionnaire-long form[50]	Physical activity assessment	A valid 27-item self-reported assessment to provide an estimate of physical activity and sedentary behaviour for adults aged 15–69 years. Participants reflect on activities over the previous 7 days across five domains: (1) occupational physical activity; (2) transportation physical activity; (3) housework, house maintenance and caring for family; (4) recreation, sport and leisure-time physical activity; (5) time spent sitting. Physical activity scores can be calculated in either categorical score (high, medium and low) or MET minutes per week.
Substudy outcomes			
MRI	Total white matter free water (diffusion MRI)		Using multishell diffusion spectral imaging with fibre orientation and compartment modelling.
	Others		MRI markers of white matter hyperintensity volume, enlarged perivascular space volume, total grey matter volume, white matter microstructure (fractional anisotropy), basal ganglia iron load and total cerebral perfusion.
Blood biomarkers	Neurodegenerative markers		Ptau-181, neurofilament light chain, Aβ42/40 and DNA extraction for apolipoprotein E genotype.
	Peripheral markers		Interleukin (IL)-6, IL-1β, NAD+, TNF-α, hsCRP

DSM-V denotes Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EQ-5D-5L EuroQoL Group 5-Dimension 5-level self-report questionnaire ; hs-CRP high-sensitivity C-reactive protein; MET metabolic equivalent (1 MET is the energy spent sitting at rest); NAD nicotinamide adenine dinucleotide; TNF tumour necrosis factor.

event assessment within the treatment group. On the 12-month follow-up, the baseline assessments are repeated.

Telephone interviews complement the inperson visits, particularly at the 6-week mark, to evaluate adverse events, medication adherence and changes in concomitant medication. Every effort is made to conduct assessments remotely for participants unable to attend inperson visits.

Outcomes

Primary outcome is processing speed, assessed by the SDMT,[35 36] which evaluates frontal lobe executive processing. Participants match numbers to symbols based on a cue of 9 abstract symbols paired with numbers. Performance is measured by the number of correct symbols within 90 s.

Secondary outcomes include a comprehensive battery of assessments covering executive functions, memory, processing speed and other domains, alongside evaluations of health status, MRI and blood biomarkers. A cost-effectiveness analysis, relative to standard care, will be executed. The table provides a detailed overview of all evaluations.

Cognitive assessments are administered by trained research psychologists specialised in cognitive measures. Importantly, these assessments can be conducted either in person or via videoconference.

Safety outcomes

This study documents expected adverse reactions to the study medication of special interest (AESI), including myalgia, nausea, elevated blood glucose, elevated creatine kinase, abdominal pain, new-onset diabetes mellitus and rhabdomyolysis. These AESIs are closely monitored at specific visits to assess participants' tolerability to study drugs, noting whether they are new or continuing from baseline, regardless of severity. Additionally, all serious adverse events (SAEs)[37] and adverse events (AEs) are reported. If treatment is discontinued as a result of any AE, serious or not, the site study team is to provide details of all events that led to the discontinuation of treatment.

Sample size

A sample of 410 patients was estimated to provide 80% power (α=0.05) to detect at least a 0.3 SD effect size difference between groups, assuming equal group participation. These calculations assume a modest 5% non-compliance and 5% dropout over 12 months of follow-up. The SDMT age-adjusted mean score is estimated at 60 (SD 13) at baseline (based on healthy control data).[35] The effect is based on trials of the use of statins for the prevention of dementia and trials of treatments for multiple sclerosis, where achieved effect sizes of 0.3–0.4 are clinically meaningful and likely to confer public health benefits.[38] For the substudy of participants undergoing MRI, a sample size of 220 (110 per group) is estimated to provide 80%

power (α=0.05) to detect an effect size of relative difference of 5.0–6.5 (variance between groups/variance within groups) for the imaging endpoints, assuming a 20% drop out. The study statistician (XW) used the software package PASS V.15 (NCSS, Kaysville, Utah, USA; http://www.ncss.com/software/pass) for these power calculations.

Data collection methods

All data entry is completed via a secure web-based data management system (IBM Clinical Development) at The George Institute for Global Health. Data entry is performed at the participating sites by authorised site staff who have completed training and been given appropriate role-based access to the system. Data logic and consistency checks are programmed into the data entry forms so that data entry errors are captured in real-time and queries are auto-generated. Authorised electronic signatures are used to lock completed data entry forms once all data queries have been resolved within the system. Data entry and all subsequent changes or deletions are captured in an accessible audit trail. Coding of outcomes is centrally performed either automatically via the IBM coding module or manually by the Central Coordinating Centre (CCC). All coding is reviewed and verified by a medical monitor. Reporting within the system is used for regular data reviews and overall trial monitoring. Data are stored and backed up on the IBM cloud servers in the USA.

Statistical analysis plan

The study will follow the intention-to-treat principle for analysis. Baseline characteristics will be summarised by treatment group. Continuous baseline characteristics will be described by means (SD), if approximately normally distributed, or by medians (IQR), if normality cannot be assumed. Categorical baseline characteristics will be presented by frequency per category. Statistical comparisons of baseline characteristics between treatment and control groups are not planned.

The primary endpoint, SDMT score, will be summarised by means (SD) if normally distributed, or by medians (IQR) if normality cannot be assumed. The primary analysis will be conducted using linear regression, with the dependent variable being SDMT and the independent variable being group allocation (treatment vs control) with adjustment for the covariates of age, sex and site. A sensitivity analysis will be undertaken with adjustment for any meaningful baseline imbalances and clinically confounders. Another sensitivity analysis will be conducted by dichotomising SDMT according to population norms (average scores of 54 in Australia and 53.2 in Chile for people aged 44 years) and use of logistic regression models with adjustment for age, sex and study site.

Continuous secondary endpoints will be analysed using linear regression, adjusting for age, sex, study site, unbalanced baseline characteristics and clinically meaningful confounders. Binary secondary endpoints will be analysed using binary logistic regression, adjusting for age, sex, study site, unbalanced baseline characteristics and clinically meaningful confounders. Ordinal secondary endpoints with more than two categories will be analysed using a cumulative logit model, adjusting for age, sex, study site, unbalanced baseline characteristics and clinically meaningful confounders and with testing of the proportional odds assumption.

Descriptive statistics will be provided for safety data, where SAEs and treatment discontinuation will be tabulated using standard terminology. Heterogeneity of the treatment on the primary endpoint will be assessed in the predefined subgroups of age (<60 vs ≥60 years), time since COVID-19 diagnosis (<6 vs ≥6 months), baseline C-reactive protein levels (0–9 vs ≥10 mg/L), ethnicity (white Caucasian vs other) and prior cardiovascular risk (no vs yes for any of a history of hypertension, hyperlipidaemia, current smoker and body mass index (height (cm)/weight (kg) ≥10).[2] The hypothesis is that there will be a larger relative treatment effect in younger people, in people with higher levels of inflammation by virtue of an earlier time from the acute COVID-19 infection, in people with raised inflammatory markers, in non-white individuals and those with elevated cardiovascular risk. A detailed outline of the statistical analyses will be specified a priori in a full statistical analysis plan prior to unblinding of the data. A modelled cost-utility analysis using trial data (health-related quality of life, captured by EuroQoL Group 5-Dimension 5-level self-report questionnaire; drug costs; health service utilisation costs, including AEs) will be conducted by comparing use of atorvastatin with standard of care. A 5-year time horizon will be undertaken, with analyses conducted in line with accepted Australian standards for use of economic evaluation in decision-making.

Data monitoring

Trial data are monitored, using central risk-based monitoring principles, to detect any unusual patterns of data that would require further investigation. During the study, representatives of the CCC monitor site performance and quality via remote methods, including via videoconference, to ensure that the study is conducted in accordance with the protocol, International Conference on Harmonisation guidelines for Good Clinical Practice (ICH-GCP) guidelines and relevant ethical and regulatory requirements.

Areas of potential bias

As this is a clinical trial, a major source of bias is *selection*, so we plan to compare the characteristics of participants with those in published cohorts and between those who were screened. Being an open trial, another main source of bias relates to *differential drop-out*, for example, participants in the control 'no treatment' group failing to return to follow-up assessments or withdrawing from the study. We will try to reduce this by ensuring that all participants fully understand the importance of participation and follow-up, irrespective of ceasing the study

medication, and in maintaining good communication and relationships with participants. A final source of bias is *behavioural*, where participants in either group may change their lifestyle and attitude simply due to participation or in response to factors outside of the trial. We will monitor this by asking questions about use of concomitant medications, diet, smoking and exercise and through use of actigraphy as a proxy measure of sleep and physical activity. There is a low likelihood that the control 'no treatment' group will receive atorvastatin (ie, *treatment crossover*) as this can only be prescribed for people who are at high risk of cardiovascular disease.

Patient and public involvement

The STRONGER study protocol was presented to the Brain Health Consumer Panel of The George Institute for Global Health at meetings in March and November of 2021. This panel comprises a dozen people with lived experience of brain health conditions or their caregivers. Feedback was sought regarding the protocol and patient-facing documents. Those with lived experience provided comments on the feasibility of the study, mode of recruitment, activities and information dissemination. This feedback was incorporated into the study where appropriate, and there was agreement to ensure that the findings of the study, along with a plain language summary, will be disseminated to participants of the trial after the study is published.

ETHICS AND DISSEMINATION

This study protocol was designed and shall be implemented and reported in accordance with the ICH-GCP, the National Health and Medical Research Council, the National Statement on Ethical Conduct in Human Research and with the ethical principles laid down in the World Medical Associations Declaration of Helsinki. Potentially eligible participants are provided with information about the study, and informed consent is obtained from all participants prior to screening assessments.

Writing committees, with oversight by the steering committee, will be formed from members of the various committees, statisticians, research fellows and investigators. Authors of publications must meet the International Committee of Medical Journal Editors[39] guidelines for authorship. The study has been approved by relevant ethics committees and regulatory bodies at country level and local sites in Australia and Chile. The current protocol is V.9.0, and all protocol updates have been approved by the Steering Committee and Ethics Committees and communicated with investigators and Data and Safety Monitoring Board members.

Author affiliations
[1]Centro de Estudios Clínicos, Instituto de Ciencias e Innovación en Medicina (ICIM), Universidad del Desarrollo Facultad de Medicina Clínica Alemana, Las Condes, Chile
[2]Faculty of Medicine, University of New South Wales, The George Institute for Global Health, Sydney, New South Wales, Australia
[3]Data science, Fudan University, Shanghai, China
[4]Charles Perkins Centre and The University of Sydney, The University of Sydney Brain and Mind Centre, Camperdown, New South Wales, Australia
[5]School of Public Health, Imperial College London, The George Institute for Global Health UK, Oxford, UK
[6]Department of Neuroscience, School of Translational Medicine, Monash University, Melbourne, Victoria, Australia
[7]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
[8]Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia
[9]Departamento de Imagenología, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Clínica Alemana de Santiago SA, Vitacura, Metropolitan Region, Chile
[10]Institute of Science and Technology for Brain-inspired Intelligence, Fudan University, Shanghai, Shanghai, China

X Cheryl Carcel @cheryl_carcel

Contributors CA, SLN, SZ, RP, MW, OH, KL, JE, ML, PM and CC made substantial contributions to the conception and the design of the work. CD, CC, PM and CA wrote the first and following drafts of this manuscript. XL contributed to the statistical analysis and methodology. NW and XS contributed to the critical revision of manuscript for intellectual content. CA is the guarantor of the study. All authors approved submission of the manuscript for publication.

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Competing interests CC is supported by an Australian National Health and Medical Research Council (NHMRC) Investigator Grant, Emerging Leadership 1 (APP2009726) and receives research support from Bayer. SN received consultancy fees from Eisai and Roche and speaker fees from Nutrica. MW has recently acted as a consultant to Freeline. RP receives grant funding from the Australian NHMRC paid to her institution. PM receives research grants from ANID Fondecyt Regular 1221837 and a Research Grant from Pfizer 76883481. SZ is employed by Monash University and receives funding from NHMRC, MRFF and the Commonwealth Department of Health and Aged Care. She reports previous payment to institution (Monash University) from Amgen Australia, AstraZeneca, Eli Lilly Australia, Moderna, MSD Australia, Sanofi and Novo Nordisk for participation in advisory and educational meetings. She is a Board Director of the Australian Clinical Trials Alliance and the Victorian Institute of Forensic Medicine. CSA reports research grants from the NHMRC, the Medical Research Council and Medical Research Foundation of the UK, and AstraZeneca. All other authors declare no conflict of interest.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Carlos Delfino http://orcid.org/0000-0002-4834-2718
Cheryl Carcel http://orcid.org/0000-0001-8942-953X
Paula Muñoz-Venturelli http://orcid.org/0000-0003-1869-2255
Karin Leder http://orcid.org/0000-0003-1368-1039
Ximena Stecher http://orcid.org/0000-0002-7962-9519

Sophia Zoungas http://orcid.org/0000-0003-2672-0949

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ADDRESS FOR ALL CORRESPONDENCE
RESEARCH ETHICS AND GOVERNANCE OFFICE
ROYAL PRINCE ALFRED HOSPITAL
CAMPERDOWN NSW 2050
TELEPHONE: (02) 9515 6766
EMAIL: SLHD-RPAEthics@health.nsw.gov.au
REFERENCE: **X21-0113 & 2021/ETH00777**
10.15/MAY21

Health
NSW GOVERNMENT Sydney Local Health District

19 May 2021

This letter constitutes ethical approval only. You must NOT commence this research project at ANY site until you have submitted a Site Specific Assessment Form to the Research Governance Officer and received separate authorisation from the Chief Executive or delegate of that site.

Dear Professor Anderson,

Re: Protocol No X21-0113 & 2021/ETH00777 - "Statin TReatment for COVID-19 to Optimise NeuroloGical recovery"

The Executive of the Ethics Review Committee, at its meeting of 18 May 2021 considered your correspondence of 12 May 2021. In accordance with the decision made by the Ethics Review Committee at its meeting of 26 April 2021, ethical approval is granted*.

- The research project meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

This approval includes the following:

- HREA (Version 2, 28 April 2021)
- Protocol (Version 2.0, 12 May 2021)
- Participant Information Sheet/Consent Form (Master Version 2.0, 5 May 2021)
- Participant Information Sheet/Consent Form - Biomarker & MRI Sub-Study (Master Version 2.0, 5 May 2021)
- Telephone Script Form C – 6 months (Version 1.0, 6 May 2021)
- Telephone Script Form E – 12 months (Version 1.0, 6 May 2021)
- SAE AESI CRF Telephone Script (Version 1.0, 6 May 2021)
- GeneActiv Instructions 1 week (Version 1.0, 6 May 2021)
- 7-day Sleep Diary (Version 1.0, 6 May 2021)
- Remote Consent GP Letter (Version 1.0, 4 May 2021)

- Screen Failure GP letter (Version 1.0, 4 May 2021)
- Randomisation GP Letter (Version 1.0, 4 May 2021)
- Lost to Follow-Up GP Letter (Version 1.0, 4 May 2021)
- Withdrawal GP Letter (Version 1.0, 4 May 2021)
- Study Completion GP Letter (Version 1.0, 4 May 2021)
- Research Data Management Plan (Version 1.0, 10 March 2021)
- Victorian Specific Module (6 May 2021)

***Additional conditions of this approval:**

- Approval from the RPA Virtual Head of Department must be sought for the RPAH Site Specific Assessment
- All advertising material for use must be submitted to the HREC for review and approval as soon as they become available.

You are asked to note the following:

- **This study requires notification to the Therapeutic Goods Administration (TGA) under the Clinical Trials Notification (CTN) Scheme.**
- The Committee noted that authorisation will be sought to conduct the study at the following sites:
    - Royal Prince Alfred Hospital, NSW
    - The Brain and Mind Centre of the University of Sydney, NSW
    - The Alfred, VIC
    - Monash University, VIC
- It is a requirement of ethics approval that, before its commencement, this clinical trial is registered on a publicly accessible register, such as the Australian New Zealand Clinical Trials Registry or another appropriate international register. The Committee therefore sought details of the Register in which the study has been included and its registration number.
- This approval is valid for five years, and the Committee requires that you furnish it with **annual reports** on the study's progress beginning in **May 2022.** If recruitment is ongoing at the conclusion of the four year approval period, a full re-submission will be required. Ethics approval will continue during the re-approval process.
- This human research ethics committee (HREC) has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review and is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

- You must immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.
- You must notify the HREC of proposed changes to the research protocol or conduct of the research in the specified format.
- You must notify the HREC and other participating sites, giving reasons, if the project is discontinued at a site before the expected date of completion.
- If you or any of your co-investigators are University of Sydney employees or have a conjoint appointment, you are responsible for informing the University's Risk Management Office of this approval, so that you can be appropriately indemnified.
- Where appropriate, the Committee recommends that you consult with your Medical Defence Union to ensure that you are adequately covered for the purposes of conducting this study.

Should you have any queries about the Committee's consideration of your project, please contact me. The Committee's Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Sydney Local Health District website.

If you are not using REGIS, a copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The Ethics Review Committee wishes you every success in your research.

Regards,

S. Thomas

Sanaa Thomas
Executive Officer
Clinical Trials Sub-committee (RPAH Zone)

for:

Merela Ghazal
A/Executive Officer
Ethics Review Committee (RPAH Zone)

HERC\EXCOR\21-05

COMITÉ ÉTICO CIENTÍFICO
FACULTAD DE MEDICINA
CLÍNICA ALEMANA DE SANTIAGO
UNIVERSIDAD DEL DESARROLLO

Facultad de Medicina
Clínica Alemana - Universidad del Desarrollo

ACTA DE APROBACIÓN
2021-75

Fecha: **Santiago, 20 de agosto 2021**
Protocolo: **"Statin Treatment for Covid-19 to Optimise Neurological Recovery" (STRONGER) N° UIEC 1074**
Investigador Responsable: **Paula Muñoz**
Institución: **Departamento de Psiquiatría y Neurología**
Clínica Alemana de Santiago

Los siguientes documentos han sido analizados a la luz de los postulados de la Declaración de Helsinski, de las Pautas éticas internacionales para la investigación relacionada con la salud con seres humanos que involucra sujetos humanos CIOMS 2016, y de las Guías de Buena Práctica Clínica de ICH 1996.

Documentación revisada en primera instancia:

1. Protocolo del estudio, versión 2.0 con fecha 12 de mayo de 2021, en inglés (incluye resumen en español)
2. Consentimiento informado para el participante, versión local 1.0 con fecha 17 de julio de 2021, en español.
3. Consentimiento informado para la realización de sub-estudio de biomarcardores y resonancia magnética, versión 1.0 con fecha 02 de julio de 2021, en español
4. Folleto de información para el profesional, ISP 24 octubre 2012
5. Guía de instrucciones para el participante del uso del actígrafo, versión 1.0 del 06 de mayo 2021, en español
6. Diario de sueño para el participante, versión 1.0 del 06 de mayo 2021, en español
7. Currículum vitae del investigador responsable para Clínica Alemana y coinvestigadores (Dra. Ximena Stecher, Dr. Carlos Delfino y Ps. Helga Welzel) y coordinador local (Flga. Francisca Urrutia).
8. Certificados de Buenas Prácticas Clínicas del equipo
9. Declaración de conflictos de interés del equipo
10. Carta de apoyo de Jefes de Departamento de Neurología y Psiquiatría y de Servicio de Neurología de Clínica Alemana
11. Material para difusión
12. Seguro está pendiente de envío

Facultad de Medicina UDD | Clínica Alemana de Santiago. Mail ceccasudd@udd.cl

Documentación revisada en respuesta a carta de observaciones de fecha 02 de agosto de 2021:

1. Carta respuesta de fecha 15 de agosto 2021
2. Consentimiento informado para el participante, versión local 1.0 de fecha 15 agosto 2021
3. Consentimiento informado para la realización de sub-estudio de biomarcardores y resonancia magnética, versión 1.0 de fecha 15 agosto 2021
4. Material para difusión: poster A4 y A5 enviados con las modificaciones solicitadas

Para otorgar la presente Acta de Aprobación, se consideraron los siguientes aspectos éticos:

1.- Valor social: este es un estudio internacional, Fase III, a realizarse en Chile y Australia, cuyo objetivo es determinar si 40 mg de atorvastatina diaria mejora la función neurocognitiva en adultos con síntomas neurológicos post COVID. La importancia radica en que se ha hecho evidente que un grupo significativo de pacientes experimenta síntomas neurológicos post COVID-19, que perduran en el tiempo, en lo que ha sido llamado COVID-largo, en el cual se postula existe un componente inflamatorio. Es en este posible mecanismo donde podrían actuar las estatinas, compuestos que mediante la inhibición de mevalonate tienen un "essential role for intracellular inflammatory signalling and pro-inflammatory cytokine responses". Asimismo, ya existe evidencia que el uso de estatinas previene el deterioro cognitivo.

2.- Validez Científica: es estudio intervencional, randomizado, abierto, ciego al evaluador, que compara dos intervenciones: uso de atorvastatina 40 mg/día vs tratamiento estándar por 18 meses, en un grupo de 410 adultos que tuvieron COVID. Tiene sub-estudio para futuros estudios de biomarcadores neurodegenerativos y resonancia magnética cerebral (n = 220).

Dentro de los estudios experimentales existen diferentes tipos de diseños que son apropiados para un ensayo clínico en fase 3. Si bien el *gold standard* son los estudios randomizados contra placebo, en este caso, el tipo de estudio planteado permite responder la pregunta de investigación mediante las evaluaciones de resultados cognitivos (evaluación ciega del desenlace por profesionales expertos) y biomarcadores (estos últimos, marcadores objetivos, por lo que no varían según la interpretación humana). Además, se contempla una adjudicación ciega de los eventos adversos por ramas, que serán considerados en los resultados finales. Los sesgos que pueden asociarse la metodología de un estudio abierto serán entonces minimizados con las evaluaciones objetivas y enmascaradas que fueron mencionadas previamente. Actualmente, y sobre todo debido a la pandemia COVID-19, este tipo de estudios están siendo utilizados, ya que es una forma más rápida y eficaz de brindar conocimiento científico de calidad ante situaciones como las que debemos enfrentar como sociedad en una emergencia sanitaria

3.- Evaluación riesgo/beneficio: favorable. El uso de atorvastatina es de bajo riesgo, toda vez que es fármaco muy usado y donde existe abundante experiencia clínica. La RNM no requiere de medio de contraste. Los tests cognitivos no son riesgosos. Con respecto a los resultados de marcadores de neurodegeneración, en el consentimiento informado se aclara que dichos procedimientos no son diagnósticos, por lo que no tendrán relevancia clínica para el paciente ni sus tratantes. Además, el procesamiento de las muestras se realizará en la última etapa del estudio.

4.- Conflictos de interés: no se observan fueran del indudable interés académico.

5.- Consentimiento informado: contempla firma del consentimiento informado por medios electrónicos y presenciales. Se entregará un incentivo a cada participante del estudio de $30.000 en

total, el cual se realizará una vez corroborados los criterios de inclusión y luego de la randomización. Este pago, tal como se manifiesta en la carta, es planteado como reembolso de gastos (se estiman 220 participantes en el estudio).

Con respecto a las muestras de sangre, el patrocinador del estudio (George Institute) aclaró que las muestras de sangre no serán transferidas a terceros u otros países. La información que podría ser compartida serán solo los datos del estudio. En el caso de que se pretendan utilizar estos datos en el futuro, se solicitará la aprobación del Comité Ético científico antes de cualquier nuevo uso, tal como se describe en el formulario de consentimiento.

6.- Protección de los derechos de los participantes: es adecuada. Hay libertad de participación, derecho a retiro, se resguardará la confidencialidad, y no hay costos asociados a los participantes.

Por lo tanto, el Comité de Ética considera que el estudio está bien justificado, que no hay objeciones éticas para la realización del estudio propuesto, y, por ende, otorga su aprobación, la que estará vigente mientras el proyecto esté en curso.

El Comité solicita que el investigador:

- Utilice los documentos de consentimiento informado versión 1.0 de fecha 15 de agosto, aprobados y timbrados por este Comité, así como el material para difusión.
- Para nuevas correspondencias referentes a este proyecto, se le solicita utilizar el número **2021-75**.
- Una vez finalizado el proyecto, el Comité deberá ser informado de los resultados del estudio.

Dr. Marcial Osorio
Presidente
Comité Ético Científico

Javiera Bellolio A.
Secretaria Ejecutiva
Comité Ético Científico

Facultad de Medicina UDD | Clínica Alemana de Santiago. Mail ceccasudd@udd.cl

Nómina de los integrantes del Comité Ético Científico de la Facultad de Medicina Clínica Alemana Universidad del Desarrollo que participaron de la reunión de fecha 29 de julio de 2021, donde se acordó la aprobación del protocolo una vez subsanadas las observaciones:

NOMBRE	PROFESIÓN	CARGO
Marcial Osorio Fuenzalida	Médico	Presidente
Bernardita Portales V.	Fonoaudióloga	Vicepresidenta
Javiera Bellolio Avaria	Abogado	Secretaria Ejecutiva
Alejandra Valdés Valdés	Matrona	Integrante
Juan Alberto Lecaros Urzúa	Abogado	Integrante
Sofía Salas Ibarra	Médico	Integrante
Andrea Schilling Redlich	Médico	Integrante
Gonzalo López Gaete	Abogado	Integrante
J. Pablo Undurraga Fourcade	Médico	Integrante
Iris Delgado Becerra	Profesora, M.Sc. Bioestadística	Integrante

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PCS/JMM
Nº Ref.:EC1707587/21

RESOLUCIÓN EXENTA RW N° 30574/21
Santiago, 17 de noviembre de 2021

VISTO ESTOS ANTECEDENTES: la presentación del Director Técnico Sra. Claudia Andrea Asenjo Lobos en representación de UNIVERSIDAD DEL DESARROLLO, la que solicita autorización para el uso provisional sin registro sanitario para el producto farmacéutico detallado en la parte resolutiva, para la realización del Estudio Clínico patrocinado por THE GEORGE INSTITUTE FOR GLOBAL HEALTH, a efectuarse en el centro CLINICA ALEMANA DE SANTIAGO y CLINICA ALEMANA DE SANTIAGO SEDE LA DEHESA, bajo la responsabilidad de la DRA. PAULA MUÑOZ VENTURELLI.

CONSIDERANDO:

· La opinión favorable del Comité Ético Científico Facultad de Medicina Clínica Alemana de Santiago - Universidad del Desarrollo, el cual se encuentra debidamente acreditado.
· El Informe Técnico Científico N° 104/21 de la Sección Estudios Clínicos.
· La constancia de cumplimiento de Buenas Prácticas de Manufactura (BPM) de la planta de fabricación, emitida por la autoridad sanitaria para el sitio de fabricación.
· Que ningún producto farmacéutico podrá ser distribuido en el país sin que haya sido registrado (art. 97° del Código Sanitario).

TENIENDO PRESENTE: las disposiciones contenidas en el artículo 96 y 99 de la Ley 20724 del 14 de febrero de 2014, que modifica el Código Sanitario, Decreto con Fuerza de Ley N° 725 de 1968, el Decreto Supremo N°3/10 , la Ley 20850 del 6/6 de 2015, del Ministerio de Salud; y los artículos 59º letra b) y 61º letra b) del DFL Nº 1 de 2005 y las facultades delegadas por la Resolución Exenta Nº 191 de 05 de febrero de 2021, del Instituto de Salud Pública de Chile, las Resoluciones N° 441/2012, 460/2015, 5161 y 5174 de 2016, y la Resolución N°403 del 2013 que aprueba la Norma Técnica N°151, dicto la siguiente:

R E S O L U C I Ó N

1.- **AUTORÍZASE** la ejecución del protocolo: "Un ensayo clínico internacional y pragmático, iniciado y conducido por investigador para determinar si 40 mg diarios de Atorvastatina pueden mejorar las funciones neurocognitivas en adultos con síntomas neurológicos prolongados producidos por el COVID", Protocolo N° NCT04904536, Fase Nº: III, de fecha 16 de septiembre de 2021 (versión 4.0), Formulario de Consentimiento Informado versión local 1.2, de fecha 22 de septiembre de 2021, sometidos a la evaluación ética del COMITÉ ÉTICO CIENTÍFICO FACULTAD DE MEDICINA CLINICA ALEMANA-UNIVERSIDAD DEL DESARROLLO, cuyo informe favorable se emitió con fecha 05 de octubre de 2021.

2.- El ensayo clínico se realizará cumpliendo los siguientes requisitos y condiciones:

a) El titular de esta autorización corresponde a UNIVERSIDAD DEL DESARROLLO.
b) El patrocinador ha presentado un documento legal de delegación de funciones en UNIVERSIDAD DEL DESARROLLO, con domicilio en Av. Plaza 680, LAS CONDES.
b) El Patrocinador THE GEORGE INSTITUTE FOR GLOBAL HEALTH ha presentado un documento legal de delegación de funciones en UNIVERSIDAD DEL DESARROLLO, con domicilio en Av. Plaza Nº 680, Las Condes, Santiago.
c) El producto autorizado a usarse en dicho ensayo clínico es el que a continuación se detalla, en su concentración, forma farmacéutica, unidad de

Av. Marathon 1.000, Ñuñoa, Santiago
Casilla 48, Correo 21 - Código Postal 7780050
Mesa Central: (56 2) 2575 51 01
Informaciones: (56 2) 2575 52 01
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medida, cantidad y presentación.

Ítem	Producto	Concentración/dosis unitaria	Forma farmacéutica	Unidad de medida	Cantidad	Presentación
1	Atorvastatina (Registro Sanitario F-19644/17)	40 mg	Comprimidos Recubiertos	Caja	2.200	Caja que contiene 30 comprimidos recubiertos
Fabricante: Laboratorio Chile S.A.						
Domicilios: Camino a Melipilla N° 9978, Maipú, Santiago, Chile.						

Almacenado a no más de 30 ºC, protegido de la luz, calor y humedad.

Procedencia: Droguería Pharmavisan (Ñuñoa, Santiago, Chile).

3.- El protocolo se llevará a cabo en los Centros: CLINICA ALEMANA DE SANTIAGO con domicilio en AVENIDA VITACURA N° 5951, VITACURA, SANTIAGO, Y CLINICA ALEMANA DE SANTIAGO SEDE LA DEHESA con domicilio en AV. JOSE ALCALDE DELANO - LA DEHESA N° 12205, LO BARNECHEA, SANTIAGO.

4.-UNIVERSIDAD DEL DESARROLLO, se responsabilizará de certificar la calidad del producto que utiliza.

5.- El producto será almacenado en la bodega de DROGUERÍA PHARMAVISAN S.A., ubicada en: Calle Los Jardines N° 261, ÑUÑOA, REGION METROPOLITANA, para su posterior distribución a los centros de estudio.

6.- El Titular tendrá las obligaciones siguientes:

- Informar al Instituto de Salud Pública de Chile las sospechas de eventos adversos serios a medicamentos acontecidos durante la ejecución del respectivo protocolo de estudio clínico.
- Remitir "Informes Periódicos de Seguridad de Productos Farmacéuticos usados en Investigación Clínica (IPSI; en ingles DSUR, Development Safety Update Report), entregando información de seguridad de un medicamento cuyo uso clínico se investiga y que, entre varios elementos, contiene información de eventos adversos acontecidos durante la ejecución del protocolo de investigación correspondiente, así como una evaluación científica al respecto.
- Cumplir en todo momento con las prescripciones del protocolo cuya ejecución se ha autorizado y con las Buenas Prácticas Clínicas; en lo que corresponda.
- Acceder a las inspecciones que puedan ser realizadas por la autoridad sanitaria y que están destinadas a la verificación del cumplimiento de la autorización y de las Buenas Prácticas Clínicas.
- Notificar cambios de orden administrativo relacionados con la ejecución del estudio clínico, y no incorporados en las menciones que más adelante se indican.
- Remitir Informe de cierre anticipado o, en su defecto, informe final al término del ensayo clínico. En el caso de los estudios que se realicen en más de un país, se deberá incluir además los antecedentes relacionados con la ejecución del estudio en el extranjero

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7.- Esta resolución tendrá vigencia por un plazo de un año, desde la fecha de la presente resolución, previo el cuál deberá, en caso de que lo requiera, solicitar una renovación de autorización a este Instituto.

INSTITUTO DE SALUD PÚBLICA DE CHILE
AGENCIA NACIONAL DE MEDICAMENTOS

10

Q.F. JUAN ROLDÁN SAELZER
JEFE (S) DEPARTAMENTO
AGENCIA NACIONAL DE MEDICAMENTOS
INSTITUTO DE SALUD PÚBLICA DE CHILE

INSTITUTO DE SALUD PÚBLICA DE CHILE
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Av. Marathon 1.000. Ñuñoa. Santiago
Casilla 48. Correo 21 - Código Postal 7780050
Mesa Central: (56 2) 2575 51 01
Informaciones: (56 2) 2575 52 01
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9.4 Supplementary material for Chapter VI

Supplementary table S1. Laboratory Characteristics of the Study Population

Parameter	Mean (SD)	p25–p75
Glucose (mmol/L)	5.1 (0.76)	4.6–5.3
Total Cholesterol (mmol/L)	5.2 (1.0)	4.5–5.8
LDL Cholesterol (mmol/L)	3.2 (0.9)	2.64–3.7
HDL Cholesterol (mmol/L)	1.5 (0.6)	1.2–1.7
Triglycerides (mmol/L)	1.3 (0.7)	0.8–1.7
Urea nitrogen (mmol/L)	7.2 (11.4)	3.6–5.6
AST, (U/L)	22.2 (7.2)	17–25
ALT, (U/L)	26 (15.5)	15–32
Creatine Kinase, (U/L)	88.7 (75.4)	52–105
Creatinine, (μmol/L)	103.1 (470.2)	61–75
Sodium (mmol/L)	136.0 (20.7)	138–141
Potassium (mmol/L)	4.54 (2.69)	4.1–4.6
C-reactive protein, (mg/L)	6.02 (27.6)	1.0–4.0
Haemoglobin, (g/L)	143.2 (104.9)	130–146
MCHC, (g/L)	346.8 (238.7)	326–339
MCV, (fL)	89.9 (4.8)	87–93
MCH (pg)	29.8 (1.9)	29–31
RDW-CV, (%)	13.6 (6.6)	12.4–13.5
Haematocrit, (%)	41.6 (3.4)	39–44
Red blood cell count, ($\times 10^6$/μL)	4.6 (0.4)	4.38–4.9
White blood cell count, ($\times 10^3$/μL)	6.4 (1.8)	5.1–7.6
Neutrophils, ($\times 10^3$/μL)	6.9 (13)	2.6–4.5
Lymphocytes, ($\times 10^3$/μL)	4.2 (7.8)	1.7–2.6
Monocytes, ($\times 10^3$/μL)	1.7 (7.1)	0.39–0.6
Eosinophils, ($\times 10^3$/μL)	0.4 (0.9)	0.1–0.3
Basophils, ($\times 10^3$/μL)	0.1 (0.3)	0.02–0.1
Platelet count, ($\times 10^3$/μL)	280.8 (68.1)	240–315

Supplementary table S2. Covid-19 Yorkshire rehabilitation scale (C19-YRS) : a. Symptoms, n (%); b. comparison pre and post COVID-19 infection.

Symptoms according to the C19-YRS scale, n (%)	
Dyspnoea	
At rest	103 (54)
While dressing	132 (69)
While walking	177 (93)
Laryngeal/airway discomfort	99 (52)
Voice changes	64 (34)
Asthenia	186 (98)
Pain/discomfort	171 (90)
Mobility issues	18 (9)
Problems with self-care	84 (44)
Problems with daily activities	151 (79)
Cognition	
Concentration issues	186 (98)
Memory issues	177 (93)
Comunication issues	173 (91)
Anxiety	169 (89)
Depression	149 (78)
Gastrointestinal	
Difficulty swallowing	39 (21)
Nutiotional issues	34 (18)
Faecal Incontinence	29 (15)
Urinary incontinence	39 (21)
PTSD screening	
Unwanted memories	63 (33)
Unpleasant dreams	31 (16)
Avoidance behaviours	61 (32)

PTSD: post-traumatic stress disorder

b. comparison pre and post COVID-19 infection.

Domain	Pre-COVID-19	Post COVID-19	Median of Change	IC95%	p
Breathlessness at rest	0 (0-0)	1 (0-3)	1	0.145 – 1.855	**<0.001**
Breathlessness on dressing	0 (0-0)	2 (0-4)	2	1.758 – 2.241	**<0.001**
Breathlessness on walking	0 (0-2)	5 (3-7)	4	3.13 – 4.686	**<0.001**
Fatigue	0 (0-2)	8 (6-9)	6	5.10 – 6.90	**<0.001**
Pain	0 (0-1)	6 (4-8)	5	4.338 – 5.662	**<0.001**
Cognition	0 (0-1)	7 (6-8)	6	5.233 – 6.767	**<0.001**
Depression	0 (0-2)	3 (0-6)	2	1.239 – 2.761	**<0.001**
Communication	0 (0-0)	6 (4-8)	5	4.483 – 5.517	**<0.001**
Self-care	0 (0-0)	0 (0-4)	0	−0.258 – 0.258	**<0.001**
Usual activities	0 (0-0)	6 (3-8)	5	4.515 – 5.485	**<0.001**
Social role	0 (0-0)	5 (0-8)	4	3.024 – 4.976	**<0.001**
Global health*	2 (1-2)	6 (5-7)	4	3.772 – 4.228	**<0.001**

Supplementary table S3. Quality of Life and Cognitive Assessments by country.

Instrument	Total (n=180)	Australia (n=155)	Chile (n=35)	p
HRQoL and Psychological Measures				
Patient Health Questionnaire (PHQ-9)	11.9 (5.7)	12 (5.7)	11 (5.9)	0.360
Generalized Anxiety Disorder Scale (GAD-7)	7.6 (5.2)	7.1(5.1)	9.7 (5.1)	**0.005**
Pittsburgh Sleep Quality Index (PSQI)	9.8 (3.8)	9.8 (3.7)	9.4 (4.2)	0.486
EQ-5D-5L utility	0.71 (0.22)	0.68 (0.22)	0.81 (0.16)	**0.001**
Cognitive Performance Tests				
Rey Auditory Verbal Learning Test (RAVLT)				
Immediate recall (A1-A5)	52.4 (9.4)	52.4 (9.6)	52.1 (8.4)	0.868
Delayed recall (A6)	11.1 (3.0)	11.1 (3.1)	11.2 (2.7)	0.798
Recognition (A7)	10.8 (3.2)	10.8 (3.2)	10.6 (3.2)	0.692
% retained (A6A5)	86.4 (15.8)	86.5 (16.3)	85.8 (13.3)	0.826
% recognition (A7A5)	84.2 (17.4)	85.1 (17.3)	80.6 (17.7)	0.174
Symbol Digit Modalities Test (SDMT)	56.6 (10.6)	56.3 (11.1)	57.7 (7.6)	0.541
Oral Trail-Making Test*				
Trail A	6 (6-8)	7 (6-8)	6 (5-8)	**0.027**
Trail B	27 (21-36)	28 (21-37)	23 (20-30)	0.082
Delis-Kaplan Executive Function System – CWIT				0.902
Colour Naming	29.7 (7.2)	30.1 (7.4)	27.8 (5.9)	**0.004**
Word Reading	22.3 (6.1)	22.9 (6.4)	19.6 (3.3)	**0.031**
Inhibition	54.3 (16.3)	55.5 (17.1)	48.9 (10.9)	**0.015**
Inhibition/Switching	63.6 (21.4)	65.4 (22.5)	55.7 (13.4)	0.067
Semantic Fluency	24.7 (6.2)	25.1 (6.2)	22.9 (6)	0.360

*Median (IQR). Higher PHQ-9, GAD-7, and PSQI scores indicate worse outcomes; higher EQ-5D utility, MoCA, RAVLT, SDMT, and SF scores indicate better performance.

Supplementary table S4. Health domain scores across EQ-5D index tertiles at baseline

Clinical characteristics (%)	Low (worst) HRQoL (n = 63)	Mid HRQoL (n = 63)	High (best) HRQoL (n = 62)	p-value*
Age, mean (SD)	43.3 (10.5)	44,9 (10.7)	44.96 (10.4)	0.588
Female, n(%)	51 (81)	53 (84)	43 (69)	0.110
Ethnic (314oce314sian vs no 314oce314sian), n (%)	48 (36)	49 (37)	37 (28)	**0.035**
Country = Chile, n (%)	6 (17)	8 (23)	21 (60)	**0.001**
Higher Education level	48 (35)	46 (33)	42 (31)	0.542
BMI (kg/m^2), mean (SD)	29.7 (7.5)	29.5 (7.8)	27.7 (5.3)	0.223
Comorbidities (Y/N), n (%)	55 (34)	58 (36)	47 (29)	**0.032**
Current smoking, n (%)	6 (23)	5 (19)	15 (57)	**0.015**
Alcohol consumption	23 (29)	24 (31)	32 (40)	0.172
Vaccine 314oce (>3 doses), (n%)	49 (77)	59 (94)	53 (85)	0.049
Time since acute infection months, n (%)	13.1 (8.4)	13.7 (9.2)	14.2 (10.8)	0.803
Anosmia, n (%)	11 (31)	10 (28)	15 (41)	0.456
MoCA, mean (SD)	20.3 (1.5)	20.6 (1.6)	20.4 (1.7)	0.690
Health domain				
EQ-5D index	0.46 (0.16)	0.77 (0.06)	0.92 (0.04)	**<0.001**
Depressive symptoms (PHQ-9)	15.6 (5.8)	11.8 (4.5)	8.1 (4.2)	**<0.001**
Anxiety symptoms (GAD-7)	9.1 (5.9)	7.6 (4.6)	6.0 (4.5)	**0.002**
Sleep quality (PSQI)	10.4 (3.6)	11.0 (3.7)	7.9 (3.5)	**<0.001**
Self-rated health (EQ-VAS)	40.6 (18.1)	59.0 (14.1)	71.8 (13.6)	**<0.001**
Cognitive Performance Tests				
RAVLT	51.8 (8.4)	52.8 (10.0)	52.7 (9.8)	0.796
Immediate recall (A1-A5)	11.0 (3.1)	11.2 (3.0)	11.2 (2.9)	0.868
Delayed recall (A6)	10.6 (3.3)	10.8 (3.2)	11.0 (3.2)	0.771
Recognition (A7)	84.3 (16.4)	87.3 (16.4)	87.9 (14.3)	0.390
% retained (A6A5)	83.7 (15.3)	83.9 (19.3)	85.6 (17.3)	0.801

% recognition (A7A5)	54.2 (11.5)	57.2 (10.2)	58.3 (9.7)	0.077
Symbol Digit Modalities Test (SDMT)	7.8 (2.9)	6.8 (2.3)	22.0 (115.1)	0.358
Oral Trail-Making Test*	29.3 (11.1)	31.6(18.4)	45.7 (115.8)	0.344
Trail A	32.3 (9.1)	28.4 (5.4)	28.3 (5.7)	0.002
Trail B	23.6 (5.8)	21.4 (7.0)	21.4 (4.4)	0.058
Delis-Kaplan Executive Function System	56.8 (18.4)	55.3 (17.1)	50.3 (12.2)	0.069
Colour Naming	66.0 (21.0)	65.1 (23.3)	59.6 (19.9)	0.210
Word Reading	23.7 (5.4)	25.5 (6.2)	25.0 (7.0)	0.264
Inhibition	51.8 (8.4)	52.8 (10.0)	52.7 (9.8)	0.796
Inhibition/Switching	11.0 (3.1)	11.2 (3.0)	11.2 (2.9)	0.868
Semantic Fluency	10.6 (3.3)	10.8 (3.2)	11.0 (3.2)	0.771
*P-values from one-way ANOVA or chi-square test comparing the three EQ-5D tertiles, as appropriate.				

Supplementary table S4. Demographic, clinical and health domain characteristics according to extreme HRQoL impairment (lowest EQ-5D utility tertile vs higher tertiles).

Demographic and clinical variables	No extreme impairment (n = 125) [a]	Extreme impairment (n = 63) [a]	Effect estimate[b] (95% CI)	p-value[c]
Age, years	45.0 (10.5)	43.3 (10.6)	1.68 (−1.53, 4.89)	0.300
BMI, kg/m²	28.7 (6.7)	29.7 (7.6)	−1.06 (−3.23, 1.12)	0.340
Days since acute COVID-19	464 (309.9)	438 (257.1)	25.7 (−63.8, 115.1)	0.570
N° of comorbidities	0.84 (0.37)	0.87 (0.34)	−0.03 (−0.14, - 0.08)	0.550
Female sex, n (%)	96 (76.8)	51 (81.0)	0.78 (0.37, 1.65) [e]	0.520
Country: Chile, n (%)	29 (23.2)	6 (9.5)	0.35 (0.14, 0.89) [e]	**0.023**
COVID-19 vaccine doses >4, n (%)[f]	15 (12.2)	6 (9.7)	0.77 (0.28, 2.10) [e]	0.610
Persistent anosmia, n (%)	25 (20.0)	11 (17.5)	0.85 (0.39 - 1.85) [e]	0.680
Current smoker, n (%)	20 (16.0)	6 (9.5)	0.55 (0.21, 1.45) [e]	0.230
Alcohol use, n (%)	56 (44.8)	23 (36.5)	0.71 (0.38, 1.32) [e]	0.280
Education level, n (%)[g]			—	0.500
– Secundary school	21 (16.9)	7 (11.1)		
– Undergraduate	36 (29.0)	24 (38.1)		
– Postgraduate	52 (40.3)	24 (38.1)		
– Technical vocational	10 (7.8)	7 (11.1)		
– Other	5 (3.9)	1 (1.6)		
Health domain measures				
PHQ-9	10.0 (4.7)	15.6 (5.8)	−5.60 (−7.16, −4.03)	**<0.001**
GAD-7	6.8 (4.6)	9.1 (5.9)	−2.34 (−3.87, −0.80)	**0.003**
PSQI total score	9.5 (3.9)	10.4 (3.6)	−0.94 (−2.11, 0.23)	0.120
EQ-5D VAS (0–100,	65.4 (15.2)	40.6 (18.1)	24.73 (19.78, 29.68)	**<0.001**

SDMT (processing speed)	57.8 (9.9)	54.2 (11.5)	3.57 (0.37, 6.77)	**0.029**

a Values are mean (SD) for continuous variables and n (%) for categorical variables, unless otherwise specified.
b For continuous variables, the effect estimate is the mean difference (no extreme impairment − extreme impairment). For binary variables, the effect estimate is the odds ratio (OR) for extreme impairment comparing the category shown with the reference group.
c p-values from independent-samples t tests (continuous variables) or Pearson's chi-square tests / univariable logistic regression (categorical variables), as appropriate.
e OR (95% CI) from univariable logistic regression models with extreme impairment as the dependent variable..
g p-value from chi-square test for the overall distribution of education levels across groups.

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Co-Designing aphasia services for regional and remote Queensland: Experiences and unmet needs of speech pathologists managing aphasia care

Mrs Lisa Anemaat[1,2], Prof Victoria Palmer[3,4], Prof David Copland[1,2], Dr Sarah Wallace[1,2]
[1]Queensland Aphasia Research Centre, The University of Queensland, Herston, Australia, [2]School of Health and Rehabilitation Sciences, The University of Queensland, St Lucia, Australia, [3]The Department of General Practice, Melbourne Medical School, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Parkville, Australia, [4]The ALIVE National Centre for Mental Health Research Translation, Australia

Background: Providing equitable post-stroke care in Australia is challenging. Geographic isolation and disparately located health services present unique challenges for care providers in regional and remote communities. Understanding the experiences of speech pathologists is crucial to determine where the pressure points and gaps in service delivery exist and where support is needed.
Aims: To identify from the perspective of speech pathologists in regional and remote Queensland: (1) positive and challenging experiences of post-stroke aphasia care management; and (2) priorities for service development.
Methods: Experience Based Co-Design (EBCD). Speech pathologists (n=23) were recruited through 10 Queensland Hospital sites and online professional affiliate groups. Maximum variation in years of experience working with people with aphasia, type of health service setting, clinical caseload (acute, subacute and chronic), and geographical remoteness was acquired. As part of the EBCD process participants shared positive and challenging experiences of managing aphasia care. Thematic analysis was applied to experiential data. Priorities for service development were established using the nominal group technique. Priorities were ranked and analysed using inductive content analysis.
Results: We conducted 7 online focus groups and 4 semi-structured interviews across remote and regional Australia. Speech pathologists (experience: <2yrs=13%; 2-10yrs=61%; >10yrs=26%) shared 54 experiences of managing care across the care continuum and health service settings. Preliminary touchpoints (themes) of unmet need include: 1) clinician competence, 2) service capacity limiting care, 3) reduced access to services, and 4) providing culturally appropriate support. Participants generated 167 potential priorities for aphasia service development.
Conclusion: In regional and remote areas negative experiences often related to providing culturally appropriate care, limitations of service contexts, and clinician competence. Unmet needs for speech pathologists included: access to supervision from experienced clinicians, resources and treatment options for culturally and linguistically diverse populations, and service constraints reducing capacity for clinicians to deliver evidence-based care.

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Understanding unmet needs after young stroke: A codesign project to develop a screening tool

Dr Karen Borschmann[1,2], Associate Professor Emma Power[3], Dr Dana Wong[4], Dr David W Lawson[1], Dr Barbara Wolfenden[1], Ms Jessica Keating[1], Professor Natasha A Lannin[5,6], Dr Toni Withiel[7], Prof Vincent Thijs[1,8], Prof Julie Bernhardt[1]
[1]The Florey, Heidelberg, Australia, [2]St Vincent's Hospital, Fitzroy, Australia, [3]University of Technology, Sydney, Australia, [4]La Trobe University, Bundoora, Australia, [5]Alfred Health, Melbourne, Australia, [6]Monash University, Melbourne, Australia, [7]Melbourne Health, Parkville, Australia, [8]Austin Health, Heidelberg, Australia

Background & Aims: Young stroke survivors (YSS) report unmet needs related to age and life stage that stroke services often overlook. Researchers, advisers with lived experience, and clinicians collaborated to develop the "Young Stroke Unmet Needs Screening Tool".
Method: Mixed-method codesign project conducted in three phases:
1. Literature review conducted and workshop held with 12 advisers (8 YSS, 4 clinicians) to develop initial tool content.
2. Online survey conducted to examine YSS preferences for methods of meeting needs, and gain feedback on tool's usability and content.
3. A version was then developed for people with communication or cognitive impairment using Principles of Supported Conversation for Adults with Aphasia, and cognitive strategies. Semi-structured interviews and focus groups held to further develop and test both versions.

Results: 171 online survey responses (68% female, mean age 45 years, IQR 36-51). Respondents' demographic and stroke-related characteristics influenced preferences for methods of meeting needs, including face-to-face contact with professionals, peer support and succinct tip sheets.
Interviews and focus groups were held online due to COVID, with 20 YSS (age 24-53yrs, 60% reported cognitive impairments and 80% had mild to moderate-severe language limitation), and 10 family members. Recruitment of people with more severe language limitations required personal invitation rather than advertising via social media or stroke groups.
The tools include six domains (Body and Mind, Emotions, Information, Daily Life, Relationships, Social) covering 53 potential needs. Also included is a distress thermometer. Use of the tool was strongly endorsed for both versions.
Conclusion: These new unmet needs screening tools could be used to identify service needs for young stroke survivors, including those with cognitive and/or communication difficulties. The tools are now being used in a large study to identify care pathway requirements, to inform the development of a bespoke health service for young stroke survivors

was no change in time from PSC Door-in to the first CSC DSA images (median 125 vs 125 minutes, p=0.79).
Within the DIDO workflow, the only significantly different metric was time from CSC advising of patient acceptance to PSC door-out, which improved (median 8 vs 14 minutes, p=0.016). DIDO times out of hours when the stroke registrar was called in also improved (median 51 vs 87 minutes, p=0.003).
Conclusion: The median DIDO times at our PSC improved during the pandemic. Further studies are required to determine if this is due to a continued quality improvement program at our centre, or due to other factors.

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TIA models of care in Melbourne and Geelong – a contemporary survey

Dr Ross Cody[1], Mr Shi-Ping Lim[1], Dr Anna Balabanksi[2,3], A/Prof Benjamin Clissold[4,5], A/Prof Douglas Crompton[6,7], A.Prof Lauren Sanders[7,8], Dr Shaloo Singhal[9,10], Prof Vincent Thijs[7,11,12], Dr Hans Tu[13], Dr Wenwen Zhang[14], Dr Philip Choi[1,15]
[1]Department of Neuroscience, Eastern Health, Box Hill, Australia, [2]Department of Neurology, Melbourne Health, Parkville, Australia, [3]Department of Neurology, Alfred Health, Melbourne, Australia, [4]Neuroscience Department, Barwon Health, Geelong, Australia, [5]Faculty of Health, School of Medicine, Deakin University, Geelong, Australia, [6]Department of Neurology, Northern Health, Epping, Australia, [7]Faculty of Medicine Dentistry and Health Sciences, University of Melbourne, Parkville, Australia, [8]Department of Neuroscience, St Vincent's Hospital Melbourne, Fitzroy, Australia, [9]Department of Neurology, Monash Health, Clayton, Australia, [10]Stroke & Aging Research, Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Australia, [11]Department of Neurology, Austin Health, Heidelberg, Australia, [12]Florey Institute of Neuroscience and Mental Health, Parkville, Australia, [13]Department of Neurology, Western Health, Footscray, Australia, [14]Department of Neurology, Peninsula Health, Frankston, Australia, [15]Eastern Health Clinical School, Monash University, Box Hill, Australia

Background: An objective of the National Strategic Action Plan for Heart Disease and Stroke 2021 is to improve access to transient ischaemic attack (TIA) clinics. It is unclear how patients with TIAs are managed by public health services in the two largest cities in Victoria.
Aims: To review models of care for managing TIAs in health services with neurology departments in Melbourne and Geelong.
Methods: Neurologists from ten health services took part in a survey by telephone or video conference. The survey consisted of 39 questions focusing on TIA management.
Results: The estimated volume of TIA presentations ranged from 13 to 39 per month. The neurology department's involvement in the ED presentation varied; two services aimed to physically review every patient, six aimed to provide at least phone advice to all, and two encouraged ED staff to call if concerned. Two services rarely admitted TIA patients (<10%), one admitted all TIA patients overnight, and the remaining seven varied, admitting on average 22% of TIAs. Six preferred CT angiography for initial vessel imaging, and four preferred Doppler ultrasound.
All services ensured an antithrombotic was prescribed. Five services routinely prescribed a statin, and three regularly prescribed antihypertensives. Five services routinely ordered outpatient cardiac investigations from ED, and six routinely ordered outpatient MRI from ED. The average wait for MRI varied from next day to multiple months.
Two had dedicated TIA clinics running every weekday if required, and eight had dedicated or mixed clinics running at least weekly. The average wait for these clinics varied from under a week to 3-6 months.
Conclusion: There is heterogeneity in models of care for managing patients with TIA. There are opportunities to benchmark a quality standard, and improve access to TIA clinics and investigations, so patients receive the same standard of care irrespective of their postcodes.

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Stroke in Latin America: A systematic review of the incidence, prevalence and case-fatality between 1997 – 2021

Dr Marilaura Nuñez[1], Dr Carlos Delfino1, Mrs. Claudia Asenjo-Lobos[1], Mrs. Francisca Gonzalez[1], Mrs. Amy Riviotta[1], Mrs. Francisca Urrutia[1], Dr. Pablo M. Lavados[3], Prof. Craig S. Anderson[1,2], Dr Carlos Delfino[1,2,3]
[1]Clinical Research Center, ICIM, Faculty of Medicine, Universidad Del Desarrollo, Santiago, Chile, [2]The George Institute for Global Health, University of New South Wales, Sydney, Australia, [3]Servicio de Neurologia, Departamento de Neurologia y Psiquiatria, Facultad de Medicina Clinica Alemana Universidad del Desarrollo, Santiago, Chile

Background: Stroke is a major global cause of death and disability but as most strokes occur in low-middle income countries (LMIC), the subsequent disease burden is greater than in high-income countries. Few epidemiological data exist for stroke in Latin America, which is primarily composed of LMIC.
Aim: To determine epidemiological measures of incidence, prevalence, and 1-month case-fatality for stroke in Latin America/Caribbean during 1997-2021.
Methods: A structured search was conducted to identify relevant references from MEDLINE, WOS, and LILACS databases for prospective observational and cross-sectional studies in Latin American populations from January 1997 to December 2021. Titles and abstracts, full-text review, and data extraction were conducted in duplicate. Crude and age-adjusted prevalence and incidence of stroke, and case fatality per 100,000 people in Latin America, and sex-disaggregated data, were collected where available. A narrative synthesis of the findings from the included studies was assessed systematically, and where meta-analysis was deemed appropriate, random-effects techniques were used to obtain pooled estimates and 95% confidence intervals. The quality of studies was evaluated according to the study risk of bias criteria in the Joanna Briggs Institute's guide to conducting prevalence and incidence review.
Results: From 9242 identified records, 7301 titles and abstracts were screened after removing duplicates. Of these, 118 met the criteria for full-text review and eligibility, for which 20 articles were selected for analyzes. Final results will be presented during the conference.
Conclusions: The results of this review are highly relevant for defining the burden of stroke in Latin America. This information will allow a better understanding of the disease characteristics and gaps in knowledge within a cultural and ethnic diverse group, to guide future preventive policies.
Systematic review registration number: PROSPERO 2022 CRD42022325247

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Haemoglobin levels and outcome following endovascular thrombectomy in large vessel occlusion stroke

Dr Joseph Donnelly[1,2], Dr Jae Beom Hong[1,2], Dr Douglas Campbell[3], Dr William Diprose[4], Ms Vivien Yong[1,2], Professor P. Alan Barber[1,2]
[1]Department of Medicine, University of Auckland, Auckland, New Zealand, [2]Department of Neurology, Auckland City Hospital, Auckland, New Zealand, [3]Department of Anaesthesiology, University of Auckland, Auckland, New Zealand, [4]Department of Neurology, Royal North Shore Hospital, Sydney, Australia

Background: In ischaemic stroke, low and elevated haemoglobin levels have been associated with poor outcome in large epidemiologic studies. It is unclear whether haemoglobin levels are prognostic in stroke patients treated with endovascular thrombectomy.
Aim: To evaluate the influence of low and elevated haemoglobin levels on patient outcome in endovascular thrombectomy treated stroke patients.

	N=50
• Age	42 yo
• Gender	Male 60% Female 40%
Comorbidities	
• Obesity	80%
• Hypertension	70%
• Diabetes	70%
• Heart disease	20%
• Nephropathies	6%
• Autoimmune	2%
Neuropsychiatric symptoms	
• Headache	100%
• Depression	100%
• Anxiety	100%
• Fatigue	100%
• Recent memory disorder	95%
• Hypersomnia	60%
• Insomnia	40%
• Distal paresthesias	40%
• Dizziness	30%
• Myalgia	30%
• Anosmia	20%
• Dysgeusia	6%
• Shaking	6%
Laboratory alterations	
• C-reactive protein (>10mg/L)	20%
• D-dimer (>500ng/ml)	60%
• Lymphopenia (<1000 cel/mcL)	30%
COVID-19 infections	
• 1	20%
• 2	30%
• 3 or more	50%
Vaccination status	
• Vaccinated	94%
• Not vaccinated	6%

Conclusions

Long COVID is an entity associated with a chronic inflammatory process after a case of COVID-19 presenting great disabling neuropsychiatric symptoms, probably favored by repeated episodes of acute infection coupled with the neurotropism of Sars Cov2 that condition greater morbidity in this area, increasing the burden of the disease globally.

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Increased risk of long-term post-COVID neurologic symptoms in women

Carlos Delfino [a], Cecilia Poli [a,b,c], Cecilia Vial [a,d], Pablo Vial [a,d], Catalina Arbat [c], Josefina Hoppe [c], Nicole Mac-Guire [c], Paula Muñoz Venturelli [a,f], [a] *Universidad del Desarrollo, Facultad De Medicina, Instituto De Ciencias E Innovación En Medicina, Región metropolitana, Chile,* [b] *Programa de Inmunogenética y Inmunología Traslacional., Instituto De Ciencias E Innovación En Medicina, Facultad De Medicina, Universidad Del Desarrollo, Región metropolitana, Chile,* [c] *Unidad de Inmunología y Reumatología, Hospital Roberto Del Río, Región metropolitana, Chile,,* [d] *Programa de Hantavirus y Zoonosis, Instituto de Ciencias e Innovación en Medicina, Facultad De Medicina, Universidad Del Desarrollo, Región metropolitana, Chile,* [e] *Clínica Alemana de Santiago, Universidad del Desarrollo, Facultad De Medicina, Región metropolitana, Chile,* [f] *The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia*

Background and aims

COVID-19 long-term sequelae have not been well characterized.

Aim

To describe long-COVID (LC) symptoms and to identify clinical and laboratory predictors of neurologic LC.

Methods

Patients < 65 years old admitted for COVID-19 at Clínica Alemana de Santiago, Chile between June 2020 and July 2021 were consecutively registered. Acute clinical data and inflammatory parameters were collected. A phone interview was performed at 6 and 12 months after discharge to assess the presence of LC symptoms. Logistic regression was performed considering statistical and clinically relevant variables, using STATA v16.1.

Results

The cohort comprised 130 patients with a mean age of 42 years (IQR 37-55), 34 % were women. At six months, 104 patients were assessed: 71/104 had LC symptoms and 34/104 were from the neurologic area. Of those who reported LC symptoms at 6 months, 52/71 had persistent LC symptoms at 12 months follow-up, of which 30/71 were neurological. When comparing patients with vs. without neurologic LC symptoms at 6 months (table 1), we found that in the first group 16/34 (52 %) were women, compared to 15/70 (22 %) in the second group ($p = 0.011$). No difference was found between the groups regarding other demographic characteristics, clinical severity, or inflammatory biomarkers. Logistic regression confirmed the higher risk for women compared to men (OR = 4.72, IC95 % 1.24–17.99).

Table 1. Demographic, clinical characteristics and inflammatory parameters of patients with and without Neurological LC symptoms

	Neurological LC symptoms (n=34)	Controls (n=70)	p
Women (n, %)	16 (52)	15 (22)	**0.011**
Age, years (median, IQR)	45 (38-59)	40 (38-55)	0.130
BMI (kg/cm²), (median, IQR)	26 (24-29)	29 (26-31)	0.060
Charlson Comorbidity Index-0 (no comorbidity), (n, %)	13 (38)	24 (34)	0.693
Length of hospitalization (days), (median, IQR)	5 (4-6)	5 (4-7)	0.411
Invasive mechanical ventilation requirement (n, %)	3 (8)	5 (7)	0.714
COVID-19 vaccine before admission (n, %)	2 (6)	9(12)	0.496
Blood exams			
WBC, /mm3 (median, IQR)	8950 (5800-10200)	7200 (5600-9700)	0.318
VHS (median, IQR)	41 (27-60)	43.5 (27.5-58)	0.901
Highest value of CRP (mg/L) (median, IQR)	7.9 (4.87-10.75)	5.86 (2.14- 12.42)	0.235
Presence of NLRP3 rs10754555 variant (n, %)			
G/G	3 (10)	2 (18)	-
G/C	6 (47)	10 (35)	-
C/C	8 (45)	9 (47)	-
Inflammatory risk genotype (G/G, G/C), (n, %)	9 (43)	12 (57)	1.000

BMI: body mass index, WBC: white blood cells, CRP: C reactive protein

Conclusions

In this cohort of admitted COVID-19 patients, women had a fourfold higher risk of long-term neurological symptoms. These findings are consistent with previous published data; future work should underpin the causes of this sex-predominance.

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ESOC 2024 – ORAL ABSTRACTS

SCIENTIFIC COMMUNICATION – ATHEROSCLEROSIS & STROKE

Abstract N°: 486

ASSOCIATIONS BETWEEN PLAQUE MORPHOLOGY AND STROKE MECHANISMS IN SYMPTOMATIC INTRACRANIAL ATHEROSCLEROTIC DISEASE

Xuan Tian*[1], Yu Liu[1], Shuang LI[1], Yuying Liu[1], Jill Abrigo[2], Bonaventure Ym Ip[1], Sze Ho MA[1], Wt Lui[1], Thomas Leung[1], Xinyi Leng[1]
[1]The Chinese University of Hong Kong, Department of Medicine and Therapeutics, Hong Kong, China, [2]The Chinese University of Hong Kong, Department of Imaging and Interventional Radiology, Hong Kong, China
On behalf of:

Background and aims: Intracranial atherosclerotic stenosis (ICAS) could cause an ischemic stroke via various mechanisms. We aimed to explore the associations between plaque morphology and stroke mechanisms in symptomatic ICAS.
Methods: We prospectively enrolled patients with acute ischemic stroke due to high-grade ICAS (60%-99%) in anterior circulation identified in three-dimensional rotational angiography (3DRA). The probable stroke mechanisms were classified into parent artery atherosclerosis occluding penetrating artery (PAO), artery-to-artery embolism (AAE), hypoperfusion and mixed mechanisms. Plaque morphology was assessed in 3DRA, including luminal stenosis, plaque thickness/length, upstream shoulder angulation, plaque eccentricity, surface contour, longitudinal plaque distribution and presence of adjoining branch atheromatous disease. We compared these morphological parameters among patients with different stroke mechanisms.
Results: Among 145 patients (median age 62 years, 69.7% males), 23 (15.9%), 14 (9.7%), 58 (40.0%) and 50 (34.5%) respectively had isolated PAO, AAE, hypoperfusion and mixed mechanisms of AAE and hypoperfusion. Upstream shoulder angulation >45° was associated with presence of AAE (45.3% versus 17.4%, p=0.018), while none of the plaque morphology metrics was associated with presence of hypoperfusion. In multinomial logistic regression among those with a single stroke mechanism (n=95), upstream shoulder angulation was an independent predictor of isolated AAE, as a continuous (adjusted odds ratio 1.03, 95% confidence interval 1.00-1.06, p=0.030) or categorical variable (>45° versus ≤45°, 8.61, 1.84-40.18, p=0.006), with isolated PAO as reference.
Conclusions: ICAS lesions with a steeper upstream plaque shoulder were more likely to cause an ischemic stroke via AAE. The mechanisms could be verified in rheological studies.
Disclosures of Interest: No

Abstract N°: 810

INTRACRANIAL ATHEROSCLEROTIC PLAQUES RISK STRATIFICATION: A RADIOMICS ANALYSIS

Elena Sagues Sese*[1], Sebastian Sanchez[2], Sricharan Veeturi[3], Diego Ojeda[1], Carlos Dier Melo[1], Vicent Tutino[3], Edgar Samaniego[1]
[1]University of Iowa Hospitals & Clinics, Neurology, Iowa City, United States, [2]Yale University, Neurology, New Haven, United States, [3]University at Buffalo (South Campus), Buffalo, United States
On behalf of:

Background and aims: High resolution vessel wall imaging (HR-VWI) enables accurate visualization of intracranial atherosclerotic plaques. Radiomics can be utilized as an objective quantification method of plaque appearance and shape. We aimed to analyze the radiomics features (RFs) obtained from 7T-HR-VWI to differentiate between culprit and non-culprit plaques in patients with intracranial atherosclerotic disease (ICAD).
Methods: Patients with ICAD as stroke etiology undergoing HR-VWI were included in the study. Culprit plaques in the vascular territory of the stroke were identified. The degree of stenosis, area degree of stenosis and

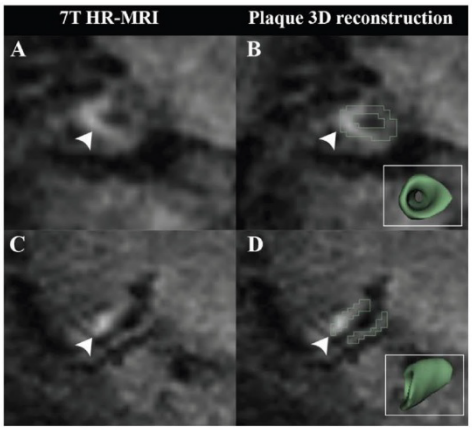


Figure 1. A-D) Plaque visualization in 7T HR-VWI, segmentation and 3D reconstruction.

Background and aims: To measure whether human UrinaryKallindinogenase (HUK) has benefits for patients with acute ischemic stroke (AIS) after discharge and the 3-months after time of onset of this disease.
Methods: In this prospective, multiple centers, real world study involving 80 hospitals in China registered with ClinicalTrials.gov (NCT02470624), patients with AIS were treated following the Chinese stroke guideline and local practice. Real-world data on treatment regimens and clinical outcomes are collected at baseline and subsequent visits. Patients were analyzed whether or not receiving preconditioned Human Urinary Kallindinogenase (HUK group) or standard treatment alone (control group). The primary outcome was the alteration of the score on the modified Rankin Scale (mRS) between the discharge and the 3 months re-investigation. Secondary measurements included alteration in NIHSS at discharge after admission and the classification of the shift of mRS(including the age and gender)
Results: A total of 10002 cases were recruited. After the criteria filter and propensity score matching (PSM), 2319 cases were ultimately analyzed in the study with 1:1 ratio of HUK or non-HUK group, seperatively. Baseline characteristics were not different between groups. There was significant difference between the groups in the shift of mRS score ($p < 0.001$) and the HUK group performed the improvement with larger numbers with statistical significance.
Conclusions: HUK treatment was associated with improvements in the shift from discharge to 3-month mRS score. However, large scale Randomized clinical trials(RCT), especially the underlying cerebral hemodynamics mechanism still need further study.
Disclosures of Interest: No

Abstract N°: 673

CHALLENGES OF RECANALIZATION THERAPY IN ACUTE STROKE PATIENTS TAKING DOACS

Jessica Seetge*[1], László Szapáry[1]
[1]University of Pécs, Department of Neurology, Pécs, Hungary
On behalf of:

Background and aims: Direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) are the recommended primary therapy for preventing acute ischemic stroke (AIS) in patients with atrial fibrillation. Nonetheless, an annual AIS risk of 1-2% endures despite their effectiveness. Intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) are interventions capable of reducing AIS-related morbidity. Herein, we assess the safety and efficacy of recanalization therapy in anticoagulated patients.
Methods: Within the prospective TINL-STROKE-registry, AIS patients admitted to the Department of Neurology, between February 2023 and March 2024 were investigated. The study's objective was to assess the association between oral anticoagulant (OAC), choice of reperfusion therapy, proportion of functionally independent patients at 90 days (modified Rankin Scale [mRS] $\leqslant 2$), and clinical improvement (National Institute of Health Stroke Scale [NIHSS] $\leqslant 1$ or change from baseline [Δ NIHSS] $\geqslant 4$) after 72 hours. Outcomes were compared with (ordinal) logistic regression analyses adjusted for confounding factors.
Results: 627 eligible patients (DOAC, n=72 and VKA, n=40 vs. non-anticoagulated, n=515) was included. 307 patients underwent reperfusion therapy (133 IVT, 131 MT, 43 IVT+MT), the remaining 320 received standard care (SC). Anticoagulated patients (n=112) showed less favorable outcomes than non-anticoagulated patients (n=515): 29,2% vs. 49,4% 90-day mRS $\leqslant 2$, 29,5% vs. 36,3% NIHSS $\leqslant 1$, 23,2% vs. 26,2% Δ NIHSS $\geqslant 4$ and 90-day mortality: 26,8% vs. 13,8%. However, this difference was no longer apparent after adjustment for baseline prognostic factors.
Conclusions: Our study adds evidence to the safety and efficacy of recanalization therapy in patients with prior therapeutic anticoagulation.
Disclosures of Interest: No

Abstract N°: 1126

CLINICAL OUTCOMES AFTER ACUTE ISCHEMIC STROKE IN PATIENTS WITH COMORBID CANCER

Ryu Matsuo*[1], Noriko Sato[2], Fumi Kiyuna[2], Fumi Irie[1], Yoshinobu Wakisaka[2], Tetsuro Ago[2], Masahiro Kamouchi[1], Takanari Kitazono[1]
[1]Kyushu University, Department of Health Care Administration and Management, Graduate School of Medical Sciences, Fukuoka, Japan, [2]Kyushu University, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Fukuoka, Japan
On behalf of: the Fukuoka Stroke Registry

Background and aims: Comorbid cancer was not uncommon in patients with stroke. This study aimed to determine whether comorbid cancer is associated with functional outcomes after acute ischemic stroke.
Methods: We investigated data on patients with acute ischemic stroke who were hospitalized in 7 stroke centers in Fukuoka, Japan, between June 2007 and September 2019. Comorbid cancer was categorized into non-active and active cancer based on its status at stroke onset. Clinical outcomes included poor functional outcome (modified Rankin Scale [mRS] score of 3-6), all-cause death, and functional dependency (mRS score of 3–5) at 3 months. Logistic regression analysis was performed to adjust for multiple confounding factors.
Results: Of 13,047 patients (aged 71.1 ± 12.3 years, 62.8% men) without pre-stroke disability, 1,384 (10.8%) patients had non-active cancer, and 622 (4.8%) had active cancer at stroke onset. Active cancer was associated with poor functional outcome (multivariable-adjusted odds ratio [95% confidence interval], 2.26 [1.85-2.76]), death (5.99 [4.42-8.14]), and functional dependency (1.62 [1.30-2.02]) even after adjusting for covariates, whereas no association was found between non-active cancer and the clinical outcomes. These associations were maintained when clinical outcomes were assessed at discharge. The associations of active cancer with 3-month unfavorable functional outcomes were still found even after excluding patients with previous stroke, or patients who had recurrent stroke within 3 months after onset.
Conclusions: Active cancer but not non-active cancer was associated with an increased risk of unfavorable functional outcomes as well as death at 3 months after acute ischemic stroke.
Disclosures of Interest: No

Abstract N°: 1386

STROKE OUTCOMES USING UTILITY-WEIGHTED MODIFIED RANKIN SCALE SCORES: RESULTS FROM A LARGE COMMUNITY-BASED STUDY IN CHILE

Carlos Delfino*[1], Paula Muñoz Venturelli[1,2,3], Gabriel Cavada[4], Lorena Hoffmeister[1], Pablo Lavados[2,4]
[1]Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile, las condes, Chile, [2]Clinica Alemana, Servicio de Neurología, Departamento de Neurología y Psiquiatría, Clínica Alemana de Santiago, Facultad de Medicina, Vitacura, Chile, [3]The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Barangaroo, Australia, [4]Unidad de Investigación y Ensayos Clínicos, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile
On behalf of:

Background and aims: A promising approach to Patient-Reported Outcome Measures in stroke is the transformation of mRS (modified Rankin Scale) scores according to respective utilities of health-related quality of life questionnaires. We aimed at mapping mRS functional status

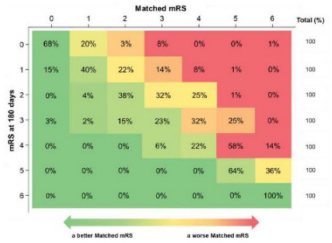
and the EQ5D-3L to derive utility-weighted (UW) stroke outcomes from a representative national cohort.

Methods: The UW-mRS was obtained by analysing the EQ5D-3L and mRS scores at 180 days after any stroke in the ÑANDU study, a large prospective community-based study in Chile. The mRS prediction was estimated using a linear regression adjusted by the EQ5D-3L tariff. A misclassification matrix was used to classify each patient into a new ''matched'' mRS category. Formal agreement between the "current" and "matched" mRS was estimated by correspondence analysis. STATA v18.0 was used.

Results: In this analysis, 958 patients with a stroke in 2015-2016 were considered: 48% were women, had a mean age of 71 (SD 13.8) years, and 85% had an ischemic stroke. UW-mRS values for mRS categories 0–6 at 180 days were 0.88, 0.69, 0.47, 0.36, 0.15, 0.03, and 0. When comparing the mRS weighted by EQ5D-3L (matched) with the current mRS, between 32-72% of patients in all mRS scores were considered in a worse mRS, with a higher discrepancy in patients with mRS 4. (figure 1)

Conclusions: Our findings, derived from a nationally representative cohort, underscore the need to develop novel outcome assessment methods for stroke patients describing their health status more comprehensively.

Proportion of patients classified in a matched mRS based on the UW-mRS value closest to their observed EQ5d-3L utility value.



Disclosures of Interest: No

Abstract N°: 1443

THE STRUCTURAL CONNECTOME IS ASSOCIATED WITH COGNITIVE PERFORMANCE OVER TIME IN YOUNG STROKE SURVIVORS

Esther Boot*[1], Mijntje Schellekens[1], Jamie Verhoeven[1], Merel Ekker[1], Hao LI[1], Roy Kessels[2], Anton Meijer[3], Frank-Erik De Leeuw[1], Anil Tuladhar[1]

[1]Radboud University Medical Centre; Donders Institute for Brain, Cognition and Behaviour, Neurology, Nijmegen, Netherlands, [2]Radboud University Medical Centre; Donders Institute for Brain, Cognition and Behaviour, Medical Psychology, Nijmegen, Netherlands, [3]Radboud University Medical Centre; Donders Institute for Brain, Cognition and Behaviour, Radiology, Nijmegen, Netherlands

On behalf of:

Background and aims: Post-stroke cognitive impairment is common among young stroke survivors, but its mechanisms remain unclear. We aimed to study the relationship between brain network measures and cognitive performance in this population, focusing on hub regions.

Methods: A cohort of young stroke survivors (ages 18-49) with confirmed cerebral ischemia from the ODYSSEY study underwent MRI and neuropsychological assessments at baseline (n=60) and follow-up (n=46). We used Diffusion Tensor Imaging (DTI) based connectivity matrices for graph analysis. Lesion impact scores (combining affected voxel percentage and mean betweenness centrality) and rich club scores (quantifying affected voxels in rich club areas) were calculated using a normative brain atlas derived from DTI data from 23 stroke-free controls. Participants were categorized as no/mild or major vascular cognitive disorder (VCD) and group differences were examined.

Results: Among 60 participants (median age: 39.2 (IQR 27.9-46.2) and 52% female), 20 had major VCD. The major VCD group exhibited larger lesions (p=0.02), lower global efficiency (p=0.03), local efficiency (p=0.047) and density (p=0.03) compared to the no/mild VCD group, persisting at follow-up. At follow-up, the major VCD group showed significantly higher lesion impact scores and rich club scores, however validation analysis in a larger cohort (n=287) could not replicate these findings.

Table 1: Characteristics of study population

	All participants (n=60)		p-value	Controls (n=23)	p-value
	No/mild VCD n=40	Major VCD n=20			
Mean age at index event, years (SD)	40.3 (31.6-46.3)	38.8 (25.-44.4)	0.67	34.5 (27.0-47.0)	0.85
Men, n (%)	25 (62.5%)	4 (20%)	**0.003**	12 (52.2%)	0.75
Mean time to follow-up assessment, days (SD)*	523.5 (105.8)	505.0 (97.0)	0.58	NA	NA
Mean interval baseline and follow-up, days (SD)*	406.3 (96.0)	394.2 (87.3)	0.68	NA	NA
Median education level (IQR)	5 (5-6)	5 (5-5)	0.07	6 (5-6.5)	0.09
Median NIHSS score at discharge (IQR) **	0 (0-1.25)	1 (0-3.5)	**0.03**	NA	NA
Median mRS at baseline (IQR)	1 (0-1)	2 (1-2)	**<0.001**	NA	NA
TOAST, n (%)			0.66	NA	NA
Atherothrombotic	0 (0)	1 (5)			
Likely atherothrombotic	2 (5)	1 (5)			
Small vessel disease	6 (15)	2 (10)			
Cardioembolic	13 (32.5)	4 (20)			
Rare causes	5 (12.5)	4 (20)			
Multiple causes	3 (7.5)	3 (15)			
Cryptogenic	11 (27.5)	5 (25)			
Mean time to MRI, days (IQR)	28.5 (4.8-80)	12.5 (4.5-94.8)	0.90		NA
Lesion location, N (%)			0.90		NA
Right supratentorial	19 (47.5)	9 (45.0)			
Left supratentorial	14 (35.0)	7 (35.0)			
Bilateral supratentorial	2 (5)	1 (5.0)			
Unilateral supratentorial and infratentorial	2 (5)	0			
Bilateral supratentorial and infratentorial	3 (7.5)	3 (15.0)			
Lesion volume on MRI, mL (IQR)	0.91 (0.4-2.6)	3.99 (0.8-16.8)	**0.01**		NA
Global Efficiency, (SD)	0.003 (0.001)	0.003 (0.001)	**0.01**	0.004 (0.001)	**<0.001**
Local Efficiency, (SD)	0.003 (0.001)	0.002 (0.001)	**0.02**	0.003 (0.000)	**<0.001**
Density, (SD)	0.11 (0.02)	0.10 (0.02)	**0.03**	0.12 (0.01)	**<0.001**
Strength, (SD)	0.005 (0.001)	0.005 (0.001)	0.10	0.006 (0.001)	**<0.001**
Clustering Coefficient, (SD)	0.001 (0.000))	0.001 (0.000)	**0.03**	0.001 (0.000)	**<0.001**
Lesion Impact Score	726.4 (167.5-3500.2)	3144.3 (411.4-9280.2)	**0.04**		NA
Rich Club score	0.0 (0.0-67.0)	41.0 (1.75-165.0)	**0.03**		NA

Education category 5, i.e. middle school / secondary vocational training. IQR: interquartile range. NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankins Scale; MMSE: Mini-Mental State Examination; MINI: Mini International Neuropsychiatric Interview; CIS-20R: Checklist Individual Strength; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.
*46 completed second neuropsychological assessment, ** 2 missing

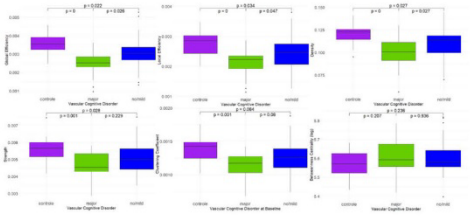


Figure 1. Boxplots of the structural network properties, divided by group (n=83), adjusted for age and gender

1° LUGAR PRESENTACION ORAL DE PÓSTER

PATIENT CENTERED OUTCOMES IN STROKE: UTILITY-WEIGHTED MODIFIED RANKIN SCALE RESULTS IN A COMMUNITY-BASED STUDY

Carlos Delfino[1†], Gabriel Cavada[2], Lorena Hoffmeister[1], Pablo Lavados[2,3], Paula Muñoz Venturelli[1,3,4]

† Principal author
[1] Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile
[2] Unidad de Investigación y Ensayos Clínicos, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile
[3] Servicio de Neurología, Departamento de Neurología y Psiquiatría, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile
[4] The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia

Background and aims: The transformation of modified Rankin Scale (mRS) scores into utility-weighted values using health-related quality of life (HRQoL) measures can enhance the capture of Patient-Centered Outcomes (PCOs) in stroke. We aimed to derive utility-weighted modified Rankin Scale (UW-mRS) values by mapping mRS functional status to EQ-5**D-3L scores in a population-based stroke cohort.**

Methods: UW-mRS values were obtained by analyzing the EQ5-D-3 L and mRS scores at 180 days post-stroke in the ÑANDU study, a large prospective community-based study in Chile. mRS prediction was estimated using a linear regression adjusted by the EQ-5D-3L values. Generalized linear and binary logistic regression models were constructed to determine influencing factors of the UW-mRS, using STATA (v18.0).

Results: We included 773 patients with any stroke between 2015–2016: 48% female, mean age 71 years (SD 13.8), 85% had an acute ischemic stroke (AIS). Overall, 82% had low socioeconomic status, 50% had <12 years of formal education, and 32% lived in urban areas. UW-mRS values for mRS categories 0–6 at 180 days were 0.913, 0.694, 0.425, 0.249, −0.102, −0.347, and 0. In multivariable analysis, significant predictors of worse UW-mRS included age >70 years (β −0.038 [SE 0.018], p = 0.032), prior mRS 3–5 (β −0.556 [SE 0.197], p < 0.001), ischemic stroke (β −0.066 [SE 0.025], p = 0.010), and NIHSS >5 at admission (β −0.015 [SE 0.002], p < 0.001), explaining 70% of the variance. Sex-disaggregated analysis showed age >70 years was significant for males (β −0.069 [SE 0.024], p = 0.006), while AIS had a greater negative impact on females (β −0.087 [SE 0.033], p = 0.010).

Conclusion: We present UW-mRS values derived from a population-based stroke study. Key determinants of health-related quality of life in post-stroke patients included age, prior disability, and stroke severity. Sex-disaggregated analysis revealed age being significant for males and AIS for females. Incorporating PCO as UW-mRS in stroke research can provide a more nuanced understanding of the impact of stroke on survivors, offering valuable insights for clinical decision-making and rehabilitation strategies across diverse healthcare contexts.

Keywords: patient-centered outcomes, stroke, utility-weighted, modified Rankin Scale

Contact: cdelfino@udd.cl

Cerebrovascular Diseases

9th World Intracranial Hemorrhage Conference (WICH) 2025 & 4th Hemorrhagic Stroke Academia Industry Meeting (HEADS)

Sydney, Australia, March 27–29, 2025

Abstracts

Guest Editors

Magdy Selim
Beth Israel Deaconess Medical Center, Boston, United States

Craig Anderson
George Institute for Global Health, University of New South Wales, Sydney, Australia

Conflict of Interest Statement
The abstracts included in this supplement were reviewed and selected by WICH 2025 Executive Committee. The committee has no conflicts of interest in connection with the conference and the selection of abstracts.

OP-10
Topic: Epidemiology and outcomes

Quality of Functional Outcome and its determinants in ICH. Insights from the INTERACT3 trial

Authors: Carlos Delfino[1], Menglu Ouyang[2], Paula Muñoz Venturelli [1], Craig Anderson[2]

Institutions: [1] Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile
[2] The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia
[3] Servicio de Neurología, Departamento de Neurología y Psiquiatría, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile

Objectives: To determine predictors of health-related quality of life (HRQoL) and to develop utility-weighted modified Rankin Scale (mRS) scores in patients who suffered an acute intracerebral haemorrhage (ICH) using data from a pragmatic international clinical trial. Methods: The INTEnsive care bundle with blood pressure Reduction in Acute Cerebral Haemorrhage trial (INTERACT3) was an international, multicentre, stepped-wedge (4 phases/3 steps), cluster randomised trial undertaken to assess a multifaceted intervention (care bundle) in a broad cohort of patients with acute spontaneous, non-traumatic ICH. Clinical outcomes included the functional status according mRS and HRQoL bases on the 3-level version of EQ-5D, were evaluated at 6 months post-ICH. Ratings from each EQ-5D subscale were synthesized into a single utility score using UK population-based preference weights. Logistic regression models were used to identify baseline predictors of poor HRQoL (≤median EQ-5D utility scores), with adjusted odds ratios (aOR) calculated. Ordinary least squares regression was used to derive utility-weighted mRS (UW-mRS) scores for participants across both trial arms. Results: A total of 7,036 patients were analyzed, with a mean age of 62 years, and 64% were male (Table 1). Among them, 3,908 (55.5%) had unfavorable HRQoL (utility scores <0.702). Predictors of lower HRQoL included older age (aOR per decade: 0.72, 95% CI: 0.67–0.76), higher NIHSS scores at admission (aOR: 0.95, 95% CI: 0.94–0.96), larger haematoma volume (aOR per mL: 0.98, 95% CI: 0.98–0.99), prestroke disability (mRS ≥1; aOR: 0.68, 95% CI: 0.57–0.81), and decompressive surgery (aOR: 0.60, 95% CI: 0.49–0.73; all p<0.0001) (Table 2). Conversely, patients from China and those residing at home 6 months post-ICH were associated with better HRQoL (p<0.001). The mRS correlated strongly with EQ-5D utility scores (Spearman R = -0.934, p<0.0001, Figure 1). For mRS levels 0 to 5, the derived UW-mRS scores were 0.98, 0.92, 0.81, 0.65, 0.39, and 0.22, respectively (Table 3). Conclusions: This study, derived from a large international clinical trial, identified key predictors of HRQoL and developed utility-weighted mRS scores for patients with ICH. These findings enhance our understanding of the long-term impact of ICH and offer a robust framework for assessing interventions and outcomes in this population.
Keywords: Intracerebral Haemorrhage,Health-Related Quality of Life,Modified Rankin Scale,utility-weighted modified Rankin Scale