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Multimorbidity in acute ischemic stroke and its impact on short-term mortality: A Chilean nationwide database analysis

Francisca González, MPH PhD(c) [a,b], Ma. Ignacia Allende, MD [a], Marilaura Nuñez, MD PhD(c) [a], Iris Delgado, PhD [c], Paula Jakszyn, PhD [b], Carlos Delfino, MD PhD(c) [a], Craig S. Anderson, MD PhD [a,d,e], Paula Muñoz Venturelli, MD PhD [a,d,f,*]

[a] Centro de Estudios Clínicos, Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile
[b] Facultad de Ciencias de la Salud Blanquerna, Universitat Ramón Llull, Barcelona, Spain
[c] Centro de Epidemiología y Políticas de Salud, CEPS, Facultad de Medicina-Clínica Alemana. Universidad del Desarrollo, Santiago, Chile
[d] The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia
[e] Institute for Science and Technology for Brain-inspired Intelligence, Fudan University, Shanghai, China
[f] Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile

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ABSTRACT

Background: Multimorbidity predicts a worse prognosis for various diseases but its impact in people after an acute ischemic stroke (AIS) in developing societies is not well established. We aimed to characterize the pattern of multimorbidity and determine its association with in-hospital mortality after AIS in the nationwide Chilean database.

Methods: A retrospective analysis of the Diagnosis-Related Groups database for hospitalized adult patients in Chile in 2019 was conducted. Association of multimorbidity, defined as the presence of ≥2 health conditions, in patients with AIS (ICD-10 code I63) on in-hospital mortality was determined in logistic regression models adjusted for confounding variables.

Results: Of 1,048,575 recorded ICD-10 codes, there were 10,440 AIS episodes in whom 7,696 (73.7 %) patients had multimorbidity. Age, female sex, and low socioeconomic status were associated with a higher multimorbidity, and the combination of comorbidities differed across age groups. Cardiometabolic multimorbidity was associated with higher in-hospital mortality (odds ratio [OR] 1.39, 95 % confidence interval [CI] 1.16-1.66; $p<0.001$). Stage 5 chronic kidney disease combined with ischemic heart disease was the comorbidity with the highest risk of death (OR 4.20, 95 %CI 1.58-11.16; $p = 0.004$). Obesity, which exhibited a predominance in early to mid-life, had the highest association with mortality when combined with other conditions.

Conclusions: Multimorbidity is common in patients with AIS and its components vary by age and sex. Cardiometabolic multimorbidity increases the likelihood of in-hospital mortality. Adopting a multimorbidity-focused approach to stroke care could improve outcomes.

Introduction

With increases in life expectancy and socioeconomic conditions worldwide, there is greater prevalence of chronic diseases and concomitant comorbidities[1]. Multimorbidity, defined by the World Health Organization (WHO) as the coexistence of two or more chronic

Abbreviation: WHO, World health organization; AIS, Acute Ischemic Stroke; AIS_{mm}, Acute ischemic stroke with multimorbidity; IR-DRG, International refined diagnosis-related groups; ICD-10, International classification of diseases-10; ICD-9, International classification of diseases-9; CKD, Chronic kidney disease; SU, Stroke unit; HT, Hypertension; DM, Diabetes mellitus; AF, Atrial fibrillation.

* Correspondence author at: Av. Plaza 680. Edificio 0. 4 piso. Las Condes. Santiago. Chile
E-mail addresses: frgonzalez@udd.cl (F. González), m.allendee@udd.cl (Ma.I. Allende), manunezm@udd.cl (M. Nuñez), idelgado@udd.cl (I. Delgado), paulagabrielajf@blanquerna.url.edu (P. Jakszyn), cdelfino@udd.cl (C. Delfino), canderson@georgeinstitute.org.au (C.S. Anderson), paumunoz@udd.cl (P. Muñoz Venturelli).

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conditions in the same individual[2], poses challenges to the organization of healthcare systems[3,4]. Patients with multimorbidity face higher risk and worse outcome due to factors such polypharmacy, poor health, advanced age, and cognitive impairment[2].

The prevalence of multimorbidity in stroke patients is notably high, ranging from 43 % to 94 %, depending on definition[5]. Common health conditions in these patients include atrial fibrillation (AF) or heart disease (HD), and secondary to stroke such as vascular dementia[5]. The additive effect of disease burden diminishes health states and increases the risk of adverse outcomes. Furthermore, the strength of the association between multimorbidity and adverse outcomes increases with the number of comorbidities,[6] and challenges the approaches to the care of those affected by stroke [7]. This is particularly relevant in Latin America where data on the significance of multimorbidity are limited despite the occurrence of rapid epidemiological transitions.[8] A better understanding of multimorbidity in countries experiencing the transition from middle to high income economies, where health access inequalities still persist, can provide insights into the re-organization of healthcare systems to better target needs.

We undertook a characterization of multimorbidity and its association with short-term mortality in patients with acute ischemic stroke (AIS) registered in the hospital nationwide healthcare database of Chile.

Methods

Study Design and Participants

A retrospective cohort study of the International Refined Diagnosis-Related Groups (IR-DRG)[9] database of Chile in 2019 was conducted according to STROBE [10] criteria (Table S1). The IR-DRG comprises records from 65 medium to high-complexity healthcare centers that represents approximately 70 % of the operational expenditure of the national public health system.[11,12] As an open and de-identified database, the IR-DRG is widely used to provide insights into casuistry, hospital complexity, and services rendered. Two authors (MIA, MN) had full access to all the data and took responsibility for the integrity of the data analysis.

All adults (age ≥18 years) with a diagnosis of AIS who were discharged from one of the registered healthcare centers in Chile between January 1 and December 31, 2019, were included in the study. The International Classification of Diseases (ICD-10)[13] was used to identify cases of AIS with codes I63.0 to I63.9. Individuals diagnosed with AIS (as the primary diagnosis) and without a registered sequelae of stroke were included.

Variables and Data Collection

Sociodemographic data including age, sex, socioeconomic level (classified according to level of personal income noted in the national public health insurance [14] system) and rurality were obtained from the IR-DRG database. Socioeconomic level was categorized as low (monthly income below the national minimum wage [i.e. $301.000.- Chilean pesos that was 462 USD/month on March 1, 2019]), medium (monthly income between 1 and 1.5 times the national minimum wage), or high (income greater than 1.5 times the national minimum wage). Rurality was designated according to the patient́s municipality of residence[15] and defined as the population in the highest interquartile range Q3-Q4 (i.e. rurality percentage >13.5 %).

Comorbidities and medical complications were characterized using ICD-10 codes, and hospital procedures were identified using the International Classification of Diseases (ICD-9)[16]. Variables of interest included days of hospitalization, admission to hospital with stroke unit (SU) and performance of diagnostic tests and treatments. Multimorbidity, was defined according to the WHO definition of ≥2 chronic health conditions in addition to AIS in the same individual [2]. The presence of a cardiometabolic pattern was also assessed [6]; this included at least 2 comorbidities of hypertension (HT), diabetes mellitus (DM), atrial fibrillation (AF), chronic kidney disease (CKD) and ischemic heart disease. In-hospital mortality was evaluated in patients with and without multimorbidity, and in patients with and without cardiometabolic pattern, considering sociodemographic, and hospital characteristics. The database search was conducted based on a predefined list of 24 chronic health conditions established through a systematic review measuring multiple chronic conditions[17] and subsequent expert consensus (Table S2).

Statistical analysis

For bivariate analysis, Pearson's chi-square test was used for categorical analysis. After verifying the distribution with the Shapiro Wilk test, quantitative analysis was performed with Student's t-test and the Mann-Whitney U test when appropriate. Three logistic regression models were performed with random effects, where the dependent variable was in-hospital mortality evaluated by presence of: individual comorbidities, multimorbidity, and cardiometabolic pattern. All models were adjusted for variables of interest that included age (continuous), sex, socioeconomic status, and rurality. The unique hospital identifier was considered as a random effect in the regression model setup to account for heterogeneity between hospitals. Considering that heterogeneity between hospitals was accounted for in this configuration, adjustment for the presence or absence of a hospital stroke unit was not included due to possible collinearity in the model. Finally, subgroup analysis in patients with multimorbidity and analysis in patients who received thrombolysis and/or endovascular thrombectomy during the hospitalization were considered. Results are reported as odds ratios (OR) with 95 % confidence intervals (CI). A significance level was set at $p < 0.05$. All analyses were conducted using STATA, version 18.0.

Role of the funding source

There was no funding source for this study.

Results

Of 1,048,575 hospital disease discharges identified in Chile in 2019, there were 10,440 (67.20 %) patients (mean age 69.5 (SD 13.4) years, men 55.4 %) with a main diagnosis of AIS. Those excluded were discharges with incomplete information or duplicated entries (Figure S1). 74.9 % of the patients had a low socioeconomic status, and the three most common comorbidities were HT (77.3 %), DM (38.0 %) and AF (16.5 %) (Table 1). The median hospital stay was 8 days (IQR 5-14). The most frequent combination of two comorbidities were HT + DM (34.3 %), HT + AF (13.6 %), HT + dyslipidemia (11.6 %) and HT + smoking (9.6 %) (Fig. 1). Of all comorbidities reviewed, 48.9 % ($n = 5,108$) had a cardiometabolic pattern.

Patients with AIS and multimorbidity (AIS_{mm}) accounted for 73.7 % ($n = 7,696$) of cases (Table 1). Compared with those without multimorbidity, AIS_{mm} was more frequent in women (45.5 % versus 42.2 %; $p = 0.003$), the elderly (71.6 ± 14.2 vs 67.9 ± 12.6; $p < 0.001$), those with lower socioeconomic status (73.3 % vs 71.9 %; $p = 0.001$) and residing in lower rurality (24.1 % vs 26.6 %; $p = 0.009$).

AIS_{mm} patients had longer hospitalization stays (9 days IQR [5-14] versus 7 days IQR [4-12]; $p < 0.001$) and more use of brain computed tomography (94.2 % vs 91.0 %; $p < 0.001$). Between all in-hospital complications analyzed, AIS_{mm} patients had a higher proportion of complications overall (25.0 % vs 19.1 %; $p < 0.001$),; albeit these were only significant for pneumonia, dysphagia, acute kidney injury and sepsis. Regarding treatment, no differences were observed in the use of thrombectomy and thrombolysis between the groups (Table 1). The three most frequent comorbidities in the AIS_{mm} group were hypertension (89.1 %), diabetes mellitus (50.1 %) and atrial fibrillation (21.1 %) (Table 1).

Table 1
Characteristics of acute ischemic stroke patients, by presence of multimorbidity

	Overall	Without multimorbidity	With multimorbidity	*P* Value
Baseline characteristics, n (%)	10,440	2,744 (26.3 %)	7,696 (73.7 %)	
Sociodemographic characteristics				
Age, mean ± SD	69.5 ± 13.4	67.9 ± 12.6	71.6 ± 14.2	**<0.001**
Age over 65 years	6,862 (65.7)	1,599 (58.3)	5,263 (68.4)	**<0.001**
Men	5,781 (55.4)	1,587 (57.8)	4,194 (54.5)	**0.003**
Low SES[a]	7,817 (74.9)	1,974 (71.9)	5,843 (73.3)	**0.001**
Rurality[b]	2,581 (24.7)	729 (26.6)	1,852 (24.1)	**0.009**
Risk Factors				
Hypertension	8,067 (77.3)	1,214 (44.24)	6,853 (89.1)	**<0.001**
Diabetes Mellitus	3,962 (38.0)	108 (3.94)	3,854 (50.1)	**<0.001**
Heart diseases				
Atrial fibrillation	1,719 (16.5)	93 (3.39)	1,626 (21.1)	**<0.001**
Ischemic heart diseases	833 (7.98)	9 (0.33)	824 (10.7)	**<0.001**
Others	603 (5.78)	27 (0.98)	576 (7.55)	**<0.001**
Dyslipidemia	1,402 (13.4)	50 (1.82)	1,352 (17.6)	**<0.001**
Current smoking	1,431 (13.7)	145 (5.28)	1,286 (16.7)	**<0.001**
Chronic kidney disease[c]	909 (8.7)	19 (0.69)	890 (11.6)	**<0.001**
Stage 1-4	712 (6.8)	13 (0.47)	699 (9.1)	**<0.001**
Stage 5	197 (1.9)	6 (0.22)	191 (2.5)	**<0.001**
Epilepsy	919 (8.8)	78 (2.84)	841 (11.0)	**<0.001**
Obesity	763 (7.3)	24 (0.87)	739 (9.6)	**<0.001**
Dementia	727 (7.0)	56 (2.04)	671 (8.7)	**<0.001**
Peripheral vascular disease	697 (6.7)	31 (1.13)	666 (8.7)	**<0.001**
Alcohol problems	519 (5.0)	32 (1.17)	487 (6.3)	**<0.001**
Number of comorbidities				
2	3,247 (31.1)	NA	3,247 (42.2)	
3	2,478 (23.7)	NA	2,478 (32.2)	
≥4	1,917 (18.9)	NA	1,971 (25.6)	
Hospitalization				
Hospitalization days, Median (IQR)	8 (5-14)	7 (4-12)	9 (5-14)	**<0.001**
Stroke care unit[d]	6,309 (60.4)	1,045 (38.1)	3,086 (40.1)	0.064
Mechanical Ventilation	340 (3.3)	90 (3.3)	250 (3.2)	0.936
Diagnostic test				
Brain MRI	1,685 (16.1)	419 (15.3)	1,266 (16.4)	0.149
Brain CT	9,742 (93.3)	2,496 (91.0)	7,246 (94.2)	**<0.001**
Angiography	2,347 (22.5)	640 (23.3)	1,707 (22.2)	0.218
Treatment				
Thrombolysis	717 (6.9)	202 (7.4)	515 (6.7)	0.234
Thrombectomy	133 (1.3)	40 (1.5)	93 (1.2)	0.317
In-hospital complications	2,442 (23.4)	523 (19.1)	1,919 (25.0)	**<0.001**
Dysphagia	960 (9.2)	190 (6.9)	770 (10.0)	**<0.001**
Pneumonia	1,170 (11.2)	277 (10.1)	893 (11.6)	**0.031**
Pressure Ulcers	358 (3.4)	83 (3.0)	275 (3.6)	0.175
ARDS	212 (2.0)	46 (1.7)	166 (2.2)	0.125
UTI	36 (0.3)	7 (0.3)	29 (0.4)	0.350
Sepsis	76 (0.7)	7 (0.3)	69 (0.9)	**0.001**
Acute Kidney Injury	451 (4.3)	54 (2.0)	397 (5.2)	**<0.001**
In-hospital Mortality	1,017 (9.7)	257 (9.4)	760 (9.9)	0.440

Abbreviations: IQR=interquartile range; SD= standard deviation; MRI= magnetic resonance imaging; CT= computed tomography; UTI =urinary tract infection; ARDS= acute respiratory distress syndrome.
[a] Among those with National Healthcare insurance.
[b] Measured at a municipality level.
[c] Numbers may not add up to a 100 % due to patients without stage registered.
[d] Measured at a hospital level. Bold denotes statistically significant results.

Most of the younger patients (age 18-34 years) did not have any comorbidity (45.7 %); only 25.2 % had ≥2 comorbidities (Fig. 2A). In patients aged ≥35 years, the presence of multimorbidity was more pronounced and progressively increased with age. In general, there were 42.6 % of all patients with ≥3 comorbidities. The most frequent combinations of multimorbidity per age range are presented in Fig. 2B and Table S5. Of all comorbidities reviewed in the AIS_{mm} group, 66.4 % had a cardiometabolic pattern.

A total of 1,017 (9.74 %) AIS patients died during hospitalization. Of those, 55.36 % were men, with average age of 75.43 years (SD=12.16) and 34.02 % were admitted to hospital with a SU. The median hospitalization days was 7 days (IQR= 3-15) and 74.73 % presented multimorbidity at the time of death, with 19.47 % having 4 or more comorbidities. (Figure S2).

The presence of multimorbidity, alone, was not a predictor of death during hospitalization for IS even after adjusting for age, sex, low socioeconomic status, and rurality (adjusted odds ratio [ORadj]=0.99 [CI: 0.85–1.15], $p = 0.933$). However, the combination of specific comorbidities (Table S6), or considering the presence of cardiometabolic pattern (HT, DM, AF, CKD, ischemic heart diseases) shown an association with higher in-hospital mortality (ORadj= 1.22 [CI: 1.07-1.40], $p = 0.003$) compared to patients without multimorbidity or with multimorbidity but with one or no cardiometabolic comorbidity. Moreover, within the IS_{mm} group, having two or more cardiometabolic comorbidities was a significant predictor of in-hospital mortality (ORadj= 1.39 [CI: 1.16-1.66], $p < 0.001$]) compared to patients with multimorbidity but none or only one cardiometabolic comorbidity.

In-hospital mortality by main comorbidities and the most frequent combination of multimorbidity are shown in Table S6 and significant findings are presented in Fig. 3. Notably, CKD Stage 5 was the comorbidity that, both individually and in combination, had the highest risk of death, with an ORadj of 4.20 (CI:1.58-11.16, $p = 0.004$) when combined with ischemic heart disease. It was noticed that dementia was a comorbidity that individually analyzed was associated to higher risk of death (ORadj= 1.28 [CI:1.03-1.60], $p = 0.026$) and this risk increased when combined with obesity (ORadj= 3.30 [CI: 1.28-8.51], $p = 0.013$) or with ischemic heart disease (ORadj= 2.50 [CI: 1.20-5.23], $p = 0.014$)

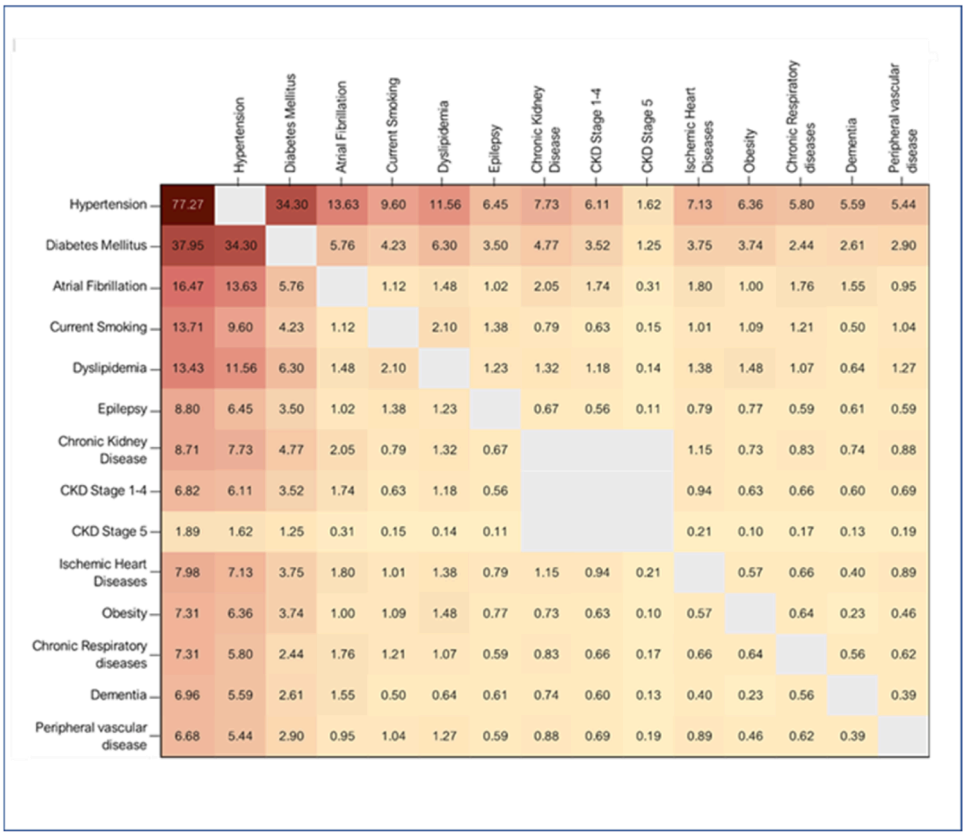

Fig. 1. Frequency of comorbidities in patients with acute ischemic stroke
Legend: Results are presented as a percentage (%) of the total population with ischemic stroke (n = 10,440). Grey squares denote not applicable correlation. Abbreviations: CKD= Chronic Kidney Disease

(Fig. 3). Some exceptions are worth mentioning, such as the case of obesity, which exhibited a predominance in the early to mid-life, being one of the most impactful comorbidities in the risk of death when combined with others. Dyslipidemia stands out, which was associated with lower risk of in-hospital mortality, analyzed individually or in combination with others.

In addition, considering only a subgroup of patients who received thrombolysis and/or thrombectomy (n = 768) during the hospitalization, the analysis showed that the presence of multimorbidity was associated with higher in-hospital mortality (ORadj= 1.89 [CI: 1.01-3.53], p = 0.044) compared to patients without multimorbidity, even after adjusting for age, sex, low socioeconomic status and rurality. In this subgroup, the cardiometabolic pattern also showed higher risk of mortality (ORadj=1.76 [CI:1.08-2.88], p = 0.022) compared to patients without multimorbidity or those with multimorbidity but only none or no cardiometabolic comorbidity.

Discussion

Our analysis of a large nationwide database delineated the frequency and characteristics of multimorbidity in adults hospitalized with AIS in Chile. Our findings show that the presence of cardiometabolic multimorbidity is significantly associated with increased in-hospital mortality.

The high frequency of multimorbidity found in adults with AIS aligns with the findings of other studies which report prevalence figures ranging from 43 % to 94 %[5], but much of this variation may be attributed to differing definitions and measurement methods. Our study identified HT, DM, and AF as the most frequent health conditions in patients with multimorbidity, consistent with the reviewed literature.[18–20] Multimorbidity poses significant challenges, including a greater treatment burden, higher risk of adverse events, and uncoordinated care, among other challenges that impact the quality of life for the patient and their families. Given that in most current health models the various health conditions require management by different specialists, these patients are likely to receive fragmented healthcare and have limited preparation for the treatment of multiple and different health conditions that require complex and interdisciplinary approaches. Therefore, new perspectives for the implementation of targeted primary and secondary stroke prevention and hospital care plans, with greater emphasis on a complex multimorbidity-focused approach centered on the patients and their needs.

Different multimorbidity patterns were described across age groups. Multimorbidity is highly prevalent among elderly, where it exerts considerable influence.[2,3,21–23] Conversely, there is global recognition of the importance of addressing stroke in younger patients who exhibit nontraditional risk factors that are generally underreported.[24] In the Chilean database, we found that half of those under the age of 55 years had none or only one reported comorbidity associated with AIS. Unraveling risk factors that are not readily measured may be of particular importance in tackling the burden of AIS, especially in younger populations which have shown increasing trends in the incidence of stroke in recent years.[25,26]

Moreover, when analyzing sex and socioeconomic status, our findings align with the literature indicating that multimorbidity is more common in women and in disadvantaged groups, contributing to health inequities.[3,4,21] It is important to consider that improvements in prevention strategies have been initiated (HEARTS program), as well as the Stroke Action Plan in Chile[11], that proposes guidelines for comprehensive and timely care for AIS patients and the goal is contribute to mortality reduction, improving the final functional condition and promoting a series of actions. In Chile, and likely in public hospitals across other

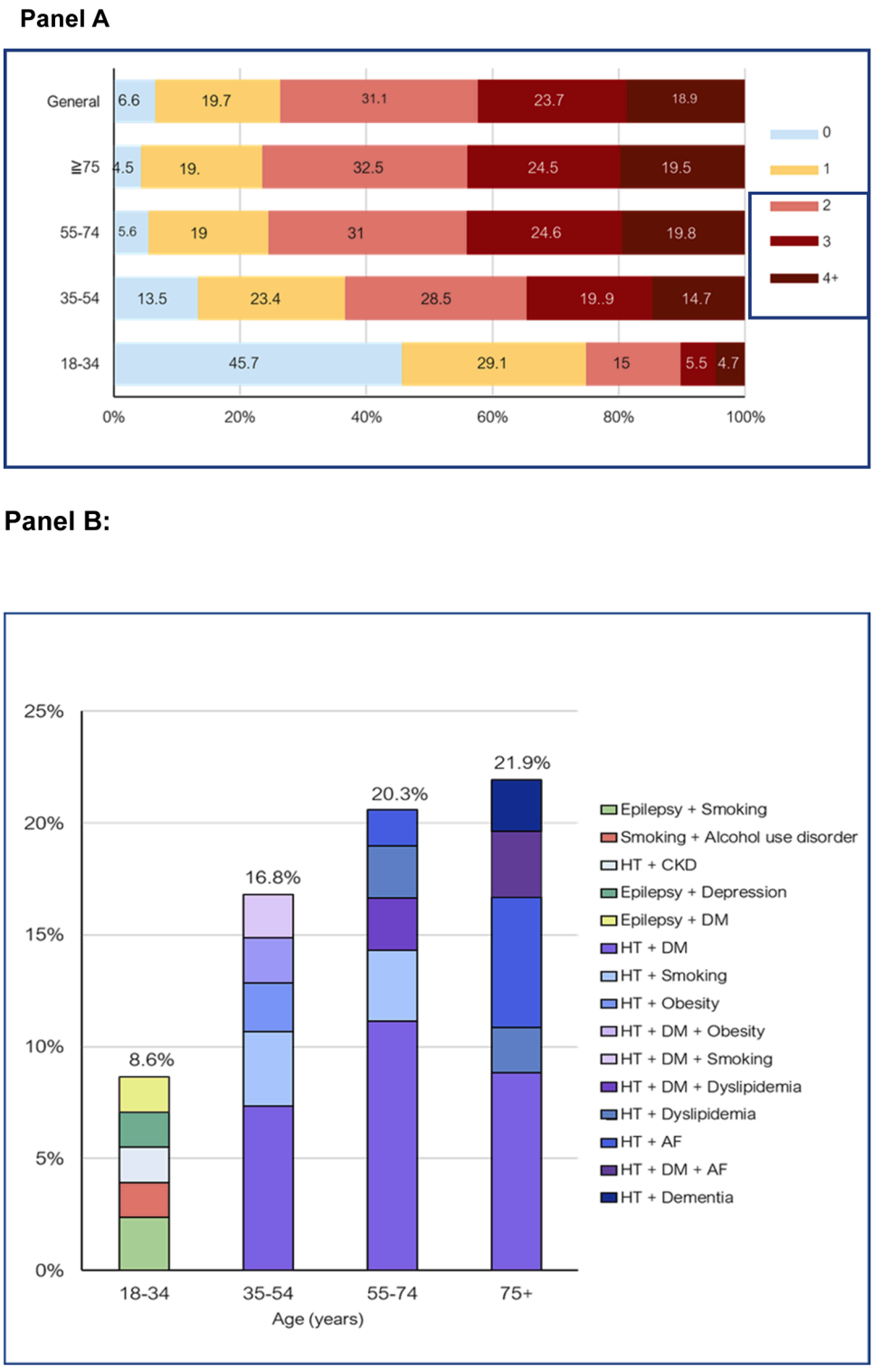

Fig. 2. Patterns of most common comorbidities across age groups
Panel A: Legend: results are presented as a percentage (%) of the total of the population with ischemic stroke (n = 10,440) and in each age group. Red colour palette denotes onset of multimorbidity. **Panel B:** Legend: Results indicates patients who exclusively have the combination indicated: HT=Hypertension; CKD=Chronic Kidney Disease; DM=Diabetes Mellitus; AF= Atrial Fibrillation

areas of Latin America, effective implementation of these initiatives is incomplete, especially in marginalized communities or rural areas [27].

Special attention must be directed towards the observed "*protective*" effect of dyslipidemia on mortality after AIS. Patients included in this database were registered to have dyslipidemia, yet their current treatment or cholesterol levels remained unknown. A conflicting body of literature exists, with several studies suggesting that elevated cholesterol levels correlate with improved clinical and functional outcomes post IS.[28] Our findings align with prior publications wherein hyperlipidemia has been linked to reduced all-cause mortality following IS, irrespective of statin therapy.[29] Notably, the same study indicates that statin therapy confers a significant additional reduction in all-cause

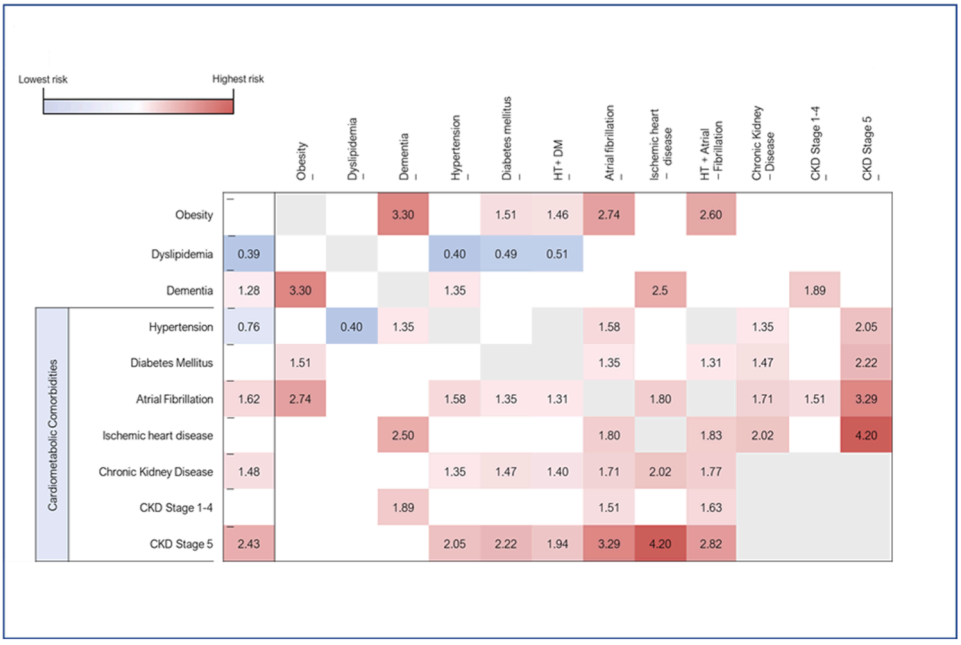

Fig. 3. In-hospital mortality main comorbidities in patients with acute ischemic stroke
Legend: Results are presented as adjusted Odds Ratio of the total population with ischemic stroke (n = 10,440). Adjusted Odds Ratio by sex, age, low socioeconomic status and high rurality percentage. Blank squares indicate non-significant results. Grey squares indicate not applicable correlation. Abbreviations: OR= Odds ratio; HT=Hypertension; CKD=Chronic Kidney Disease; DM= Diabetes Mellitus; AF= Atrial Fibrillation

mortality post-stroke. It is plausible that our dyslipidemia cohort comprises a mix between individuals with elevated cholesterol levels and those undergoing statin therapy, potentially contributing to their lower in-hospital mortality rates.

Strengths and limitations

This study has several strengths. To the best of our knowledge, this is the first analysis of multimorbidity associated with AIS in Latin America. It is also a relevant topic for Chile, a country with a high prevalence of stroke and where the population is undergoing advanced demographic transition, which is leading to increases in older adults with complex, specific, and costly diseases.

We also recognize this study has limitations that are worth mentioning. This analysis was conducted using a widely utilized national database considered a representative registry of the Chilean population. However, the IR-DRG was designed for other purposes and does not contain all information relevant to the outcomes from AIS, such functional prognosis. Furthermore, there is likely to have been an underreporting of mental health and other medical diagnoses in the reviewed database, such as the presence of depression — a prevalent condition in Chile — which has been associated with AIS and has a much higher prevalence in other similar studies (for example, the reported 11.7 % national prevalence of risky alcohol consumption[30] and 15.8 % of depression[31]). Moreover, the registry of a previous stroke might not have been accurate because of the lack of a special code, preventing the analysis of first or recurrent stroke.

Knowledge about multimorbidity in stroke is currently limited, and the impact of multimorbidity in stroke outcome should be comprehensively tackled. Some countries in Latin America have established national clinical guidelines for stroke, although much more has to be done in the organization of care[32]. There is a need to place greater emphasis on the management of this disease with a multimorbidity perspective and improve stroke prevention strategies focused on higher risk patients with a comprehensive approach.

Statement of ethics

The project has been exempted from evaluation and supervision by the Research Ethics Committee of Clínica Alemana- Universidad del Desarrollo since contemplates the use of de-identified public data (08/12/2023).

CRediT authorship contribution statement

Francisca González: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Ma. Ignacia Allende:** Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Formal analysis, Data curation. **Marilaura Nuñez:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Data curation, Conceptualization. **Iris Delgado:** Writing – review & editing, Software, Methodology, Formal analysis, Conceptualization. **Paula Jakszyn:** Writing – review & editing, Visualization, Validation, Supervision, Methodology. **Carlos Delfino:** Writing – review & editing, Visualization, Supervision, Methodology, Conceptualization. **Craig S. Anderson:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Conceptualization. **Paula Muñoz Venturelli:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

PMV receives research grants from ANID Fondecyt Regular 1221837, Pfizer and Boehringer Ingelheim. CA: Receives Grants and fellowship from the National Health and Medical Research Council (NHMRC) of Australia, Medical Research Foundation of the UK, Consulting fees as Advisory Board for AstraZeneca Australia, is the Vice-President of the World Stroke Organisation and the Editor-in-Chief of Cerebrovascular Diseases journal; the other authors have no competing interests.

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Supplementary materials

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Glossary

AIS_{mm}: AIS with multimorbidity.