Long-term effects of COVID-19 in patients with primary immunodeficiency: An IPOPI worldwide survey

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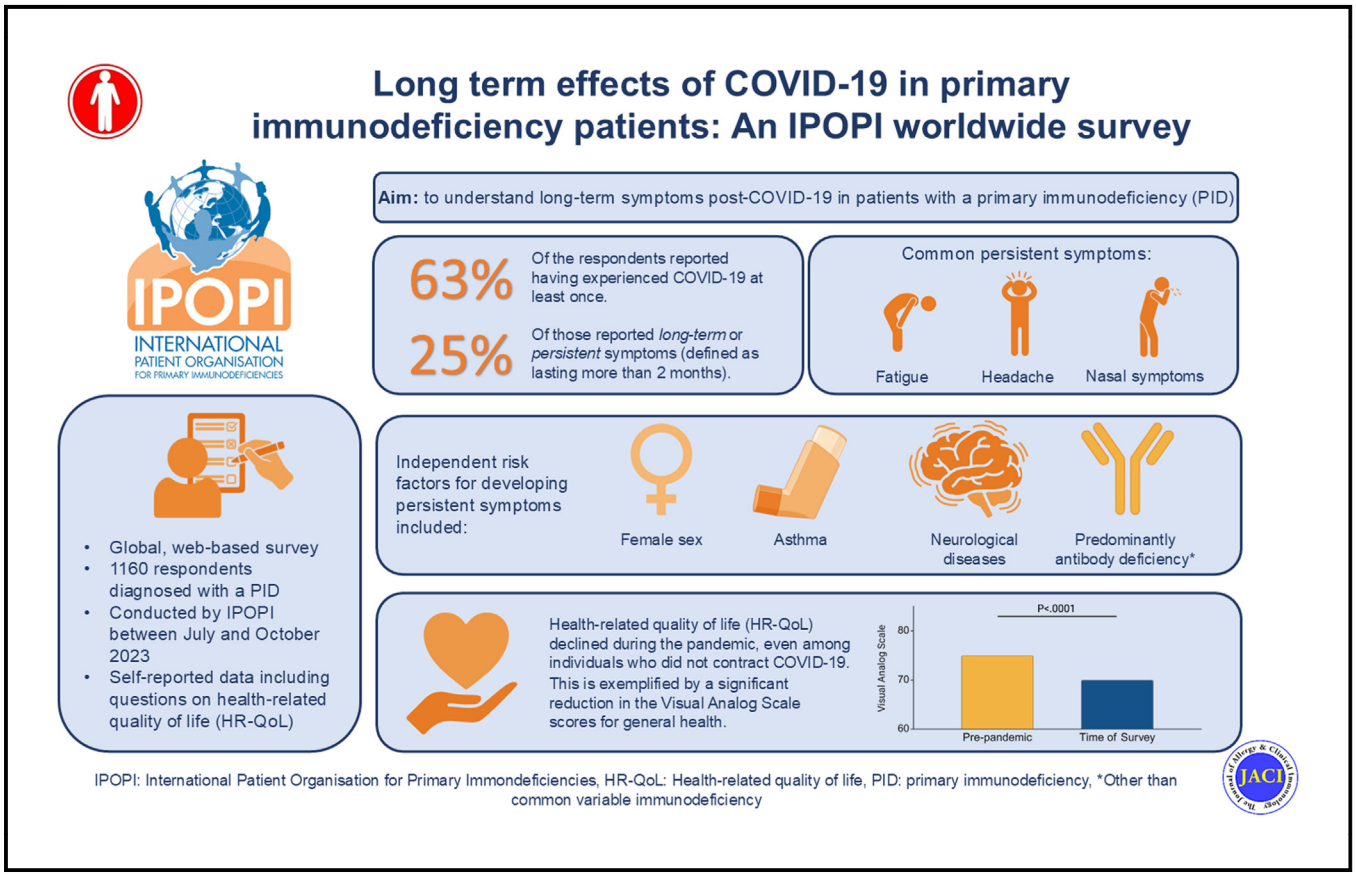
GRAPHICAL ABSTRACT



Capsule summary: Persistent symptoms after COVID-19 are prevalent among patients with primary immunodeficiency (PID). The COVID-19 pandemic had a considerable negative impact on the health-related quality of life of patients with PID, regardless of COVID-19 status.

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Long-term effects of COVID-19 in patients with primary immunodeficiency: An IPOPI worldwide survey

Leanne P. M. van Leeuwen, MD,[a] Samya Van Coillie, PhD,[b]* Johan Prévot, BA,[b] Jose Drabwell,[b,†] Nizar Mahlaoui, MD, PhD,[b,c,d] Silvia Sánchez-Ramón, MD, PhD,[e] M. Cecilia Poli, MD, PhD,[f,g,h] Isabelle Meyts, MD, PhD,[i,j] Adli Ali, MD, PhD,[k,l] David M. Lowe, FRCP, PhD,[m,n] Virgil A. S. H. Dalm, MD, PhD,[o,p] and Martine Pergent, MSc[b]

Rotterdam, The Netherlands; Brussels and Leuven, Belgium; Paris, France; Madrid, Spain; Santiago, Chile; Kuala Lumpur, Malaysia; and London, United Kingdom

Background: During the coronavirus disease 2019 (COVID-19) pandemic, many individuals developed persistent symptoms after COVID-19. The data on these long-term effects in the primary immunodeficiency (PID) community are limited.
Objective: This study aimed to understand long-term symptoms after COVID-19 in patients with PID, focusing on prevalence, risk factors, viral persistence, and the impact of COVID-19 on their health-related quality of life (HR-QoL).
Methods: A global, multilingual web-based survey was conducted by the International Patient Organization for Primary Immunodeficiencies between July and October 2023. Self-reported data on demographics, PID diagnosis, comorbidities, COVID-19, and HR-QoL were collected using the EuroQol 5-Dimensions 5-Level (EQ-5D-5L) survey and analyzed.
Results: Of the 1160 respondents, 25% reported persistent symptoms after COVID-19. Common symptoms included fatigue, headache, and nasal symptoms. Compared with those respondents without persistent symptoms, those with persistent symptoms after COVID-19 reported a significantly higher prevalence of symptoms across all categories—systemic, pain, cardiopulmonary, gastrointestinal, neurologic, psychological, neurocognitive, and others—except for upper respiratory tract symptoms. Independent risk factors for development of persistent symptoms included female sex, asthma, neurologic diseases, and predominantly antibody deficiency other than common variable immunodeficiency or agammaglobulinemia. In 30% of patients with persistent symptoms, viral clearance was not achieved within 1 month. During the pandemic, HR-QoL declined across all PID categories—even in those without COVID-19, but especially in those with a symptom duration of more than 6 months.
Conclusion: Persistent symptoms after COVID-19 are prevalent among patients with PID, with various risk factors identified. The COVID-19 pandemic had a considerable impact on the HR-QoL of patients with PID regardless of COVID-19 status. (J Allergy Clin Immunol 2025;156:449-62.)

Key words: *COVID-19, persistent symptoms, primary immunodeficiencies, PID, health-related quality of life, HR-QoL, viral persistence, survey, long COVID, patient-reported*

Shortly after the onset of the coronavirus 2019 (COVID-19) pandemic, it became clear that some patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) developed long-term symptoms. These ranged from general manifestations such as fatigue to more severe pulmonary, cardiovascular, and neurologic conditions.[1,2] Initially, there was no standardized terminology for this illness, resulting in the use of various terms, including *postacute sequelae of COVID-19*, *chronic COVID-19*, *persistent COVID-19 symptoms*, *long-term sequelae*, and *long-haulers*.[3] The World Health Organization refers to this illness as "post–COVID-19 condition" or "long COVID" and specifies its clinical case definition as "the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation."[4]

The aforementioned World Health Organization definition is very broad, encompassing everything from mild persistent symptoms to severe long-term multiple organ dysfunction. It may include patients with psychosomatic complaints, post–intensive care syndrome, or true viral persistence, as observed in immunocompromised patients.[5] In these cases, inability to clear the virus can lead to continued viral replication, causing repeated clinical relapses and hospitalizations.[6]

From [a]the Department of Viroscience, [o]the Department of Internal Medicine, Division of Allergy and Clinical Immunology, and [p]the Department of Immunology, Erasmus MC University Medical Center Rotterdam; [b]the International Patient Organization for Primary Immunodeficiencies, Brussels; [c]the Pediatric Hematology-Immunology and Rheumatology Unit and [d]the French National Reference Center for Primary Immune Deficiencies, Necker-Enfants malades University Hospital, Assistance Publique-Hôpitaux de Paris; [e]the Department of Clinical Immunology, IML and IdISSC, Health Research Institute of the Hospital Clínico San Carlos Madrid; [f]the Facultad de Medicina Clínica Alemana de Santiago, Universidad del Desarrollo; [g]the Programa de Inmunogenética e Inmunología Traslacional, Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina, Santiago; [h]the Unidad de Inmunología y Reumatología, Hospital Roberto del Río, Santiago; [i]the Department of Pediatrics, University Hospitals Leuven; [j]the Department of Microbiology, Immunology and Transplantation, Laboratory for Inborn Errors of Immunity, Katholieke Universiteit (KU) Leuven; [k]the Department of Paediatrics, Faculty of Medicine, and [l]the Hospital Tunku Ampuan Besar Tuanku Aishah Rohani, UKM Specialist Children's Hospital, Universiti Kebangsaan Malaysia, Kuala Lumpur; [m]the Department of Immunology, Royal Free London NHS Foundation Trust; and [n]the Institute of Immunity and Transplantation, University College London.
*These authors share first authorship.
†Deceased.
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Corresponding author: Martine Pergent, MSc, International Patient Organization for Primary Immunodeficiencies, Avenue Louise 65, BTE 111050 Brussels, Belgium. E-mail: martine.pergent@gmail.com.

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Abbreviations used

CID: Combined immunodeficiency
COVID-19: Coronavirus disease 2019
CTLA-4: Cytotoxic T lymphocyte–associated protein 4
CVID: Common variable immunodeficiency
EQ-5D-5L: EuroQol 5-Dimension 5-Level
HR-QoL: Health-related quality of life
IPOPI: International Patient Organization for Primary Immunodeficiencies
LRBA: LPS-responsive and beige-like anchor protein
LSS: Level sum score
OR: Odds ratio
PID: Primary immunodeficiency
SCID: Severe combined immunodeficiency
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
STAT: Signal transducer and activator of transcription
VAS: Visual Analog Scale
XIAP: X-linked inhibitor of apoptosis

Patients with primary immunodeficiencies (PIDs), also referred to as inborn errors of immunity, represent an important group of immunocompromised patients. During the acute phase of COVID-19, specific subgroups of PIDs were associated with a higher risk of severe disease, including combined immunodeficiencies, immune dysregulation disorders, and defects in innate immunity that impair type I interferon responses.[7-9] Furthermore, various PID-related comorbidities, including chronic lung disease (eg, asthma, bronchiectasis, interstitial diseases) and cardiomyopathy, increasing the risk of severe disease.[10-12]

Although the prevalence and clinical manifestations of persistent COVID-19 symptoms are increasingly being investigated in the general population, few studies have focused on the PID community.[2,3] A survey in Italian patients with PIDs showed that 115 of the 175 enrolled patients (66%) experienced persistent symptoms, with the most common being fatigue, arthralgia, myalgia, and dyspnea.[13] However, this cohort included only patients with common variable immunodeficiency (CVID).

Therefore, the aim of this study was to better understand the long-term impact of the COVID-19 pandemic in a heterogeneous group of patients with various types of PID. The prevalence, clinical presentation, and risk factors of persistent symptoms after COVID-19 were investigated, and an assessment of viral persistence was conducted to evaluate the impact of persistent viral replication on these symptoms. It was previously shown that patients with PID, regardless of SARS-CoV-2 infection status, are known to have significantly poorer physical health than the general population and to also experience reduced psychosocial well-being and health-related quality of life (HR-QoL).[14-16] Therefore, this study also assessed in more detail the impact of the COVID-19 pandemic on HR-QoL in a large group of patients with PID.

METHODS

A web-based survey was conducted by the International Patient Organization for Primary Immunodeficiencies (IPOPI) between July and October 2023. The survey was conducted using the online survey software SurveyMonkey (Momentive, San Mateo, Calif). Patients with PID were globally addressed through IPOPI's national member organizations, network of physicians, and nurses and social media. Before participation, patients received detailed information about the survey's objectives and were subsequently requested to provide informed consent. After providing informed consent, patients with PID or their caregivers were enrolled in the survey irrespective of their SARS-CoV-2 infection status. No age limitations were imposed; no identifying information of patients or caregivers was needed to participate in the survey. Surveys completed with the help of a family caregiver were not analyzed separately. A copy of the survey can be found in the Online Repository (available at www.jacionline.org).

The objectives of this study were to investigate the prevalence, clinical presentation, risk factors, and impact of viral clearance on persistent symptoms after COVID-19, as well as to assess the impact of the COVID-19 pandemic on HR-QoL of patients with PID. Persistent symptoms were defined as self-reported symptoms lasting at least 2 months following the onset of acute COVID-19 disease.

The survey collected baseline characteristics, including demographics, PID diagnosis, PID treatment regimens, and presence of 1 or multiple PID-related and other comorbidities. Subsequent sections focused on self-reported history of SARS-CoV-2 infection, if any, and included questions about symptoms experienced, duration of symptoms, treatment received, viral clearance, and SARS-CoV-2 vaccination status. Participants with a symptom duration longer than 6 months also received questions about their current symptoms or symptoms during the month preceding the survey. The symptoms included in the survey correspond to those in the meta-analysis on long-term health effects of long COVID published by O'Mahoney et al.[3] All participants completed questions regarding their QoL using the EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire (produced by the EuroQoL Group), modified for 2 time points: before the pandemic and at the time of survey administration. This instrument measures 5 dimensions of health: mobility, self-care, activities, pain and/or discomfort, and anxiety and/or depression, each with 5 levels of severity. Additionally, a Visual Analog Scale (VAS) score, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state), was used to capture respondents' self-rated health.

The various PID diagnoses were classified into categories according to the International Union of Immunological Societies criteria. Here, severe combined immunodeficiencies (SCIDs) and combined immunodeficiencies (CIDs) were grouped together as immunodeficiencies affecting cellular and humoral immunity. Within the category of combined immunodeficiencies with associated and syndromic features, ataxia-telangiectasia, cartilage-hair hypoplasia, Di George syndrome, hyper-IgE syndrome, and Wiskott-Aldrich syndrome were grouped together. Autoimmune lymphoproliferative syndrome, cytotoxic T lymphocyte–associated protein-4 (CTLA4) haploinsufficiency, LPS-responsive and beige-like anchor protein (LRBA) deficiency, signal transducer and activator of transcription-3 (STAT3) gain of function, and X-linked inhibitor of apoptosis (XIAP) deficiency formed a group termed *diseases of immune dysregulation*. Chronic granulomatous disease and congenital neutropenia were categorized as phagocyte defects. IL-17F deficiency; STAT1 gain-of-function; and warts hypogammaglobulinemia, infections, and myelokathexis syndrome constituted the defects of intrinsic and innate immunity. CVID and agammaglobulinemia each formed their own category owing to the large number of respondents with these disorders. Other (predominantly) antibody deficiencies, including hyper-IgM

syndrome, IgA deficiency, IgG subclass deficiency, other hypogammaglobulinemia, and specific antibody deficiency, were grouped together.

Descriptive statistics were presented as percentages for categoric variables and medians (including interquartile ranges) for continuous variables. Associations between individual variables and the presence of persistent symptoms were assessed by using chi-square tests. The Fisher exact test was applied when any cell had an expected count of less than 5. Continuous variables were compared using the Mann-Whitney *U* test. Power and sample size calculations were not performed before the study.

A mixed-effects logistic regression model was used to analyze the relationship between baseline variables and the outcome of having persistent symptoms after COVID-19. To mitigate the risk of overfitting, the model size was adjusted to the number of respondents experiencing persistent symptoms (10 events per degree of freedom). Covariates were chosen on the basis of their clinical relevance and prevalence. For the analysis, smaller PID groups, including SCIDs and/or CIDs, CIDs with associated and syndromic features, defects of intrinsic and innate immunity, diseases of immune dysregulation, phagocyte defects, and others/unknown, were combined into a single category. The largest PID group, CVID, was used as the reference category for this variable. The variables representing the use of anti-inflammatory and immunosuppressive medications were combined into a single variable termed *immunomodulatory medication*. Vaccination status was omitted from this analysis owing to the unknown time relationship between vaccination and infection. To account for clustering of patients by geographic region, continent was included as a random effect.

The results for the 5 domains of the EQ-5D-5L questionnaire were summarized as percentages and visualised using bar charts. The VAS scores were compared using the Mann-Whitney *U* test for paired data. Initially, the results of the EQ-5D-5L of all respondents were analyzed. The respondents were then categorized into 4 groups based on symptom duration: respondents without COVID-19, respondents with COVID-19 and symptoms lasting less than 2 months, those with COVID-19 and symptoms lasting between 2 and 6 months, and those with COVID-19 and symptoms lasting more than 6 months. Level sum scores (LSSs) were calculated from the EQ-5D-5L responses by summing the scores for each dimension. The LSS ranges from 5 (indicating no problems in any dimension) to 25 (indicating extreme problems in all dimensions). Differences in VAS scores and LSSs were calculated by subtracting a respondent's prepandemic score from the score at the time of survey. These differences in VAS score and LSS were compared between respondents with and without COVID-19 by using the Mann-Whitney *U* test for unpaired data. For these calculations, Bonferroni correction for multiple testing was applied.

Statistical significance was defined as a P value less than .05 (2 tailed). All analyses were performed using R (R Foundation, Vienna, Austria). Graphs were created using GraphPad (version 10.2.3, GraphPad Software, San Diego, Calif).

RESULTS

Baseline characteristics of the survey respondents

A total of 1392 patients provided informed consent for participation in the study. However, 232 patients did not initiate the questionnaire following informed consent, resulting in a final respondent count of 1160 (691 females and 461 males) who completed the survey either fully or partially (Fig 1). In all, 7 participants chose not to disclose their sex, and 1 participant identified as "other." The median age of the cohort was 43 years (interquartile range = 20-56) (see Table E1 in the Online Repository at www.jacionline.org). The respondents originated from 51 different countries, with Germany, China, and Canada being the countries with the highest numbers of respondents (n = 126, 125, and 117, respectively) (Fig 2).

The most prevalent PID diagnosis observed was CVID (n = 539), followed by other predominantly antibody deficiencies (n = 220), and agammaglobulinemia (n = 167) (see Tables E1 and E2 in the Online Repository at www.jacionline.org). Regarding COVID-19, a total of 285 participants reported no history of COVID-19, 97 were uncertain, and 52 opted to not respond to this question. A total of 479 respondents reported experiencing COVID-19 once, 220 reported contracting COVID-19 twice or 3 times, and 27 reported having had COVID-19 more than 3 times.

Prevalence and clinical presentation of persistent symptoms after SARS-CoV-2

Of the 726 respondents diagnosed with COVID-19, a total of 181 (25% [95% CI = 22%-28%]) reported having persistent symptoms after COVID-19 (symptom duration > 2 months), 454 (63% [95% CI = 59%-66%]) reported that their symptoms resolved within 2 months, and 91 (13% [95% CI = 10%-15%]) did not provide information regarding symptom duration. Among the participants with a PID diagnosis, those with other predominantly antibody deficiencies had the highest frequency of persistent symptoms (40%) (see Table E3 in the Online Repository at www.jacionline.org).

Among those with persistent symptoms, the most common COVID-19–related symptoms (occurring at any time during the illness or its sequelae) included fatigue, headache, and nasal symptoms, whereas those without persistent symptoms reported fatigue, fever, and nasal symptoms most frequently (Fig 3, *A* and *B*). Patients with PID with persistent symptoms after COVID-19 exhibited a significantly higher prevalence of symptoms across all categories (systemic, pain, cardiopulmonary, gastrointestinal, neurologic, psychological, neurocognitive, and others), with the exception of upper respiratory symptoms. The most pronounced differences were observed in the prevalence of neurocognitive symptoms (29% in those without persistent symptoms vs 70% in those with persistent symptoms), followed by psychological and other symptoms (43% vs 80% and 36% vs 73%, respectively [$P < .0001$ for all 3 categories]) (Fig 4, *A* and Table I). For those with persistent symptoms, the most frequent other symptoms were impaired exercise capacity (n = 81), hair loss (n = 61), and vertigo (n = 47). The median number of symptoms in this group was 18, which was higher than the median number (ie, 12) in the group of respondents without persistent symptoms ($P < .0001$). The most prevalent COVID-19–related symptoms in hospitalized respondents versus in nonhospitalized are shown in Fig E1 (available in the Online Repository at www.jacionline.org).

Severity of acute COVID-19 and treatment of respondents with persistent symptoms

Acute COVID-19 was more severe among respondents with persistent symptoms than in those without persistent symptoms

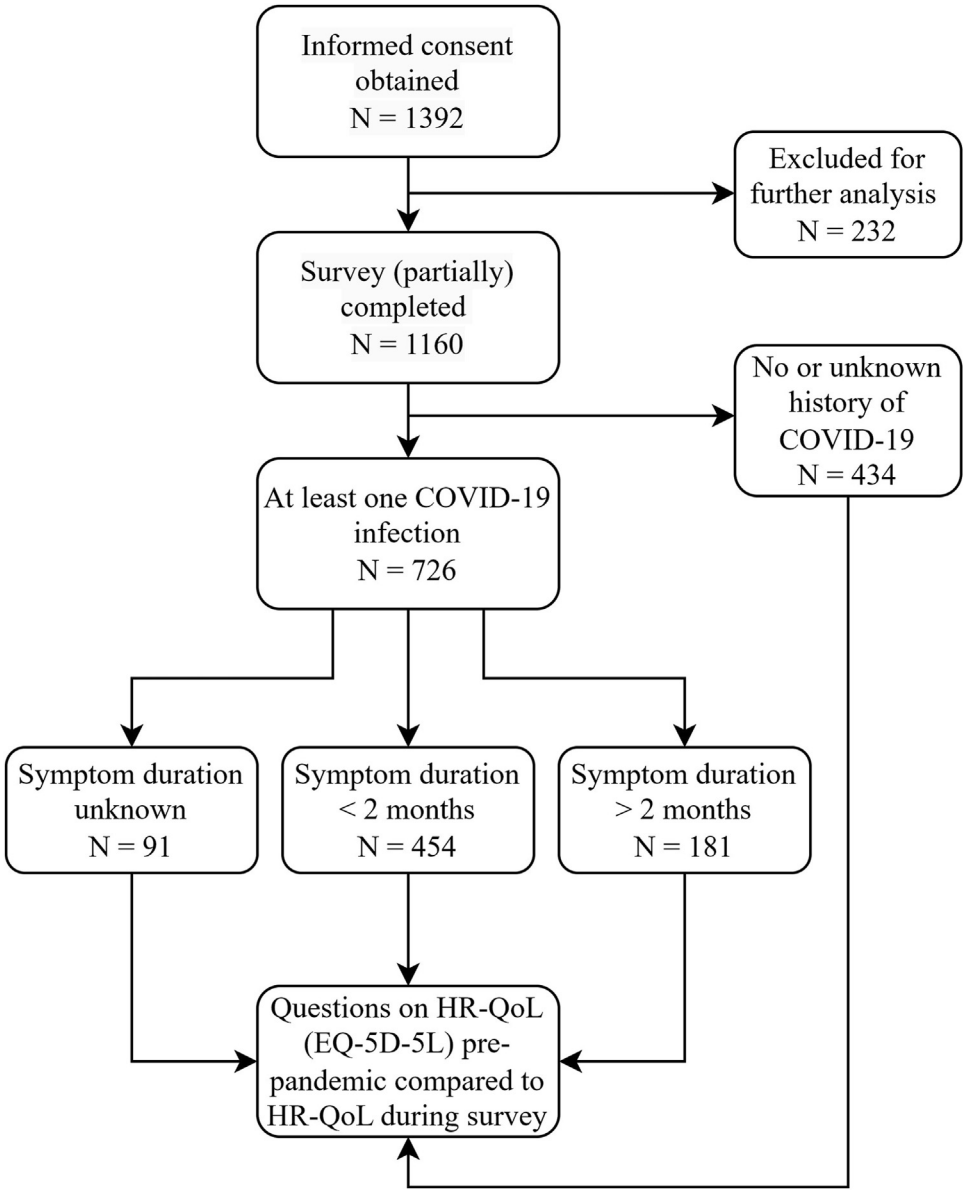

FIG 1. Flowchart of study participants and survey completion. A total of 1392 participants were enrolled in the survey. In all, 232 participants were excluded for analysis because they did not (even partially) complete the survey, resulting in 1160 patients at least partially completing the survey. Among these participants, 726 reported at least 1 episode of COVID-19. Participants were further categorized on the basis of duration of their symptoms. All respondents answered questions on HR-QoL by using the EuroQoL Group EQ-5D-5L questionnaire comparing their HR-QoL at 2 different time points: before the pandemic and during the survey period.

($P < .0001$). Only 31% of respondents with persistent symptoms (n = 55) experienced mild-to-moderate illness versus 67% (n = 303) of those without persistent symptoms (Table I). Among those with persistent symptoms, 49% (n = 89) experienced severe symptoms without requiring hospitalization, 20% (n = 37) required hospital admission, and 4% (n = 7) were admitted to an intensive care unit.

A larger proportion of respondents with than without persistent symptoms received therapy for COVID-19 (Table I and see also Table E4 in the Online Repository at www.jacionline.org). Specifically, 14% versus 9% received multiple rounds of antiviral therapy ($P = .03$), 22% versus 16% received combination therapy (ie, ≥2 COVID-19 treatments given contemporaneously) ($P = .07$), and 21% versus 3% received some sort of long-term maintenance therapy to manage COVID-19–related symptoms ($P < .0001$). The use of anti–SARS-CoV-2 mAbs in the 2 groups was comparable (in 11% of those with persistent symptoms vs in 12% of those without [$P = .82$]). Additionally, 15% percent of respondents with long-term symptoms reported developing an autoimmune disorder after COVID-19 versus 8% of respondents without persistent symptoms ($P = .004$).

Risk factors for developing persistent symptoms after SARS-CoV-2 infection

The respondents with persistent symptoms were predominantly female (77% vs 22% male), and they tended to be older than those

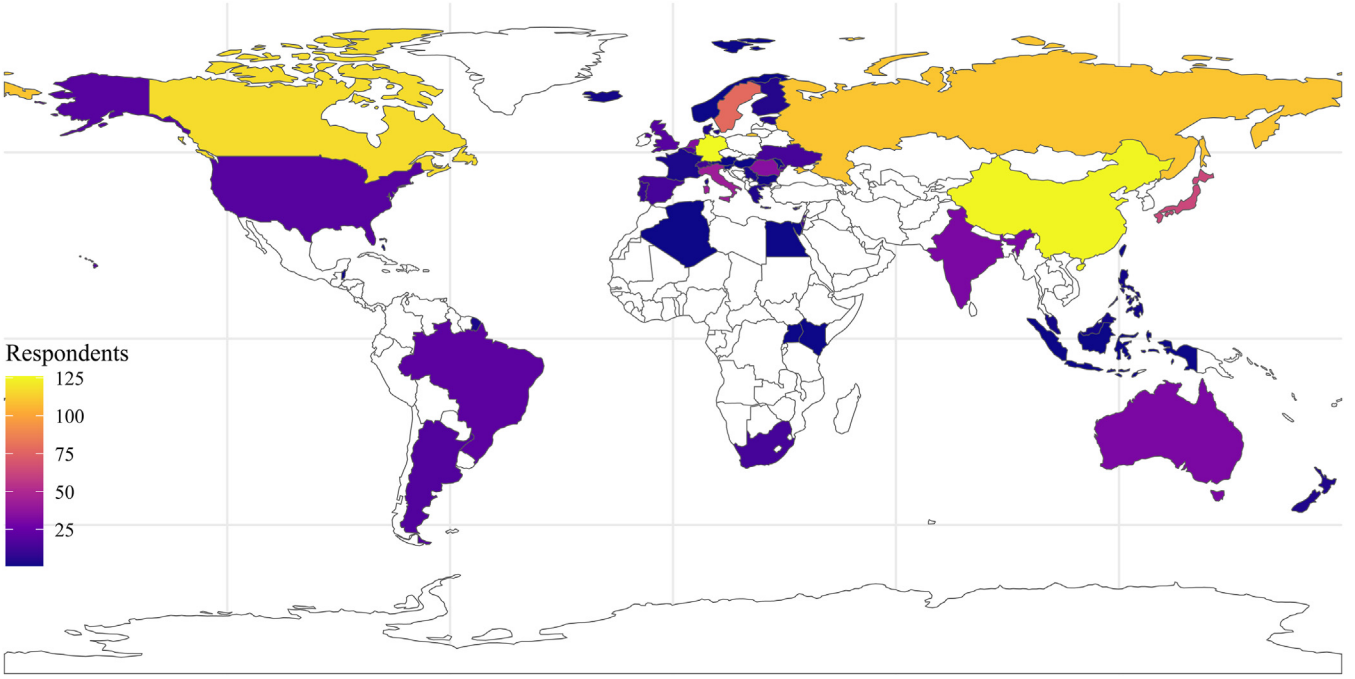

FIG 2. World map indicating the number of respondents by country. The color gradient from purple to yellow represents the number of respondents across different countries. Purple indicates those countries with the lowest number of respondents. Yellow indicates those countries with the highest number of respondents. White indicates countries with no respondents.

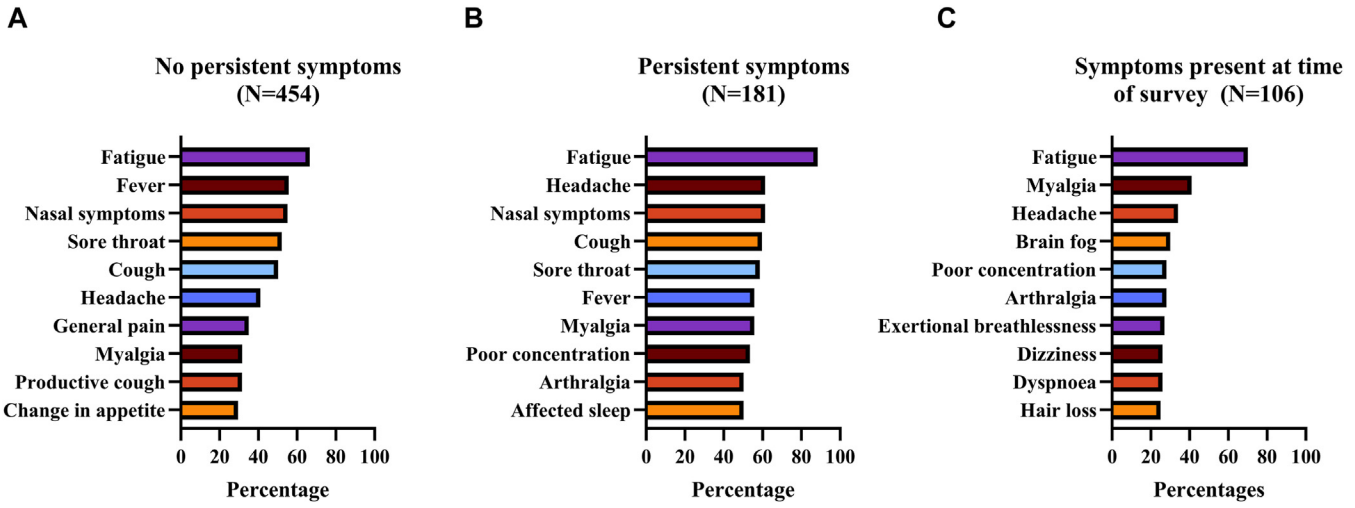

FIG 3. Prevalence of the most common COVID-19–related symptoms in respondents without persistent symptoms, with persistent symptoms, and with symptoms present at the time of the survey. A visual comparison of the prevalence of the most common symptoms between the 3 groups is provided. Symptoms are listed on the vertical axis, and the percentage of patients reporting each symptom is shown on the horizontal axis. The color-coded bars represent different symptoms. **A,** Prevalence of symptoms in patients without persistent symptoms (ie, symptoms resolved in <2 months) (n = 454). The most common symptoms reported include fatigue, fever, and nasal symptoms. **B,** Prevalence of symptoms in patients who experienced persistent symptoms (for >2 months) (n = 181). The most common symptoms reported include fatigue, headache, and nasal symptoms. **C,** Persistent symptoms present at the time of survey of participants with a symptom duration longer than 6 months. These participants were asked additional questions about their current symptoms or symptoms experienced in the month preceding the survey. **B** and **C,** The participants shown in (**C**) represent a subgroup of the patients depicted in (**B**).

without persistent symptoms (median age 44 vs 37 years) (Table II). The majority of respondents in both groups used immunoglobulin replacement therapy; however, the use of anti-inflammatory medication was reported more frequently in those with persistent symptoms (33% vs 23% in those without persistent symptoms).

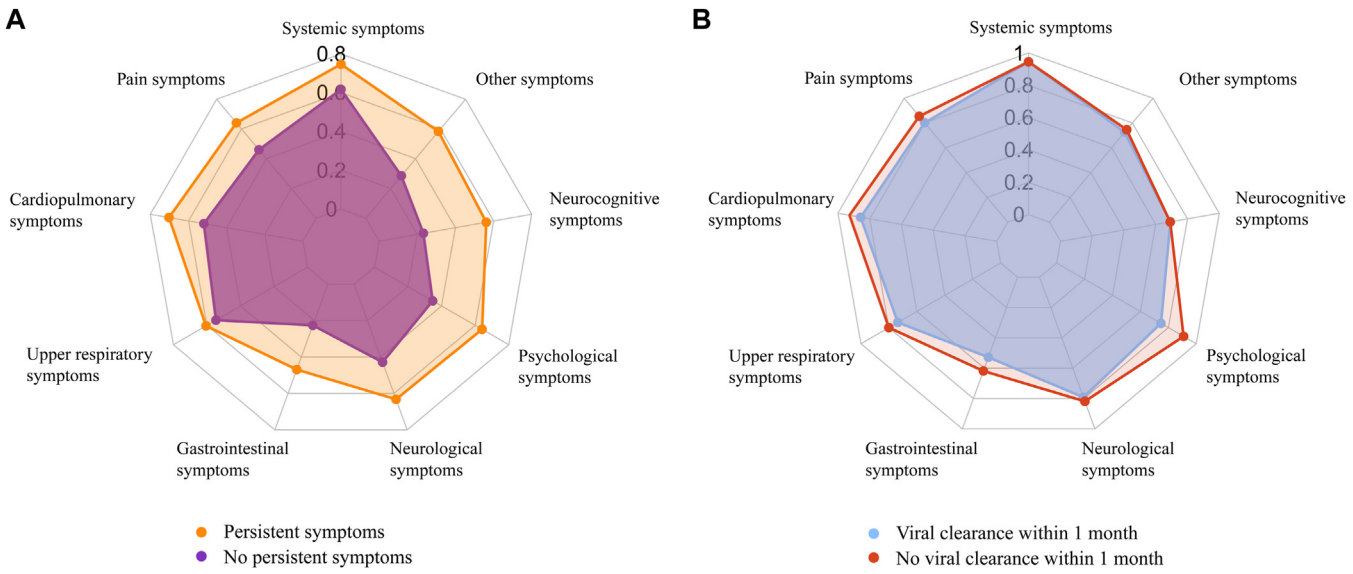

FIG 4. Radar charts comparing symptom prevalence after COVID-19. **A,** Symptom prevalence in respondents with (*orange line* [n = 181]) and without persistent symptoms (*purple line* [n = 454]). **B,** Symptom prevalence in respondents with persistent symptoms based on viral clearance within 1 month. Blue line indicates those with persistent symptoms and achieved viral clearance within 1 month (n = 91). Red line indicates those who had persistent symptoms and did not achieve viral clearance within 1 month (n = 55). Systemic symptoms include fatigue and/or weakness, fever, heavy sweating and/or night sweats, change in appetite, weight loss, and dizziness. Pain symptoms include muscle pain, joint pain, and general pain and/or discomfort. Cardiopulmonary symptoms include dyspnea, exertional breathlessness, chest pain and/or tightness, palpitations, sputum cough, and wheezing. Upper respiratory symptoms include sore throat and nasal symptoms. Gastrointestinal symptoms include diarrhea, gastrointestinal symptoms, nausea and/or vomiting, abdominal pain, and constipation. Neurologic symptoms include headache, smell dysfunction, taste dysfunction, affected vision, affected hearing, epilepsy and/or seizures, and paraesthesia. Psychological and social symptoms include affected sleep, anxiety, depression, posttraumatic stress disorder, impaired walking and/or mobility, problems with self-care, impaired usual activity, and reduced quality of life. Neurocognitive symptoms include impaired memory, poor concentration, and confusion and/or brain fog. Other symptoms include hair loss, skin changes, impaired exercise capacity, chills, vertigo, limb edema, and urinary symptoms.

Before the COVID-19 pandemic, various comorbidities were present in those respondents who later contracted COVID-19. Among those without persistent symptoms, lung diseases other than asthma were the most prevalent comorbidity (25%), whereas asthma was the most prevalent comorbidity among those with persistent symptoms (40%).

To further analyze the relationship between baseline variables and likelihood of developing persistent symptoms after COVID-19, a mixed-effects logistic regression model was used. The fixed effects included sex, age, PID group (with the groups other than CVID, agammaglobulinemia, and other predominantly antibody deficiencies combined into the category other), use of immunomodulatory medication, and comorbidities present before the pandemic. Continent was included as a random effect to account for clustering by geographic region (Table III). This model found that being female (odds ratio [OR] = 1.8 [95% CI = 1.1-2.9]; P = .017), having other predominantly antibody deficiencies (OR = 1.70 [95% CI = 1.0-2.7]; P = .031), having asthma (OR = 2.2 [95% CI = 1.4-3.4]; P = .0005), or having a neurologic disease (OR = 3.0 [95% CI = 1.5-5.9]; P= .0015) significantly increased the odds of development of persistent symptoms (Table III). Having a psychiatric condition at baseline was found to lower the odds of developing persistent symptoms (OR = 0.31 95% [CI = 0.12-0.77]; P = .011).

Persistent symptoms at the time of the survey

Participants with a symptom duration of more than 6 months (n = 106) were also asked about their symptoms as experienced in the past month. In 28% of the respondents, symptoms fluctuated after initial onset, whereas symptoms persisted in 22% of the respondents, increased in 16%, relapsed (returned after a period of improvement) in 11%, and were of new onset in 8%, with 15% of the respondents having an unknown status. The most commonly reported symptoms were fatigue, myalgia, headache, brain fog, and poor concentration (Fig 3, *C*).

When stratifying the respondents with persistent symptoms into those with symptoms lasting between 2 and 6 months and those with symptoms lasting more than 6 months, we observed no differences in terms of underlying PID diagnosis, sex, age, comorbidity, or disease severity (see Tables E5 and E6 in the Online Repository at www.jacionline.org). However, the group with symptoms lasting more than 6 months exhibited a higher median number of symptoms (20 vs 16 [P = .03]) and more frequent use of maintenance therapy for COVID-19 related symptoms (26% vs 13% [P = .03]). Additionally, respondents from Asia reported symptoms lasting more than 6 months less frequently (P = .04). Conversely, respondents with symptoms lasting between 2 and 6 months reported relatively higher antibiotic use (61% vs 41% [P = .006]). Analysis

TABLE I. Descriptive statistics of outcome variables stratified by COVID-19 symptom duration (<2 mo vs >2 mo)

Variable	Descriptive statistics		*P* value
	COVID-19 symptom duration < 2 mo (n = 454)	COVID-19 symptom duration > 2 mo (n = 181)	
No. of COVID-19 infections, no. (%)			.0027*
1	302 (67%)	104 (58%)	
2 or 3	140 (31%)	62 (34%)	
≥3	12 (3%)	15 (8%)	
COVID-19 severity, no. (%)			<.0001†
Mild	122 (27%)	10 (6%)	
Moderate	181 (40%)	45 (25%)	
Severe (no hospital admission)	110 (24%)	89 (49%)	
Hospital admission (non-ICU), no. (%)	39 (9%)	30 (17%)	
ICU admission	2 (0.4%)	7 (4%)	
COVID-19 symptom categories, no. (%)			
Systemic	350 (77%)	169 (93%)	<.0001*
Pain	261 (58%)	145 (80%)	<.0001*
Cardiopulmonary	295 (65%)	159 (88%)	<.0001*
Upper respiratory	310 (68%)	137 (76%)	.08*
Gastrointestinal	128 (28%)	106 (59%)	<.0001*
Neurologic	243 (54%)	143 (79%)	<.0001*
Psychological	197 (43%)	145 (80%)	<.0001*
Neurocognitive	132 (29%)	127 (70%)	<.0001*
Other	162 (36%)	132 (73%)	<.0001*
No. of symptoms (median)	12	18	<.0001‡
Viral clearance within 1 mo, no. (%)			<.0001†
Yes (clearance in <1 mo)	317 (70%)	91 (50%)	
No, clearance after 1 month	52 (12%)	32 (18%)	
No, clearance after 3 mo	7 (2%)	17 (9%)	
No, clearance after 6 mo	3 (1%)	6 (3%)	
Unknown	75 (17%)	35 (19%)	
Positive self-test result at >1 m, no. (%)			.0008*
No, tested negative within 1 mo (reference)	297 (65%)	96 (53%)	
Yes, tested positive after 1 mo	54 (12%)	42 (23%)	
Unknown	102 (23%)	43 (24%)	
Treatment, no. (%)			
Multiple (≥2) rounds of antivirals	39 (9%)	26 (14%)	.03*
Combination treatment	73 (16%)	40 (22%)	.07*
Maintenance therapy	14 (3%)	38 (21%)	<.0001*
mAbs (symptomatic use)	53 (12%)	20 (11%)	.82*
Autoimmune disease after COVID-19, no. (%)	34 (8%)	27 (15%)	.004*

Systemic symptoms include fatigue and/or weakness, fever, heavy sweating and/or night sweats, change in appetite, weight loss, and dizziness. Pain symptoms include muscle pain, joint pain, and general pain and/or discomfort. Cardiopulmonary symptoms include dyspnea, exertional breathlessness, chest pain and/or tightness, palpitations, sputum cough, and wheezing. Upper respiratory symptoms include sore throat and nasal symptoms. Gastrointestinal symptoms and diarrhea, gastrointestinal symptoms, nausea and/or vomiting, abdominal pain, and constipation. Neurologic symptoms include headache, smell dysfunction, taste dysfunction, affected vision, affected hearing, epilepsy and/or seizures, and paraesthesia. Psychological and social symptoms include affected sleep, anxiety, depression, posttraumatic stress disorder, impaired walking and/or mobility, problems with self-care, impaired usual activity, and reduced quality of life. Neurocognitive symptoms include impaired memory, poor concentration, confusion and/or brain fog. Other symptoms include hair loss, skin changes, impaired exercise capacity, chills, vertigo, limb edema, urinary symptoms, and other. For the different treatment options, the chi-square calculation compared the yes responses with the combined no, unknown, and missing responses. See Table E4 for the exact respondent counts per answer.
ICU, Intensive care unit.
*The chi-square test.
†The Fisher exact test.
‡The Mann-Whitney *U* test.

of open-ended responses regarding antibiotic use did not reveal increased use of any specific antibiotic (data not shown).

Persistent symptoms after COVID-19 and viral clearance

In all, 30% of respondents with persistent symptoms after COVID-19 (n = 55) failed to achieve viral clearance after 1 month (Table II). Compared with those respondents who achieved viral clearance within 1 month, those who did not were significantly more likely to have experienced severe acute illness requiring hospitalization ($P < .0001$ [see Table E7 in the Online Repository at www.jacionline.org]). The respondents without viral clearance received multiple rounds of antiviral therapy (27% vs 7%, [$P = .0006$]) and combination therapy for COVID-19 (36% vs 12% [$P = .0005$]) more frequently, but no difference in the administration of long-term maintenance therapy for COVID-19–related symptoms or mAbs for symptomatic disease was observed. Respondents without viral

TABLE II. Descriptive statistics of the baseline variables stratified by COVID-19 symptom duration (<2 mo vs >2 mo)

	Descriptive statistics		
Variable	**COVID-19 symptom duration < 2 mo (n = 454)**	**COVID-19 symptom duration > 2 mo (n = 181)**	***P* value**
Sex, no. (%)			<.0001*
Female	252 (56%)	140 (77%)	
Male	200 (44%)	40 (22%)	
Prefer not to answer	2 (0.4%)	1 (0.6%)	
Age (y), median	37	44	.0003†
Time since PID diagnosis (y), median	8	8	.38†
PID group			
CVID	205 (45%)	81 (45%)	.99‡
(S)CID	12 (3%)	7 (4%)	.44*
Agammaglobulinemia	78 (17%)	9 (5%)	<.0001‡
CID with associated and syndromic features	15 (3%)	3 (2%)	.43*
Defects of intrinsic and innate immunity	2 (0.4%)	0 (0%)	NA
Diseases of immune dysregulation	12 (3%)	1 (0.6%)	.12*
Other/unknown	40 (9%)	17 (9%)	.94‡
Other predominantly antibody deficiencies	77 (17%)	59 (33%)	<.0001‡
Phagocyte defects	13 (3%)	4 (2%)	.79*
IGRT	389 (86%)	153 (85%)	.81‡
Antibiotics	214 (47%)	89 (49%)	.64‡
Antivirals	58 (13%)	26 (14%)	.59‡
Antifungal	61 (13%)	32 (18%)	.17‡
Anti-inflammatory medication	102 (23%)	60 (33%)	.005‡
Immunosuppressive medication	44 (10%)	24 (13%)	.19‡
Comorbidity before COVID-19			
Asthma	77 (17%)	72 (40%)	<.0001‡
Autoimmune disease	102 (23%)	51 (28%)	.16‡
Cancer and/or lymphoproliferative disease	23 (5%)	13 (7%)	.40‡
Coronary artery disease	6 (1%)	5 (3%)	.31*
Diabetes	13 (3%)	11 (6%)	.09‡
Gastrointestinal disease	87 (19%)	58 (32.0%)	.0007‡
Heart disease	22 (5%)	8 (4%)	.98‡
Hypertension	51 (11%)	37 (20%)	.004‡
Inflammatory disease	48 (11%)	34 (19%)	.008‡
Kidney disease	14 (3%)	14 (8%)	.018‡
Liver disease	23 (5%)	8 (4%)	.89‡
Lung disease other than asthma	115 (25 %)	45 (25%)	.98‡
Neurologic disease	21 (5%)	29 (16%)	<.0001‡
Obesity (BMI > 30 kg/m^2)	41 (9%)	37 (20%)	.0001‡
Psychiatric condition	29 (6%)	7 (4%)	.29‡
Continent			
Europe	264 (58%)	107 (59%)	.89‡
Africa	8 (2%)	4 (2%)	.75*
Asia	99 (22%)	16 (9%)	.0002‡
Australia	11 (2%)	9 (5%)	.16‡
North America	62 (14%)	44 (24%)	.002‡
South America	10 (2%)	1 (1%)	.19*
Vaccination, no. (%)			.009*
Fully vaccinated	273 (60%)	127 (70%)	
Partially vaccinated	73 (16%)	18 (10%)	
Not vaccinated	107 (24%)	33 (18%)	
Status unknown	1 (0.2%)	3 (2%)	

For the different prepandemic treatment options, the chi-square calculation compared the yes responses with the combined no, unknown, and missing responses. See Table E4 in the Online Repository for the exact respondent counts per answer.

BMI, Body mass index; *IGRT*, immunoglobulin replacement therapy; *(S)CID*, SCID and/or CID.

*The Fisher exact test.

†The Mann-Whitney *U* test.

‡The chi-square test.

clearance reported a higher number of symptoms (median 20 vs 17 [P = .006]). Their clinical profiles were largely similar. However, those respondents with persistent symptoms who did not achieve viral clearance reported significantly more psychological problems than those who cleared the virus rapidly (91% vs 75% [P = .03]) (Fig 4, *B*).

TABLE III. Mixed-effects logistic regression analyses of baseline variables stratified by COVID-19 symptom duration (<2 mo vs >2 mo)

	Multivariate regression analysis		
Variable	**Exp(B) = OR**	**95% CI**	***P* value**
Sex (female vs male), no.	1.8	1.1-2.9	**.017**
Age (y), median	1.0	0.99-1.0	.68
PID group, no.			
CVID	Reference		
Agammaglobulinemia	0.64	0.28-1.5	.29
Other predominantly antibody deficiencies	1.7	1.0-2.7	**.031**
Other	1.1	0.61-1.8	.83
Immunomodulatory medication (yes vs no),* no.	1.4	0.95-2.2	.083
Comorbidity before COVID-19 (yes vs no), no.			
Asthma	2.2	1.4-3.4	**.0005**
Autoimmune disease	0.84	0.52-1.4	.49
Cancer and/or lymphoproliferative disease	0.96	0.41-2.2	.93
Diabetes	0.96	0.35-2.6	.94
Gastrointestinal disease	1.2	0.78-2.0	.36
Hypertension	1.3	0.73-2.3	.38
Inflammatory disease	1.4	0.78-2.6	.25
Lung disease other than asthma	0.84	0.54-1.3	.45
Neurologic disease	3.0	1.5-5.9	**.0015**
Obesity (BMI > 30 kg/m^2)	1.3	0.72-2.3	.40
Psychiatric condition	0.31	0.12-0.77	**.011**

Continent was included as a random effect in the mixed-effects logistic regression model to account for clustering of patients by geographic region. Boldface indicates statistical significance.

BMI, Body mass index.

*For the variable immunomodulatory medication, the no option (total n = 424) also included the unknown responses (n = 5).

HR-QoL and preventive measures before the pandemic versus at time of the survey

From the time before the pandemic to the time of completion of the survey by the respondents, HR-QoL (assessed using the EQ-5D-5L instrument produced by the EuroQoL Group and modified for 2 time points) decreased across all 5 domains (Fig 5, *A*). This decrease was most prominent in the domains activity and anxiety and/or depression. The median VAS score for overall health was 75 before the pandemic, but it declined to 70 at the time of the survey ($P < .0001$) (Fig 5, *A* and see Table E8 in the Online Repository at www.jacionline.org). The median LSS, which was 6.0 before the pandemic, deteriorated to 7.0 ($P < .0001$). Those respondents who experienced symptoms for more than 6 months demonstrated the greatest deterioration across all domains and in VAS score when compared with the those without COVID-19, those with COVID-19 and symptoms lasting less than 2 months, and those with symptoms lasting between 2 and 6 months (see Fig E2 in the Online Repository at www.jacionline.org).

Compared with those participants without COVID-19, those with symptom durations longer than 6 months experienced significantly greater decreases in VAS score ($P < .0001$). The worsening of LSS was significantly less in respondents with symptom durations less than 2 months than in those without COVID-19 ($P = .004$). However, the deterioration in LSS was significantly greater in those with symptom durations longer than 6 months than in those without COVID-19 ($P < .0001$) (Fig 5, *B*).

Behavior related to avoiding infection was assessed by using the same scale as the EQ-5D-5L, which categorizes measures into no, slight, moderate, severe, and extreme. Prepandemic measures to avoid infections were compared with the measures at the time of survey. Before the pandemic, 58% of respondents without persistent symptoms took no or slight measures to avoid infections. This proportion decreased to 44% at the time of survey. On the other hand, the percentage of those taking moderate-to-extreme measures increased from 42% before the pandemic to 56% during the time of survey ($P = .0001$). A similar trend was observed for respondents with persistent symptoms. The percentage of these respondents taking no or slight measures decreased from 47% to 23%, whereas the percentage of those taking moderate-to-extreme measures increased from 53% to 77% ($P < .0001$).

DISCUSSION

This study investigated the long-term effects experienced by patients with PID in response to COVID-19. A significant number of the survey respondents reported persistent symptoms lasting more than 2 months after SARS-CoV-2 infection, with a considerable number of them (self)-reporting viral persistence beyond 1 month. The most commonly reported persistent symptoms included fatigue, nasal symptoms, and headache. Independent risk factors for developing persistent symptoms included female sex, asthma, neurologic disease, and a PID diagnosis classified as other predominantly antibody deficiency.Individuals with psychiatric conditions appeared to have a lower risk of developing persistent symptoms. Those with persistent symptoms experienced higher disease severity and more symptoms across most categories. The pandemic has had a significant negative impact on overall HR-QoL for patients with PID, even among those who were not infected with SARS-CoV-2.

The survey used the term *persistent symptoms after COVID-19* instead of *long COVID* (also referred to as postacute sequelae of COVID-19). Long COVID encompasses a broad spectrum of symptoms following an acute SARS-CoV-2 infection. The pathogenesis of long COVID is still poorly understood, with several hypotheses reported.[17,18] Persistent symptoms may sometimes be caused by a persistent SARS-CoV-2 infection, particularly in immunocompromised individuals.[19-21] These persistent infections are often unrecognized, as their clinical symptoms overlap with those of other suggested causes of long COVID.[17,19] However, it is important to distinguish cases of persistent symptoms with or without viral clearance, as the treatment options differ. Because this study involved patients with PIDs, the hypothesis was that some of the persistent symptoms could be explained by persistent SARS-CoV-2 infections. Therefore, cases of persistent symptoms were not automatically designated as long COVID. However, to put our results in perspective, we compared our results with those of other studies that did use the term *long COVID*.

In all, 25% of respondents who contracted SARS-CoV-2 experienced persistent symptoms. Although it is alarming that 1 in 4 patients with PID experience long-term symptoms after COVID-19, the percentage is comparable to the prevalence of long COVID in the general (nonhospitalized) population, which is estimated to be between 10% and 30%.[17] A survey of 1974 patients with rheumatic diseases also found a similar prevalence

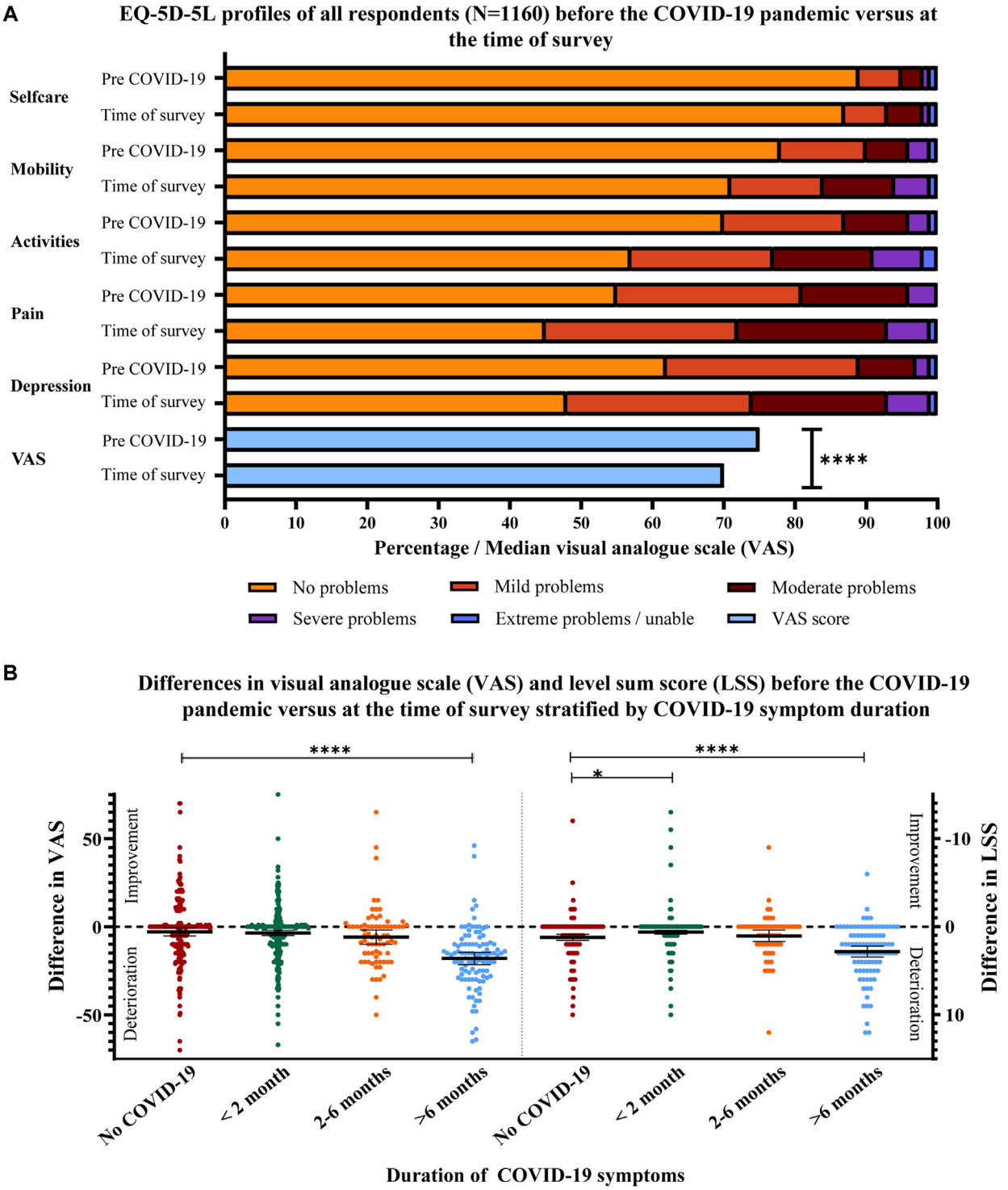

FIG 5. EQ-5D-5L profiles before the COVID-19 pandemic versus at the time of the survey. **A,** The first 5 pairs of bars represent the percentages of responses across the domains of self-care, mobility, activity, pain, and depression. Respondents could choose from 5 levels of severity: no problems, mild problems, moderate problems, severe problems, and extreme problems or inability. The last pair of bars (*blue*) indicate mean VAS score of overall health on a scale from 0 to 100. The Wilcoxon signed-rank test was used to compare the prepandemic situation with the situation at the time of the survey. **B,** Differences in VAS scores (*left*) and LSSs (*right*) before the pandemic versus at the time of survey, stratified by COVID-19 symptom duration. Every dot represents the difference from before the pandemic to time of the survey for 1 respondent. Scores below the zero line indicate a deterioration. Scores above the line indicate an improvement. Black horizontal lines indicate the mean difference of the group with the 95% CI. The Y-axis on the right side is reversed, as negative differences indicate an improvement and positive differences indicate a decline. *$P < .05$; ****$P < .0001$.

of 21%.[22] On the other hand, another survey that included 175 patients with CVID reported higher prevalence (66%).[13] The persistent clinical symptoms of our PID cohort (including fatigue, arthralgia, myalgia, and dyspnea) largely overlap with those in other studies of individuals with immune deficiency.[13,22] The identified risk factors for persistent symptoms also correspond with those in the existing literature, which often identifies female sex[3,13,22] and asthma[23] as significant predictors. Although obesity is widely recognized as a risk factor, it was not identified in our multivariate analysis.[13,22,23]

Having a PID characterized by predominantly antibody deficiency but other than CVID and agammaglobulinemia formed an independent risk factor for developing persistent symptoms (with CVID as the reference category). Because this survey is, as far as we know, the first study to investigate multiple categories of PID diagnosis, these data are difficult to validate against the existing literature. These other predominantly antibody deficiencies may be associated with a relatively lower burden of chronic disease, which might have led to a greater perceived severity of COVID-19–related symptoms. Additionally, this patient group uses immunoglobulin replacement therapy less frequently. Especially in the later phase of the pandemic, they might have missed the protective effect of SARS-CoV-2 antibodies provided by this therapy.[24]

The largest difference in COVID-19–related symptoms between respondents with and without persistent symptoms was observed in the category of neurocognitive symptoms, including impaired memory, poor concentration, and confusion/brain fog. Similar results have been found in other (non-PID) studies, underscoring the negative impact of COVID-19 on neurocognitive functioning.[25] Additionally, this survey found that having a neurologic disease as a comorbidity before the COVID-19 pandemic is a risk factor for developing persistent symptoms. Although the survey did not differentiate between prepandemic neurologic or neurocognitive comorbidity, this result suggests that respondents with these comorbidities were particularly vulnerable to long-term symptoms following COVID-19. Furthermore, previous studies in the general population have found that COVID-19 is associated with an increased risk of developing autoimmune diseases, which is also among the suggested causes of long COVID.[17,26,27] This finding aligns with those of this study, in which significantly more autoimmune conditions were reported in respondents with persistent symptoms. The finding that preexistent psychiatric conditions are associated with fewer persistent symptoms contrasts with findings from previous studies. For instance, a survey conducted with 6015 respondents in the general population reported a slight increase in the prevalence of persistent symptoms among respondents with preexisting psychiatric conditions.[28]

In our survey, 30% of respondents with persistent symptoms reported failing to achieve viral clearance within 1 month. It is important to acknowledge that viral persistence was self-reported, which introduces a degree of unreliability to these data. Respondents without viral clearance within 1 month also reported higher use of multiple rounds of antivirals and combination therapy for COVID-19, although the outcomes of these treatments in our cohort are unknown. Another study investigating persistent SARS-CoV-2 PCR positivity in 103 patients with immune deficiency also reported persistent PCR positivity in 30% of those studied regardless of treatment. In this study, lower B-cell counts and lower IgA and IgM concentrations were identified as risk factors for persistent PCR positivity.[21] In a case-control study involving participants without PID, blood transcriptomic analyses identified persistent presence of SARS-CoV-2 RNA as an independent predictor of long COVID.[29] Further investigation into persistent viral replication is essential to gain insights that could guide the development of future therapeutic options.

HR-QoL decreased for all PID categories. The most prominent decline in HR-QoL was observed in the activity and anxiety/depression domains, indicating that many respondents struggled with performing their usual activities and/or felt more anxious or depressed than before the pandemic. As respondents without COVID-19 also experienced this deterioration, a considerable part of the decline in HR-QoL could be attributed to the impact of COVID-19 on daily life, including the implementation of preventive measure such as lockdowns. Although a direct comparison with the general population cannot be made, patients with PID might have experienced more anxiety owing to their vulnerability to infectious diseases, leading to stricter adherence to preventive measures and increased social isolation. They may have also faced greater uncertainty regarding the efficacy of vaccines, as several PID conditions are known for poor immunologic response after vaccination in general. Additionally, persistent symptoms after COVID-19 significantly affected HR-QoL, with those experiencing the longest symptom duration showing the greatest decline in HR- QoL when compared with respondents without COVID-19. This finding aligns with the findings of other studies that assessed the HR-QoL in the general population.[30,31]

A unique feature of this study is the diverse geographic representation of its respondents. To our knowledge, this is also the largest study of the long-term effects of COVID-19 in patients with PID. By including a wide variety of PID diagnoses, this study provides a broad perspective on how patients with PID have experienced and managed long-term COVID-19 symptoms. However, the study has several limitations. First, the absence of a control group limited the ability to compare our findings with those regarding the broader (PID-free) population. It would have been particularly interesting to compare comorbidity profiles with those of individuals without PID to better understand what contributes most to the persistent symptoms: the PID itself, the (associated) comorbidities, or the combination of both. Second, although the overall sample size is substantial, the number of respondents within many specific PID diagnosis was relatively small, limiting the statistical power to conduct detailed analyses for each individual diagnosis. Additionally, our data were self-reported and have not been verified with the respondents' medical records (including COVID-19 test results, therapies, and vaccination records). As a result, it was not possible to perform analyses based on specific viral variants, which might have varied across different regions and affected symptom severity and duration; in addition, the unknown timing of vaccinations in relation to infection made it impossible to investigate their protective effects. Moreover, we observed a higher reported use of antiviral and combination therapies among participants who indicated experiencing viral persistence. However, because of the lack of precise data on the timing of these treatments in relation to COVID-19 infection, we were unable to analyze the relationship between the initiation of these therapies, the persistence of viral symptoms, and their outcomes. Furthermore, the lack of a baseline (prepandemic) measurement of the EQ-5D-5L questionnaire introduces the risk for recall bias. Despite these limitations, the questionnaire still offers valuable insights into how patients

with PID have experienced the pandemic. Future studies could explore the influence of sex as a potential effect modifier in the relationship between risk factors and prolonged COVID-19 symptoms. Investigating sex-specific biologic and social factors may provide valuable insights into differences in disease progression and recovery.

In summary, this large international survey demonstrated the impact of the COVID-19 pandemic on patients with PID. Experiencing persistent symptoms after COVID-19 is common. Regardless of whether they individuals experienced COVID-19, the pandemic had a notable negative impact on overall HR-QoL. This study provides clinicians with valuable insights into their patients' experiences during the pandemic. Future research should continue monitoring the long-term effects of the pandemic in this patient group. Additionally, ongoing research in antiviral therapy is crucial, as viral persistence is prevalent in this population. Improved therapeutic options could potentially alleviate some of the clinical burden caused by COVID-19 or future viral outbreaks.

DISCLOSURE STATEMENT

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Clinical implication: Recognizing and addressing the high prevalence of persistent symptoms after COVID-19 and associated risk factors in patients with PID is crucial for improving their management and HR-QoL.

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