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MAJOR ARTICLE

Respiratory, Cardiac, and Neuropsychiatric Manifestations of Postacute Sequelae of Coronavirus Disease 2019 in Lima, Peru

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Background. Few studies have examined the burden of postacute sequelae of coronavirus disease 2019 (COVID-19) (PASC) in low- and middle-income countries. We sought to characterize PASC with self-reported questionnaires and clinical examinations of end-organ function in Lima, Peru.

Methods. From January to July 2021, we recruited participants at least 8 weeks after COVID-19 diagnosis from a case registry in Lima, Peru. We evaluated participants for PASC with questionnaires, neuropsychiatric evaluations, chest X-ray, spirometry, electrocardiogram, and echocardiogram. We used multivariable models to identify risk factors for PASC.

Results. We assessed 989 participants for PASC at a median 4.7 months after diagnosis. Clinically significant respiratory symptoms were reported by 68.3% of participants, particularly those who had been severely ill during acute COVID-19, and were associated with cardiac findings of ventricular hypertrophy or dilation on echocardiogram. Neuropsychiatric questionnaires were consistent with depression in 20.7% and cognitive impairment in 8.0%. Female sex and older age were associated with increased risk of respiratory (adjusted odds ratio [aOR], 2.36 [95% confidence interval {CI}, 1.69–3.31] and aOR, 1.01 [95% CI, 1.00–1.03], respectively) and neuropsychiatric sequelae (aOR, 2.99 [95% CI, 2.16–4.18] and aOR, 1.02 [95% CI, 1.01–1.03], respectively).

Conclusions. COVID-19 survivors in Lima, Peru, experienced frequent postacute respiratory symptoms and depression, particularly among older and female participants. Clinical examinations highlighted the need for cardiopulmonary rehabilitation among persons with severe COVID-19; psychosocial support may be required among all COVID-19 survivors.

Keywords. COVID-19; Peru; postacute; SARS-CoV-2; sequelae.

Following acute coronavirus disease 2019 (COVID-19), many develop postacute sequelae of COVID-19 (PASC), including persistent symptoms, evidence of cardiopulmonary disease on imaging, and limitations in ability to resume work or recreational activities [1–5]. Few studies have evaluated PASC in low- and middle-income countries (LMICs) in South America [6–8]. In Peru, limitations in access to hospital beds, supplemental oxygen, and ventilators have contributed to disproportionate COVID-19 mortality [9] and may portend a heavy PASC burden. PASC risk factors include greater severity of acute COVID-19 illness [1, 4, 8, 10–16], preexisting comorbidities [11, 14], increasing age [2, 13, 15], elevated body mass index (BMI) [2], female sex [2, 8, 12–14, 17], and low income [18]. PASC may also be frequent in people with asymptomatic acute COVID-19 and younger persons [11, 13].

Here, we sought to evaluate the prevalence of PASC in Peru through self-reported questionnaires on respiratory status and mental health and through objective clinical examinations of end-organ function. Through multivariable analysis, we identified risk factors associated with the development of PASC.

METHODS

Patient Consent Statement

The study was approved by the ethics committee of Asociación Benéfica PRISMA and the Mass General Brigham Institutional

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Review Board. All participants provided written informed consent.

Study Design and Participants

We enrolled adult participants (aged ≥18 years) with COVID-19 who had been registered in a database of the Directorate of Integrated Health Networks Lima Norte and Socios En Salud using a 2-stage telephone screening and enrollment process. First, potential participants were contacted to assess eligibility. Only those who lived within the catchment area in northern Lima, Peru and who were at least 8 weeks after confirmed diagnosis of COVID-19 by reverse-transcription polymerase chain reaction (RT-PCR) were eligible for enrollment. Subsequently, eligible potential participants were contacted again and scheduled for an in-person enrollment visit.

Data Collection and Procedures

Participants completed a screening questionnaire to evaluate demographics and to retrospectively record their self-report of comorbidities prior to COVID-19, as well as symptoms and hospitalization course during the acute COVID-19 presentation. Participants were classified as "symptomatic" if they self-reported the presence of any of the following during their acute COVID-19 presentation: fever, chills, cough, dyspnea, nasal congestion, sore throat, malaise, fatigue, loss of appetite, nausea/emesis, diarrhea, anosmia, ageusia, headache, musculoskeletal pain, chest pain, abdominal pain, and altered mental status. We categorized participants as either asymptomatic, symptomatic without requiring hospitalization, or symptomatic requiring hospitalization during acute COVID-19 presentation.

The in-person PASC evaluation entailed respiratory questionnaires including the chronic obstructive pulmonary disease assessment test (CAT) and the St George's Respiratory Questionnaire (SGRQ); neuropsychiatric questionnaires including the Patient Health Questionnaire-2 (PHQ-2), Patient Health Questionnaire-9 (PHQ-9), and Mini-Mental State Examination (MMSE); and quality-of-life (QOL) questionnaires including the Euro-QOL–5 dimensions–3 levels (EQ-5D-3L) and EUROHIS-QOL 8-item index (see Supplementary Material). Clinical examinations included chest X-ray (CXR), spirometry, electrocardiogram (ECG), and echocardiogram (see Supplementary Material). We recorded data in a Microsoft SQL Server 2019 database (Microsoft Corporation, Redmond, Washington).

Statistical Analyses

We defined respiratory, cardiac, and neuropsychiatric PASC as outlined in Table 1. Presence of at least 1 of the features described in Table 1 was used to classify participants as having a specific type of PASC. We reported demographics and health outcomes as median and interquartile range (IQR) for continuous variables and as absolute values with percentages for categorical variables. We reported results of QOL questionnaires separately. First, we evaluated the association between comorbidities (independent variable) and the results of questionnaires and clinical assessments (dependent variables), adjusting for age, sex, and BMI as potential confounders, using linear and logistic regression models for continuous and binary dependent variables, respectively. We also evaluated the association between severity of acute COVID-19 (independent variable) and the results of questionnaires and clinical assessments (dependent variables), adjusting for age, sex, BMI, and comorbidities as potential confounders, using linear and logistic regression models as described above. We reported beta (β) coefficients for linear models and adjusted odds ratios (aORs) for logistic models. Second, we assessed for predictors of PASC by fitting a multivariable logistic model using a backward selection method where we considered age, sex, BMI, comorbidities, and the presence of symptoms during acute COVID-19 as potential predictors of PASC. We retained covariates with a P value <.10 in the final model. Third, we performed an exploratory analysis on potential effect modification by time from COVID-19 diagnosis to PASC evaluation on the risk factors identified in the multivariable model. All tests were 2-sided with a significance level of 5%. Fourth, we conducted an exploratory analysis using Spearman correlation and matrix plots to quantify the correlation between self-reported PASC questionnaires and objective clinical evaluations, using the Bonferroni method to adjust for multiple

Table 1. Definitions of Respiratory, Cardiac, and Neuropsychiatric Postacute Sequelae of Coronavirus Disease 2019

Category	Definition
Respiratory	• Restrictive or obstructive ventilatory patterns on spirometry • CXR abnormalities including parenchymal opacities, atelectasis or volume loss, fibrosis, emphysematous change, pleural abnormalities, cardiomegaly, and calcifications • Clinically significant respiratory symptoms as defined by score of ≥10 on the CAT or ≥25 on the SGRQ
Cardiac	• Echocardiographic abnormalities including atrial abnormalities, ventricular hypertrophy/dilation, systolic dysfunction or hypokinesis, diastolic dysfunction or impaired ventricular relaxation, valvular abnormalities, pulmonary hypertension, or elevated filling pressures • Elftaleectrocardiogram abnormalities including arrhythmia, evidence of strain or ischemia, conduction abnormalities, ventricular hypertrophy, and axis deviations
Neuropsychiatric	• Clinically significant depression, as defined by score of ≥10 on PHQ-9 • Cognitive impairment, as defined by score ≤23 on MMSE

Abbreviations: CAT, chronic obstructive pulmonary disease assessment test; CXR, chest x-ray; MMSE, Mini-Mental State Examination; PHQ-9, Patient Health Questionnaire-9; SGRQ, St George's Respiratory Questionnaire.

testing. We performed complete case analysis for all analyses. We performed statistical analyses in R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) and created forest plots with GraphPad Prism version 8.4.3 (GraphPad Software, San Diego, California).

RESULTS

Between 4 January and 14 July 2021, we assessed 7856 individuals for eligibility (Figure 1), among whom 1526 met enrollment criteria. We enrolled 1357 individuals who had COVID-19 confirmed by nasopharyngeal RT-PCR; of these, 989 (72.9%) attended the in-person PASC evaluation. Comparison of enrolled participants who did or did not complete the in-person PASC evaluation revealed grossly similar proportions of self-reported comorbidities prior to COVID-19 and symptoms at acute COVID-19 presentation (Supplementary Table 1). The median duration from date of COVID-19 diagnosis to PASC evaluation was 4.7 (IQR, 4–6) months (Table 2, Supplementary Figure 1).

Table 2 shows characteristics of participants who attended the PASC evaluation, stratified by severity of acute COVID-19 presentation. The median age was 47 (IQR, 35–58) years; 568 (57.4%) were females. The most common self-reported comorbidity preceding COVID-19 was hypertension or other cardiovascular disease in 100 (10.1%) participants, followed by diabetes in 71 (7.2%). Participants with comorbidities prior to COVID-19 had higher median age (59 vs 46 years), symptomatic COVID-19 (83.2% vs 72.0%), and proportion of hospitalization (18.3% vs 11.1%) compared to those without comorbidities (Supplementary Table 2). During acute COVID-19 presentation, 727 (73.5%) participants were symptomatic, with 119 (12.0%) requiring hospitalization for a median duration of 14 (IQR, 10–20) days. Among hospitalized participants, 18 (15.1%) required intensive care unit support with 14 (11.8%) requiring mechanical ventilation.

During PASC evaluation, 790 (81.1%) participants demonstrated respiratory sequelae, 765 (79.4%) cardiac sequelae, and 252 (25.5%) neuropsychiatric sequelae (Table 3). In multivariable analysis, female sex and older age were associated with increased risk of respiratory sequelae (aOR, 2.36 [95% confidence interval {CI}, 1.69–3.31] and aOR, 1.01 [95% CI, 1.00–1.03], respectively) and neuropsychiatric sequelae (aOR, 2.99 [95% CI, 2.16–4.18] and aOR, 1.02 [95% CI, 1.01–1.03], respectively) (Figure 2*A* and 2*C*). Factors associated with greater risk of cardiac sequelae included being symptomatic during acute COVID-19 presentation (aOR, 1.75 [95% CI, 1.22–2.49]), older age (aOR, 1.05 [95% CI, 1.04–1.06]), and greater BMI (aOR, 1.04 [95% CI, 1.00–1.08]) (Figure 2*B*). Time from COVID-19 diagnosis to PASC evaluation did not modify the effect of any risk factor identified in multivariable analysis on the risk of respiratory, cardiac, or neuropsychiatric sequelae (Supplementary Table 3).

CAT screening revealed clinically significant respiratory symptoms among 675 (68.3%) participants (Table 3). Participants with comorbidities had more severe respiratory symptoms, including cough and phlegm, compared to those without comorbidities (Supplementary Table 4). Participants who had been symptomatic during acute COVID-19 presentation had greater severity of respiratory symptoms, including cough, phlegm, chest tightness, breathlessness, and diminished confidence leaving home, as compared to those with asymptomatic COVID-19 (Supplementary Table 4). Participants who had been hospitalized during acute COVID-19 presentation had greater severity of respiratory symptoms, including cough, chest tightness, breathlessness, and diminished confidence leaving home, as compared to those with asymptomatic COVID-19 (Supplementary Table 4). A total of 613 (62.0%) participants had clinically significant respiratory symptoms as defined by score of ≥25 on SGRQ (Table 3, Supplementary Table 5). Participants who had been hospitalized during acute COVID-19 presentation had greater severity of respiratory symptoms on SGRQ as compared to those with asymptomatic COVID-19 (Table 3). Clinically significant respiratory symptoms as defined by SGRQ correlated with those identified by CAT (Spearman rho [ρ] = 0.43; $P < .0001$) (Supplementary Figure 2).

A total of 110 (11.1%) participants had abnormal findings on CXR with parenchymal opacities in 78 (7.9%) and fibrosis in 47 (4.8%) (Supplementary Table 6). Neither the presence of comorbidities nor greater severity of acute COVID-19 presentation was associated with increased risk of abnormalities on CXR (Table 3). CXR abnormalities did not correlate with the presence of clinically significant respiratory symptoms on CAT or SGRQ (Supplementary Figure 2). A total of 125 (12.9%) participants had impaired ventilation on spirometry with 96 (9.9%) restrictive patterns and 29 (3.0%) obstructive patterns (Supplementary Table 7). Participants who had been symptomatic during acute COVID-19 presentation had a lower risk of ventilatory impairment on spirometry (aOR, 0.65 [95% CI, .43–.99]) as compared to those with asymptomatic COVID-19 (Table 3). Those who had been hospitalized during acute COVID-19 had similar risk of ventilatory impairment as compared to those with asymptomatic COVID-19. Abnormalities on spirometry were not correlated with the presence of clinically significant respiratory symptoms on CAT or SGRQ (Supplementary Figure 2).

A total of 375 (38.2%) participants had an abnormal ECG with ventricular hypertrophy or strain in 142 (14.5%) and ischemic patterns in 129 (13.1%) (Supplementary Table 8). Participants with comorbidities had greater risk of ECG abnormalities as compared to those without comorbidities (Table 3). Participants who had been symptomatic or hospitalized with

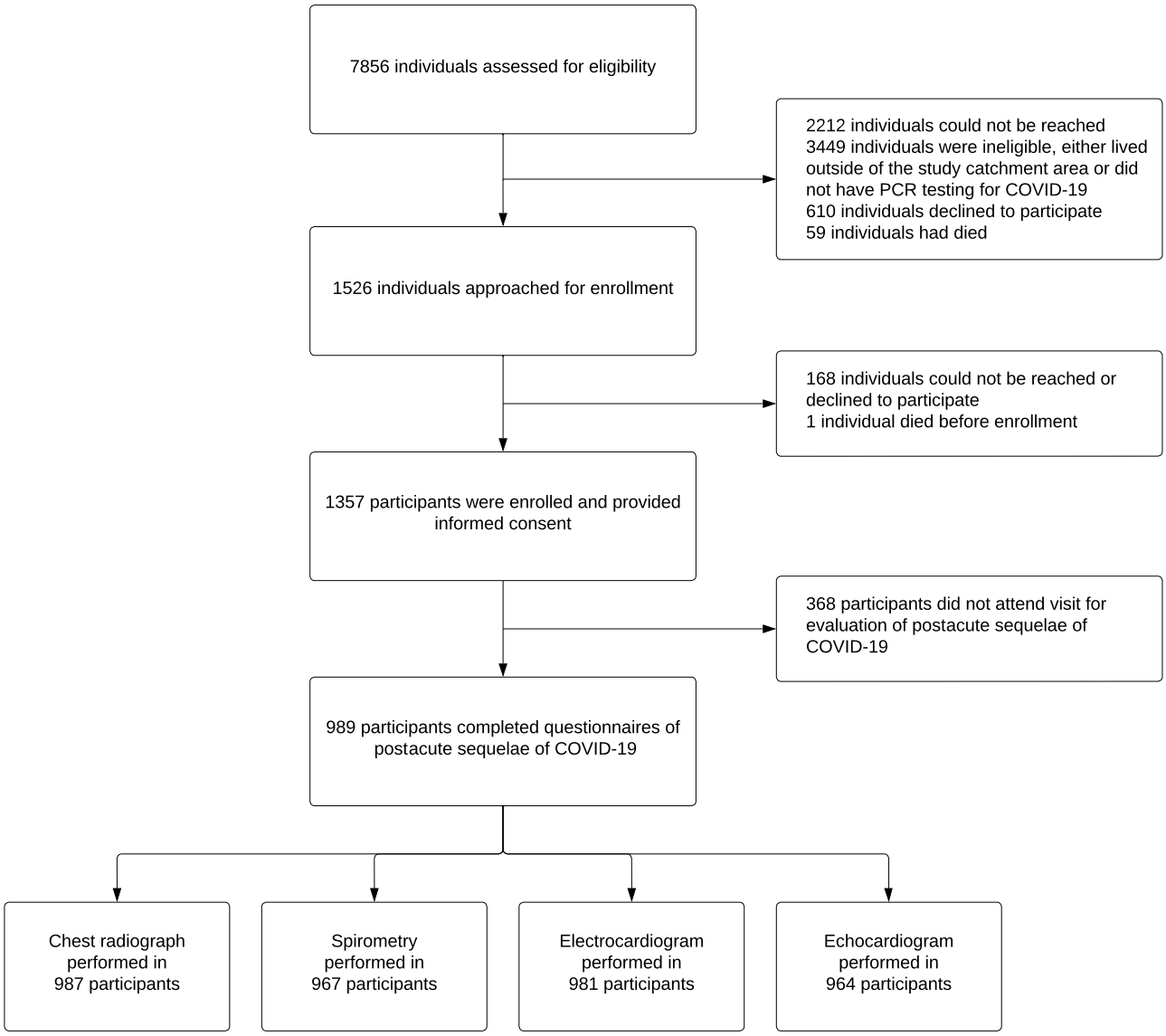

Figure 1. Participant flow diagram. Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

acute COVID-19 had similar risk of ECG abnormalities as compared to those with asymptomatic COVID-19. A total of 694 (72.0%) participants had an abnormal echocardiogram with ventricular hypertrophy or dilation in 402 (41.7%), diastolic dysfunction or impaired ventricular relaxation in 331 (34.3%), and valvular disease in 307 (31.8%) (Supplementary Table 9). Participants who had been symptomatic or hospitalized with acute COVID-19 had greater risk of echocardiographic abnormalities as compared to those with asymptomatic COVID-19 (Table 3). The presence of ventricular hypertrophy or dilation was associated with the presence of clinically significant respiratory symptoms on CAT (Spearman $\rho = 0.15$, $P < .0001$) (Supplementary Figure 2).

On the PHQ-2 and PHQ-9 questionnaires, 408 (41.3%) participants endorsed anhedonia, 579 (58.7%) endorsed depressed mood, and 204 (20.7%) had survey responses consistent with clinically significant depression (Table 3). Neither the presence of comorbidities nor greater severity of acute COVID-19 presentation was associated with increased risk of clinically significant depression (Table 3). Cognitive impairment was noted in 79 (8.0%) participants with mild impairment noted in 60 (6.1%) (Supplementary Table 10). The presence of prior comorbidities was associated with a greater degree of cognitive impairment (Table 3).

On the EQ-5D-3L questionnaire, 731 (73.9%) participants reported pain or discomfort, 608 (61.5%) screened positive for anxiety or depression, 239 (24.2%) reported problems with mobility, and 236 (23.9%) reported problems with usual activities (Supplementary Tables 4 and 11). Participants with comorbidities had diminished QOL scores

Table 2. Characteristics of Participants Evaluated for Postacute Sequelae of Coronavirus Disease 2019

Characteristic	Severity of COVID-19 Presentation			
		Symptomatic[a]		
	Asymptomatic (n = 262)	Not Hospitalized (n = 608)	Hospitalized (n = 119)	Total (N = 989)
Age, y, median (IQR)	44 (32.2–55)	47 (34–58)	54 (45–61)	47 (35–58)
Sex				
Female	164 (62.6)	358 (58.9)	46 (38.7)	568 (57.4)
Male	98 (37.4)	250 (41.1)	73 (61.3)	421 (42.6)
Months between COVID-19 diagnosis and screening phone call for study enrollment, median (IQR)	4.2 (3.7–5.4)	4.5 (3.7–5.8)	4.6 (3.8–6.0)	4.4 (3.7–5.7)
Months between COVID-19 diagnosis and PASC evaluation, median (IQR)	4.55 (3.9–6.2)	4.7 (4.0–6.0)	5.0 (3.9–6.4)	4.7 (4.0–6.0)
BMI, kg/m^2, median (IQR)	27.6 (24.7–31.2), n = 259	28.1 (25.3–31.2), n = 592	29.8 (26.5–33.1), n = 118	28.1 (25.3–31.5), n = 969
Underweight	2/259 (0.8)	3/592 (0.5)	0	5/969 (0.5)
Normal weight	68/259 (26.3)	138/592 (23.3)	17/118 (14.4)	223/969 (23.0)
Overweight	106/259 (40.9)	246/592 (41.6)	45/118 (38.1)	397/969 (41.0)
Obesity	83/259 (32.0)	205/592 (34.6)	56/118 (47.5)	344/969 (35.5)
Contact with presumptive or known COVID-19 case in the past 4 wk	15 (5.7)	68 (11.2)	11 (9.2)	94 (9.5)
1 or more self-reported comorbidity prior to COVID-19 diagnosis	22 (8.4)	85 (14.0)	24 (20.2)	131 (13.2)
Diabetes	14 (5.3)	39 (6.4)	18 (15.1)	71 (7.2)
Any immunodeficiency including HIV	1 (0.4)	0	0	1 (0.1)
Cancer	0	4 (0.7)	1 (0.8)	5 (0.5)
Tuberculosis	0	3 (0.5)	1 (0.8)	4 (0.4)
Hypertension or other cardiovascular disease	17 (6.5)	63 (10.4)	20 (16.8)	100 (10.1)
Chronic neuropsychiatric disease	1 (0.4)	6 (1.0)	1 (0.8)	8 (0.8)
Chronic lung disease	5 (1.9)	14 (2.3)	1 (0.8)	20 (2.0)
No. of symptoms during acute COVID-19 presentation[a], median (IQR)	0	3 (2–4)	3 (2.5–5)	2 (0–4)
Days of hospitalization, median (IQR)	…	…	14 (10–20)	…
Self-reported interventions provided for acute COVID-19 hospitalization				
Non-ICU, no supplemental oxygen required	…	…	14 (11.8)	…
Non-ICU, supplemental oxygen required	…	…	84 (70.6)	…
ICU without mechanical ventilation	…	…	4 (3.4)	…
ICU with mechanical ventilation	…	…	14 (11.8)	…
Unknown	…	…	3 (2.5)	…

Data are presented as No. (%) unless otherwise specified. Denominators are specified for cells containing missing data.

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; PASC, postacute sequelae of COVID-19.

[a]Symptoms potentially consistent with acute COVID-19 were defined as any of the following: fever, chills, cough, dyspnea, nasal congestion, sore throat, malaise, loss of appetite, nausea/emesis, diarrhea, anosmia, ageusia, headache, musculoskeletal pain, chest pain, abdominal pain, and altered mental status.

(Supplementary Table 4). Participants who had been symptomatic or hospitalized during acute COVID-19 presentation had greater odds of pain or discomfort as compared to those with asymptomatic COVID-19 (Supplementary Table 4). On the EUROHIS-QOL questionnaire, 548 (55.4%) participants reported little money or not enough money to meet daily needs, 325 (32.9%) reported dissatisfaction with their health, and 307 (31.0%) reported little to no energy for everyday life (Supplementary Tables 4 and 12). Participants hospitalized during acute COVID-19 had diminished QOL on the EUROHIS-QOL total score as compared to those with asymptomatic COVID-19 (Supplementary Table 4).

DISCUSSION

This cohort study from the prevaccination era in Lima, Peru, is one of the first evaluating PASC in South America [6–8]. During the conduct of the study, Peru had the highest global mortality from COVID-19 at 555 per 100 000 population; however, the burden of PASC among COVID-19 survivors in Peru has not been fully elucidated [19].

Our evaluations revealed high prevalence of respiratory, cardiac, and neuropsychiatric PASC among this cohort in Lima, Peru. In line with multiple reports, older age was identified as a risk factor for cardiac, respiratory, and neuropsychiatric PASC [2, 13, 15]. Female sex was a risk factor for respiratory

Table 3. Results of Questionnaires and Clinical Assessments at Evaluation for Postacute Sequelae of Coronavirus Disease 2019

PASC Assessment	Severity of COVID-19 Presentation				Adjusted OR or β (95% CI)[b]		
		Symptomatic[a]					
	Asymptomatic (n = 262)	Not Hospitalized (n = 608)	Hospitalized (n = 119)	Total (N = 989)	Comorbidities vs No Comorbidities[c]	Symptomatic vs Asymptomatic[d]	Hospitalized vs Asymptomatic[d]
Sequelae[e]							
Respiratory sequelae	203/258 (78.7)	489/591 (82.7)	98/118 (83.1)	790/967 (81.7)	1.32 (0.76–2.42), n = 967	1.07 (0.78–1.45), n = 967	1.12 (0.67–1.95), n = 376
Cardiac sequelae	179/256 (69.9)	481/591 (81.4)	105/119 (89.7)	765/964 (79.4)	**2.12 (1.10–4.52)**, n = 948	**1.75 (1.22–2.49)**, n = 948	1.95 (0.98–4.11), n = 370
Neuropsychiatric sequelae	65/261 (24.9)	162/607 (26.7)	25/119 (21.0)	252/987 (25.5)	1.46 (0.95–2.24), n = 969	1.05 (0.75–1.49) n = 969	0.81 (0.44–1.45), n = 377
Questionnaires							
Respiratory							
CAT[f]	12 (7–16)	13 (9–18)	14 (9–19.5)	13 (8–18)	**β = 1.36 (0.03–2.69)**, n = 969	**β = 1.80 (0.83–2.77)**, n = 969	**β = 2.34 (0.72–3.97)**, n = 377
CAT score ≥10	163 (62.2)	431 (70.9)	81 (68.1)	675 (68.3)	1.23 (0.80–1.93), n = 969	**1.44 (1.06–1.95)**, n = 969	1.36 (0.83–2.27), n = 377
SGRQ[g]	27.2 (18.2–36.6)	29.2 (20.4–38.0)	33.6 (21.3–41.8)	29.0 (20.2–38.4)	β = 1.18 (−1.43 to 3.79), n = 969	β = 1.85 (−0.07 to 3.77), n = 969	**β = 4.37 (1.06–7.69)**, n = 377
SGRQ score ≥25	153 (58.4)	382 (62.8)	78 (65.5)	613 (62.0)	1.12 (0.74–1.71), n = 969	1.25 (0.92–1.69), n = 969	1.56 (0.94–2.60), n = 377
Neuropsychiatric							
PHQ-2							
Any anhedonia	111/261 (42.5)	256/607 (42.2)	41/119 (34.5)	408/987 (41.3)	1.18 (0.79–1.77), n = 969	0.97 (0.72–1.31), n = 969	0.89 (0.54–1.47), n = 377
Any depressed mood	151/261 (57.9)	367/607 (60.5)	61/119 (51.3)	579/987 (58.7)	1.35 (0.89–2.08), n = 969	1.07 (0.78–1.45), n = 969	0.82 (0.50–1.35), n = 377
PHQ-9[h] score ≥10	52/261 (19.9)	131/607 (21.6)	21/119 (17.6)	204/987 (20.7)	1.25 (0.77–1.98), n = 969	1.11 (0.77–1.62), n = 969	1.11 (0.58–2.08), n = 377
MMSE[i]	28 (27–29)	28 (27–30)	28 (26–29)	28 (27–29)	**β = −0.58 (−1.11 to −0.05)**, n = 969	β = 0.25 (−0.14 to 0.64), n = 969	β = 0.54 (−0.05 to 1.13), n = 377
MMSE ≤23	18 (6.9)	53 (8.7)	8 (6.7)	79 (8.0)	1.19 (0.63–2.20), n = 969	1.23 (0.70–2.27), n = 969	0.77 (0.28–1.96), n = 377
Clinical assessments[j]							
Abnormal CXR	32/261 (12.3)	54/607 (8.9)	24/119 (20.2)	110/987 (11.1)	1.03 (0.57–1.79), n = 969	0.68 (0.43–1.10), n = 969	1.25 (0.65–2.35), n = 377
Abnormal spirometry	41/258 (15.9)	62/591 (10.5)	22/118 (18.6)	125/967 (12.9)	1.56 (0.92–2.55), n = 967	**0.65 (0.43–0.99)**, n = 967	1.03 (0.55–1.89), n = 376
Abnormal electrocardiogram	83/261 (31.8)	238/601 (38.6)	60/119 (50.4)	375/981 (38.2)	**1.53 (1.02–2.30)**, n = 964	1.25 (0.92–1.72), n = 964	1.41 (0.86–2.30), n = 372
Abnormal echocardiography	156/256 (60.9)	439/591 (74.3)	99/117 (84.6)	694/964 (72.0)	1.48 (0.86–2.66), n = 948	**1.80 (1.29–2.51)**, n = 948	**2.02 (1.09–3.88)**, n = 370

Data are presented as No. (%) or median (interquartile range) unless otherwise specified. The differing denominators used indicate missing data. Values with a *P* value < .05 are shown in bold.

Abbreviations: CAT, chronic obstructive pulmonary disease assessment test; CI, confidence interval; COVID-19, coronavirus disease 2019; CXR, chest x-ray; MMSE, Mini-Mental State Examination; OR, odds ratio; PASC, postacute sequelae of coronavirus disease 2019; PHQ-2, Patient Health Questionnaire-2; PHQ-9, Patient Health Questionnaire-9; SGRQ, St George's Respiratory Questionnaire.

[a]Symptoms potentially consistent with acute COVID-19 illness were defined as any of the following: fever, chills, cough, dyspnea, nasal congestion, sore throat, malaise, fatigue, loss of appetite, nausea/emesis, diarrhea, anosmia, ageusia, headache, musculoskeletal pain, chest pain, abdominal pain, and altered mental status.

[b]Adjusted OR unless otherwise indicated.

[c]Adjusted for age, sex, and body mass index (BMI).

[d]Adjusted for age, sex, BMI, and comorbidities.

[e]Definitions of respiratory, cardiac, and neuropsychiatric PASC are shown in Table 1.

[f]Scored 0 to 40, with higher scores corresponding to greater severity of respiratory symptoms.

[g]Scored 0 to 100, with higher scores corresponding to greater severity of respiratory symptoms.

[h]PHQ-9 was performed on the subset of participants who screened positive on PHQ-2.

[i]Scored 0 to 30, with lower scores corresponding to greater impairment of cognitive function.

[j]Definitions of abnormal clinical assessments are shown in Table 1.

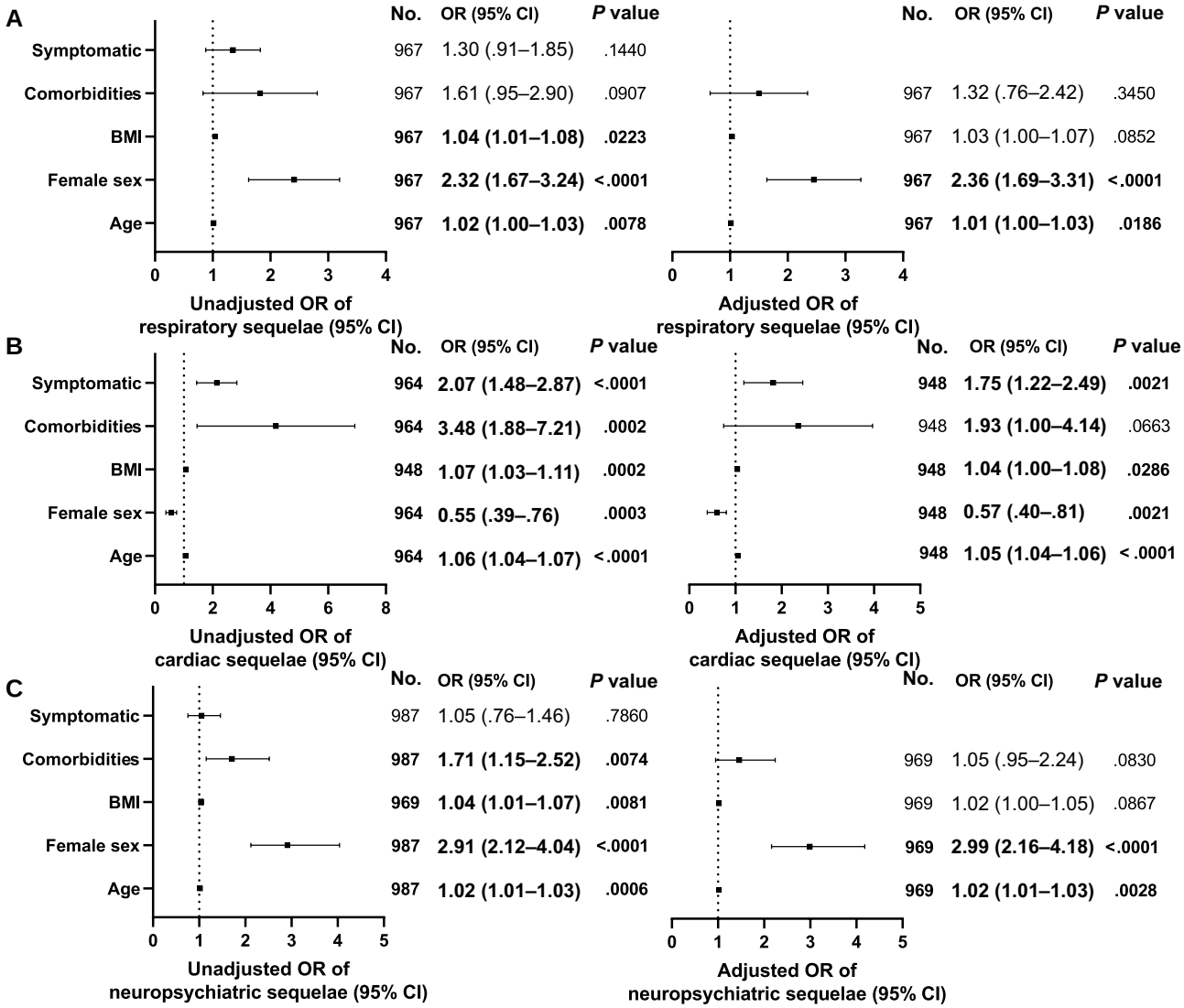

Figure 2. Risk factors associated with postacute sequelae of coronavirus disease 2019 (PASC). *A*, Respiratory sequelae. *B*, Cardiac sequelae. *C*, Neuropsychiatric sequelae. Adjusted multivariable analysis included all covariates associated with sequelae with $P < .1$ in univariable analysis. Rows with $P < .05$ are shown in bold. Definitions of respiratory, cardiac, and neuropsychiatric PASC are shown in Table 1. Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

and neuropsychiatric PASC [2, 12–14]. Participants who had been symptomatic during acute COVID-19 had greater risk of cardiac PASC, consistent with reports that PASC are more common among persons with greater severity of acute COVID-19 [1, 4, 11–15].

A large fraction of our cohort (68.3%) had clinically significant respiratory symptoms, higher than estimates seen in a study from the United Kingdom (52%) despite a lower prevalence of comorbid lung disease (2.0% in our cohort as compared to 30.5%) [20]. Similarly, our cohort demonstrated greater severity of respiratory QOL outcomes across all severities of acute COVID-19 presentation as compared to a study from China [4]. These findings suggest potential differences in the risk of respiratory PASC by region, whether through direct causes such as the prevalent COVID-19 variant or host immune responses, or indirect causes such as burden of chronic diseases, health system constraints, or air pollution [21].

Consistent with previous reports [4, 10], clinically significant respiratory symptoms were more prevalent among participants who had been more severely ill during acute COVID-19 presentation. Participants with greater severity of acute COVID-19 presentation were not found to have greater likelihood of abnormalities on CXR or spirometry. CXR may be insensitive to detect granular abnormalities associated with PASC, as evidenced by other studies that have demonstrated greater severity of abnormalities on chest computed tomography among persons with severe acute COVID-19 disease [4, 12].

Our study did not evaluate for diffusion abnormalities on spirometry, which correlate with severity of acute COVID-19 [4, 5, 12]. While the pathophysiology of PASC remains unclear, studies have suggested immune dysregulation as a mechanism for persistent chest imaging abnormalities and ventilatory impairment [22]. Overall, the respiratory symptom burden of PASC in our cohort appears to be disproportionate to the rates of abnormalities captured by spirometry or radiography [3, 4]. Our data support the implementation of comprehensive respiratory rehabilitation services, particularly among individuals who are convalescent from symptomatic COVID-19.

Previous studies have reported that more than half of persons with acute COVID-19 may have abnormalities on echocardiogram [23], including diastolic dysfunction [24, 25], which can persist up to 100 days following COVID-19 diagnosis [26]. The contribution of these findings to symptomatology is unclear. In our cohort, systolic dysfunction was rare, consistent with 1 study demonstrating resolution of left ventricular systolic dysfunction following acute COVID-19 [27]. Ventricular hypertrophy/dilation was common and weakly correlated with the presence of clinically significant respiratory symptoms. While pericardial effusions have been noted during acute COVID-19 [28], our study did not identify pericardial effusions among participants evaluated at a minimum of 2 months following acute COVID-19. ECG abnormalities, namely ventricular hypertrophy/strain and ischemic patterns, were frequently observed. These findings must be interpreted with caution in the absence of ECGs prior to COVID-19 diagnosis. One study demonstrated similar rates of ECG abnormalities at 6 months after COVID-19 as compared to matched controls [3].

The frequency of any depressive symptoms (64.5%) and clinically significant depression (20.7%) in our cohort exceeds estimates from a systematic review of persons with PASC at 3 months (11%–28% and 3%–12%, respectively) [29]. This may reflect a high burden of undiagnosed depression in our cohort and/or that COVID-19 survivors in low-resource settings may be at disproportionate risk of depression, potentially in relation to limited availability of mental healthcare and social support or heightened economic vulnerability due to COVID-19 illness and isolation. Consistent with other reports [29–31], severity of acute COVID-19 presentation was not associated with risk of depression. The burden of depressive disorders, even among participants who had been asymptomatic during acute COVID-19, highlights the need for psychosocial services among this population.

Cognitive impairment on the MMSE was relatively uncommon in our cohort. While "brain fog" and neurocognitive symptoms have been reported in PASC [32], the rates of objective cognitive impairment have been variable [33–38]. The Montreal Cognitive Assessment has been proposed as a more sensitive modality and should be employed in future studies evaluating neurocognitive PASC [33, 35].

Participants who had been hospitalized during acute COVID-19 presentation were at greater risk for diminished QOL as compared to those with asymptomatic COVID-19. Participants who had been more severely ill during acute COVID-19 presentation had greater risk for pain or discomfort. Economic insecurity, dissatisfaction with health, and limited energy for everyday life were commonly endorsed. In comparison to a meta-analysis of 4828 individuals with PASC in the United States, Europe, and China, our cohort reported a greater frequency of problems with pain or discomfort (73.9% vs 41.5%) [39].

This study had several limitations. We did not have information on the cohort prior to COVID-19 diagnosis, nor did we have a control group for comparison. The reported PASC cannot be definitively attributed to COVID-19 and may reflect chronic impairments. However, the proportion of participants with preexisting pulmonary, cardiac, or neuropsychiatric comorbidities was low, although self-report and underdiagnosis may have led to underestimation. For example, the prevalence of hypertension in Lima in 2021 was estimated at 22.4%, whereas self-reported hypertension or other cardiovascular disease in our cohort was present in 10.1% [40]. We were unable to infer temporal or directional aspects of observed associations. Given that participants self-reported their preexisting comorbidities and acute COVID-19 symptoms during PASC evaluation, there is potential for recall or desirability bias. Participants who attended the in-person PASC evaluation may reflect a biased sample, despite overall comparable rates of preexisting comorbidities and of being symptomatic at acute COVID-19. Potential confounders that were not accounted for in our analyses included education, employment, income, smoking status, and treatments for COVID-19.

In summary, respiratory, cardiac, and neuropsychiatric PASC were common among participants evaluated at least 2 months after COVID-19. Female sex and older age were risk factors for PASC. Risk of respiratory symptoms was elevated in participants with severe acute COVID-19, arguing for prioritization of pulmonary rehabilitation in this population. Depression screening may be required regardless of severity of acute COVID-19. Future studies should evaluate PASC in the postvaccination era, particularly in LMICs where limited access to healthcare may exacerbate PASC.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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