Health-Related Quality of Life Mildly Affected Following COVID-19: a Retrospective Pre-post Cohort Study with a Propensity Score–Matched Control Group

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IMPORTANCE: Long-term health effects have been indicated following COVID-19; however, the impact of COVID-19 on health-related quality of life (HRQOL), including who may experience ongoing symptoms, is unknown.
OBJECTIVE: To identify change in HRQOL following COVID-19 compared to pre-infection HRQOL and a matched control group, and identify predictors of patients who worsen.
DESIGN: Retrospective pre-post cohort study with a matched control group.
SETTING: Large healthcare system in northeast Ohio.
PARTICIPANTS: A total of 3,690 adult patients diagnosed with COVID-19 who completed HRQOL surveys during routine care for ambulatory visits before and after infection. Propensity-score 1:1 match was utilized to identify controls without COVID who completed HRQOL at two time points.
MAIN OUTCOMES: HRQOL was assessed with PROMIS Global Health: global mental and physical health summary scores. Pre- and post-COVID PROMIS Global Health was completed as part of routine care from 1/1/2019 to 2/29/2020 and 4/4/2020 to 11/1/2021, respectively, and extracted from the electronic health record.
RESULTS: COVID-19 patients (mean age 53±15; 66% female) completed PROMIS Global Health in the year prior (median 11.1 months) and after diagnosis (median 7.8 months). Compared to before infection, COVID-19 patients had a significant reduction in global mental health and stable global physical health (−0.85 and 0.05 T-score points, respectively) with clinically meaningful reduction (≥5 T-score points) experienced by 27% and 23% of patients, respectively. Predictors of worsening global health included being female, having depression, being hospitalized for COVID-19, and better pre-COVID global health. Compared to the control group, there was significantly worse global mental and physical health decline following COVID-19 (−0.53 and −0.37 T-score points, respectively).
CONCLUSIONS AND RELEVANCE: A quarter of patients with COVID-19 experienced meaningful reductions in HRQOL. Reductions in global mental and physical health were modest, although significantly worse than a control group. Additionally, identified predictors of patients who worsen may assist clinicians when counseling patients of their risk of worse HRQOL following COVID-19.

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INTRODUCTION

A large proportion of people experience long-term health effects following COVID-19 infection, such as persistent fatigue, difficulty concentrating, anxiety, and depression[1–5]. Findings from studies comparing rates of depression and mental well-being to normative values pre-COVID have been inconsistent, with some indicating significant worsening following COVID-19[4,6] and another demonstrating no change[7]. Studies have been hindered by a lack of pre-infection data, and it is unknown whether patients' symptoms pre-date COVID-19 or are exacerbated by the illness. Investigating the health status of patients with COVID-19 compared to prior to infection is paramount for understanding the impact of COVID-19 on health-related quality of life (HRQOL).

Despite studies demonstrating high rates of post-COVID symptoms, knowledge of who may be prone to experience persistently worse HRQOL post-infection is largely unknown. It has been posited that pre-existing psychiatric disorders may exacerbate long-term symptoms and worsen prognosis[3,4,8,9]. Women and those with prior conditions such as obesity seem more likely to suffer long-haul symptoms[2,10,11]. Some research has indicated those who have been hospitalized or had more severe COVID-19 are more likely to experience prolonged symptoms[12,13]; however, others have demonstrated symptoms persist or worsen over time for those with initially mild infection[11,14,15].

Studies assessing the effect of COVID-19 and its persistent symptoms on HRQOL have mostly consisted of surveys conducted with convenience samples, and pre-post analyses have relied on historical norms[7,13] or self-reports of pre-illness HRQOL[12,16,17]. As studies in non-COVID patients and the general population have also demonstrated higher rates of anxiety and depression during the pandemic[18,19], it is

unknown whether reductions in HRQOL in COVID+ patients are differentially worse than those without COVID-19.

Patient-reported measures of HRQOL have been collected routinely at our institution as standard care, providing a unique resource for interpreting the change in symptoms due to COVID-19. Our study aimed to identify change in HRQOL following COVID-19 compared to pre-infection HRQOL and a matched control group, and identify predictors of patients who worsen.

METHODS

This study was approved by the Institutional Review Board at Cleveland Clinic (IRB 20-1331). Because the study consisted of analyses of pre-existing data, the requirement for patient informed consent was waived. The study followed STROBE reporting guidelines for cohort studies.

Population

Patient Sample with COVID-19 Infection. The study cohort included adults (≥18 years) who tested positive for COVID-19 at Cleveland Clinic as documented in the electronic health record (EHR) between 3/13/2020 and 12/31/2020. COVID-19 test results, presenting symptoms, and hospitalization outcomes were included from Cleveland Clinic's COVID-19 Registry[20]. COVID-19 samples were obtained through naso- and oropharyngeal swabs, and were tested with the use of the Centers for Disease Control and Prevention assay using Roche magnapure extraction (Roche Life Science) and ABI 7500 DX PCR machines (Applied Biosystems/ThermoFisher Scientific), as per the standard laboratory testing in our institution. For patients with multiple COVID tests, the date of the first positive test was used as the date of testing.

Patients were included in the study analyses if they completed PROMIS Global Health in the year prior to their diagnosis (between 1/1/2019 and 2/29/2020) as well as following their diagnosis (between 4/4/2020 and 11/1/2021).

Patient Comparison Sample. A comparison sample of adult patients seen at Cleveland Clinic was included in the study if they were not tested for or diagnosed with COVID-19 at our institution and had completed PROMIS Global Health in the year prior to and again during the COVID-19 pandemic.

Demographic and Clinical Data

Patient demographics were extracted from the EHR, and median household income was estimated from 2010 census data by zip code. Clinical characteristics included whether the patient had a primary care provider at Cleveland Clinic, the Charlson comorbidity index (a measure of 19 conditions related to the potential for mortality and morbidity)[21], and binary indicators for 14 comorbidities.

Patient-Reported Outcomes

Patient-reported information, including PROMIS Global Health, is completed as part of standard care, and is collected through an electronic platform[22] and available in the EHR at the point of care. PROMIS Global Health v1.0 is collected in most departments at Cleveland Clinic. Patients are asked to complete the PROMIS Global Health scale prior to an office visit if not previously completed elsewhere in the health system within the previous 3 months. The inclusion of additional condition-specific surveys differs by department. Questionnaires are administered either on tablets immediately prior to an ambulatory patient visit or at home before their appointment via a patient portal (MyChart; Epic Systems, Verona, WI). Starting 5/6/2020, patients diagnosed with COVID-19 could also complete questionnaires, including PROMIS Global Health, through the "Home Management of COVID-19" research study.

PROMIS Global Health includes 10 items, with 9 of the items scored on a Likert scale from 1 to 5, where 5 represents the best response. One item (pain intensity) is answered on a scale from 0 to 10, but was recoded to a 5-point scale as recommended in the scoring manual[23]. PROMIS Global Health produces two summary scores: global mental and physical health[24]. Global mental health includes 4 items on overall quality of life, mental health, satisfaction with social activities and relationships, and emotional problems. Global physical health comprises 4 items on physical health, physical functioning, pain intensity, and fatigue. Two items, general health and social roles, are not used to calculate the summary scores. Global mental and physical summary scores are transformed to a T-score metric, with 50 representing the mean (standard deviation of 10) of the US general population[25]. Clinically meaningful differences in PROMIS Global Health summary scores are estimated to be between 2 and 5 T-score points[26].

Statistical Analysis

Propensity score (PS) matching was utilized to match COVID+ patients to patients without COVID-19. PSs for the probability of having COVID-19 were estimated with a multivariable logistic regression model including the variables presented in Table 1. The greedy nearest neighbor method matched one COVID-19 patient to one control patient (1:1 matching) using the smallest within-pair difference between the PS logit using a caliper of 0.5[27]. In the matched sample, balance of covariates was assessed between COVID+ patients and controls using standardized mean differences. Change between the two time points was summarized and compared within group using paired *t*-test. Change in summary scores and items following COVID-19 was compared with the matched controls using generalized estimating equations

Table 1. Characteristics of Propensity Score–Matched COVID+ Patients and Controls

Characteristics	Total (*N*=7,380)	COVID+ (*N*=3,690)	Controls (*N*=3,690)	Standardized difference
Age, mean ± SD	52.3 ± 15.7	52.7 ± 15.4	51.9 ± 15.9	0.051
Female, *n* (%)	4,889 (66.2)	2,418 (65.5)	2,471 (67.0)	0.030
Race, *n* (%)				
White	5,768 (78.2)	2,901 (78.6)	2,867 (77.7)	0.028
Black/African American	1,147 (15.5)	550 (14.9)	597 (16.2)	
Other	282 (3.8)	146 (4.0)	136 (3.7)	
Missing	183 (2.5)	93 (2.5)	90 (2.4)	
Hispanic, *n* (%)	256 (3.5)	151 (4.1)	105 (2.8)	0.055
Married, *n* (%)				
Married	4,377 (59.3)	2,219 (60.1)	2,158 (58.5)	0.046
Single	2,043 (27.7)	987 (26.7)	1,056 (28.6)	
Other	960 (13.0)	484 (13.1)	476 (12.9)	
Median household income [q1, q3]	55015.0 [43288.0, 67669.0]	56832.0 [43288.0, 67669.0]	54722.0 [43288.0, 67669.0]	0.008
Insurance, *n* (%)				
Medicaid	588 (8.0)	288 (7.8)	300 (8.1)	0.024
Medicare	1,711 (23.2)	869 (23.6)	842 (22.8)	
Private	4,926 (66.7)	2,451 (66.4)	2,475 (67.1)	
Self-Pay	155 (2.1)	82 (2.2)	73 (2.0)	
Body mass index, mean ± SD	31.7 ± 7.9	31.6 ± 7.8	31.7 ± 8.1	0.013
Obesity (30+ kg/m^2)	3,873 (52.5)	1,936 (52.5)	1,937 (52.5)	0.001
Smoking status, *n* (%)				
Current	253 (3.4)	127 (3.4)	126 (3.4)	0.021
Former	2,470 (33.5)	1,255 (34.0)	1,215 (32.9)	
Never	4,657 (63.1)	2,308 (62.5)	2,349 (63.7)	
Charlson Comorbidity Index, median [q1, q3]	2.0 [0.00, 4.0]	2.0 [0.00, 4.0]	2.0 [0.00, 4.0]	0.046
History of comorbidities, *n* (%)				
COPD/emphysema	729 (9.9)	370 (10.0)	359 (9.7)	0.010
Asthma	2,725 (36.9)	1,355 (36.7)	1,370 (37.1)	0.008
Diabetes	2,695 (36.5)	1,356 (36.7)	1,339 (36.3)	0.010
Hypertension	5,354 (72.5)	2,683 (72.7)	2,671 (72.4)	0.007
Coronary artery disease	580 (7.9)	291 (7.9)	289 (7.8)	0.002
Atrial fibrillation	1,145 (15.5)	574 (15.6)	571 (15.5)	0.002
Heart failure	1,303 (17.7)	656 (17.8)	647 (17.5)	0.006
Cancer	3,773 (51.1)	1,889 (51.2)	1,884 (51.1)	0.003
Depression	3,530 (47.8)	1,774 (48.1)	1,756 (47.6)	0.010
Chronic kidney disease	1,314 (17.8)	665 (18.0)	649 (17.6)	0.011
Migraine	2,212 (30.0)	1,097 (29.7)	1,115 (30.2)	0.011
Fibromyalgia	638 (8.6)	322 (8.7)	316 (8.6)	0.006
Low back pain	4,205 (57.0)	2,090 (56.6)	2,115 (57.3)	0.014
Primary care provider at Cleveland Clinic	6,772 (91.8)	3,386 (91.8)	3,386 (91.8)	0.000
Institute where baseline PROMIS Global Health was completed				
Internal Medicine	4,015 (54.4)	1,968 (53.3)	2,047 (55.5)	*0.133*
Neurologic	1,997 (27.1)	945 (25.6)	1,052 (28.5)	
Other	1,368 (18.5)	777 (21.1)	591 (16.0)	
Baseline Global Mental Health T-score	49.0 ± 9.1	49.1 ± 9.0	49.0 ± 9.2	0.010
Baseline Global Physical Health T-score	47.0 ± 8.7	46.9 ± 8.7	47.1 ± 8.6	0.015
Months between PROMIS Global Health completions	18.9 ± 5.1	19.0 ± 5.3	18.7 ± 4.8	0.055

SD, standard deviation; q, quartile

accounting for the match identifier and adjusting for variables with standardized differences >0.10[28]. Lastly, meaningful reductions were compared between COVID+ patients and controls using McNemar test.

Predictors of COVID-19 patients and their matched controls who meaningfully worsened on the summary scores (≥5 T-score points) were evaluated separately through multivariable logistic regression models. Characteristics included in the models were determined a priori.

Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) at significance level 0.05. As the results of our study are exploratory and focused on estimates of effect, there was no formal adjustment for multiple comparisons.

Data Availability

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

RESULTS

There were 3,926 patients diagnosed with COVID-19 between March and December 2020 who completed PROMIS Global Health prior to and following diagnosis. Of these, 3,690 were PS matched 1:1 to controls (Table 1). COVID+ patients had a mean age of 52.7 (SD=15.4), with 65.5% female, 78.6% white race, 60.1% married, and 90.0% had private insurance or

Medicare. COVID+ patients completed PROMIS Global Health a median 11.1 (interquartile range: 9.2–14.4) months prior to their diagnosis and a median of 7.8 (3.3–10.4) months after their diagnosis. Controls were well matched to cases, with standardized mean differences <0.10 for all variables except institute where baseline PROMIS Global Health was completed (standardized difference = 0.133).

Global mental health significantly worsened over time for both COVID+ cases and controls (−0.85 (standard error = 0.12), and −0.29 (0.11) T-score points, respectively) (Table 2). Global physical health remained stable in cases and significantly improved in controls (0.05 (0.12) and 0.40 (0.10), respectively). Adjusting for institute and accounting for the match identifier, COVID+ patients had significantly worse scores over time as compared to the controls for both global mental health (mean difference (standard error): −0.53 (0.16)) and global physical health (−0.37 (0.15)). COVID+ patients had significantly more patients with meaningful worsening (≥5 T-score points) over time for global mental and physical health compared to controls (mental health: 26.8% vs 23.8%, p=0.003; physical health: 22.6% vs 18.4%, p<0.001, respectively).

At the item-level, COVID+ patients had significant worsening on 7 of the 10 items compared to the year prior to COVID (Table 2). When compared to controls, COVID+ patients had significantly worse declines on 8 of the 10 items although the effect size was small for all changes (range 0–0.15) (Fig. 1). COVID+ patients and controls both had significant reductions on the items evaluating mental health and social roles; however, COVID+ patients worsened significantly on items assessing general health and physical health, while controls demonstrated significant improvement. Control patients also had significant improvement in fatigue over time while COVID+ patients improved significantly on the item assessing pain (effect size = 0.14).

Multivariable predictors of meaningful worsening on global mental and physical health were evaluated separately in COVID+ patients and their matched controls. Predictors of the COVID+ patients who worsened on global mental health included age <50 years, being female, having higher body mass index, higher Charlson comorbidity index, diagnosis of asthma, depression, being hospitalized for COVID-19, and better baseline global health (Table 3). Independent predictors of worsening on global physical health for COVID+ patients were similar to global mental health but also included low back pain; age and asthma were not associated with worsening on global physical health (Table 4). Interestingly, predictors of worsening on global mental and physical health in the control group were similar to patients with COVID-19. Exceptions of note were that female sex and Charlson comorbidity index were not associated with worsening on global physical health for controls.

DISCUSSION

Our study utilized longitudinally collected patient-entered data from standard care in a large healthcare system to quantify the change in HRQOL following COVID-19 infection. Compared to before the pandemic, a quarter of patients experienced meaningful reductions in mental and physical global health a median of 7.8 months following their first positive COVID-19 test. When compared to matched controls without COVID-19, COVID+ patients experienced greater reductions in global mental and physical health, with a significantly greater proportion of COVID+ patients having meaningful declines in both mental and physical health compared to control patients.

Table 2. Change in PROMIS Global Health in COVID+ Patients Versus Controls, n=3690 Matched Pairs

PROMIS Global Health summary scores and items	Change in COVID+ Mean (SE)	Change in Controls Mean (SE)	Difference between COVID+ vs controls Estimate (SE)	p-value comparing difference
Global Mental Health T-score	−0.85 (0.12)**	−0.29 (0.11)*	−0.53 (0.16)	0.001
Global Physical Health T-score	0.05 (0.12)	0.40 (0.10)**	−0.37 (0.15)	0.016
Global Health Items				
1. General health	−0.10 (0.01)**	0.09 (0.01)**	−0.18 (0.02)	<0.001
2. Quality of life‡	−0.09 (0.01)**	0.01 (0.01)	−0.10 (0.02)	<0.001
3. Physical health†	−0.07 (0.01)**	0.07 (0.01)**	−0.13 (0.02)	<0.001
4. Mental health‡	−0.12 (0.02)**	−0.03 (0.01)*	−0.08 (0.02)	<0.001
5. Social discretionary‡	−0.13 (0.02)**	−0.06 (0.02)**	−0.06 (0.02)	0.005
6. Physical function†	−0.05 (0.02)*	0.00 (0.01)	−0.06 (0.02)	0.005
7. Pain†	0.15 (0.02)**	0.00 (0.01)	0.14 (0.02)	<0.001
8. Fatigue†	−0.02 (0.01)	0.05 (0.01)**	−0.06 (0.02)	0.001
9. Social roles	−0.14 (0.02)**	−0.08 (0.01)**	−0.06 (0.02)	0.005
10. Emotional problems‡	0.02 (0.02)	−0.03 (0.02)	0.04 (0.02)	0.070

*Mean with standard error (se) presented for change in PROMIS summary scores and items; negative estimates indicate worse health-related quality of life for patients at time point 2 compared to baseline; *p<0.05, **p<0.001, based on paired t-test; difference between COVID+ patients versus controls with p-value based on GEE models accounting for institute of baseline completion and match identifier; ‡questions comprise PROMIS Global Mental Health summary score; †questions comprise PROMIS Global Physical Health summary score*

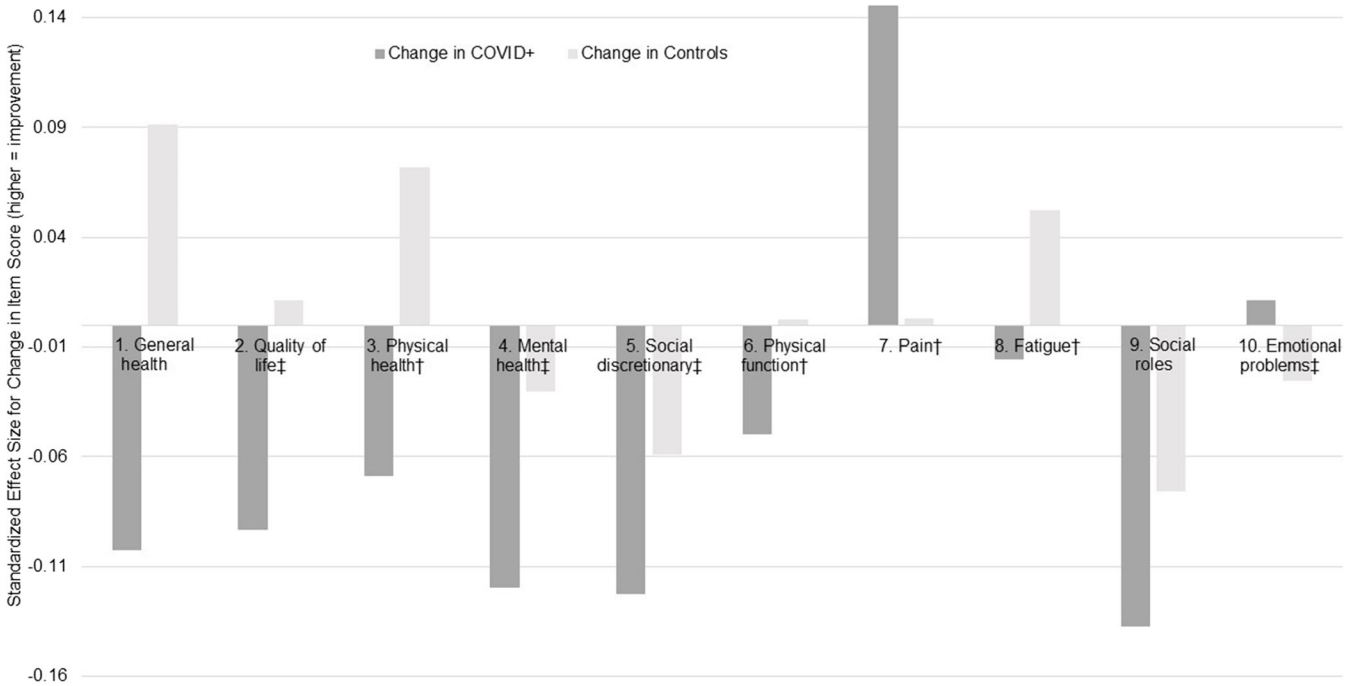

Figure 1. Standardized effect size for change in PROMIS Global Health items for COVID+ patients versus propensity score–matched controls. Cohen D's effect size for change in PROMIS Global Health items for COVID+ patients versus matched controls. ‡Questions comprise PROMIS Global Mental Health summary score; †questions comprise PROMIS Global Physical Health summary score

To our knowledge, no other study has measured HRQOL before and after COVID-19 infection. Prior pre-post studies have relied on patients to think back to their status pre-illness[12,16,17], which introduces substantial recall bias. Additionally, the majority of studies assessing HRQOL following COVID-19 did not have a control group, rendering it difficult to determine if declines are due to COVID-19 or general byproducts of the pandemic[14,17,29–31]. Our study adds new insight through the inclusion of a comparison group of matched controls who did not have COVID-19 but completed two HRQOL assessments. Approximately a quarter of COVID+ patients had meaningful worsening in both mental and physical health post-infection. A significantly larger proportion of patients with COVID-19 had meaningful worsening in global mental health compared to controls (26.8% cases vs 23.8% controls), suggesting that the effects of COVID-19, and not just the pandemic-itself, contribute to reduced mental health in some patients. A meaningful reduction in physical health also occurred more frequently in COVID+ patients (22.6%) than controls (18.4%) although there was overall positive change in the mean scores of both groups (0.05 T-score points for cases and 0.40 for controls). The mean differences in summary scores were modest, however, with changes of less than 1 T-score point, far lower than previously reported measures of minimal clinically important change[26]. Our findings help to quantify the change in HRQOL following COVID-19 infection.

In the evaluation of individual items over time, mental health and social activities and roles were significantly reduced compared to pre-pandemic for both COVID+ patients and controls. Much has been written about the effects of the pandemic on social and mental health in the general population[3,18,19]. Depressive symptoms have been shown to increase 3-fold during the COVID-19 pandemic compared to before[18], and feelings of loneliness have increased due to social isolation[32–34]. Compared to controls in our study, COVID+ patients had significantly larger reductions in items assessing general health, quality of life, physical health and function, mental health, social discretionary and social roles, and fatigue. These findings are generally consistent with those of other studies assessing HRQOL in COVID-19 patients, which have demonstrated worse scores in the areas of fatigue, general health, and functional impairment in daily life[14,29]. Fatigue has been one of the most prevalent symptoms identified during and following COVID-19 infection[6,35–37] and there is growing concern that COVID-19 could trigger post-viral fatigue syndromes[9]. However, in our study the greater worsening of fatigue in COVID+ patients compared to controls was due to a slight improvement in the control group's scores over time. In fact, COVID+ patients did not have significantly worse fatigue scores following COVID-19 compared to pre-pandemic.

Predictors of worsening on global mental health in COVID+ patients in our study included younger age, being female, having high body mass index and Charlson comorbidity index, having depression, being hospitalized for COVID-19, and having better pre-pandemic global health. These findings are consistent with other studies which have assessed predictors of worse mental health, including

Table 3. Multivariable Predictors of Meaningful Worsening on PROMIS Global *Mental* Health in COVID+ Patients and Controls

	COVID+ Patients, n=3690		Matched Controls, n=3690	
Meaningful worsening, n (%)	*987 (26.8%)*		*877 (23.8%)*	
	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Age categorization (reference = 50–64)				
18-34	1.70 (1.30–2.21)	<0.001	1.55 (1.19–2.02)	0.001
35-49	1.31 (1.06–1.63)	0.013	1.25 (0.99–1.57)	0.054
65+	1.00 (0.81–1.25)	0.97	1.14 (0.91–1.42)	0.25
Female (vs male)	1.20 (1.01–1.43)	0.044	1.29 (1.07–1.55)	0.007
Race (reference = White)				
Black/African American	1.02 (0.79–1.30)	0.91	0.70 (0.55–0.91)	0.006
Other	0.95 (0.62–1.47)	0.82	1.27 (0.83–1.94)	0.28
Unreported	1.27 (0.77–2.09)	0.34	0.77 (0.44–1.37)	0.38
Married (vs other)	0.85 (0.71–1.01)	0.070	0.75 (0.63–0.89)	0.001
Median household income	0.98 (0.94–1.03)	0.42	0.96 (0.91–1.01)	0.081
Body mass index (per 5kg/m^2)	1.07 (1.01–1.13)	0.018	1.00 (0.94–1.05)	0.88
Comorbidities				
Charlson Comorbidity Index	1.04 (1.01–1.07)	0.012	1.04 (1.01–1.08)	0.008
Asthma	1.19 (1.00–1.41)	0.045	1.10 (0.93–1.31)	0.27
Hypertension	0.97 (0.80–1.18)	0.75	1.11 (0.91–1.36)	0.31
Atrial fibrillation	0.94 (0.75–1.18)	0.58	1.02 (0.81–1.28)	0.89
Depression	1.29 (1.08–1.53)	0.004	1.30 (1.09–1.55)	0.004
Migraine	0.95 (0.79–1.15)	0.61	1.08 (0.89–1.31)	0.42
Fibromyalgia	0.89 (0.65–1.22)	0.48	1.19 (0.87–1.62)	0.27
Low back pain	1.16 (0.98–1.37)	0.090	1.11 (0.93–1.31)	0.25
Primary care provider at Cleveland Clinic	0.93 (0.70–1.24)	0.61	0.96 (0.72–1.28)	0.77
Institute (reference = Internal medicine)				
Neurologic	1.21 (0.99–1.47)	0.060	1.15 (0.94–1.40)	0.17
Other	1.13 (0.92–1.39)	0.25	1.32 (1.05–1.65)	0.017
Number of COVID presenting symptoms	1.01 (0.96–1.05)	0.84	n/a	
Hospitalized for COVID	1.40 (1.12–1.76)	0.004	n/a	
Baseline PROMIS Global Health	1.11 (1.10–1.13)	<0.001	1.11 (1.10–1.12)	<0.001
Months between PROMIS Global Health completions	1.01 (0.99–1.03)	0.11	1.01 (0.99–1.03)	0.29

aOR (95% CI) = adjusted odds ratio presented with confidence interval; meaningful worsening defined as reduction of 5+ T-score points. Models conducted separately in COVID+ patients and controls. Variables included in the models were determined a priori; comorbidities were included if they were not also included in the Charlson comorbidity index. Due to multicollinearity with age categories, which were categorized based on data distribution and clinical relevance, insurance status was not included

depression and anxiety[2,8]. Without a comparison group, it is not possible to know if patients with COVID-19 experience differentially worse mental health than the general population. Because our control group was matched to the cases, we were unable to evaluate predictors in the same model, but our stratified analysis elucidated similar predictors in the control group: younger age, being female, higher Charlson comorbidity index, and having depression. Interestingly, higher body mass index was only associated with worsening following COVID-19.

Studies assessing predictors of worse functional status following COVID-19 have identified older age, more comorbidities including obesity, psychiatric conditions, more severe COVID-19 infection, and ICU stay[7,10,12,16,30,38]. Our study found similar predictors, with the exception of age which was not associated with worse global physical health. While most of these predictors were significant for both COVID+ patients and controls, female sex and higher Charlson comorbidity index were only associated with worsening global physical health following COVID-19 infection.

Our study has implications for clinical care. Given the significant reductions in mental and social HRQOL seen in both COVID+ outpatients and controls, healthcare systems should prioritize access to psychological support for those more likely to suffer from adverse effects of the pandemic. This could potentially entail ramping up efforts to screen for depression and anxiety at primary care visits, especially those patients with characteristics associated with decline in mental and social HRQOL identified in our study. It may also be beneficial to reach out to patients who may have avoided going to their healthcare providers during the pandemic, irrespective of their COVID status. Additionally, we found patients who suffered from COVID-19 were more likely to have worse physical and mental health, compared to controls. Some of these patients may have long COVID and would benefit from multidisciplinary treatment and ongoing care. In February 2021, our institution developed a COVID-19 recovery clinic to help triage care to patients based on continued COVID symptoms. One of the methods to identify symptoms is the PROMIS Global Health, and our study supports the use of the PROMIS Global Health as a screener. Improving the understanding of symptoms and symptom duration, particularly in outpatients, will help direct care, inform interventions, and tailor treatment plans.

Our study has many strengths, including the large sample size, availability of pre-infection patient-reported data, and a PS-matched control group. The patients included in this study completed PROMIS Global Health as standard care, and not

Table 4. Multivariable Predictors of Meaningful Worsening on PROMIS Global *Physical* Health in COVID+ Patients and Controls

	COVID+ patients, *n*=3690		Matched controls, *n*=3690	
Meaningful worsening, n (%)	*833 (22.6%)*	*678 (18.4%)*		
	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Age categorization (reference = 50–64)				
18-34	0.83 (0.62–1.10)	0.19	0.72 (0.54–0.96)	0.027
35-49	0.99 (0.79–1.24)	0.93	1.04 (0.83–1.21)	0.73
65+	1.12 (0.89–1.40)	0.33	1.22 (0.97–1.55)	0.096
Female (vs male)	1.24 (1.03–1.50)	0.022	1.19 (0.98–1.44)	0.082
Race (reference = White)				
Black/African American	1.21 (0.94–1.56)	0.15	0.97 (0.76–1.25)	0.84
Other	1.13 (0.72–1.76)	0.60	1.30 (0.83–2.04)	0.25
Unreported	0.87 (0.50–1.51)	0.61	1.48 (0.87–2.51)	0.15
Married (vs other)	0.91 (0.76–1.10)	0.34	0.94 (0.78–1.13)	0.49
Median household income	0.96 (0.91–1.01)	0.11	0.91 (0.86–0.95)	<0.001
Body mass index (per 5kg/m^2)	1.11 (1.05–1.18)	<0.001	1.13 (1.07–1.20)	<0.001
Comorbidities				
Charlson Comorbidity Index	1.07 (1.04–1.10)	<0.001	1.03 (0.99–1.06)	0.13
Asthma	1.08 (0.90–1.29)	0.41	0.99 (0.82–1.19)	0.88
Hypertension	1.01 (0.82–1.24)	0.95	0.94 (0.76–1.17)	0.57
Atrial fibrillation	0.90 (0.71–1.14)	0.38	0.86 (0.67–1.11)	0.25
Depression	1.31 (1.10–1.57)	0.003	1.39 (1.16–1.67)	<0.001
Migraine	1.01 (0.83–1.22)	0.95	1.19 (0.97–1.45)	0.089
Fibromyalgia	0.96 (0.69–1.35)	0.82	1.24 (0.91–1.71)	0.18
Low back pain	1.27 (1.07–1.52)	0.008	1.28 (1.07–1.54)	<0.001
Primary care provider at Cleveland Clinic	1.27 (0.93–1.75)	0.14	1.11 (0.81–1.54)	0.51
Institute (reference = Internal medicine)				
Neurologic	1.13 (0.92–1.39)	0.25	1.20 (0.97–1.48)	0.10
Other	0.93 (0.74–1.17)	0.55	1.01 (0.79–1.30)	0.92
Number of COVID presenting symptoms	1.01 (0.96–1.05)	0.84	n/a	
Hospitalized for COVID	1.52 (1.20–1.93)	<0.001	n/a	
Baseline PROMIS Global Health	1.11 (1.10–1.13)	<0.001	1.08 (1.07–1.10)	<0.001
Months between PROMIS Global Health completions	1.01 (0.99–1.03)	0.21	1.01 (0.99–1.03)	0.29

aOR (95% CI) = adjusted odds ratio presented with confidence interval; meaningful worsening defined as reduction of 5+ T-score points. Models conducted separately in COVID+ patients and controls. Variables included in the models were determined a priori; comorbidities were included if they were not also included in the Charlson comorbidity index. Due to multicollinearity with age categories, which were categorized based on data distribution and clinical relevance, insurance status was not included.

part of a research study, increasing the generalizability of our results. There are, however, some limitations which deserve mention. There is selection bias in that COVID+ patients included in the study were Cleveland Clinic patients who completed patient-entered data longitudinally, and were therefore more likely to be older, White, have higher income, and more comorbidities than patients who were not seeking healthcare. Similarly, our control group may also not be representative of outpatient populations, although the overall change in PROMIS Global Health from pre-pandemic to during the pandemic is similar to previous reports by our group of 71,117 patients seeking medical care[39]. Lastly, it is possible controls were diagnosed with COVID-19 outside of our health system; however, if they were seen at Cleveland Clinic to complete their second PROMIS Global Health, it is assumed a positive COVID-19 diagnosis could have been entered into the EHR.

In conclusion, a quarter of patients with COVID-19 experienced meaningful reductions in global health from pre-pandemic to 8 months following infection. Compared to a matched control group, reductions in global mental and physical health were modestly worse following COVID-19. The social and mental impact of the COVID-19 pandemic affected both cases and controls, with COVID-19 patients differentially affected in the areas of general health and physical function. Lastly, we identified predictors of patients who worsen, which can assist clinicians in identifying patients who may be at an increased risk of worse HRQOL following COVID-19.

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REFERENCES

1. **Krishnamoorthy Y, Nagarajan R, Saya GK, Menon V**. Prevalence of psychological morbidities among general population, healthcare work and COVID-19 patients amidst the COVID-19 pandemic: a systematic review and meta-analysis. *Psychiatry Res*. 2020;293:113382.
2. **Hu Y, Chen Y, Zheng Y, et al.** Factors related to mental health of inpatients with COVID-19 in Wuhan, China. *Brain Behav Immun*. 2020;89:587-593.
3. Liu CH, Stevens C, Conrad RC, Hahm HC. Evidence for elevated psychiatric distress, poor sleep, and quality of life concerns during the COVID-19 pandemic among U.S. young adults with suspected and reported psychiatric diagnoses. *Psychiatry Res*. 2020;292:113345.
4. **Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ**. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. 2021;8(5):416-427.
5. **Carvalho-Schneider C, Laurent E, Lemaignen A, et al.**Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect*. 2021;27(2):258-263.

6. **Willi S, Luthold R, Hunt A, et al.**COVID-19 sequelae in adults aged less than 50 years: a systematic review. *Travel Med Infect Dis.* 2021;40:101995.
7. **Arnold DT, Hamilton FW, Milne A, et al.** Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax.* 2020.
8. **Wang C, Pan R, Wan X, et al.** Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. *Int J Environ Res Public Health.* 2020;17(5).
9. **Townsend L, Dyer AH, Jones K, et al.** Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One.* 2020;15(11):e0240784.
10. **Tenforde MW, Kim SS, Lindsell CJ, et al.** Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(30):993-998.
11. **Davido B, Seang S, Tubiana R, de Truchis P**. Post-COVID-19 chronic symptoms: a postinfectious entity? *Clin Microbiol Infect.* 2020;26(11):1448-1449.
12. **Halpin SJ, McIvor C, Whyatt G, et al.** Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J Med Virol.* 2021;93(2):1013-1022.
13. **Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G**. Prevalence and determinants of fatigue after COVID-19 in non-hospitalized subjects: a population-based study. *Int J Environ Res Public Health.* 2021;18(4).
14. **van den Borst B, Peters JB, Brink M, et al.** Comprehensive health assessment three months after recovery from acute COVID-19. *Clin Infect Dis.* 2020.
15. **Petersen MS, Kristiansen MF, Hanusson KD, et al**. Long COVID in the Faroe Islands - a longitudinal study among non-hospitalized patients. *Clin Infect Dis.* 2021;73(11):e4058-4063.
16. **Taboada M, Carinena A, Moreno E, et al.**Post-COVID-19 functional status six-months after hospitalization. *J Infect.* 2021;82(4):e31-e33.
17. **Weerahandi H, Hochman KA, Simon E, et al.**Post-discharge health status and symptoms in patients with severe COVID-19. *J Gen Intern Med.* 2021;36(3):738-745.
18. **Ettman CK, Abdalla SM, Cohen GH, Sampson L, Vivier PM, Galea S**. Prevalence of depression symptoms in US adults before and during the COVID-19 pandemic. *JAMA Netw Open.* 2020;3(9):e2019686.
19. **Ferreira LN, Pereira LN, da Fe Bras M, Ilchuk K**. Quality of life under the COVID-19 quarantine. *Qual Life Res.* 2021;30(5):1389-1405.
20. **Jehi L, Ji X, Milinovich A, et al.**Individualizing risk prediction for positive COVID-19 testing: results from 11,672 patients. *Chest.* 2020.
21. **Charlson ME, Pompei P, Ales KL, MacKenzie CR**. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.
22. **Katzan I, Speck M, Dopler C, et al.** The Knowledge Program: an innovative, comprehensive electronic data capture system and warehouse. *AMIA Annu Symp Proc.* 2011;2011:683-692.
23. Global Health, A brief guide to the PROMIS© Global Health instruments: http://www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Global_Scoring_Manual.pdf. Accessed 11/19/2021.
24. **Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D**. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. *Qual Life Res.* 2009;18(7):873-880.
25. **Liu H, Cella D, Gershon R, et al.** Representativeness of the Patient-Reported Outcomes Measurement Information System Internet panel. *J Clin Epidemiol.* 2010;63(11):1169-1178.
26. Meaningful Change for PROMIS®. https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/meaningful-change. Accessed 02/10/2021.
27. **Yuan Y, Yung Y.F., Stokes M**. *Propensity Score Methods for Causal Inference with the PSMATCH Procedure.* Cary, NC SAS Institute Inc.;2017.
28. **Nguyen TL, Collins GS, Spence J, et al.**Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. *BMC Med Res Methodol.* 2017;17(1):78.
29. **Temperoni C, Grieco S, Pasquini Z, et al.** Clinical characteristics, management and health related quality of life in young to middle age adults with COVID-19. *BMC Infect Dis.* 2021;21(1):134.
30. **Garrigues E, Janvier P, Kherabi Y, et al.**Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect.* 2020;81(6):e4-e6.
31. **Carfi A, Bernabei R, Landi F**Gemelli Against C-P-ACSG. Persistent symptoms in patients after acute COVID-19. *JAMA.* 2020;324(6):603-605.
32. **Nogueira J, Gerardo B, Silva AR, et al.** Effects of restraining measures due to COVID-19: pre- and post-lockdown cognitive status and mental health. *Curr Psychol.* 2021:1-10.
33. **Mazza C, Ricci E, Biondi S, et al.** A nationwide survey of psychological distress among Italian people during the COVID-19 pandemic: immediate psychological responses and associated factors. *Int J Environ Res Public Health.* 2020;17(9).
34. **Sams N, Fisher DM, Mata-Greve F, et al.** Understanding psychological distress and protective factors amongst older adults during the COVID-19 pandemic. *Am J Geriatr Psychiatry.* 2021.
35. **Goertz YMJ, Van Herck M, Delbressine JM, et al.** Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? *ERJ Open Res.* 2020;6(4).
36. **Blair PW, Brown DM, Jang M, et al**. The clinical course of COVID-19 in the outpatient setting: a prospective cohort study. *Open Forum Infect Dis.* 2021;8(2):ofab007.
37. **Mizrahi B, Shilo S, Rossman H, et al.** Longitudinal symptom dynamics of COVID-19 infection. *Nat Commun.* 2020;11(1):6208.
38. **Fisher KA, Olson SM, Tenforde MW, et al.** Symptoms and recovery among adult outpatients with and without COVID-19 at 11 healthcare facilities-July 2020, United States. *Influenza Other Respir Viruses.* 2021;15(3):345-351.
39. **Lapin BR, Tang WHW, Honomichl R, Hogue O, Katzan IL**. Evidence of stability in patient-reported global health during the COVID-19 pandemic. *Value Health.* 2021;24(11):1578-1585.