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Life stressors significantly impact long-term outcomes and post-acute symptoms 12-months after COVID-19 hospitalization

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ABSTRACT

Background: Limited data exists evaluating predictors of long-term outcomes after hospitalization for COVID-19. The following outcomes were collected at 6 and 12-months post-diagnosis: disability using the modified Rankin Scale (mRS), activities of daily living assessed with the Barthel Index, cognition assessed with the telephone Montreal Cognitive Assessment (t-MoCA), Neuro-QoL batteries for anxiety, depression, fatigue and sleep, and post-acute symptoms of COVID-19. Predictors of these outcomes, including demographics, pre-COVID-19 comorbidities, index COVID-19 hospitalization metrics, and life stressors, were evaluated using multivariable logistic regression.

Results: Of 790 COVID-19 patients who survived hospitalization, 451 (57%) completed 6-month (N = 383) and/or 12-month (N = 242) follow-up, and 77/451 (17%) died between discharge and 12-month follow-up. Significant life stressors were reported in 121/239 (51%) at 12-months. In multivariable analyses, life stressors including financial insecurity, food insecurity, death of a close contact and new disability were the strongest independent predictors of worse mRS, Barthel Index, depression, fatigue, and sleep scores, and prolonged symptoms, with adjusted odds ratios ranging from 2.5 to 20.8. Other predictors of poor outcome included older age (associated with worse mRS, Barthel Index, depression, fatigue, and sleep scores, and prolonged symptoms), female sex (associated with worse Barthel index, prolonged symptoms), and index COVID-19 severity (associated with worse Barthel index, prolonged symptoms).

Conclusions: Life stressors contribute substantially to worse functional, cognitive and neuropsychiatric outcomes 12-months after COVID-19 hospitalization. Other predictors of poor outcome include older age, female sex, baseline disability and severity of index COVID-19.

1. Introduction

Long term sequelae of COVID-19 are increasingly recognized as major public health issues. We have previously reported that 87% of patients who survived COVID-19 hospitalization had abnormal scores on functional, cognitive, quality of life and/or activities of daily living batteries at 12-months [1]. Others have reported post-acute symptoms of COVID-19 in 33–90% of hospitalized patients [2-6]. Among non-hospitalized cohorts, post-acute sequelae have been estimated to occur in 25–69% [3,7–9]. This variable prevalence can be explained by differences in study design, ascertainment, symptoms assessed, timing of assessment and whether objective metrics (in addition to subjective
symptom reporting) were evaluated [10]. Despite a plethora of literature reporting prevalence rates of post-COVID-19 symptoms, there is a paucity of data reporting predictors of long-term functional, cognitive and quality of life quantitative outcomes.

In this prospective study, we evaluated the impact of four categories of predictors on 6- and 12-month outcome metrics including: demographics, pre-COVID-19 comorbidities, index COVID-19 hospitalization metrics, and life stressors within the month prior to interview. Outcome measures included not only long-term COVID-19 symptoms, but functional outcomes (modified Ranking Score), activities of daily living (Barthel Index), cognitive outcomes (telephone Montreal Cognitive Assessment [t-MoCA]) and NIH/PROMIS Neurological Quality Of Life (NeuroQoL) self-reported measures of anxiety, depression, fatigue and sleep.

2. Methods

2.1. Study design and patient cohort

We conducted a prospective, observational study of consecutive COVID-19 patients hospitalized at four New York City area hospitals within the same hospital system between March 10, 2020 and May 20, 2020. Follow-up interviews were performed at 6 and 12 months after initial SARS-CoV-2 diagnosis. Detailed enrollment, methodology and outcome measures have been previously reported [1,11–13]. Inclusion criteria were: RT-PCR positive SARS-CoV-2 infection, age ≥ 18 years, hospital admission, and consent to participate in a follow-up interview. Exclusion criteria were: evaluation in an outpatient or emergency department setting only.

2.2. Standard protocol approvals and patient consents

This study was approved by the NYU Grossman School of Medicine Institutional Review Board. All patients or their surrogates provided informed consent for participation.

2.3. Predictor variables

Demographic data, past medical/neurological history, new neurological events or other complications during hospitalization, and COVID-19 specific medications administered during the acute phase of illness were recorded. Severity of illness during hospitalization was graded based on the Sequential Organ Failure Assessment (SOFA) score [14] and requirement for intubation. Pre-COVID baseline functional status was assessed with modified Rankin Scale (mRS) [15] scores as reported by patients and/or their surrogate. Subjects were also asked to indicate if they had experienced any of 15 life stressors [7] within the month prior to the 12-month interview (Supplemental Table 1).

2.4. Study outcomes

Longitudinal follow-up assessments were conducted by telephone interview among patients or their surrogates who consented to participate. Contact was attempted at 6-months (±1 month) and 12-months (±2 months) from the onset of COVID-19 symptoms. Three attempts at contact were required before patients/surrogates were coded as “unreachable”. Patients who were “unreachable” at 6-months, were also contacted at 12-months for participation. Functional status and disability were assessed using the modified Rankin Scale (mRS; 0 = no symptoms, 6 = dead, dichotomized as 0–3 versus 4–6) [15], activities of daily living were evaluated with the Barthel Index of activities of daily living (0 = completely dependent, 100 = independent for all activities, dichotomized as completely independent with a score of 100 versus 100) [16], cognition was assessed with the telephone-MoCA (t-MoCA; 22 = perfect score; ≤18 = abnormal cognition) [17], and Quality of Life in Neurological Disorders [18] (NeuroQoL) short form self-reported health measures of anxiety, depression, fatigue and sleep were collected. NeuroQoL raw scores were converted into T-scores with a mean of 50 and standard deviation of 10 in a reference population (U.S. general population or clinical sample) [19]. Higher T-scores indicate worse self-reported health for the anxiety, depression, fatigue and sleep metrics. NeuroQoL scores were dichotomized at the mean ± 1 standard deviation (T-scores ≥60 versus <60). Patients with fewer than 13 years of education received an additional point when scoring the t-MoCA [20]. With the exception of the t-MoCA, all of the above batteries have been validated for surrogate completion, and surrogates were asked to complete these metrics for patients who were unable to do so.

The outcome of post-acute symptoms of COVID-19 was defined according to Centers for Disease Control and Prevention (CDC) criteria as new or persistent symptoms occurring ≥4 weeks after SARS-CoV-2 infection [21]. Symptoms were categorized following the World Health Organization (WHO) clinical case report form for post-acute COVID-19 symptoms [22] (Supplemental Table 2). Post-acute symptom data was only collected at the 12-month follow-up interview.

2.5. Statistical analyses

Demographic variables, past medical/neurological history, life stressors, and hospital clinical variables were evaluated as predictors of dichotomized 6- and 12-month outcomes using univariate logistic regression analyses. Data on life stressors and post-COVID-19 symptoms were only available from the 12-month interview. Multivariable backward, stepwise logistic regression models were constructed utilizing univariate variables with \( P \) values <0.05. Discharge metrics including length of stay, and discharge disposition (home, skilled nursing facility, acute rehabilitation facility) were not entered into multivariable models due to collinearity. Receiver operating characteristic curves were used to determine the area under the curve (AUC) for each multivariable model.

For patients who died, a mRS score of 6 was assigned, but no other outcome variables were scored or imputed. Incomplete or partial responses to a given metric were excluded from analysis. All analyses were conducted using IBM SPSS Statistics for Mac version 25 (IBM Corp., Armonk, NY).

3. Results

Follow-up interviews were attempted in 790 and 590 patients at 6 and 12 months post COVID-19 hospitalization, respectively [1]. A total of 451 patients completed follow-up either time point and were included in analyses. Fewer patients were eligible for the 12-month call due to language barrier, missing or defunct contact information or indication at the 6-month call that the respondent did not wish to be re-contacted. Interviews were completed in 382/790 (48%) patients at 6 months, 242/590 (41%) patients at 12-months and 174 patients completed follow-up at both time points. There were no differences in sex, race, education level, pre-COVID-19 history of psychiatric disease or dementia, pre-COVID-19 mRS scores, index COVID-19 severity, or rates of neurological events during index hospitalization between those who completed the 6-month versus 12-month follow-up interview. However, patients who completed only 6-month follow-up (and were then lost to follow-up) were significantly older than those who completed 12-month follow-up (median age 69 years versus 65 years, \( P < 0.001 \)) and had slightly higher body mass index (Table 1). Among those who completed 12-month follow-up, the most common neurological post-COVID-19 symptoms reported were headache (22%), cognitive abnormalities (20%), anxiety (12%), depression (11%), sleep disturbance (11%) and fatigue (10%, Supplemental Table 2) [23].

The mean values for outcome metrics and percent of patients who had poor or abnormal test results at 6- and 12-months post COVID-19 are shown in Table 2. As previously reported [1,12], 90% of patients at 6 months and 87% of patients at 12 months had abnormalities on at
least one of the metrics assessed (e.g. mRS > 0, Barthel Index <100, t-MoCA <18, or a NeuroQoL T-score ≥60), with abnormalities in t-MoCA and mRS being most prevalent. There was a small but significant correlation between abnormal 12-month NeuroQoL anxiety scores ≥60 and post-acute symptoms of COVID-19 (Pearson correlation coefficient 0.191, P = 0.005). There were no other significant correlations of post-acute symptoms with other 6- or 12-months outcomes (mRS 4–6, Barthel Index <100, t-MoCA scores <18, or depression, fatigue or sleep t-scores ≥60).

Tables 3a and 3b demonstrate univariate demographic and pre-COVId comorbidity predictors of 6- and 12-month outcomes. Older age was consistently associated with worse mRS, Barthel Index and t-MoCA scores at both time points, as well as NeuroQoL depression scores at 12-months. Female sex was associated with worse Barthel scores at 6- and 12-months and higher anxiety scores at 12-months. Lower education levels were associated with worse cognitive scores at 6- and 12-months [13], as well as worse depression and fatigue NeuroQoL scores at 12-months. Pre-COVId disability (as measured by baseline mRS) was a strong predictor of worse mRS and Barthel scores at both time points, and was associated with worse NeuroQoL fatigue scores at 12-months. A pre-COVId history of dementia/cognitive disorder or psychiatric disease were associated with worse mRS and Barthel scores. A history of dementia/cognitive disorder was also associated with worse t-MoCA scores and higher anxiety NeuroQoL scores. The presence of post-acute COVID-19 symptoms was not associated with any demographic or comorbidity predictors.

Tables 4a and 4b delineate index COVID-19 hospitalization metrics and their association with 6- and 12-month outcomes. Neurological complications including toxic metabolic encephalopathy and hypoxic ischemic brain injury were strong predictors of worse mRS and Barthel Index at 6 and 12 months and worse depression and fatigue scores at 12 months, while mechanical ventilation and worse SOFA scores (markers of severe COVID) were only predictive of worse Barthel Index at 6-months, and with much lower odds ratios. There was no consistent effect of COVID-19 related pharmaceuticals on outcome metrics, however, nitazoxanide (used in N = 14 patients) was associated with worse fatigue, depression and anxiety scores at 6 months. There were significantly worse Barthel Index scores in univariate analysis with corticosteroid use, but this medication was preferentially utilized in the most severely ill patients, suggesting a bias by indication. Post-acute COVID-19 symptoms at 12-months were more common in those with severe COVID-19 illness, as measured by the requirement for mechanical ventilation and worse SOFA scores. Worse mRS and Barthel scores were associated with discharge to a nursing home, but cognitive and NeuroQoL scores did not significantly vary with discharge disposition. We evaluated inflammatory markers collected during hospitalization including blood IL-6 (N = 300), D-dimer (N = 398), C-reactive peptide (N = 420) and ferritin levels (N = 414), but did not find any correlations with 6- or 12-month outcome metrics.

Next, we evaluated the impact of life stressors (Table 5 and SupplemenTable 1) on 12-month outcomes. Over 50% (121/239) of subjects reported experiencing at least one life stressor within the month prior to the 12-month follow-up interview (median 1 stressor, range 0–7 stressors). The most common stressors were: new personal illness within the month prior to the 12-month interview (23%), financial insecurity (17%), social isolation (13%) and death or illness of a close contact. The presence and number of stressors were strongly related to worse anxiety, depression, fatigue and sleep NeuroQoL scores and PASC. Social isolation, financial insecurity, unemployment, food insecurity, personal illness (within the month prior to 12-month interview), new disability and death of a close contact were all significantly associated with worse NeuroQoL measures, while personal illness, new disability and increased caregiver responsibilities were the only life stressors associated with mRS and Barthel scores. We did not identify associations with any of the measured stressors and cognitive scores.

Results of multivariable analyses for each outcome at 6 and 12 months, including variables entered into each model, are shown in Table 6 and Fig. 1. Older age and baseline disability (pre-COVId-19 mRS scores) were significantly predictive of worse mRS and Barthel Index scores at both 6 and 12 months. Older age was also associated with worse cognitive scores and worse NeuroQoL depression scores at 12-months. Neurological complications during index hospitalization, specifically hypoxic ischeamic encephalopathy, were independently associated with worse mRS scores at both timepoints. Severity of index COVID-19 illness was only associated with 6-month Barthel Index (SOFA scores) and post-acute COVID-19 symptoms at 12 months (mechanical ventilation). COVID-19 severity was not associated with mRS, t-MoCA or NeuroQoL anxiety, depression, fatigue or sleep scores at any time point. The presence of a variety of life stressors were independently associated with a number of 12-month outcomes including worse mRS, Barthel,
Table 3a

Association of demographic and comorbidity variables and 6- and 12-month mRS, Barthel Index, T-MoCA and post-acute COVID-19 symptoms. Univariate logistic regression odds ratios, 95% confidence intervals (CI) and P values are shown.

| Demographics                  | 6 months   | 12 months  | Barthel <100 | Barthel <100 | T-MoCA (≥18) 6-months | T-MoCA (≥18) 12-months | 12-month Post-acute COVID-19 symptoms |
|-------------------------------|------------|------------|--------------|--------------|------------------------|-------------------------|---------------------------------------|
| N                             | 381        | 236        | 304          | 236          | 215                    | 170                     |                                      |
| mRS 4-6                       |            |            |              |              |                        |                         |                                      |
| mRS 4-6                       |            |            |              |              |                        |                         |                                      |
| 6 months                      |            |            |              |              |                        |                         |                                      |
| P ≤ 0.001                     |            |            |              |              |                        |                         |                                      |
| Age                           | 1.04 (1.02-1.05) | 1.04 (1.02-1.06) | 1.04 (1.02-1.05) | 1.05 (1.03-1.08) | 1.03 (1.01-1.05) | 1.03 (1.01-1.06) | 1.00 (0.98-1.02) P < 0.162 |
| Sex (male)                    |            |            |              |              |                        |                         |                                      |
| Race (white)                  |            |            |              |              |                        |                         |                                      |
| Education level > 12 years    |            |            |              |              |                        |                         |                                      |
| BMI                           | P = 0.035  | P = 0.253  | P = 0.315    | P = 0.331    | P = 0.009               | P = 0.050               | P = 0.009                            |
| Comorbidities                 |            |            |              |              |                        |                         |                                      |
| Pre-COVID disability (mRS)    |            |            |              |              |                        |                         |                                      |
| P ≤ 0.001                     |            |            |              |              |                        |                         |                                      |
| Hypertension                  | 1.32 (1.00-1.69) | 1.32 (1.00-1.76) | 1.32 (1.00-1.77) | 1.32 (1.00-1.81) | 1.32 (1.00-1.85) | 1.32 (1.00-1.88) | 1.32 (0.99-1.38) P < 0.001 |
| Diabetes                      | 1.03 (0.94-1.10) | 1.03 (0.94-1.11) | 1.03 (0.94-1.11) | 1.03 (0.94-1.12) | 1.03 (0.94-1.12) | 1.03 (0.94-1.12) | 1.03 (0.99-1.12) P < 0.001 |
| COPD/ Asthma                  | 2.13 (0.62-2.42) | 2.13 (0.62-2.43) | 2.13 (0.62-2.43) | 2.13 (0.62-2.43) | 2.13 (0.62-2.43) | 2.13 (0.62-2.43) | 2.13 (0.62-2.43) P < 0.001 |
| Headache Disorder             | 1.25 (0.33-4.86) | 1.25 (0.33-4.86) | 1.25 (0.33-4.86) | 1.25 (0.33-4.86) | 1.25 (0.33-4.86) | 1.25 (0.33-4.86) | 1.25 (0.33-4.86) P < 0.001 |
| Dementia                      | 4.02 (1.86-8.69) | 4.02 (1.86-8.69) | 4.02 (1.86-8.69) | 4.02 (1.86-8.69) | 4.02 (1.86-8.69) | 4.02 (1.86-8.69) | 4.02 (1.86-8.69) P < 0.001 |
| Psychiatric history           | 1.94 (1.03-3.66) | 1.94 (1.03-3.66) | 1.94 (1.03-3.66) | 1.94 (1.03-3.66) | 1.94 (1.03-3.66) | 1.94 (1.03-3.66) | 1.94 (1.03-3.66) P < 0.001 |
| Bold indicates P < 0.05; mRS = modified Rankin Scale, t-MoCA = telephone Montreal Cognitive Assessment; BMI = body mass index; COPD = chronic obstructive pulmonary disease.

4. Discussion

In this prospective, longitudinal cohort study we identified independent predictors of 6- and 12-month functional (mRS, Barthel Index), cognitive (t-MoCA), quality of life (NeuroQol depression, anxiety, fatigue and sleep) outcomes and post-acute COVID-19 symptoms following COVID-19 hospitalization. While predictors of disability (mRS, Barthel) were similar and largely consisted of age, baseline functional status, neurological complications during hospitalization and markers of higher severity of COVID-19 illness, life stressors, which were present in >50% of subjects, played a larger role in predicting NeuroQol measures of depression, fatigue, sleep and post-acute symptoms of COVID-19. Indeed, the adjusted odds ratios for life stressors (including financial insecurity, food insecurity, death of a loved one and new disability) for predicting a variety of 12-month outcomes ranged from 2.5 to 20.8. While there are several reports of predictors of short term outcomes during hospitalization or within the first months following COVID-19 (e.g. mortality or discharge disposition) [24–26], as well as reports describing qualitative subjective post-acute COVID symptoms [2,8,9,27–39], this study is distinct in that it prospectively explores the impact of life stressors along with demographic, comorbid, and neurological events as predictors of quantitative long-term cognitive, functional, quality of life and post-acute symptoms outcomes in a large population.

Life stressors were significantly associated with several 12-month outcomes, including worse mRS scores, activities of daily living, NeuroQol depression, fatigue and sleep measures, and post-acute COVID-19 symptoms. The incorporation of pandemic-related stressors and related social determinants of health into predictive models is critical because these may represent areas of potential intervention. In a prior study of risk factors for post-acute COVID-19 symptoms among U.S. community dwellers with and without mild COVID-19 (not requiring hospitalization) conducted in February 2021, we identified multiple stressors (present within the month prior to interview) that were associated with the development of post-acute symptoms, most notably financial insecurity and unemployment [7]. In that study, multivariable models predicting NeuroQol measures of cognition, anxiety, depression, fatigue and sleep, demonstrated that several stressors were stronger predictors of abnormalities on quality of life testing than was SARS-CoV-2 infection itself. These data suggest an interplay of environmental and pandemic-related factors that may impact functional and neuropsychiatric outcomes.

We found that older age was a consistent and prominent predictor of worse functional status (mRS and Barthel scores), cognitive abnormalities and depression. While these findings may appear intuitive, some have identified a paradoxical relationship, wherein older patients hospitalized with COVID-19 were more likely to make greater improvements in functional status and return to pre-hospitalization status at 18 weeks compared to patients <45 years old [33]. Female subjects and those who considered themselves “very fit” pre-COVID-19 were also less likely to recover to pre-hospitalization functional status [31]. These data may reflect a ceiling effect in frailty assessments that have limited ability to detect nuanced differences in functional status. Others have found that post-acute COVID-19 symptoms were more prevalent in older individuals [27,34]. However, the types of post-acute COVID-19 symptoms may vary by age. For example, one study found that older individuals were more likely to have “any” post-acute COVID-19 feature (notably cognitive and respiratory symptoms), while younger patients more often reported headaches, anxiety/depression and abdominal symptoms [28]. We also found that poor baseline functional status (pre-COVID mRS score) was a strong, independent predictor of 6- and 12-month mRS and Barthel Index scores and fatigue. Indeed, some studies have found that baseline frailty or disability scores are more closely associated with poor outcomes than age [40].

depression, fatigue, and sleep scores, as well as post-acute COVID-19 symptoms. The AUCs for each model ranged from 0.664 to 0.903. Generally, 12-month models that included life stressors yielded more robust AUCs, however, models predicting cognitive outcomes and post-acute symptoms performed less well than models for other outcomes.
Table 3b

Association of Demographic and Comorbid variables and 6- and 12-month patient-reported NeuroQoL outcomes. Univariate logistic regression odds ratios, 95% confidence intervals (CI) and P values shown.

|         | Anxiety T-score ≥ 60 at 6-months N = 280 | Anxiety T-score ≥ 60 at 12-months N = 225 | Depression T-score ≥ 60 at 6-months N = 279 | Depression T-score ≥ 60 at 12-months N = 225 | Fatigue T-score ≥ 60 at 6-months N = 272 | Fatigue T-score ≥ 60 at 12-months N = 223 | Sleep T-score ≥ 60 at 6-months N = 278 | Sleep T-score ≥ 60 at 12-months N = 221 |
|---------|------------------------------------------|-------------------------------------------|---------------------------------------------|-------------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| Demographics |                                           |                                           |                                             |                                             |                                      |                                      |                                      |                                      |
| Age     | 1.03                                     | 1.00                                      | 1.05                                        | 1.10                                       | 0.99                                 | 1.02                                 | 0.99                                 | 1.00                                 |
| (1.00–1.06) | P = (0.96–1.03) P –                     | (0.99–1.11) P –                         | (1.03–1.17) P =                            | (0.96–1.03) P                             | (0.99–1.06) P                         | (0.97–1.02) P                         | (0.96–1.02) P                         | (0.96–1.02) P                         |
| Sex (male) | 0.72                                     | 0.17                                      | 0.31                                        | 0.28                                       | 0.40                                 | 0.54                                 | 0.92                                 | 0.56                                 |
| Race (white) | 0.479                                    | 0.67                                      | 0.118                                       | 0.075                                      | 0.101                                | 0.188                                | 0.838                                | 0.192                                |
| (0.29–1.78) | P = (0.05–0.55) P =                    | (0.07–1.34) P –                         | (0.07–1.14) P –                            | (0.14–1.19) P                             | (0.21–1.35) P                         | (0.40–0.29) P                         | (0.23–1.34) P                         |                                     |
| Education level | 0.875                                    | 0.473                                    | – 0.348                                    | – 0.169                                    | – 0.765                               | – 0.563                               | 0.140                                | – 0.885                               |
| > 12 years | 0.50                                     | 0.59                                      | 0.96                                        | 0.22                                       | 0.78                                 | 0.36                                 | 0.59                                 | 0.54                                 |
| (0.20–1.25) | P = (0.17–0.60) P =                    | (0.19–0.85) P –                         | (0.06–0.87) P =                            | (0.24–2.58) P                             | (0.13–0.95) P                         | (0.25–1.39) P                         | (0.19–1.36) P                         |                                     |
| Anxiety T-score ≥ 60 at 6-months | 0.137                                    | 0.406                                    | 0.957                                       | 0.031                                      | – 0.687                               | 0.039                                | 0.231                                | – 0.178                               |
| Anxiety T-score ≥ 60 at 12-months |                                           |                                           |                                             |                                             |                                      |                                      |                                      |                                      |
| Depression T-score ≥ 60 at 6-months |                                           |                                           |                                             |                                             |                                      |                                      |                                      |                                      |
| Depression T-score ≥ 60 at 12-months |                                           |                                           |                                             |                                             |                                      |                                      |                                      |                                      |
| Fatigue T-score ≥ 60 at 6-months |                                           |                                           |                                             |                                             |                                      |                                      |                                      |                                      |
| Fatigue T-score ≥ 60 at 12-months |                                           |                                           |                                             |                                             |                                      |                                      |                                      |                                      |
| Sleep T-score ≥ 60 at 6-months |                                           |                                           |                                             |                                             |                                      |                                      |                                      |                                      |
| Sleep T-score ≥ 60 at 12-months |                                           |                                           |                                             |                                             |                                      |                                      |                                      |                                      |

**Bold indicates P < 0.05; mRS = modified Rankin Scale; NeuroQoL = neurological quality of life; BMI = body mass index; COPD = chronic obstructive pulmonary disease.**

We identified female sex as an independent predictor of both anxiety and limitations in activities of daily living. Others have identified that female sex may be a predictor of post-acute COVID-19 symptoms [8,9,27,28,31–39,41]. In a survey of 999 community dwellers across the U.S, female sex, along with younger age, racial/ethnic minority status, baseline disability, fewer years of formal education, and/or a history of psychiatric diagnosis were significant predictors of post-acute COVID-19 symptoms [12,32]. Mechanisms of injury more common in women, such as autoimmune disease, might explain some of these differences. Indeed, women have higher basal levels of immunoglobulins and respond more robustly to both infections and vaccines, with increased cytokine production and T-cell response, compared to men [42–44]. Additionally, baseline pre-COVID prevalence rates of anxiety and depression are nearly two-fold higher in women than men [45,46]. It is possible that subclinical or undiagnosed mood disorders may have been unmasked in the context of pandemic- or illness-related stressors.

We found that severity of index COVID-19 illness (SOFA scores or intubation) was a predictor of limited activities of daily living and post-acute COVID-19 symptoms. Indeed, many others have identified index COVID-19 severity as a predictor of protracted COVID symptoms [28,36,37,47–50]. Some studies have suggested that the severity of acute respiratory failure, rather than the pathogen involved, predicts neuropsychiatric sequelae. One study compared electronic medical records of patients hospitalized for COVID-19 or a severe acute respiratory infection, to a reference population of hospitalized and non-hospitalized patients without these conditions [51], and found significantly higher rates of new onset anxiety, depression, bipolar disorder or psychotic disorder compared to the reference population. However, rates of neuropsychiatric sequelae were similar in COVID-19 and non-COVID-19 acute respiratory infection patients, suggesting that the prime driver of long-term events is disease severity, and not the specific pathogen.

Conversely, other cohorts have found higher rates of post-acute symptoms among patients with COVID-19 compared to seasonal influenza, even after adjusting for severity of illness, suggesting that these long-term sequelae may be unique to SARS-CoV-2 [47,48]. We did not identify index COVID-19 severity as a predictor of NeuroQoL metrics such as anxiety, depression, fatigue or sleep outcomes. Others have also failed to find an association of severity of index illness (defined by oxygen requirement or intubation status) when evaluating certain outcomes of hospitalized patients [34]. Differing relationships of COVID-19 severity with sequelae may be explained by differences in comparator groups, e.g. some studies evaluated hospitalized versus non-hospitalized COVID-19 patients, whereas we compared mechanically ventilated hospital patients to non-intubated hospitalized patients. Additionally, these incongruities may simply reflect the fact that the sickest patients died or were too impaired to participate in long-term outcome batteries. Because we did not have a non-COVID-19 comparator group, we cannot make any assertions regarding whether outcomes were driven by...
Table 4a

Association of index COVID-19 hospitalization variables with 6 and 12 month mRS, Barthel, T-MoCA and PASC outcomes. Univariate logistic regression odds ratios, 95% confidence intervals (CI) and P values shown.

| Index COVID-19 Hospitalization | mRS 4-6 | mRS 4-6 6 months | mRS 4-6 12 months | Barthel <100 | Barthel <100 6 months | Barthel <100 12 months | T-MoCA (=18) | T-MoCA (=18) 6 months | T-MoCA (=18) 12 months | COVID-19 symptoms 12-month Post-acute |
|--------------------------------|---------|------------------|------------------|-------------|----------------------|----------------------|--------------|----------------------|----------------------|--------------------------------------|
| Neuro complication             | 1.61    | 1.31 (0.76-2.25) | 1.71             | 1.21 (0.71-2.05) | 1.32 (0.77-2.26) | 0.92                 | 0.74 (0.44-1.24) | P = 0.251             | 0.790                 |                                      |
| Hypoxic/ischemic brain injury  | 2.70    | 3.52             | 3.51             | 3.00         | 1.16 (0.45-2.97) | 1.51                 | 0.88 (0.34-2.29) | P = 0.788             | 0.493                 |                                      |
| Toxic-Metabolic                | 2.02    | 2.73             | 2.03             | 2.39         | 1.70 (0.88-3.28) | 1.72                 | 1.01 (0.53-1.92) | P = 0.982             | 0.212                 |                                      |
| Encephalopathy                 | 1.24    | 1.10 (0.62-1.94) | 1.62             | 1.10 (0.63-1.93) | 0.75 (0.43-1.32) | 0.90                 | 3.63 (2.01-6.58) | P < 0.001             | 0.756                 |                                      |
| Worst Sequential Organ Failure | 1.03    | 1.03 (0.96-1.10) | 1.07             | 1.02 (0.96-1.09) | 0.98 (0.92-1.05) | 1.03                 | 1.10 (1.03-1.18) | P = 0.006             | 0.373                 |                                      |
| Failure (SOFA) score           | 1.00    | 1.00 (0.98-1.02) | 1.00             | 1.01 (0.99-1.02) | 1.00 (0.98-1.01) | 0.99                 | 0.98 (0.96-1.00) | P = 0.035             | 0.408                 |                                      |
| Lowest % oxygen saturation     | 0.94    | 0.94             | 0.83             | 0.98         | 0.99 (0.97-1.01) | 0.99                 | 0.99 (0.97-1) | P = 0.015             | 0.243                 |                                      |
| Lowest mean arterial blood     | 0.69    | 0.50 (0.37-1.61) | 0.54             | 0.47         | 0.54 (0.36-0.80) | 0.47                 | 0.188 (0.11-0.31) | P = 0.188             | 0.079                 |                                      |
| pressure (mmHg)                | 0.27    | 0.27             | 0.21             | 0.26         | 0.25 (0.16-0.41) | 0.26                 | 0.26 (0.17-0.44) | P = 0.002             | 0.001                 |                                      |
| Acute renal failure            | 0.88    | 0.88             | 0.83             | 0.85         | 0.86 (0.67-1.09) | 0.85                 | 0.86 (0.37-2.04) | P = 0.349             | 0.743                 |                                      |
| Medications during Index       | 0.70    | 0.70             | 0.68             | 0.68         | 0.68 (0.56-0.84) | 0.68                 | 0.68 (0.54-0.84) | P = 0.006             | 0.001                 |                                      |
| Hospitalization                | 0.57    | 0.57             | 0.57             | 0.57         | 0.57 (0.43-0.75) | 0.57                 | 0.57 (0.43-0.75) | P = 0.001             | 0.001                 |                                      |

**Bold** indicates P < 0.05; mRS = modified Rankin Scale, t-MOCA = telephone Montreal Cognitive Assessment; SNF = skilled nursing facility.
Table 4b

Association of index COVID-19 hospitalization variables and 6- and 12-month patient-reported NeuroQol outcomes. Univariate logistic regression odds ratios, 95% confidence intervals (CI) and P values shown.

| Index COVID-19 | Hospitalization |
|----------------|-----------------|
| Anxiety T-score ≥ 60 at 6-months | N = 280 |
| Anxiety T-score ≥ 60 at 12-months | N = 225 |
| Depression T-score ≥ 60 at 6-months | N = 279 |
| Depression T-score ≥ 60 at 12-months | N = 223 |
| Fatigue T-score ≥ 60 at 6-months | N = 272 |
| Fatigue T-score ≥ 60 at 12-months | N = 227 |
| Sleep T-score ≥ 60 at 6-months | N = 218 |
| Sleep T-score ≥ 60 at 12-months | N = 221 |

| Variable | Odds Ratio | 95% CI | P-value |
|----------|------------|--------|---------|
| Neuro complication | 0.51 (0.20–1.31) | P = 0.015 | 0.33 (0.01–0.93) | P = 0.084 |
| Hyponic/hypothermic brain injury | 1.02 (0.23–4.70) | P = 0.973 | 0.97 (0.19–4.77) | P = 0.960 |
| Toxic-Metabolic | 0.97 (0.34–2.76) | P = 0.817 | 0.98 (0.30–3.44) | P = 0.941 |
| Mechanically ventilated | 0.60 (0.21–1.68) | P = 0.329 | 0.60 (0.13–2.99) | P = 0.537 |
| Worst Sequential Organ Failure Score | 0.90 (0.78–1.03) | P = 0.476 | 0.89 (0.68–1.17) | P = 0.353 |
| Failure Assessment (SOFA) score | 0.90 (0.80–1.00) | P = 0.086 | 0.90 (0.80–1.00) | P = 0.086 |
| Lowest % oxygen saturation | 1.01 (0.98–1.05) | P = 0.772 | 1.01 (0.95–1.06) | P = 0.772 |
| Lowest mean arterial blood pressure | 1.03 (1.00–1.06) | P = 0.038 | 1.03 (1.00–1.06) | P = 0.038 |
| Acute renal failure | 2.64 (0.96–7.26) | P = 0.061 | 2.64 (0.96–7.26) | P = 0.061 |

### Medications during Index Hospitalization

| Medication | Odds Ratio | 95% CI | P-value |
|------------|------------|--------|---------|
| Ticlofizumab/ clazakizumab | 0.89 (0.29–2.76) | P = 0.737 | 0.89 (0.29–2.76) | P = 0.737 |
| Corticosteroids | 0.64 (0.21–1.95) | P = 0.887 | 0.64 (0.19–1.97) | P = 0.887 |
| Remdesivir | 0.73 (0.28–1.88) | P = 0.509 | 0.73 (0.28–1.88) | P = 0.509 |
| Nizatidine | 5.37 (0.97–29.41) | P = 0.054 | 5.37 (0.97–29.41) | P = 0.054 |
| Zinc | 0.68 (0.27–1.73) | P = 0.417 | 0.68 (0.27–1.73) | P = 0.417 |
| Ascorbic acid | 1.23 (0.48–3.16) | P = 0.672 | 1.23 (0.48–3.16) | P = 0.672 |
| Lopinavir/ritonavir | 1.71 (0.47–6.24) | P = 0.705 | 1.71 (0.47–6.24) | P = 0.705 |
| Azithromycin | 0.53 (0.22–1.29) | P = 0.162 | 0.53 (0.22–1.29) | P = 0.162 |
| Therapeutic anticoagulation | 2.3 (0.49–10.50) | P = 0.675 | 2.3 (0.49–10.50) | P = 0.675 |

### Discharge metrics

| Metric | Odds Ratio | 95% CI | P-value |
|--------|------------|--------|---------|
| Length of stay | 0.99 (0.96–1.01) | P = 0.546 | 0.99 (0.96–1.01) | P = 0.546 |
| Discharge home | 0.77 (0.31–1.94) | P = 0.190 | 0.77 (0.31–1.94) | P = 0.190 |
| Discharge SNF | 1.39 (0.49–4.00) | P = 0.538 | 1.39 (0.49–4.00) | P = 0.538 |
| Discharge rehab | 0.87 (0.19–3.96) | P = 0.860 | 0.87 (0.19–3.96) | P = 0.860 |

**Bold** indicates P < 0.05; NeuroQol = neurological quality of life; SNF = skilled nursing facility.
severity of illness or are specific to the SARS-CoV-2 pathogen.

Finally, most COVID-19 specific medications used during index hospitalization did not independently predict 12-month outcomes, with the exception of azithromycin, which was protective against severe fatigue scores. Since this cohort represents the first SARS-CoV-2 wave in the U.S., many subsequent studies that identified effective acute therapies were not yet published [52–56]. Indeed, many critically ill patients were treated with anticoagulation based on ferritin and D-Dimer levels per hospital protocol, while decedent was sporadically, and inconsistently used. There were too few patients who received remdesivir to even perform statistical analyses. Because certain COVID-19 specific medications may have variable beneficial or harmful impact depending on the population treated, it is likely we were unable to detect any effect due to both underpowering and poor patient selection. The relationship of in-hospital azithromycin use and 12-month fatigue scores is intriguing, since azithromycin has been reported to provide symptomatic relief to patients with chronic fatigue syndrome [57]. Azithromycin has been shown to have immune modulating capacity and its utility in chronic fatigue syndrome patients is thought to be linked to its effect on chronically primed immune cells in the brain [57]. Additionally, azithromycin has anti-inflammatory and anti-viral properties [58], which may play a role in the pathophysiology of post-COVID-19 chronic fatigue. While acute COVID-19 studies did not demonstrate a beneficial effect of azithromycin on symptoms at 14–28 days [59,60], post-infection, hospitalization rates [60], requirement for invasive mechanical ventilation [61], discharge disposition [61], clinical recovery [62], or mortality [61,63], further study of azithromycin for the treatment of PASC fatigue may be warranted.

Strengths of this study include the prospective ascertainment of data from hospitalization through 12-month follow-up, the robust characterization of neurological events during index hospitalization, accounting of pre-COV functional status, assessment of life stressors, and the use of both quantitative and patient-reported long-term outcome metrics. There are also several limitations to this study that should be noted. First, we did not a priori investigate certain factors that may be important outcome predictors. For example, a multi-omic study of 309 patients (51% were hospitalized for index COVID-19) examined predictors of post-acute symptoms (most commonly fatigue, cough, and anosmia/dysgeusia) at 2–3 months post SARS-CoV-2 infection. In this study, type 2 diabetes, Epstein-Barr virus (EBV) viremia, SARS-CoV-2 RNAemia and several autoantibodies were identified as risk factors for post-acute symptoms [64]. Because index hospitalization occurred early in the pandemic in our study, we did not have measures of SARS-CoV-2 viral load, nor did we assess autoantibodies or EBV levels. Though we evaluated the impact of diabetes on our outcome measures, we did not find any significant associations. Differences in study populations

| Table 5 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | mRS 4-6 | Barthel < 100 | t-MoCA ≤ 18 | Anxiety T-score ≥ 60 | Depression T-score ≥ 60 | Fatigue T-score ≥ 60 | Sleep T-score ≥ 60 | 12-month Post-acute COVID-19 symptoms N |
| | N = 236 | N = 236 | N = 170 | N = 225 | N = 225 | N = 223 | N = 221 |
| Stressors | | | | | | | | |
| At least one | | | | | | | | |
| J.A. Frontera et al. | | | | | | | | |
| Social Isolation | 1.28 | 1.91 | 1.09 | 4.22 | 2.27 | 1.47 | 2.43 | 1.29 |
| Financial | 0.10 | 0.10 | 0.09 | 0.72 | 0.14 | 0.00 | 0.00 | 1.31 |
| Education | 0.38 | 0.38 | 0.38 | 0.72 | 0.14 | 0.00 | 0.00 | 0.43 |
| Political conflict | 0.38 | 0.38 | 0.38 | 0.72 | 0.14 | 0.00 | 0.00 | 0.43 |
| Food Insecurity | 0.38 | 0.38 | 0.38 | 0.72 | 0.14 | 0.00 | 0.00 | 0.43 |
| None | | | | | | | | |
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Multivariable predictors of 6- and 12-month outcomes calculated using multivariable, backwards, stepwise logistic regression analyses. Adjusted odds ratios (OR), 95% confidence intervals (CI), p values, and area under the curve (AUC) for the entire model are shown.

| Variable | Adjusted OR (95% CI) | p | Model AUC (95% CI) |
|----------|----------------------|---|-------------------|
| 6-month mRS 4-6 | 1.02 (1.00–1.04) | 0.021 | 0.755 (0.697–0.813) |
| Age | 1.04 (1.01–1.06) | 0.002 | 0.789 (0.737–0.841) |
| Baseline mRS | 2.05 (1.59–2.65) | <0.001 | 0.573 (0.415–0.780) |
| Hypoxic ischemic encephalopathy during index hospitalization | 3.58 | 0.037 | 0.608 (0.462–0.793) |
| Stressor: new disability | 4.88 | 0.007 | 0.682 (0.537–0.875) |
| 6-month Barthel < 100 | 1.06 (1.03–1.09) | <0.001 | 0.644 (0.573–0.715) |
| Age | 1.11 (1.02–1.20) | 0.011 | 0.731 (0.592–0.870) |
| Male sex | 0.21 (0.06–0.74) | 0.015 | 0.821 (0.654–0.993) |
| History of dementia | 6.42 | 0.011 | 0.684 (0.574–0.814) |
| Education: >12 years | 0.30 (0.12–0.77) | 0.012 | 0.840 (0.732–0.948) |
| 6-month t-MoCA ≤ 18 | 0.41 (0.21–0.83) | 0.012 | 0.573 (0.415–0.780) |
| White race | 6.82 | 0.019 | 0.608 (0.462–0.793) |
| History of dementia | 1.38 (1.33–1.67) | 0.018 | 0.608 (0.462–0.793) |
| Education: >12 years | 0.30 (0.12–0.77) | 0.012 | 0.684 (0.574–0.814) |
| 6-month t-MoCA ≥ 18 | 1.04 (1.01–1.07) | 0.003 | 0.731 (0.592–0.870) |
| Education: >12 years | 0.34 (0.15–0.78) | 0.014 | 0.731 (0.592–0.870) |
| Male sex | 0.21 (0.06–0.74) | 0.015 | 0.821 (0.654–0.993) |
| History of dementia | 6.42 | 0.011 | 0.684 (0.574–0.814) |
| Education: >12 years | 0.30 (0.12–0.77) | 0.012 | 0.840 (0.732–0.948) |
| Male sex | 0.21 (0.06–0.74) | 0.015 | 0.821 (0.654–0.993) |
| History of dementia | 6.42 | 0.011 | 0.684 (0.574–0.814) |
| Education: >12 years | 0.30 (0.12–0.77) | 0.012 | 0.840 (0.732–0.948) |
| Male sex | 0.21 (0.06–0.74) | 0.015 | 0.821 (0.654–0.993) |
| History of dementia | 6.42 | 0.011 | 0.684 (0.574–0.814) |
| Education: >12 years | 0.30 (0.12–0.77) | 0.012 | 0.840 (0.732–0.948) |
| Male sex | 0.21 (0.06–0.74) | 0.015 | 0.821 (0.654–0.993) |
| History of dementia | 6.42 | 0.011 | 0.684 (0.574–0.814) |
| Education: >12 years | 0.30 (0.12–0.77) | 0.012 | 0.840 (0.732–0.948) |

mRS = modified Rankin Scale; t-MoCA = telephone Montreal Cognitive Assessment; NeuroQoL = neurological quality of life; SOFA = Worst Sequential Organ Failure Assessment.

Multivariable logistic regression analyses of 6-month NeuroQoL metrics not performed due to <2 univariate predictors with P < 0.05. Variables (univariate predictors with P < 0.05) assessed in each backwards, stepwise logistic regression model by outcome of interest:

6-month mRS: age, education >12 years, pre-COVID disability, history of dementia, history of psychiatric disorder, any neurological complication during hospitalization, hypoxic ischemic brain injury, toxic-metabolic encephalopathy, azithromycin use during hospitalization.

12-month mRS: age, pre-COVID disability, history of dementia, hypoxic ischemic brain injury, toxic-metabolic encephalopathy, increased caregiver responsibility, personal illness, new disability stressor.

6-month Barthel Index: age, sex, pre-COVID disability, history of dementia, history of psychiatric disorder, any neurological complication during hospitalization, hypoxic ischemic brain injury, toxic-metabolic encephalopathy, mechanical ventilation, worst SOFA score, use of corticosteroids during hospitalization.

12-month Barthel Index: age, sex, pre-COVID disability, hypoxic ischemic brain injury, toxic-metabolic encephalopathy, increased caregiver responsibility, personal illness, new disability stressor.

6-month t-MoCA: age, race, education >12 years, history of dementia, tocilizumab use during hospitalization.

12-month t-MoCA: age.

12-month Anxiety: sex, history of dementia, at least one life stressor, number of stressors, social isolation, financial insecurity, food insecurity.

12-month Depression: age, education >12 years, toxic-metabolic encephalopathy, number of stressors, death of a close contact.

12-month Fatigue: education >12 years, pre-COVID disability, any neurological complication during hospitalization, ascorbic acid use during hospitalization, azithromycin use during hospitalization, at least one life stressor, number of stressors, food insecurity, personal illness, new disability.

12-month Sleep: at least one life stressor, number of stressors, financial insecurity, personal illness, new disability, political conflict with close contacts.

Post-acute COVID-19 symptoms: mechanical ventilation during index hospitalization, worst Sequential Organ Failure Assessment (SOFA) score during hospitalization, oxygen saturation during hospitalization, tocilizumab, corticosteroid, hydroxychloroquine, zinc, azithromycin or therapeutic anti-coagulation during hospitalization, at least one life stressor, number of stressors, unemployment, personal illness.

In adults hospitalized with COVID-19, we found that traditional predictors of poor outcome, including older age, poor pre-COVID (hospitalized versus not) and time frame of outcome assessments, may in part explain this discrepancy. While most of our models demonstrated robust AUCs, models for cognition and post-acute COVID-19 symptoms yielded middling AUC values, suggesting there are important factors that we did not account for in these models. We did not have baseline pre-COVID cognitive testing to evaluate change over time. It is also likely that sicker patients may not have been able to participate in cognitive testing or review of post-acute symptoms. Second, there were some differences in the number participants between the two time points, and the same individuals are not represented at each time point. However, aside from older age in those lost to follow-up at 12-months, there were no other significant differences between those who completed only 6-month follow-up and those who completed 12-month follow-up. Third, we did not collect life stressor data at the 6-month visit, so we were unable to account for these variables in 6-month outcome models. Fourth, some medications utilized to treat COVID-19 appeared to be associated with worse outcomes in univariate analyses. This is likely related to bias by indication, since many of these medications were reserved for the sickest patients, and little data existed to guide standardized management during the first wave of the pandemic. Last, we dichotomized NeuroQoL scores at ≥1 standard deviation above the mean. There is some data to suggest that a clinically meaningful threshold for dichotomization may be 0.5 standard deviations (SD) above the mean [65,66]. Utilization of a more liberal 0.5 SD threshold would increase the prevalence of worse NeuroQoL measures and could lead to differences in multivariable models.

5. Conclusions
Fig. 1. Independent predictors of outcome 6- and 12-months after COVID-19 hospitalization. Life stressors, age, female sex, baseline disability, and index COVID-19 severity were the most common predictors of functional status (measured by the modified Rankin Scale [mRS]), activities of daily living (ADLs, measured by the Barthel Index), cognition (measured by the telephone MoCA) and patient-reported anxiety, depression, fatigue and sleep (assessed using NeuroQoL metrics).

Functional status (mRS)
ADLs (Barthel Index)
Cognition (telephone MoCA)
Depression (NeuroQoL)

Age
Female
COVID Severity
Baseline Disability
Life Stressors

Functional status (mRS)
ADLs (Barthel Index)
Fatigue (NeuroQoL)

IA DLs (Barthel Index)
Post-acute symptoms

Author contributions

JAF contributed to conception, study design, data analysis and drafting of the manuscript.
SS, DY, AL, ASL, KM, ST contributed to data curation, investigation, writing- review and editing of the manuscript.
AdH, SY, AL, ASL, KM, LB, TW and SLG contributed to study conception and design, data interpretation and critical revision of the manuscript.

Declaration of Competing Interest

Potential conflict of interest: JAF receives funding for the following COVID-19-related grants: NIH/NIA R01AG077422, NIH/NINDS 3U24NS11384401S1, NIH/NHLBI 1OT2HL161847-01; LB and ST receive funding for the following COVID-19-related grant: NIH/NHLBI 1OT2HL161847-01. TW receives funding for the following COVID-19-related grant: NIH/NHLBI 3U24NS11384401S1, NIH/NHLBI 1OT2HL161847-01; LJB and ST contribute to study conception and design, data interpretation and critical revision of the manuscript.

Data availability

De-identified data will be made available to qualified investigators upon written request to the corresponding author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2022.120487.

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