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# Elevated risk of new-onset chronic fatigue syndrome/myalgic encephalomyelitis up to four years after SARS-CoV-2 infection

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## Abstract

**Background** Fatigue is a common sequela of SARS-CoV-2 infection, with many COVID-19 patients subsequently developing chronic fatigue syndrome and myalgic encephalomyelitis (CFS/ME). Long-term associations between COVID-19, new-onset CFS/ME, and other independent predictors such as vaccination for SARS-CoV-2, re-infection, and blood biomarkers at time of infection remain unclear. This study investigated the incidence and independent predictors of developing new-onset CFS/ME up to 4 years post SARS-CoV-2 infection in comparison to COVID− controls.

**Methods** This retrospective analysis conducted within the Montefiore Health System from February 1, 2020, to January 12, 2024 included adults without a prior diagnosis of fatigue or CFS/ME who were hospitalized for COVID-19 (n = 10,667), not hospitalized for COVID-19 (n = 25,409), and non-COVID-19 controls (n = 111,301). The observation time was between 30 days and 4 years post index date. The outcome was new-onset CFS/ME. Multivariate adjusted hazard ratios (HR) with 95% confidence intervals were calculated, assessing risk posed by SARS-CoV-2 infection, re-infection, and vaccination. Whether abnormal levels of aspartate aminotransferase, creatinine, D-dimer, lactate dehydrogenase, ferritin, hemoglobin, platelets, neutrophil/lymphocyte ratio, and temperature during hospitalization were associated with future CFS/ME risk was examined.

**Results** Compared to COVID− controls, the risk of developing new-onset CFS/ME was higher among both COVID-19 hospitalized (adjusted HR = 1.46 [1.07, 1.99]) and non-hospitalized patients (1.56 [1.25, 1.93]). Females (1.54 [1.27, 1.89]), patients with liver disease (1.61 [1.29, 2.00]), autoimmune disorders (1.57 [1.18, 2.08]), and anxiety disorders (1.35 [1.04, 1.74]) were more likely to develop CFS/ME ($p < 0.05$). Re-infection with SARS-CoV-2 was not associated with increased risk of incident CFS/ME. COVID-19 vaccination status during the initial phase of the rollout (prior to 2022) was associated with an increased risk of new-onset CFS/ME ($p < 0.05$). None of the blood biomarkers during acute COVID-19 were associated with new-onset CFS/ME risk ($p > 0.05$).

**Conclusion** SARS-CoV-2 infection is associated with an increased risk of new-onset CFS/ME, independent of hospitalization status. Females, and individuals with autoimmune and anxiety disorders were more susceptible. These findings highlight the need for ongoing surveillance and management of fatigue-related symptoms in COVID-19 survivors.

**Keywords** Chronic fatigue syndrome, Myalgic encephalomyelitis, Post-acute sequelae, COVID-19, Long-COVID, Risk factors, Epidemiology

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## Introduction

Chronic fatigue syndrome, also known as myalgic encephalomyelitis (CFS/ME), is a complex and debilitating condition characterized by persistent, unexplained fatigue that is not alleviated by rest and is often accompanied by cognitive dysfunction, post-exertional malaise, unrefreshing sleep, pain, and autonomic abnormalities [1]. The etiology of CFS/ME remains elusive, although viral infections have been strongly implicated as potential triggers [2]. Historically, post-infectious fatigue syndromes have followed acute illnesses caused by Epstein–Barr virus, Ross River virus, and Coxiella burnetii, among others [2]. In this context, the global SARS-CoV-2 pandemic has reignited interest in post-viral syndromes and their potential overlap with CFS/ME.

Emerging evidence suggests that SARS-CoV-2 may also act as a trigger for CFS/ME, contributing to a broader constellation of symptoms now referred to as post-acute sequelae of SARS-CoV-2 infection or long-COVID [3]. Fatigue is one of the most prevalent and persistent symptoms among COVID-19 survivors, and in many cases, it presents with orthostatic intolerance, "brain fog," and post-exertional symptom exacerbation, clinical features that mirror those of CFS/ME [1].

Several biological mechanisms have been proposed to explain the potential link between COVID-19 and subsequent development of CFS/ME [4]. These include systemic inflammation, immune dysregulation, mitochondrial dysfunction, and persistent viral reservoirs. Notably, elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), common in both CFS/ME and post-COVID cohorts, may promote neuroinflammation and central nervous system disruption [5, 6]. In addition, autonomic nervous system dysfunction has been observed in both conditions and may play a key role in symptom persistence [7].

Although a few studies have investigated self-reported post-COVID fatigue [8–16], few have focused specifically on clinically diagnosed CFS/ME. To our knowledge, only three prior studies have assessed the risk of new-onset CFS/ME in COVID-19 survivors compared to unexposed individuals, all with follow-up periods limited to one year or less [14–16]. Furthermore, these studies often did not adjust for key factors such as social determinants of health, vaccination status, SARS-CoV-2 re-infection, and clinical biomarkers at the time of infection, which may modify risk. Another common limitation is that a few studies did not exclude patients with pre-existing fatigue, which can confound the attribution of CFS/ME diagnoses to post-COVID pathophysiology.

In this study, we investigated the incidence of clinically diagnosed CFS/ME over an extended follow-up period of up to four years post-infection in the Montefiore Health System, a large urban health system in the Bronx, New York. This setting serves a racially and ethnically diverse, predominantly low-income population, which experienced disproportionately high COVID-19 burden during both early and subsequent waves of the pandemic. In addition to evaluating overall incidence, we examined how demographic and socioeconomic factors, COVID-19 vaccination status, re-infection, blood-based biomarkers at the time of initial infection, and unmet social needs may modify risk for post-COVID CFS/ME. By integrating long-term follow-up with clinical diagnoses and granular health system data, this study provides a novel and rigorous contribution to the understanding of post-viral fatigue syndromes in the aftermath of SARS-CoV-2.

## Methods

### Data sources

This retrospective cohort study was approved by the Einstein-Montefiore Institutional Review Board (#2021–13658) with an exemption for informed consent. The data came from the Montefiore Health System, which consists of multiple hospitals and outpatient clinics in the Bronx, the lower Hudson Valley, and Westchester County. Data was extracted from Montefiore's electronic health record (EHR) as previously described [17–34].

### Study cohort

Data extraction queried the EHR for all polymerase chain reaction (PCR) SARS-CoV-2 tests performed on adults (≥ 21 years old) in the Montefiore Health System from February 1, 2020, to January 12, 2024. COVID+ patients consisted of those who tested positive at least once and index date was defined as date of first positive test. COVID− patients consisted of those who never tested positive and index date was defined as date of first negative test. To ensure adequate follow up, patients who died or were lost to follow up within the first 30 days of index date were excluded. Patients were also excluded if they had a history of fatigue, defined as a diagnosis code of "Fatigue", "Chronic fatigue syndrome", or "Postviral fatigue syndrome" prior to index date or during the first 30 days after index date. A sensitivity analysis was also conducted in which these 30-day exclusions were not applied.

### Variables

Demographic data included age at index date, sex, race, and ethnicity. Insurance and median household income of each patient's Zone Improvement Plan (ZIP) code. Pre-existing comorbidities at index date included hypertension (HTN), type-2 diabetes (T2DM), chronic obstructive pulmonary disease (COPD), asthma, chronic

kidney disease (CKD), liver disease, cardiovascular disease (CVD, defined as a composite of a history of myocardial infarction, coronary artery disease, or congestive heart failure), any autoimmune disease, depressive disorder, and anxiety disorder. To assess severity of SARS-CoV-2, the COVID+ patients were stratified based on hospitalization during the acute phase of the infection. We also collected data on vaccination for COVID-19 and considered patients vaccinated if they had received at least one dose prior to index date. Among those who were COVID+, we also collected data on re-infection with SARS-CoV-2. Sociodemographic data was available for all patients and those who had no diagnosis of comorbidities or outcomes in the EHR were assumed to not have experienced the outcome or had the comorbidity.

### Outcomes

The outcome event consisted of the first documented occurrence of any of the following Systematized Nomenclature of Medicine diagnostic codes: Chronic fatigue syndrome (52702003) or Postviral fatigue syndrome (51771007), typically diagnosed using the 2015 Institute of Medicine (IOM) criteria [35]. Follow-up time was calculated in months from the index date to either the date of first diagnosis (for patients who developed the outcome), death, or last recorded visit (for patients who did not develop the outcome) up to January 12, 2024.

### Statistical analysis

Python (v3.10.12) and RStudio (v4.3.2) were used for data processing and statistical analyses. *p*-values less than 0.05 were considered statistically significant. For group comparison of categorical variables, the chi-square test was used and for group comparison of continuous variables, the independent t-test was used. Cumulative incidence curves were plotted for > 30 days post-index date test CFS/ME. The risk of the outcome was assessed using multivariate Fine-Gray subdistribution hazards models, accounting for all-cause mortality as a competing risk. We assessed the proportional hazards assumption for COVID-19 status in all models and found no violation. The multivariate models adjusted for all collected variables regardless of statistical significance. Covariates adjusted for included SARS-CoV-2 infection and hospitalization status (COVID− patients as reference), vaccination for SARS-CoV-2 prior to index date, age at index date (continuous), sex (males as reference), race (non-Hispanic Whites as reference), Hispanic ethnicity, all pre-existing comorbidities, insurance (private insurance as reference), and median income of ZIP code (divided into quartiles and top quartile as reference). Re-infection with SARS-CoV-2 was modeled as a time-varying covariate. Subgroup analyses were performed across age groups, sex, race, ethnicity, pre-existing psychiatric disorder, insurance, median income of ZIP code quartile, and vaccination status and interaction terms were used to assess effect modification.

## Results

From February 1, 2020, to January 12, 2024, 204,144 adults (≥ 21 years old) had a SARS-CoV-2 PCR test performed (Fig. 1). After applying exclusion criteria, 36,076 COVID+ and 111,301 COVID− patients without a history of fatigue were available for long-term follow up.

Table 1 shows the characteristics of patients without a history of fatigue by SARS-CoV-2 positivity status. On average, patients were followed up for approximately 1.78 years. COVID− patients had slightly longer follow up time (1.81 vs. 1.69 years, $p < 0.005$) and were on average younger (50.96 vs. 52.44 years old, $p < 0.005$) than COVID+ patients. COVID+ patients had slightly higher prevalence of pre-existing comorbidities and 10,667 (29.57%) were hospitalized during the acute phase of the infection. Supplementary Table 1 shows the demographics of those with and without at least one dose of COVID-19 vaccination by index date. Those who were

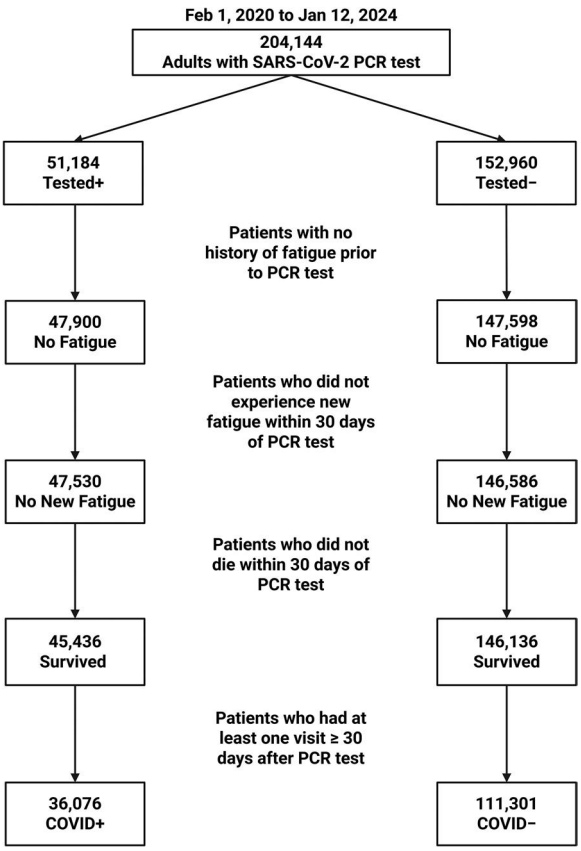


**Fig. 1** Patient selection flowchart. PCR, polymerase chain reaction

**Table 1** Characteristics of COVID+ and COVID− patients without history of fatigue

| | COVID+ (n = 36,076) | COVID−(n = 111,301) | *p*-value |
|---|---|---|---|
| Follow-up time (years), mean ± SD | 1.69 ± 0.99 | 1.81 ± 1.01 | **< 0.005** |
| Age at index date, mean ± SD | 52.44 ± 18.10 | 50.96 ± 17.01 | **< 0.005** |
| Female, n (%) | 22,094 (61.24%) | 68,027 (61.12%) | 0.68 |
| Race and ethnicity, n (%) | | | |
| Non-Hispanic White | 3667 (10.16%) | 11,811 (10.61%) | **0.020** |
| Black | 11,969 (33.18%) | 33,931 (30.49%) | **< 0.005** |
| Asian | 1624 (4.50%) | 4129 (3.71%) | **< 0.005** |
| Other race | 18,816 (52.16%) | 61,430 (55.19%) | **< 0.005** |
| Hispanic | 14,863 (41.20%) | 43,472 (39.06%) | **< 0.005** |
| Pre-existing comorbidities, n (%) | | | |
| Hypertension | 18,211 (50.48%) | 46,263 (41.57%) | **< 0.005** |
| Type-2 diabetes | 11,116 (30.81%) | 23,867 (21.44%) | **< 0.005** |
| COPD | 1512 (4.19%) | 1192 (1.07%) | **< 0.005** |
| Asthma | 7624 (21.13%) | 17,677 (15.88%) | **< 0.005** |
| Chronic kidney disease | 6218 (17.24%) | 9256 (8.32%) | **< 0.005** |
| Liver disease | 5950 (16.49%) | 12,992 (11.67%) | **< 0.005** |
| Cardiovascular disease | 7843 (21.74%) | 12,715 (11.42%) | **< 0.005** |
| Autoimmune disease | 2774 (7.69%) | 5787 (5.20%) | **< 0.005** |
| Depressive disorder | 5970 (16.55%) | 13,149 (11.81%) | **< 0.005** |
| Anxiety disorder | 6235 (17.28%) | 12,985 (11.67%) | **< 0.005** |
| Insurance, n (%) | | | |
| Medicaid | 12,729 (35.28%) | 43,750 (39.31%) | **< 0.005** |
| Medicare | 6782 (18.80%) | 17,519 (15.74%) | **< 0.005** |
| Private | 13,041 (36.15%) | 40,704 (36.57%) | 0.15 |
| Self pay | 3524 (9.77%) | 9328 (8.38%) | **< 0.005** |
| Income group, n (%) | | | |
| Lower 25 th percentile (< $38,768) | 7708 (21.37%) | 26,901 (24.17%) | **< 0.005** |
| 25 th–50 th percentile ($36,730–$56,327) | 8945 (24.79%) | 24,990 (22.45%) | **< 0.005** |
| 50 th–75 th percentile ($56,327–$63,048) | 10,497 (29.10%) | 30,665 (27.55%) | **< 0.005** |
| Top 25 th percentile (≥ $63,048) | 8926 (24.74%) | 28,745 (25.83%) | **< 0.005** |
| Hospitalized due to COVID-19, n (%) | 10,667 (29.57%) | – | – |
| Vaccinated for COVID-19 prior to index date, n (%) | 13,037 (36.14%) | 29,727 (26.71%) | **< 0.005** |
| New-onset CFS/ME, n (%) | 171 (0.47%) | 336 (0.30%) | **< 0.005** |

SD, standard deviation; ZIP, Zone Improvement Plan; COPD, chronic obstructive pulmonary disease; CFS/ME, chronic fatigue syndrome/myalgic encephalomyelitis

unvaccinated were more likely to experience hospitalized COVID-19 (8.06%) compared to those who were vaccinated (5.24%, $p < 0.05$).

Figure 2 shows the cumulative incidence of new-onset CFS/ME > 30 days post-index date among COVID+ hospitalized, COVID+ non-hospitalized, and COVID− patients. Over a median follow-up time of 21 months, the incidence of new-onset CFS/ME was 2.74 per 1000 patient-years among hospitalized COVID+ patients, 2.84 among non-hospitalized COVID+ patients, and 1.67 among COVID− patients.

The risk of new-onset CFS/ME among COVID+ hospitalized patients (multivariate Fine-Gray adjusted HR = 1.46 [1.07, 1.99]) and COVID+ non-hospitalized patients was higher (1.56 [1.25, 1.93]) than that of COVID− patients (Table 2). Those with vaccination for COVID-19 (1.52 [1.24, 1.85]), females (1.54 [1.27, 1.89]), those with liver disease (1.61 [1.29, 2.00]), autoimmune disease (1.57 [1.18, 2.08]), depressive disorder (1.28 [0.99, 1.66]), and anxiety disorder (1.35 [1.04, 1.74]) were at elevated risk of new-onset CFS/ME. Blacks (0.70 [0.52, 0.96]) and those of other races (0.70 [0.50, 0.98]) were at lower risk of CFS/ME compared to non-Hispanic Whites. Risk of incident CFS/ME was not associated with age, most comorbidities, insurance, and neighborhood median income.

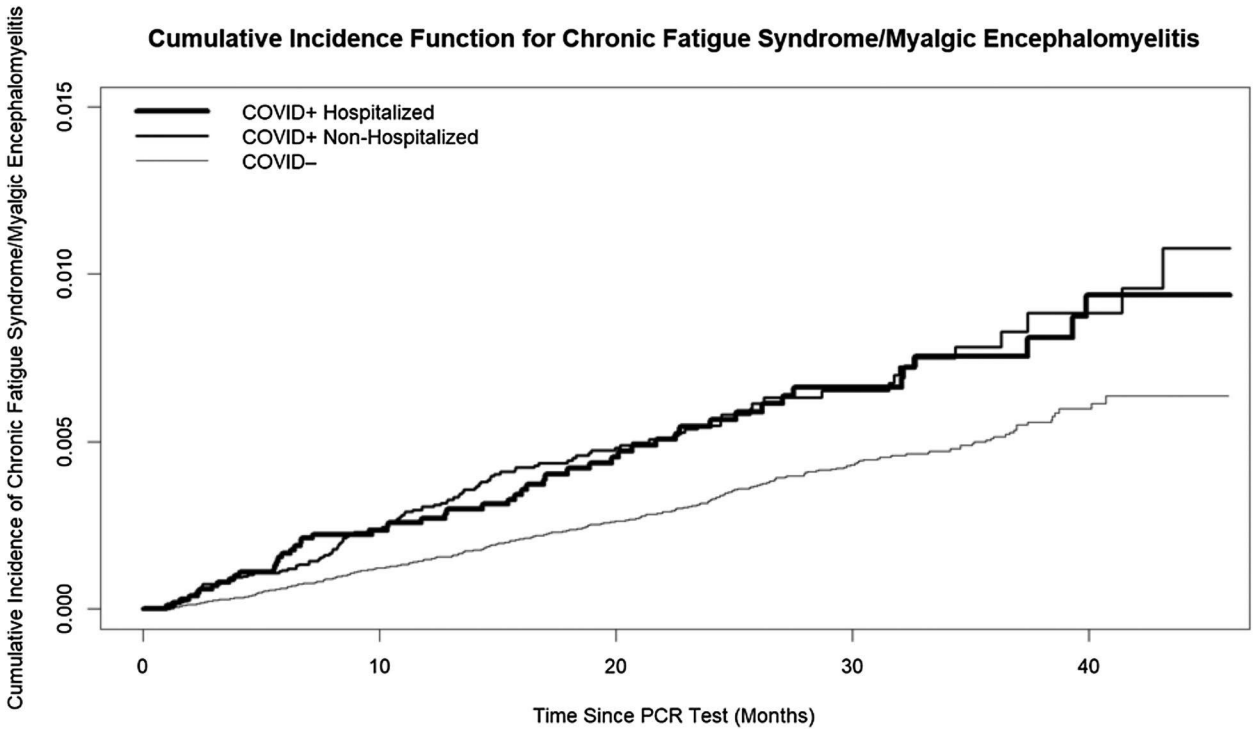


**Fig. 2** Cumulative incidence curve of new-onset chronic fatigue syndrome/myalgic encephalomyelitis > 30 days after polymerase chain reaction COVID-19 test

To investigate the potential association of incident CFS/ME with biomarkers, we evaluated CFS/ME risk with respect to biomarkers obtained during acute COVID-19 in hospitalized patients (see Table 3). We did not find any association between biomarkers at infection and subsequent long-term risk of incident CFS/ME.

### Sensitivity analyses

Our main analysis excluded patients who were lost to follow-up, died, or experienced CFS/ME or fatigue within 30 days of the index date, which might have introduced survivor biases. We thus performed sensitivity analysis in which these exclusions were not applied (Appendix 1). The results were largely consistent with this main analysis.

We also examined the association between SARS-CoV-2 re-infection and risk of incident CFS/ME and found no increased risk among those who were re-infected (Appendix 2).

To further investigate the association between COVID-19 vaccination and the outcome, we assessed the risk posed by being vaccinated during 2020 and 2021 versus being vaccinated during 2022 and onward (Supplementary Table 2). Those who were vaccinated prior to 2022 were at higher risk of new-onset CFS/ME, but not those were vaccinated after.

To assess if the association between COVID-19 and incident CFS/ME is more pronounced among specific sociodemographic subgroups, a subgroup analysis is presented in Supplementary Fig. 1. The only notable finding is that the association appeared more pronounced among Whites compared to other racial and ethnic groups.

## Discussion

Our findings revealed that, compared to COVID− patients, both hospitalized (adjusted HR = 1.46 [1.07, 1.99]) and non-hospitalized (adjusted HR = 1.56 [1.25, 1.93]) COVID-19 patients are at significantly higher risk of new-onset CFS/ME up to four years post-infection. Females, patients with liver, autoimmune disorders, and anxiety disorders were more likely to develop the outcome. Re-infection with SARS-CoV-2 was not associated with increased risk of incident CFS/ME. Vaccination for COVID-19 was associated with an increased risk of new-onset CFS/ME, but only among individuals who received the vaccine during the initial phase of the rollout. Levels of commonly acquired blood biomarkers at acute infection were not predictive of new-onset CFS/ME risk.

The adjusted risk for new-onset CFS/ME among COVID+ compared to COVID− individuals were lower than two prior studies, one reported an incidence rate

**Table 2** Multivariate Cox-proportional hazards model showing adjusted hazard ratios (HR) for developing new-onset chronic fatigue syndrome/myalgic encephalomyelitis > 30 days post-index date

| Covariate | Adjusted HR | *p*-value |
|---|---|---|
| SARS-CoV-2 | | |
| COVID+ Hospitalized vs COVID– | 1.46 [1.07, 1.99] | **0.016** |
| COVID+ Non-Hospitalized vs COVID– | 1.56 [1.25, 1.93] | **< 0.005** |
| Vaccinated for COVDI-19 | 1.52 [1.24, 1.85] | **< 0.005** |
| Age and sex | | |
| Age at Index Date (Years) | 1.00 [1.00, 1.01] | 0.49 |
| Female vs Male | 1.54 [1.27, 1.89] | **< 0.005** |
| Race and ethnicity | | |
| Black vs Non-Hispanic White | 0.70 [0.52, 0.96] | **0.025** |
| Asian vs Non-Hispanic White | 1.02 [0.65, 1.62] | 0.93 |
| Other Race vs Non-Hispanic White | 0.70 [0.50, 0.98] | **0.039** |
| Hispanic vs Non-Hispanic | 1.09 [0.84, 1.41] | 0.51 |
| Pre-existing comorbidities | | |
| Hypertension | 0.90 [0.72, 1.12] | 0.35 |
| Type-2 diabetes | 0.90 [0.72, 1.12] | 0.35 |
| COPD | 0.93 [0.54, 1.60] | 0.79 |
| Asthma | 1.10 [0.89, 1.37] | 0.38 |
| Chronic kidney disease | 1.02 [0.77, 1.36] | 0.89 |
| Liver disease | 1.61 [1.29, 2.00] | **< 0.005** |
| Cardiovascular disease | 1.19 [0.92, 1.55] | 0.18 |
| Autoimmune disease | 1.57 [1.18, 2.08] | **< 0.005** |
| Pre-existing psychiatric disorders | | |
| Depressive disorder | 1.28 [0.99, 1.66] | 0.056 |
| Anxiety disorder | 1.35 [1.04, 1.74] | **0.022** |
| Insurance | | |
| Medicaid vs. private insurance | 0.93 [0.75, 1.16] | 0.54 |
| Medicare vs. private insurance | 1.00 [0.76, 1.31] | 0.99 |
| Self Pay vs. private insurance | 0.80 [0.55, 1.15] | 0.23 |
| ZIP code income percentile | | |
| Lower 25 th percentile vs. Top 25 th percentile | 0.90 [0.68, 1.18] | 0.43 |
| 25–50 th percentile vs. Top 25 th percentile | 0.94 [0.73, 1.21] | 0.63 |
| 50–75 th percentile vs. Top 25 th percentile | 0.95 [0.75, 1.21] | 0.69 |

COPD, chronic obstructive pulmonary disease

**Table 3** Fine-Gray subdistribution hazards model showing adjusted hazard ratios (HR) for biomarkers at time of hospitalization and risk of chronic fatigue syndrome/myalgic encephalomyelitis > 30 days after post-index date

| Predictor | Adjusted HR [95% CI] | *p*-value |
|---|---|---|
| Aspartate aminotransferase ≥ 100 U/L | 1.06 [0.47, 2.41] | 0.88 |
| Creatinine ≥ 1.1 mg/dL | 0.76 [0.38, 1.53] | 0.45 |
| C-Reactive Protein ≥ 15 mg/dL | 1.69 [0.92, 3.10] | 0.092 |
| D-dimer ≥ 1.5 µg/mL | 1.31 [0.71, 2.41] | 0.39 |
| Lactate dehydrogenase ≥ 400 U/L | 1.01 [0.55, 1.85] | 0.98 |
| Ferritin ≥ 700 µg/L 1.34 | 0.75 [0.39, 1.44] | 0.38 |
| Hemoglobin ≤ 9.2 g/dL | 0.81 [0.42, 1.55] | 0.52 |
| Platelets ≤ $110 \times 10^9$ cells/L | 2.64 [0.62, 11.18] | 0.19 |
| Neutrophil/lymphocyte ratio ≥ 10 | 1.52 [0.88, 2.64] | 0.14 |
| Temperature ≥ 38.0 °C | 1.21 [0.70, 2.10] | 0.49 |

In addition to the biomarker, each model adjusted for age, sex, race, ethnicity, all pre-existing comorbidities and psychiatric conditions collected, insurance, and income quartile of Zone Improvement Plan code

ratio of 3.04 [2.66, 3.48] from Germany [14], and the other reported a HR of 4.32 [2.90, 6.43] from the United States [16]. The study from Germany did not exclude individuals with prior history of fatigue [14], whereas our definition of CFS/ME was limited to new-onset cases only. Follow-up time in the previous analyses was on average one year or less, whereas we had an average follow-up time of 21 months and up to four years post-infection. Additionally, our analysis was adjusted for additional potential confounders such as vaccination and history of psychiatric or autoimmune disorders and this cohort from the Bronx, a predominantly Black and Hispanic population in a largely underinsured urban center in the United States, differed from the German population [14] and most Caucasians in the United States [16]. Notably, our subgroup analysis demonstrated that the association between COVID-19 and incident CFS/ME was slightly more pronounced among Whites, consistent with the higher HR in the existing literature on majority Caucasian populations.

Our HRs were similar in patients hospitalized for COVID-19 and those not hospitalized for COVID-19 compared to COVID− controls, suggesting that even patients with mild COVID-19 were at similar risk to of developing CFS/ME as hospitalized patients. Post-COVID fatigue has previously reported to be similarly independent of COVID-19 hospitalization status [8, 9]. These prior studies of post-COVID CFS/ME did not stratify COVID-19 groups based on hospitalization status and were shorter in follow-up duration [14–16]. Interestingly, when comparing patients infected SARS-CoV-2 and other respiratory infections, Unger et al. found no difference in risk of CFS/ME onset [15], suggesting COVID-19 per se may not exert higher risk of CFS/ME compared to other respiratory infections. Nonetheless, given the sheer number of individuals infected with SARS-CoV-2, post-infection CFS/ME could result in a large number of people affected [36].

Moreover, CFS/ME may be more widespread than currently reported in the literature because of the considerable overlap between long-COVID and CFS/ME, which share hallmark symptoms such as fatigue, post-exertional malaise, cognitive dysfunction, and autonomic

dysregulation [37]. While CFS/ME has more established diagnostic criteria such as those from the IOM [35], long-COVID remains more heterogeneous and lacks standardized definitions across providers and institutions. The true burden of post-COVID fatigue may be underestimated and could pose a major global public health challenge, as suggested by recent analyses from the UK Biobank and other national registries [38–41]..

Females were at higher risk for new-onset CFS/ME, consistent with prior studies indicating a higher prevalence of CFS/ME in women, potentially due to sex-based immune and hormonal differences [42]. We also found that pre-existing conditions such as depressive disorder, anxiety disorder, and autoimmune disorders are associated with elevated CFS/ME post-index date, which are known independent predictors for CFS/ME [43–46]. Pre-existing anxiety and depressive disorders may influence both healthcare-seeking behavior and diagnostic labeling, potentially contributing to reverse causality [43, 47, 48]. However, our subgroup analyses suggest that the association between COVID-19 and incident CFS/ME is the same regardless of baseline psychiatric status. Further investigation using longitudinal mental health trajectories is warranted.

Our findings also showed that CFS/ME was associated with some comorbidities (autoimmune disorders and liver disease) but not others (HTN, T2DM, COPD, CKD, and CVD), whereas CFS/ME has been reported to be associated with many common comorbidities [49–54]. The current study was not designed to investigate the association between CFS/ME and comorbidities and the relatively low incidence of CFS/ME diagnosis could have contributed to this discrepancy. Nonetheless, these findings underscore the relative contribution of COVID-19 to CFS/ME risk relative to other predictors.

Black patients and those of other racial groups were observed to have a lower risk of new-onset CFS/ME compared to non-Hispanic Whites. One possible explanation is the existence of underlying biological or genetic differences in susceptibility to CFS/ME across racial and ethnic groups [55–57]. Alternatively, the observed lower incidence in non-White populations may reflect diagnostic disparities driven by systemic bias in healthcare settings [58]. Minority patients may experience underdiagnosis or misdiagnosis, either due to implicit bias among healthcare providers or differences in health-seeking behavior, cultural perceptions of fatigue, or trust in the medical system [59, 60]. Furthermore, structural barriers such as limited access to specialty care, insurance disparities, and geographic inequalities may disproportionately affect racial and ethnic minorities, reducing the likelihood of receiving a formal diagnosis [61, 62]. Future studies should investigate whether these differences reflect true variations in disease incidence or are artifacts of healthcare access and diagnostic processes [63].

Re-infection with SARS-CoV-2 did not contribute to increased risk of new-onset CFS/ME. This may have been due to the very low occurrence of re-infection and CFS/ME. Some prior studies have reported a higher risk of long-COVID in patients re-infected with SARS-CoV-2 [64–66], but none investigated risk of CFS/ME. Further studies are needed.

Vaccination for COVID-19 appeared to be associated with increased risk of new-onset CFS/ME, but this association was only present during the initial phase of the rollout and disappeared after 2021. It is possible that the patients prioritized to receive COVID-19 vaccines in the early phases of vaccine rollout were those who were more vulnerable to severe COVID-19 (i.e., individuals who were older, were immunologically compromised or those who work in healthcare with high risk of exposure) [67, 68]. Many of these individuals might have inherently been at higher risk of developing CFS/ME.

We found no association between CFS/ME risk and key blood biomarkers obtained during acute COVID-19. Some prior studies have reported an association between CFS/ME and lactate dehydrogenase, ferritin, platelets, and neutrophil/lymphocyte ratio [69–72]. This is consistent with the findings that patients hospitalized for COVID-19 and those not hospitalized for COVID-19 had similar risk for outcomes compared to COVID− controls.

#### Strengths and limitations

As CFS/ME incidence is relatively low, this study's large sample size is a strength. The follow-up period in this study was much longer than previous analyses, extending up to January 2024. We also analyzed outcomes with stratification by COVID-19 hospitalization, adjusted for pre-existing psychiatric and autoimmune disorders, investigated the contribution of COVID-19 vaccination and re-infection, and explored the role of biomarkers at acute infection and social determinants of health. Our cohort also consisted of a unique diverse population in the Bronx [56, 73].

This study has several limitations. We relied on the accuracy of the EHR, which in datasets of this size could result in inaccuracies or misdocumentations going unnoticed. To confirm accuracy, we have performed manual chart review of all variables on subsets of patients over the last few years.

We did not use antibody test and at-home COVID-19 tests because they were less reliable and/or not well-documented. Patients could be misclassified as COVID− if they were tested positive elsewhere and such misclassification likely underestimated any potential impact of the infection on the outcome. However,

cases of severe COVID-19 were unlikely to have been missed due to the need for inpatient admission, as Montefiore Health System is the predominant healthcare provider in the Bronx. Some COVID-19 vaccination records were performed outside our system and reconciled into our EHR from the New York State Immunization Information System. There could be potential errors if patients obtained COVID-19 vaccines elsewhere.

Reliance on EHR data also likely resulted in some underreporting of CFS/ME, as some patients may have experienced symptoms but did not seek medical attention or were not formally diagnosed. Diagnosis of CFS/ME in this study could reflect more severe and persistent cases, as milder forms may have gone underdiagnosed. Furthermore, the criteria for diagnosing CFS/ME vary across studies and clinical settings, leading to discrepancies in prevalence estimates between studies [74]. However, such factors affected both COVID+ and COVID− groups and are therefore unlikely to alter key conclusions.

To reduce misclassification, we excluded all patients with any diagnosis of "Fatigue," "Chronic fatigue syndrome," or "Postviral fatigue syndrome" recorded prior to or within 30 days of the index date. We did not analyze CFS/ME relapse or exacerbation of fatigue symptoms post-COVID because of the low number of patients with pre-existing CFS/ME at index date and difficulty in capturing exacerbation or relapse from the existing diagnostic codes.

As this cohort is diverse, consisting of large proportions of racial minorities in an underserved population, these findings may not be representative of less diverse populations. Future research should include multicenter studies to enhance generalizability, particularly in populations with different demographic and socioeconomic characteristics. The use of median household income based on ZIP code as a proxy for individual socioeconomic status (SES) is a limitation. Area-level SES measures may not accurately reflect individual-level income, education, or financial security. This ecological fallacy may dilute associations between SES and health outcomes. Although we included insurance status as a secondary SES indicator, variables such as education level, employment status, or income, which were not available in our dataset at the individual level, could have offered a more precise measure of SES.

While the proportional hazards assumption was not violated, the possibility that the risk of CFS/ME varies over time post-infection could not be ruled out. Future studies with flexible time-varying models or landmark analyses could help further elucidate temporal patterns of risk.

Although we corrected for all major confounders using multivariate Fine-Gray subdistribution hazards regression, unintentional patient selection biases and residual confounding are always possible in observational studies. Prospective cohort studies with standardized diagnostic assessments for CFS/ME are needed to validate these findings.

## Conclusions

Both hospitalized and non-hospitalized COVID-19 is associated with elevated risk of developing CFS/ME up to four years post-infection. Females, and individuals with autoimmune and anxiety disorders were more susceptible. Re-infection with SARS-CoV-2 was not associated with increased risk of incident CFS/ME. These findings highlight the critical need for clinical surveillance tools to identify patients at risk for post-viral fatigue syndromes.

## Supplementary Information

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Additional file 1

Additional file 2

Additional file 3

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**Author contributions**
Concept and design: RH, JM, TQD. Data collection/validation/analysis: RH, AL. Drafting of the manuscript: RH, BP, JM, TQD. Critical review of the manuscript for important intellectual content: All authors. Statistical analysis: RH. Supervision: TQD.

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**Availability of data and materials**
The datasets generated during and/or analyzed during the current study are not publicly available due to patient data privacy concerns but are available from the corresponding author on reasonable request. Code used to perform analysis in this study are available at https://github.com/hadidchi/CFS-ME-COVID-19.

## Declarations

**Ethics approval and consent to participate**
This retrospective cohort study was approved by the Einstein-Montefiore Institutional Review Board (#2021–13658) with an exemption for informed consent.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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## Publisher's Note