half of the originally randomized sample. However, almost half (43.8%) of the omitted participants simply did not receive the assessment needed to diagnose PGD, and another 38% were excluded because it was too soon (six months to one year since the loss) to receive a PGD diagnosis. Further, those assessed showed no differences in demographic or clinical characteristics from participants in the parent study.

We endorse continued study of effective treatments for PGD. In the meantime, we believe that clinicians will benefit from knowing that CGT, a strongly validated intervention[6-8], can be appropriately re-labeled as prolonged grief disorder therapy (PGDT).

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Supplementary information on the study is available at http://christinemauro.com/downloads/tables_17.02.2022.pdf.

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DOI:10.1002/wps.20991

Risk of new-onset psychiatric sequelae of COVID-19 in the early and late post-acute phase

Recent publications have documented that a proportion of COVID-19 patients develop psychiatric symptoms during or after acute infection[1]. We investigated this risk in the context of the National COVID Cohort Collaborative (N3C) – a centralized, harmonized, high-granularity electronic health record (EHR) repository[2] – using the largest retrospective cohort reported to date.

Two previous large-scale EHR studies examined psychiatric sequelae 90 and 180 days after COVID-19 diagnosis. A cohort of 44,779 individuals with COVID-19 was propensity score-matched to control cohorts with conditions such as influenza and other respiratory tract infections (RTI). In the 90 days following the initial presentation, the incidence proportion of new-onset psychiatric conditions was 5.8% in the COVID-19 group vs. 2.5% to 3.4% in the control groups[3]. A follow-up study also included individuals with a prior history of mental illness and similarly showed an increased risk of psychiatric conditions in the six months following initial presentation[4].

To validate these findings, we leveraged data from N3C, which at our cutoff date of October 20, 2021 had 1,834,913 COVID-19 positive patients and 5,006,352 comparable controls. Our data set was drawn from 51 distinct clinical organizations. We included patients in the COVID-19 cohort if they had a confirmed diagnosis of SARS-CoV-2 infection by polymerase chain reaction or antigen test after January 1, 2020. Controls were selected from patients with a diagnosis of a RTI other than COVID-19. We excluded from this analysis patients with a history of any mental illness prior to 21 days after COVID-19 diagnosis, as well as patients without a medical record extending back a year prior to COVID-19. There were 245,027 COVID-19 positive individuals available for propensity matching.

Each COVID-19 patient was matched with a control patient from the same institution whose age differed by no more than 5 years. Propensity score matching was done on 34 factors using a logistic regression model including main effect terms, resulting in 46,610 matched patient pairs. Multivariable Cox regression was performed to compare the incidence of new-onset mental illness for all psychiatric conditions, mood disorders and anxiety disorders for 21 to 365 days following initial presentation. We additionally considered dyspnea as a positive control.

We tested the Cox regression proportional hazard assumption for comparisons of COVID-19 patients and controls[5]. Schoenfeld residual analysis yielded a significant p-value and led us to reject the null hypothesis of a constant proportional hazard over the full time period of 21-365 days. We therefore separated the cohort into two time intervals (before and after 120 days) in which the proportional hazard assumption was not violated.

We identified a statistically significant difference in the hazard rate of new-onset psychiatric sequelae between COVID-19 and RTI in the early post-acute phase (from 21 to 120 days), but not in the late post-acute phase (from 121 to 365 days). The estimated incidence proportion (as modeled on the log-hazard scale over time) of a new-onset psychiatric diagnosis in the early post-acute phase for the COVID-19 group was 3.8% (95% CI: 3.6-4.0), significantly higher than the 3.0% (95% CI: 2.8-3.2) for the RTI group, with a hazard ratio (HR) of 1.3 (95% CI: 1.2-1.4). The HR for new-onset mental illness in the late post-acute phase was not significant in the COVID-19 compared to the RTI group (HR: 1.0; 95% CI: 0.97-1.1).

Similar findings were obtained for anxiety disorders, but not for mood disorders. The estimated incidence proportion of a new-onset anxiety disorder diagnosis was significantly increased for COVID-19 patients (2.0%; 95% CI: 1.8-2.1) compared to RTI patients (1.6%; 95% CI: 1.5-1.7) in the early post-acute phase (HR: 1.3; 95% CI: 1.1-1.4). However, the estimated incidence proportion

of a new-onset mood disorder diagnosis in the same period was not significantly increased for COVID-19 patients (1.2%; 95% CI: 1.1-1.3) in comparison to RTI patients (1.1%; 95% CI: 1.0-1.2).

New-onset anxiety and mood disorders were not significantly increased in the interval of 121-365 days following initial presentation (HR: 1.0, 95% CI: 0.91-1.1; and HR: 1.1, 95% CI: 0.97-1.2, respectively). In contrast, the HR for dyspnea, a known post-acute COVID-19 sequela[1], increased in both time periods (1.4, 95% CI: 1.2-1.5; and 1.2, 95% CI: 1.0-1.3, respectively).

We reasoned that patients might be followed more closely after COVID-19 as compared with other RTIs, and that a higher visit frequency might increase the probability of a mental illness being recorded in the EHR. To assess this, we repeated our analysis but added the frequency of visits 21 days or more after initial presentation as a factor to the Cox regression. The HR for any mental illness in the early post-acute phase was still significant ($p<0.0001$), but reduced to 1.2 (95% CI: 1.1-1.3).

Our results confirm the conclusion of the above-cited study[3] that patients are at significantly increased risk of psychiatric conditions after a COVID-19 diagnosis. However, the degree of increased risk documented in our study is substantially lower than previously found.

There are several potential reasons for the differences between our results and those of the above-mentioned study. The previous study included data from January 20, 2020 (first recorded COVID-19 case in the US) to August 1, 2020, while our study includes data through October 20, 2021. It is conceivable that perceptions of COVID-19 by patients have shifted or that clinical practice has changed in the intervening time. It is possible that improved treatment options available later in the pandemic have reduced the risk of psychiatric illness. Finally, COVID-19 vaccination may reduce rates of anxiety and depression and alleviate symptoms in persons with post-acute sequelae[6,7]. Thus, the increasing availability of vaccines might have reduced the rate of mental illness following COVID-19. The data available in N3C do not include comprehensive information about vaccination status, so we could not test this hypothesis.

Many cohort studies have documented a high prevalence of mental illness in individuals with long COVID. For instance, in our recent analysis, the prevalence of depression was 21.1% (median reported percentage in 25 studies) and that of anxiety was 22.2% (median over 24 studies)[1]. However, it is possible that the reported prevalence of these and other conditions was inflated by a sampling bias toward long COVID patients who joined support groups or chose to participate in cohort studies[8]. This, and the fact that inclusion criteria for long COVID studies vary, has made it difficult to characterize the natural history of psychiatric manifestations of long COVID. Our study did not focus specifically on long COVID, but instead investigated a cohort of patients following a diagnosis of acute COVID-19. It is difficult to know what proportion of these patients went on to develop long COVID; the recent introduction of ICD-10 codes for long COVID[9] may enable studies on this topic in the future.

In summary, we support previously published reports of an increased risk of new-onset psychiatric illness following acute COVID-19 infection. In contrast to the nearly doubled risk identified by the earlier study, we found the relative risk to be increased by only about 25% (3.8% vs. 3.0% following other RTI). We did not find a significant difference in risk in the late post-acute phase, suggesting that the increased risk of new-onset psychiatric illness is concentrated in the early post-acute phase.

Our results have important implications for understanding the natural history of psychiatric manifestations of COVID-19. If confirmed by independent studies, our findings suggest that health services should consider mental health screening efforts early in the post-COVID clinical course.

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This work was supported by the US National Center for Advancing Translational Sciences (grant no. U24 TR002306).

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DOI:10.1002/wps.20992

Evidence-informed is not enough: digital therapeutics also need to be evidence-based

We are witnessing exponential growth in a heavily capitalized digital health industry which promises to transform behavioral and mental health care[1,2]. Consequently, it is critical that there is no ambiguity about the evidence standards necessary for the safe and effective treatment of psychiatric disorders through digital approaches. In our opinion, these standards should be essentially the same as for any other form of treatment, or even arguably higher, given the intrinsic likelihood of placebo effects in software