

MENTAL HEALTH OUTCOMES IN COVID-19 SURVIVORS: ROLE OF CLINICAL PREDICTORS

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Summary

Background: The COVID-19 pandemic had a major worldwide impact resulting in more than 7 million deaths due to COVID-19. Mental health issues, including anxiety, depression, and post-traumatic stress disorder (PTSD) have been observed in COVID-19 survivors worldwide. This study aimed to investigate the psychological impact of COVID-19 survivors three months after discharge from hospital and examine associated risk factors.

Subjects and Methods: 186 COVID-19 patients were assessed at baseline and three months after hospital discharge using questionnaires for depression, anxiety, insomnia, and post-traumatic stress symptoms (PTSD). Medical data, including comorbidities, complications, and psychiatric history, were collected, and analyzed.

Results: The study found a prevalence of PTSD, anxiety, and depression symptoms of 14%, 14% and 10.8% respectively three months after hospital discharge. Female gender was a risk factor for PTSD (OR 4.54), depression (OR 3.55) and anxiety (OR 3.06). Patients with psychiatric history were at higher risk of depression (OR 8.46) and anxiety (OR 4.00) but not of PTSD. No association was found with other clinical variables including inflammation markers.

Discussion: The prevalence of psychopathological outcomes in COVID-19 survivors in this study was increased compared to the general population and in line with previous research. Female gender and psychiatric history increased the risk of anxiety and depression. The absence of correlation between inflammation or other clinical variables and psychopathological outcome measures is discussed in comparison with prior research. More research is needed to understand these associations and the long-term effects of COVID-19 on mental health.

Keywords: COVID-19, PTSD, depression, anxiety, inflammation

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INTRODUCTION

The Coronavirus disease-19 (COVID-19) pandemic quickly spread throughout the world, leading to a global pandemic. As the pandemic phase was concluded by the WHO, the global cumulative cases reached 765,222,932 (WHO 2023), resulting in nearly seven million fatalities (Wise 2023). During hospital admission, patients were placed in isolation, while visitation from family was restricted and direct contact with healthcare personnel was reduced to a minimum (Hugelius et al. 2021). Previous research has demonstrated mental health complications following COVID-19 infection (Shanbehzadeh et al. 2021, Bourmistrova et al. 2022). The study samples varied greatly, ranging from the general population (Xiong et al. 2020), psychiatric patients (Hao et al. 2020), healthcare workers (Pappa et al. 2020, Danet 2021) to patients admitted to the intensive care unit (Hatch et al. 2018, Vlaker et al. 2021, Claus et al. 2022). Studies with hospitalized patients found a high prevalence of anxiety (6.5% to 63%),

depression (4% to 31%) and PTSD (12% to 46%) (Guo et al. 2020, Einvik et al. 2021, Janiri et al. 2021, Méndez et al. 2021, Shanbehzadeh et al. 2021, Tarsitani et al. 2021, Moseholm et al. 2022, Rass et al. 2022, Spada et al. 2022, Stavem et al. 2022, Li et al. 2023). The variation in prevalence of psychopathology was explained by differences in instruments, as well as differences in coping strategies and cultural beliefs regarding the psychological effect of the COVID-19 pandemic (Shanbehzadeh et al. 2021).

Several risk factors for developing psychopathology after acute COVID-19 infection have been identified, such as female gender (Einvik et al. 2021, Gramaglia et al. 2022), previous history of psychiatric diagnosis (Janiri et al. 2021, Mazza et al. 2021a, Méndez et al. 2021, Tarsitani et al. 2021, Huarcaya-Victoria et al. 2023), obesity (Tarsitani et al. 2021, Gramaglia et al. 2022), severity of COVID-19 symptoms (Liu et al. 2020, Einvik et al. 2021), persistent COVID-19 symptoms (Tomasoni et al. 2021, Huarcaya-Victoria et al. 2023), and history of chronic disease (Li et al. 2023). However, not all studies

have found previous factors to be risk factors for developing mental health problems; for example, some studies did not find an association between female gender and psychopathology in COVID-19 survivors (Grover et al. 2021, Moseholm et al. 2022). Contrasting findings have been found regarding the correlation between young age and psychopathology (Shanbehzadeh et al. 2021). Other possible factors contributing to psychopathology in COVID-19 survivors are a history of chronic disease, drinking, smoking, lower education (Li et al. 2023), and loss of a family member due to COVID-19 (Liu et al. 2020, Huarcaya-Victoria et al. 2023).

One upcoming research area is the role of inflammation pathways as possible mechanism involved in psychopathology in COVID-19 survivors (Raony et al. 2020). Immune dysregulation has been proposed as an underlying pathophysiological mechanism in several psychiatric disorders (Gibney & Drexhage 2013). Research has shown that SARS-CoV-2 infection is associated with a release of pro-inflammatory cytokines involved in a cytokine storm (Conti et al. 2020, Coperchini et al. 2020), leading to the hypothesis that psychiatric problems in patients with COVID-19 are mediated through changes and interactions in the immune, endocrine, and nervous systems (Raony et al. 2020, Troyer et al. 2020). One study found that inflammation measured by systemic immune-inflammation index (SII) is associated with higher rates of depression in COVID-19 survivors and that baseline SII predicted severity of depression at three months follow-up. (Mazza et al. 2020, Mazza et al. 2021a) Another study used the neutrophil-to-lymphocyte ratio (NLR) to measure inflammation response and demonstrated a higher NLR in COVID-19 survivors with depression (Huarcaya-Victoria et al. 2023). Additionally, CRP levels have also been correlated with Patient Health Questionnaire-9 (PHQ-9) and Hamilton Rating Scale for Depression (HAM-D) scores in COVID-19 patients with depression (Guo et al. 2020, de Azevedo Cardoso et al. 2023).

Although numerous studies investigating the psychological impact of COVID-19 survivors have been performed, carrying out studies to assess the impact of COVID-19 in each affected country remains important due to the specific measures implemented per country to reduce the spread of COVID-19. Furthermore, the role of inflammation has mostly been studied in relation to depression, but not with other psychiatric disorders. The aim of this study was to measure the prevalence of psychopathology in COVID-19 survivors in Belgium and investigate the association between sociodemographic, clinical, and inflammatory variables with psychiatric disorders in COVID-19 survivors.

SUBJECTS AND METHODS

All patients hospitalized at the University Hospital Brussels (UZ Brussel, Belgium) with positive COVID-19 PCR-testing between March 2020 and May 2020 were invited for a multidisciplinary check-up three months after discharge. During this visit, participants received self-reported questionnaires to measure symptoms of depression and anxiety as assessed by the Hospital Anxiety and Depression Scale (HADS), insomnia as assessed by the Insomnia Severity Index (ISI), and PTSD symptoms as assessed by the PTSD Checklist for DSM-5 (PCL-5). For the PCL-5, a cut-off score of 33 indicated PTSD symptoms (Blevins et al. 2015); for the HADS, a score >10 indicated symptoms of anxiety and/or depression (Bjelland et al. 2002); for the ISI, a cut-off score of 15 indicated insomnia symptoms (Bastien et al. 2001). All patients participating in the multidisciplinary check-up three months after discharge and giving informed consent were included in the study. Only patients unable to fill in self-reported questionnaires were excluded from the study.

Medical data were derived from medical records and included pre-existing physical comorbidities, history of psychiatric disorders, medication use, the length of in-hospital and Intensive Care Unit (ICU) stay, the type of respiratory support, and inflammatory markers (leukocyte/neutrophil/lymphocyte/platelet count, C-reactive protein, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index).

Statistical analyses were performed with SPSS 29.0.1 (IBM Statistics). Descriptive data were presented as frequencies (%) or as mean \pm standard deviation (SD). For every diagnosis, PTSD, anxiety and depression, the group with the tentative diagnosis was compared with the group without the tentative diagnosis (e.g. PTSD versus no PTSD). Tentative diagnosis was made based on cut-off score of HADS, ISI and PCL-5. Univariate analyses (Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables) were used to test for differences in demographic, social, clinical, and psychometric variables between different groups. Factors significantly associated with PTSD, anxiety or depression were subjected to binary logistic regression analysis. A value of $p < 0.05$ was considered as statistically significant. Bonferroni correction was applied to regression analysis, resulting in a significance threshold of $p < 0.017$.

The study was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the Ethical Board of the University Hospital Brussels (registration number B1432020000291). Written informed consent was received from all participants.

RESULTS

A total of 186 participants were included in the study, 71 (48.2%) were female. The mean age was 54.61 years (SD 12.89). The demographic and clinical characteristics of the study population are described in *Table 1*. 65% of participants had co-morbidities, the most common co-morbidities were arterial hypertension (35.5%) and diabetes mellitus (18.3%). A total of 32 (17.2%) patients suffered from somatic complications during hospital stay. 14 (7.5%) patients had a history of psychiatric disorder, predominantly mood disorders (5.9%), while 12.4% of patient were currently using psychotropic medication.

Table 1 Characteristics of the study population (n=186)

Characteristic	N (%)
Gender, male	115 (61,8%)
Age, years (SD)	54.6 (12.9)
Comorbidities	121 (65,1%)
• Arterial hypertension	66 (35,5%)
• Diabetes mellitus	34 (18,3%)
• Chronic lung disease	17 (9,1%)
• Cardiovascular disease	11 (5,9%)
• Chronic kidney disease	10 (5,4%)
• Active oncological disease	1 (0,5%)
Somatic complications	32 (17,2%)
• Bacterial superinfection or hospital acquired pneumonia	23 (12,4%)
• Neuropsychiatric (delirium or encephalopathy)	9 (4,8%)
History of psychiatric disorder	14 (7,5%)
• Mood disorders	11 (5,9%)
• Substance use disorder	2 (1,1%)
• Intellectual disability	1 (0,5%)
Current use of psychotropic medication	23 (12,4%)
• Antidepressants	11 (5,9%)
• Benzodiazepines	11 (5,9%)
• Antipsychotics	2 (1,1%)
Type of respiratory support	
• Oxygen need	153 (82,3%)
• Non-invasive ventilation	28 (15,1%)
• Intubation	11 (5,9%)
ICU stay	37 (19,9%)
Length of hospital stay (SD)	9,1 days (8,9)

Measures

26 (14.0%) patients met the criteria of probable diagnosis of PTSD (PCL-5 > 32). On the Hospital Anxiety and Depression Scale, 20 (10.8%) and 26 (14.0%) patients met the cut-off for the Depression and Anxiety subscale respectively. 14 (7.5%) patients met criteria for all three disorders. 40 (21,1%) patients experienced complaints of insomnia.

Table 2 describes a selection of studied variables according to the relevant study population.

Female gender appears to be significantly associated with PTSD ($p < 0.001$), depression ($p = 0.009$) and anxiety ($p = 0.008$). Furthermore, there is a significant relationship between use of psychotropic medication and depression ($p = 0.005$) and anxiety ($p = 0.024$), but not with PTSD. History of psychiatric condition also appears to be associated with depression ($p = 0.001$) and anxiety ($p = 0.03$). Amongst ICU survivors, 16.2% (6 out of 37) met criteria for PTSD, with a mean PCL-5 score of 18.2 (± 12.5). 13.4% of non-ICU survivors (20 out of 149) met criteria for PTSD, with a mean PCL-5 score of 15.7 (± 15.5).

No significant associations were found for age, length of in-hospital or ICU stay, pre-existing comorbidities, complications. Univariate analyses conducted for inflammatory markers (leukocyte count, neutrophil count, lymphocyte count, platelet count, C-reactive protein, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index) and types of respiratory support (oxygen need, non-invasive ventilation, intubation) did not show any significant associations.

Risk factors for mental health outcomes

Binary logistic regression analysis was conducted for the following variables: gender, use of psychotropic medication and history of psychiatric condition.

• Gender

Regression analysis showed an association between female gender and tentative PTSD, depression, and anxiety symptoms. Patients with PTSD symptoms were 4.54 times more likely to be female (OR 4.54, 95% CI 1.86-11.12, $p < 0.001$), 3.55 times in case of depression symptoms (OR 3.55, 95% CI 1.31-9.15, $p = 0.012$) and 3.06 times in case of anxiety symptoms (OR 3.06, 95% CI 1.30-7.19, $p = 0.010$).

• Use of psychotropic medication

Patients with depression symptoms were 8.46 times more likely to use of psychotropic medication (OR 8.46, 95% CI 2.57-27.858, $p < 0.001$), and 3.32 times more likely

Table 2 variables, described as part of the total population, and in patients with PTSD, depression or anxiety

Variable	Total population	PTSD	Depression	Anxiety
	(n=186)	(n=26)	(n=20)	(n=26)
	n° (%)	n° (p-value ^a)	n° (p-value ^b)	n° (p-value ^c)
Gender, female	71 (38,2%)	18 (<0,001)	13 (0,009)	16 (0,008)
Age, median (IQR), years	58 (46-66)	53 (43-62) p=0,508	58.5 (45-64) p=0,720	54.5 (43-64) p=0,254
Length of stay, median (IQR), days	6 (4-11)	6.5 (4-13) p=0,136	5.5 (3.5-10) p=0,224	6.5 (4-14) p=0,136
Any comorbidity, n°	121 (65,1%)	18 (0,674)	15 (0,348)	17 (0,981)
ICU stay, n°	37 (19,9%)	6 (0,661)	4 (1,000)	7 (0,333)
Use of psychotropic medication, n°	23 (12,4%)	6 (0,102)	7 (0,005)	7 (0,024)
Psychiatric history, n°	14 (7,5%)	4 (0,112)	6 (0,001)	5 (0,030)

^a Comparison between patients with PTSD diagnosis and patients without PTSD diagnosis

^b Comparison between patients with depression diagnosis and patients without depression diagnosis

^c Comparison between patients with anxiety diagnosis and patients without anxiety diagnosis

in case of anxiety symptoms (OR 3.32, 95% CI 1.21-9.09, $p = 0.02$). The association with anxiety symptoms was not statistically significant after Bonferroni correction. No significant association could be found with PTSD symptoms (OR 2.524, 95% CI 0.890-7.152, $p = 0.082$).

History of psychiatric condition

Similarly, patients with depression symptoms were 8.46 times more likely to have a history of psychiatric condition (OR 8.46, 95% CI 2.57-27.858, $p < 0.001$) and 4 times more likely in case of anxiety symptoms (OR 4.00, 95% CI 1.22-13.06, $p = 0.022$), although not statistically significant after Bonferroni correction in case of anxiety symptoms. No significant relationship between PTSD symptoms and history of psychiatric condition was found (OR 2.727, 95% CI 0.787-9.452, $p = 0.114$).

DISCUSSION

In our study, the prevalence of PTSD, anxiety, and depression symptoms in COVID-19 survivors at three months after hospitalization was 14%, 14% and 10.8% respectively. Prevalences in this study are in line with most studies and systematic reviews reporting these numbers at three months after hospital discharge (Einvik et al. 2021, Tarsitani et al. 2021, Bourmistrova et al. 2022, Stavem et al. 2022). However, some studies have also reported higher numbers (Shanbehzadeh et al. 2021), for example a study in the Netherlands reported similar PTSD prevalence but higher prevalence of anxiety (20%) and depression (24%) at three months (Vlake et al. 2021).

In this case a lower HADS cut-off score for anxiety and depression was used. Other possible explanations for differences in prevalence of mental health symptoms between studies are the use of different outcome measures, study population and geographical location (Shanbehzadeh et al. 2021).

Female gender was associated with PTSD, anxiety, and depression, corresponding to existing research establishing female gender as risk factor for psychopathology in COVID-19 survivors (Janiri et al. 2021, Mazza et al. 2021a, Tarsitani et al. 2021, Stavem et al. 2022). Among COVID-19 survivors, patients with psychiatric history (through history of psychiatric diagnosis and use of psychotropic medication) are at higher risk for anxiety and depression, but not for PTSD at three months after hospital discharge. After Bonferroni correction, the association with anxiety was under the significance threshold. While not seen in the present study, previous research has found psychiatric history to be a risk factor for PTSD (Janiri et al. 2021, Mazza et al. 2021a, Tarsitani et al. 2021). We hypothesized that the prevalence of PTSD may be underestimated in the present study, as PTSD does not always develop within the first three months of the traumatic event, and research in PTSD patients has shown up to 25% of patients have delayed-onset PTSD after six months (Smid et al. 2009). This was seen in ICU survivors showing significant increase in PTSD prevalence over 12 months (Rigny et al. 2019). Although no significance was found, the percentage of patients with PTSD having stayed in the ICU was higher than those who didn't. This is not the first study that did not find a clear association between ICU stay and PTSD (Vlake

et al. 2021). The lack of association between psychiatric history and PTSD in our sample might also be explained by the role of ICU admission as a traumatic event causing PTSD (Horn et al. 2020).

There is few research on the course of PTSD symptoms in COVID-19 survivors after hospitalization, and the few existing studies have inconclusive results. Some studies showed a decrease in PTSD symptoms over time (Mazza et al. 2021b, Vlaker et al. 2021), whereas other studies showed no difference in PTSD symptoms over time (Moseholm et al. 2022) or even an increase in PCL-5 scores by 20% from three to six months after hospital discharge (Tu et al. 2021). These conflicting results show the need for uniformity in measures for PTSD in research studies and the need for larger cohort studies in COVID-19 survivors, as point-prevalence for PTSD might not adequately reflect the number of patients suffering from PTSD.

In contrast to earlier research on the association between inflammatory markers and psychopathology in COVID survivors (Guo et al. 2020, Mazza et al. 2020, Mazza et al. 2021a, Huarcaya-Victoria et al. 2023), we did not find an association between baseline inflammatory markers during hospitalization and psychopathological consequences at three months follow-up. Although aforementioned studies hypothesized the role of systemic and persistent inflammation in the pathogenesis of psychiatric disorders after COVID-19 infection, these studies are rare and based on cross-sectional studies with a low number of subjects. Consistent with our study, a Spanish study could also not find an association between systemic inflammation and development of psychiatric symptoms (Méndez et al. 2021). In Mazza's study only baseline systemic immune-inflammation index, in contrast to other baseline inflammatory markers, was associated with anxiety and depression at one-month follow-up (Mazza et al. 2020). The role of the immune system in psychopathology is still being researched (Blume et al. 2011), and the inconclusive findings of inflammatory markers in psychiatric disorders in COVID-19 survivors highlights the need for further research studying the role of inflammation in psychopathology after COVID-19 infection.

Additionally, this study found no significant associations between mental health problems and physical comorbidities, or length of hospital stay. This is in line with earlier research on this topic (Wu et al. 2020, De Lorenzo et al. 2020, Tomasoni et al. 2021), although some studies suggest that longer length of hospital stay might be associated with mental health conditions such as anxiety, depression, schizophrenia, and bipolar disorder in hospitalized COVID-19 patients (Koyoma et al. 2022)

Limitations in this study include response bias as patients were invited to follow-up consultations after hospitalization without obligation. Selection bias could also be present as some patients who were not able to present at follow-up consultation (e.g. with less physical mobility) have been excluded. The execution of this study in a single center limits the generalizability of the findings. Another limitation is the use of assessment methods through self-reporting questionnaires, without formal diagnosis by a medical doctor. Consequently, other risk factors for psychiatric disorders not available in clinical records and rating scales were not studied. Furthermore, the follow-up of patients was limited to three months. Longer cohort studies are needed to study the long-term neuropsychiatric sequelae of COVID-19 survivors.

CONCLUSION

Psychopathological outcomes in COVID-19 survivors are more prevalent than in the general population. Female patients and patients with a psychiatric history have an increased risk for developing anxiety and depression after COVID-19, while an association with PTSD was not found in this study. More studies are necessary to identify risk factors for developing psychiatric disorders in a pandemic. This will increase chances to identify and treat patients at risk and therefore reducing burden of disease during and after a pandemic.

Ethical Considerations: Does this study include human subjects? NO

Conflict of interest: No conflict of interest

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