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Prevalence of post-traumatic stress disorder among survivors of severe COVID-19 infections: A systematic review and meta-analysis

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ABSTRACT

Background: Post-traumatic stress disorder (PTSD) develops after a person has experienced a traumatic event which can be highly accounted for amidst the ongoing COVID-19 pandemic. This study aims to estimate the prevalence of PTSD among the severe cases of COVID-19.

Methods: We included the observational studies done to estimate the burden of PTSD among severe COVID-19 patients. Data was extracted manually using structured data extraction form and analyzed in STATA version 14.2. A random-effects model was applied, and the final pooled data was reported as proportion with a 95% confidence interval. Multivariable meta-regression analysis was carried out, and a forest plot was utilized to represent the study-specific and pooled estimates for overall and subgroup analysis.

Results: We included 13 articles with 1,093 participants in our analysis. The pooled prevalence was estimated to be 16% (95%CI: 9% to 23%). We found a substantial heterogeneity between the studies that reported the outcome ($I^2=87.9\%$, $p<0.001$). In subgroup analysis, the difference in prevalence estimate between the regions was statistically significant.

Limitations: We found significant between-study variability for the outcome. In addition, our review was found to have substantial publication bias. We also found that the lower quality of the majority of the studies being included in our review.

Interpretation: Our study states that the risk of PTSD is higher following severe COVID-19 infection. Understanding this burden will help us in diverting the resources and adapting necessary interventions to control the situation.

1. Introduction

A coronavirus is a group of viruses primarily affecting the respiratory tract. Most viruses that cause human infections result in mild to moderate respiratory tract infections (Zheng, 2020). COVID-19 was first notified to the WHO by the Chinese government in the second half of December 2019. Following the investigation, a novel coronavirus, SARS-CoV-2, was found to be the causative factor. It later spread across the world (World Health Organization 2021).

This pandemic has also faced various strict public health measures to limit transmission. Some of these are regular use of outdoor masks, following physical distancing, adapting handwashing techniques, and getting vaccinated against the disease (Ministry of Health and Family Welfare [Internet]. Government of India 2021; World Health Organization. Coronavirus Disease (COVID-19) Pandemic [Internet] 2021). Strict lockdown measures were implemented in various countries globally, and most of the population was advised to adapt to work from home (World Health Organization 2021). Many people have also lost their jobs in this process. People who got infected were isolated from others while quarantining their contacts to avoid disease transmission. This has also led to increased stigma in society. All these factors have increased psychological morbidities in the general population (Krishnamoorthy et al., 2020).

As per American Psychiatric Association, Posttraumatic stress...
disorder is a psychiatric disorder that may occur in people who have experienced or witnessed a traumatic event. Events such as a natural disaster, a severe accident, a terrorist act, war/combat, or rape or who have been threatened with death, sexual violence, or severe injury are factors associated with PTSD (Felix Torres 2020). Many people exposed to a traumatic event experience symptoms of PTSD in the days following the event (Felix Torres 2020).

Due to the disease, social stigma, prolonged hospital stays, economic loss, etc., some COVID-19 patients developed severe infections and required ICU admission during the treatment. These ICU admissions can be traumatic experiences for the patients. As a result, some might also develop the condition Post Traumatic Stress Disorder (PTSD). Hence, we conducted this systematic review and meta-analysis to estimate the prevalence of PTSD among the severe cases of COVID-19.

2. Methods

2.1. Design and registration

We conducted this systematic review and meta-analysis by including the observational studies (cross-sectional, prospective, or retrospective studies) on the prevalence of PTSD among severe COVID-19 patients. The review was registered under the "International prospective register of systematic review (PROSPERO)" (PROSPERO ID: CRD42021256948). The latest 2020 checklist of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) was used for reporting our review (Title TT 2020).

2.2. Eligibility criteria

2.2.1. Study design

We included observational studies (cross-sectional/prospective/retrospective studies) reporting the prevalence estimate of PTSD among severe COVID-19 patients. There wasn't any restriction in age/study setting/country/region/any specific comorbidities. Studies were included without considering the mode of interview (online/offline). Abstracts, preprints, full-text articles met the inclusion criteria, while case reports, case series, and gray literature (unpublished data/articles) were excluded.

2.2.2. Study participants

We included studies conducted among the survivors following severe COVID-19 infection. We used the following criteria to identify the studies conducted on severe COVID-19: patients with the respiratory rate (RR) > 30 breaths/min (or) oxygen saturation (SpO2) < 93% (or) oxygenation index (PaO2/FiO2) ≤ 300 mmHg (or) requirement of ICU (or) mechanical ventilation (Cascella et al., 2021). Studies must have followed up these patients after four weeks of COVID-19 diagnosis to be eligible for inclusion (Post-COVID Conditions [Internet]. Centre for Disease Control 2021). Studies conducted among patients with only mild to moderate COVID-19 infection were excluded from the systematic review.

2.2.3. Outcome measures

We included the studies reporting the prevalence of PTSD irrespective of the scale used for measurement.

2.3. Search strategy

An extensive electronic database search was done in the following search engines: MEDLINE, EMBASE, Google Scholar, and ScienceDirect. Search terms were built using MESH terms in MEDLINE and EMTREE terms in EMBASE. The terms used to construct the search strategy were ‘Stress Disorders, Post-Traumatic’ ‘Posttraumatic stress Disorder’ ‘Post Traumatic Stress Syndrome’ ‘COVID-19’ ‘hospitalization’ ‘severe COVID-19’ ‘ICU admission.’ Supplementary Appendix 1 shows the detailed search strategy used to extract the studies for the review. The search was restricted from Jan 2020 to May 2021, and only English-language articles were included.

2.4. Study selection

This process has involved three stages:

2.4.1. Primary screening

Two independent investigators (RN & YK) have performed the preliminary screening of title, abstract, and keywords during the literature search. Full-text articles were retrieved for the studies relevant to the eligibility criteria.

2.4.2. Secondary screening

The two investigators (RN & YK) again screened the full text of these retrieved studies and assessed it against the review’s eligibility criteria. Studies satisfying the eligibility criteria in terms of design, participants, and outcome were considered eligible to be included in our review.

2.4.3. Finalizing the study selection

Disagreements during the primary and secondary screening process between the investigators were resolved by another investigator (VB). The final consensus on study inclusion was also reached with the help of the investigator (VB). "PRISMA flowchart" was utilized to represent the screening and selection process (Fig. 1).

2.5. Data extraction and management

Data was extracted manually by the primary investigator (RN). A structured data extraction form was developed and pilot-tested during the protocol stage itself. It consisted of the following information: general information (author, study title, publication year, country), details related to methods section (study design, study setting, study participants, sample size, diagnostic tool, and interview mode), and outcome (number of participants with PTSD).

The data was transferred by the primary investigator (RN) into the software STATA version 14.2. The data entered was double-checked by the second investigator (YK) to ensure correct entry by comparing the data presented in the review and the primary articles.

2.6. Risk of bias assessment

All the included studies were assessed by two authors (RN and YK) independently to look for the quality using the "Newcastle-Ottawa (NO) scale utilized for cross-sectional studies." (Shea et al., 2012) It was assessed using two criteria (selection and outcome). Under selection criteria following domains were employed to evaluate the risk of bias: sample representativeness, sample size justification, rate of non-respondents and their characteristics, and use of validated measurement tool. To assess the risk of bias under outcome criteria, assessment of outcome through independent blind assessment or record linkage was used. Every outcome was rated as having high risk (1 point) or low risk (0 points) depending upon the quality of evidence and availability of information. An increased risk of bias was considered for studies with a score of ≥3 points.

2.7. Statistical analysis

Meta-analysis was performed using the STATA 14.2 (StataCorp, College Station, TX, USA) software. Standard error was calculated using the reported number of outcomes and the sample size for each study. The "Metaprop" function in STATA was used for performing the pooled analysis (Nyaga and Arbyn, 2014) To minimize the effect of extremely small or large prevalence on the overall estimate, "Freeman Tukey double arcsine transformation" was done to stabilize the variance.
Nyaga and Arbyn, 2014) Random-effects model was applied to account for heterogeneity between the included studies. The final pooled data was reported as proportion with a 95% confidence interval (CI).

Following methods were used to assess the evidence of heterogeneity: Chi-square test to identify the heterogeneity and \( I^2 \) statistic to quantify the heterogeneity. \( I^2 \) value < 25% considered to be mild, 25–75% moderate, and >75% was considered substantial heterogeneity (Higgins et al., 2021). In our analysis, since all the included outcomes had significant heterogeneity, additional subgroup analysis, and meta-regression were performed. The potential covariates for performing meta-regression were geographical region, study design, measurement tool, mode of interview, mean age, sample size, and quality of the study. Multivariable meta-regression analysis included the study-level factors with p-value less than 0.20 in the univariable model.

Forest plot was used for graphical representation of the study-specific and pooled estimates for overall and subgroup analysis. Publication bias was checked and graphically represented by funnel plot and Doi plot. Asymmetry of the plot was tested using Egger’s test and LFK index. P-value less than 0.10 in Egger’s test is indicative of a possible publication bias. Based on the LFK index value, the possibility of publication bias is classified as no asymmetry (value within ±1), minor asymmetry (value out of ±1 but within ±2), and significant asymmetry (value ≥ ±2) (Egger et al., 1997).

3. Results

3.1. Study selection

During the primary screening, a total of 1597 records were obtained, in which 50 articles relevant to our review were extracted for full-text search. During the secondary screening, we went through the full-text of these articles and found 13 articles with 1093 participants satisfying our inclusion criteria and included as a part of the analysis (Fig. 1) (Janiri et al., 2021; Morin et al., 2021; Naidu et al., 2021; Rass et al.,

![Fig. 1. PRISMA Flowchart.](image-url)
3.2. Characteristics of the studies included

Most of the studies were carried out in the European region (3 studies in Italy, two each in Netherlands and United Kingdom, each in France and Turkey). The remaining studies were carried out in China, Iran, and the United States of America. More than 50% of the studies (7 out of 13) conducted amidst the COVID-19 pandemic were cross-sectional, while the rest were prospective studies (cohort studies). The studies were undertaken after the patient got discharged from the hospital following admission for severe COVID-19. The follow-up or data collection time interval following discharge has ranged from 4 weeks to 16 weeks. The mean age of the participants ranges from 39.7 years to 60.9 years. The majority of the studies (8 out of 13) used PCL-5 (PTSD Checklist for DSM-5) to diagnose PTSD. In contrast, the rest of the studies used IES-R (Impact of Event Scale-Revised), CAPS-5 (Clinician-Administered PTSD Scale for DSM-5), PTSS-14 (Post Traumatic Stress Syndrome), and TSQ (Trauma Screening Questionnaire) to diagnose PTSD among the severe COVID-19 patients. The interview mode was a telephonic interview (5 out of 13 studies), an offline interview by following up the patient in a hospital setting (5 out of 13 studies), and online applications in the rest of the studies. (Table 1).

3.3. Risk of bias assessment

All the studies had a high risk of bias concerning the representativeness of the sample and outcome assessment given the nature of data collection and mode of interview. In contrast, all the studies had a low risk of bias concerning using the validated tool. Only four studies reported a non-response rate and its characteristics, while the sample size justification is provided in most studies (8 out of 13). Finally, the review included 13 studies, out of which nine were of lower quality as per the NO scale (Table 2).

3.4. Prevalence of PTSD among severe COVID-19 patients

In total, 13 studies were included to find out the prevalence of PTSD.

Table 1

| S. No. | Author and Year | Country       | Study design    | Sample Size | PTSD among SCP | Follow up duration | Assessment tool | Severity Criteria | Mode of interview | Mean Age (in years) |
|--------|-----------------|---------------|-----------------|-------------|----------------|--------------------|----------------|-------------------|-------------------|---------------------|
| 1      | Beck 2021       | Switzerland   | Cohort study    | Overall: 126 SCP: 18 | 2 | 4 weeks | IES-R | ICU admissions | Telephone | 58.2               |
| 2      | Graff 2020      | Netherlands   | Cross-sectional study | Overall: 81 SCP: 34 | 2 | 6 weeks | PCL-5 | ICU admissions | Offline | 60.8               |
| 3      | Janiri 2021     | Italy         | Cross-sectional study | Overall: 381 SCP: 65 | 23 | 4 weeks | CAPS-5 | ICU admissions | Offline | 55.26              |
| 4      | Khademi 2021    | Iran          | Cross-sectional study | Overall: 602 SCP: 418 SCP: 35 | 16 | 4 weeks | PCL-5 | Hospitalization with severe illness | Telephone | 53.2               |
| 5      | Liu 2020        | China         | Cross-sectional study | Overall: 675 SCP: 35 | 5 | 4 weeks | PCL-5 | ICU admissions | Online | 53.58              |
| 6      | Martillo 2021   | USA           | Cohort study    | Overall: 45 SCP: 760 SCP: 177 | 8 | 4 weeks | PCL-5 | ICU admissions | Telephone | 53.9               |
| 7      | Mazza 2020      | Italy         | Cohort study    | Overall: 402 SCP: 220 SCP: 117 SCP: 94 SCP: 760 SCP: 90 SCP: 36 SCP: 17 | 40 | 4 weeks | PCL-5 | Hospitalization with severe illness | Offline | 57.8               |
| 8      | Morin 2021      | France        | Cohort study    | Overall: 117 SCP: 94 SCP: 760 SCP: 90 SCP: 36 SCP: 17 | 7 | 16 weeks | PCL-5 | ICU admissions | Offline | 60.9               |
| 9      | Naidu 2021      | United Kingdom| Cross-sectional study | Overall: 760 SCP: 90 SCP: 36 SCP: 17 | 12 | 8 weeks | TSQ | ICU admissions | Online | 57                 |
| 10     | Parker 2021     | United Kingdom| Cross-sectional study | Overall: 36 SCP: 34 SCP: 284 SCP: 34 SCP: 135 SCP: 31 SCP: 26 | 8 | 12 weeks | PTSS-14 | ICU admissions | Telephone | 52.5               |
| 11     | Poyraz 2021     | Turkey        | Cross-sectional study | Overall: 284 SCP: 34 SCP: 135 SCP: 31 SCP: 26 | 14 | 4 weeks | IES-R | Hospitalization with severe illness | Online | 39.7               |
| 12     | Rass 2021       | Austria       | Cohort study    | Overall: 135 SCP: 31 SCP: 26 | 4 | 12 weeks | PCL-5 | ICU admissions | Offline | 56                 |
| 13     | Tarstitani 2021 | Italy         | Cohort study    | Overall: 115 SCP: 26 | 2 | 12 weeks | PCL-5 | ICU admissions | Telephone | 57                 |

ICU: Intensive Care Unit.
PTSD: Post Traumatic Stress Disorder.
IES-R: Impact of Event Scale-Revised.
PCL-5: PTSD Checklist for DSM-5.
CAPS-5: Clinician-Administered PTSD Scale for DSM-5.
TSQ: Trauma Screening Questionnaire- PTSD.
PTSS-14: Post Traumatic Stress syndrome-14.
USA: United States of America.
SCP: Severe COVID-19 Patients.
among severe COVID-19 patients. The pooled prevalence was estimated to be 16% (95%CI: 9% to 23%) (Fig. 2). We found substantial heterogeneity between the studies that reported the outcome ($I^2=87.9\%$, $p<0.001$). Subgroup analysis was carried out in terms of geographical region, study design, follow-up duration, measurement tool, and interview mode (Table 3).

### 3.4.1. Additional subgroup analysis

Subgroup analysis based on the geographical region could not reveal much information. Most of the studies were carried out in the European region, and only one study was from the American, Western Pacific, and Eastern Mediterranean regions. However, the difference in prevalence estimate between the areas was statistically significant ($p<0.001$) (Supplementary Figure 1). Analysis based on study design revealed a higher pooled prevalence amongst the cross-sectional studies (19%) compared to cohort studies (13%). However, the difference was not statistically significant (Supplementary Figure 2).

Based on data collection time point, the analysis showed that the prevalence of PTSD was similar irrespective of the time point or follow-up period (4 weeks period = 18%; 12 weeks period = 20%) (Supplementary Figure 3). Based on interview mode, the Subgroup analysis showed the highest pooled prevalence of PTSD (21%) for the studies conducted online. In comparison, the studies conducted through the offline interview (15%) and telephonic interview (14%) had almost similar estimates (Supplementary Figure 4). Analysis based on the assessment tool to diagnose PTSD revealed that the pooled prevalence of PTSD while using PCL-5 was 10% and 29% for the IES-R scale, and this difference was statistically significant (Supplementary Figure 5).

### Table 2

| No | Study            | Representativeness of the sample | Justification of sample size | Non-response rate | Use of a validated tool | Outcome assessment | Overall Quality |
|----|------------------|---------------------------------|------------------------------|-----------------|-------------------------|-------------------|-----------------|
| 1  | Beck 2021        | High                            | Low                          | Low             | High                    | High              | High            |
| 2  | Graff 2020       | High                            | Low                          | Low             | High                    | Low               | Low             |
| 3  | Janiri 2021      | High                            | High                         | Low             | High                    | Low               | Low             |
| 4  | Khademi 2021     | High                            | Low                          | Low             | High                    | High              | Low             |
| 5  | Liu 2020         | High                            | High                         | High            | High                    | Low               | Low             |
| 6  | Martillo 2021    | High                            | High                         | High            | High                    | Low               | Low             |
| 7  | Mazza 2020       | High                            | Low                          | Low             | High                    | Low               | Low             |
| 8  | Morin 2021       | High                            | Low                          | Low             | High                    | Low               | High            |
| 9  | Naidu 2021       | High                            | High                         | High            | Low                     | Low               | High            |
| 10 | Parker 2021      | High                            | Low                          | Low             | High                    | Low               | Low             |
| 11 | Poyraz 2021      | High                            | Low                          | High            | High                    | Low               | Low             |
| 12 | Ras 2021         | High                            | Low                          | Low             | High                    | High              | High            |
| 13 | Tarsitani 2021   | High                            | High                         | High            | Low                     | Low               | Low             |

Fig. 2. Forest plot showing the pooled prevalence of PTSD among severe COVID-19 patients ($N=13$).
3.5. Meta-regression

We also performed meta-regression to look for the heterogeneity sources with the study-level characteristics such as geographical region, study design, measurement tool, mode of interview, mean age, sample size, and quality of the study. Neither of the factors was significantly explaining the effect estimate. However, multivariable meta-regression analyses were performed with factors with a p-value less than 0.20, such as sample size, geographical region, measurement tool, and interview mode. Though the adjusted model could explain 100% of the heterogeneity, it was not statistically significant (Table 4).

3.6. Additional analysis

Publication bias was graphically assessed by funnel plot (Supplementary Figure 6) and Doi plot (Supplementary Figure 7). Both the plots showed signs of asymmetry, statistically confirmed by Egger’s test (p = 0.07) and the LFK index (3.18). Sensitivity analysis was carried out to check the robustness of the estimates. It has shown no significant variation in the magnitude or direction of the outcome, indicating that a single study failed to influence the overall pooled estimate (Supplementary Figure 8).

4. Discussion

PTSD can occur in people who experience a traumatic event in their lifetime (Felix Torres 2020). The risk of increased prevalence of PTSD has also been observed in previous coronavirus pandemics, making its occurrence during this COVID-19 pandemic highly explainable (Yuan et al., 2021). Some of the severe cases of COVID-19 result in mortality. The fear of death might be among the many reasons responsible for PTSD amongst these patients. The death of any close relative in the family may also lead to the occurrence of PTSD. Therefore, it is necessary to understand the prevalence of PTSD amongst these patients to highlight its importance in every aspect of health during such testing times.

Our review showed that 16% of the severe COVID-19 patients globally had PTSD. Geographic distribution of the prevalence did not reveal any additional information due to limited studies in regions other than Europe. The evidence is limited on the post mental effects of severely COVID-19 affected individuals. The estimated prevalence of PTSD in our study was higher than the existing literature focusing on all severe COVID-19 affected individuals. The estimated prevalence of PTSD can occur in people who experience a traumatic event in their lifetime (Felix Torres 2020).

A meta-analysis on the survivors of ICU-admitted patients with SARS and MERS infection has revealed that about 39% of them had suffered from PTSD. There could be plenty of reasons for such contrasting differences in the prevalence across these studies. However, some critical reasons were; high lethality and lower epidemic spread of the SARS and MERS compared to COVID-19, the difference in the follow-up period for PTSD, measurement tool, study region, study quality across these reviews (Ahmed et al., 2020). However, a large-scale web-based survey conducted by the Center for Disease Control and Prevention (CDC) among 5000 US adults showed that almost all suffered from at least one adverse mental or behavioral health problem concerned with this pandemic. The survey also reported that more than one-fourth of them had symptoms of trauma and stress-related disorder (Dietze et al., 2021). Some of the severe cases of COVID-19 result in mortality. The fear of death might be among the many reasons responsible for PTSD amongst these patients. The death of any close relative in the family may also lead to the occurrence of PTSD. Therefore, it is necessary to understand the prevalence of PTSD amongst these patients to highlight its importance in every aspect of health during such testing times.

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zones. Such variations in mental disorders should occur as they take a more significant toll on individuals exposing them to vulnerability as well as the methodological differences in the individual studies.

These findings further necessitate the need for having a more significant number of longitudinal studies assessing the prevalence of PTSD amongst severe COVID-19 patients. We have also carried out additional subgroup analysis, meta-regression, and sensitivity analysis to find the source of heterogeneity and check the robustness of the results. However, our review has certain limitations. We found significant between-study differences between the included studies can be held accountable, such as type of patients categorized as severe COVID-19, geographical region, sample size, tools used for diagnosis, quality of the studies, etc. In addition, our review was found to have substantial publication bias. We also found that the lower quality of the majority of the studies included in our review might further limit the generalisability of our study findings.

Irrespective of the limitations seen in our review, the findings did show some important implications for clinical management. PTSD is a psychiatric disorder in individuals who have experienced severe life-threatening incidents, war/ combat, rape, serious trauma. It affects all age groups and both genders (Torres, 2020). In our case, the COVID-19 pandemic has been threatening the lives of millions of people, which makes it a traumatic event by itself irrespective of suffering from the disease. On top of this, hospitalization with severe COVID-19 infection or admission in ICU under critical condition might further amplify the risk associated with PTSD. Apart from the disease, hospitalized patients also face other difficulties such as financial prevalence pertaining to the treatment, staying away from home, stigma in society, etc. This meta-analysis helps identify this vital aspect and urges clinicians and psychiatrists worldwide to provide extra attention and care for patients admitted or discharged following severe COVID-19 conditions.

Though our results provide some crucial information for better understanding the prevalence of PTSD following severe COVID-19, it is still needed to perform a substantial number of high-quality longitudinal studies to establish the prevalence of PTSD more precisely. Nevertheless, understanding this prevalence will help us divert the resources and adapt necessary interventions to control the situation.

Contributions

Nagarajan R, acquisition of data, analysis, and interpretation of data, drafting the article, final approval; Krishnamoorthy Y, conception and design of the study, acquisition of data, analysis, and interpretation of data, drafting the article, final approval; Basavarachar V revising the article, final approval; Dakshinamoorthy R, critical revision, final approval.

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Declaration of Competing Interest

None.

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Supplementary materials

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Declaration of Competing Interest

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