Risk factors of PTSD, depression and anxiety in patients with previous COVID-19 infection: A systematic review and meta-analysis

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Abstract

Introduction Studies showed that those who tested positive for COVID-19 have a 65% risk for a psychiatric disorder, while those undergoing isolation or quarantine are put at risk for anxiety and depression. The objective of this study was to appraise studies that determine the risk factors for psychiatric disorder post-COVID-19 infection.

Methods All cross-sectional and cohort studies from 2019 onwards that had COVID-19 survivors that developed anxiety, depression and/or post-traumatic stress disorder (PTSD), were included. Medline, Cochrane Library and ClinicalKey were searched using MeSH terms including "COVID-19", "depression", "anxiety", "post-traumatic stress disorder", and "risk factor". The risk of bias was assessed using the Newcastle-Ottawa scale. The data extracted from the studies were characteristics of the participants, risk factors, outcome measures and outcomes.

Results Four cohort and four cross-sectional studies involving 1438 COVID-19 survivors who developed depression, anxiety and/or depression were included. The risk factors that were statistically significant were 1) female sex (RR = 1.86; 95% CI 1.06, 2.04; Z = 2.32; p = 0.02) for depression, 2) having family members infected with COVID-19 (RR = 1.56; 95% CI 1.32, 1.85; Z= 5.17; p = <0.01) for depression, 3) steroid administration during hospital admission (RR = 1.62; 95% CI 1.07, 2.47; Z = 2.26; p = 0.02) for anxiety and 4) female sex (RR = 2.13; 95% CI 1.16, 3.91; Z = 2.45, p = 0.01) for PTSD.

Conclusion Female sex increases the risk of depression and PTSD. A family history of COVID-19 increases the risk of depression. Steroid administration is a risk factor for anxiety.

Key words: COVID-19, risk factors, depression, anxiety, post traumatic stress disorder

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The COVID-19 outbreak has claimed millions of lives worldwide and continues to infect the population. As of March 14, 2022, there have been 457 million cases reported with 6.04 million deaths. While there are numerous studies on mental health among healthy populations during the pandemic, data on mental health outcomes of individuals previously diagnosed with COVID-19 are limited. The effects of COVID-19 may last beyond the present infection

and have been implicated in the development of neuropsychiatric disorders such as depression, anxiety and post-traumatic stress disorder (PTSD) through direct viral infection of the central nervous system (CNS) or indirectly via an immune response.[1] Those who tested positive for COVID-19 have a 65% risk for a psychiatric disorder, while those undergoing isolation or quarantine are at risk for anxiety and depression.[2] In order to predict the patient's risk for having the aforementioned disorders, a number of studies from 2019 to 2021 looked into the prevalence, demographics, and predictors of psychiatric disorder in patients who had previous COVID-19 infections.[3-5] A literature search showed that no systematic review or meta-analysis regarding the risk factors or predictors of developing psychiatric disorders in patients with previous COVID-19 infection has been published.

Due to the increasing number of psychiatric cases reported after a COVID-19 infection, a meta-analysis will be a valid evidence-based guide for physicians that can help in predicting the onset of psychiatric disorders and providing appropriate management.[4] This study aimed to determine the risk factors associated with PTSD, depression and anxiety among patients with previous COVID-19 infection.

Methods

This meta-analysis and systematic review was done according to the guidelines set in the Cochrane Handbook for Systematic Reviews of Prognosis Studies and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist.[6,7] The studies were selected according to the study design, participants, risk factors or predictors, outcome, timing, setting and language. Case control, cohort, and cross-sectional studies reported in English from 2019 to the present were targeted research for this study. The studies must have participants with previously confirmed post-COVID-19 infection, and were screened for PTSD, anxiety and/or depression Studies which identified risk factors associated with psychiatric disorders post-COVID-19 infection were retrieved from August to October 2021 at Elsevier/Science Direct, Clinical Key, EBSCO, MEDLINE (PubMed), and CINAHL using the following medical subject headings (MeSH) terms: "COVID-19", "depression", "anxiety", "post-traumatic stress disorder", "risk factor", "determinant" and "predictor".

Using REVMAN 5.4.1, three author reviewers extracted the data from each eligible study. To ensure consistency across reviewers, the researchers conducted training exercises using the REVMAN training guide. Data that were collected from each study included the sociodemographic characteristics of the subjects and their clinical features. All reported outcomes including the effect size and the statistical analysis done for the outcomes were evaluated. Reviewers resolved disagreements through discussions. The three author reviewers were also the main authors who adjudicated unresolved disagreements. Study authors were contacted for any uncertainties. The authors extracted the number of participants who had depression, anxiety, PTSD, risk factors, outcome, and outcome measurement. Risk factor for the development of the aforestated disorders were collected.

The Newcastle-Ottawa Scales for Cohort and Cross-sectional Studies was used in assessing the risk of bias. The data set was encoded in RevMan 5.4.1 for analysis, while the Mantel Haenszel method was used to pool together the effect of individual data using risk ratios. A risk factor with a result of $p < 0.05$ was considered statistically significant. A risk ratio of > 1.00 is deemed as a positive outcome for a risk factor of a psychiatric disorder post-COVID-19 infection. Statistical heterogeneity was evaluated by chi-square and I^2 tests. The authors used an $I^2 > 75\%$ and a x^2 $p < 0.1$ as indicative of statistical heterogeneity. A random or fixed effects model was used for summary effect analysis depending on the statistical heterogeneity.[7-8]

Results

Study selection

A primary database search yielded 499 results from Elsevier, MEDLINE, CINAHL and Clinical Key; 16 additional studies were identified through other sources, for a total of 515 articles. Four hundred fifty-six articles were excluded due to irrelevance and duplication. From the remaining 59 full-text articles, 51 were excluded because they did not meet the eligibility criteria, leaving eight studies for this systematic review and meta-analysis (Figure 1).

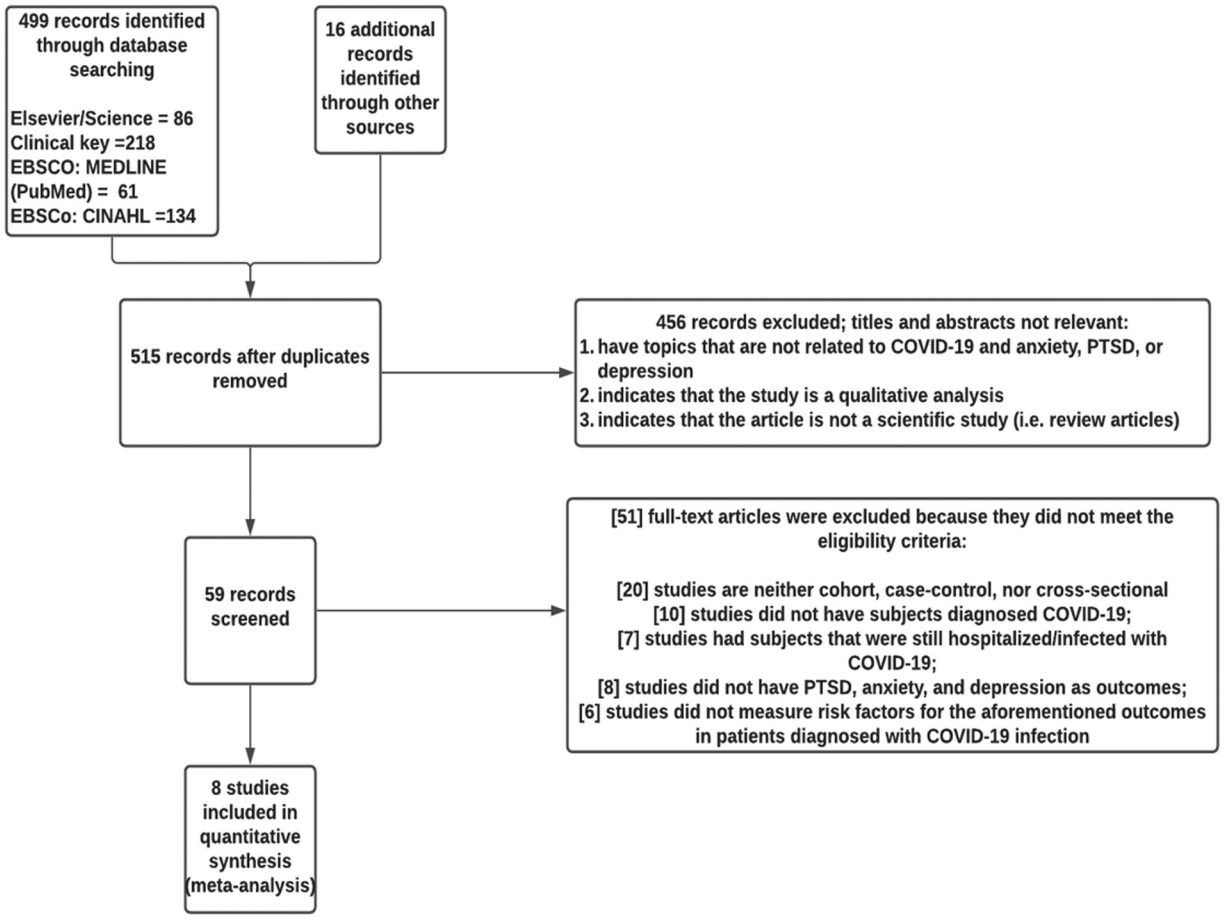

Figure 1. Study selection process.

Study Characteristics

The characteristics of the four cohort and four cross-sectional studies are summarized in Table 1.[9-6] Four articles had depression outcomes, three studies had anxiety outcomes, and seven studies had PTSD outcomes.[10-16] The eight studies had a total of 1438 participants of whom 115 participants had anxiety, 183 had depression, and 211 had PTSD. Risk factors identified in the studies were gender (6 studies); age (4 studies); marital status (3 studies); steroid administration (2 studies); educational status (3 studies); ICU hospitalization (2 studies); and a family member who was infected with COVID-19 (2 studies).

Risk of bias

The risk of bias for cohort and cross-sectional studies, respectively, was assessed using the Newcastle-Ottawa Quality Assessment Scale. The risk of bias was tabulated using the Risk of Bias Table in RevMan 5.4. Figures 2 to 5 show the summary of the risk of bias.

The criteria used in evaluating selection bias were 1) representativeness of exposed cohort, 2) selection of the non-exposed cohort, 3) ascertainment of exposure, and 4) demonstration that outcome of interest was not present at the start of the study. A study was considered low risk based on the first criterion if it included subjects who did not have an active COVID-19 infection (with serum levels that

Table 1. Study characteristics.

Reference	Methods	Participants	Number of Total Participants	Number of Participants w/ Anxiety	Number of Participants w/ Depression	Number of Participants w/ PTSD	Risk Factors	Outcome Measure	Outcome
Beck 2021	Cohort	Patients previously diagnosed with COVID-19 with confirmed by reverse transcriptase polymerase chain reaction from nasopharyngeal swabs, 18 y/o and above (mean: 58.2)	126	0	0	10	Married	Impact of Event Scale -revised (to German)	PTSD
Benzakour 2021	Cohort	Post-discharged patients diagnosed with COVID-19 infection, 18 years old and above (mean 56.8 (+/- SD 18-86 y/o)	109	17	20	15	Age, Gender, ICU hospitalization	Posttraumatic stress disroder checklist-5 (PCL-5), Hospital anxiety and depression scale (HADS)	PTSD, Depression, Anxiety
Cai 2020	Cohort	Post-discharged patients diagnosed with COVID-19 infection, 18 years old and above (mean ± SD: 45.7 ±14)	126	28	48	39	Older age, retirement, gender, social support, family members or close relatives infected, post-infection physical discomfort, educational status, history of psychiatric disorder	Post-traumatic stress disorder self-reating scale (PTSD-SS), Self-rating depression scale (SDS), Self-rating anxiety scale (SAS)	PTSD, Depression, Anxiety
Ju 2021	Cohort	Post-discharged patients diagnosed with COVID-19 infection, 18 years old and above (median 41, 31-53y/o)	114	0	0	41	Age, Gender, Marital Status, Edication, Clinical characteristics (Comorbidity, Duration of hospitalization,. severity of pneumonia, isolation site), Mental status during hospitalization	Impact of Event Scale-6 (IES-6)	PTSD
Chang 2020	Cross-sectional	discharged COVID-19 patients, 18 y/o and above (38-71; mean age=64.7	64	0	0	13	Female	Posttraumatic stress disroder checklist-5 (PCL-5)	PTSD
Imran 2021	Cross-sectional	previously hospitalized COVID-19 patients (23-60; mean age=40)	103	0	0	9	Steroid administration, Mechanical ventilator	Posttraumatic stress disroder checklist-5 (PCL-5)	PTSD
Liu 2020	Cross-sectional	Recovered COVID-19 patients who had been discharged from the hospital, 18 y/o and above (mean: 53.58)	675	70	103	84	Steroid administration; Female; Married; Higher Education; Family member infected with COVID-19; Family member died from COVID-19; Smoker	Generalized Anxiety Disorder Scale (GAD-7), Patient Health Questionnaire (PHQ-9, Posttraumatic stress disroder checklist-5 (PCL-5)	PTSD, Depression, Anxiety
Xu 2020	Cross-sectional	Post-discharged patients diagnosed with COVID-19 infection, 18 y/o and above (Mean ±SD: 41.72 ±13.61)	121	0	12	0	age, gender, ICU	Center for epidemiology scale for depression (CES-D)	Depression

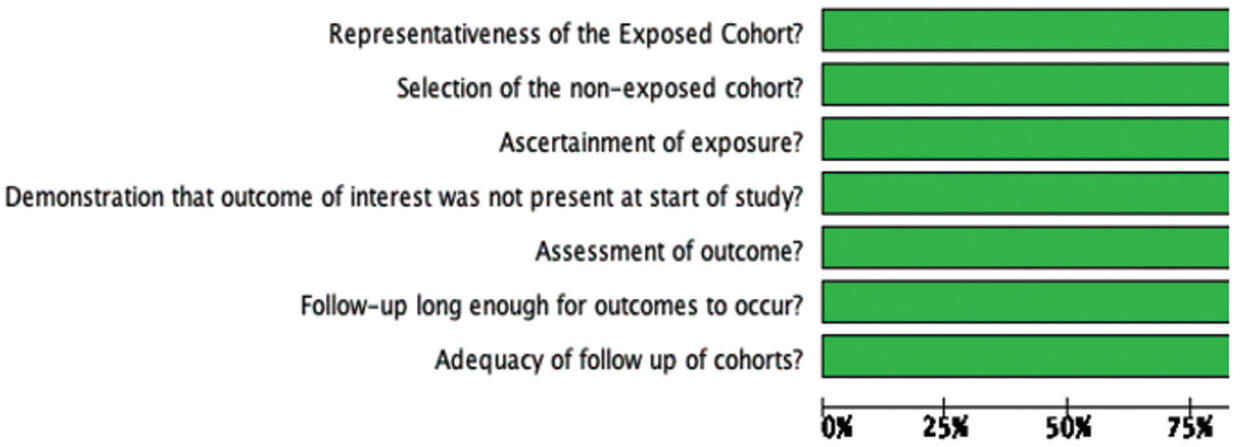

Figure 2. Risk of bias graph for cohort studies

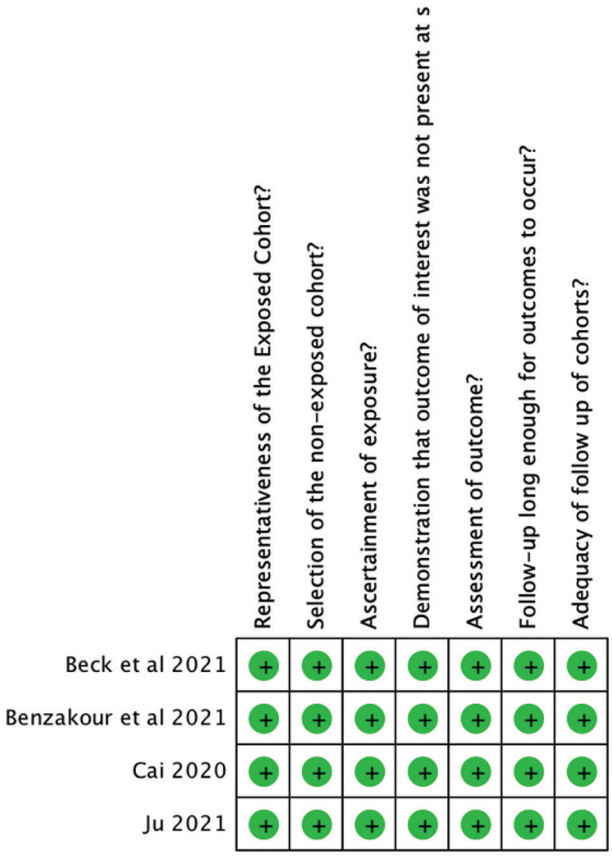

Figure 3. Risk of bias of individual cohort studies.

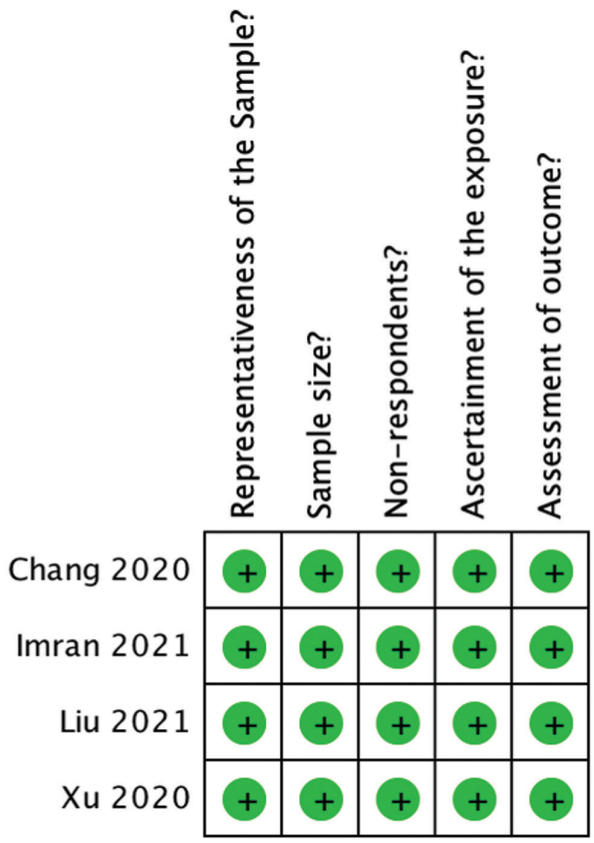

Figure 5. Risk of bias of individual cross-sectional studies.

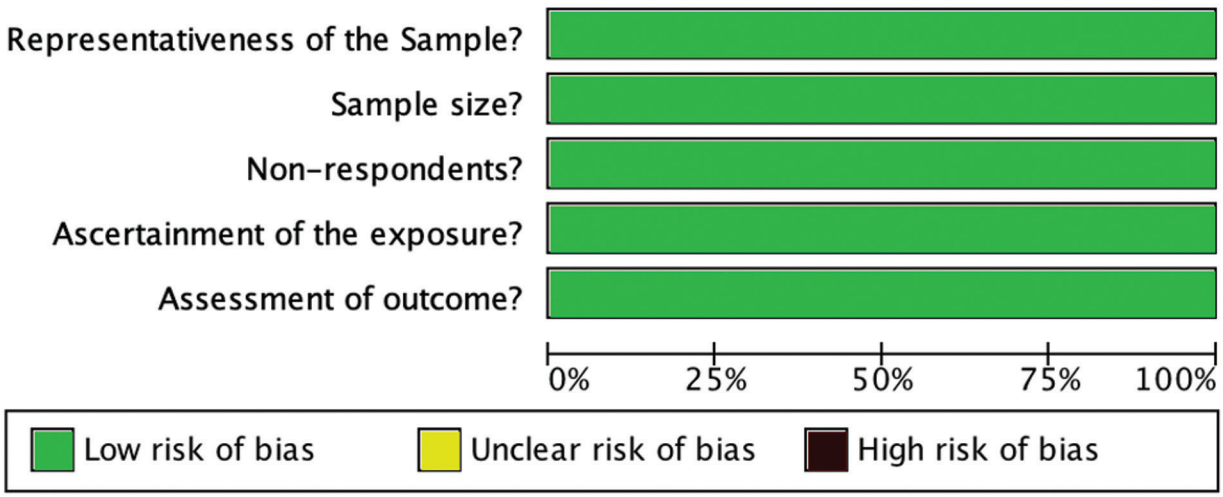

Figure 4. Risk of bias graph for cross-sectional studies.

were undetectable by RT-PCR). All the studies were low risk because they evaluated only patients who had undetectable COVID-19 by RT-PCR. A study was considered low risk based on the second criterion if all non-exposed subjects came from the same population as the exposed cohorts. All studies were low risk because the unexposed subjects also came from the same population as the exposed cohorts. A study was considered low risk based on the third criterion if validated questionnaires were used to determine the risk factors. All studies were considered low risk since validated questionnaires were used to measure the risk factors. A study was considered low risk based on the fourth criterion if the patients were screened during their hospital stay, supported by records that they did not show any symptoms of PTSD, anxiety, and/or depression. All studies were low risk based on this criterion. (See Figures 2 & 3)

The criteria used to assess outcome bias in cohort studies were: 1) assessment of outcome, 2) follow up long enough for outcomes to occur, and 3) adequacy of follow up of cohorts. A study was considered low risk if outcomes were measured using validated questionnaires, which was done in all included studies. All studies were considered low risk in terms of follow-up since they were conducted for a minimum of one month after the patients' discharge. For the adequacy of follow up to cohort, a study was considered low risk if the study stated the reasons for the loss to follow up. All the studies were considered low risk because descriptions of the loss to follow up were provided.

The criteria used for evaluating selection bias in cross-sectional studies were: 1) representativeness of the sample, 2) sample size, 3) non-respondents, and 4) ascertainment of the exposure. A study was considered low risk based on the first criterion if the subjects had serum levels that were not detectable by RT-PCR after their COVID-19 infection. All the studies were low risk because they only evaluated patients without detectable COVID-19 by RT-PCR swab tests. A study was low risk based on the second criterion if the sample size was satisfactory. All studies were low risk because they all had adequate sample sizes. A study was considered low risk based on the third criterion if the non-respondents were accounted for. All studies were considered low risk since all studies documented reasons for non-response. A study was considered low risk based on ascertainment of the exposure if the outcome was measured with a validated measuring tool. All studies were low risk based on this criterion. (See Figures 4 & 5)

Results of individual studies and synthesis of results

Individual studies tested several risk factors such as ICU stay, gender or sex, severity of COVID-19 infection, patient's knowledge of a relative infected with COVID-19, and post-discharge symptoms, however the pooled data suggested that not all were statistically significant or associated with psychiatric disorder development. Studies which assessed similar outcomes and risk factors were grouped and synthesized.

Depression Three studies showed a positive association between female sex and depression.[10,14,15,16] Females were 1.47 times more likely to have depression than males. Seventy-nine out of 469 (16.8%) females developed depression after COVID-19 infection, compared with 11.2% of males. The summary data showed a statistically significant effect ($Z = 2.32$, $p = 0.02$) as shown in Figure 6. Two studies showed that patients with family members also infected with COVID-19 were 1.56 times more likely to have depression than patients without infected family members.[11,15] Fifty-five percent of 229 patients with infected family members developed depression. The summary data showed a statistically significant association ($Z = 5.17$, $p < 0.001$) as shown in Figure 7. One study showed a positive but not statistically significant association between ventilator use and development of depression ($RR = 1.15$, $Z = 0.29$, $p = 0.77$). One study showed a positive association between ICU stay and depression ($RR = 2.29$), however the overall effect showed a negative association ($RR = 0.93$, $Z = 0.04$, $p = 0.97$).[15]

Anxiety Two studies showed a positive, statistically significant increased risk ($RR = 1.62$; 95% CI = 1.07, 2.47; $p = 0.02$) for developing anxiety in patients who were administered steroids as shown in Figure 8.[14,15] Three studies showed an increased risk of females developing anxiety that was not statistically significant ($RR = 1.14$; 95% CI = 0.77, 1.69; $p = 0.52$).[10,14,15] Three studies showed positive but not statistically significant ($RR = 1.20$; 95% CI = 0.68, 2.12; $p = 0.52$) increased risk for patients to develop anxiety after ICU admission.[14,15]

PTSD Seven studies showed a statistically significant increased risk for patients to develop PTSD

if they were female (RR = 2.13; 95% CI = 1.16, 3.91; p < 0.01), as shown in Figure 9).[9-15] Two studies showed a negative but statistically significant association between corticosteroid use during admission and PTSD (RR = 0.33; 95% CI = 0.15, 0.73; p = 0.006), as shown in Figure 10.[14,15] Three studies showed a positive but not statistically significant association between ICU admission and PTSD (RR = 1.29; 95% CI = 0.72, 2.31; p = 0.40).[9,10,14,15] Three studies showed a negative and statistically insignificant association between PTSD and use of a mechanical ventilator during admission (RR = 0.21, Z = 2.63; p = 0.65).[9,14,15] Three studies showed no association between being married and developing PTSD after COVID-19 infection (RR = 1.04; 95% CI = 0.96, 1.12; p = 0.36).[9,12,15]

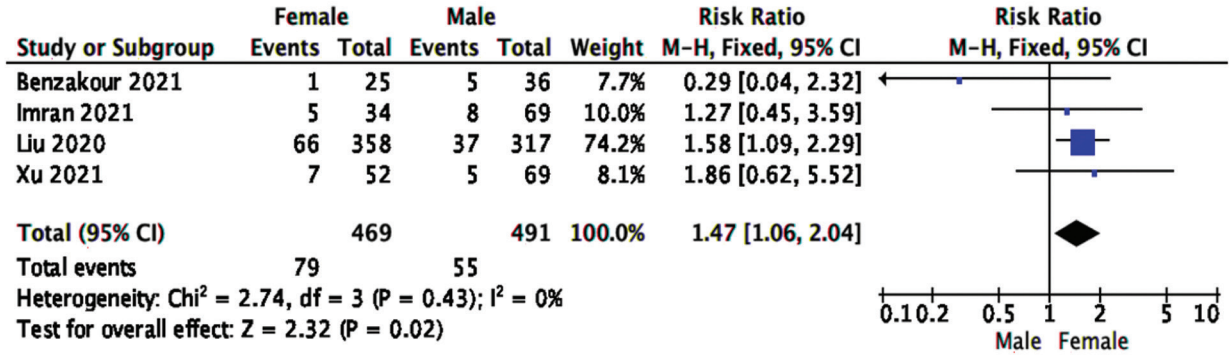

Figure 6. Association between female sex and depression.

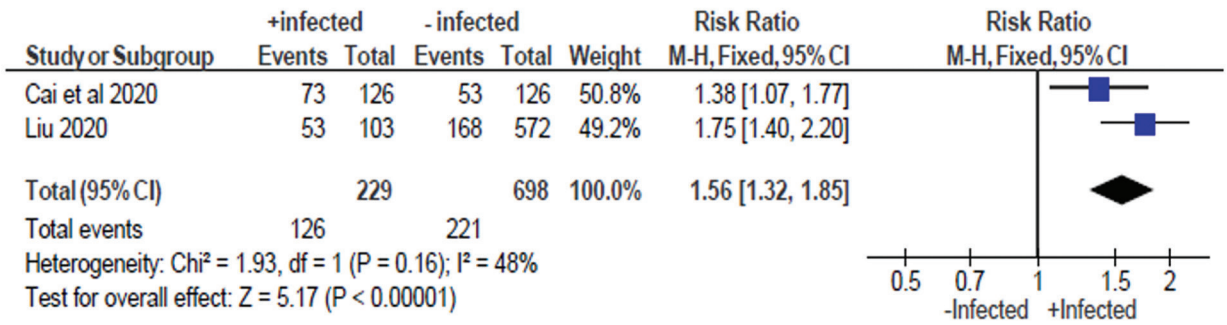

Figure 7. Association between infected family member and depression.

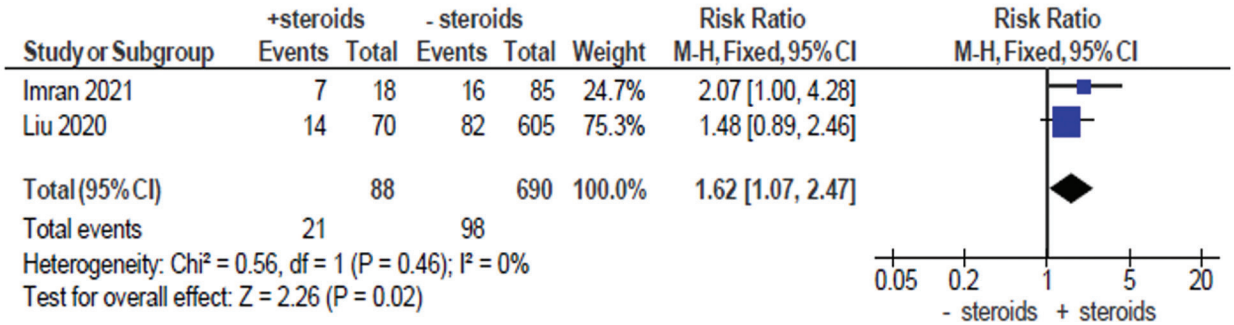

Figure 8. Association between steroid administration and anxiety.

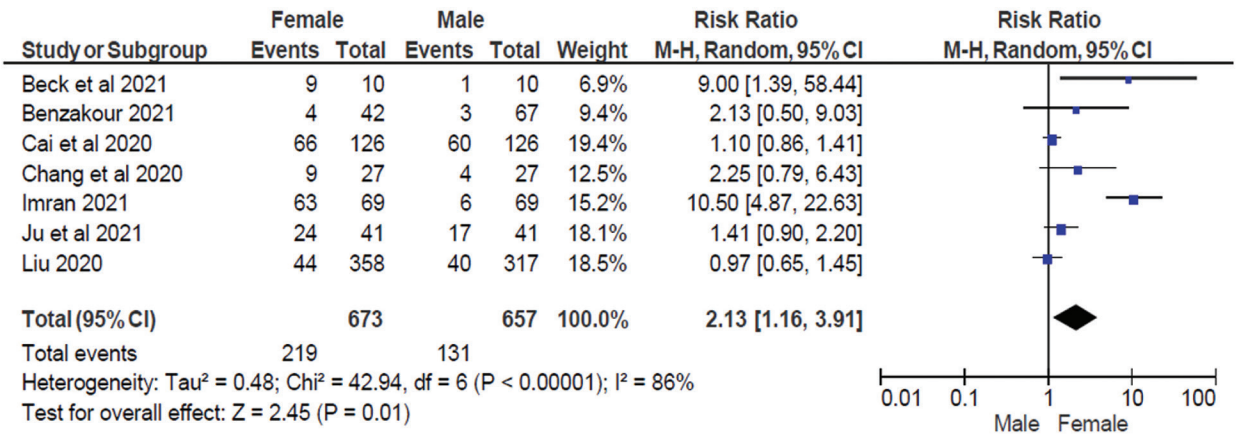

Figure 9. Association between female sex and PTSD.

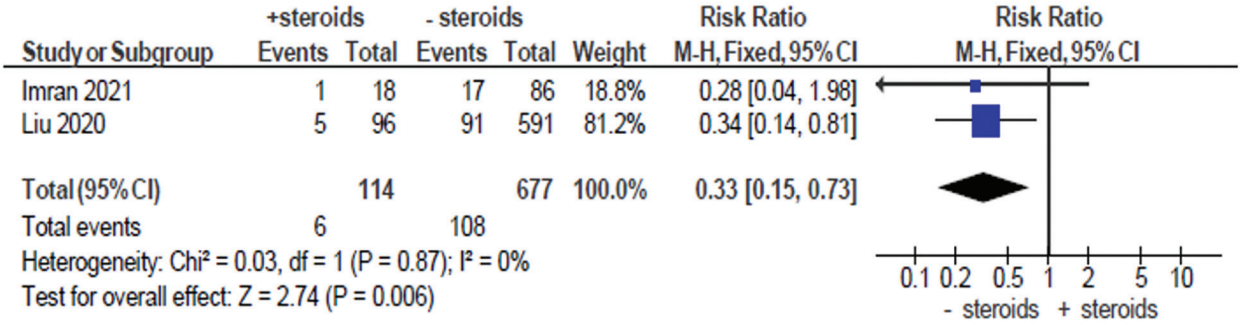

Figure 10. Association between steroid administration and PTSD.

Discussion

COVID-19 has affected not only the physical health of those infected, but their mental health and well-being as well. A rise in mental health problems among vulnerable groups has been observed, and it is important to be knowledgeable of predictive factors that may be used to screen them for psychiatric disorders.[17] The findings show that female sex and having one or more family members infected with COVID-19 were risk factors for depression; female sex for PTSD; and steroid administration during hospital admission for anxiety.

Female sex was determined as a risk factor for both depression and PTSD post-COVID-19 infection, supporting majority of the studies showing females suffering more psychiatric symptoms after COVID-19 infection. An increase in NF-κB inhibitor expression in females, due to an infection-triggered disturbance in the immune system, may play a part in the development of depression.[18] Differences in gender roles may also play a significant role in this. Participants who took on more traditionally feminine gender roles in their daily lives were less likely to experience emotional distress regardless of whether they were male or female.[19]

Having one or more family members previously or currently infected with COVID-19 was also identified as a risk factor for depression in COVID-19 survivors. That patients may have experienced guilt due to the possibility of being the source of infection, and an accompanying concern for the health status of the infected family member were proposed as explanations for the development of the psychiatric disorder.[11] The COVID-19 infection of the family member may also lead to his/her subsequent death, resulting in depression, stress and/or anxiety.[20]

Steroid administration was identified as a risk factor for anxiety. There is an association between corticosteroid administration and higher mortality in critically-ill patients.[15] Exposure to dexamethasone (6 mg/day) was also related to induced psychosis in patients.[21] One mechanism to explain this manifestation is the activation of the hypothalamic-pituitary adrenal axis, triggering a change in the production and regulation of neurotransmitters, such as a decrease in serotonin and increase in dopamine activity in the brain, leading to psychotic, mood or anxiety disorders.[21]

Risk factors that had a positive association but were not statistically significant for depression include ventilator use, non-psychiatric comorbidity, ICU admission, and steroid use. The risk factors for PTSD that had a positive association but were not statistically significant were psychiatric comorbidity, ICU admission, and marital status. Studies showed these as predictors for PTSD, however, their overall effects were not statistically significant. The risk factors for anxiety that were not statistically significant were female sex and ICU admission. Two studies identified female sex as a predictor for anxiety, however the overall effect was not statistically significant.[14,15] ICU admission was found to be a predictor in two studies, but the overall effect was not statistically significant.

A systematic review and meta-analysis of eight studies involving 1438 COVID-19 survivors showed that particular risk factors are associated in predicting depression, anxiety and/or PTSD: female sex and having one or more family members infected with COVID-19 are risk factors for depression; female sex, for PTSD; and steroid administration during hospital admission, for anxiety. Other risk factors assessed were positively associated with depression, anxiety and/or PTSD, but were not statistically significant.

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