Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Prevalence of depression in SARS-CoV-2 infected patients: An umbrella review of meta-analyses

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ABSTRACT

Objective: The COVID-19 pandemic is still spreading worldwide two years after its outbreak. Depression has been reported in around 30% of SARS-CoV-2 infected patients. We aim to synthesize the available meta-analytical evidence in an umbrella review exploring the prevalence of depression during and after SARS-CoV-2 infection.
Methods: First, we performed a narrative umbrella review including only meta-analyses providing a quantitative summary of the prevalence of depression during or after SARS-CoV-2 infection. Then we extracted the prevalence and sample size from the original studies included in each meta-analysis, and after removing duplicate studies, we performed a random-effects model meta-analysis based on single original study estimates. Heterogeneity, publication bias, leave-one-out sensitivity, and subgroup analyses were performed.
Results: 14 meta-analyses were included in the umbrella review. The prevalence of depression ranged from 12% to 55% in the presence of high heterogeneity. The meta-analysis based on 85 original studies derived from the included 14 meta-analyses showed a pooled prevalence of depression of 31% (95% CI:25–38%) in the presence of high and significant heterogeneity ($Q = 8988$; $p < 10^{-6}$; $I^2 = 99\%$) and publication bias ($p < 0.001$).
Conclusion: The burden of post-COVID depression substantially exceeds the pre-pandemic prevalence. Health care services for COVID-19 survivors should monitor and treat emergent depression, reducing its potential detrimental long-term effects.

1. Introduction

The Coronavirus Disease 2019 (COVID-19) has affected >600 million people and resulted in 6 million deaths two years from its outbreak (WHO) [1].

After Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection, approximately 20% of patients develop severe illness [2]. Furthermore, persistent and prolonged symptoms have been observed after the acute infection regardless of the COVID-19 severity [2]. The post-acute sequelae of COVID-19 (PASC) are now recognized and defined as a condition pertaining to those who still have signs and symptoms for weeks after the onset of the illness [3].

Since the pandemic spread, acute and post-acute psychopathological consequences have been reported in COVID-19 survivors [4,5]. Available evidence indicates depression as a major adverse psychiatric outcome COVID-19 survivors struggle with during infection and for several months after the infection itself [6]. Clinically significant depression during and after COVID-19 was reported in one out of three patients, with a higher risk of presenting post-COVID depressive symptomatology in females and patients with preexisting psychiatric disorders [7–9]. COVID-19-related depression, characterized by depressed mood and decreased interest and pleasure, displays similar psychopathological brain imaging correlates [10] and negative thinking styles [11] as major depression and affects fatigue syndrome [12], neurocognitive functioning [13], and quality of life [14] in PACS. The mechanisms underlying post-COVID depression have been associated with infection-related neuroinflammation as well as persistent psychological distress in the peri-infection period [15,16]. Furthermore, preexisting depression during SARS-CoV-2 infection was found to detrimentally affect COVID-19 outcome, being associated with

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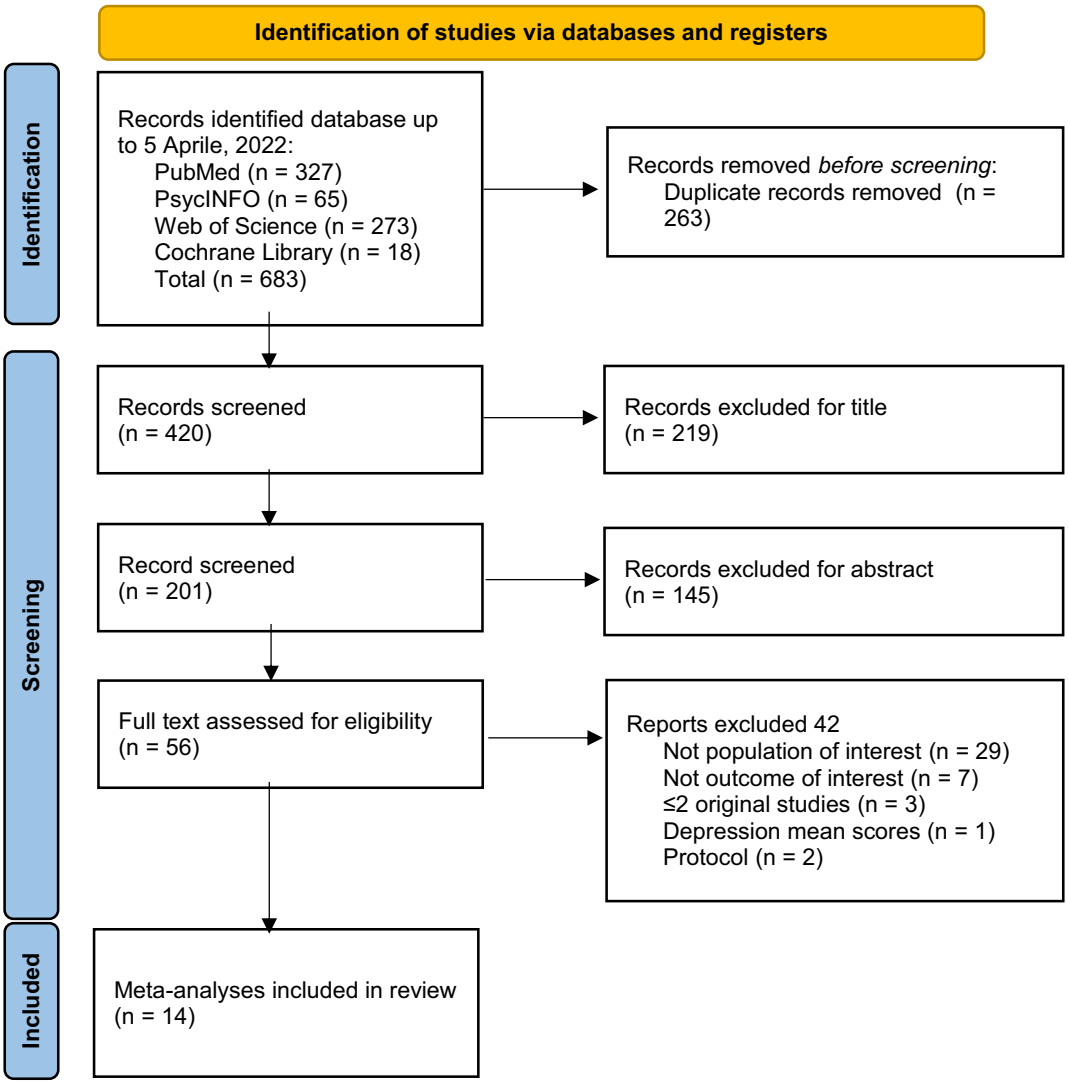

Fig. 1. PRISMA 2020 flow diagram for the selection process.

hospitalization, intensive care unit admission, and mortality [17].

Notwithstanding the impact of depression on SARS-CoV-2 infected patients' quality of life, a more precise estimate of its prevalence and associated risk factors is still lacking. Considering the overall burden of COVID-19 triggered depressive psychopathology and the previous efforts to quantitatively meta-analyze data about its epidemiology, we aim to systematically synthesize the available meta-analytical evidence of the prevalence of depression in COVID-19 patients during acute and post SARS-CoV-2 infection by providing an umbrella review.

2. Materials & methods

We performed an umbrella review exploring the prevalence of depression in COVID-19 infected patients according to the state-of-the-art methodological guidance, namely the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [18] and specific empirical recommendations for conducting umbrella reviews [19]. PRISMA checklist for meta-analysis and systematic reviews is available in eTable1. In accordance with the guidelines, we registered the protocol in the International Prospective Register of Systematic Reviews (PROSPERO) under the code CRD42022310693. Any critical protocol amendments were noted in eMethod 1.

2.1. Search strategy and study eligibility criteria

We conducted a systematic literature search of all eligible articles updated to April 5, 2022, on PubMed, Ovid/PsycINFO, Web of Science (Clarivate Analytics), and the Cochrane Library databases (eMethods 2 for the search strategy in each database). Furthermore, the reference lists of included papers were manually screened for further eligible articles.

Medical databases were queried using relevant keywords and MeSH terms with Boolean Logic operators (OR and AND). The following keywords were adapted to the database's rules: (depress* OR mood OR affective OR psychiatric OR mental health OR neuropsychiatric OR psychopathol*) AND (COVID-19 OR SARS-CoV-2 OR coronavirus) AND (prevalence OR incidence OR epidemiology OR rate OR occurrence OR frequency OR percentage OR burden) AND (meta-analysis).

In this umbrella review, meta-analyses were included if they provided a quantitative summary of the prevalence of depression in patients who contracted the SARS-CoV-2, both considering patients in acute and post-acute infection. Only systematic reviews with a meta-analytical approach including at least three studies were considered. We only included studies reporting a categorical definition of depression according to questionnaire cut-off scores or clinical diagnosis. Studies with only mean scores of depressive symptoms were excluded. Meta-analyses utilizing multiple populations or outcomes were included only if they

Table 1
The characteristics of included studies.

Study	Number of included original studies	Total sample size	Sources searched	Data collection period	Instruments used to measure depressive symptoms	Overall prevalence and 95% CI	Heterogeneity	AMSTAR-2	JBI	Class of evidence
Deng et al., 2020 [23]	23	4028	PubMed, Embase, Web of Science, Medline CINAHL, Wangfang Data, WangFang Med Online, CNKI, and CQVIP	From 2019 to August 18, 2020	ZSDS, PHQ-9, HADS, SCL-90, or unvalidated custom questionnaires or interviews	45% (37–54%)	96%	Moderate	High	NS
Dong et al., 2021 [24]	27	6002	PubMed, Embase, PsycInfo, Wanfang Data, CNKI, CQVIP, and Sinomed	From January 1, 2020 to October 7, 2020	ZSDS, PHQ-9, HADS, SCL-90, HAMD, or PHQ-2	38% (29–46%)	98%	Critically low	High	III
Dorri et al., 2021 [25]	7	2393[a]	PubMed, Embase, Google Scholar	Up to January 16, 2021	ZSDS, PHQ-9, HADS, BDI-13, clinical diagnosis, or a single question on depression	12% (8–17%)	92%	Critically low	High	II
Dragioti et al., 2021 [30]	9	2088[a]	PubMed, PsycInfo, Who COVID-19	Up to September 29, 2020	ZSDS, PHQ-9, DASS-21, GADS	28% (21–36%)	96%	Low	High	NS
Iqbal et al., 2021 [31]	3	621[a]	MEDLINE, Embase, PsycInfo, HMIC	Up to March 6, 2021	ZSDS, BDI-13, or self-reported symptom questionnaire	20% (9–33%)	92%	Critically low	High	IV
Khraisat et al., 2021 [6]	20	8478[a]	PubMed, Google Scholar, MedRxiv, ScienceDirect	Up to February 2021	na	21% (16–28%)	97%	Critically low	High	II
Krishnamoorty et al., 2020 [32]	3	398[a]	MEDLINE, CNKI, Cochrane Library, ScienceDirect, Google Scholar	Up to April 22, 2020	ZSDS, PHQ-9, or HADS	42% (28–57%)	88%[b]	Moderate	High	NS
Lao et al., 2020 [27]	8	2206	PubMed, Embase, Chocrane Library	Up to July 30, 2020	ZSDS, PHQ-9, or HADS	44% (30–57%)	98%	Critically low	High	NS
Liu C. et al., 2021 [26]	20	3716[a]	PubMed, Embase, Web of Science, PsycInfo	From January 1, 2020, to December 26, 2020	ZSDS, PHQ-9, HADS, SCL-90, BDI, DASS-21	38% (25–51%)	98%	Moderate	High	NS
Liu X. et al., 2021 [33]	4	444[a]	PubMed, Embase, Web of Science, Cochrane Library, EBSCO, Wangfang Data, CNKI, and Chinese biomedical literature service system	From January 1, 2020, to July 1, 2020	ZSDS or SCL-90	55% (33–76%)	95%[b]	Moderate	High	NS
Premraj et al., 2022 [29]	8	3104	PubMed, Embase, Web of Science, Google Scholar, Scopus	From January 1, 2020 to August 1, 2021	na	12% (7–22%)	98%	Low	High	II
Rogers et al., 2021 [34]	10	43,128	MEDLINE, Embase, PsycInfo, CINAHL	From January 1, 2020, to July 18, 2020	na	23% (12–40%)	99%	Low	High	IV
Wu et al., 2021 [28]	4	480	PubMed, Embase, Web of Science, Ovid, CNKI, Wanfang Data, SSRN, bioRxiv, MedRxiv	From January 1, 2020, to March 16, 2020	ZSDS, HAMD, GHQ, or self-made questionnaire	42% (26–58%)	90%	Moderate	High	IV
Yan et al., 2022 [35]	5	137[a]	PubMed, Embase, Web of Science, PsycINFO, Scopus, CNKI, Academic Search Premier, PsycARTICLES, Psychology and Behavioral Sciences Collection, Wanfang Standards Database, CQVIP, MedRxiv	Up to March 2021	ZSDS, PHQ-9, HADS	27% (14–48%)	75%	Moderate	High	IV

Beck Depression Inventory-13 (BDI-13); Cumulative Index of Nursing and Allied Health Literature (CINAHL); China National Knowledge Infrastructure (CNKI); Chongqing VIP Information (CQVIP); Depression Anxiety Stress Scales-21 (DASS-21); General Health Questionnaire (GHQ); Goldberg Anxiety and Depression Scale (GADS); Hospital Anxiety and Depression Scale (HADS); Hamilton Rating Scale for Depression (HAMD); Healthcare Management Information Consortium (HMIC); Patient Health Questionnaire-2 (PHQ-2); Patient Health Questionnaire-9 (PHQ-9); Social Science Research Network (SSRN); Symptom Checklist-90 (SCL-90); Zung Self-Rating Depression Scale (ZSDS).

[a] Sample size calculated.

[b] I^2 Calculated.

provided separate data for depression prevalence in COVID-19 patients. Original studies, clinical case reports, abstracts, conference proceedings, preprints, or comprehensive studies that did not undergo a peer-review process were excluded. The language was restricted to English.

2.2. Study selection and data extraction

After removing duplicates, two independent researchers (MP and EA) completed the preliminary screening based on titles, abstracts, and full text according to the eligibility criteria. Any disagreement between the researchers was resolved through discussion with a third reviewer (MGM). A PRISMA flowchart describes the selection process (Fig. 1).

Two authors (GV and EA) independently extracted the data using a standardized pre-defined template discussed among the authors. A third author (MGM) cross-checked the data extraction. From each of the eligible meta-analyses, the following information was extracted: first author, year of publication, type of assessment of depressive symptoms, the number of studies included in the meta-analysis, sample size, the pooled prevalence and 95% confidence interval of depression in SARS-CoV-2 infected patients, heterogeneity, publication bias, and list and findings of subgroup analyses. When sample sizes of the primary studies were not available in the meta-analyses, the information was retrieved and calculated from the original papers.

2.3. Narrative review and statistical analysis

All included meta-analyses were summarized and a narrative data synthesis was reported, discussing the findings from subgroup analyses of each meta-analysis to investigate potential risk and protective factors (Table 1 and Table 2).

Additionally, to better summarize the reported prevalence of depression in SARS-CoV-2 infected patients, we extracted the prevalence and sample size from the original studies included in each meta-analysis. We then performed our own meta-analysis based on all single original study estimates, removing duplicates. In doing so, we amplified the power of the analysis considering a large number of single studies and patients included. We applied random-effects models, considering the high heterogeneity observed in included meta-analyses. Between-study heterogeneity was assessed using Cochran's Q and I^2 statistics [20]. Publication bias was assessed using visual inspection of funnel plots and Egger linear regression tests [20]. To test the prevalence of depression at different stages of COVID-19, when data were available in the original studies, a subgroup analysis was performed according to the time of depression assessment (during SARS-CoV-2 infection, one to three months after infection, and more than three months after infection). Finally, we did leave-one-out sensitivity analyses to investigate the effect of single studies on the overall estimate. All analyses were two-sided and were done using Comprehensive Meta-Analysis (version 3.3.070).

2.4. Quality assessment and credibility criteria

The methodological quality of included meta-analyses was independently assessed by two investigators (MP and EA) using A Measurement Tool to Assess Systematic Reviews version 2 (AMSTAR-2) [21] and the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Systematic Reviews and Research Syntheses [22].

The credibility of associations was classified into five levels according to the strength of the meta-analytical evidence: i) convincing (when the number of cases>1000, $p < 10^{-6}$, $I^2 < 50\%$, 95% prediction interval excluding the null, no small-study effects, and no excess significance bias); ii) highly suggestive (when the number of cases>1000, $p < 10^{-6}$, largest study with a statistically significant effect, and class I criteria were not met); iii) suggestive (when the number of cases>1000, $p < 10^{-3}$ and class I–II criteria were not met); iv) weak (when $p < 0.05$ and class I–III criteria were not met); v) non-significant (when $p > 0.05$) [19]. When data to assess the strength of evidence were unavailable in the published meta-analysis, we reran the meta-analysis with the reported sample size and prevalence to calculate, when necessary, overall significance, I^2, publication bias, and small-study effects. Regardless of methodological quality, all studies were included in the review.

3. Results

3.1. Umbrella narrative review of meta-analyses

The literature search identified 683 studies. After excluding duplicate, non-relevant titles, and abstracts, 56 full-text articles were screened. 14 meta-analyses [6,23–35] met our inclusion criteria and were included in this umbrella review (Fig. 1, Table 1, eTable 2 for excluded meta-analyses after full-text assessment). The median number of original studies included in the meta-analyses was 8 (ranging from 3 [32] to 27 [24] studies), while the median sample size of each meta-analysis was 2299 (ranging from 137 [35] to 43,128 [34] patients). Among the included meta-analyses, the prevalence of depression in SARS-CoV-2 infected patients ranged from 12% (95% CI 7–22%) [29] to 55% (95% CI 33–76%) [33]. All the included meta-analyses showed high heterogeneity (I [2] ranging from 88 to 99%). The complete list of original studies for each included meta-analysis is available in eTable 3.

Some meta-analyses explored the effect of covariates known to affect depression prevalence in subgroup analyses (Table 2). Three meta-analyses consistently found that females showed a higher prevalence of depressive symptoms after SARS-CoV-2 infection compared to males [23,25,26]. Stratifying by depression severity, three meta-analyses consistently reported a higher prevalence of mild depression (prevalence from 29% to 33%), followed by moderate depression (prevalence from 13% to 17%) and, ultimately, severe depression (prevalence from 5% and 10%) [23,26,27]. When subgrouping the prevalence of screening tools for depression, the highest occurrence of depressive psychopathology was recorded through the Patient-Health Questionnaire-9 (PHQ-9) and Zung Self-Rating Depression Scale (ZSDS), while a lower prevalence was found using the Hospital Anxiety and Depression Scale (HADS-depression subscale), Symptom Checklist-90 (SCL-90), and Hamilton Rating Scale for Depression (HAMD) [23–25]. Two meta-analyses consistently revealed an impressive higher prevalence of depression in cohort studies (74%–88%) compared to cross-sectional investigations (34%–44%) [23,26]. The prevalence of depression in patients with severe COVID-19 was consistently higher than the prevalence in patients with milder forms in two meta-analyses [24,25]. Inconsistent findings were reported on the effect of setting of care for acute COVID-19 in two studies, with depression prevalence being alternately higher or lower in inpatients compared to outpatients [23,29]. Stratifying by the stage of COVID-19 inflection also revealed mixed evidence, highlighting higher depression burden during the ongoing infection or, conversely, after hospital discharge [26,27]. One meta-analysis investigating the effect of quality of study [26] and another exploring the follow-up duration [25] found no differences

Table 2
Subgroup analyses and relative findings performed in the included meta-analyses.

Subgroup analysis	Study	Findings from subgroup analysis
Country	Deng et al., 2020 [23]	The prevalence in 20 studies conducted in China was 45% (36–55%). The prevalence for Italy, Ecuador, and Iran was 38% (29–47%), 60% (55–66%), and 38% (28–49%), respectively, as reported by one study in each subgroup
	Dragioti et al., 2021 [30]	Prevalence was higher in low/middle income countries
	Liu C. et al., 2021 [26]	The prevalence reported in 13 studies conducted in China was 39% (25–54%), the prevalence reported in 2 studies conducted in Iran was 65% (0–100%, 95% CI). The prevalence for South Korea, Ecuador, Jordan, Turkey, and Italy was 39% (23–57%), 23% (18–28%), 44% (32–56%), 32% (17–50%), and 11% (6–18%), respectively, as reported by one study in each subgroup
Sex	Deng et al., 2020 [23]	Stratified data for gender were available in 9 studies, prevalence was higher in females 50% (38–62%) than in males 39% (26–53%)
	Dorri et al., 2021 [25]	Stratified data for gender were available in 2 studies, prevalence was higher in females 19% (15–22%) than in males 12% (9–15%)
	Liu C. et al., 2021 [26]	Stratified data for gender were available in 11 studies, prevalence was higher in females 46% (32–60%) than in males 32% (17–47%)
Study design	Deng et al., 2020 [23]	The prevalence of one cohort-study (74%, 62–83%) was higher than the prevalence of 22 cross-sectional studies (44%, 36–53%)
	Dorri et al., 2021 [25]	The prevalence was similar between 4 retrospective (12%, 5–18%) and 3 prospective (12%, 9–15%) cohort studies
	Liu C. et al., 2021 [26]	The prevalence of 3 cohort-studies (88%, 44–100%) was higher than the prevalence of 17 cross-sectional studies (34%, 21–46%)
Severity of depression	Deng et al., 2020 [23]	The prevalence of mild, moderate, and severe depression was 33% (26–39%, 11 studies), 14% (11–16%, 11 studies), and 7% (4–10%, 12 studies), respectively.
	Lao et al., 2020 [27]	The prevalence of mild, moderate, and severe depression was 31% (19–43%, 5 studies), 13% (11–15%, 4 studies), and 5% (2–8%, 4 studies), respectively.
	Liu C. et al., 2021 [26]	The prevalence of mild, moderate, and severe depression was 29% (24–34% 9 studies), 17% (11–22% 9 studies), and 10% (2–20% 11 studies), respectively.
Depression screening tool	Deng et al., 2020 [23]	The prevalence according to different depression screening tools were PHQ-9 (n = 9, 52% (45–59%)), HADS (n = 2, 20% (16–23%)), ZSDS (n = 6, 53% (42–65%)), and SCL-90 (n = 2, 19% (17–22%)). The remaining studies used unvalidated custom questionnaires or interviews (n = 4, 47% (15–80%)).
	Dong et al., 2021 [4]	The prevalence according to different depression screening tools were PHQ-9 (n = 9, 33%), ZSDS (n = 6, 22%), HADS (n = 4, 15%), SCL-90 (n = 4, 15%), HAMD (n = 2, 7%), and PHQ-2 (n = 2, 7%).
	Dorri et al., 2021 [25]	The prevalence according to different depression screening tools were PHQ-9 (n = 2, 16% (13–18%)), HADS (n = 2, 16% (13–20%)), ZSDS (n = 1, 31% (26–36%)), Self-reported questionnaire (n = 1, 4% (3–6%)), DSM-IV (n = 1, 10% (7–13%)), BDI-13 (n = 1, 11% (8–15%))
Disease stage	Liu C. et al., 2021 [26]	17 studies had reported the prevalence of 42% (29–56%) in patients who were experiencing SARS-CoV-2 infection, and 3

between groups.

3.2. Meta-analysis of the original studies

Based on 85 single original studies derived from the included 14 meta-analyses (eTable3), the estimated pooled prevalence of depression in 62,318 COVID-19 infected patients was 31% (95% CI:25–38%) (Fig. 2). Significantly high heterogeneity was observed among included studies (Q = 8988; $p < 0.001$; $I^2 = 99\%$).

Subgroup analysis showed a significantly lower prevalence of depression at longer post-COVID follow-ups ($T = 14.20$, $p < 0.001$). Specifically, the prevalence was 44% during infection (39 studies; 95% CI 32–55%; $I^2 = 99.47$), 20% one to three months after infection (14 studies; 95%CI 10–35%; $I^2 = 91.34$), and 15% more than three months after infection (18 studies; 95%CI 8–26%; $I^2 = 94.11$) (eFigure 1). Sensitivity analysis leaving out single studies revealed that no single study had a significant impact on the pooled prevalence that lay between the value of 30% and 32% always remaining statistically significant (p ranging from <0. 0000001 to 0.0000007) (eTable 4). Visual examination of the funnel plot (eFigure 2) and Egger's and Begg's tests revealed evidence of publication bias ($p < 0.001$).

3.3. Quality assessment and credibility of evaluation

Based on the AMSTAR-2 assessment, six meta-analyses (43%) met the moderate quality level, three (21%) were of low quality, and finally, five (36%) were rated as critically low quality (Table 1, eTable 5). On the other hand, when considering JBI Checklist for Systematic Reviews and Research Syntheses, six meta-analyses met all 11 criteria for quality assessment, and all the included meta-analyses were classified as high quality, satisfying at least eight items (Table 1, eTable 6).

The credibility of associations was found to be highly suggestive in three (21%) meta-analyses, suggestive in one (7%) meta-analysis, and weak in four (29%) meta-analyses. Moreover, six (43%) meta-analyses were classified as non-significant reporting an overall p-value >0.05 (Table 1, eTable 7). Due to the high rate of heterogeneity in all the included meta-analyses, none of them was classified as convincing.

4. Discussion

To our knowledge, this is the first umbrella review that systematically provides a comprehensive synthesis of the prevalence of depression during and after SARS-CoV-2 infection. Fourteen existing meta-analyses met the inclusion criteria, and the narrative review showed that the prevalence of depression in SARS-CoV-2 infected patients is relatively high, ranging from 12% up to 55%. Moreover, after removing duplicate studies, the overall meta-analysis of 85 single original studies derived from the 14 included meta-analyses showed a prevalence of 31% (95% CI:25–38%) in 62,318 patients in the presence of high heterogeneity.

The available prevalence estimates indicate a remarkable boost in the burden of COVID-19-related depression [36]. Globally, an increase of 27% in the cases of major depressive disorder was estimated due to the COVID-19 pandemic, potentially causing almost 50 million disability-adjusted life-years in 2020 [37]. Two COVID-19 pandemic severity indicators, daily SARS-CoV-2 infection rates and reductions in human mobility, were significantly associated with an increased prevalence of major depression [37]. Interesting, depressive episodes were significantly more common in patients who had COVID-19 than in those who had influenza (hazard ratio [HR] 1.47, 95% CI 1.42–1.53) and those who had other respiratory tract infections (HR 1.23, 1.20–1.26) [4]. Moreover, a significant difference in depression prevalence was found between SARS-CoV-2 infected and non-infected patients during the COVID-19 pandemic. Infected individuals were at higher risk of developing depressive symptoms than both healthcare workers and the general population during the COVID-19 outbreak [28].

Current insight into immunopsychiatry suggests that SARS-CoV-2

Table 2 (*continued*)

Subgroup analysis	Study	Findings from subgroup analysis
		studies conducted reported a prevalence of 14% (0–48%, 95% CI) in patients who were at the recovery stage
	Lao et al., 2020 [27]	The prevalence of depressive symptoms in discharged patients was higher (55%, 34–77%, 2 studies) than the prevalence in hospitalized patients was (40%, 28–52%, 6 studies)
COVID-19 severity	Dong et al., 2021 [4]	The prevalence of depression in patients with severe COVID-19 was 66% (16–117%, 2 studies), higher than 31% (7–55%, 4 studies) with clinically stable COVID-19. prevalence for discharged patients was 52% (25–79%, 2 studies).
	Dorri et al., 2021 [25]	The prevalence of depression in patients with severe COVID-19 was 22% (16–28%, 2 studies), higher than 15% (11–18%, 2 studies) with moderate and 13% (8–18%, 2 studies) mild forms.
Setting of care for COVID-19	Deng et al., 2020 [23]	The prevalence was higher in 12 study reporting prevalence for inpatients (48%, 35–61%) than for the single study reporting prevalence for outpatients (35%, 22–48%)
	Premraj et al., 2022 [29]	The prevalence was higher in studies reporting prevalence for outpatients (25%) than for the studies reporting prevalence for inpatients (14%)
Quality	Liu C. et al., 2021 [26]	7 high-quality studies had reported a prevalence of 38% (17–60%) and the remaining 13 low-quality studies reported a prevalence of 34% (16–54%)
Follow-up duration	Dorri et al., 2021 [25]	The prevalence was similar between studies with mean/median follow-up duration ≤31 days and those with longer follow-up time (>31): 16% (13–18%, 3 studies) vs. 15% (2–28%, 4 studies) respectively

infection-triggered perturbation of the immune-inflammatory system can foster depressive psychopathology, serving as a biological risk factor alongside COVID-19 pandemic related psychological stressors for depression [38]. In particular, from a biological perspective, the dysregulation of the innate and adaptive immune systems induced by SARS-CoV-2 infection, which leads to neurotransmitter dysregulation, is a proposed mechanism underpinning depressive psychopathology [39]. In addition to the immunological mechanisms, social isolation, quarantine, uncertainty of the future, massive media exposure, and survivor's guilt experienced by patients during the COVID-19 pandemic are all significant psychological stressors that may define psychopathological outcome [40,41].

We observed a decreasing depression prevalence at post-COVID follow-ups. The depression prevalence decreased from 44% during acute COVID-19 infection to 15% at three or more months follow-up after infection. These findings are consistent with prevalence patterns of depression during previous outbreaks of other coronaviruses [42]. Sparse longitudinal studies have directly investigated the trajectory of depression after SARS-CoV-2 infection, reporting inconsistent findings suggesting both persistent [8,9,43] and decreasing [44] depressive psychopathology over follow-ups. The subgroups meta-analysis however did not explain the heterogeneity that remained high even stratifying the studies according to the time of depression assessment. To better understand the course of depression over time long-term longitudinal follow-up studies on large cohorts of patients are needed. However, given the global burden of COVID-19 that has affected >500 million patients, the reported prevalence of depression represents an urgent clinical need that merits the attention of mental health services. Preliminary small studies suggest the potential efficacy and tolerability of pharmacological [45] and psychological [46] treatment of depressive symptomatology in SARS-CoV-2 infected patients.

Notably, in our findings, the reported high prevalence of depression was systematically accompanied by high heterogeneity thus indicating a potential effect of several clinical variables on the prevalence in the included single studies. The included studies examined very different populations in terms of COVID-19 severity, site of care, premorbid mental health history, also using different assessment instruments. When data were available in the included meta-analyses, we investigated the effect of these factors to better dealing with the source of heterogeneity. Accordingly, various meta-analyses suggested that sex, the severity of depressive symptoms, and screening tools for depressive psychopathology assessment consistently affected the prevalence estimate (Table 2). However, other risk factors potentially affecting depressive psychopathology in COVID-19 survivors where not investigated in previous meta-analyses and need to be addressed. In this context, social isolation, pandemic related psychological stressor, previous psychiatric history, pre-infection psychopharmacological treatment, medical comorbidity, and COVID-19 severity could influence the risk of presenting post-COVID depressive psychopathology directly or by interacting with the neuro-immune pathway. Although it is reasonable that all these factors could contribute to a single point estimate for depression prevalence in infected patients, no clear answers can be concluded from meta-analytical evidence and further studies are needed to investigate the reported high heterogeneity.

To check for the risk of methodological biases, we rated the included meta-analyses according both the AMSTAR-2 and JBI checklist. Discrepancies emerged between the two quality assessment tools as all included meta-analyses were rated as high quality according to the JBI checklist. In contrast, the lack of justification for excluding individual studies (item 7) in 13 of the 14 included meta-analyses prevented the studies from being classified as high quality according with AMSTAR-2. The JBI critical appraisal checklist seems to be one of the most accurate assessment tools for descriptive studies reporting prevalence data [47]. On the other hand, AMSTAR-2, one of the most commonly used tools, was designed and recommended for randomized or non-randomized studies on healthcare interventions [21]. The differing purposes of the study quality rating methods could partially explain inconsistencies in our results. Moreover, we graded the strength of associations by using well-recognized credibility criteria [19]. The high heterogeneity prevented all the meta-analyses from being classified as convincing. Moreover, six out of 14 meta-analyses had an overall p-value >0.05 and thus were classified as non-significant. However, these methodological weaknesses do not significantly bias the main findings that the burden of COVID related depression substantially exceeds the pre-pandemic prevalence of depression [37] in the general population using the same rating scales [48], and are similar to the prevalence observed in patients with immune-inflammatory diseases [49,50].

Despite the rigour in which this umbrella review was conducted, the emerging framework must be interpreted in light of some limitations. First, all the included meta-analyses as well our meta-analysis of the original studies were characterized by high heterogeneity, thus limiting the generalizability of our findings. Second, the prevalence estimates were based on observational studies, which do not imply causality but only association. Finally, the majority of reviewed studies, used self-rated questionnaires for depressive psychopathology without a psychiatric interview, thus preventing the clinical diagnosis of a major depressive episode.

5. Conclusion

In conclusion, considering the COVID-19 pandemic is still spreading worldwide two years from its outbreak and given the alarming prevalence of potentially persistent depression in infected patients, there is an urgent need for clinical intervention. According to current literature [3], mental-health follow-up services for COVID-19 survivors should be implemented to monitor emergent symptoms and provide early treatment in order to reduce the impact of psychopathology on global functioning and quality of life. The worrying rise of clinically relevant

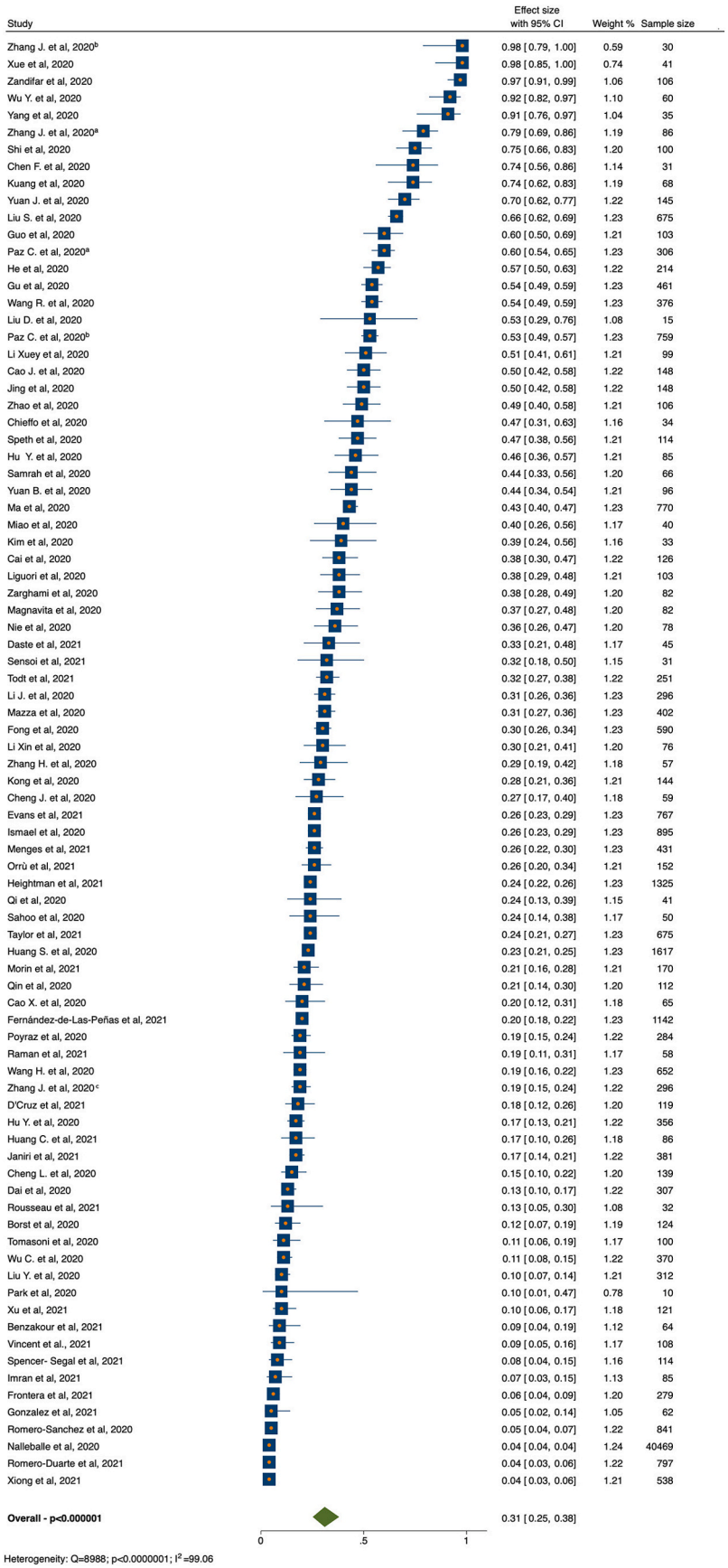

Fig. 2. Forest plot of depression prevalence in SARS-CoV-2 infected patients.

depression prevalence in acute and post-COVID stages places a new challenge on mental care services that needs to be addressed. Finally, given the reported significant heterogeneity further studies are needed to investigate the relevance of different risk and protective factors able to affect the COVID-related depression prevalence.

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Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2022.12.002.

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