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Depresja a wskaźniki stanu zapalnego u pacjentów hospitalizowanych z powodu COVID-19 – przegląd systematyczny i metaanaliza

Depression and inflammation in COVID-19 patients during and after hospitalisation – a systematic review and meta-analysis

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Streszczenie

Wstęp: Nasilenie objawów depresji u pacjentów z COVID-19 różni się w badanych populacjach i zmienia się w czasie. Coraz więcej dowodów potwierdza hipotezę o udziale stanu zapalnego w rozwoju depresji. **Metody:** Przegląd systematyczny i metaanalizę badań przekrojowych oraz badań kohortowych opublikowanych w latach 2019–2023 przeprowadzono według kryteriów PRISMA. Analizowanymi zagadnieniami były proporcja łagodnych, umiarkowanych i ciężkich objawów depresji w trakcie i po hospitalizacji oraz powiązania między depresją a stanem zapalnym u pacjentów z COVID-19. **Wyniki:** Do systematycznego przeglądu włączono trzydzieści artykułów. W ilościowej metaanalizie ogólny odsetek umiarkowanej do ciężkiej oraz lekkiej do ciężkiej depresji oszacowano na poziomie odpowiednio 0,21 (95% CI: 0,13–0,31) i 0,35 (95% CI: 0,23–0,48). W modelu efektów stałych wykazano różnicę w poziomie markerów stanu zapalnego między pacjentami z COVID-19 z depresją i bez niej, przy wyższych stężeniach białka C-reaktywnego, jak również stosunku neutrofili do limfocytów u osób z objawami obniżenia nastroju. W wynikach modeli efektów losowych dla białka C-reaktywnego nie uzyskano istotności, a dla wskaźnika neutrofilowo-limfocytowego wskaźnik ten znajdował się na granicy istotności (p = 0,053). **Wnioski:** Jak wynika z badań, odsetek osób doświadczających objawów depresji maleje w miarę upływu czasu od diagnozy COVID-19. Związek między depresją i stanem zapalnym pozostaje niejasny i wymaga dalszych badań.

Słowa kluczowe: SARS-CoV-2, zdrowie psychiczne, markery zapalne

Abstract

Introduction: The severity of depression symptoms in COVID-19 patients differs among populations investigated and changes over time. Increasing evidence supports the hypothesis about the involvement of inflammation in the development of depression. **Methods:** A systematic review and a meta-analysis of the cross-sectional and cohort studies published between 2019 and 2023 were conducted according to the PRISMA criteria. The outcomes of interest were the proportions of mild, moderate, and severe depression symptoms during and after hospitalisation, and associations between depression and inflammation in COVID-19 patients. **Results:** Thirty articles were included in the systematic review. In the quantitative meta-analysis, the overall proportions of moderate-to-severe and mild-to-severe depression were estimated at 0.21 (95% CI: 0.13–0.31) and 0.35 (95% CI: 0.23–0.48), respectively. The fixed effects model of the meta-analysis of inflammatory markers showed a difference between COVID-19 patients with and without depression, with higher concentrations of both C-reactive protein and neutrophil-lymphocyte ratio detected among people suffering mood disturbances. However, in random effects models, findings for C-reactive protein lost significance, and for neutrophil-lymphocyte ratio were on the boundary of significance (p = 0.053). **Conclusions:** According to the study results, the proportion of depression decreases over time after a COVID-19 diagnosis. The relationship between depression and inflammation is still uncertain and requires further research.

Keywords: SARS-CoV-2, mental health, inflammatory markers

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has become a challenge for the world of medicine. At the same time, it was a source of motivation for research on epidemiology, symptomatology, and the course of the disease, as well as for deepening knowledge about the psychological consequences, treatment, and the process of recovery after infection. Numerous authors conducting studies in different populations suffering from COVID-19 have drawn attention, on the one hand, to the occurrence of symptoms such as depression, anxiety, and a sense of trauma in patients (Mazza et al., 2023; Rogers et al., 2020; Santomauro et al., 2021; Schou et al., 2021; da Silva Lopes et al., 2021; Vindegaard and Benros, 2020) and, on the other hand, to psychological resources contributing to recovery, such as resilience, post-traumatic growth, and social support networks (Kunzler et al., 2021; Penninx et al., 2022).

The research also focused on the role of inflammation in the development of psychopathological symptoms such as depression or stress-related symptoms in short- and long-term observations (Beurel et al., 2020; Cruz-Pereira et al., 2020; Del Giudice and Gangestad, 2018; Gałecki and Talarowska, 2018; Haapakoski et al., 2015; Harsanyi et al., 2022; Kofod et al., 2022). Very often, the studies also addressed post-acute sequelae of COVID-19 (PASC) (Mahase, 2020; Montani et al., 2022; Thaweethai et al., 2023).

There remains a risk of further pandemic outbreaks in the future. The knowledge accumulated as a result of the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) pandemics (Debnath et al., 2020; Mak et al., 2009; Postolache et al., 2021; Rogers et al., 2020) has set directions for COVID-19 research in the fields of changes in human functioning on the individual, social, and global levels. Therefore, in the post-COVID-19 era, it is important to analyse factors significant for better understanding psychological reactions to the disease, risk factors for adaptation difficulties, and resources that support recovery and the return to bio-psycho-social balance.

Globally, the increase in major depressive disorder due to the COVID-19 pandemic in 2020 was estimated at 27.6% (Santomauro et al., 2021); however, the results of longitudinal population-based studies remain inconsistent (Penninx et al., 2022). Evidence of predictive factors for psychiatric sequelae, including depression symptoms, among COVID-19 patients is still limited (Liu et al., 2020). Multiple studies were conducted on the general population, those under home quarantine, and medical professionals, but not on hospitalised COVID-19 patients (Mazza et al., 2023; Vindegaard and Benros, 2020). Also, the results of research on inflammation in COVID-19 are very heterogeneous. Although common pathophysiological mechanisms between COVID-19 and depression are being examined (Beurel et al., 2020; da Silva Lopes et al., 2021), the relationship between COVID-19 and the development of depressive symptoms remains unclear.

Therefore, the objectives of this review were to determine the proportions of COVID-19 patients with depression during hospitalisation and after hospital discharge, and to investigate the moderating effects of inflammatory markers on the prevalence of depression.

The following key questions were addressed:

1. What are the proportions of depressive symptoms in COVID-19 patients during and after hospitalisation, considering the severity of the symptoms?
2. In COVID-19 patients, is the level of inflammatory markers associated with the severity of depressive symptoms?

MATERIALS AND METHODS

Eligibility criteria and search strategy

We included cross-sectional and cohort studies published in English reporting the prevalence of depression in adult patients (age ≥18 years) during hospitalisation for COVID-19 and after discharge. Studies that also reported inflammatory markers were prioritised. We excluded case reports, letters, conference abstracts, and qualitative studies. Studies that focused on somatic or neurological outcomes of COVID-19, depression in quarantined at-home patients, and specific populations such as healthcare workers, psychiatric inpatients, students, and the general population were also excluded.

We performed searches in the EBSCO, EMBASE, Medline, PsycInfo, and PubMed databases for studies published between 2019 and 2023. Reference lists of eligible study reports were hand-searched for additional studies, and Google Scholar was used for the identification of studies. The terms were: (patients OR survivors AND hospitali* AND inflammation OR inflammatory AND psych* OR depressive OR depression) AND Covid-19. For PubMed, COVID-19 filters from PubMed Clinical Queries were used to refine the search. We followed the PRISMA guidelines (Supplementary Tab. 1), although the study protocol was not registered.

Titles and abstracts were screened for eligibility, and duplicate references were removed manually. The process of retrieving and reviewing full-text articles for inclusion, conducted by two researchers (ALW, KOT), involved discussions, consensus-building, and consultations with a third researcher (BBK) in case of disagreements, with reasons for exclusion being collected.

Data collection

Two independently working researchers (ALW, KOT) conducted data extraction using an extraction form that was previously pilot tested on randomly selected studies. Further information from the authors of the studies was not required, as the data was found in supplementary materials. Descriptive variables were extracted as follows: reference ID,

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country, study design, sample size (at each investigated time point), mean age, number of male participants, outcomes, depression assessment tools and cut-off scores, population studied, number of depression cases, depression assessment timepoints, and main findings related to depression. Additionally, we extracted the mean, standard deviation, median, and range (if available) for inflammatory marker levels.

Methods of outcome measurement

Depression

The inclusion criteria for the studies were narrowed to ensure that depression assessment was conducted with reliable tools such as the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), Beck Depression Inventory (BDI) (Beck et al., 1961; Beck et al., 1996), and the Patient Health Questionnaire (PHQ) (Kroenke et al., 2001). In two papers (Mazza et al., 2020, 2021), Zung Self-Rating Depression Scale (ZSDS) (Zung, 1965) was used alongside the BDI-13. For this review, we operationalised depression as a patient's reported symptoms severity ranking above the scale's cut-off score.

Inflammation

Included studies should report baseline or peak inflammatory marker levels measured in blood during patient hospitalisation. We included studies reporting the following parameters: systemic immune-inflammation index (SII), neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), C-reactive protein (CRP), interleukin 1β (IL-1β), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 10 (IL-10), tumour necrosis factor-α (TNF-α), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, neutrophil, lymphocyte, platelet, D-dimer, procalcitonin, ferritin, fibrinogen, and lactate dehydrogenase (LDH).

Timepoint of outcome assessment

We categorised the included studies based on whether they measured depression during hospitalisation and/or after discharge, collecting data on follow-up timepoints. We took the length of follow-ups after discharge into consideration when interpreting the data to examine short- and long-term effects. In studies reporting multiple psychiatric outcomes, measures of depression were prioritised.

Study risk of bias assessment – assessment of methodological quality

Two researchers (ALW, KOT) independently assessed the included studies to determine potential bias in the study design, using the Joanna Briggs Institute (JBI) critical appraisal checklists for analytical cross-sectional studies and cohort studies (Aromataris et al., 2020; Moola et al., 2020). In cases of disagreements, consensus was reached through discussion or consultation with a third researcher (BBK), if necessary. High-methodological-quality studies met ≥80% of the criteria; moderate-quality studies met at least 50% but less than 80% of the criteria. There were no low-quality studies meeting <50% of the criteria. Overall, 29 studies were deemed to be of high quality (Supplementary Tab. 2). Assessed domains in each checklist are listed in the *JBI Manual for Evidence Synthesis* (Aromataris et al., 2020).

Effect measures, synthesis method, and reporting bias assessment

For at least mild and at least moderate depression, the proportions of prevalence were extracted from eligible studies. The inverse variance method and the generalised linear mixed model (GLMM) were applied to determine the overall effect size with 95% confidence interval (CI) for each outcome separately. For individual studies, CIs were computed with the Clopper–Pearson technique, and Freeman–Tukey double arcsine (F-T) transformation was implemented before pooling the proportions. Subgroup analyses were performed based on the time since hospitalisation when depression was measured (i.e. during hospitalisation, up to 6 months after discharge, and at least 6 months after discharge) and the depression assessment tool used (BDI, HADS-D, PHQ) as grouping variables. Differences between subgroups were assessed using meta-regression analyses by incorporating each of the moderators into separate models. The robustness of the pooled estimates was checked via influential analyses in which one study at a time was omitted to assess its impact on the overall effect. Publication bias was tested by Egger's regression test and by visual inspection of the funnel plots where the F-T transformed proportions were plotted against their standard errors.

Additionally, studies reporting inflammation in association with depression were planned to be grouped for separate analysis. We calculated both common and random effects estimates for meta-analyses with inflammation markers using inverse variance weighting for pooling. To test the differences between groups of patients with and without depression symptoms, we used the unstandardised mean score as the measure of effect size. Only for CRP and NLR were there at least three studies available with the detailed parameters needed for the computation of mean differences (MD). Specifically, for this purpose within each group we extracted the number of participants, mean and standard deviation for each continuous outcome (CRP and NLR) or other data sufficient for recalculation (e.g. confidence intervals, standard errors, medians with ranges/quartiles). Relevant transformations were conducted using standard mathematical procedures (Hozo et al., 2005). In one study (Guo et al., 2020), inflammatory marker measurements in two time points were available; therefore, for compatibility with the remaining studies, only that one which was reported 15 days after discharge was chosen, while data collected during hospitalisation was omitted. Due to the very limited number of studies included (three studies), we did not formally check regression using Egger's test.

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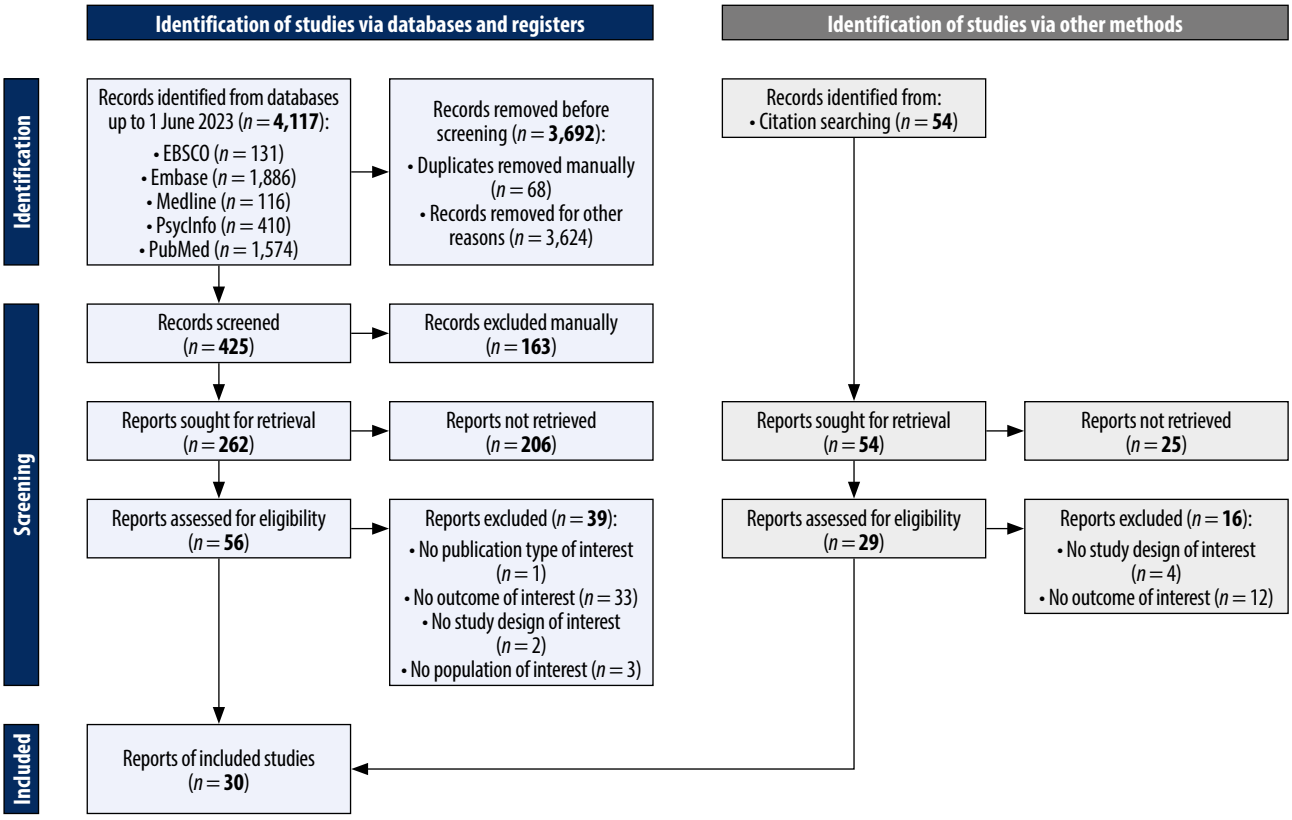

From: Page MJ, McKenzie JE, Bossuyt PM et al.: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71.
For more information: http://www.prisma-statement.org/

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

In the meta-analysis of proportions of depression and mean differences between inflammatory markers, both the fixed effects and the random-effects model with DerSimonian and Laird's estimator of between-study variance were applied. Heterogeneity between studies was estimated using I^2 statistic and Cochran's Q test. We considered the presence of significant heterogeneity when $p < 0.10$ and I^2 value of 25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively (Higgins et al., 2019). The meta-analysis was conducted using the "meta" package (Balduzzi et al., 2019) and R project version 4.3.0.

RESULTS

Characteristics of included studies

The study search resulted in 4,117 references. After duplicates were removed, a total of 3,624 references were excluded during the title screening process as irrelevant to the subject of this review. Selection after the title-abstract screening process resulted in 56 references eligible for full-text screening. Of these, we excluded 39 studies for the following reasons: not reporting the outcome of interest (n = 33); not reporting the population of interest (n = 3); not having the study design of interest (n = 2); and one article was excluded for publication type reason. Additionally, 13 studies were included after the selection process of records identified from reference list searches. The selection process resulted in the inclusion of 30 articles (Fig. 1).

Depression during hospitalisation was reported in 11 articles (Boyraz et al., 2022; Fiore et al., 2021; Guo et al., 2020; Hu et al., 2020; Kahve et al., 2021; Kang et al., 2021; Li et al., 2021; Ngasa et al., 2021; Satapathy et al., 2020; Tuna et al., 2023; Zhang et al., 2020). Depression measured before 6 months from hospital discharge was reported in 16 articles (Beck et al., 2021; Chen et al., 2021; Demiryürek et al., 2022; Fiore et al., 2021; Gramaglia et al., 2021; Houben-Wilke et al., 2022; Huang et al., 2022; Imran et al., 2021; Liu et al., 2020; Mazza et al., 2020, 2021; Méndez et al., 2021; Poyraz et al., 2021; Raman et al., 2021; Vlake et al., 2021; Xiao et al., 2022). Five of the included studies reported on depression in COVID-19 patients 6 months post-discharge (Boyraz et al., 2022; Damiano et al., 2022; Gramaglia et al., 2022; Huang et al., 2022; Huarcaya-Victoria et al., 2023). The follow-up time ranged from 8 (Huarcaya-Victoria et al., 2023) to 22 months (Boyraz et al., 2022). In cohort studies reporting two follow-up timepoints, we included only data for the latter follow-ups in this section.

Study characteristics, including study settings, design, and depression assessment timepoints are summarised in Tab. 1, and study outcomes are summarised in Tab. 2.

Study	Setting	Study design	Sample size (*n*)	Age, years	Male cases (%)	Depression assessment, cut-off scores	Outcomes
Beck et al. (2021)	Switzerland	Prospective observational cohort	126	Mean 58.2 (*SD* 16.35)	76 (60.3)	HADS-D ≥8	Depression, anxiety, PTSD
Boyraz et al. (2022)	Turkey	Retrospective cohort	172	Mean 53.23 (*SD* 13.63)	83 (48.3)	HADS-D ≥7	Depression, anxiety
Chen et al. (2021)	China	Cross-sectional	898	Mean 39.40 (*SD* 14.05)	382 (42.5)	PHQ-9 ≥10	Depression, PTSD, anxiety, trauma exposure, resilience, perceived social support
Damiano et al. (2022)	Brazil	Observational cohort	425	Mean 55.7 (*SD* 14.2)	219 (51.53)	HADS-D ≥8	Psychiatric and cognitive impairment
Demiryürek et al. (2022)	Turkey	Cross-sectional	109	Median 63 (52–72)	56 (51)	BDI ≥17	Depression, anxiety and inflammatory biomarkers
Fiore et al. (2021)	Italy	Longitudinal monocentric	48	Mean 64 (*SD* 17.6)	32 (66.7)	BDI-II ≥20	Depression, sleep impairment, comorbidities other stressors and inflammation markers
Gramaglia et al. (2021)	Italy	Prospective	238	Median 61 (50–71)	142 (59.7)	BDI-II >13	Depression, anxiety, PTS, and resilience
Gramaglia et al. (2022)	Italy	Longitudinal monocentric	196	Median 61.5 (51.0–70.5)	120 (61.2)	BDI-II >13	Depression, anxiety, PTS, peritraumatic distress in relation to COVID-19 pandemic
Guo et al. (2020)	China	Mixed method	103	Mean 42.50 (*SD* 12.53)	59 (57.3)	PHQ-9 ≥5	Depression, anxiety, PTSS and peripheral inflammatory biomarkers
Houben-Wilke et al. (2022)	Netherlands, Belgium	Longitudinal observational	239	Median 50 (39–56)	41 (17.2)	HADS-D ≥8	Depression, PTSD, anxiety
Hu et al. (2020)	China	Cross-sectional	85	Mean 48.8 (*SD* 14.3)	43 (51.5)	PHQ-9 ≥5	Depression, anxiety, insomnia, self-perceived illness severity and inflammatory markers
Huang et al. (2022)	China	Cohort	511	Mean 56.23 (*SD* 12.18)	265 (51.9)	PHQ-9 >9	Depression, PTSD, anxiety, and resilience, perceived social support, personality traits
Huarcaya-Victoria et al. (2023)	Peru	Cross-sectional single centre	318	Mean 53.1 (51.8–54.4)[1]	196 (61.3)	PHQ-9 ≥5	Depression, anxiety, somatic symptoms, PTSD, and inflammatory variables
Imran et al. (2021)	United Arab Emirates	Prospective cross-sectional multicentric	103	Median 40 (23–60)	69 (67)	PHQ-9 ≥10	Depression, anxiety, PTSD
Kahve et al. (2021)	Turkey	Cross-sectional	175	Mean 52.2 (*SD* 12.6)	106 (60.6)	BDI ≥17	Depression, anxiety, and inflammatory markers
Kang et al. (2021)	Korea	Retrospective observational	107	NR	51 (47.7)	PHQ-9 ≥5	Depression, anxiety, PTSD, suicidal ideation, somatic symptoms, COVID-19 stigma
Li et al. (2021)	China	Cross-sectional	99	Median 51.4 (30–73)	54 (54.5)	HADS-D ≥8	Depression, anxiety, and dyspnoea
Liu et al. (2020)	China	Cross-sectional	675	Median 55 (ICQ = 41.66)	317 (47)	PHQ-9 ≥10	Depression, anxiety, PTSD
Mazza et al. (2020)	Italy	Cross-sectional	402	Mean 57.8 (18–87)	265 (63.68)	BDI-13 ≥9	Depression, PTSD, anxiety, insomnia, obsessive-compulsive symptoms, social support, and inflammatory markers
Mazza et al. (2021)	Italy	Prospective	226	Mean 58.52 (*SD* 12.79)	149 (65.92)	BDI-13 ≥9	Depression, PTSD, anxiety, insomnia, obsessive-compulsive symptoms; cognitive functions and inflammatory markers
Méndez et al. (2021)	Spain	Cross-sectional	179	Median 57 (49, 67)[2]	105 (58.7)	PHQ-2 ≥3	Depression, anxiety, PTSD; neurocognitive functions and quality of life
Ngasa et al. (2021)	Cameroon	Cross-sectional single centre	285	Mean 48.47 (*SD* 16.01)	193 (67.72)	HADS-D >11	Symptoms: depression, anxiety
Poyraz et al. (2021)	Turkey	Cross-sectional	284	Mean 39.7 (*SD* 12.7)	140 (50.2)	HADS-D ≥10	Depression, psychological distress, perceived social support
Raman et al. (2021)	Great Britain	Cross-sectional single centre	58	55.4 (13.2)	34 (58.6)	PHQ-9 ≥10	Depression, anxiety, quality of life and symptom (dyspnoea, fatigue) burden

Tab. 1. Characteristics of included studies

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Study	Setting	Study design	Sample size (*n*)	Age, years	Male cases (%)	Depression assessment, cut-off scores	Outcomes
Satapathy et al. (2020)	India	Prospective observational	446	Mean 35.94 (*SD* 11.71)	350 (78.5)	HADS-D ≥8	Depression, anxiety, psychological distress, perceived social support
Sharma et al. (2021)	India	Cross-sectional	135	Mean 41.86 (*SD* 15.09)	91 (67.4)	PHQ-9 ≥5	Depression
Tuna et al. (2023)	Turkey	Cross-sectional single centre	238	Mean 52.8 (*SD* 17.6)	122 (51.3)	HADS-D ≥8	Depression, anxiety
Vlake et al. (2021)	Netherlands	Observational cohort multicentre	118	Median 61 (36–77)	79 (68)	HADS-D ≥8	Depression, PTSD, anxiety, and quality of life
Xiao et al. (2022)	China	Cross-sectional	199	Mean 42.72 (*SD* 17.53)	93 (46.7)	PHQ-9 ≥5	Depression, anxiety, posttraumatic growth
Zhang et al. (2020)	China	Cross-sectional descriptive correlational	296	NR	173 (58.4)	HADS-D ≥8	Depression, anxiety, resilience

[1] Mean and 95% confidence intervals.
[2] 1st, 3rd quartile.
BDI – Beck Depression Inventory; **BDI-II** – Beck Depression Inventory-II; **BDI-13** – Beck Depression Inventory-13; **HADS-D** – Hospital Anxiety and Depression Scale; **NR** – not reported; **PHQ-2** – Patient Health Questionnaire-2; **PHQ-9** – Patient Health Questionnaire-9; **PTS** – post-traumatic stress; **PTSD** – post-traumatic stress disorder; **PTSS** – post-traumatic stress symptoms.

Tab. 1. Characteristics of included studies (cont.)

Pooled proportion of depression symptoms

In the main analysis, we examined moderate or severe depression as an outcome. We meta-analysed fifteen individual estimates of depression (at moderate or severe level) based on data from 5,316 participants who experienced 1,173 events. The overall proportion was estimated at 0.21 (95% CI: 0.13–0.31), and significant heterogeneity between individual studies was detected (I^2 = 98.0%, p_{heter} < 0.01). Subgroup analyses showed that the occurrence of moderate or severe depression decreased with increasing time after hospitalisation (p_{pooled} = 0.30, 95% CI: 0.07–0.61 during hospitalisation, p_{pooled} = 0.18, 95% CI: 0.13–0.23 in studies with measurements undertaken up to 6 months after discharge and p_{pooled} = 0.12, 95% CI: 0.09–0.14 in studies with measurements undertaken at least 6 months after discharge) (Fig. 2). There was no difference between studies using various tools to measure depression (Supplementary Fig. 1). Only after restricting to the subgroup of studies in which depression was measured at least 6 months after discharge was the heterogeneity significantly reduced (I^2 = 0%). Influential analysis depicted the stability of the findings, with the overall proportion oscillating between 0.17 and 0.23 (within a confidence interval range of 0.12 to 0.33) (Supplementary Fig. 2). Funnel plots did not show evidence of asymmetry, in agreement with the result of Egger's test (p = 0.695) (Supplementary Fig. 3). Additionally, a sensitivity analysis with mild, moderate, or severe depression as an outcome was conducted. Based on 21 included studies, the overall proportion of depression was estimated at 0.35, with 95% CI: 0.23–0.48 (Supplementary Fig. 4). The results of subgroup analyses were generally in agreement with the main analysis. A trend of decreasing proportion of depression across three sequential categories of time after diagnosis was found: (p_{pooled} = 0.47, 95% CI: 0.23–0.73 during hospitalisation, p_{pooled} = 0.30, 95% CI: 0.08–0.58 up to 6 months after discharge and p_{pooled} = 0.24, 95% CI: 0.14–0.35 at least 6 months after discharge) (Supplementary Fig. 4). However, no significant differences were detected between subgroups of time after hospitalisation (p = 0.24), nor between tools used to assess depression (p = 0.86) (Supplementary Fig. 4 and Supplementary Fig. 5). There were no signs of small-study effects (Egger's test p = 0.620), and no influential points were detected (Supplementary Fig. 6). Details were presented in the supplementary materials.

Inflammatory markers

Eight articles (Demiryürek et al., 2022; Guo et al., 2020; Hu et al., 2020; Huarcaya-Victoria et al., 2023; Kahve et al., 2021; Mazza et al., 2020, 2021; Raman et al., 2021) investigated the association between depression and inflammation in COVID-19 patients during and after hospitalisation. The subsequent paragraphs provide the detailed outcomes.

Systemic immune-inflammation index (SII)

Associations between SII and depression were reported in three papers (Demiryürek et al., 2022; Mazza et al., 2020, 2021). According to Demiryürek et al. (2022), at 15 days follow-up, the mean baseline SII score was higher in patients with depression compared to those without depression (p = 0.032). However, there was no significant association between inflammatory parameters and BDI scores (p = 0.363) in patients with depression. At one month follow-up, Mazza et al. (2020) found a significant baseline SII influence on the patients' current psychopathological status (p = 0.0357). Consistent with these results, at the three-month follow-up, baseline SII predicted depressive symptoms, and changes in SII predicted changes in both measures of depression scores (p = 0.0013 and p = 0.0204 for BDI-13 and ZSDS, respectively) (Mazza et al., 2021).

Tab. 2. Outcome findings

Reference	Population(s) studied	Sample size (*n*)	Cases (*n*)	Depression assessment, cut-off scores	Depression assessment timepoint	Depression Prevalence (%)	Findings
Beck et al. (2021)	COVID-19 patients hospitalised in two Swiss tertiary-care hospitals and their relatives, 2020	126	10	HADS-D ≥8	30 days after discharge	7.9	Prevalence of psychological distress 30 days after hospital discharge: 24 (19.1%). Depression cases: 10 (7.9%). Factors independently associated with psychological distress: resilience, high levels of perceived stress, and low frequency of contact with relatives
Boyraz et al. (2022)	COVID-19 patients hospitalised in Bezmialem Vakıf University Hospital, 2020	172	68 during hospitalisation; 63 at the follow-up	HADS-D ≥7	During hospitalisation and 20–22 months after discharge	39.5 during hospitalisation; 36.6 at the follow-up	Mean HADS-A ($p = 0.484$) and HADS-D ($p = 0.011$) scores were increased compared to scores during hospitalisation. Being >50 years old, having lower financial status, and being vaccinated were associated with symptoms of depression (adjusted $R^2 = 0.168$)
Chen et al. (2021)	COVID-19 patients hospitalised in Wuhan, China, 2020	898	189	PHQ-9 ≥10	2–4 months after discharge	21	Depression prevalence: 21%. Moderate, severe, very severe depression prevalence: 11.5, 6.3, 3.2%, respectively. Patients who were more impacted by negative news reports, had greater exposure to traumatic experiences, and lower levels of perceived social support were at a higher risk of depression
Damiano et al. (2022)	Moderate or severe COVID-19 patients hospitalised in Hospital das Clínicas da Faculdade de Medicina da Universidade de Saõ Paulo, Brazil, 2020	425	34	HADS-D ≥8	6–9 months after discharge	8	Diagnosis of "depression": 8% of the sample. Psychiatric or cognitive outcomes were not associated with any clinical variables related to the severity of acute-phase disease, nor by disease-related psychosocial stressors
Demiryürek et al. (2022)	COVID-19 patients discharged with full recovery after the treatment in the Sakarya University Training and Research Hospital, 2020–2021	109	38	BDI ≥17	15 days after discharge	35	Patients with depression: significantly younger than the group without depression ($p < 0.001$). Female patients: significantly higher incidence of depression ($p = 0.028$). Lymphocyte counts, D-dimer, ferritin, sedimentation, CRP, fibrinogen, and LDH levels significantly higher in the group with depression as compared with the group without depression ($p = 0.007$, $p = 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.012$, respectively). The mean NLR score in patients without depression was lower than in patients with depression ($p = 0.047$). The mean SII score in the group without depression was lower than in the group with depression ($p = 0.032$). No significant association between inflammatory parameters and BDI scores in patients with depression. No correlation between BAI scores and inflammatory lab tests in patients with anxiety except for the moderate positive correlation between BDI and ferritin levels ($r = 0.24$, $p = 0.035$)
Fiore et al. (2021)	COVID-19 patients hospitalised >7 days in Infectious Disease Unit in Sassari, Italy, 2020	48	21	BDI-II ≥20	1 week after admission (T0) and 1 week after discharge (T1)	43.7;T1 total not reported	21 (43.7%) reported depressive symptoms at T0, 8 (16.7%) had minimal symptoms. Mild, moderate, and severe depressive symptoms were found in 24 (50%), 14 (29.2%), and 2 (4.2%) patients, respectively, at T0. The comparison of the BDI-II questionnaire at T0 with T1 showed a significant improvement in the total score ($p < 0.0001$), as well as in 4 out of the 5 selected questions of interest ($p < 0.05$)
Gramaglia et al. (2021)	COVID-19 patients hospitalised in the University Hospital Maggiore della Carità, Novara, Italy, 2020	238	45	BDI-II >13	3–4 months after discharge	29.5	At the psychiatric assessment, the participants showed: 29.5% depressive symptoms, 5% mild to severe depression
Gramaglia et al. (2022)	COVID-19 patients hospitalised in the University Hospital Maggiore della Carità, Novara, Italy, 2020	196	24 (at 4 months) 27 (at 12 months)	BDI-II >13	4 and 12 months after discharge	12.3 (at 4 months) 13.8 (at 12 months)	Depressive symptoms registered at the clinical interview showed a significant improvement during the 4 to 12-months follow-up ($p < 0.0003$). Female gender ($p = 0.02$) and depressive symptoms at 4-months follow-up ($p = 0.01$) were associated with depressive symptoms after 12 months

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Tab. 2. Outcome findings (cont.)

Reference	Population(s) studied	Sample size (*n*)	Cases (*n*)	Depression assessment, cut-off scores	Depression assessment timepoint	Depression Prevalence (%)	Findings
Guo et al. (2020)	Patients hospitalised with mild COVID-19 in Shanghai Public Health Clinical Center, 2020	103	62 in patients group	PHQ-9 ≥5	During hospitalisation	60.2	COVID-19 patients with depression: 62 (60.2%). Proportion of non-COVID controls who displayed depression: 32 (31.1%) symptoms was significantly lower ($\chi^2 = 17.61$, $p < 0.001$); 18 (17.5%) patients had moderate to severe depression symptoms
Houben-Wilke et al. (2022)	Data from confirmed COVID-19 patients (hospitalised and non-hospitalised), members of online long COVID-19 peer support groups	239	112 (3 months) 97 (6 months)	HADS-D ≥8	3 and 6 months after the onset of COVID-19	46.9 (3 months) 40.6 (6 months)	3-month follow-up: 46.9% had symptoms of depression. 6-month follow-up: depression 40.6% ($p = 0.08$) respectively versus the 3-month follow-up. TSQ scores and HADS anxiety and depression scores were strongly correlated at the 3- and 6-month follow-ups ($r = 0.63–0.71$, $p < 0.001$). Symptoms of depression were comparable between hospitalised and non-hospitalised patients
Hu et al. (2020)	Severe COVID-19 patients hospitalised in Tongji Hospital, Wuhan in 2020	85	39	PHQ-9 ≥5	Prior to discharge	45.9	45.9% of patients had symptoms of depression. Female sex, a higher level of interleukin 1β, greater self-perceived illness severity significantly associated with higher PHQ-9 scores. Sex ($\beta = 0.313$, $p < 0.001$), self-perceived illness severity ($\beta = 0.411$, $p < 0.001$) and levels of inflammatory markers ($\beta = 0.358$, $p = 0.002$) had direct effects on patients' mental health. Disease duration ($\beta = 0.163$, $p = 0.003$) and levels of inflammatory markers ($\beta = 0.101$, $p = 0.016$) indirectly affected patients' mental health, with self-perceived illness severity acting as a mediator
Huang et al. (2022)	COVID-19 patients hospitalised in Jinyintan Hospital, Wuhan, 2020	511	104 (6 months) 61 (12 months)	PHQ-9 >9	6 and 12 months postdiagnosis	20.35 (6 months) 11.94 (12 months)	Higher neuroticism (OR = 1.30, 95% CI = 1.15–1.46, $p < 0.001$) and depression scores at T1 (OR = 1.15, 95% CI = 1.04–1.26, $p = 0.007$) increased the probability of depression at T2; higher openness (OR = 0.91, 95% CI = 0.82–1.00, $p = 0.048$) and higher agreeableness (OR = 0.80, 95% CI = 0.70–0.92, $p = 0.002$) at T1 reduced the likelihood of depression at T2
Huarcaya-Victoria et al. (2023)	COVID-19 patients hospitalised in Hospital Nacional Guillermo Almenara Irigoyen, 2020	318	96	PHQ-9 ≥5	6–8 months after discharge	30.9	Variables associated with a higher frequency of clinically relevant mental symptoms: female sex, self-perception of greater COVID-19 severity, presence of persistent COVID-19 symptoms, loss of a family member due to COVID-19, prior psychiatric diagnosis, or treatment. NLR: significantly higher in patients with depression. Women: higher frequency of symptoms of depression (PRa = 2.11; 95% CI: 1.16–3.84), anxiety and somatic. Severe or critical COVID-19: more likely to have depression compared to mild infection. No association between NLR (≥6.5) and MLR (≥0.364) with adverse mental health outcomes. Patients with persistent COVID-19 symptoms during the interview: more likely to have a higher frequency of depression (PRa = 7.80; 95% CI: 2.16–28.15)
Imran et al. (2021)	Patients with moderate-to-critical COVID-19 from two tertiary care hospitals in Dubai, 2020	103	13 (30 days) 6 (60 days)	PHQ-9 ≥10	At 30 and 60 days of discharge	12.7 (30 days) 7.1 (60 days)	Prevalence rate of clinically significant depression was 12.7% and 7.1% at 30 and 60 days, respectively
Kahve et al. (2021)	Patients with COVID-19, hospitalised in Ankara City Hospital, 2020	175	N/A	BDI ≥17	During hospitalisation	N/A	Correlation between blood sedimentation rate and BDI levels: $p = 0.504$. Correlation between CRP and BDI levels: $p = 0.117$. Correlation between IL-6 and BDI levels: $p = 0.450$. Correlation between patients' age and their depression levels: $r = –0.1312$, $p = 0.084$. Depression levels in women were higher than in men, and their NLR, ferritin, IL-6 levels were found to be lower compared to men

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Tab. 2. Outcome findings (cont.)

Reference	Population(s) studied	Sample size (*n*)	Cases (*n*)	Depression assessment, cut-off scores	Depression assessment timepoint	Depression Prevalence (%)	Findings
Kang et al. (2021)	Patients with COVID-19 admitted to community treatment centre (CTC) in Seoul, Korea, 2020	107 (1st week) 93 (2nd week) 62 (3rd week) 32 (4th week)	7 (1st week) 4 (2nd week) 3 (3rd week) 2 (4th week) 19 (1st week) 13 (2nd week) 12 (3rd week) 3 (4th week)	PHQ-9 ≥10 PHQ ≥5	At 1st ,2nd, 3rd and 4th week of isolation in CTC	6.5 (1st week) 4.3 (2nd week) 4.8 (3rd week) 15.6 (4th week) 17.8 (1st week) 14 (2nd week) 19.4 (3rd week) 9.4 (4th week)	Prevalence of more-than-moderate depression during first week of isolation: 24.3% of total population. Depression significant risk factors: previous psychiatric history and stigma of COVID-19 infection. Prevalence of depression remained similar across the four weeks. Prevalence of severe depression increased after four weeks. Previous psychiatric history was significantly associated with a depressed mood (adjusted OR [aOR]: 11.76; 95% CI: 2.67–51.92). COVID-19 stigma was also related to a depressed mood (aOR: 7.66; 95% CI: 2.76–21.29)
Li et al. (2021)	Patients with COVID-19, hospitalised in Leishenshan Hospital, Wuhan, 2020	99	50	HADS-D ≥8	During hospitalisation	50.01	No significant difference between male and female patients in depressive symptoms ($\chi^2 = 0.264$, $p = 0.688$). Patients 46–60 years old: higher rate of depressive symptoms than 30–45 years old ($\chi^2 = 6.154$, $p = 0.013$). No interaction effect between age and hospital stays in depressive symptoms ($F = 0.134$, $p = 0.969$). The risk of depressive symptoms in patients who stayed >14 days, was 4.89 times (95% CI: 1.72–13.94) higher than those stayed ≤7 days in hospital. For depressive symptoms, correlation between levels of dyspnoea and depression scores: $p = 0.184$
Liu et al. (2020)	Patients with COVID-19 (including 13.3% medical staff who had been ill) hospitalised in Wuhan, 2020.	675	128	PHQ-9 ≥10	3 months after discharge (average 36.75 days)	19	The odds of severe depression significantly increased by: higher educational level (OR: 1.54, 95% CI: 1.07–2.22), living with children (OR: 4.75, 95% CI: 2.20–10.23), smoking (OR: 4.89, 95% CI: 2.05–11.66), higher disease severity (OR: 4.40, 95% CI: 2.51–7.74), higher total number of symptoms after discharge (OR: 1.92, 95% CI: 1.47–2.50), and perceived discrimination (OR: 1.55, 95% CI: 1.37–1.75)
Mazza et al. (2020)	Patients with COVID-19, hospitalised in IRCCS San Raffaele Hospital, Milan, 2020	402	113 42	ZSDS ≥50 BDI-13 ≥9	1 month after discharge	31 10.5	The proportion of patients self-rated in the psychopathological range of depression: 31%. Despite significantly lower levels of baseline inflammatory markers, females suffered more for both anxiety and depression. Patients with a positive previous psychiatric diagnosis showed increased scores on most psychopathological measures, with similar baseline inflammation. Baseline SII positively associated with scores of depression at follow-up. Effects of baseline inflammatory markers (CRP, NLR, MLR, and SII) on the current psychopathological status revealed a significant effect of SII (Wilks'$\lambda = 0.92$; $F = 2.12$; *df* 8,185; $p = 0.0357$), with no effect of the other markers surviving the statistical threshold.
Mazza et al. (2021)	Patients with COVID-19, hospitalised in IRCCS San Raffaele Hospital, Milan, 2020	226	51 20	ZSDS ≥50 BDI-13 ≥9	3 months after discharge	28 9	Persistent depressive symptomatology was found during follow-up. Sex, previous psychiatric history, and the presence of depression at one month affected the depressive symptomatology at three months. SII predicted self-rated depressive symptomatology at three-month follow-up; and changes of SII predicted changes of depression during follow-up. Significant interaction of delta SII with time on the pattern of change of both BDI-13 ($F = 12.37$, *df* 1,32, $p = 0.0013$) and ZSDS ($F = 5.95$, *df* 1,32, $p = 0.0204$) was found
Méndez et al. (2021)	Patients with COVID-19, hospitalised in Valencia, Spain, 2020	179	48	PHQ-2 ≥3	2 ± 1 months after discharge	26.8	Rate of positive screening for depression: 26.8%

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Tab. 2. Outcome findings (cont.)

Reference	Population(s) studied	Sample size (*n*)	Cases (*n*)	Depression assessment, cut-off scores	Depression assessment timepoint	Depression Prevalence (%)	Findings
Ngasa et al. (2021)	Patients with COVID-19, hospitalised in the Laquintinie Hospital, Douala, Cameroon, 2021	285	232	HADS-D >11	During hospitalisation	81.40	The prevalence of depression: 81.40%. Age >35 years (OR: 2.03, $p = 0.02$), presence of comorbidity (OR: 1.68, $p = 0.01$), BMI ≥ 30 kg/m^2 (OR: 1.78, $p = 0.02$), presence of COVID-19 complications (OR: 1.28, $p = 0.01$) and anxiety (OR: 4.60, $p < 0.001$) were independently associated with depression
Poyraz et al. (2021)	Patients with "probable" and "confirmed" COVID-19, population of outpatients and inpatients of Cerrahpaşa Medical Faculty, Istanbul, 2020	284	51	HADS-D ≥10	Mean 50 days since diagnosis	18.8	After a mean of almost 50 days following the diagnosis, 34.5% reported clinically significant PTSD, anxiety, and/or depression. 44.3% reported one or more protracted symptom(s). COVID-19 patients were prone to psychological distress in the first few months after the infection, with frequent protracted symptoms in this period
Raman et al. (2021)	Patients with moderate to severe COVID-19, hospitalised in Oxford University Hospitals National Health Service Foundation Trust, and 30 uninfected controls, 2020	58	11	PHQ-9 ≥10	2–3 months from disease onset	19	Patients had a higher burden of self-reported symptoms of depression compared to controls ($p < 0.0001$ to 0.044), 19% of hospitalised COVID-19 patients had moderate to severe self-reported symptoms of depression. The severity of depression and anxiety did not consistently associate with markers of inflammation (except for monocyte count) or multiorgan injury among patients. Moderate correlation was seen between the extent of mood symptoms and anxiety and ongoing breathlessness (PHQ-9 and MRC dyspnoea score: $r = 0¢58$, $p < 0.0001$, GAD-7 and MRC dyspnoea score: $r = 0.41$, $p = 0.002$)
Satapathy et al. (2020)	Patients with mild to moderate COVID-19, hospitalised in a tertiary care level hospital in Delhi-NCR, 2020	446	86	HADS-D ≥8	During hospitalisation	19.28	Prevalence of depression: 19.28%. Females, patients aged 31–45 years, and lower SES: significantly higher psychological distress as compared to their counterparts. Higher HADS-A and HADS-D scores, female gender and low SES were significant risk factors for psychological distress. Depression: more prevalent in male, however males and females had statistically same levels of depression on HADS. Distress, anxiety, male gender and younger age were the risk factors for an increase in depression. Increased social support was correlated significantly with decreased depression
Sharma et al. (2021)	Patients with COVID-19, hospitalised in the tertiary care hospital in Jabalpur, 2020	135	68	PHQ-9 ≥5	Post discharge period, timepoint not specified	50.4	Depression was found to be 50.4%, out of which, 29.6% were in mild depression, 8.9% were in moderate depression and 11.8% were in moderately severe to severe depression. Females had approximately four times higher risk for depressive symptoms ($p < 0.001$), and for an age group, more than 45 was found to be significantly associated with depression
Tuna et al. (2023)	Patients hospitalised with COVID-19 and 168 participants hospitalised for reasons other than COVID-19, Istanbul, 2020	238	116	HADS-D ≥8	During hospitalisation	50.8	In the COVID-19 sample, 50.8% of the patients had subsyndromal depressive symptoms. Depression levels in patients with COVID-19 were not higher than those in the internal medicine inpatient unit at the same time. Worries about transmission to others, uncertainty, social media news, and health anxiety increased the psychiatric symptoms of participants with COVID-19. Disruptions in social relationships and health also influence depression symptom levels

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Reference	Population(s) studied	Sample size (*n*)	Cases (*n*)	Depression assessment, cut-off scores	Depression assessment timepoint	Depression Prevalence (%)	Findings
Vlake et al. (2021)	Patients with COVID-19, hospitalised in intensive care units of three hospitals in Rotterdam, 2020–2021 and historical control cohort	118	8 of 57 (48%, 6 weeks) 19 of 107 (80%, 3 months) 18 of 80 (68%, 6 months)	HADS-D ≥8	6 weeks, 3 months, and 6 months after discharge	14 (6 weeks) 18 (3 months) 22 (6 months)	COVID-19 patients reported less severe symptoms of depression than the historical critical illness cohort
Xiao et al. (2022)	Patients with COVID-19, hospitalised in Wuhan, Shenzhen, Zhuhai, Dongguan and Nanning, 2020	199	46	PHQ-9 ≥5	6 months after discharge	23.1	The proportions of depressive symptoms <5, ≥5 and <10, ≥10 were 76.9%, 12.0% and 11.1%, respectively. Receiving mental health care services during hospitalisation, somatic symptoms after discharge, perceived impact of being infected with COVID-19, and perceived affiliate stigma were significantly associated with probable depression. Post-hospitalisation and psychosocial factors had relatively stronger associations with depression than pre-hospitalisation and hospitalisation factors
Zhang et al. (2020)	Patients with mild COVID-19 hospitalised in FangCang Hospital, Wuhan, China, 2020	296	55	HADS-D ≥8	During hospitalisation	18.6	Approximately 18.6% of the patients had depression (subthreshold depression and major depression). Risk factors for depression: having family members with COVID-19. Resilience was inversely associated with and was a protective factor for both anxiety and depression

BAI – Beck Anxiety Inventory; **BDI** – Beck Depression Inventory; **BDI-II** – Beck Depression Inventory-II; **BDI-13** – Beck Depression Inventory-13; **BMI** – body mass index; **CRP** – C-reactive protein; **HADS-A** – Hospital Anxiety and Depression Scale – Anxiety; **HADS-D** – Hospital Anxiety and Depression Scale – Depression; **IL-6** – interleukin 6; **LDH** – lactate dehydrogenase; **MLR** – monocyte/lymphocyte ratio; **MRC** – Medical Research Council; **N/A** – not available; **NLR** – neutrophil/lymphocyte ratio; **PHQ** – Patient Health Questionnaire; **PHQ-2** – Patient Health Questionnaire-2; **PHQ-9** – Patient Health Questionnaire-9; **PRa** – adjusted prevalence ratio; **SES** –socioeconomic status; **SII** – systemic immune-inflammation index; **TSQ** – Trauma Screening Questionnaire; **ZSDS** – Zung Self-Rating Depression Scale.

Tab. 2. Outcome findings (cont.)

Neutrophil/lymphocyte ratio (NLR) and monocyte/lymphocyte ratio (MLR)

The role of the NLR in depression symptomatology was investigated in six papers (Demiryürek et al., 2022; Hu et al., 2020; Huarcaya-Victoria et al., 2023; Kahve et al., 2021; Mazza et al., 2020, 2021). Three articles reported on associations between MLR and depression (Huarcaya-Victoria et al., 2023; Mazza et al., 2020, 2021). In one study (Demiryürek et al., 2022), the mean NLR score in patients with depression was higher than in patients without depression ($p = 0.047$).

Regarding the severity of depression symptoms, it was found that NLR, measured upon hospital admission, was significantly higher in patients with depressive symptoms ($p = 0.041$) compared to those without clinically relevant symptoms (Huarcaya-Victoria et al., 2023). Results of two cross-sectional studies conducted during hospitalisation (Hu et al., 2020; Kahve et al., 2021) are contradictory. Baseline NLR was not related to BDI scores in one study ($p = 0.427$) (Kahve et al., 2021), while it was found to be significantly related to PHQ-9 score for depression in the second study ($p < 0.01$) (Hu et al., 2020). Baseline NLR and MLR did not correlate with BDI-13 ($p = 0.130$ and $p = 0.103$) or with ZSDS scores ($p = 0.860$, $p = 0.761$, respectively) at one month and at three months follow-up (Mazza et al., 2020, 2021).

C-reactive protein (CRP)

Associations between CRP and depression were examined in seven articles (Demiryürek et al., 2022; Guo et al., 2020; Hu et al., 2020; Kahve et al., 2021; Mazza et al., 2020, 2021, Raman et al., 2021). There are discrepancies between the results of two studies. In the first study (Demiryürek et al., 2022), baseline CRP levels were significantly higher in patients with depression ($p < 0.001$), while the difference between groups was not significant in the second study ($p = 0.417$) (Hu et al., 2020). During hospitalisation, no significant correlation was found between CRP and BDI levels ($p = 0.117$) (Kahve et al., 2021). The PHQ-9 total score of patients with depression symptoms was found to be significantly related to CRP levels ($p = 0.003$) (Guo et al., 2020). Baseline CRP did not correlate with BDI-13 or with ZSDS scores at one month ($p = 0.098$, $p = 0.076$, respectively) or at the three-month follow-up (Mazza et al., 2020, 2021). Similarly, at the 2–3-month follow-up (Raman et al., 2021), there was no significant correlation between CRP and PHQ-9 scores ($p = 0.16$) in patients with depression. Interestingly, a significant improvement in CRP levels was shown in patients without depression symptoms ($p = 0.001$), whereas patients with depression symptoms did not show a significant change ($p = 0.179$) (Guo et al., 2020).

Results of syntheses: inflammatory markers and depression

The fixed effects model of meta-analysis of inflammatory markers showed a difference between COVID-19 patients with and without depression, with higher concentrations of both CRP and NLR detected among those experiencing

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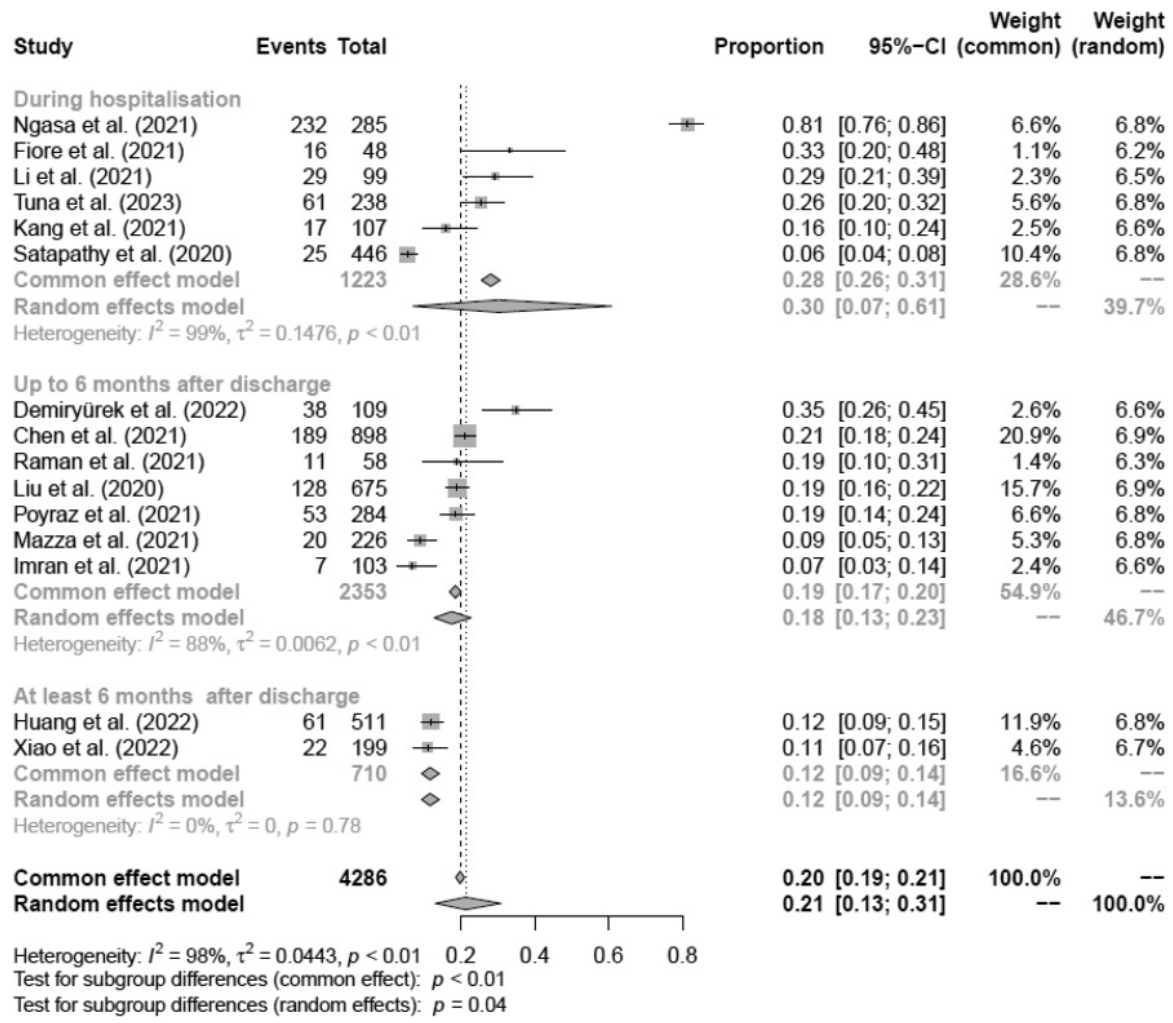
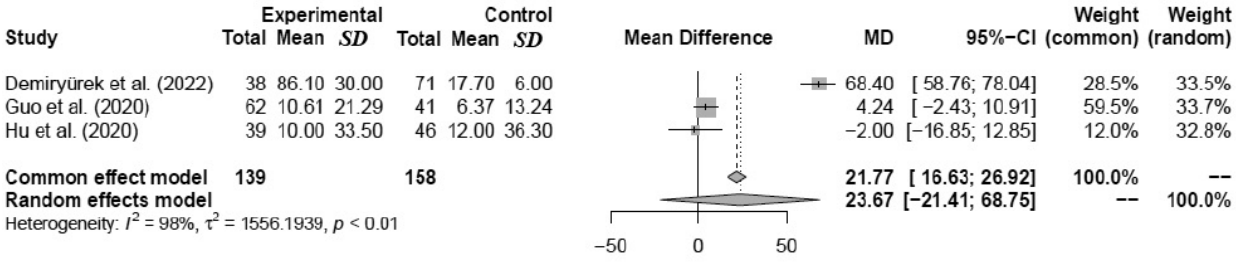


Fig. 2. Proportions of moderate or severe depression in individual studies and pooled results by time after hospitalisation

A



B

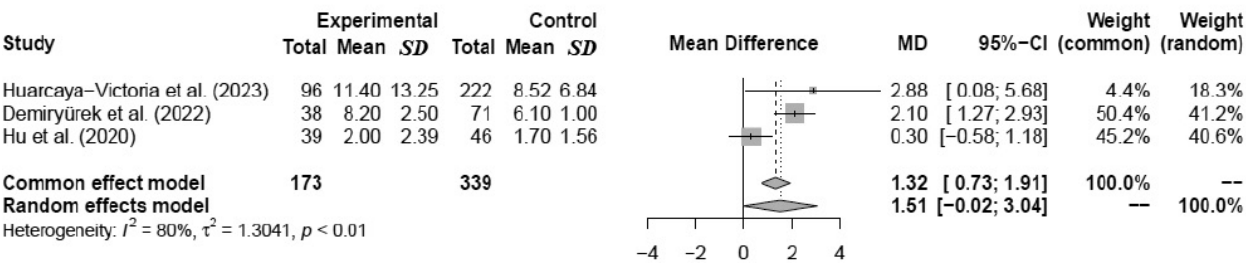


*Fig. 3. Mean differences of **A.** CRP, **B.** NLR between the experimental (patients with depression symptoms) and control (patients without depression symptoms) groups*

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mental disturbances. However, in the random effects model, the findings for CRP lost significance, and those for NLR were on the boundary of significance ($p = 0.053$) (Fig. 3). Influential analysis revealed that omitting the study by Demiryürek et al. (2022) from the CRP analysis and the study by Hu et al. (2020) from the NLR analysis reduced heterogeneity to 0%, with estimated results MD = 3.19, 95% CI: −2.89–9.28, $p = 0.304$ and MD = 2.16, 95% CI: 1.37–2.96, $p < 0.001$, respectively, showing robust findings only for NLR.

DISCUSSION

Depression symptoms in COVID-19 patients

According to evidence (Mazza et al., 2023), the prevalence of depression in COVID-19 patients is around 30%; therefore the research on this group should be prioritised. Furthermore, we should evaluate the prevalence of depression, considering the infection stage and the severity of depression symptoms. Rogers et al. (2020) grouped data in such a manner, finding evidence for improved depression symptoms over time; however, preliminary data for COVID-19 patients restricted the conclusions for this group.

To our knowledge, only three of the meta-analyses conducted to date stratified the data by the severity of depression symptoms or the stage of SARS-CoV-2 infection (Deng et al., 2021; Lao et al., 2020; Liu et al., 2021). Lao et al. (2020) found that the prevalence of depression symptoms was 44% (95% CI: 30–57%) in hospitalised, and 55% (95% CI: 34–77%) in discharged patients. Subgroup analysis based on depression severity showed a decreasing trend of prevalence: 31% (95% CI: 19–43%) for mild, 13% (95% CI: 11–15%) for moderate, and 5% (95% CI: 2–8%) for severe. In the meta-analysis conducted by Deng et al. (2021), the pooled prevalence of depression was 45% (95% CI: 37–54%), and no significant differences in depression prevalence between inpatients and outpatients ($p = 0.16$) were found. Compared to this result, in the meta-analysis performed by Liu et al. (2021), the pooled prevalence of depression was estimated at 38% (95% CI: 25–51%). The pooled prevalence in terms of symptom severity was 29%, 17% and 10% for mild, moderate, and severe depression, respectively. The prevalence of depression in the acute stage of the COVID-19 was 42% and 14% in the post-illness stage, showing an improvement in symptoms with time.

In our analysis, the estimated 0.22 (95% CI: 0.15–0.30) proportion of at least moderate depression symptoms was lower compared to the aforementioned studies. Subgroup analyses showed that the occurrence of moderate or severe depression decreased with increasing time after hospitalisation, what is in line with the results of Liu et al. (2021) and Rogers et al. (2020). Our results contradict the evidence of a higher depression burden after hospital discharge (Lao et al., 2020) and the results of Deng et al. (2021). However, it should be taken into consideration that in the study by Deng et al. (2021) only one study reported depression prevalence for outpatients, and in the meta-analysis by Lao et al. (2020), publication bias analysis or meta-regression were not conducted.

Relationship between inflammation and depression in COVID-19

Research based on the inflammatory theory of depression explores three causal pathways: depression causing inflammation, inflammation causing depression, and bidirectional relationships (Howren et al., 2009). Elevated pro-inflammatory cytokines are linked to specific symptoms of depressive disorder, including decreased mood, anhedonia, somatic fatigue, and alterations in sleep and appetite (Harsanyi et al., 2022; Kappelmann et al., 2021; Milaneschi et al., 2021).

The COVID-19 pandemic has set new directions for research into the inflammatory mechanisms underlying the development of depression. Studies investigating the pathophysiology of COVID-19 provide evidence for oxidative stress, peripheral hyperinflammation, and neuroinflammation in the development and progression of depression symptoms (Mingoti et al., 2022). Specifically, the inflammatory cytokines and type 2 angiotensin converting enzyme (ACE-2) receptors are hypothesised to play a role of a common pathophysiological mechanism between COVID-19 and depression (da Silva Lopes et al., 2021). Our analysis showed a difference between groups, with higher levels of CRP and NLR in COVID-19 patients experiencing depression symptoms; however, in random effects models, only NLR remained on the boundary of significance ($p = 0.053$). The clinical picture of depression is heterogeneous, and low-grade inflammation is not a generalised feature of depression. Moreover, inflammation is usually associated with atypical symptoms, and depressed patients with melancholic features may show an anti-inflammatory profile, for instance, with a normal or slightly elevated CRP levels (Del Giudice and Gangestad, 2018).

Strengths and limitations of the evidence and review processes

In this review, the severity of depressive symptoms in patients hospitalised with COVID-19 was taken into consideration, along with the link between inflammation and depression. This provides for a thorough examination of the subject matter. However, this study also has certain limitations. First, we detected very high heterogeneity between individual studies. Second, regarding the associations between depression and different inflammatory markers, only for CRP and NLR there were at least three studies with detailed parameters available for computation, limiting the generalisation of our findings.

Implications of study results for practice, policy, and future research

Future research should track the trajectory of depression symptoms over time to distinguish depressed mood as part of a stress response and the development of major depressive disorder (MDD) after experiencing a potentially

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life-threatening event such as SARS-CoV-2 infection. Patients with COVID-19 should be screened for depression not only during hospitalisation, but also after discharge. Furthermore, as screening tools tend to generate higher prevalence estimates than those obtained from diagnostic interviews (Levis et al., 2019), complementing self-report questionnaires with interviews conducted by professionals is worth considering. Interviewing patients could also help identify atypical depression symptoms associated with elevated inflammatory markers (Del Giudice and Gangestad, 2018).

Researchers should focus on understanding how the dysregulation of the immune system contributes to the development and persistence of depression symptoms in COVID-19 patients. Routine testing for inflammatory markers like CRP or NLR may help track the progression of viral infection; however, it may also serve as a predictor of depression. COVID-19 patients experiencing depression may benefit from antidepressant medication, though it is worth investigating whether anti-inflammatory treatment could support the alleviation of depression symptoms or prevent relapse.

CONCLUSIONS

This systematic review provides a comprehensive meta-analysis of the prevalence of depression in COVID-19 patients during hospitalisation and after hospital discharge, and the moderating effects of inflammatory markers.

According to our results, the proportion of depression decreases over time after a COVID-19 diagnosis. However, the relationship between depression and inflammation requires further research, with NLR emerging as the most promising marker for future research.

Conflict of interest

The authors declare that there are no potential conflicts of interest due to any commercial or financial dependencies.

Author contribution

Original concept of study: ALW, BBK. Collection, recording and/or compilation of data: ALW, KOT, AM. Analysis and interpretation of data: ALW, KOT, AM, BBK. Writing of manuscript: ALW, KOT, AM, BBK. Critical review of manuscript: AM, BBK. Final approval of manuscript: ALW, BBK.

Availability of data

The template data collection forms; data extracted from included studies; data used for all the analyses; and any other materials used in the review will be made available by the authors without unwarranted objection.

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