ELSEVIER

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.

Review Article

Psychological problems and reduced health-related quality of life in the COVID-19 survivors

Mahya Dorri [a,1], Mohamad Hossein Mozafari Bazargany [a,1], Zeinab Khodaparast [b],
Soroush Bahrami [a], Mahnaz Seifi Alan [b], Fariba Rahimi [a], Zeinab Kamipoor [c],
Mohammad Mahdi Niksima [c], Hanieh Dehghan [c], Hadis Rastad [b,*]

[a] *Cardiovascular Research Center, Alborz University of Medical Sciences, Karaj, Iran*
[b] *Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran*
[c] *Social Determinants of Health Research Center, Alborz University of Medical Sciences, Karaj, Iran*

A B S T R A C T

Background: COVID-19 survivors are predicted to experience the long-term consequences, including pulmonary, neurologic, cardiovascular, and mental health sequelae. This systematic review and meta-analysis was performed on studies assessing the health-related quality of life (HRQoL) and psychiatric problems in COVID-19 survivors.
Methods: A systematic search was performed on PubMed, Embase, and Google scholar databases using key terms COVID-19, PTSD, depression, anxiety, HRQoL, survivors. Pooled estimates were calculated using the random-effects models.
Results: A total of 21 eligible articles were included. The pooled prevalence of PTSD, depression, and anxiety among COVID-19 survivors were 18% (95% CI: 13 to 23%, I^2=88.23%), 12% (8 to 17%, I^2=91.84%), and 17% (12 to 22%, I^2=97.07%), respectively. COVID-19 survivors compared to pre-COVID-19 time and controls showed reduced HRQoL and a lower score in Social Functioning (SF) and Role Physical (RP), and Role Emotional (RE) health. Females compared to males had a higher risk of experiencing mental health problems. Also, patients with severe disease had a higher prevalence of depression and anxiety, but not PTSD.
Limitations: Regarding HRQoL, we were not able to perform a subgroup analysis due to a lack of data. Also, the included studies mainly used a self-rating scale to detect psychological problems in their study population.
Conclusion: A significant number of patients who survived from COVID-19 might suffer from PTSD, depression, and anxiety beyond one month. Our systematic review also found evidence of reduced HQOL and limited social role in these survivors

1. Introduction

SARS-CoV-2 is the third member of the coronavirus family, with less fatality but more transmissibility and infectivity than other family members (Pal et al., 2020). It has infected over 106 million people worldwide, of whom over 59 million people have survived as of 7 February 2021 (Asghari et al., 2020). Given the prior experience with coronavirus outbreaks, it has been supposed that COVID-19 survivors may not fully recover, and some of them are supposed to be affected by the long term sequels (O'Sullivan, 2021), psychological problems, such as post-traumatic stress disorder (PTSD), depression, and anxiety, and reduced quality of life are probably among the key health issues facing

survivors (O'Sullivan, 2021; Ahmed et al., 2020; Raghu and Wilson, 2020). A high prevalence of these psychological sequelae was reported in survivors of other coronavirus infections, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) (Rogers et al., 2020). Also, post-illness stage patients infected by other epidemic diseases, such as MERS and H1N1 Influenza have frequently experienced the short-term or long-term quality of life problems (Ahmed et al., 2020). COVID-19 is likely to have the similar mental health sequelae in a group of survivors (Makara-Studzinska et al., 2021).

Currently, the exact mechanistic pathways underlying psychological and psychiatric symptoms after COVID-19 are unclear. Infection-triggered perturbation of the immune system is suggested to play a

main pathophysiological role for the post-COVID-19 mental health issues (Yuan et al., 2020). In addition to the immunological mechanisms, treatment for COVID-19, the psychological stress of enduring a potentially fatal disease, stigma, and social isolation experienced by patients during the COVID-19 may have an adverse effect on the mental health and contribute to mood disorders, psychosis, and anxiety disorders (Borst et al., 2020). Furthermore, COVID-19 mental health sequelae might be induced directly through the viral infection of the central nervous system (CNS) (Holmes et al., 2020).

Follow-up studies have measured the psychological distress and the health-related quality-of-life (HRQoL) among COVID-19 survivors to identify the clinical needs of COVID-19 survivors to rehabilitation and mental health services. However, to our best knowledge, no systematic reviews have been conducted in this regard.

Therefore, this review aimed to summarize the available evidence on the reduced HRQoL and the prevalence of psychiatric problems, including PTSD, depression and anxiety, and HRQoL among COVID-19 survivors.

2. Methods

This systematic review was conducted in accordance with the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Knobloch et al., 2011). As no human subjects were involved, no ethical approval was required for conducting this study. The study protocol was registered on PROSPERO (ID: CRD42020224773).

All eligible studies assessing post-trauma stress disorder (PTSD), anxiety, depression, or Health-related quality of life (HRQoL) in COVID-19 patients during the post-acute phase were included in this study.

2.1. Search

A systematic search of three electronic databases such as, PubMed, Embase, and Google Scholar, was performed on 12 November 2020 and updated on 16 January 2021.

While tailoring for each database, the following key terms were combined by Boolean "OR" in each domain, and these domains were combined by "AND":

(1) The population studied: "survivors" OR "recovered patients" OR "discharged patients."
(2) Exposure: "COVID-19″, "sars-COV-2″, "novel corona", "2019-nCOV"
(3) Outcome: PTSD, anxiety, depression, or HQOL

The reference list of each relevant article was manually checked to retrieve potentially eligible items which were not captured by electronic database searches.

2.2. Study selection

Two independent researchers [HM & MD] initially screened articles by titles and abstracts, followed by full texts to identify studies that met the eligible criteria. Disagreements were resolved by consulting a third researcher (HR or MS).

2.3. Eligibility criteria

We included the observational studies that fulfilled all five following inclusion criteria:

(1) Having a case series or cohort design
(2) Written in English and published in a peer-review journal
(3) Including adult COVID-19 out/inpatients who were discharged from the hospital or recovered

(4) Evaluating at least one of the following outcomes: PTSD, anxiety, depression, or HQOL
(5) A sample size of ≥30 participants

2.4. Outcomes and measures

We assessed four outcomes, such as PTSD, depression, anxiety, and HRQoL, measured using clinical diagnosis, standardized and validated scales, or self-report.

2.4.1. Data extraction

Three independent researchers [FR, ZK & HD] extracted the following data from the eligible studies and recorded them in a 'Data Extraction Form' generated using Microsoft Excel:

First author's name, country, study design, sample size, age, sex ratio, response rates, presence of comorbidities, follow-up duration (from diagnosis or discharge), assessed outcomes, assessment tools, and main findings. Extracted data were organized and presented at the systematic review tables.

2.5. Quality (risk of bias) assessment

Two members of the research team [ZKh &MMN] independently evaluated the quality of the included articles using the Newcastle – Ottawa scale (NOS) for the cohort studies, (Wells et al., 2014) and any disagreement was resolved through involving a third researcher [HR, MS, MD, or MHM].

This appraisal tool contained nine items, and their total score ranged from 0 to 9; based on the total score, the studies fell into one of the following quality-categorizes: Poor (0–3 scores), Fair (4–6 scores), or Good (7–9 scores). (Table 1)

2.6. Statistical analysis

We used a random-effects model to estimate pooled means or proportions of relevant COVID-19 outcomes, including PTSD, anxiety, depression, and HRQoL,

We assessed for heterogeneity using the I2-statistic. Overall, $I^2 \geq 50\%$ was considered to have significant heterogeneity. The following subgroup analyses were performed to determine the source of the observed heterogeneity: gender, follow-up duration, study design, clinical severity, and hospitalization status. We employed Egger's test to assess the presence of publication bias. A univariate meta-regression analysis was performed to explore the impact of some covariates on each psychological outcome's pooled prevalence. Our covariates of interest included mean/median age, sex ratio, study design, sample size, and the mean/median follow-up duration of the prevalence of psychological outcomes. In the meta-analysis performed on the prevalence of psychological consequences, subgroup analyses were performed to explore the possible heterogeneity sources based on the categories of the following variables: sex, disease severity, hospitalization status, follow-up duration, assessment tool, and study design.

All statistical analyses were conducted using the STATA's METAN package (version 16).

3. Results

3.1. Study selection process

A total of 1320 items were identified by the original search from three databases, of which 350 were duplicates and a further 949 were excluded after screening titles/abstracts ($n = 830$) or full texts ($n = 119$). The reasons for the exclusion of the articles are provided in Table 2.

Hence, we included 21 articles which met the study eligibility criteria, including 8 prospective and 13 retrospective cohort studies. Fig. 1 shows the selection process in detail.

Table 1
Quality of the included studies.

N	Study	Selection				Comparability (**)	Outcome			Total Of 9 scores	Class
		1	2	3	4		a	b	c		
1	Taquet et al.	*	*	*	*	**	*	*	*	9	Good
2	Akter et al.	*	–	*	–	–	*	*	*	5	Fair
3	D. Liu et al.	*	–	–	–	–	*	*	*	4	Fair
4	Xiong et al.	*	*	*	–	**	*	*	*	8	Good
5	Mazza et al.	*	–	–	–	–	*	*	*	4	Fair
6	Chen et al.	*	*	*	–	*	*	*	*	7	Good
7	Y Liu et al.	*	*	*	–	**	*	*	*	8	Good
8	Poyraz et al.	*	–	*	–	–	*	*	*	5	Fair
9	Guo et al.	*	–	*	*	–	*	*	*	6	Fair
10	Jacobs et al.	*	–	*	–	–	*	*	*	5	Fair
11	Zhou et al.	*	*	*	–	**	*	*	*	8	Good
12	De Lorenzo et al.	*	–	*	–	–	*	*	*	5	Fair
13	Carfi et al.	*	–	–	–	–	*	*	*	4	Fair
14	Borst et al.	*	–	*	–	–	*	*	*	5	Fair
15	Garrigues et al.	*	–	*	–	–	*	*	*	5	Fair
16	Arnold et al.	*	–	*	–	–	*	*	*	5	Fair
17	Halpin et al.	*	–	*	–	–	*	*	*	5	Fair
18	Wong et al.	*	–	*	–	–	*	*	*	5	Fair
19	Chang et al.	*	–	*	–	–	*	*	*	5	Fair
20	Janiri et al.	*	–	*	–	–	*	*	*	5	Fair
21	Raman et al.	*	*	*	–	**	*	*	*	8	Good

1- Representativeness of exposed cohort (★).
2- Selection of non-exposed cohort (★).
3- Ascertainment of exposure (★).
4- The outcome of interest was not present at start of study (*).
a) Assessment of outcome (★).
b) Enough follow-up to occur outcomes (*).
c) Adequacy of follow up (★).

Table 2
Reasons for excluding the papers.

Reasons	Number
Duplicates	350
Unrelated outcome	391
Including healthy people such as health care workers	262
including patients at acute phase of the disease or having Insufficient follow-up duration	144
Outcome measures	52
Incomplete data	33
Full text not in English	27
Not having a case series or cohort design	19
Sample size less than 30	12
Age of participants	9
Total	1299

3.2. Study characteristics

Overall, the included studies addressed psychological problems (*n* = 11), (Borst et al., 2020; Akter et al., 2020; Chang and Park, 2020; Janiri et al., 2020; Liu et al., 2020a; Mazza et al., 2020; Taquet et al., 2020; Xiong et al., 2021; Liu et al., 2020b; Wong et al., 2020; Poyraz et al., 2021) HRQoL (*n* = 7), (Arnold et al., 2020; Carfi et al., 2020; Chen et al., 2020; Garrigues et al., 2020; Guo et al., 2020; Zhou et al., 2020; Jacobs et al., 2020) or both of them (*n* = 3) as COVID-19 sequelae (De Lorenzo et al., 2020; Halpin et al., 2021; Raman et al., 2021) in survivors. Table 3 presents the detailed characteristics of all the eligible studies.

These studies all focused on the general population and involved a total of 49,650 COVID-19 survivors aged 18 years or older from 10 countries around the world. In detail, the sample size varied from 58 in the Raman et al.'s study (Raman et al., 2021) to 44,779 to the Taquet et al.'s study (Taquet et al., 2020). Studies were carried out in China (*n* = 6), Italy (*n* = 4), United Kingdom (UK; *N* = 3), United States (USA, *N* = 2), Canada (*N* = 1), Netherlands (*N* = 1), France (*N* = 1), Korea (*N* = 1), Turkey (*N* = 1), and Bangladesh (*N* = 1). Three stdies failed to provide data on the eligible participants' response rate (Akter et al.,
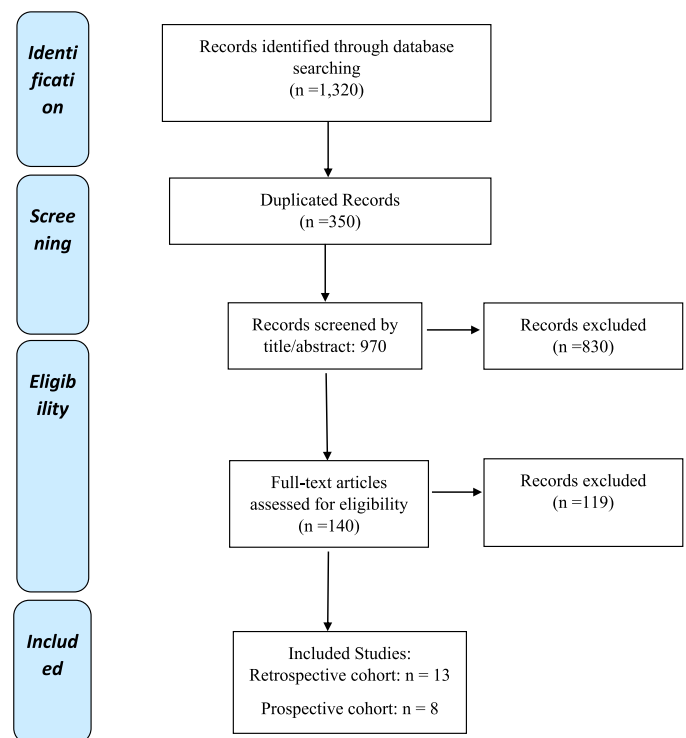
Fig. 1. PRISMA flowchart of literature search and selection process.

2020; Zhou et al., 2020; Raman et al., 2021), which ranged from 24% to 98% across remained studies.

The mean/median age of COVID-19 patients mainly fell in the fifth to seventh decades, with a male predominance in 16 out of 21 studies. Median/mean time from diagnosis/discharge to the follow-up assessment varied from 23 days to 111 days across the studies, and nearly half

Table 3
Characteristics of the included studies.

ID	Author	Country	Design	Sample size	Reported PMH	Resp. rate	The severity of the disease	Hospitalized [LOS] / ICU	% Male	Age (year) Mean (SD) /median (IQR)	Follow-up (days) Mean (SD) /median [IQR]	Quality
1	Taquet et al.	USA	RC	44,779	Psy.: 0.0%	NA	NR	NR	47.10%	47.1 (19.2)	14 to 90*	
2	Akter et al.	Bangladesh	RC	734	DM: 19.9% CVD: 9.1% Cancer:1.4% LD: 2.2%, RD: 6.1%	NR	NR	100% [NR]	76%	20–50 (in 70%)	all: 28†	
3	D. Liu et al.	China	RC	675	Any CO.: 37.2%	90%	Mild:21.5%, Moderate: 60.1% Severe:17.2% Critical:1.2%	100% [27.9 (NR)]	47%	55 [41–66]	37 (NR)†	
4	Xiong et al.	China	RC	538	Any CO.: 32.9%	76%	Mild/ moderate: 57% Severe: 33.5% / Critical:5%	100% [14.6 (8.8)]	46%	52 [41–62]	all: 30†	
5	Mazza et al.	Italy	PC	402	Psy.: 26%	>85%	NR	75% [15(10)]	66%	57.8 (13.3)	31 (16)†	
6	Chen et al.	China	RC	361	Any CO.: 31.9%	72%	Mild: 90.6% Severe: 9.4%	100% [9.1(7.6)]	52%	47.2 (13.0)	all: 30†	
7	Y Liu et al.	China	RC	312	Any CO: 40.1% DM: 8.7% HTN: 19.2%	71%	NR	100% [14.6(8.5)] ICU: 1%	52%	45•2 (11•5)	24•4 (4•7)†	
8	Poyraz et al.	Turkey	RC	284	NR	24%	Asym.:2.8% Mild: 50.8% Moderate: 32.5% Severe: 12.6% Critical:1.2%	39.90% [NR]	50%	39.7 (12.7)	48.7 (20.4)*	
9	Guo et al.	China	PC	259	Psy.: 0.0%	75%	NR	100% [NR]	47%	Med ~ 46	all: 30†	
10	Jacobs et al.	USA	PC	183	Psy.: 4.4% DM: 28.4% Cancer:9.8% CVD: 28% COPD: 3.8% HTN: 47.5%	52%	Mild: 21.5% moderate: 60.1% Severe: 14%	100% [7 (5 to 10)] IV: 5%	61.50%	57 [48–68]	35 (5)†	
11	Zhou et al.	China	PC	174	DM: 19% CVD: 12% HTN:37% CKD: 2% Cancer: 2%	NR	Asym.: 16.1% Mild/ moderate: 29.3% Severe/critical: 54.6%	84% [NR] ICU: 2% IMV: 2%	43%	58.2 (12.3)	all: 90†	
12	De Lorenzo et al.	Italy	RC	144	Psy.: 21.6% CAD:6.5% DM: 11.4% CKD: 1.6% Cancer:1.6% COPD: 1.1% HTN:38%	78%	NR	68.1% [9.5 (6 −15)] ICU: 2.2%	65%	57 [48-67]	23 [20 – 29]†	
13	Carfi et al.	Italy	RC	143	DM: 7% CKD: 2.1% HF: 2.8% CHD: 4.9% COPD: 9.1% Cancer: 3.5%	91%	NR	100% [13.5 (9.7)] ICU:12.6% IV: 5%	63%	56.5 (14.6)	36 (13)†	
14	Borst et al.	Netherlands	PC	124	Any Co.: 67.7%	63%	Mild: 22% Moderate:41% Severe:37%	100% [8 (5 −14)]	60%	59 ± 14	70 (12)†	
15	Garrigues et al.	France	RC	120	DM: 21.7% HTN: 46.7%	98%	NR	100% [11.2 (13.4)] ICU: 20%	62%	63.2 (15.7)	111 (11.1) *	
16	Arnold et al.	UK	PC	110	DM:18% HD: 18% RD: 25% CKD: 6% HTN: 25%	76%	Mild: 24.5% Moderate: 59.1% Severe: 16.4%	100% [5.1 (NR)]	61%	60 [44–76]	90 [80 – 97]*	
17	Halpin et al.	UK	RC	100	Psyc.:19% DM:28% HF:5% CAD:10% HTN:41% COPD:8%	63%	NR	100%[NR] ICU: 32%	54%	66.7 (range: 18 to 93)	48 (10.3)†	

(continued on next page)

Table 3 (*continued*)

ID	Author	Country	Design	Sample size	Reported PMH	Resp. rate	The severity of the disease	Hospitalized [LOS] / ICU	% Male	Age (year) Mean (SD) /median (IQR)	Follow-up (days) Mean (SD) /median [IQR]	Quality
18	Wong et al.	Canada	PC	78	CKD:15% Cancer: 21% DM: 26% CAD: 8% RD: 8% Any Co.: 41%	81%	NR	100% [NR]	64%	62 (16)	91 [77-98][*]	
19	Chang et al.	Korea	RC	64	NR	60%	NR	100% [31.2 (18.1)]	44%	54.7 (16.6)	76 (20)[†]	
20	Janiri et al.	Italy	RC	61	Psy.: 28%	97%	NR	100% [16.5 (10.6)] ICU: 15%	59%	67.3(6.5)	41(19)[†]	
21	Raman et al.	UK	PC	58	Depression:5.2% DM: 15.5 HTN: 37.9 CVD:5.2% COPD: 5.2% Cancer: 3.4%	NR	Moderate/ severe:100%	100% [8.5 (5 −17)] ICU: 36% IV: 21%	59%	55(13)	69 [62 – 76][*]	

CAD: coronary artery disease. **CHD:** chronic heart disease. **CKD.** Chronic kidney disease. **CO:** comorbidity. **COPD:** chronic obstructive pulmonary disease. **DM.** Diabetes mellitus. **HF:** heart failure. **HTN,** Hypertension. **IV:** invasive ventilation. **ICU,** intensive care unit. **IQR:** Interquartile range. **LD:** liver disease. **LOS:** length of stay. **NIV:** non-invasive ventilation. **NR:** not reported. **Psy:** psychiatric. **PMH:** Past medical history. **PC:** a prospective cohort. **RC:** a retrospective cohort. **RD:** respiratory disease. **SD:** standard deviation.

[*] After diagnosis.
[†] After discharge.

of them were greater than 31 days.

In 16 studies, inpatients constituted 100% of the study participants, and in remaining studies but one, the proportion of outpatients ranged from 16% to 40%. The exception was the large study conducted by Taquet et al. (2020) that included both inpatients and outpatients but failed to provide more information about their ratio. Besides, ten studies provided data on the severity of disease at the acute phase experienced by the participants. In these studies, patients with a severe form of the disease constituted at least 9.4% to a maximum of 54% of the study population.

3.3. Quality assessment

All studies had a quality score greater than four and fell in the good ($n = 6$) or fair ($n = 15$) category.

3.4. Main findings

3.4.1. Psychological and mental impacts

Overall, of 14 studies investigating the psychiatric sequelae of COVID-19 as an outcome, only Liu et al. (2020) and Taquet et al. (2020) examined the presence of an actual disorder based on clinical diagnoses rather than self-reported symptoms. Nine out of twelve remaining studies used the validated instruments, of which seven studies utilized corresponding cut-off values for the evaluation. Table 4 summarizes results of studies investigating psychological outcomes at the total study population.

Table 5 and Fig. 2 also present meta-analysis results for each psychological outcome, overall and by subgroups.

3.4.2. PTSD

A total of eight studies reported the prevalence of PTSD among COVID-19 survivors. This indicator of psychological distress was measured using validated scales ($n = 5$), including PTSD Checklist for DSM-5 (PCL −5) and/or Impact of Event Scale-Revised (IES-R), Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria ($n = 1$), or a single question on "having PTSD" (yes/no, $n = 1$) (Table 4)

Mazza et al. (2020) and Borst et al. (2020) measured the presence of PTSD using the two scales, namely PCL-5 and IES-R, and utilized a cut-point value of 33 for both of them. As the optimal cut-off score for IES-R is 46 scores (Murphy et al., 2017), the results of the PCL-5 were

included in the meta-analysis to reduce the overestimation of the overall prevalence.

Overall, the prevalence of PTSD ranged from 7.3% in the Netherlands (Borst et al., 2020) to 31% in the UK (Halpin et al., 2021).

The pooled prevalence of PTSD was 18% (ranging from 13 to 23%) with a substantial heterogeneity ($I^2 = 88.23\%$, P-value < 0.001). The prevalence of PTSD was higher among female patients than males ((23% (95% confidence interval (CI): 10 to 35%) vs. 12% (7 to 16%) respectively, P-value < 0.001) and among outpatients (28% (22 to 34%) than inpatients (22% (17 to 28%). Based on the pooled results from three studies, in the subgroup analysis by the disease severity, the similar prevalence of PTSD was observed in patients with mild (15% (0 to 30%)), moderate (14% (6 to 22%), and severe disease (13% (6 to 21%)). (P-value = 0.99) Besides, a higher pooled prevalence of PTSD was obtained from the retrospective cohort studies compared to prospective ones (21% (15 to 27%) vs. 11% (8 to 14%) respectively, P-value < 0.001). However, in the subgroup analysis by the follow-up duration, approximately the similar prevalence was obtained from the studies with a mean/median follow-up duration ≤ 31 days and those with a longer follow-up time (P-value = 0.58) (Table 5).

3.4.3. Depression

Eight studies measured depression as a psychiatric consequence of COVID-19 in patients who survived, using a validated questionnaire ($n = 6$), clinical diagnosis (DSM-IV) ($n = 1$), or a single question on depression (yes-no, $n = 1$). The validated scales included the Hospital Anxiety and Depression Scale (HADS), the Patient Health Questionnaire—9 (PHQ-9), the Beck Depression Inventory −13 (BDI-13), Temperament Evaluation of Memphis, Pisa, and San Diego Auto questionnaire. (TEMPS-A), and/or the Zung Self-Rating Depression Scale (ZSDS). Seven out of eight studies reported the prevalence of depression and were included in the meta-analysis. Mazza et al. (2020) utilized two scales, BDI-13 (Cut point: ≥ 9) and ZSDS (≥ 50). As cut point value 50 for ZSDS involved patients with mild depression, (Smarr and Keefer, 2011) the results of the BDI-13 scale were included in the meta-analysis to prevent the potential overestimation of the pooled estimate.

Among eligible studies, the prevalence of depression ranged from 4.3% (self-reported) in the Xiong et al.'s study (Xiong et al., 2021) to 30.7% (ZSDS ≥ 50) in Mazza et al.'s study (Mazza et al., 2020) (Table 4).

The overall pooled prevalence of depression was 12% (95% CI: 8 to 17%) with substantial heterogeneity 91.84%, P-value <0.001). The

Table 4
Psychological impacts of COVID-19 and their risk factors.

ID	Author	Outcome	The tool, Cut point	%	Mean ±SD Median [IQR]	Risk factors (RF) for the higher psychological impact of COVID-19 and other more findings
1	D. Liu et al.	PTSD	PCL5, NR	12.4%	12 [4,16]	- **RF**: Disease severity, Live with children, Symptoms after discharged, Perceived Discrimination
		Depression	PHQ-9, ≥ 10	15.3%	5 [3,8]	-Being female, age, Marital status, income, education, having comorbidity.: **NS**
		Anxiety	GAD-7, ≥ 10	10.4%	4 [2,6]	
2	Mazza et al.	PTSD	PCL5, ≥ 33	12.9%	14.49 ± 15.85	- **RF**: Being outpatients (NS for depression), female, and having positive PMH of psychiatric
			IES-R, ≥ 33	28.5%	23.83 ± 20.02	diagnoses
		Depression	ZSDS, ≥ 50	30.7%	44.24 ± 11.40	
			BDI-13 ≥ 9	11.2%	3.28 ± 4.40	
		Anxiety	STAI-Y	42.0%	38.32 ± 114.47	
3	Borst et al.	PTSD	PCL5, ≥ 33	7.3%	NR	- **RF**: Any
			IES-R, ≥ 33	9.8%	NR	Disease severity: **NS**
		Depression	HADS, > 10	12.1%	NR	Other: **NA**
		Anxiety	HADS, >10	10.0%	NR	
4	Poyraz et al.	PTSD	IES-R, ≥ 33	25.3%	22.2 ± 14.8	-**RF** (for PTSD): Being female, number of active and Protracted symptoms, duration and
		Depression	HADS, >10	18.7%	6.3 ± 4.3	(**Perceived**) severity of the disease, having positive PMH of psychiatric
		Anxiety	HADS, >10	18.4%	6.2 ± 4.6	Age, Marital status, Education, Clinical Severity, and Hospitalization status: **NS**
5	Y Liu et al.	PTSD	DSM-IV	12.8%	IES-R: 17•54±16•5	**RF**: Being Female, Lower education, lower income, Age, marital status, hospitalization Duration, having comorbidity: **NS**
		Depression	DSM-IV	9.62%	NR	-**More findings: 1)** A higher prevalence of depression and PTSD in COVID-19 survivors than controls.
		Anxiety	DSM-IV	4.8%	NR	**2) No** significant difference in **mean IES-R score** between patients (17•54±16•5) and controls (15•91±14•28)
6	De Lorenzo et al.	PTSD	IES-R, ≥ 33	28.4%	NR	- **RF**: Being outpatients and Females
		Anxiety	STAI-Y, ≥ 40	41.0%	NR	- Other: **NA**
7	Raman et al.	Depression	PHQ-9, ≥ 10	19.0%	3.0 [1.0,7.5]	-**More findings:** A higher prevalence of (and symptom score for) depression and anxiety in
		Anxiety	GAD-7, ≥ 10	14.0%	2.0 [0.0, 7.5]	COVID-19 survivors than controls
8	Xiong et al.	Depression	Self-reported	4.3%	NA	**More findings:** A higher prevalence of depression and anxiety in COVID-19 survivors than
		Anxiety	Self-reported	6.5%	NA	controls
9	Halpin et al.	PTSD	Self-reported	31.0%	NA	**More findings: 1)** A higher prevalence of PTSD Among ICU admitted patients than others
		Dep. or Anx.	Self-reported	35.0%	NA	(46.9% vs. 23.5%). **2)** About 74% of participants reporting anxiety/depression post-COVID-19 had no previously diagnosed mental health condition
10	Chang et al.	PTSD	PCL5, ≥ 33	20.3%	± 17.1	**RF**: Any / Being Female, Age, Hospitalization and Follow-up durations: **NS**; Other: **NA**
11	Taquet et al.	Anxiety	ICD-10	12.8%	NA	**More findings: 1-**COVID-19 survivors had a higher risk of a psychiatric diagnosis than six control with other health events. 2- Anxiety disorder was the most frequent psychiatric diagnosis following COVID-19
12	Akter et al.	Dep. or Anx.	Self-reported	22.0%	NA	–
13	Janiri et al.	Depression	TEMPS-A	NR	1.13 ± 1.9	**More findings:** Psychological distress (K10>19) was detected in 29% (*n* = 18) of subjects,
		Anxiety	TEMPS-A	NR	1.01 ± 0.89	more frequently in females than males (61% vs. 39%)
14	Wong et al.	Dep. or Anx.	Self-reported	14%	NA	RF: Having (Charlson) comorbidity

BDI: Beck Depression Inventory. **DSM**: Diagnostic and Statistical Manual of Mental Disorders. **Dep. or Anx**: depression or anxiety. **HADS**: Hospital Anxiety and Depression Scale. **ICD: International classification of disease. IES-R**: Impact of Event Scale-Revised. **IQR**: Interquartile range. **NA**: not assessed. **NR**: not reported. **NS**: not significant. **RF**: risk factor. **PTSD**: Post-traumatic stress disorder. **PCL −5**: PTSD Checklist for DSM-5. **PHQ-9**: Patient Health Questionnaire—9. **SD**: standard deviation. **TEMPS-A**: Temperament Evaluation of Memphis, Pisa and San Diego Auto questionnaire. **ZSDS**: Zung Self-Rating Depression Scale.

prevalence of depression was higher among female patients than males (19% (15 to 22%) vs. 12% (9 to 15%) respectively, (P value < 0.001)) and in patients with severe disease (22% (16 to 28%)) than those with moderate (15% (11 to 18%)) and mild forms (13% (8 to 18%)), (P value = 0.04). Furthermore, the pooled prevalence was similar between studies with mean/median follow-up duration ≤ 31 days and those with longer follow-up time (>=31) (16% (13 to 18%) vs. (15% (2 to 28%) respectively, P value= 0.86) and between retrospective (12% (5 to 18%)) and prospective (12% (9 to 15%)) cohort studies (P value =0.94). (Table 5)

3.4.4. Anxiety

Overall, nine studies evaluated anxiety as an indicator for psychological sequelae of COVID-19 among survivors. Studies used different methods to measure anxiety, including clinical diagnosis (DSM-IV or ICD-10) (*n* = 2), a single question on "having anxiety" (yes-no, *n* = 1) or one of the following validated scales (*n* = 6): The Generalized Anxiety Disorder-7 (GAD-7), The State-Trait Anxiety Inventory (STAI), TEMPS-A, OR HADS. Eight out of nine studies reported the prevalence of anxiety, its prevalence ranged from 4.8% in Y Liu et al.'s study (Liu et al., 2020b) (China) to 42% in Maaza et al.'s study (Mazza et al., 2020) (Italy). (Table 4)

Overall, the pooled prevalence of anxiety was 17% (95% CI: 12 to 22%) with a significant heterogeneity (I^2=97.07%, P-value < 0.001).

The pooled prevalence of anxiety was higher among females compared to males (19% (16 to 22%) vs. 8% (6 to 11%) respectively, (P-value < 0.001)) and in patients with a severe form of the disease (16% (10 to 21%)) compared to those with moderated (8% (6 to 11%)) and mild forms (8% (4 to 12%)), (P-value = 0.04). In the subgroup analysis by the assessment tools, the highest pooled prevalence was obtained from studies that used the STAI-Y scale (42% (38 to 46%)).However, in the subgroup analysis by follow-up duration and study design, the pooled prevalence was higher in studies with mean/median follow-up duration ≤ 31 days than those with longer follow-up time (>=31) (24 (16 to 32) vs. 13% (9 to 17%)respectively, P-value = 0.03 was statistically significant in prospective studies than retrospective studies (27% (10 to 45%) vs 14% (9 to 18%) respectively, P-value = 0.14). (Table 5)

Besides, a total of three studies evaluated the presence of "anxiety or depression" as a single outcome based on the patients self-reporting of having at least one of them; the proportion of patients who reported having anxiety/depression, in order by frequency, was 35% in Halpin et al.'s study (Halpin et al., 2021) (UK), 22% in Akter et al.'s study (Akter et al., 2020) (Bangladesh), and 14% in the Wong et al. study (Wong et al., 2020) (Canada). (Table 4) A meta-analysis of these studies

Table 5
Pooled prevalence of PTSD, Depression, and Anxiety among patients who survived COVID-19, overall and by subgroups.

Group	PTSD Category	N	Pooled estimated	I^2, P-Value	Depression Category	N	Pooled estimate	I^2, P-Value	Anxiety Category	N	Pooled estimate	I^2, P-Value
Overall	All	8	18 (13 −23)	88.23%, <0.001	All	7	12 (8–17)	91.84% <0.001	All	9	17 (12 −22)	97.07%, <0.001
Sex	Male	3	12 (7 – 16)	–	Male	2	12(9–15)	–	Male	2	8 (6 – 11)	–
	Female	3	23 (10 −35)	–	Female	2	19 (15 −22)	–	Female	2	19 (16–22)	–
Follow-up duration	≤ 31 days	3	17 (10 −24)	–	≤ 31 days	3	15 (2 −28)	–	≤ 31 days	6	24 (16–32)	98.70%, <0.001
	>31 days	5	19 (11 −26)	89.14%, <0.001	>31 days	4	16 (13 – 18)	18.35%, 0.30	>31 days	4	13 (9–17)	70.02%, 0.02
Assessment tool	IES-R	4	23 (14 – 32)	90.71%, <0.001	HADS	2	16 (13–20)	–	HADS	2	15 (11–18)	–
	PCL-5	4	12 (9–15)	59.94%, 0.06	PHQ-9	2	16 (13 −18)	–	GAD-7	2	11 (8–13)	–
	Self-Reported	1	31 (23 −41)	–	ZSDS	1	31 (26 – 36)	–	STAY-Y	2	42 (38–46)	–
	DSM-IV	1	13 (10–17)	–	Self-Reported	1	4 (3 −6)	–	ICD-10	1	13 (12–13)	–
					DSM-IV	1	10 (7–13)	–	Self-Reported	1	7(5 - 9)	–
					BDI-13	1	11 (8 – 15)	–	DSM-IV	1	5(3–8)	–
Severity	Mild	3	15 (0–30)	–	Mild	2	13 (8 – 18)	–	Mild	2	8 (4–12)	–
	Moderate	3	14 (6 – 22)	–	Moderate	2	15 (11 −18)	–	Moderate	2	8(6–11)	–
	Sever	3	13 (6 −21)	–	Sever	2	22 (16 −28)	–	Sever	2	16 (10–21)	–
Study Design	Retrospective cohort	6	21 (15 −27)	89.14%, <0.001	Retrospective cohort	4	12 (5 −18)	95.49%, <0.001	Retrospective cohort	6	14 (9–18)	96.16% <0.001
	Prospective cohort	2	11 (8 - 14)	–	Prospective cohort	3	12 (9 – 15)	NA	Prospective cohort	4	27 (10–45)	97.27% <0.001
Hospitalization status	Inpatients	2	22 (17–28)	–	Inpatients	–	–	–	Inpatients	1	55 (40–69)	+
	Outpatients	2	28 (22–34)	–	Outpatients	–	–	–	Outpatients	1	35 (26–45)	–

BDI: Beck Depression Inventory. **DSM:** Diagnostic and Statistical Manual of Mental Disorders. **HADS:** Hospital Anxiety and Depression Scale. **ICD:** International classification of disease. **IES-R:** Impact of Event Scale-Revised. **NA:** not applicable. **PTSD:** Post-traumatic stress disorder **PCL −5:** PTSD Checklist for DSM-5. **PHQ-9:** Patient Health Questionnaire—9, **TEMPS-A:** Temperament Evaluation of Memphis, Pisa, and San Diego Auto questionnaire. **ZSDS:** Zung Self-Rating Depression Scale.

yielded an overall pooled prevalence equaling 23% (14 to 32%).

3.4.5. Risk factors of psychological impacts: a qualitative assessment

Risk factors for a more significant psychological impact of COVID-19 among its survivors were substantially similar for indicators of PTSD, anxiety, and depression. Common associated factors were mainly being female and the severity of the disease. Other significant risk factors reported with less frequency were being outpatient, having comorbidity, previous psychological distress, length of stay (LOS) at the hospital, having lower income, lower level of education, and perceived discrimination. However, not all studies detected these significant associations. Besides, studies consistently reported no significant association between the presence of these COVID-19 psychological sequelae with the survivors' age and marital status. (Table 4)

3.5. Meta-regression results and publication bias

We detected no significant correlations between the pooled prevalence of each psychological outcome and study-level factors, including mean/median age, sex ratio, study design, sample sizes, and mean/median follow-up duration (all $P > 0.05$) in the meta-regression analyses. Also, according to Egger's regression test, there was no evidence of publication bias (for all psychological outcomes, $P > 0.05$).

3.6. HRQoL outcome

Ten studies evaluated HRQoL in COVID-19 survivors. In terms of the assessment tool, all studies but one used a validated scale, including short-form 36 health survey (SF-36; $N = 4$), (Arnold et al., 2020; Chen et al., 2020; Guo et al., 2020; Raman et al., 2021) St George's Respiratory Questionnaire (SGRQ; $n = 1$), (Zhou et al., 2020) World Health Organization Quality of Life (WHOQOL)-BREF ($n = 1$), (De Lorenzo et al., 2020) or 5-level EuroQol five-dimension (EQ-5D-5 L; $n = 3$), (Carfi et al., 2020; Garrigues et al., 2020; Halpin et al., 2021). The exception was the Jacobs et al.'s study showing that patients' quality of life was determined using one single item, self-rated on a four-point scale (poor, fair, excellent, good), of the Patient-Reported Outcomes Measurement Information System (PROMIS) instrument (Jacobs et al., 2020) (Table 6).

Four out of ten studies reported a mean (SD) of SF-36 domains [Fig. 2], conducted in two countries, the UK ($n = 2$) (Arnold et al., 2020; Raman et al., 2021) and China ($n = 2$) (Chen et al., 2020; Guo et al., 2020). In contrast to other studies, the study of Guo et al. (2020) measured only four domains, including Vitality (VT), Mental Health (MH), social functioning (SF), and role emotional (RE). Based on both studies conducted in the UK (20, 29), the mean scores of all of the eight domains of the SF36 in COVID-19 survivors were lower than those in matched controls and the normative values of the general population were derived from the existing literature. However, Chinese studies failed to observe this reduction in score of COVID-19 survivors in four domains, including physical function (PF), VT, bodily pain (BP), and general health (GH), and MH (Chen et al., 2020; Guo et al., 2020) (Table 6).

The meta-analysis was conducted on these four studies, based on the pooled estimations of standardized mean differences (SMDs), three domains SF (SMD (95% CI: −1.01 (−1.24 to −0.78) and Role Physical (RP)
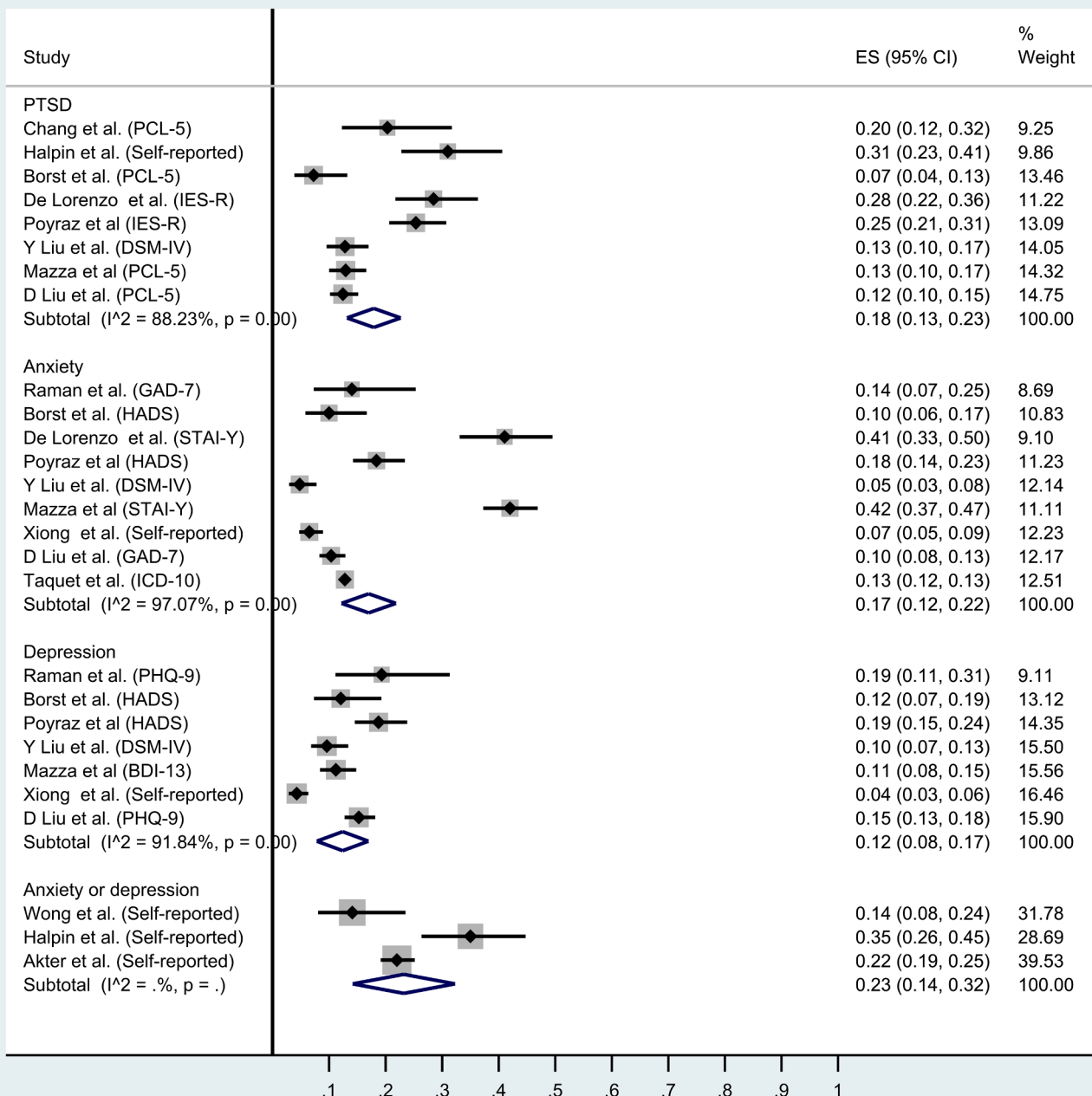
Fig. 2. Forest plot showing an overall pooled estimate of prevalence (ES) of different psychological distress in COVID-19 survivors
BDI: Beck Depression Inventory. **CI:** Confidence Interval. **DSM:** Diagnostic and Statistical Manual of Mental Disorders. **HADS:** Hospital Anxiety and Depression Scale. **ICD:** International classification of disease. **IES-R:** Impact of Event Scale-Revised. **NA:** not applicable. **PTSD:** Post-traumatic stress disorder **PCL −5:** PTSD Checklist for DSM-5. **PHQ-9:** Patient Health Questionnaire—9, **TEMPS-A:** Temperament Evaluation of Memphis, Pisa, and San Diego Auto questionnaire. **ZSDS:** Zung Self-Rating Depression Scale.

(−1.37 (−2.44 TO −0.29), and RE (−0.64 (−1.39 to 0.10) scores substantially lower in COVID-19 survivors than controls. [Fig. 3]

The radar plot shows a lower pooled estimate of mean scores of the different domains of SF-36 in COVID-19 survivors than controls. (Fig. 4)

Other studies that utilized other tools also reported that a HRQoL was reduced in survivors at follow-up time compared to pre-COVID-19 time or controls. Some studies found that the severity of disease and persistent symptoms of COVID-19 might be associated with reduced HRQoL among COVID-19 survivors. Other identified associated factors

included female gender, age, and LOS (Table 6).

4. Discussion

4.1. Main findings

The main objectives of the current systematic review and meta-analysis were to: (1) assess the HRQoL status of COVID-19 survivors and (2) provide an overall estimate of the prevalence of PTSD, depression,

Table 6
Quality of life impairments in COVID-19 survivors and its associated factors: A qualitative assessment of the findings from the included studies.

Author	Tool	Follow D. (days) Mean/med	Reduced QOL	The main findings
Chen et al.	SF-36	30*	+	-COVID19 survivors had reduced HRQoL, except in PF, compared to Chinese population norms -Negative association: LOS with RE and RP, Age with PF and RP, Female sex with PF, BP, and RE -Positive association: Age and LOS with VT **-RF:** overweight and obesity for a low PCS, female sex for a low MCS, severity for MH
Raman et al	SF-36	69[†]	+	-COVID19 survivors had lower HRQoL in all domains than controls
Arnold et al.	SF-36	90[†]	+	-COVID19 survivors had reduced HRQoL, all domains, compared to age-matched population norms[§] - Physical scores were significantly lower in the severe cohort compared to mild/moderate
Gue et al.	SF-36[‡]	30*	+	-No association: sex, age, smoking, and alcohol habit with VT, MH, SF, RE - Negative association Duration of positive PCR ≤ 20 with RE but not with others -COVID19 survivors had poorer HRQoL, only in SF than Chinese population norms[§]
Carfi et al.	EQ-5D-5L	36*	+	-Overall, 44.1% of survivors experienced Worsened QOL, defined as a 10-point reduction in EQ-VAS**
Halpin et al.	EQ-5D-5L	48*	+	- 53% of survivors had at least 0.05 MCIDc reduction in Mean EQ-5D-5 L index value** more frequently in ICU patients than ward patients. (68.8% versus 45.6%)
Garrigues	EQ-5D-5L	111[†]	NR	-Mean EQ-VAS was 70.3% and mean EQ-5D index 0.86, **no** difference between ICU and ward patients
Zhou et al.	SGRQ	90*	+	- COVID-19 patients had a significantly lower health status (higher SGRQ scores) than controls - Patients with severe disease had higher SGRQ scores than their counterparts - A significant negative correlation between SGRQ scores and lung ventilatory function variables.
De Lorenzo	WHOQOL	23*	+	- Outpatients had lower WHOQOL scores (lower QOL), only in the psychological domain, than inpatients
		35	+	

Table 6 (*continued*)

Author	Tool	Follow D. (days) Mean/med	Reduced QOL	The main findings
Jacobs et al.	Self-report			- "poor/fair" QOL: 23.2% - poor HRQoL was associated with persistent symptoms of COVID-19, but not with pre-COVID-19 General Health

* after discharge.
† after diagnosis/onset.
‡ they measured only four domains: VT, MH, SF, and RE.
§ we make this comparison.
** screen time compared to pre-COVID-19

AF: associated factors. **BP:** Bodily pain. **D.:** Duration. **EQ-5D-5L:** 5-level EuroQol five-dimension. **EQ-VAS:** EuroQol Visual Analogue Scale. **HQOL:** Health quality-of-life. **ICU:** intensive care unit. **LOS:** Length of stay. **MCIDc:** Minimal clinically significant difference as validated in respiratory disease. **MCS:** mental component summary. **Med:** median. **MH:** Mental health. **NR:** not reported. **NS:** not significant. **PCS:** physical component summary. **PF:** Physical function. **QOL:** quality-of-life. **RE:** Role emotional. **RF:** risk factor. **RP:** Role physical. **SF:** Social functioning. **SF-36:** 6-Item Short Form Health Survey. **VT:** Vitality. **WHOQOL:** World Health Organization quality-of-life.

and anxiety among them by combining the data of 21 observational studies with a total of 49,650 patients. Based on our findings, the overall prevalence of PTSD, depression, and anxiety among COVID-19 survivors were 18% (95 CI: 13 to 23%), 12% (8 to 17%), and 17% (12 to 22%), respectively. Our findings highlighted that COVID-19 survivors showed a reduction in HRQoL, measuring using different scales.
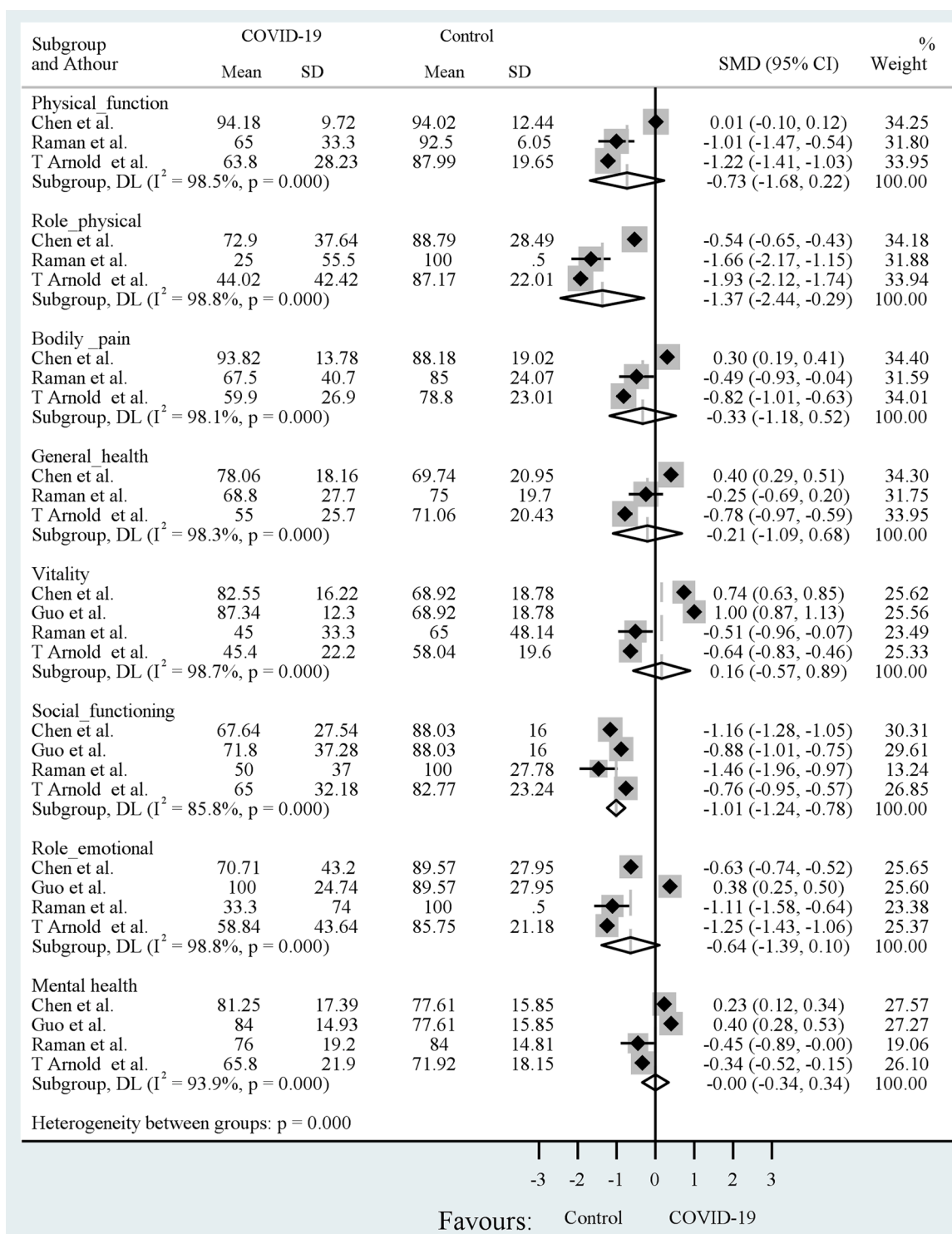
Our subgroup analysis revealed a higher prevalence of depression and anxiety, but not PTSD, in patients with severe disease compared to others. Also, all three mental health problems were more common in females than males. Based on our systematic review of the literature, other potential risk factors for the mental health sequelae of COVID-19 included being outpatient, having comorbidity, a history of psychological distress, hospital length of stay, a low level of education, income levels, and perceived discriminations.

4.2. Mental health sequelae of COVID-19

Our meta-analysis showed that about one out of five to ten COVID-19 patients might suffer from psychological conditions, such as PTSD, depression, or anxiety during the post-acute phase of the disease or after recovery. In line with our findings, a recent meta-analysis revealed that PTSD (32•2% (95% Confidence Interval (CI): 23•7–42•0)), anxiety disorders (14•8% (95% CI: 11•1–19•4)), and depression (14•9% (95% CI: 12•1–18•2)) were prevalent among survivors of other coronaviruses at a mean follow up of 35 months (Rogers et al., 2020).

A recent systematic review and meta-analysis conducted by Deng et al. on COVID-19 patients during the acute phase of the disease revealed that about half of them suffered from depression and/or anxiety, and one-third of them had sleep disturbances (Deng et al., 2020). A higher prevalence of psychological outcomes detected by Deng et al. in comparison with our study can be justified by this methodological issue that they focused on patients during the acute phase of the disease.

The exact Mechanism underlying mental health sequelae of COVID-19 are unknown. Viral invasion of the CNS, (Holmes et al., 2020) neural effects of the immune response, (Yuan et al., 2020) and psychological stress of enduring a potentially fatal disease (Borst et al., 2020) are supposed to be the main potential mechanisms for COVID-19 mental health sequels. Also, as reported in previous studies on SARS survivors, people may avoid interacting with recovered patients for fear of infection (Person et al., 2004); this perceived discrimination and feeling isolated could contribute to developing mental health problems in COVID-19 survivors (Liu et al., 2020a).

Subgroup and Athour	COVID-19		Control		SMD (95% CI)	% Weight
	Mean	SD	Mean	SD		
Physical_function						
Chen et al.	94.18	9.72	94.02	12.44	0.01 (-0.10, 0.12)	34.25
Raman et al.	65	33.3	92.5	6.05	-1.01 (-1.47, -0.54)	31.80
T Arnold et al.	63.8	28.23	87.99	19.65	-1.22 (-1.41, -1.03)	33.95
Subgroup, DL ($I^2 = 98.5\%$, p = 0.000)					-0.73 (-1.68, 0.22)	100.00
Role_physical						
Chen et al.	72.9	37.64	88.79	28.49	-0.54 (-0.65, -0.43)	34.18
Raman et al.	25	55.5	100	.5	-1.66 (-2.17, -1.15)	31.88
T Arnold et al.	44.02	42.42	87.17	22.01	-1.93 (-2.12, -1.74)	33.94
Subgroup, DL ($I^2 = 98.8\%$, p = 0.000)					-1.37 (-2.44, -0.29)	100.00
Bodily _pain						
Chen et al.	93.82	13.78	88.18	19.02	0.30 (0.19, 0.41)	34.40
Raman et al.	67.5	40.7	85	24.07	-0.49 (-0.93, -0.04)	31.59
T Arnold et al.	59.9	26.9	78.8	23.01	-0.82 (-1.01, -0.63)	34.01
Subgroup, DL ($I^2 = 98.1\%$, p = 0.000)					-0.33 (-1.18, 0.52)	100.00
General_health						
Chen et al.	78.06	18.16	69.74	20.95	0.40 (0.29, 0.51)	34.30
Raman et al.	68.8	27.7	75	19.7	-0.25 (-0.69, 0.20)	31.75
T Arnold et al.	55	25.7	71.06	20.43	-0.78 (-0.97, -0.59)	33.95
Subgroup, DL ($I^2 = 98.3\%$, p = 0.000)					-0.21 (-1.09, 0.68)	100.00
Vitality						
Chen et al.	82.55	16.22	68.92	18.78	0.74 (0.63, 0.85)	25.62
Guo et al.	87.34	12.3	68.92	18.78	1.00 (0.87, 1.13)	25.56
Raman et al.	45	33.3	65	48.14	-0.51 (-0.96, -0.07)	23.49
T Arnold et al.	45.4	22.2	58.04	19.6	-0.64 (-0.83, -0.46)	25.33
Subgroup, DL ($I^2 = 98.7\%$, p = 0.000)					0.16 (-0.57, 0.89)	100.00
Social_functioning						
Chen et al.	67.64	27.54	88.03	16	-1.16 (-1.28, -1.05)	30.31
Guo et al.	71.8	37.28	88.03	16	-0.88 (-1.01, -0.75)	29.61
Raman et al.	50	37	100	27.78	-1.46 (-1.96, -0.97)	13.24
T Arnold et al.	65	32.18	82.77	23.24	-0.76 (-0.95, -0.57)	26.85
Subgroup, DL ($I^2 = 85.8\%$, p = 0.000)					-1.01 (-1.24, -0.78)	100.00
Role_emotional						
Chen et al.	70.71	43.2	89.57	27.95	-0.63 (-0.74, -0.52)	25.65
Guo et al.	100	24.74	89.57	27.95	0.38 (0.25, 0.50)	25.60
Raman et al.	33.3	74	100	.5	-1.11 (-1.58, -0.64)	23.38
T Arnold et al.	58.84	43.64	85.75	21.18	-1.25 (-1.43, -1.06)	25.37
Subgroup, DL ($I^2 = 98.8\%$, p = 0.000)					-0.64 (-1.39, 0.10)	100.00
Mental health						
Chen et al.	81.25	17.39	77.61	15.85	0.23 (0.12, 0.34)	27.57
Guo et al.	84	14.93	77.61	15.85	0.40 (0.28, 0.53)	27.27
Raman et al.	76	19.2	84	14.81	-0.45 (-0.89, -0.00)	19.06
T Arnold et al.	65.8	21.9	71.92	18.15	-0.34 (-0.52, -0.15)	26.10
Subgroup, DL ($I^2 = 93.9\%$, p = 0.000)					-0.00 (-0.34, 0.34)	100.00

Heterogeneity between groups: p = 0.000

-3 -2 -1 0 1 2 3

Favours: Control   COVID-19

Fig. 3. Forest plot of standardized mean difference (SMD) (and their 95% CI and weights for individual studies) determined from the results of the studies comparing mean scores for different domains of SF-36 in COVID-19 survivors with controls.
CI: Confidence Interval. **SD:** Standard Deviation.

Some factors may put patients at a higher risk for the development of psychological and psychiatric symptoms after recovery of COVID-19. In this systematic review study, four out of six included studies reported that female gender was a significant risk factor for experiencing psychiatric sequelae of COVID-19 after hospital discharge. Some also found that the female gender is associated with the increased severity of PTSD symptoms (Liu et al., 2020b; Poyraz et al., 2021) A previous longitudinal study on SARS survivors revealed that female gender and the presence of

chronic comorbidities are the independent predictors of PTSD. (Mak et al., 2010) It is well known that females are more prone to emotional distress and traumatization subsequent to major stressors. They are more likely to suffer from depressive and anxiety disorders and have a higher risk for PTSD for traumatic events than males (Sareen, 2014).

Overall, females are also at higher risk of disorders of anxiety and depression (Altemus et al., 2014). This greater vulnerability may be explained by the immune-neuro-endocrine interactions and/or their
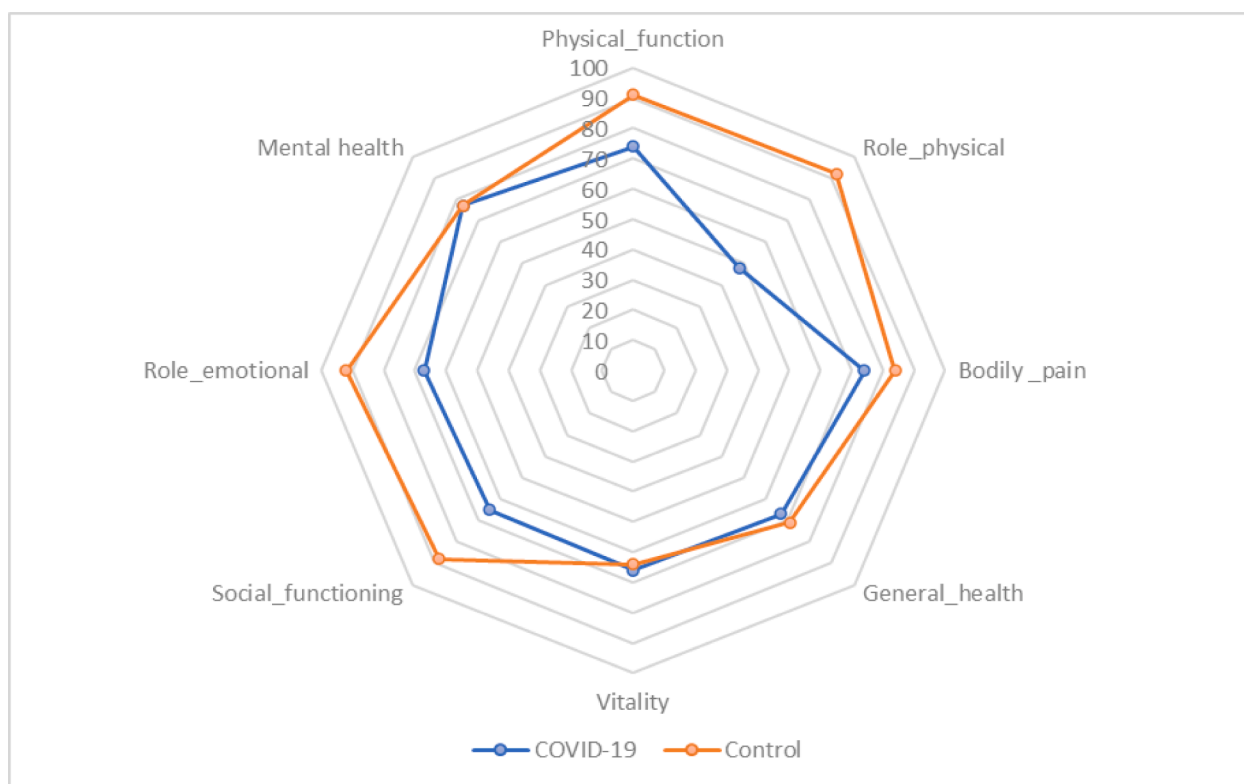
Fig. 4. Radar plot showing a pooled estimate of mean scores for different domains of SF-36 in COVID-19 survivors (blue) compared to Controls (orange).

different innate and adaptive immune system functioning. (Canady, 2020)

Two out of five studies assessing the association between hospitalization status and psychological sequelae in COVID −19 survivors observed that outpatients are at a higher risk of developing PTSD and anxiety disorder (Mazza et al., 2020; De Lorenzo et al., 2020), which may be explained by the lack of healthcare support for the non-hospitalized patients. However, others failed to detect any significant association (Chang and Park, 2020; Liu et al., 2020b; Poyraz et al., 2021). These findings showed that the psychological sequelae not only suffered from serious illness, but also from factors, such as fear (Tsai et al., 2004) and stigma (Lam et al., 2009) that may play a key role. Also, based on the available evidence, the pre-existing psychiatric history of subjects is a risk factor for the COVID-19 mental health sequelae; therefore, this factor is well known as a predictive factor for the occurrence of psychological problems later in life (Karsten et al., 2011; Ozer et al., 2003).

Given the population size of COVID-19 survivors, the prevalence of psychological problems could be fairly characterized as massive in a public health sense. According to the available evidence, stress-related disorders are associated with having suicidal ideation, suicide attempts, and suicide death. (Sher, 2019) Hence, it is suggested that COVID-19 survivors be regarded as a high-risk group for suicide. (Sher, 2020) Further, individuals with depression are at a higher risk of all-cause and cause-specific mortality (Cuijpers et al., 2014).

Also, as a large proportion of the study populations were patients with mild to moderate SARS-CoV-2 infection, our findings can be alerting as the presence of psychiatric sequelae which may be more easily discounted in this group of survivors.

Hence, COVID-19 survivors would need the long-term psychological interventions. It implicates the need to provide mental health care for millions of survivors globally with the depressive and related disorders. Specific strategies should be considered to enhance the mental health of COVID-19 survivors and reduce suicidality (i.e., suicidal ideation and suicide attempts) in this population (Sher, 2020).

4.3. HRQoL outcome

Most of the included studies in this review reported that survivors had a lower quality of life than controls or their status at pre-COVID-19. Our Meta-analysis revealed that three domains such as, SF, RP, and RE scores significantly lower in COVID-19 survivors than controls. In line with our findings, Ahmed et al. found that HQOL was significantly reduced in survivors of other coronaviruses compared to normative values for healthy and people with chronic diseases (Ahmed et al., 2020). They mainly observed lower SF-36 scores for role limitations in the survivors of other coronaviruses compared to healthy individuals.

Persistent symptoms of the disease may be responsible for such reduced social functioning experienced by survivors of COVID-19. Jacobs et al. studied 184 COVID-19 survivors at 35 days after discharge and found that fatigue, pain, and/or dyspnea were present in over half of them (Jacobs et al., 2020). They also found that persistent symptoms are inversely associated with odds of a socially active role. Zhou et al. found the significant negative correlations between SGRQ scores and lung ventilator function variables in COVID-19 survivors (Zhou et al., 2020).

4.4. Limitations and strengths

As the first main limitation, we observed a large between-study heterogeneity for all psychological outcomes that its source was not identified by subgroup analysis and meta-regression analysis. None of the study-level factors, such as sample size and follow-up duration, could explain the large heterogeneity observed between the studies. However, a random-effects model was performed to address the observed heterogeneity.

Second, our results should be interpreted with caution because the included studies mainly used self-rating scales to assess the prevalence of psychological problems that mostly have lower sensitivity and specificity than observer-rated scales (Möller, 2000) and structured clinical interviews (Stuart et al., 2014).

Finally, regarding the HRQOL outcome, we could not perform a

subgroup analysis to compare subgroups, such as male and female patients with different severity of the disease due to lack of subgroup data.

However, our systematic review and meta-analysis highlighted the burden of psychological issues in COVID-19 survivors. Our findings inform public health to plan the appropriate interventions and prepare mental health and social care services for the utilization of healthcare services after COVID-19.

There is a need for future comparative studies to identify the effective early interventions that may decrease psychiatric morbidity in COVID-19 survivors.

5. Conclusion

Our findings suggest that a group of COVID-19 survivors would have reduced HQOL and limited social role beyond one month. Psychological distress, including PTSD, depression, and anxiety, should be expected in a large number of them.

Author contribution

HR had the idea for designing the study, performed all statistical analyses, and critically reviewed and revised the manuscript. MHM and MD performed database searches, supervised and performed article screening and data extraction, and drafted the manuscript. MS, ZKH, FR, HD, ZK, MMN, SB performed article screening and data extraction. All authors read and approved the final version of the manuscript to be submitted. HR accepts responsibility for the integrity of the data analyzed.

Funding

Declaration of Competing Interest

The authors declare that there is no conflict of interest

Acknowledgments

References

Ahmed, H., et al., *Long-term clinical outcomes in survivors of coronavirus outbreaks after hospitalisation or ICU admission: a systematic review and meta-analysis of follow-up studies.*medrxiv, 2020.

Akter, F., et al., 2020. Clinical characteristics and short term outcomes after recovery from COVID-19 in patients with and without diabetes in Bangladesh. Diabetes Metabolic Syndrome 14 (6), 2031–2038.

Altemus, M., Sarvaiya, N., Epperson, C.N., 2014. Sex differences in anxiety and depression clinical perspectives. Front. Neuroendocrinol. 35 (3), 320–330.

Arnold, D.T., et al., 2020. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. Thorax.

Asghari, A., et al., 2020. The novel insight of SARS-CoV-2 molecular biology and pathogenesis and therapeutic options. DNA Cell Biol. 39 (10), 1741–1753.

Borst, B., et al., 2020. Comprehensive health assessment three months after recovery from acute COVID-19. Clin. Infect. Dis.

Canady, V.A., 2020. Study finds COVID-19 survivors exhibit MH signs one month after treatment. Ment. Health Wkly. 30 (32), 1–3.

Carfì, A., Bernabei, R., Landi, F., 2020. Persistent symptoms in patients after acute COVID-19. JAMA 324 (6), 603–605.

Chang, M.C., Park, D., 2020. Incidence of post-traumatic stress disorder after coronavirus disease. Healthcare. Multidisciplinary Digital Publishing Institute.

Chen, K.-.Y., et al., 2020. Predictors of health-related quality of life and influencing factors for COVID-19 patients, a follow-up at one month. Front. Psychiatry 11, 668.

Cuijpers, P., et al., 2014. Is excess mortality in depression generic or specific? A comprehensive meta-analysis of community and patient studies. Am. J. Psychiatry.

De Lorenzo, R., et al., 2020. Residual clinical damage after COVID-19: a retrospective and prospective observational cohort study. PLoS One 15 (10), e0239570.

Deng, J., et al., 2020. The Prevalence of Depression, Anxiety, and Sleep Disturbances in COVID-19 Patients: a Meta-Analysis. Annals of the New York Academy of Sciences.

Garrigues, E., et al., 2020. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J. Infect. 81 (6), e4–e6.

Guo, L., et al., 2020. Correlation study of short-term mental health in patients discharged after coronavirus disease 2019 (Covid-19) infection without comorbidities: a prospective study. Neuropsychiatr. Dis. Treat. 16, 2661.

Halpin, S.J., et al., 2021. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. J. Med. Virol. 93 (2), 1013–1022.

Holmes, E.A., et al., 2020. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. Lancet Psychiatry 7 (6), 547–560.

Jacobs, L.G., et al., 2020. Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. PLoS One 15 (12), e0243882.

Janiri, D., et al., 2020. Psychological distress after covid-19 recovery: reciprocal effects with temperament and emotional dysregulation. An exploratory study of patients over 60 years of age assessed in a post-acute care service. Front. Psychiatry 11, 1210.

Karsten, J., et al., 2011. Psychiatric history and subthreshold symptoms as predictors of the occurrence of depressive or anxiety disorder within 2 years. Br. J. Psychiatry 198 (3), 206–212.

Knobloch, K., Yoon, U., Vogt, P.M., 2011. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and publication bias. J. Cranio-Maxillofacial Surg. 39 (2), 91–92.

Lam, M.H.-B., et al., 2009. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. Arch. Intern. Med. 169 (22), 2142–2147.

Liu, D., et al., 2020a. Risk factors associated with mental illness in hospital discharged patients infected with COVID-19 in Wuhan, China. Psychiatry Res. 292, 113297.

Liu, Y., et al., *Mental disorders, fatigue, perceived event impact, and coping in post-illness patients with COVID-19 within 1 month after discharge: a case-controlled study.*2020b.

Mak, I.W.C., et al., 2010. Risk factors for chronic post-traumatic stress disorder (PTSD) in SARS survivors. Gen. Hosp. Psychiatry 32 (6), 590–598.

Makara-Studzinska, M., Zaluski, M., Lickiewicz, J., 2021. Are the COVID-19 survivors future patients of psychiatrists and psychologists A rapid literature review. Psychiatria 140–151.

Mazza, M.G., et al., 2020. anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. Brain Behav. Immun. 89, 594–600.

Möller, H., 2000. Rating depressed patients: observer-vs self-assessment. Eur. Psychiatry 15 (3), 160–172.

Murphy, D., et al., 2017. Exploring optimum cut-off scores to screen for probable post-traumatic stress disorder within a sample of UK treatment-seeking veterans. Eur. J. Psychotraumatol. 8 (1), 1398001.

O'Sullivan, O., 2021. Long-term sequelae following previous coronavirus epidemics. Clin. Med. 21 (1), e68.

Ozer, E.J., et al., 2003. Predictors of post-traumatic stress disorder and symptoms in adults: a meta-analysis. Psychol. Bull. 129 (1), 52.

Pal, M., et al., 2020. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): an update. Cureus 12 (3).

Person, B., et al., 2004. Fear and stigma: the epidemic within the SARS outbreak. Emerging Infect. Dis. 10 (2), 358.

Poyraz, B.Ç., et al., 2021. Psychiatric morbidity and protracted symptoms after COVID-19. Psychiatry Res. 295, 113604.

Raghu, G., Wilson, K.C., 2020. COVID-19 interstitial pneumonia: monitoring the clinical course in survivors. Lancet Respir. Med. 8 (9), 839–842.

Raman, B., et al., 2021. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine 31, 100683.

Rogers, J.P., et al., 2020. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 7 (7), 611–627.

Sareen, J., 2014. Post-traumatic stress disorder in adults: impact, comorbidity, risk factors, and treatment. Canadian J. Psychiatry 59 (9), 460–467.

Sher, L., 2019. Resilience as a focus of suicide research and prevention. Acta Psychiatr. Scand. 140 (2), 169–180.

Sher, L., 2020. Are COVID-19 survivors at increased risk for suicide? Acta Neuropsychiatr. 32 (5), 270-270.

Smarr, K.L., Keefer, A.L., 2011. Measures of depression and depressive symptoms: beck depression inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), geriatric depression scale (GDS), hospital anxiety and depression scale (HADS), and patient health Questionnaire-9 (PHQ-9). Arthritis Care Res. (Hoboken) 63 (S11), S454–S466.

Stuart, A.L., et al., 2014. comparison of self-report and structured clinical interview in the identification of depression. Compr. Psychiatry 55 (4), 866–869.

Taquet, M., et al., 2020. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry.

Tsai, L.-.K., et al., 2004. Neuromuscular disorders in severe acute respiratory syndrome. Arch. Neurol. 61 (11), 1669–1673.

Wells, G., et al., 2014. Newcastle-Ottawa Quality Assessment Scale Cohort Studies. University of Ottawa.

Wong, A.W., et al., 2020. Patient-reported outcome measures after COVID-19: a prospective cohort study. Eur. Respir. J. 56 (5).

Xiong, Q., et al., 2021. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. Clin. Microbiol. Infect. 27 (1), 89–95.

Yuan, B., et al., 2020. Correlation between immune response and self-reported depression during convalescence from COVID-19. Brain Behav. Immun. 88, 39–43.

Zhou, M., et al., *Multifaceted examination and assessment of COVID-19 convalescent patients in Wuhan, China: a follow-up study of survivors three months after discharge.* 2020.