



Prevalence and risk factors of erectile dysfunction in COVID-19 patients: a systematic review and meta-analysis

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Abstract

Purpose Studies have found that erectile dysfunction (ED) may be a short-term or long-term complication in coronavirus disease 2019 (COVID-19) patients, but no relevant studies have completed a pooled analysis of this claim. The purpose of the review was to comprehensively search the relevant literature, summarize the prevalence of ED in COVID-19 patients, assess risk factors for its development, and explore the effect of the COVID-19 infection on erectile function.

Methods Medline, Embase, and the Cochrane Library was performed from database inception until April 14, 2022. Heterogeneity was analyzed by χ^2 tests and I^2 was used as a quantitative test of heterogeneity. Subgroup analyses, meta-regression, and sensitivity analyses were used to analyze sources of heterogeneity.

Results Our review included 8 studies, 4 of which functioned as a control group. There were 250,606 COVID-19 patients (mean age: 31–47.1 years, sample size: 23–246,990). The control group consisted of 10,844,200 individuals (mean age: 32.76–42.4 years, sample size 75–10,836,663). The prevalence of ED was 33% (95% CI 18–47%, $I^2 = 99.48\%$) in COVID-19 patients. The prevalence of ED based on the international coding of diseases (ICD-10) was 9% (95% CI 2–19%), which was significantly lower than the prevalence of ED diagnosed based on the International Index of Erectile Function (IIEF-5) (46%, 95% CI 22–71%, $I^2 = 96.72\%$). The pooling prevalence of ED was 50% (95% CI 34–67%, $I^2 = 81.54\%$) for articles published in 2021, significantly higher than that for articles published in 2022 (17%, 95% CI 7–30%, $I^2 = 99.55\%$). The relative risk of developing ED was 2.64 times in COVID-19 patients higher than in non-COVID-19 patients (RR: 2.64, 95% CI 1.01–6.88). The GRADE-pro score showed that the mean incidence of ED events in COVID-19 patients was 1,333/50,606 (2.6%) compared with 52,937/844,200 (0.4%) in controls; the absolute impact of COVID-19 on ED was 656/100,000 (ranging from 4/100,000 to 2352/100,000). Anxiety (OR: 1.13, 95% CI 1.03–1.26, $I^2 = 0.0\%$) in COVID-19 patients was a risk factor for ED.

Conclusion COVID-19 patients have a high risk and prevalence of ED, mainly driven by anxiety. Attention should be paid to patient's erectile functioning when treating COVID-19.

Keywords COVID-19 · Erectile dysfunction · Prevalence

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Introduction

The coronavirus disease 2019 (COVID-19) broke out in countries around the world beginning in 2019 [1]. The COVID-19 outbreak was listed by the World Health Organization as a major global public health problem [2]. Current studies indicate that COVID-19 has multiple site mutations, and the epidemic has still not been completely controlled [3–5]. Epidemiological data show that a large portion of the population is susceptible to COVID-19, but disease incidence appears to be positively correlated with age and underlying diseases, (i.e., hypertension, diabetes, and cardiovascular disease) [6]. There were 500,186,525 confirmed

COVID-19 cases worldwide and 6,190,349 deaths attributed to the disease as of April 15, 2022 [7].

The American Urological Association (AUA) guidelines define erectile dysfunction (ED) as the persistent or repeated inability to achieve and/or maintain penile sexual needs, and ED is one of the most common manifestations of male sexual dysfunction [8]. It appears that psychological, vascular, endocrine, and neurological factors can lead to ED, which is most common in males [9, 10]. The prevalence of ED has been found to fluctuate between 0.48% and 75% in COVID-19 patients [11, 12]. Studies have reported that COVID-19 can invade host cells through the Spike-Angiotensin converting enzyme 2 (ACE2) binding pathway [13]. In Leydig cells, seminiferous tubules, and germ cells, ACE2 is highly expressed [14, 15]. COVID-19 could thus directly invade testicular tissue via these ACE2 receptors and cause ED [16]. Additionally, other studies have found that the virus persists in the penis long after the initial COVID-19, and have argued that widespread endothelial cell dysfunction caused by COVID-19 could lead to ED [17]. However, there is no current consensus on the effects of COVID-19 on ED. This review aimed to comprehensively search relevant literature and summarize the prevalence and risk factors of ED after COVID-19 infection.

Methods

The study followed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was registered in PROSPERO (ID: CRD42022327263) [18].

Data search

Embase, Medline, and the Cochrane Library were searched using Ovid SP until April 14, 2022. The search strategies are listed in Table S1. References of included studies were searched manually. There were no restrictions for the literature search. Two reviewers independently conducted the process of records search, study selection, quality assessment, and data extraction. Disagreements between the 2 reviewers were resolved by a third reviewer.

Inclusion and exclusion criteria

All types of studies that reported ED's prevalence in COVID-19 were included. The diagnosis of COVID-19 was based on reverse transcription polymerase chain reaction (RT-PCR) or any measurement was provided in each study's methodology. The assessment of ED according to any measurement [i.e., the international coding of diseases (ICD-10) or International Index of Erectile Function (IIEF-5)] was provided in each study's methodology. The question

that directed the review was “Does COVID-19 increase the risk of ED?”, and it followed a Patients, Interventions, Comparisons, Outcomes, and Study Design (PICOS).

P: COVID-19 patients.

I: diagnosis of ED.

C: healthy population.

O: prevalence and risk factors for ED.

S: all studies.

In addition, studies that provided odds ratios (ORs), relative risks (RRs), hazard ratios, and 95% confidence intervals (CIs) were included. Studies that did not examine the prevalence of or assessment methods related to ED, duplicate studies, studies using the same population, reviews, commentaries, letters, editorials, conference abstracts, case reports, studies with < 10 participants and animal studies were excluded.

Study selection

We started by removing duplicate studies. We then filtered all articles by title and abstract. Next, full-text studies were screened based on our criteria. Finally, studies included were reviewed and finalized.

Data extraction

Data were extracted from eligible studies using preformatted tables, reviewed, and finalized. The extracted data included the first author's name, year of publication, the region, study design, sample size, age, diagnostic method of COVID-19, and the methods of assessing ED, determining ED's prevalence, and determining risk factors of ED (ORs and 95% CI).

Quality and evidence assessment

The quality assessment of case–control/cohort studies and cross-sectional studies was assessed using the Newcastle–Ottawa Scale (NOS) [19] and the cross-sectional study quality methodology checklist [20], respectively. The evidence's overall quality was ranked using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [21].

Outcomes

The outcomes of the review were (1) the prevalence of ED in included studies, (2) RR for developing ED in COVID-19 patients compared with non-COVID-19 patients, and (3) risk factors for ED's development in COVID-19 patients.

Statistical analyses

A meta-analysis was used to calculate the weight of prevalence of ED and risk factors for ED in COVID-19 patients using STATA 12.0 (StataCorp, College Station, TX, USA). ORs and 95% CIs of risk factors were extracted from multivariate analyses. A p value < 0.05 was considered statistically significant. Heterogeneity was quantitatively assessed using I^2 , and heterogeneity was analyzed using chi-square tests [22]. If there was no statistical heterogeneity, a fixed-effects model was used for meta-analysis [23]. If there was statistical heterogeneity, a random-effects model was used, and subgroup analysis [24], meta-regression, and sensitivity analysis were used to further analyze heterogeneity. Funnel plots, Begg-Mazumdar Kendall's tau tests [25], and Egger bias tests [26] were performed to evaluate publication bias, and, if there was any publication bias, the trim-and-fill approach was used [27].

Results

Literature Search

In total, 392 records were retrieved. After removing 66 duplicate articles, 326 articles were screened by read-through of abstracts and titles. Then, 11 studies were read in

full text. After reading the full text, 3 articles were excluded, 1 article was because there was no data on the prevalence of ED, and 2 articles were for they were studies of sexual function in female patients. A total of 8 studies met our inclusion and exclusion criteria [11, 12, 28–33]. Figure 1 shows the specific screening process and results.

Study characteristics and quality assessment

A total of 250,606 COVID-19 patients were included, with an average age of 31–47.1 years and a sample size of 23–246,990. Four of the included studies had control groups, which, when combined, comprised 10,844,200 individuals, with mean ages ranging between 32.76 and 42.4 years and sample sizes ranging from 75 to 10,836,663 persons. The prevalence of ED ranged from 0.48 to 75.0%. The characteristics of the included studies are shown in Table 1. Three studies were retrospective, 2 were prospective studies, 2 were cross-sectional studies, and 1 was a case–control study. Two studies were from North America, 2 studies were from Europe, 2 studies were from Asia, and 2 studies were from Africa. The quality assessment of the studies included is listed in Table S2 and Table S3, with 3 studies rated as moderate and 5 studies rated as high quality. The GRADE-pro score showed that the mean incidence of ED in COVID-19 patients was 1,333/50,606 (2.6%) compared with 52,937/844,200 (0.4%) in controls, and the absolute impact

Fig. 1 Flow diagram of study selection process

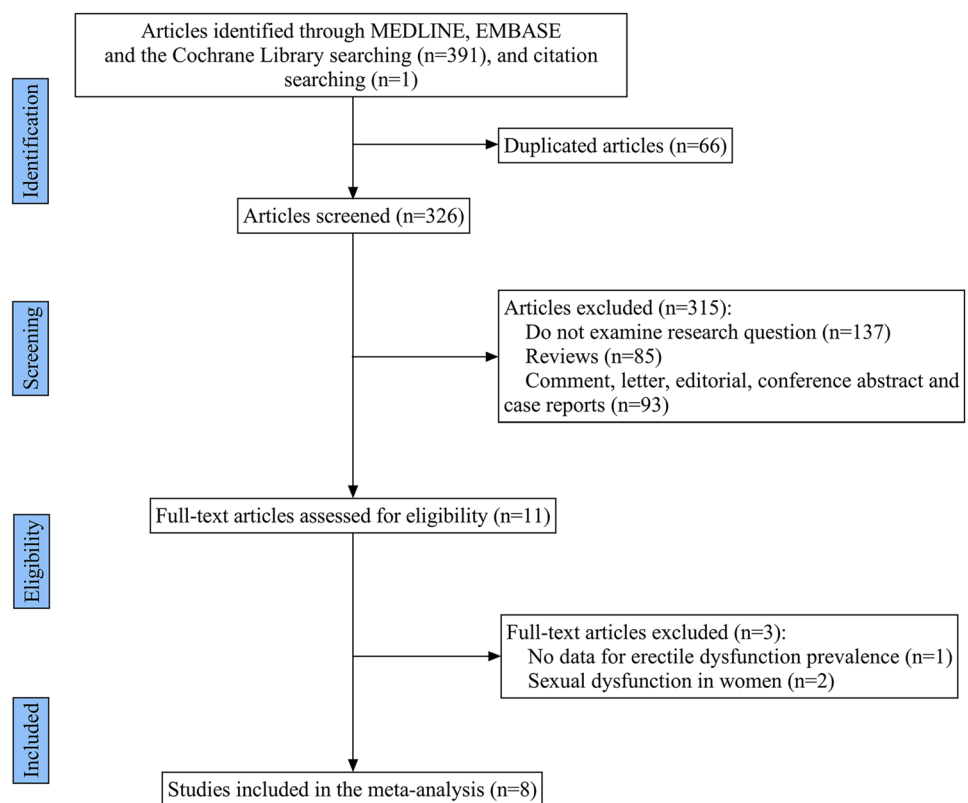


Table 1 Studies included characteristics

Study, year, country	Study design	Sample size (study group)	Sample Size (control group)	Mean age (years) study group	Mean age (years) control group	Assessment of ED	Diagnosis of COVID-19	Prevalence of ED	
								Study group (%)	Control group (%)
Chu et al. [11] (2022) USA	Retrospective cohort	246,990	10,836,663	47.1 ± 21.4	42.4 ± 24.3	ICD-10	ICD-10	0.48	0.39
Sivritepe et al. [12] (2022) Turkey	Prospective	80	–	42 ± 3.9	–	IIEF-5	RT-PCR	75.00	–
Harirugsakul et al. [28] (2021) Thailand	Cross-sectional	153	–	40.80	–	IIEF-5	–	64.70	–
Hu et al. [29] (2021) China	Prospective cohort	67	7372	31.00	33.79 ± 11.20	IIEF-5	RT-PCR	44.80	17.10
Katz et al. [30] (2022) USA	Cross-sectional	3,098	1,063,010	–	–	ICD-10	ICD-10	4.67	0.89
Rabie [31] (2021) Egypt	Retrospective	23	–	40.70	–	ICD-10	RT-PCR	60.90%	–
Saad et al. [32] (2022) Egypt	Case-control	107	90	32.66 ± 4.83	32.76 ± 5.02	IIEF-5	RT-PCR	17.10	–
Sansone et al. [33] (2021) Italy	Retrospective	25	75	39.00	42.00	SHI IIEF-5	Patient self-report	28.00	9.33

ED erectile dysfunction, COVID-19 coronavirus disease 2019, USA United States of America, ICD, international coding of diseases, IIEF International Index of Erectile Function, RT-PCR reverse transcription polymerase chain reaction, SHI sexual health inventory

of COVID-19 on ED was 656/100,000 (from 4/100,000 to 2352/100,000). The evidence's overall quality was considered to be low (Table 2).

Prevalence of ED and subgroup analysis

After pooling, the prevalence of ED was 33% (95% CI 18–47%, $I^2 = 99.48\%$, Fig. 2) in COVID-19 patients. When the four studies with a control group were combined, the risk of developing ED was 2.64 times in COVID-19 patients that in patients without COVID-19 (RR: 2.64, 95% CI 1.01–6.88, Fig. 3). Subgroup analysis showed that the prevalence of ED diagnosed according to ICD-10 was 9% (95% CI 2–19%), which was significantly lower than the prevalence of ED diagnosed based on IIEF-5 (46%, 95% CI 22–71%, $I^2 = 96.72\%$, Figure S1). Further, this difference was statistically significant, with a p -value less than 0.05, indicating that ED diagnosis was a source of between-study heterogeneity. In addition, the pooling prevalence of ED was 50% (95% CI 34–67%, $I^2 = 81.54\%$)

for articles published in 2021, significantly higher than that for articles published in 2022 (17%, 95% CI 7–30%, $I^2 = 99.55\%$, Figure S2), the difference was statistically significant ($P < 0.05$), suggesting that publication year may be one of the sources of inter-study heterogeneity. Such heterogeneity can be due to the larger sample size of more recent studies, or to different outcomes for different COVID-19 variants, or to the increasing rates of vaccination.

Meta-regression and sensitivity analysis

Sample size (regression coefficient: 1.507, 95% CI 1.157–1.965, $p = 0.009$) was one of the sources of between-study heterogeneity in meta-regression analyses (Figure S3). Sensitivity analyses indicated that the omission of any of the included studies did not significantly affect the prevalence of ED (Figure S4).

Table 2 GRADE summary of evidence for the effects of COVID-19 on erectile dysfunction

Certainty assessment		Effect				Certainty		Importance				
No. of studies	Study design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	COVID-19	Control	Relative (95% CI)	Absolute		
4	Observational studies	Not serious	serious	Not serious	Not serious	None	1,333/250,606 (2.6%)	52,937/10,844,200 (0.4%)	RR 2.64 (1.01–6.88)	656 more per 100,000 (from 4 more to 2352 more)	⊕○○○LOW CRITICAL	CRITICAL

GRADE Working Group grades of evidence. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect
CI confidence interval, *RR* risk ratio

Risk factors for ED in COVID-19 patients

Four studies provided data on anxiety, suggesting that anxiety (OR: 1.13, 95% CI 1.03–1.26, $I^2 = 0.0\%$) was a risk factor for ED in COVID-19 patients. However, age (OR: 1.03, 95% CI 0.98–1.09, $I^2 = 68.3\%$, 4 studies), body mass index (BMI) (OR: 0.98, 95% CI 0.87–1.11, $I^2 = 44.3\%$, 3 2 studies) and depression (OR: 1.01, 95% CI 0.86–1.19, $I^2 = 64.0\%$, 3 studies) were not risk factors for ED in COVID-19 patients (Fig. 4). Other risk factors that could not be analyzed using meta-analysis are listed in Table S4. The study also found that COVID-19 was one of the risk factors for ED, and OR was higher with increasing severity of illness [32, 33].

Publication bias

The funnel plot of our study is asymmetric (Figure S5). Begg’s test showed *p* value is 0.71, and Egger’s test showed *p* value is 0.006, suggesting the existence of publication bias. The trim-and-fill method showed that five additional studies would be needed to eliminate publication bias in the future (Figure S6). The results of the five studies were similar to previous work [i.e., Harirugsakul et al. (2021) [28], Hu et al. (2021) [29], Rabie et al. (2021) [31], Sansone et al. (2021) [33] and Sivritepe et al. (2022) [12].

Discussion

This study pooled all studies on ED in COVID-19 patients, performed a meta-analysis of the prevalence and risk factors for ED, and explored whether COVID-19 increases the risk of ED. A meta-analysis of the 8 included articles showed that the prevalence of ED was 33% in patients with COVID-19, of which the prevalence of ED diagnosed by ICD-10 was 9%, and the prevalence of ED diagnosed by IIEF-5 was 46%. The diagnostic method used to determine ED has a great impact on its prevalence, which may be due to the high sensitivity of IIEF-5 for diagnosing ED (i.e., 0.98.) [34] and/or two studies (Chu et al. and Katz et al.) [11, 30] using ICD-10 to diagnose ED had significantly larger sample sizes than the other included studies. The pooling prevalence of ED for articles published in 2021 was 50%, higher than that for articles published in 2022 (17%). The effect of publication year on ED prevalence may be due to the larger sample size of articles published in 2022 than in 2021 (250,338 vs. 268) and/or possibly the effect of COVID-19 variants. In a meta-regression, the sample size was one of the reasons for the high heterogeneity of this study. The included studies’ sample was uneven and varied greatly, which might be due to differences in each study’s capabilities in obtaining COVID-19 patients’ case data. When pooling studies with a control group, we found that in COVID-19 patients

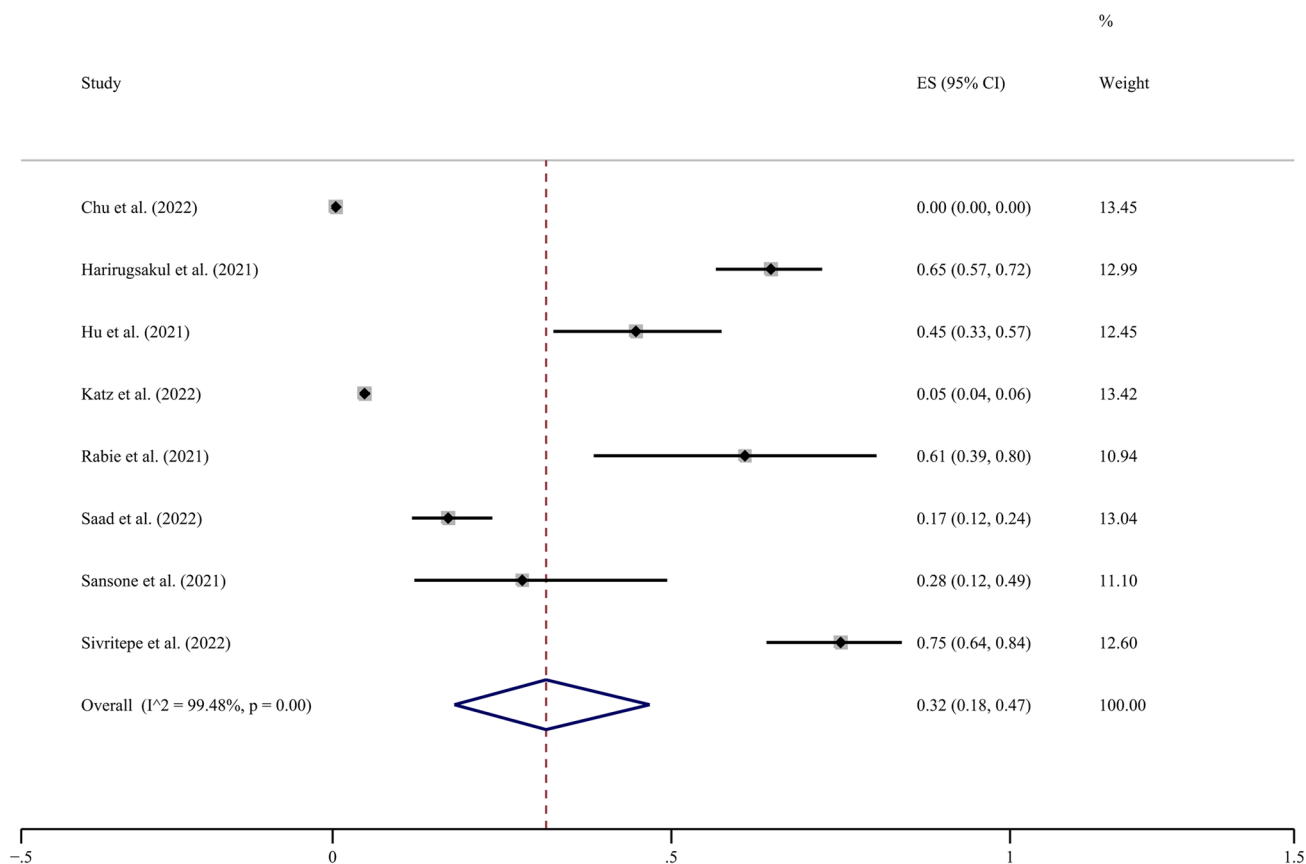


Fig. 2 Prevalence of erectile dysfunction in COVID-19 patients. *ES* effect size

the relative risk of developing ED was 2.64 times greater than in patients without COVID-19. The GRADE-pro score showed that the mean incidence of ED events in COVID-19 patients was 1,333/50,606 (2.6%), and the absolute impact of COVID-19 on ED was 656/100,000 (increased from 4/100,000 to 2352/100,000). Taken together, COVID-19 appears to increase the risk of ED.

We found that anxiety in patients with COVID-19 was a risk factor for ED, whereas age, BMI, and depression were not risk factors for ED. A large number of existing studies have found the negative impact of psychological factors on ED [29, 35–38]. However, studies have found that sexual activity has a protective effect against the quarantine-related plague of anxiety and mood disorders during the COVID-19 outbreak [39]. Given the bidirectional interaction between sexual activity and mental health [39, 40]. Excluding possible effects of anxiety and depression, Sansone et al. confirmed that the increased prevalence of ED was not only a result of the psychological burden, but was also clearly attributable to other truly organic factors, of which endothelial dysfunction was the most likely culprit. Moreover, the study was also highly suggestive of the role of infection in ED development and the possible clinical relevance of

COVID-19 as an additional risk factor for ED development [33]. Additionally, due to the limited number of included studies, some studies which did determine statistically significant risk factors could not be meta-analyzed. Hu et al. [29] found that the Global Severity Index was the only independent risk factor for ED in newly diagnosed COVID-19 patients (OR: 8.697, $P = 0.015$), suggesting an important role of ED on disease at the time of the first diagnosis. Saad et al. [32] showed that smoking, moderate COVID-19, baseline IIEF-5 scores, and severe COVID-19 in patients with COVID-19 were independent risk factors for ED. A logistic regression, adjusted for age and BMI (Sansone et al.), showed that COVID-19 infection [odds ratio: 5.27 (95% CI 1.49–20.09)] was an independent risk factor for ED and that ED may be a short- and a long-term risk factor for complications in COVID-19 [33]. The possible mechanisms of ED caused by COVID-19 in the current study are as follows: (1) Endothelial dysfunction [41]: the nitric oxide synthase's expression levels in the cavernous endothelium and the average level of endothelial progenitor cells in patients with COVID-19 were decreased [17]. (2) Direct testicular injury: novel coronaviruses have been found in COVID-19 patients semen and testes in acute and convalescent periods

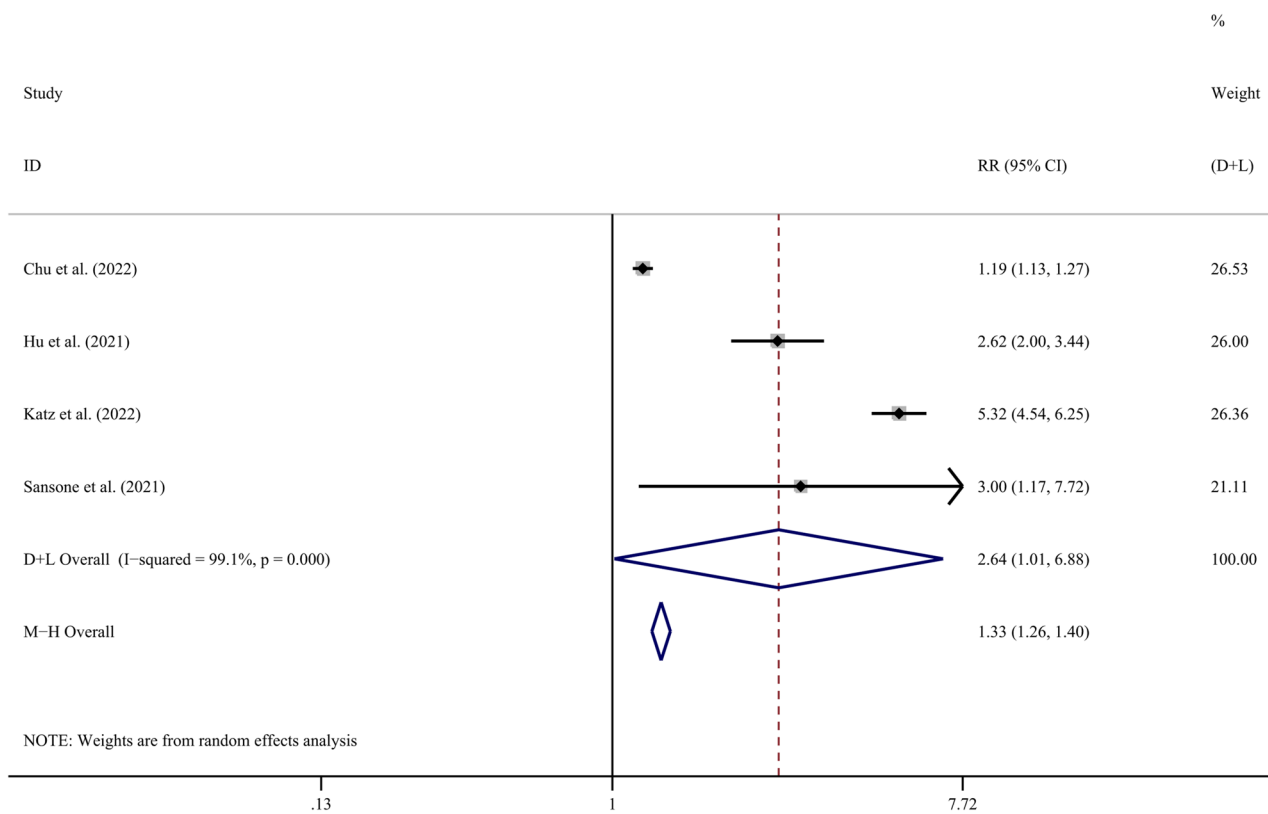


Fig. 3 The association between COVID-19 and erectile dysfunction. *CI* confidence interval, *RR* risk ratio

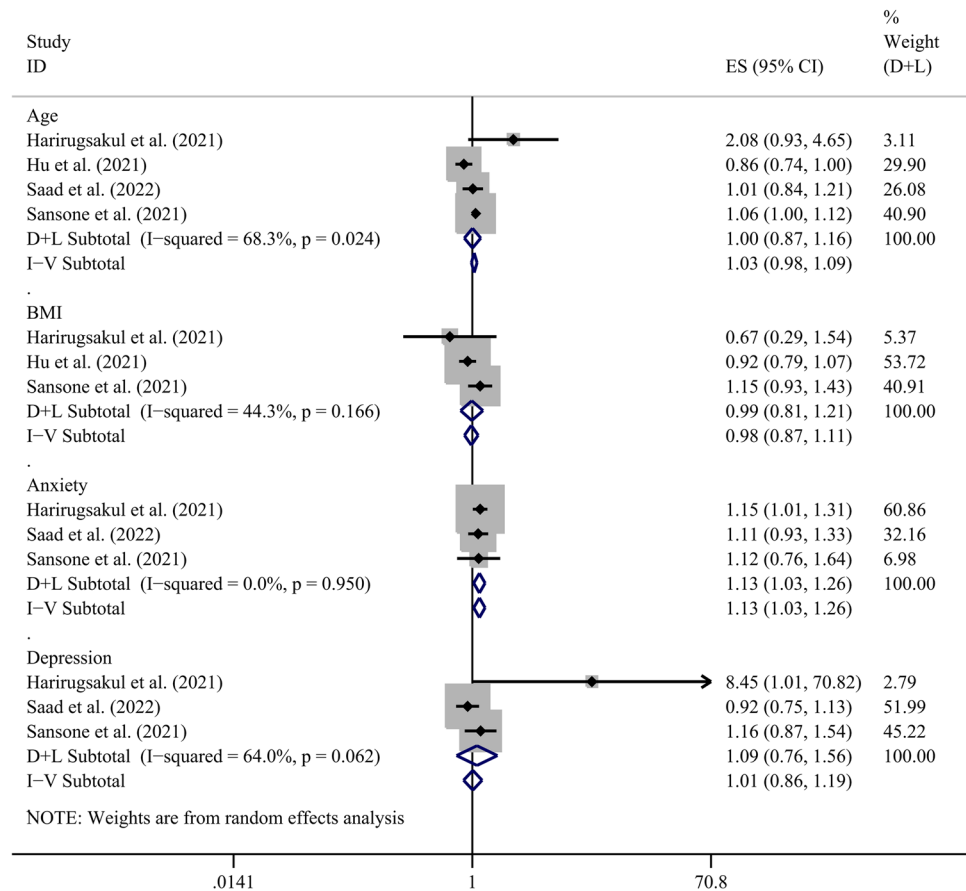
[42]. Autopsy reports have revealed that patients' testes have edema, mild lymphocytic infiltration, marked leukopenia, and seminiferous tubule damage [43]. (3) Hypogonadism [41]: a large study found that COVID-19 was related with decreased testosterone, with secondary hypogonadism in 85% of patients [44]. (4) Inflammatory cytokines: IL-1 β , IL-6, and TNF- α were associated to the clinical progression of sexual dysfunction [44, 45]. In COVID-19 patients, IL-6 could be used as a marker for ED, and when its cut-off point was 14.2 ng/ml, the sensitivity for detecting ED risk was 0.78 and the specificity was 0.72 [12]. (5) Psychological dysfunction [41, 46]. (6) Impaired pulmonary hemodynamics [41]. (7) Anosmia and ageusia: it has been suggested that anosmia and ageusia may play an important role in the etiology of temporary ED associated with COVID-19 [47].

To our knowledge, the study was the first meta-analysis of the prevalence and risk factors for ED in COVID-19 patients. We summarized the current prevalence of ED in COVID-19 patients and found that studies' number in this field was relatively small, and the related research was still needed, especially for the occurrence, development, and treatment of ED after recovery from COVID-19. However, we also provided data for future interventional studies. Furthermore, in COVID-19 patients, anxiety was a risk factor for ED's development. ED might be the first

symptom of an otherwise asymptomatic cardiovascular disease, and all patients with ED without an apparent cause should undergo a comprehensive cardiovascular examination [48, 49]. We recommend that special attention needs to be paid to the mental health of COVID-19 patients to reduce ED incidence, and comprehensive cardiovascular examinations should be conducted for patients with ED of unknown cause.

This study had some limitations. First, the included studies were highly heterogeneous ($I^2 = 99.48\%$). Thus, we used subgroup analyses, meta-regression, and sensitivity analyses to determine potential heterogeneity, and found that methods of diagnosing ED and the size of the study sample were partially responsible for the high heterogeneity. Second, related to risk factors for ED, the number of studies on some variables was limited, and the application of the combined results was limited. Additionally, due to the small number of included studies, some risk factors could not be combined. Third, there was publication bias amongst the studies included in our review, and further attention should be paid to newer work that could supplement and update our findings. Fourth, as some original literatures did not provide relevant data, we could not explore the potential link between the time span from COVID-19 infection to the onset of ED and ED.

Fig. 4 Risk factors of erectile dysfunction in COVID-19 patients. *CI* confidence interval, *ES* effect size (odds ratio), *BMI* body mass index



Conclusion

In conclusion, ED's prevalence was higher in COVID-19 patients, and anxiety played a driving role in the development of ED. Thus, to reduce the occurrence of ED, it is very important to evaluate the psychological function of patients while treating COVID-19.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40618-022-01945-w>.

Author contributions Jinzhi Zhang and Wei Shi have contributed equally to this work. Design: Jinzhi Zhang, Wei Shi and Huatian Gan. Data search and selection: Jinzhi Zhang and Wei Shi. Data analysis and manuscript writing: All authors.

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Declarations

Conflict of interest All authors have no conflicts of interest to disclose.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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