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ORIGINAL ARTICLE

Impact and prevalence of comorbidities and complications on the severity of COVID-19 in association with age, gender, obesity, and pre-existing smoking: A meta-analysis

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Abstract

Background: **COVID-19 patients usually present multiple comorbidities and complications associated with severe forms of SARS-CoV-2 infection. This study aimed to assess the risk factors and prevalence of comorbidities and complications contributing to the severity of COVID-19.**

Methods: **This meta-analysis was performed according to PRISMA guidelines. We searched various databases, including PubMed, Google Scholar, and Scopus (between 2020 and 2023), for eligible studies for this meta-analysis.**

Results: **Thirty-three studies were eligible, including 85,812 patients, of which 36 % (30,634/85,812) had severe disease, whereas 64 % (55,178/85,812) had non-severe disease. Severe cases were potentially correlated with the following factors: gender (male) (odd ratio (OR) = 1.52, 95 % CI: 1.34−1.73), advanced age (OR = 3.06, 95 % CI: 2.18−4.40) pre-existing smoking (OR = 1.33, 95 % CI: 1.01−1.75), obesity (OR = 2.11, 95 % CI: 1.47−3.04), diabetes (OR = 1.81, 95 % CI: 1.35−2.43), hypertension (OR = 2.22, 95 % CI: 1.72−2.87), coronary heart disease (OR = 2.17, 95 % CI: 1.42−3.31), CKD (OR = 2.27, 95 % CI: 1.26−4.06), COPD (OR = 1.95, 95 % CI: 1.22−3.09), malignancy (OR = 1.63, 95 % CI: 1.07−2.49) and cerebrovascular disease (OR = 2.76, 95 % CI: 1.63−4.62). All these comorbidities were significantly higher in the severe COVID-19 group compared with the non-severe COVID-19 group. In addition, the most severe complications were associated with shock (OR = 28.08, 95 % CI: 3.49−226.03), ARDS (OR = 13.09, 95 % CI: 5.87−29.18), AKI (OR = 16.91, 95 % CI: 1.87−152.45) and arrhythmia (OR = 7.47, 95 % CI: 2.96−18.83). However, these complications were the most likely to prevent recovery in patients with severe affections compared with non-severe affection groups.**

Conclusion: **All the comorbidities and complications listed above are more likely to cause severe forms of COVID-19 in some patients and hinder recovery. They are therefore risk factors to be controlled to minimize the undesirable effects of the disease.**

Keywords: Severe COVID-19, Non-severe COVID-19, Comorbidities, Complications, Risk factors

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1. Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused high morbidity and mortality around the world. More than 0.67 billion people have been infected and more than 6.8 million deaths around the world [1,2]. The clinical presentation of SARS-CoV-2 infection is very wide, ranging from asymptomatic infection in the first phases of infection to severe symptomatic forms of infection, sometimes implying dyspnea, organ dysfunction and, in the worst case, death ensues [2].

Several studies have reported that there are many clinical risk factors associated with the development of severe or even potentially fatal forms of the disease (COVID-19). These risk factors included demographic characteristics such as gender, advanced age, smoking history; comorbidities such as diabetes mellitus, hypertension, cardiovascular diseases, and chronic obstructive pulmonary disease (COPD), as well as complications such as acute respiratory distress syndrome (ARDS), septic shock, and, in the most extreme cases, neurological complications [3]. In addition, recent studies have highlighted the syndemic concept in the severity of COVID-19 [4,5]. Defined (syndemic) as two or more health conditions or diseases which, by their synergy, aggravate the consequences of these diseases on a sick person, specifically, an unhealthy lifestyle behaviors (i.e., physical inactivity, poor diet, increased sedentariness, obesity etc.)—chronic diseases—COVID-19 syndemic [4,5]. Indeed, emerging evidence in the scientific literature has suggested that some regions of the world suffer from the syndemic rather than the pandemic [4]. This syndemic would be one of the main causes of hospitalizations and high mortality worldwide during the COVID-19 pandemic [4–6].

Nevertheless, a good understanding of the risk factors associated with COVID-19 severity is useful for public health and clinicians to implement appropriate preventive measures and guidance of emerging treatment protocols to better identify patients at high risk of severe COVID-19 for priority treatment to prevent disease progression and unfavorable outcomes [7].

The aim of this study was to exhaustively evaluate the risk factors and prevalence of demographic characteristics, comorbidities, and complications associated with the severity of COVID-19 and the correlation between these risk factors.

2. Methods

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (Supporting information: S1 PRISMA 2020 checklist) and the statement by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group were employed to design and describe this study [8,9].

2.1. Search strategy

To minimize bias, two investigators (S.D and NN) independently examined the data (titles, abstracts, and extraction of potentially eligible articles). Eligible articles were stored in a “Zotero” citation manager. Literature searches were performed using the international databases PubMed Central, Google Scholar, and Scopus, using the following search terms:

“SARS-CoV-2″ OR “COVID-19″ AND “Severity and non-severity of COVID-19″ OR “Severity of COVID-19″ OR “Intensive Care Unit” OR “clinical features of COVID-19". The articles selected for this study are those published between 2020 and 2023.

2.2. Selection criteria

Studies fulfilling the following selection criteria were included in the meta-analysis: - Inclusion criteria: (1) study type: case series, cohort study, or prospective study in relation to the severe form of COVID-19; (2) COVID-19-positive patients with comorbidities and associated studies reporting complications following the severity of COVID-19; (3) randomized clinical trials, observational studies, and case series involving $\geq$70 patients, written in English or French.

- Exclusion criteria were: (1) systematic reviews and meta-analyses; (2) unpublished articles; (3) studies with sample sizes $\leq$70 patients; (4) insufficient or incomplete data; (5) animal experiment reports, and (6) pediatric reports.

2.3. Quality assessment

The evaluation of the quality of studies included in this meta-analysis was based on the Newcastle-Ottawa Scale (NOS) [10]. The main elements include: selection (representativeness of the exposed cohort, selection of the nonexposed cohort,

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Ascertainment of exposure, demonstration that the outcome of interest was not present at the start of the study); comparability (comparability of cohorts on the basis of design or analysis); and outcome (assessment of outcome, follow-up time, Adequacy of follow-up of cohorts). The quality score ranges from 0 to 10 stars, with a score≥ 7 stars indicating high-quality articles (Table 1).

2.4. Statistical analysis

All statistical tests were performed using Review Manager (RevMan) version 5 (Cochrane Collaboration, Copenhagen, Denmark) [11]. Odds ratios (ORs) were calculated for dichotomous variables, while standardized mean differences (SMDs) and 95 % confidence intervals (CIs) were calculated for continuous data. The Mantel-Haenszel random-effects model was used to calculate effect sizes. Heterogeneity was estimated using the chi-square test and the Higgins I^2 test. Z-score was calculated to detect the overall effect, with significance set at $P < 0.05$. Publication bias was examined using funnel plots. The 95 % CI in the funnel plots is based on the hypothesis that all studies have only one true effect. Consequently, the 95 % CI in the fixed-effects model (based on this hypothesis) represents the expected distribution of studies in the absence of heterogeneity and bias. The random-effects model, on the other hand, supposes that these studies have different true effects, and there is therefore no need to add a 95 % CI. For all analysis, significant levels were two-tailed, and $p < 0.05$ was considered significant for OR and SMD summarized. Population-attributable risk fractions (PAF) for COVID-19-positive patients for the effect of the outcome of different comorbidities were also calculated for all groups. The formula used to calculate PAF was:

$$\mathbf{PAF = P_1\ (OR\text{-}1)\ /OR}$$

P 1 = proportion of risk factors in the population and OR = odds ratio [12].

For continuous variables for which SMD has been calculated, the odd ratio is determined according to the equation: ln (OR) = $\pi/\sqrt{3}$ X SMD [13].

3. Results

3.1. Study selection and characteristics

Fig. 1 shows the flow chart for study selection according to PRISMA guidelines. According to the predefined search strategies, a total of 22,005 articles were initially identified, of which 21,972 were excluded following evaluation of the eligibility criteria. COVID-19 patients were divided into severe and non-severe groups. Study characteristics are shown in Table 1.

A total of 85,812 patients were included in this meta-analysis. The characteristics of all studies included are listed in Table 1. The rate of severe cases was 36 % (30,634/85,812), while the rate of non-severe cases was 64 % (55,178/85,812).

3.2. Quality of the included studies

The results of the quality assessment of all the studies included in this meta-analysis are presented in Table 2. The majority of studies were high-quality, with the exception of two studies with a NOS score of 6. The NOS scores of the thirty-one other studies with high quality were distributed as follows: nine studies had a NOS score of 7, nine other studies had a NOS score of 8, and thirteen studies had a NOS score of 9.

3.3. Summary of the meta-analysis for primary outcomes

In Table 3, sixteen risk factors for COVID-19 have been listed in three categories. These are demographic characteristics, comorbidities, and complications that have an impact on the severity of COVID-19.

3.4. Publication bias

In order to estimate publication bias in addition to heterogeneity (chi-square test and Higgins' I^2 test), funnel plots were generated (Fig. 2). Funnel plots of demographics, comorbidities, and complications in this meta-analysis showed that nearly all the funnel plots were asymmetrical with the exception of chronic liver disease, cerebrovascular disease, asthma/allergy, and AKI, implying that the publication bias existed to some extent.

3.5. Demographic characteristics

Demographic characteristics in this study included gender, age, pre-existing smoking, and body mass index (BMI≥ 25–30 kg/m^2) (BMI is the most useful measure of overweight and obesity in a population, because in adults, the scale is the same regardless of the subject's gender or age (according to World Health Organization (WHO), there is overweight when BMI ≥25 kg/m^2; and there is obesity when BMI is ≥ 30 kg/m^2)). The results of the analysis of demographic characteristics are

Table 1. Clinical and demographic characteristics of the patients with severe and non-severe COVID-19.

Reference	Publication year	Country	Samples (Male/Female)	Severe	Non-severe	Overall age (Median age/ Mean age, range/SD)	Risk factor outcomes
Al-Numair et al., 2022 [14]	2022	Saudi Arabia	598 (352/246)	300	298	57 (46–65)	①, ②, ④, ⑦, ⑨, ⑫, ⑭, ⑮
Almarashda et al., 2022 [15]	2022	United Arab Emirates	585 (386/199)	154	431	49 (39–59)	①, ②, ③, ④, ⑥, ⑦, ⑨, ⑪, ⑮
Cai et al., 2020 [16]	2020	China	298 (145/153)	58	240	47,5 (33–61)	①, ②, ④, ⑦, ⑫
Chen et al., 2023 [17]	2023	China (Taiwan)	127 (70/57)	39	88	52,3 (SD = 14.1)	①, ②, ④, ⑦, ⑫
El Aidaoui et al., 2020 [18]	2020	Morocco	134 (73/61)	45	89	53 (36–64)	①, ②, ③, ④, ⑤, ⑥, ⑦, ⑩, ⑪, ⑫, ⑬, ⑭, ⑯
Feng et al., 2020 [19]	2020	China	476 (271/205)	124	352	53 (40–64)	①, ②, ③, ④, ⑤, ⑥, ⑦, ⑧, ⑨, ⑪
Hermosa et al., 2023 [20]	2023	Spain	2217 (1210/1007)	872	1145	62.2 (SD = 12.8)	①, ②, ③, ④, ⑤, ⑥, ⑦, ⑨, ⑫, ⑯
Hong et al., 2020 [21]	2020	Korea	98 (38/60)	13	85	55.4 (SD = 17.1)	①, ②, ④, ⑤, ⑥, ⑦, ⑧, ⑨, ⑩, ⑫, ⑬, ⑭
Ishii et al., 2020 [22]	2020	Japan	345 (198/147)	112	233	54 (32–68)	①, ②, ④, ⑤, ⑥, ⑦, ⑨, ⑪, ⑫
Kabuto et al., 2023 [23]	2023	Italy	192 (138/54)	44	148	68.5 (65.2–71.8)	①, ②, ③, ④, ⑦, ⑨, ⑭, ⑮
Kantri et al., 2021 [24]	2021	Morocco	138 (73/61)	45	89	53 (36–64)	①, ②, ③, ④, ⑤, ⑥, ⑦, ⑩, ⑪, ⑫, ⑭, ⑯
Lenoir et al., 2023 [25]	2023	Swiss	584 (332/252)	228	356	58 (SD = 14.1)	①, ②, ③, ④, ⑤, ⑥, ⑦, ⑨, ⑪, ⑭, ⑯
Namayandeh et al., 2023 [26]	2023	Iran	19,576 (10,291/9285)	2559	17,017	56.2 (SD = 20.71)	①, ②, ③, ④, ⑤, ⑥, ⑦, ⑨, ⑪, ⑫, ⑯
Ozel et al., 2022 [27]	2022	Turkey	728 (392/336)	37	691	54 (44–65)	①, ②, ④, ⑤, ⑥, ⑦, ⑨, ⑪, ⑫, ⑭, ⑯
Pecorelli et al., 2023 [28]	2023	Switzerland	168 (125/43)	91	77	63 (SD = 12)	①, ②, ④, ⑤, ⑥, ⑦, ⑧, ⑨, ⑪, ⑯
Ren et al., 2020 [29]	2020	China	129 (62/67)	40	89	50 (34.5–61)	①, ②, ④, ⑤, ⑥, ⑦, ⑪
Reyes et al., 2022a [30]	2022	Colombia	40,440 (25,501/14,939)	20,044	20,396	67 (55–78)	①, ②, ④, ⑤, ⑥, ⑦, ⑨, ⑪, ⑫, ⑭, ⑮, ⑯
Reyes et al., 2022b [31]	2022	Colombia	3008 (1817/1191)	1934	1074	56 (43–67)	①, ②, ③, ④, ⑤, ⑥, ⑦, ⑧, ⑨, ⑪, ⑭, ⑯
Ryan et al., 2021 [32]	2021	USA	556 (296/260)	164	392	57 (SD = 17)	①, ②, ③, ④, ⑤, ⑥, ⑦, ⑧, ⑨, ⑪, ⑫, ⑮, ⑯
Shu et al., 2020 [33]	2020	China	293 (135/158)	86	207	57.1 (SD = 16.3)	①, ②, ④, ⑥, ⑦, ⑧, ⑪
Su et al., 2023 [34]	2023	Canada	417 (217/200)	175	242	65.3 (18.4)	①, ②, ③, ④, ⑥, ⑦, ⑨, ⑪, ⑫
Suleyman et al., 2020 [35]	2020	USA	463 (165/298)	141	214	57.5 (SD = 16.8)	①, ②, ③, ④, ⑥, ⑦, ⑨, ⑪, ⑬, ⑮, ⑯
Takács et al., 2023 [36]	2023	Hungary	83 (53/30)	32	51	70.1 (SD = 12.8)	①, ②, ④, ⑥, ⑦, ⑨
Uzum et al., 2023 [37]	2023	Turkey	272 (144/128)	114	158	65 (SD = 14)	①, ②, ④, ④, ⑥, ⑦, ⑪
Wang et al., 2020 [38]	2020	China	138 (75/102)	36	102	56 (42–68)	①, ②, ④, ⑥, ⑦, ⑧, ⑨, ⑩, ⑪, ⑫, ⑬, ⑭
Wei et al., 2020 [39]	2020	China	276 (155/121)	14	262	51 (41–58)	①, ②, ③, ④, ⑥, ⑦, ⑧, ⑨
Xiong et al., 2020 [40]	2020	China	116 (80/36)	55	61	58.5 (47–69)	①, ②, ④, ⑥, ⑦, ⑧, ⑨, ⑩, ⑫, ⑬, ⑭
Xu et al., 2023 [41]	2023	China	11,566 (6959/4607)	2422	9144	65.45 (SD = 15.61)	①, ②, ⑤, ⑥, ⑦, ⑨, ⑩, ⑫, ⑮
Yahyaoui et al., 2023 [42]	2023	Morocco	521 (272/249)	185	336	64 (SD = 16.3)	①, ②, ④, ⑥, ⑦, ⑨, ⑪, ⑮
Yang et al., 2021 [43]	2021	China	78 (37/41)	17	61	45.5 (34–55.8)	①, ②, ③, ④, ⑥, ⑦, ⑭
Yousif et al., 2022 [44]	2022	Sudan	418 (279/139)	279	139	66,3 (SD = 13)	①, ②, ③, ④, ⑥, ⑦, ⑧, ⑨, ⑪
Zhichao Feng et al., 2020 [45]	2020	China	564 (284/280)	69	495	47 (36–58)	①, ②, ③, ④, ⑥, ⑦, ⑧, ⑨, ⑪, ⑫, ⑮
Zhou et al., 2021 [46]	2021	China	120 (49/71)	16	104	51.6 (SD = 10.8)	①, ②, ③, ④, ⑥, ⑦

①: sex; ②: age; ③: smoking history; ④: hypertension; ⑤: malignancy; ⑥: coronary heart disease; ⑦: diabetes; ⑧: cerebrovascular disease; ⑨: chronic obstructive pulmonary disease (COPD); ⑩: shock; ⑪: chronic kidney disease (CKD); ⑫: chronic liver disease; ⑬: acute kidney injury (AKI); ⑭: acute respiratory distress syndrome (ARDS); ⑮: body mass index (BMI); ⑯: asthma/Allergy.

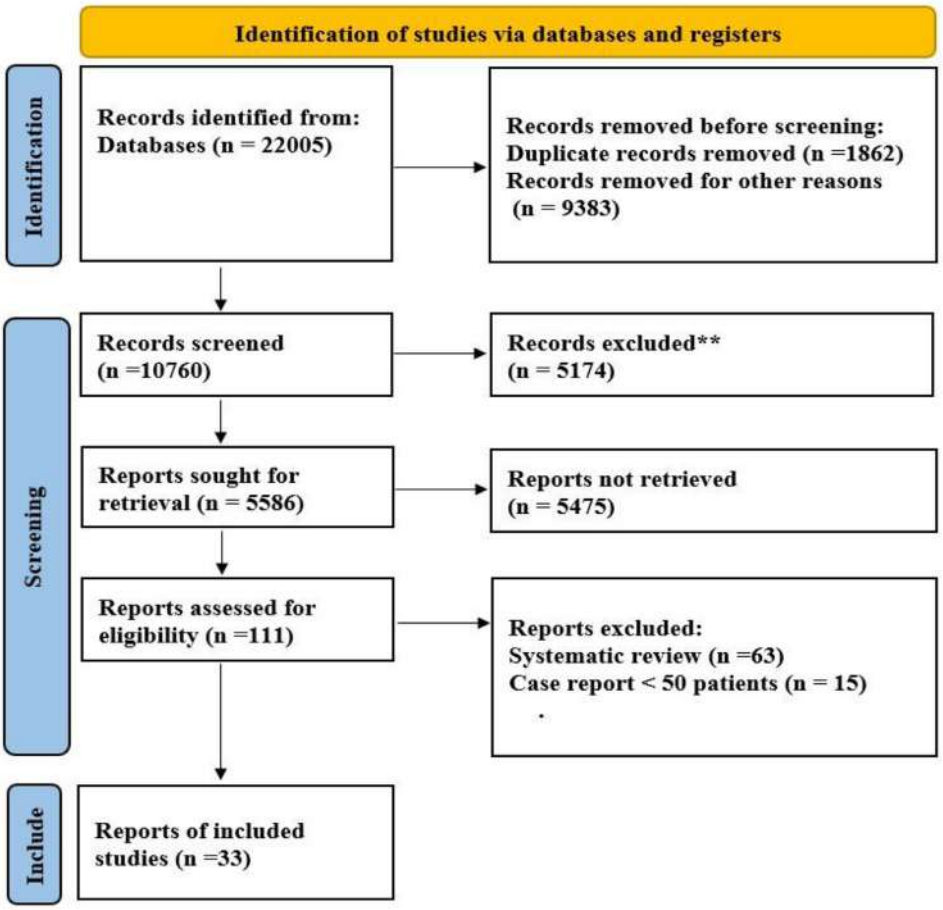

Fig. 1. PRISMA flow diagram of study selection.

presented in Fig. 3. All thirty-three studies reported gender differences (men were taken as reference group in this study), and the result of our analysis showed that men were more likely to have severe disease than women (OR = 1.52, 95 % CI:1.34−1.73; I^2 = 85 %, p < 0.001) [14−46]. In this study, age was statistically significant (SMD = 0.62, 95 % CI: 0.43−0.82 of which OR = 3.06, 95 % CI: 2.18−4.40; I^2 = 97 %; p < 0.001) [14−25,27−46]. Of all articles included in this study, the mean age of patients with severe affection was higher than that of patients with non-severe affection, except for the studies of Takacs et al., 2023 and Xu et al., 2023 [36,41]. Patients' pre-existing smoking status was positively correlated with severe coronavirus disease (OR = 1.33, 95 % CI: 1.01−1.75; I^2 = 67 %, P < 0.001) [15,18−20,23−26,31,32,34,35,39,43−46]. Analyses based on BMI (BMI ≥25−30 kg/m2) revealed that overweight and obesity (overweight if BMI ≥25 kg/m^2; and obesity if BMI ≥30 kg/m^2) were higher in patients with the severe form of the disease compared to the group of patients with non-severe affection (OR = 2.11, 95 % CI: 1.47−3.04; I^2 = 96 %; P < 0.001) [14,15,23,30−32,35,41,42,45]. Fig. 3 shows forest plots of the meta-analysis of the association between demographic characteristics of the severity and non-severity of COVID-19 disease: (a) gender, (b) age, (d) smoking history, and (e) BMI.

3.6. Comorbidities

In this study, Fig. 4 shows the potential association between nine comorbidities and the risk of severe COVID-19. In comparison with patients with a non-severe form of COVID-19 disease, there was a higher risk in patients with the severe form of COVID-19 with several comorbidities associated. Our results showed that cerebrovascular disease had the highest OR value of 2.76 (95 % CI: 1.65−4.62; I^2 = 44 %; p = 0.06) [19,21,28,31−33,38−40,44,45] despite the fact that no significant difference between patients with severe and non-severe cerebrovascular disease was reported after analysis. This risk is followed by chronic kidney disease (CKD), with an OR of 2.27 (95 % CI: 1.26−4.06]; I^2 = 96 %; P < 0.001) [15,18,19,22,24,26−35,37,38,42,44,45], hypertension with an OR of 2.22

Table 2. Evaluation of the methodological quality of studies according to the NOS score.

Study	Selection				Comparability	Outcome			Total score
	Represent ativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Followup time	Adequacy of follow- up of cohorts	
Al-Numair et al., 2022 [14]	*	*	*	*	**	*	*	*	9
Almarashda et al., 2022 [15]	*	*	*	*	**	*		*	8
Cai et al., 2020 [16]	*	*	*	*	**	*	*	*	9
Chen et al., 2023 [17]	*	*	*	*	*			*	6
El Aidaoui et al., 2020 [18]	*	*	*	*	*	*	*	*	8
Feng et al., 2020 [19]	*	*	*	*	**	*	*	*	9
Hermosa et al., 2023 [20]	*	*	*	*	**	*	*		7
Hong et al., 2020 [21]	*	*	*	*	*	*	*		7
Ishii et al., 2020 [22]	*	*	*	*	**	*	*	*	9
Kabuto et al., 2023 [23]	*	*	*	*	**	*	*	*	9
Kantri et al., 2021 [24]	*	*	*	*	**	*	*	*	9
Lenoir et al., 2023 [25]	*	*	*	*	**	*	*	*	9
Namayandeh et al., 2023 [26]	*	*	*	*	*			*	6
Ozel et al., 2022 [27]	*	*	*	*	**	*	*	*	9
Pecorelli et al., 2023 [28]	*	*	*	*	*	*		*	7
Ren et al., 2020 [29]	*	*	*	*	**	*	*	*	9
Reyes et al., 2022a [30]	*	*	*	*	**	*		*	8
Reyes et al., 2022b [31]	*	*	*	*	*	*		*	7
Ryan et al., 2021 [32]	*	*	*	*	**	*	*	*	9
Shu et al., 2020 [33]	*	*	*	*	**	*	*	*	9
Su et al., 2023 [34]	*	*	*	*	*	*		*	7
Suleyman et al., 2020 [35]	*	*	*	*	**	*	*	*	9
Takács et al., 2023 [36]	*	*	*	*	*	*		*	7
Uzum et al., 2023 [37]	*	*	*	*	*		*	*	7
Wang et al., 2020 [38]	*	*	*	*	*	*	*	*	8
Wei et al., 2020 [39]	*	*	*	*	**	*	*	*	9
Xiong et al., 2020 [40]	*	*	*	*	*	*	*	*	8
Xu et al., 2023 [41]	*	*	*	*	*	*	*	*	8
Yahyaoui et al., 2023 [42]	*	*	*	*	**	*		*	8
Yang et al., 2021 [43]	*	*	*	*	*	*		*	7
Yousif et al., 2022 [44]	*	*	*	*	**	*		*	8
Zhichao Feng et al., 2020 [45]	*	*	*	*	**	*		*	8
Zhou et al., 2021 [46]	*	*	*	*	*		*	*	7

Table 3. Results of meta-analysis for primary outcomes.

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2
(a) Sex	33	85,812	Odds Ratio (M–H, Random, 95 % CI)	1.52 [1.34, 1.73]	85 %
(b) Age	28	24,168	Std. Mean Difference (IV, Random, 95 % CI)	0.62 [0.43, 0.82]	99 %
(c) Asthma/allergy	13	68,323	Odds Ratio (M–H, Random, 95 % CI)	1.04 [0.79, 1.36]	71 %
(d) Body mass index (BMI)	10	58,388	Odds Ratio (M–H, Random, 95 % CI)	2.11 [1.47, 3.04]	96 %
(e) Smoking history	17	29,870	Odds Ratio (M–H, Random, 95 % CI)	1.33 [1.01, 1.75]	67 %
(f) Diabetes	33	85,812	Odds Ratio (M–H, Random, 95 % CI)	1.81 [1.35, 2.43]	97 %
(g) Hypertension	32	74,248	Odds Ratio (M–H, Random, 95 % CI)	2.22 [1.72, 2.87]	96 %
(h) Malignancy	22	81,894	Odds Ratio (M–H, Random, 95 % CI)	1.63 [1.07, 2.49]	94 %
(i) Chronic kidney disease (CKD)	21	70,243	Odds Ratio (M–H, Random, 95 % CI)	2.27 [1.26, 4.06]	96 %
(j) Chronic obstructive pulmonary disease (COPD)	24	84,227	Odds Ratio (M–H, Random, 95 % CI)	1.95 [1.22, 3.09]	98 %
(k) Cerebrovascular disease	11	6111	Odds Ratio (M–H, Random, 95 % CI)	2.76 [1.65, 4.62]	44 %
(l) Coronary heart disease	29	84,597	Odds Ratio (M–H, Random, 95 % CI)	2.17 [1.42, 3.31]	98 %
(m) Chronic liver disease	17	78,254	Odds Ratio (M–H, Random, 95 % CI)	1.33 [0.82, 2.16]	91 %
(n) Shock	7	12,541	Odds Ratio (M–H, Random, 95 % CI)	28.08 [3.49, 226.03]	86 %
(o) Acute kidney injury (AKI)	4	397	Odds Ratio (M–H, Random, 95 % CI)	16.91 [1.87, 152.45]	63 %
(p) Acute respiratory distress syndrome (ARDS)	12	46,248	Odds Ratio (M–H, Random, 95 % CI)	13.09 [5.87, 29.18]	94 %
(q) Neurological complications	6	64,504	Odds Ratio (M–H, Random, 95 % CI)	0.95 [0.35, 2.64]	97 %
(r) Arrhythmia	5	41,444	Odds Ratio (M–H, Random, 95 % CI)	7.47 [2.96, 18.83]	34 %

(95 % CI:1.72–2.87; $I^2 = 96$ %; $p < 0.001$) [14–40,42–46] and coronary heart disease with an OR of 2.17 (95 % CI:1.42–3.31; $I^2 = 98$ %; $p < 0.001$) [15,18–22,24–46]. Other significant judgment criteria for risk factors of the comorbidities involved in the severe form of COVID-19 included chronic obstructive pulmonary disease (COPD) (OR: 1.95, 95 % CI:1.22–3.09; $I^2 = 98$ %, $p < 0.001$) [14,15,19–23,25–28,30–32,34–36,38–42,44,45], diabetes mellitus (OR = 1.81, 95 % IC: 1.35–2.43; $I^2 = 97$ %, $p < 0.001$) [14–46], malignancy (OR = 1.63, 95 % CI: 1.07–2.49; $I^2 = 94$ %; $p < 0.001$) [18–22,24–32,35,36,38–41,44,45], Chronic liver disease (CLD) with an OR of 1.33 (95 % CI: 0.82–2.16; $I^2 = 91$ %, $p < 0.001$) [14,16–18,20–22,24,26,27,30,32,34,38,40,41,45] and Asthma/allergy (OR = 1.04, 95 % CI: 0.79–1.36; $I^2 = 71$ %, $p < 0.001$) [18,20,22,24–28,30–33,35]. However, there were fewer patients with asthma or allergies in the severe COVID-19 group compared to the non-severe COVID-19 group with a significant number of patients with asthma or allergies.

3.7. Complications

In Fig. 5, our results indicate that shock with an OR of 28.08 (95 % CI: 19,99–78,41; $I^2 = 86$ %, $p < 0.001$) [18,21,24,35,38,40,41], acute kidney injury (AKI) with OR = 16.91 (95 % CI:1.87–152.45; $I^2 = 63$ %; $p = 0.07$) [18,21,38,40] and acute respiratory distress syndrome (ARDS) with OR = 13.09 (95 % IC: 5.87–29.18; $I^2 = 94$ %, $P < 0.001$) [14,18,21,23–25,27,30,31,38,40,43] were the principal complications associated with severe and life threatening disease in COVID-19 patients. In addition to the aforementioned complications, cardiac rhythm disturbance (arrhythmia) (OR = 7.47; 95 % CI: 2.96–18.83; $I^2 = 34$ %, $p = 0.20$) [14,18,24,30,38] was one of the complications associated with the severity of COVID-19 disease in some patients, although the result was not statistically significant. Despite the fact that the studies we examined provided insufficient evidence to support other findings of complications other than shock, acute renal failure (AKI), acute respiratory distress syndrome (ARDS), and arrhythmia, the data that we have are very consistent in severe cases of COVID19. However, neurological complications with an OR of 0.95 (95 % CI: 0.35–2.64; $I^2 = 97$ %, $p < 0.001$) did not show any potential risk of complication in the group of patients with severe COVID-19 disease [26,30–32,42,44].

3.8. Population attributable risk

In this meta-analysis, we calculated the proportion of risk attributed to the population infected with SARS-CoV-2. The Population Attributable Fraction (PAF) represents the proportion of cases in the population that can be attributed to exposure to risk factors associated with severe infections of the coronavirus disease (COVID-19). In this study, the PAFs ranged from 0.10 % to 18.47 % (Table 4). The estimated attributable fraction for COVID-19 patients was 18.47 % for acute respiratory distress syndrome (ARDS), 14.29 % for hypertension, 9.47 % for body mass index (obesity), 9.39 % for diabetes,

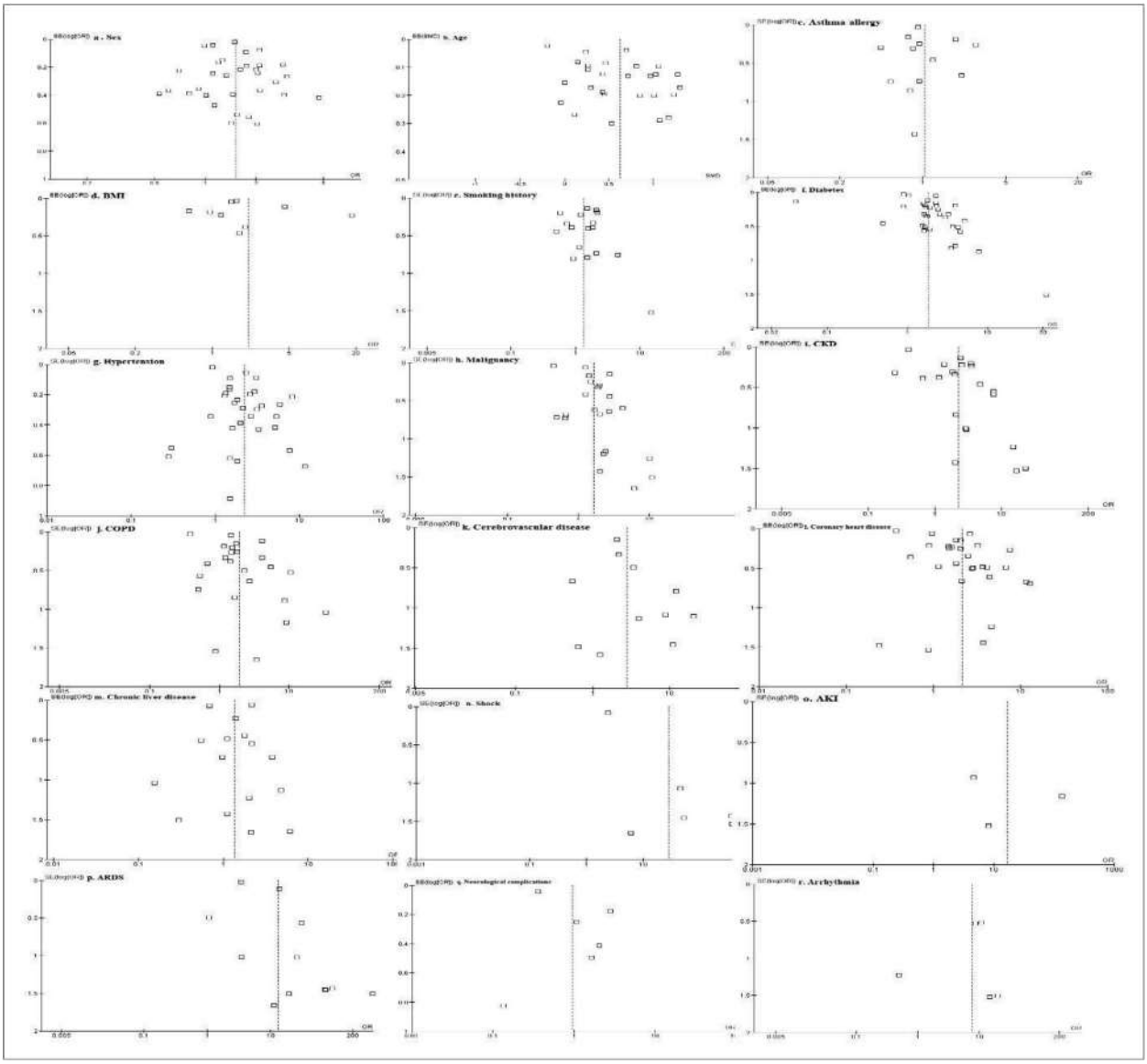

*Fig. 2. Funnel plot representing publication bias of each meta-analysis: (a) sex, (b) age, (d) smoking history, (e) BMI, (e) asthma/allergy, (f) diabetes, (g) hypertension, (h) malignancy, (i) CKD, (j) COPD, (k) cerebrovascular disease, (l) coronary heart disease, (m) chronic liver disease, (n) shock, (o) acute kidney injury (AKI), (p) acute respiratory distress syndrome (ARDS), (q) neurological complications and (r) arrhythmia. *SE (log [OR]) = Standard error multiplied log scale of odd ratio (OR).*

and 8.62 % for coronary heart disease. It is estimated that reducing the prevalence of ARDS, hypertension, BMI, diabetes, and coronary heart disease could have prevented up to 8.62 %–18.47 % of severe cases.

4. Discussion

To our knowledge, this is one of the most comprehensive studies demonstrating the impact of various comorbidities and complications on the severe cases of COVID-19, as well as estimating the prevalence of these risk factors. Identifying potential risk factors involved in severe coronavirus disease is crucial for public health professionals to better target high-risk patients requiring prioritized treatment to prevent unfavorable disease outcomes [7]. In this study, potential risk factors contributing to severe form included demographic characteristics such as age, gender, obesity (BMI $\geq$25–30 kg/m^2) and smoking history, as well as comorbidities and complications listed in Table 3. The different risk factors reported in this meta-analysis are predictive of a severe and critical form of the disease, requiring patients' admission to intensive care units (ICU). Our analysis has shown that the association between age, gender (male), obesity, and smoking status appeared with numerous comorbidities as

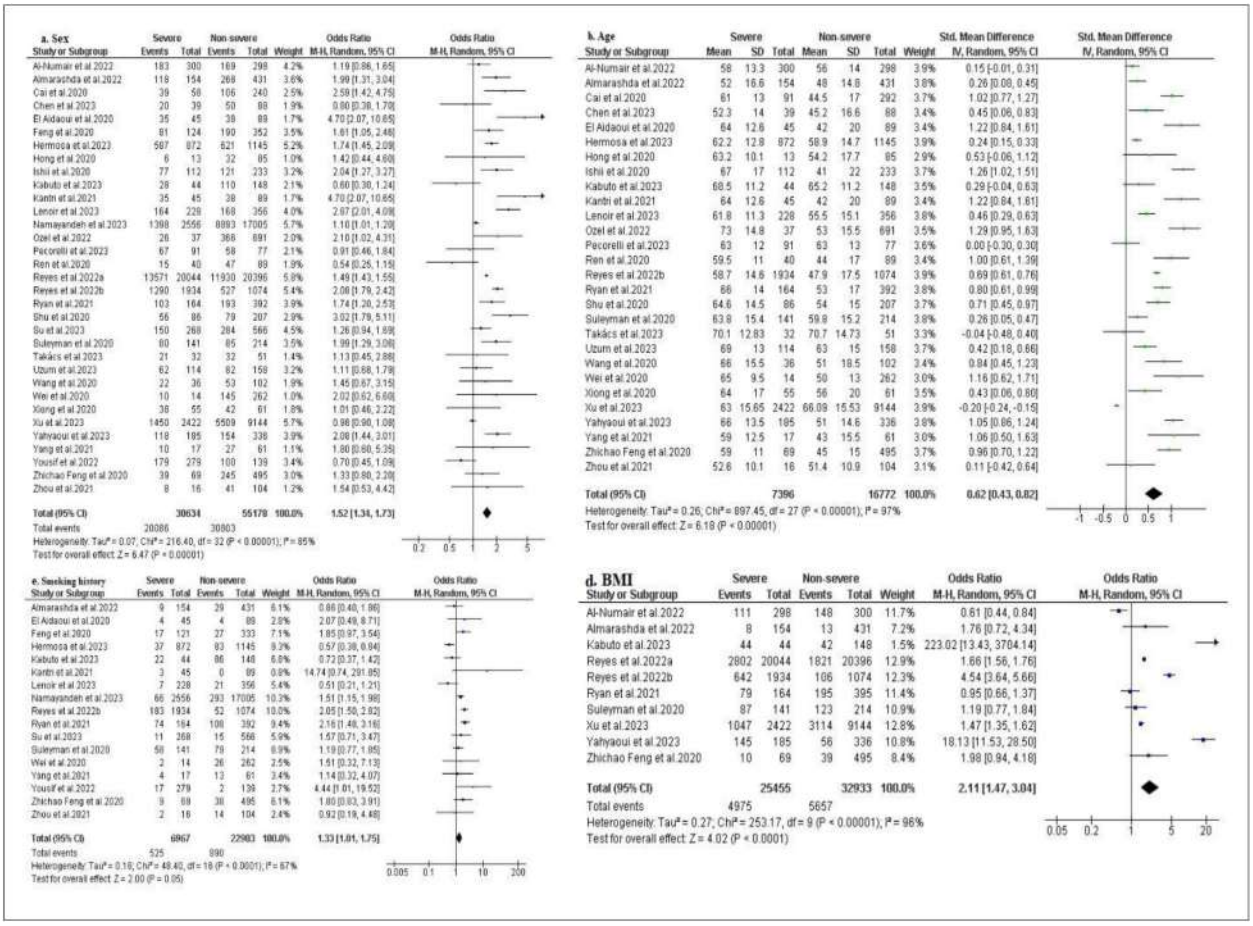

Fig. 3. Forest plots comparing demographic characteristics between severe and non-severe groups. (a) sex, (b) age, (d) smoking history, (e) BMI and severe COVID-19 disease.

risk factors for severe COVID-19 [47,48]. Indeed, several studies have reported that advanced age is associated with the severity of COVID-19, primarily due to physiological changes accompanying aging, a weakened immune system and underlying health issues [7,49,50]. In agreement with these studies, the advanced age of patients in our study appeared strongly as a potential risk factor associated with the severe form of COVID-19 compared to non-severe COVID-19 patients (SMD = 0.62; OR = 3.06, $P < 0.001$), and the result was statistically significant. However, age alone does not explain the variability in disease severity. In agreement with the results from the general population in this study, it was evident that the elderly had a higher prevalence of comorbidities including diabetes (OR = 1.81), hypertension (OR = 2.22), and COPD (OR = 1.95) as observed in our study (Fig. 4), while complications including ARDS (OR = 13.09, PAF = 18.47 %), shock (OR = 28.08, PAF = 5.78 %), AKI (OR = 16.91, PAF = 5.64 %) and arrhythmia (OR = 7.47, PAF = 0.17 % %) were the main obstacles to recovery in patients with the severe form of COVID-19 (Fig. 5 and Table 3). In addition, our study supports the hypothesis of some studies which have reported that, cancer (OR = 1.63), CKD (OR = 2.27), cerebrovascular disease (OR = 2.76), and coronary heart disease (OR = 2.17), are also associated with the severity of COVID-19 [49,51,52]. These risk factors increase the risk of admission to intensive care units, and could be life-threatening [49,51,52]. In contrast to some studies, our study reported several comorbidities [47,52–54]. Interestingly, previous studies such as that of Ross Arena and his colleagues have indicated that unhealthy lifestyle behaviors, comorbidities, and COVID-19 syndemic in severe cases raise the question of a complex interaction of health factors, acting synergistically to worsen the overall consequences of the disease [4–6]. It is reported that physical inactivity can contribute to obesity, which in turn can increase the risk of diabetes and other noncommunicable diseases (NCDs) [4–6]. Our study supports this hypothesis, which is consistent with our results

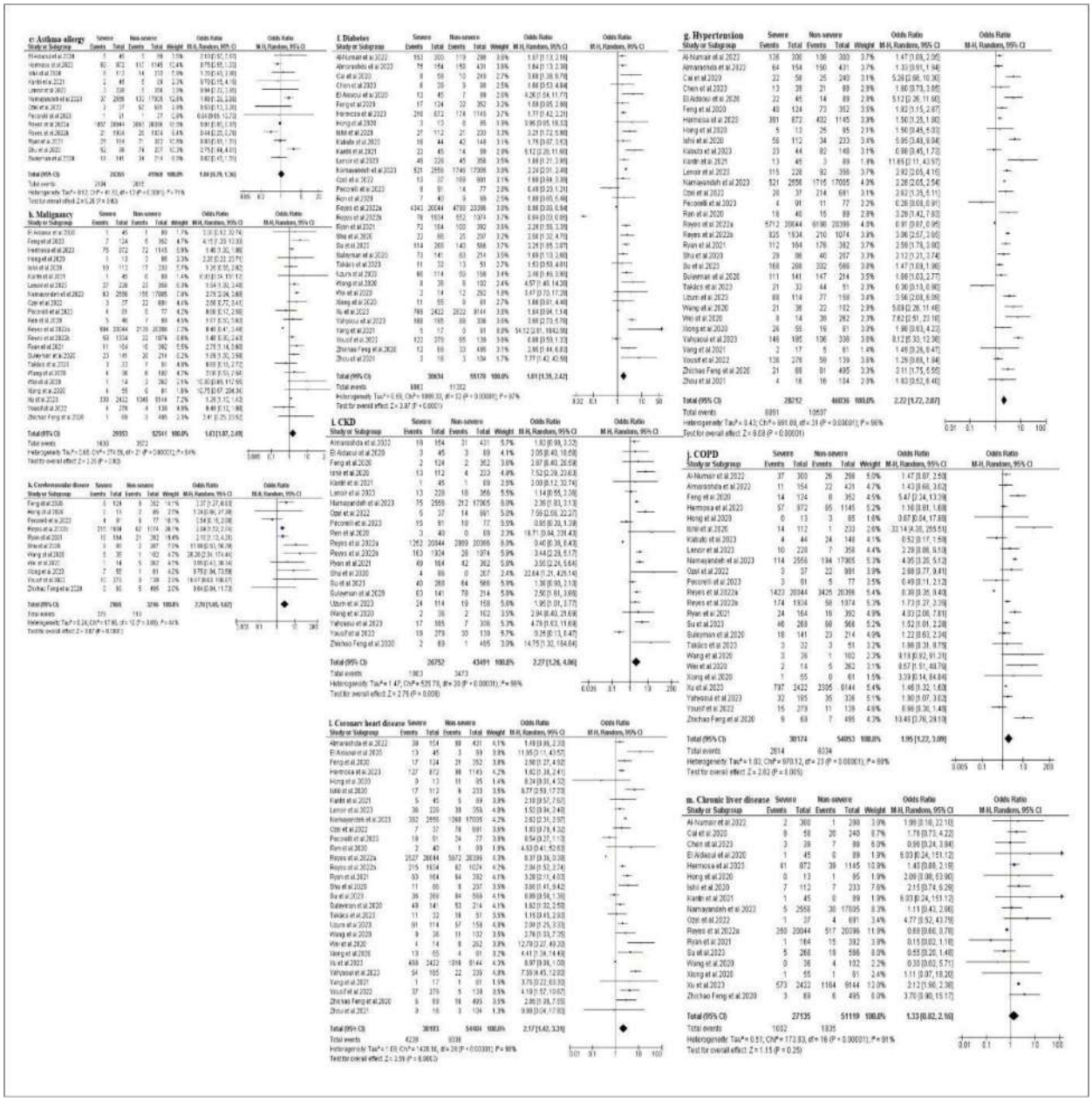

Fig. 4. Forest plots of the meta-analysis of the association between comorbidities in patients with severe and non-severe COVID-19 disease. (e, f, g, h, i, j, k, l, m) forest plots of the association between (e) asthma/allergy, (f) diabetes, (g) hypertension, (h) malignancy, (i) CKD, (j) COPD, (k) cerebrovascular disease, (l) coronary heart disease, and (m) chronic liver disease.

showing that patients with comorbidities such as obesity, diabetes, and cardiovascular disease were at high risk of developing the severe form of COVID-19. Therefore, raising awareness of healthy lifestyles could strengthen human resilience and could protect some people against certain noncommunicable diseases as well as health deterioration due to viral infection [4–6].

Advanced age and comorbidities such as diabetes, hypertension, and asthma have been found to have a significant impact on the health of COVID-19 patients. Previous meta-analysis studies have shown that pre-existing diabetes, hypertension, obesity, and smoking were associated with severe cases of COVID-19 and higher mortality, representing up to 30 % of cases [47]. Therefore, it is essential to pay particular attention to obese elderly patients with a history of smoking, as well as those with comorbidities or complications such as shock, ARDS, AKI, and arrhythmia because they are likely to develop a

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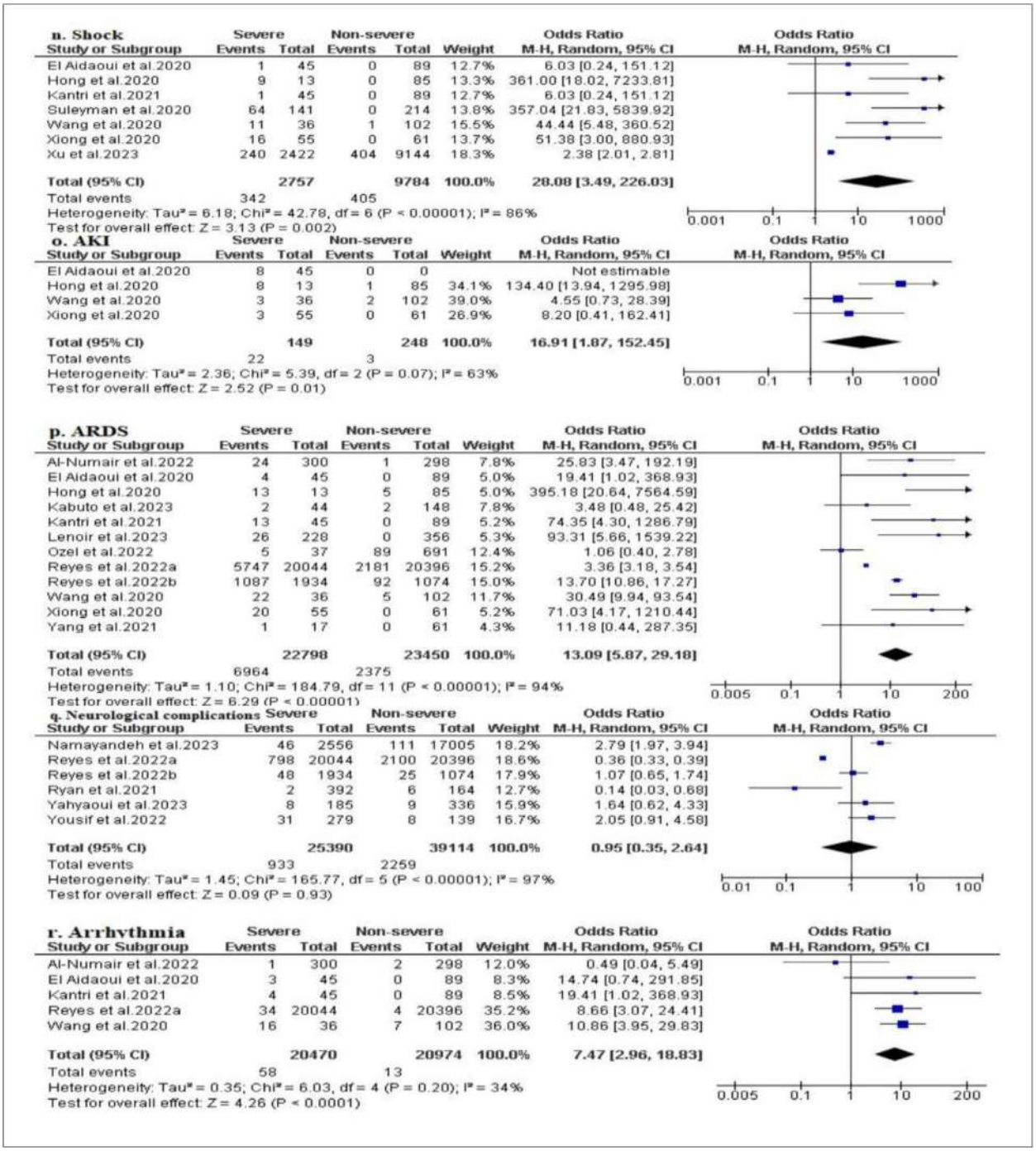

Fig. 5. Forest plots of complications reported in severe and non-severe groups of patients with COVID-19: (n) shock, (o) acute kidney injury (AKI), (p) acute respiratory distress syndrome (ARDS), (q) neurological complications, (r) arrhythmia.

severe form of COVID-19 [47]. According to some reports, the proportion of COVID-19 cases is approximately equal between the genders [55], but men are more likely to develop a severe form of the disease [52]. Our analysis is in agreement with the fact that male gender (OR = 1.65) is one of the risk factors associated with the severity of COVID-19 unlike female gender [56]. Nevertheless, it is reported that the severity of COVID-19 which mainly affects elderly men is strongly associated with frequent consumption of tobacco [56]. Moreover, certain genes regulating the immune system are located on the X chromosome, of which women possess two copies. These genes located on the X chromosome contain the largest number of genes regulating the immune system in the entire human

Table 4. Proportion of risk attributable to different risk factors for severe forms of the disease.

Outcome or Subgroup	Prevalence	PAF	OR (95 % CI)
(c) Asthma/allergy	0.07	0.27 %	1.04 [0.79, 1.36]
(d) Body mass index (BMI)	0.18	9.47 %	2.11 [1.47, 3.04]
(e) Smoking history	0.05	1.24 %	1.33 [1.01, 1.75]
(f) Diabetes	0.21	9.39 %	1.81 [1.35, 2.43]
(g) Hypertension	0.26	14.29 %	2.22 [1.72, 2.87]
(h) Malignancy	0.06	2.32 %	1.63 [1.07, 2.49]
(i) Chronic kidney disease (CKD)	0.07	4 %	2.27 [1.26, 4.06]
(j) Chronic obstructive pulmonary disease (COPD)	0.11	5.35 %	1.95 [1.22, 3.09]
(k) Cerebrovascular disease	0.06	3.82 %	2.76 [1.65, 4.62]
(l) Coronary heart disease	0.16	8.62 %	2.17 [1.42, 3.31]
(m) Chronic liver disease	0.04	0.10 %	1.33 [0.82, 2.16]
(n) Shock	0.06	5.78 %	28.08 [3.49, 226.03]
(o) Acute kidney injury (AKI)	0.06	5.64 %	16.91 [1.87, 152.45]
(p) Acute respiratory distress syndrome (ARDS)	0.20	18.47 %	13.09 [5.87, 29.18]
(r) Arrhythmia	0.002	0.17 %	7.47 [2.96, 18.83]

genome, theoretically conferring women a double advantage in stimulating an effective and rapid immune response [57]. In addition, the female hormones estrogen and progesterone would boost women's immunity against severe COVID-19, while, lower expression of the androgen receptor (AR) in women might contribute to reduced vulnerability to complications like acute respiratory distress syndrome [58,59]. Angiotensin-converting enzyme 2 (ACE2) an essential receptor for cell entry of SARS-CoV-2 is known to be influenced by sex hormones and is present in greater quantity in men than in women, which could increase sensitivity to SARS-CoV-2 [60,61]. In addition, the host transmembrane serine protease 2 (TMPRSS2) also plays an important role in the entrance of SARS-CoV-2 into cells. Its expression is associated with an increase in androgen receptors [62,63]. Our study showed that pre-existing diabetes was a risk factor (OR = 1.81) associated with severe disease in patients with COVID-19 compared to patients with non-severe forms of the disease. This finding is in agreement with several related studies [64,65]. Diabetic patients suffer from altered immunological and inflammatory pathways after hyperglycemia, which could make them more susceptible to developing a severe COVID-19 infection [66]. In other words, high blood glucose levels in diabetic patients could make them more vulnerable to severe COVID-19 infection. On the other hand, COVID-19 infection can influence glucose levels and worsen outcomes in diabetic patients. The severe form of COVID-19 can stimulate the liberation of stress hormones such as cortisol and adrenalin, temporarily raising blood glucose levels by stimulating glucose production in the liver [66]. In addition, the systemic inflammation associated with infection can disrupt insulin regulation, leading to insulin resistance and increased glucose levels [66], therefore, this suggests a bidirectional association between diabetes/glycemia and COVID-19 [67]. In addition to the comorbidities previously mentioned, obesity is identified as another metabolic comorbidity associated with severe COVID-19. We considered obesity as a risk factor on the basis of this meta-analysis (OR = 2.11) with a prevalence of 9.47 % associating obesity with risk factors for severe COVID-19. Obesity is implicated in significant changes in the distribution of immune cells in adipose tissue, with a decrease in regulatory T cells (Treg), Th2 cells, and M2 macrophages, as well as a decrease in M1 macrophage cells and an increase in CD8+ T lymphocytes, hampering immune defense and T cell activity [47,66,68]. The high level of ACE2 receptor expressed in adipocytes may transform adipose tissue into a viral vector, which could facilitate the spread of SARS-CoV-2 to other organs [69].

Hypertension was one of the major predominant factors for disease severity of COVID-19. It is a chronic disease that generally occurs in the elderly. In the severe form of COVID-19, there is a strong correlation between hypertension and age, on the one hand, and coronary heart disease on the other hand. This correlation could explain the high prevalence of hypertension in patients with severe COVID-19 [70,71]. Considered the leading reversible risk factor for cardiovascular morbidity and mortality, contributing to the development of vulnerable cardiovascular areas and acute myocardial affections favoring severe and fatal forms of COVID-19 [72]. Recent reports have shown that the prevalence of hypertension in patients with COVID-19 is considerable, ranging from 9.6 % to 40.8 % [70]. According to our results, most patients with severe COVID-19 were older than those with non-severe COVID-19 and the prevalence of hypertension in

our study was 14.29 % with an OR of 2.22 and with an OR of 2.17 for coronary heart disease and arrhythmic complications (OR = 7.47) implicated in the worsening of COVID-19 in patients. These results were consistent with related studies [70,71]. SARS-CoV-2 infection is therefore associated with a high inflammatory load that can induce vascular inflammation, myocarditis, and cardiac arrhythmias. This suggests that myocardial and vascular damage may be direct or indirect after SARS-CoV-2 infection through myocarditis and endothelial dysfunction [73]. Furthermore, in subjects with severe COVID-19, systemic inflammation, elevated cytokine levels and hypercoagulability could contribute to atherosclerotic plaque rupture [71]. In addition, sympathetic hyperactivity and hypoxemia can lead to myocardial ischemia and ventricular dysfunction by disturbing the balance between the heart's oxygen supply and consumption [71]. In normal physiological conditions, the antagonistic effects of ACE 1 and ACE 2 maintain homeostasis. However, in patients with severe coronavirus disease, angiotensin-1 is converted to angiotensin-2 by ACE, leading to inflammation, oxidative stress, fibrosis, vasoconstriction and increased vascular permeability contributing to ARDS [71]. In addition, it has been reported that some antihypertensive drugs can affect hemoglobin levels in hypertensive patients with diabetes mellitus, which could be associated with the severity of COVID-19 [70]. In general, comorbidities such as hypertension, diabetes, obesity, and smoking are strongly associated with vascular endothelial damage, dysfunction of the hemostatic system, and chronic inflammation. This can lead to increased cytokines, multiple organ failure (MOF), which can lead to acute respiratory distress syndrome (ARDS) and aggravation of the patient's condition in case of SARS-CoV-2 infection [71]. According to our estimations, between 8.62 % and 18.47 % of severe cases could have been avoided if the prevalence of hypertension (OR = 2.22; PAF = 14.29 %), coronary heart disease (OR = 2.17; PAF = 8.62 %) and complications such as acute respiratory distress syndrome (ARDS) (OR = 13.09; PAF = 18.47 %) had been reduced. In our meta-analysis, cerebrovascular disease was one of the predominant factors in the severity of COVID-19. Cerebrovascular disease was found to be associated with a 2.76-fold increased risk of severe COVID-19 in patients infected with SARS-CoV-19. However, there was a non-significant trend with cerebrovascular disease in COVID-19 patients in our study. Our results are in agreement with those of Aggarwal and his colleagues [74]. Some studies have shown that comorbidity such as COPD in patients with COVID-19 was one of the potential risk factors associated with the severity of COVID-19 compared with asthmatic/allergic patients [47,52]. In asthmatics, the upper and lower airways are mainly affected, whereas in COPD patients, the altered lesions extend from the small peripheral airways to the alveolar tissues, which can lead to the severe form of coronavirus disease (COVID-19). The lesions caused by COPD are similar to those caused by SARS-CoV-2 and this could increase the risk of severe COVID-19. However, longterm use of inhaled corticosteroids to control asthma may have a beneficial modulatory effect on patients with COVID-19 by reducing epithelial damage and enhancing T-cell immune responses [47,52]. The results of our analysis were in agreement with these related studies, showing that the risk of severe COVID-19 was higher in patients with pre-existing COPD (OR = 1.95; 95 % CI: 1.22–3.09) with a prevalence of 5.35 % in contrast to asthmatic or allergic patients who did not present an increased risk of severe COVID-19 (OR = 1.04; 95 % CI: 0.79–1.36) with a prevalence of 0.27 %. COPD can engender airway obstruction and respiratory complications such as ARDS [69,75,76].

As reported by Fang and his colleagues, among the comorbidities, whether malignancy contributes to the worsening of coronavirus disease remains controversial [51]. Some studies have shown that patients with malignancy did not show an increased risk of developing a severe form of COVID-19 [69,77]. This could be due to the attenuated flow of cytokines caused by their compromised immune systems [69,77]. However, some studies have shown that cancer patients are more likely to develop a severe form of the disease [78]. Our study showed that malignancy was a risk factor for disease worsening (OR = 1.63). Furthermore, we observed a low prevalence of severe COVID-19 in patients with malignancy in our study (PAF = 2.32 %). These results are in agreement with related studies such as Desai and his colleagues and Elgohary and his colleagues [78,79]. However, it is not easy to make strong conclusions for several reasons, such as the small number of cancer patients with a severe form of COVID-19, the lack of information on cancer staging, treatment phase, comorbidities, type of cancer treatment, planned treatment for COVID-19 infection and the ability of the healthcare system to manage these patients [78]. All these factors can influence patient outcomes. Regarding the risk of developing the severe COVID-19 associated with chronic liver disease, we observed an OR of 1.33 with a 95 % CI: 0.82–2.16. Compared with the results of Nagarajan and his colleagues, who found an

OR of 2.44 with a 95 % CI:1.8–3.16 for chronic liver disease, our result suggests a weaker association between chronic liver disease and the risk of developing the severe form of COVID-19 [53]. Furthermore, chronic kidney disease (CKD) (OR = 2.22) and pre-existing acute kidney injury (AKI) (OR = 16.91) were risk factors for disease worsening and hampered recovery in patients with severe COVID-19 compared to patients with non-severe COVID-19. Previous studies with similar results to ours suggested that it was likely that patients with CKD had a disorder of the immune system, suggesting that CKD and pre-existing AKI complications could be involved in the severe COVID-19 disease [54,69]. Shock (OR = 28.08), AKI (OR = 16.91), ARDS (OR = 13.09), and arrhythmia (OR = 7.47) were principal complications associated with the severity of COVID-19. Al-Mutair and his colleagues reported that excessive lung inflammation, increased pulmonary capillary permeability and alveolar fluid accumulation induced by SARS-CoV-2 were associated with ARDS, for this reason, some ARDS patients required respiratory assistance, particularly diagnosed in patients with severe COVID-19, and this could be due to increased levels of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) found in these patients [80]. Nevertheless, daily assessment of the Sequential Organ Failure Assessment (SOFA) score and the Multiple Organ Dysfunction (MOD) score associated with septicemia is essential for early diagnosis, treatment and prevention of the consequences of shock and multi-organ dysfunction in patients with severe COVID-19 [80].

Interestingly, the population-attributable risk fractions (PAFs ≥8 %) in this study were statistically significant. Like Li and his colleagues, we found that the highest prevalence of comorbidities was hypertension [69]. However, the prevalence of hypertension in our study (PAF = 14 %) was higher than that reported by Li and his colleagues (PAF = 11.3 %). Among the complications listed in this study, ARDS was the complication contributing to the severity of COVID-19 with a high prevalence in our study (PAF = 18.47 %) compared to the study of Li and his colleagues, in which the complications implicated in the severity of COVID-19 were ARDS (PAF = 10 %) and AKI (PAF = 7.4 %) [69]. Therefore, the risk of severe cases could decrease with the reduction of the prevalence of these factors. In addition, factors such as obesity (PAF = 9.47 %), diabetes (PAF = 9.39 %), and coronary heart disease (PAF = 8.62 %) should be controlled. It is important to be cautious about public health guidelines for the management of patients with these comorbidities. However, the other risk factors had PAFs ranging from 0.10 % to 5.78 %, which suggests that these PAFs exerted less effect on the severity of COVID-19 (Table 4).

Our study has several limitations. Eligible studies were limited to articles written in English and French. We were unable to assess the impact of SARS-CoV-2 variants on COVID-19 risk or the effect of vaccination on decreasing severe cases in patients; although all the studies reviewed compared severe and non-severe cases. However, some articles did not specify their definition criteria for severe and non-severe cases, which could bias the results of these studies. Comorbidities and complications can be measured differently from one study to another, which can introduce measurement bias. The quality of the data included in the meta-analysis depends on the quality of the original studies. Unmeasured or unaccounted confounding factors could exist in the included studies, which could influence the results. If some studies have significant methodological flaws, this can affect the validity of the aggregated results.

5. Conclusion

In this meta-analysis, the group of patients with severe COVID-19 had a higher prevalence of demographic characteristics, comorbidities, and complications compared to the group of nonsevere COVID-19 patients. However, several risk factors associated with an increased risk of worsening coronavirus disease (COVID-19) have been reported. These included advanced age, sex, obesity, pre-existing smoking, as well as comorbidities such as diabetes, hypertension, malignancy, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), cerebrovascular disease, and coronary artery disease. In addition, complications such as septic shock, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), and arrhythmia can have lasting consequences on patients' health, leading to an undesirable disease course. These outcomes are crucial in guiding timely treatment decisions and assessing disease prognosis.

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Conflicts of interest

The authors declare no competing interests.

Authors' contributions

Study Design: AB, AM, and BK. Data Collection and analysis: SD and NN. Data analyses and interpretation: SD, NN, and JN. Manuscript Writing: SD and NN. All authors contributed to revisions and have read and approved the final manuscript.

Ethical statement

The institutional review board and patient consent were not required because of the review nature of this study.

Support information

S1 PRISMA 2020 Checklist.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P7-8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P4-10
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	P11-16
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P7-9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P5-6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P6-16
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P5 -10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P9-10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P10
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P10
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P10-16

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P6
Study characteristics	17	Cite each included study and present its characteristics.	P7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	P10
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P9-16
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P9-16
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P10-15
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P9-16
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	P9-16
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	P9-16
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	P9-16
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P17-22
	23b	Discuss any limitations of the evidence included in the review.	P22
	23c	Discuss any limitations of the review processes used.	P22
	23d	Discuss implications of the results for practice, policy, and future research.	P22
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	NA
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	P6, P23
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P23
Competing interests	26	Declare any competing interests of review authors.	P23
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	P6-9, P23

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For more information, visit: http://www.prisma-statement.org/

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