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REVIEW

The epidemiological burden and overall distribution of chronic comorbidities in coronavirus disease-2019 among 202,005 infected patients: evidence from a systematic review and meta-analysis

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Abstract

Purpose The main purpose of this study was to examine the overall distribution of chronic comorbidities in coronavirus disease-19 (COVID-19) infected populations and the risk of the underlying burden of disease in terms of the case fatality ratio (CFR).

Methods We carried out a systematic review and meta-analysis of studies on COVID-19 patients published before 10th April 2020. Twenty-three studies containing data for 202,005 COVID-19 patients were identified and included in our study. Pooled effects of chronic comorbid conditions and CFR with 95% confidence intervals were calculated using random-effects models.

Results A median age of COVID-19 patients was 56.4 years and 55% of the patients were male. The most prevalent chronic comorbid conditions were: any type of chronic comorbidity (37%; 95% CI 32–41%), hypertension (22%; 95% CI 17–27%), diabetes (14%; 95% CI 12–17%), respiratory diseases (5%; 95% CI 3–6%), cardiovascular diseases (13%; 95% CI 10–16%) and other chronic diseases (e.g., cancer) (8%; 95% CI 6–10%). Furthermore, 37% of COVID-19 patients had at least one chronic comorbid condition, 28% of patients had two conditions, and 19% of patients had three or more chronic conditions. The overall pooled CFR was 7% (95% CI 6–7%). The crude CFRs increased significantly with increasing number of chronic comorbid conditions, ranging from 6% for at least one chronic comorbid condition to 13% for 2 or 3 chronic comorbid conditions, 12% for 4 chronic comorbid conditions, 14% for 5 chronic comorbid conditions, and 21% for 6 or more chronic comorbid conditions. Furthermore, the overall CFRs also significantly increased with higher levels of reported clinical symptoms, ranging from 14% for at least four symptoms, to 15% for 5 or 6 symptoms, and 21% for 7 or more symptoms.

Conclusions The chronic comorbid conditions were identified as dominating risk factors, which should be considered in an emergency disease management and treatment choices. There is urgent need to further enhance systematic and real-time sharing of epidemiologic data, clinical results, and experience to inform the global response to COVID-19.

Keywords COVID-19 · Coronavirus · Chronic cormobidity · Disease · Fatality

Abbreviations

CFR	Case fatality ratio
CI	Confidence intervals
JBI	Joanna Briggs Institute
WHO	World Health Organisation
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Introduction

On December 31, 2019, China reported a series of pneumonia cases with an unknown cause that was later identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1–3]. Subsequently, a novel coronavirus that is

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phylogenetically in the SARS-CoV clade was reported as the causative agent of the outbreak. The disease was named a novel coronavirus disease-2019 (COVID-19) and was declared a global pandemic by the Director General of the World Health Organisation (WHO) on March 11, 2020 [1]. Patients with the disease commonly present with fever, cough, and shortness of breath within an incubation period of 2–14 days [3].

So far, the majority of COVID-19 cases (80%) are milder respiratory infections and pneumonia [4]. The risk of severe illness and associated death with COVID-19 infection is considered high among the elderly and individuals with underlying chronic health conditions [4]. Some studies have reported a high proportion of COVID-19 infected individuals (30 to 48%) had at least one chronic comorbid condition [2, 5–8], including hypertension [7, 8], cardiovascular diseases [9–11], diabetes [12, 13], respiratory system diseases, and other chronic diseases [14]. Chronic diseases lead to several clinical features with complications, including the proinflammatory state and the reduction of the innate immune response [15, 16]. Chronic comorbid conditions of patients contribute to major clinical challenges in terms of diagnosis, ill health and disease management, which adversely influence treatment choices and outcomes [17]. Ultimately, the severity of comorbidity leads to poor health conditions and outcomes, an increased risk of hospitalisation, and an increased financial burden on the healthcare system [18–20].

Measuring the prevalence of chronic comorbid conditions can be a basis for mitigating complications in patients with COVID-19 infection. Therefore, using a systematic review and meta-analysis, we aimed to estimate the pooled prevalence of comorbidities in all patients and to investigate the risk of underlying diseases in terms of crude case fatality ratio (CFR). Unlike previous systematic review studies [21–23] that focussed on specific regions, our study is unique in that it includes published studies with vast data on COVID-19 patients from different regions. The large pool of data and wide geographical coverage represents various populations giving insight into how different populations and regions respond to COVID-19. We anticipate that our study findings will provide comprehensive understanding of COVID-19 and will inform prevention, control, and response policies and practices.

Methods

Search strategy

We conducted a comprehensive search for academic studies that reported in COVID -19 patients published between January 2020 and 9th April 2020 from the following electronic bibliographic databases: PubMed, Scopus, EBSCOhost (CINAHL, Medline), Web of Science, and the first 20 pages of Google Scholar. The following search terms were used with no language restrictions:

> ["2019 novel coronavirus or COVID-19"] AND ["comorbidities" OR "chronic comorbidity" OR "chronic diseases" OR "diabetes" OR "hypertension" OR "respiratory diseases" OR "cardiovascular diseases" OR "cancer" OR "malignancy" OR "asthma" OR "bronchitis" OR "kidney disease"].

Study participants

Our study scope comprise of patients that were clinically presented with COVID-19 characteristics and were hospitalised.

Inclusion and exclusion criteria

Eligible studies were included if they 1) were original articles; 2) published between January 2020 and April 9th, 2020; focused on 3) epidemiological perspective, 4) reported clinical characteristics of the COVID-19 among infected people, and 5) reported the prevalence of chronic comorbid conditions in infected patients. Reviews, editorials, letters, perspectives, commentaries, reports, and studies with 'insufficient related data' were excluded. The reference lists of studies included were checked for eligible studies.

Data extraction

Data were independently extracted into EndNote libraries by two researchers (RAM and AMNR) who later compared their results. Emerging differences in the data were discussed and resolved by consensus and where the two researchers could not agree, a third researcher (JKK) was consulted for adjudication. Extracted data captured author's name, year, settings, design or approach, age, gender, number of participants, the overall number of deaths, the prevalence of clinical symptoms such as fever, cough, fatigue, polypnea, nausea or vomiting, sputum, dyspnoea, headache, and diarrhea together with chronic comorbid conditions including any type of comorbidity, diabetes, hypertension, respiratory disease and cardiovascular diseases. We also extracted data on CFR.

Study screening and selection

The eligibility of studies included was determined following a three-stage screening process. The first stage involved screening studies by title to eliminate duplicates. The second stage required reading of abstracts to determine their

relevance to our study. The third stage necessitated reading of full texts of the retained studies and those that met the set criteria were retained for our study as reflected in Fig. 1. RAM carried out and recorded the above process, and shared the record with AMNR and JKK for verification. Discrepancies were discussed and resolved by consensus.

Quality assessment

Quality assessment was independently conducted by two authors (RAM and JKK) who applied four quality assessment tools due to the heterogeneity of included studies designs. Discrepancies in the two author's quality assessments were referred to the AMNR for adjudication. The included studies designs were cohort, cross-sectional, case series, and case controls. The four critical appraisal tools applied were from the Joanna Briggs Institute (JBI). The JBI tools have been used widely in academic studies [24–26]. The tools provide a subjective assessment of risk of bias (ranked as low, moderate, or high) [27]. Higher quality indicates greater confidence that future research is unlikely to change or contradict the results, while lower quality indicates higher likelihood that future research may not replicate. The first JBI tool used was the checklist for cohort studies. The checklist assesses critical areas of studies' methodologies for biasness in design, implementation and analysis (Appendix Table 5). The JBI tool for cohort studies was applied to ten cohort studies include in our systematic review and meta-analysis. The second tool of quality assessment used was the JBI checklist for analytical cross-sectional studies. The checklist was applied to two cross-sectional studies included in this review. The checklist consists of eight items that enables the critical appraisal of studies for potential biasness (Appendix Table 6). The third JBI tool applied was the checklist for case series and this was applied to ten studies included in this review (Appendix Table 7). The checklist comprises of ten items that examines the criteria for inclusion in the case series, reliability of the condition of measured, validity of methods used in identification of the condition for participants, consecutive inclusion of participants, completeness of participants inclusion, clarity of reporting on study demographics, clarity of clinical information reporting, clarity of results reporting and the clarity of information on the study site(s). The fourth and last tool used was the JBI checklist for case control studies and was applied to one study included in our review (Appendix Table 8). The checklist comprises of ten items measuring comparability of study groups, matching of cases and controls, identification criteria for cases and controls, reliability and validity of exposure measurement, similarities in exposure measurement for case and control, identification of confounding factors, addressing the confounding factors, assessment of outcomes, length of exposure period and statistical analysis.

Data analysis

The case fatality rate (CFR) was derived for COVID-19 infected populations for all studies, which describes the ratio of deaths to cases. We investigated the association between

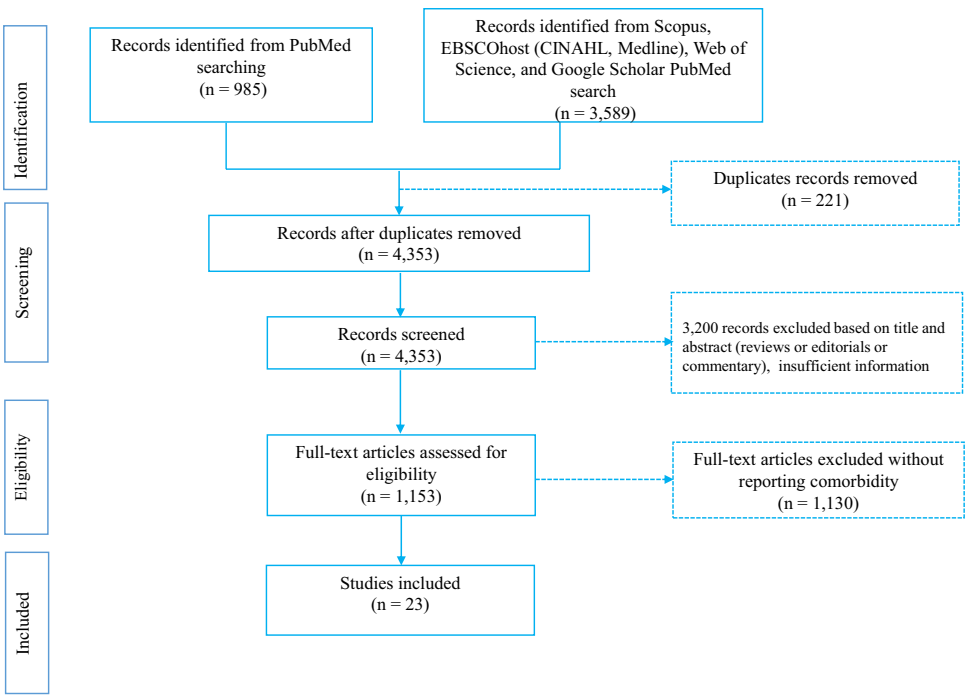


Fig. 1 Steps of study selection procedures

the case fatality ratio and the chronic comorbid conditions among the COVID-19 infected population. Given the high heterogeneity between studies ($I^2 > 50\%$) [28], we used random effect models with the 95% confidence intervals (CI) of estimates, complemented with a sensitivity analysis to examine the effects of outliers. The I^2 statistic enabled us determine whether the percentage of variance was attributable to the heterogeneity of the data in studies included using the random-effects model. We used forest plots to show the distribution of chronic comorbid conditions in coronavirus disease-2019 patients. All statistical analyses were performed by STATA/SE version 14.0. Furthermore, publication bias was assessed using the Begg's test [29] and Egger's test [30]. Both of the tests are widely used to assess the tendency for the effects estimated in small sample size studies to differ from those estimated in larger studies. The risk of publication bias was analysed in terms of chronic comorbid conditions and CFR due to number of comorbidities. Subgroup and meta-regression analyses were conducted to verify the association of CFR and chronic comorbid conditions among COVID-19 infected patient, where moderate or higher heterogeneity was reported [31, 32]. Additionally, a permutation test was employed based on Monte Carlo simulation by controlling the risk of spurious findings from meta-regression [33], wherein unadjusted and adjusted estimation approaches were also used to calculate p values in meta-regression. In a permutation test, the covariates were randomly reallocated to the outcomes for 10,000 times to adjust for multiple testing to compare the observed t-statistic for every covariate with the largest t-statistic for any covariate in each random permutation.

Results

Description of studies included

Our primary search of databases yielded 4453 studies of which 23 met our criteria and were included in this study (Fig. 1), giving a total sample of 202,005 coronavirus disease-2019 confirmed cases and 3,895 confirmed deaths (Table 1). The average age of participants (55% male and 45% female) was 56.4 years, whereas the overall incubation period was 7.8 days.

Distribution of comorbidities

Our findings suggest the predominant clinical symptoms were fever (87.5%; 95% CI 87.5–87.5%), cough (57.1%; 95% CI 57.1–57.1%), and fatigue (32.7%; 95% CI 32.7–32.7%) (Table 2). Our analysis shows, the most prevalent of chronic comorbid conditions were (Fig. 2): any type of chronic comorbidity (37%; 95% CI 32–41%; $p < 0.001$), hypertension (22%; 95% CI 17–27%; $p < 0.001$), diabetes (14%; 95% CI 12–17%; $p < 0.001$), cardiovascular (13%; 95% CI:10–16%; $p < 0.001$), respiratory disease (5%; 95% CI 3–6%; $p < 0.001$), and other chronic diseases (8%; 95% CI 6–10%; $p < 0.001$).

Mortality among COVID-19 patients

The overall pooled CFR was 7% (95% CI 6–7%; $p < 0.001$; $I^2 = 97.7\%$) (3895 deaths among 202,005 confirmed cases) and significantly increased ($p = 0.01$) with higher levels of chronic comorbid conditions (Fig. 3), ranging from 7% for at least one chronic comorbid condition ($p < 0.001$), to 13% for 2 or 3 chronic comorbid conditions ($p < 0.001$), 12% for 4 chronic comorbid conditions ($p < 0.001$), 14% for 5 chronic comorbid conditions ($p < 0.001$, $I^2 = 98.2\%$), and 21% for 6 or more chronic comorbid conditions ($p < 0.001$). Furthermore, the overall CFRs also significantly increased with higher levels of reported clinical symptoms (Fig. 4), ranging from 14% for at least four symptoms ($p < 0.001$), to 15% for 5 or 6 symptoms ($p < 0.001$), and 21% for 7 or more symptoms ($p < 0.001$).The results of Egger's test were presented in terms of bias coefficient (Table 3). Publication bias was only observed in studies identified to estimate the prevalence of any type of chronic disease ($p = 0.002$), hypertension ($p < 0.001$), diabetes ($p = 0.015$) and CVD ($p = 0.050$). However, the p values for the Egger's test were 0.177 (for respiratory system disease) and 0.120 (for other chronic disease), respectively, denoting absent of publication bias (Table 3).

Our analysis shows that a high heterogeneity ($I^2 > 75\%$) was also observed for meta-regression (96.86%) in terms of CFR (Table 3). To examine the sources of heterogeneity, we conducted stratified analysis across chronic comorbid conditions, study design (e.g., case series vs cohort vs cross-sectional), sample size (i.e., ≤ 200 or > 200), age of the total sample (i.e., < 50 years or ≥ 50 years). We found that the risk of mortality varied and significantly associated with chronic comorbid conditions, aged patients and increased incubation period. For instance, the CFR was significantly higher for COVID-19 patients with pre-existing any type of chronic disease (beta, $\beta = 0.014$, $p = 0.007$), hypertension ($\beta = 0.055$, $p = 0.054$), diabetes ($\beta = 0.188$, $p = 0.023$), respiratory system diseases ($\beta = 0.331$, $p = 0.022$). A similar association was also observed among patients with higher levels of chronic comorbid conditions ($p < 0.050$) and increased incubation period in day ($p = 0.043$) (Table 4).

Quality of included studies

Our findings suggest that eleven ($n = 11$) of the included studies were of high quality implying that they were robust studies; twelve of the studies were ranked as medium

Table 1 Characteristics of selected studies

Selected studies by study design	Settings	Infected population (*n*)	Age (year)	% of male	Incubation period (days)	Total number of deaths, n	Case fatality ratio (95% CI)	% Weight
Cohort study								
Zhou et al. [34]	Wuhan, China	191	56.00	62.00	11.00	54	0.28 (0.22, 0.35)	1.33
Zhang et al. [12]	Wuhan, Hubei	258	64.00	53.50	12.00	15	0.06 (0.03, 0.09)	4.50
Wu et al. [35]	Wuhan, China	188	51.90	63.60	9.00	43	0.23 (0.17, 0.30)	1.49
Cheng et al. [36]	Wuhan, China	701	63.00	52.40	10.00	113	0.16 (0.13, 0.19)	4.76
Chen et al. [6]	Huanan, China	99	55.50	68.00	6.50	11	0.11 (0.06, 0.19)	1.41
Fu et al. [37]	Wuhan, Hubei	200	65.00	49.30	8.00	34	0.17 (0.12, 0.23)	1.89
Shi et al. [38]	China	416	64.10	49.30	5.00	57	0.14 (0.11, 0.17)	3.75
Guan et al. [39]	China	1099	47.00	58.10	4.00	15	0.01 (0.01, 0.02)	10.21
Yan et al. [40]	Wuhan, China	193	64.00	59.10	13.00	108	0.56 (0.49, 0.63)	1.13
Wang et al. [41]	Wuhan, China	69	42.00	46.00	4.00	5	0.07 (0.02, 0.16)	1.44
Sub-total (pooled)	$n=10$	3414	57.24	56.13	8.25	455	0.18 (0.10, 0.25)	**31.90**
Cross-sectional study								
Pan et al. [42]	China	204	52.90	52.40	8.10	36	0.18 (0.13, 0.24)	1.88
Cao et al. [43]	Shanghai, China	198	50.10	51.00	4.00	1	0.01 (0.00, 0.03)	9.42
Sub-total (pooled)	$n=2$	402	51.50	51.70	6.05	37	0.01 (0.00, 0.02)	**11.30**
Case series study								
Guan et al. [44]	China	1590	48.90	57.30	3.60	50	0.03 (0.02, 0.04)	9.78
Wang et al. [5]	Wuhan, China	138	56.00	54.30	5.00	6	0.04 (0.02, 0.09)	3.60
Chen et al. [45]	Wuhan, China	799	62.00	62.00	10.00	113	0.14 (0.12, 0.17)	5.41
Liu et al. [46]	Hubei, China	137	57.00	44.50	7.00	16	0.12 (0.07, 0.18)	1.79
CDC [8]	USA	122,653	–	–	–	2112	0.02 (0.02, 0.02)	11.05
McMichael et al. [2]	Washington, USA	167	72.00	32.90	9.00	35	0.21 (0.15, 0.28)	1.42
Wu et al. [47]	China	72,314	44.00	–	–	1023	0.01 (0.01, 0.02)	11.05
Guo et al. [48]	Wuhan, China	174	59.00	43.70	7.00	9	0.05 (0.02, 0.10)	3.77
Wan et al. [49]	Chongqing, China	135	47.00	53.30	5.00	1	0.01 (0.00, 0.04)	8.05
Huang et al. [7]	Wuhan, China	41	49.00	73.00	8.00	6	0.15 (0.06, 0.29)	0.50
Sub-total (pooled)	$n=10$	198,148	54.99	52.63	6.83	3371	0.03 (0.02, 0.04)	56.43
Case–control study								
Su et al. [50]	Huanan, China	41	70.00	75.00	14.00	32	0.78 (0.62, 0.89)	0.37
Total	$N=23$	202,005	56.38	55.27	7.77	3895	0.07 (0.06, 0.07)	**100.00**
I-squared (I^2), % (p value)							97.69% ($p<0.001$)	

quality implying that their methods were of moderate quality based on the JBI quality assessment criteria. There was no study excluded based on poor scoring on the quality assessment scales. Notably, one ($n=1$) cohort study [12] was assed as high on the JBI checklist for cohort studies; the rest ($n=9$) studies were found to be of medium quality on the same scale [6, 34–41]. Neither of the ten ($n=10$) cohort studies articulated how they dealt with confounding factors nor did they articulate strategies to address incomplete follow-up of participants. Furthermore, only two ($n=2$) of the cohort studies reported that their follow-up time was sufficient and long enough to observe outcomes. Furthermore, the two cross-sectional studies [42, 43] included in our study scored seven out of eight ($n=8$) items on the JBI quality assessment checklist used. Both studies did not state how they dealt with confounding factors. Eight out of ten ($n=8/10$) case series studies included [2, 5, 7, 8, 44–49], ware found to be of high quality based on the JBI quality assessment scale for case series. However, four ($n=4$) of the case series studies [2, 8, 47, 48] statistical analyses were assessed to be unsatisfactory. Lastly, the only one case–control study [50] included in our review was found to be of medium quality with eight ($n=8/10$) items on the JBI quality assessment scale of case controls.

Table 2 Distribution of reported symptoms in coronavirus disease-2019 infected populations

Selected studies	Most reported symptoms in the studies								
	Fever	Cough	Fatigue	Polypnea	Nausea or vomiting	Sputum	Dyspnoea	Headache	Diarrhea
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Cohort study									
Zhou et al. [34]	94.00 (93.45, 94.55)	79.00 (78.44, 79.55)	23.00 (22.44, 23.55)	–	4.00 (3.44, 4.55)	23.00 (22.44, 23.55)	–	–	5.00 (4.45, 5.55)
Zhang et al. [12]	82.20 (82.09, 82.31)	67.10 (66.98, 67.21)	38.00 (37.88, 38.11)	48.10 (47.98, 48.21)	8.50 (8.38, 8.61)	5.40 (5.28, 5.51)	48.10 (47.98, 48.21)	10.90 (10.78, 11.01)	21.30 (21.18, 21.41)
Wu et al. [35]	92.60 (92.15, 93.05)	83.50 (83.05, 83.94)	32.50 (32.05, 32.95)	38.30 (37.85, 38.74)	–	39.40 (39.95, 39.84)	12.80 (12.35, 13.25)	33.50 (33.05, 33.94)	–
Cheng et al. [36]	32.50 (32.18, 32.82)	–	–	–	–	–	–	–	–
Chen et al. [6]	83.00 (82.78, 83.22)	82.00 (81.78, 82.21)	–	–	1.00 (0.78, 1.22)	–	–	8.00 (7.78, 8.21)	2.00 (1.78, 2.22)
Fu et al. [37]	88.00 (87.67, 88.33)	46.30 (45.96, 46.63)	52.20 (51.86, 52.53)	–	–	–	–	–	59.70 (59.36, 60.03)
Shi et al. [38]	80.30 (80.03, 80.57)	34.60 (34.33, 34.86)	13.20 (12.93, 13.46)	–	–	–	–	2.20 (1.93, 2.47)	3.80 (3.53, 4.07)
Guan et al. [39]	–	67.80 (67.77, 67.82)	38.10 (38.07, 38.12)	18.70 (18.67, 18.72)	4.80 (4.77, 4.83)		–	13.60 (13.57, 13.63)	3.80 (3.77, 3.83)
Yan et al. [40]	89.60 (88.50, 90.69)	69.90 (68.80, 71.99)	52.30 (51.20, 53.39)	5.00 (3.90, 6.09)	–	–	59.60 (58.50, 60.69)	10.90 (9.80, 11.99)	26.40 (25.30, 27.49)
Wang et al. [41]	87.00 (86.86, 87.14)	55.00 (54.85, 55.14)	42.00 (41.85, 42.14)	9.00 (8.85, 9.14)	–	–	29.00 (28.85, 29.14)	14.00 (13.85, 14.14)	14.00 (13.86, 14.14)
Sub-total (pooled)	81.56 (81.49, 81.64)		38.03 (38.01, 38.06)	19.92 (19.89, 19.95)	4.93 (4.91, 4.96)	8.06 (7.94, 8.17)	39.68 (39.60, 39.78)	13.36 (13.34, 13.39)	5.29 (5.26, 5.32)
Cross-sectional study									
Pan et al. [42]	92.23 (91.88, 92.57)	34.00 (33.65, 34.35)	–	–	–	–	–	14.56 (14.21, 14.91)	33.98 (33.63, 34.32)
Cao et al. [43]	86.90 (86.89, 86.91)	46.40 (46.39, 46.41)	31.30 (31.29, 31.30)	–	–	23.20 (23.19, 23.21)	–	12.10 (12.09, 12.11)	4.40 (4.39, 4.41)
Sub-total (pooled)			31.30 (31.29, 31.31)	–		23.20 (23.19, 23.21)		12.10 (12.09, 12.11)	4.42 (4.41, 4.43)
Case-series study									
Guan et al. [44]	88.00 (87.94, 88.06)	70.20 (70.13, 70.26)	42.80 (42.73, 42.86)	14.70 (14.63, 14.76)	5.80 (5.73, 5.86)	–	–	15.40 (15.34, 15.46)	4.20 (4.13, 4.26)
Wang et al. [5]	98.60 (98.52, 98.68)	59.40 (59.31, 59.48)	69.60 (69.51, 69.68)	17.40 (17.31, 17.48)	3.60 (3.51, 3.68)	2.20 (2.11, 2.29)	31.20 (31.11, 31.29)	6.50 (6.42, 6.59)	10.10 (10.01, 10.19)
Chen et al. [45]	91.00 (90.72, 91.28)	68.00 (67.72, 68.28)	50.00 (49.72, 50.27)	4.00 (3.72, 4.27)	9.00 (8.72, 9.28)	30.00 (29.72, 30.28)	44.00 (43.72, 44.29)	11.00 (10.72, 11.28)	28.00 (27.72, 28.28)
McMichae et al. [2]	–	–	–	–	–	–	–	–	–
Wu et al. [47]	–	–	–	–	–	–	–	–	–
Guo et al. [48]	78.20 (78.09, 78.30)	32.20 (32.09, 32.30)	27.00 (26.89, 27.10)	5.20 (5.09, 5.30)	–	–	–	6.90 (6.79, 7.00)	12.10 (11.99, 12.20)
Wan et al. [49]	88.90 (88.89, 88.92)	76.50 (76.48, 76.51)	32.50 (32.48, 32.51)	17.70 (17.68, 17.71)	–	8.80 (8.78, 8.82)	13.30 (13.28, 13.31)	32.50 (32.48, 32.52)	13.30 (13.28, 13.32)
Liu et al. [46]	48.20 (47.97, 48.43)	32.10 (31.87, 32.32)	32.10 (31.87, 32.32)	–	–	–	19.00 (18.77, 19.22)	9.50 (9.27, 9.73)	8.00 (7.77, 8.23)
CDC [8]	–	–	–	–	–	–	–	–	–
Huang et al. [7]	98.00 (97.71, 98.29)	76.00 (75.71, 76.28)	44.00 (43.71, 44.28)	–	–	28.00 (27.71, 28.29)	55.00 (54.71, 55.29)	8.00 (7.71, 8.29)	3.00 (2.71, 3.29)
Sub-total (pooled)	88.79 (88.77, 88.80)	74.74 (74.72, 74.76)	33.94 (33.93, 33.96)	17.27 (17.26, 17.29)		8.71 (8.70, 8.73)	14.01 (13.99, 14.02)	30.31 (30.29, 30.32)	12.73 (12.72, 12.75)

Table 2 (continued)

Selected studies	Most reported symptoms in the studies								
	Fever	Cough	Fatigue	Polypnea	Nausea or vomiting	Sputum	Dyspnoea	Headache	Diarrhea
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Case–control study									
Su et al. [50]	81.30 (79.77, 82.83)	59.30 (57.77, 60.83)	43.80 (42.27, 45.33)	–	3.10 (1.57, 4.63)	–	–	15.00 (13.47, 16.53)	3.10 (1.57, 4.63)
Inverse variance (I–V) pooled estimate, % (95% CI)	87.47 (87.46, 87.48)	57.09 (57.08, 57.09)	32.73 (32.72, 32.74)	17.87 (17.86, 17.89)	4.98 (4.96, 5.01)	18.44 (18.43, 18.45)	14.67 (14.66, 14.69)	17.86 (17.85, 17.87)	7.08 (7.07, 7.09)
I-squared I^2, %	100%	99·6%	100%	99·9%	99·9%	97·9%	100%	100%	100%
(*p* value)	($p < 0{\cdot}001$)	($p < 0{\cdot}001$)	($p < 0{\cdot}001$)	($p < 0{\cdot}001$)	($p < 0{\cdot}001$)	($p < 0{\cdot}001$)	($p < 0{\cdot}001$)	($p < 0{\cdot}001$)	($p < 0{\cdot}001$)

p value for heterogeneity, *CI* confidence interval

Discussion

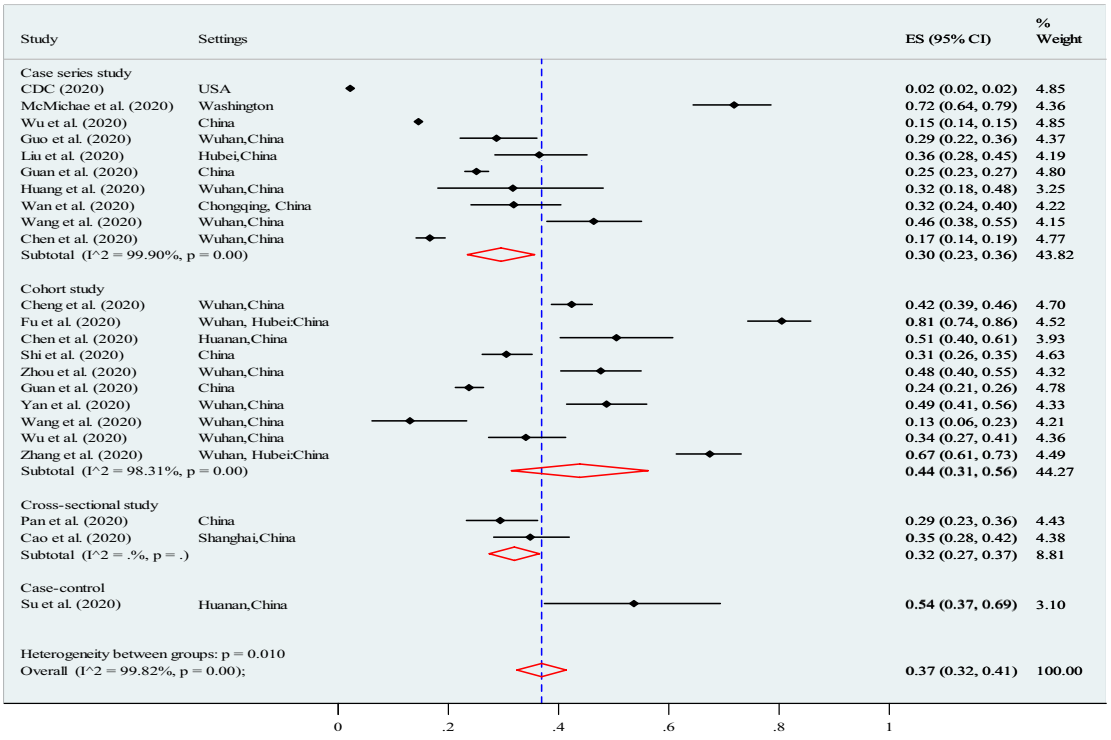
Our meta-analysis was based on data from 23 studies with laboratory-confirmed 202,005 COVID-19 infected patients. The patients average age was 56.4 years and almost 55% of the patients were men. This finding suggests age and gender were critical determinants in COVID-19 infection. This finding is consistent with earlier studies that found approximately 60 to 70% of COVID-19 patients were elderly men [51–53].

Our findings suggest that the most predominant clinical symptoms of COVID-19 were fever (87.5%), cough (57.1%), and fatigue (32.7%). This finding differs from earlier studies that associated COVID-19 symptoms with viral pneumonia, fatigue, and lymphopenia [3, 14, 16, 51, 53, 54]. A recent study observed that 10% of COVID-19 patients presented with diarrhea and nausea initially [5]. An earlier study conducted in China argued that nausea or vomiting and diarrhea were low (5.0% and 3.8%) [44]. However, another study reported diarrhea (80%) and nausea (50%) were more common symptoms in COVID-19 infected populations [51]. Such discrepancies could be a result of limited understanding of the disease, methodological inconsistencies, inadequate classification of the disease, inadequate differential diagnosis and, classification biases caused by small sample sizes. In addition, the discrepancies in clinical symptoms could lead to misdiagnosis of the symptoms when patients seek clinical attention. A misdiagnosis of the symptoms implies patients who should be placed in high risk isolation wards could be mixed with other patients causing further transmissions to non COVID-19 patients and their careers.

Our analysis shows, the most prevalent of chronic comorbid conditions among COVID-19 infected population were at least one underlying chronic comorbid condition (37%), hypertension (22%), diabetes (14%), cardiovascular diseases (13%), respiratory disease (5%), and other chronic diseases (8%). This is consistent with a previous studies that noted 40% of patients had at least one underlying chronic disease [55] and that approximately 23% of infected individuals suffered from hypertension [11], followed by diabetes mellitus (17%), and cardiovascular diseases (10%) [55]. Chronic diseases lead to several clinical features with severe complications, including the proinflammatory state, and the reduction of the innate immune response [15, 16]. For instance, diabetes mellitus occurs in part due to accumulation of stimulated innate immune cells in metabolic tissues that contribute to the release of inflammatory mediators, particularly, IL-1β and TNFα, which develop systemic insulin resistance and β-cell damage [15, 56, 57]. Furthermore, metabolic disorders may associate with low immune function due to damaged function of macrophage and lymphocyte [7, 15, 56–59], which make patients susceptible to disease complications. However, chronic comorbid conditions of COVID-19 patients presents major clinical challenges in terms of diagnosis, ill health, the course of treatment and disease management, which adversely influences treatment choices and outcomes.

In this meta-analysis, the overall pooled crude CFR was 7% (95% CI 6–7%), which was significantly increased with a higher level of chronic comorbid conditions. A recent study estimated the overall CFR for Chinese and Italian patients aged > 48 years were 6.93% and 24.8%, respectively [54], which were comparatively higher than our estimate. The distribution of CFR can vary across countries in terms of age-stratified data as well as chronic comorbid conditions [54]. COVID-19 patients who reported no chronic comorbid

(a) Any type of chronic comorbid condition



(b) Hypertension

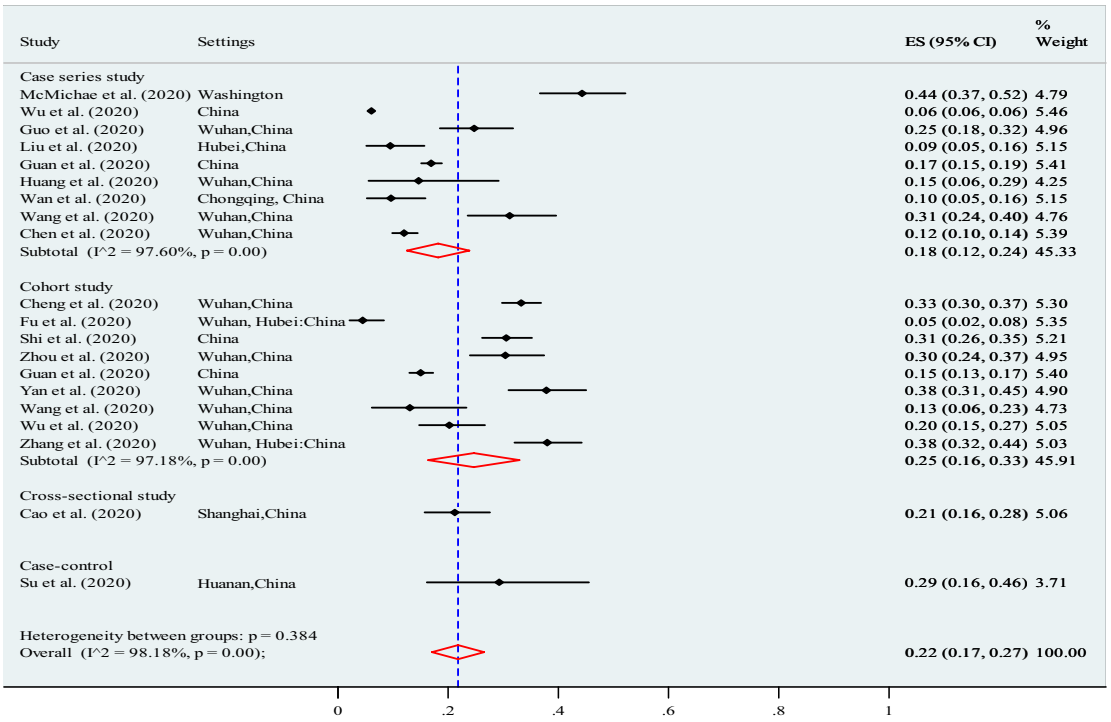
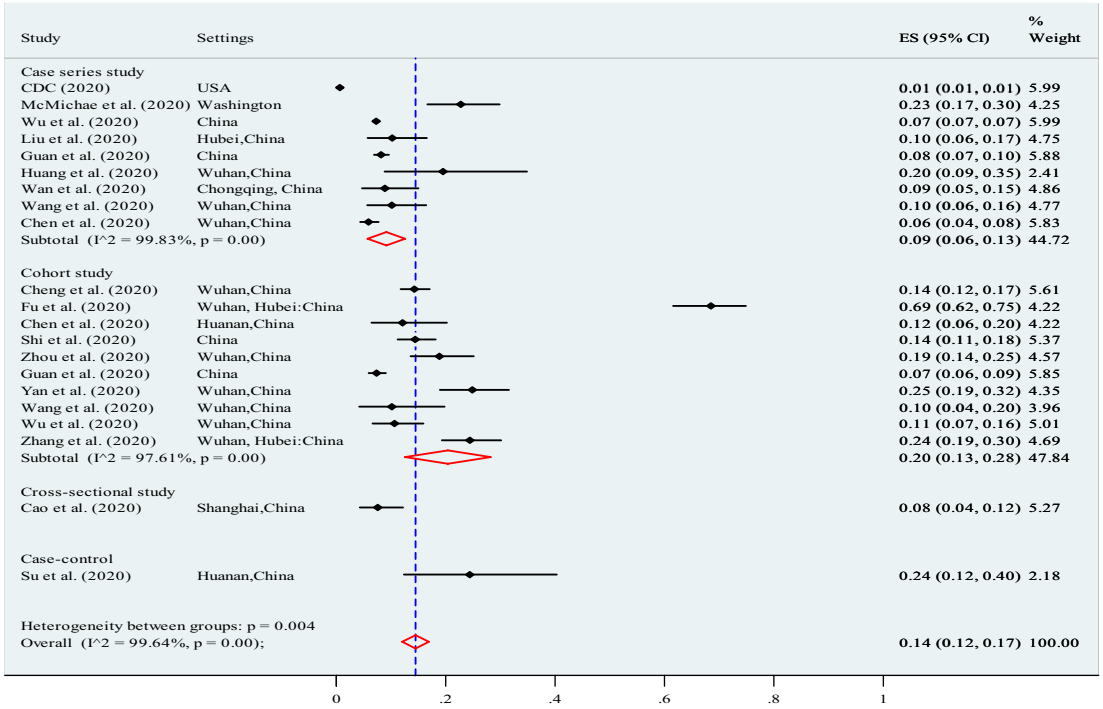


Fig. 2 Meta-analysis of the proportion of comorbidities in COVID-19 infected populations. **a** Any type of chronic diseases. **b** Hypertension. **c** Diabetes. **d** Cardiovascular disease (CVD). **e** Respiratory system diseases. **f** Other chronic diseases

(c) Diabetes



(d) Cardiovascular disease (CVD)

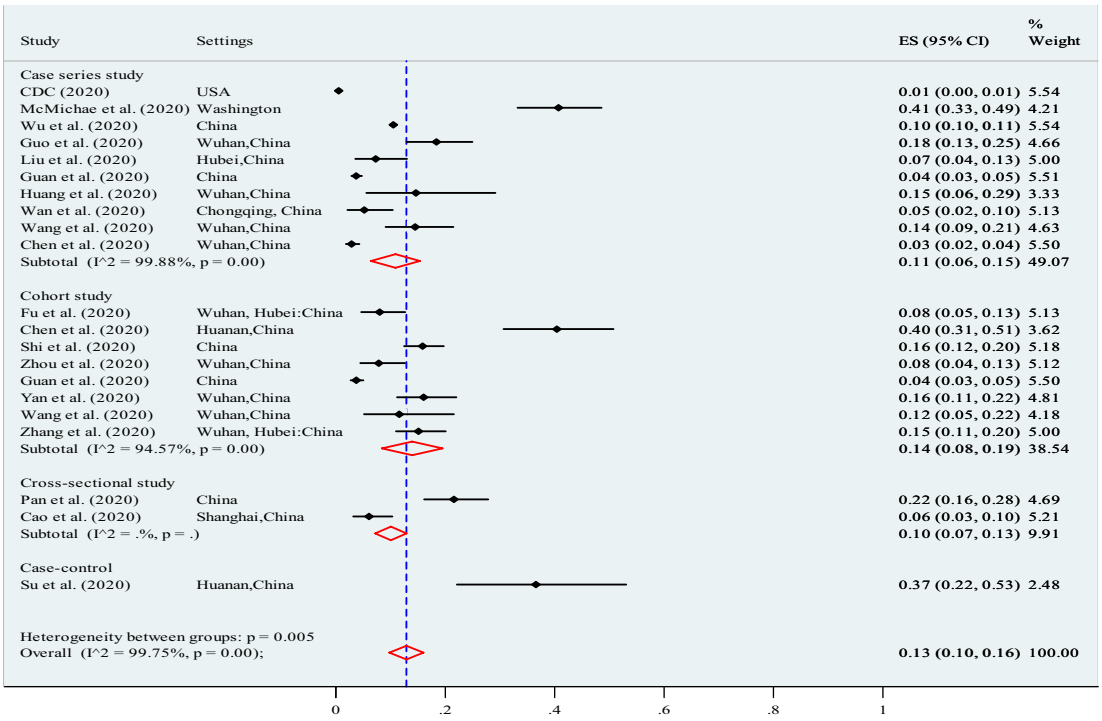
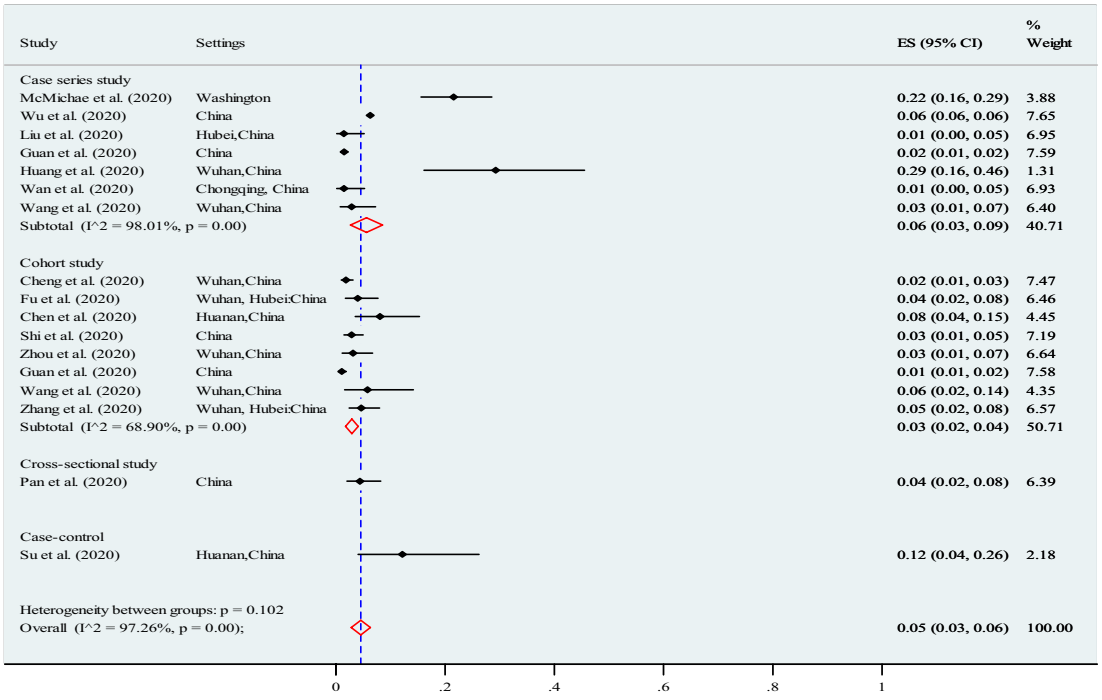


Fig. 2 (continued)

(e) Respiratory System Disease



(f) Other chronic diseases

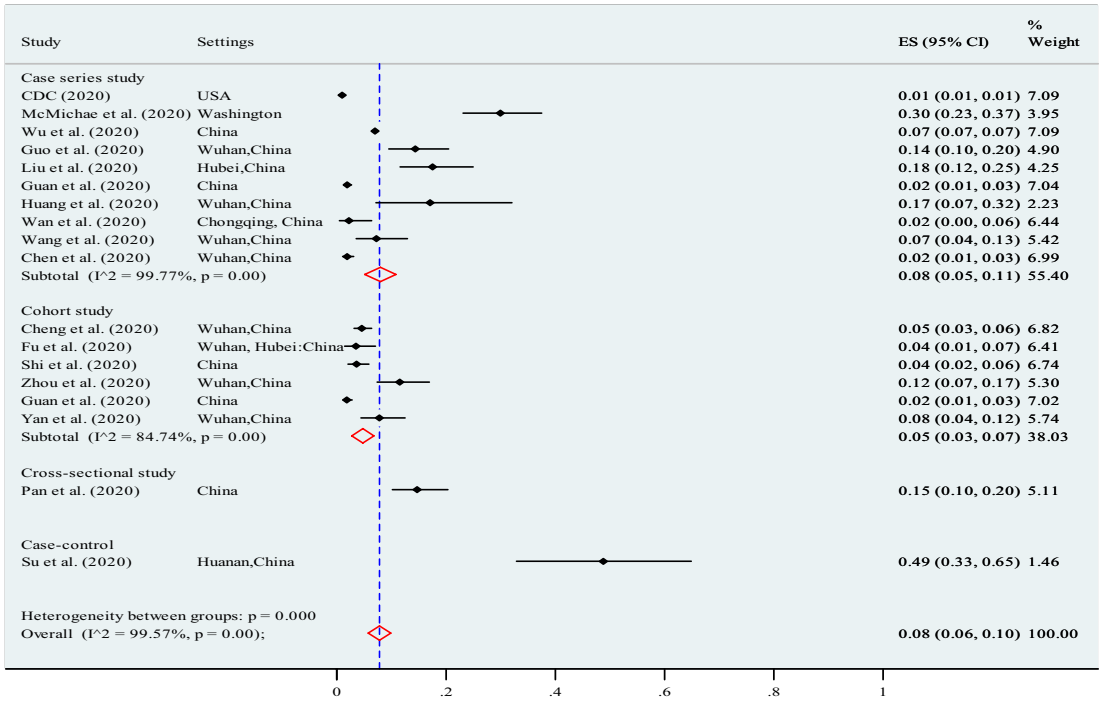
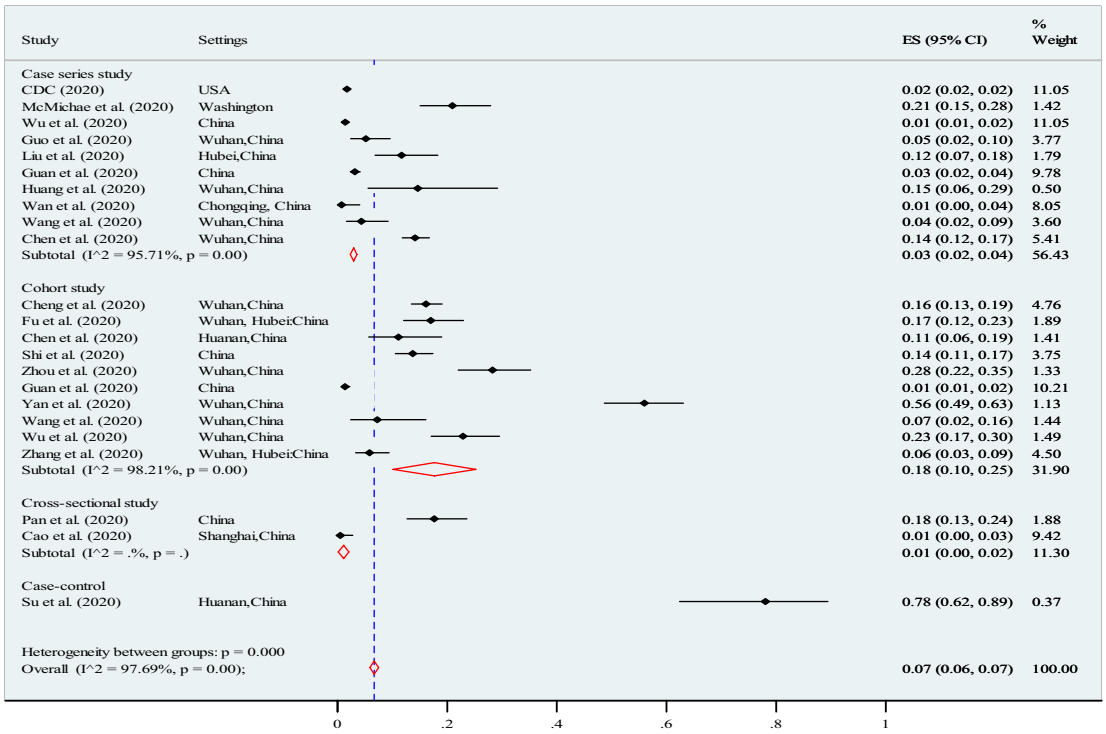


Fig. 2 (continued)

(a) CFR for at least one chronic comorbid condition



(b) CFR for two chronic comorbid conditions

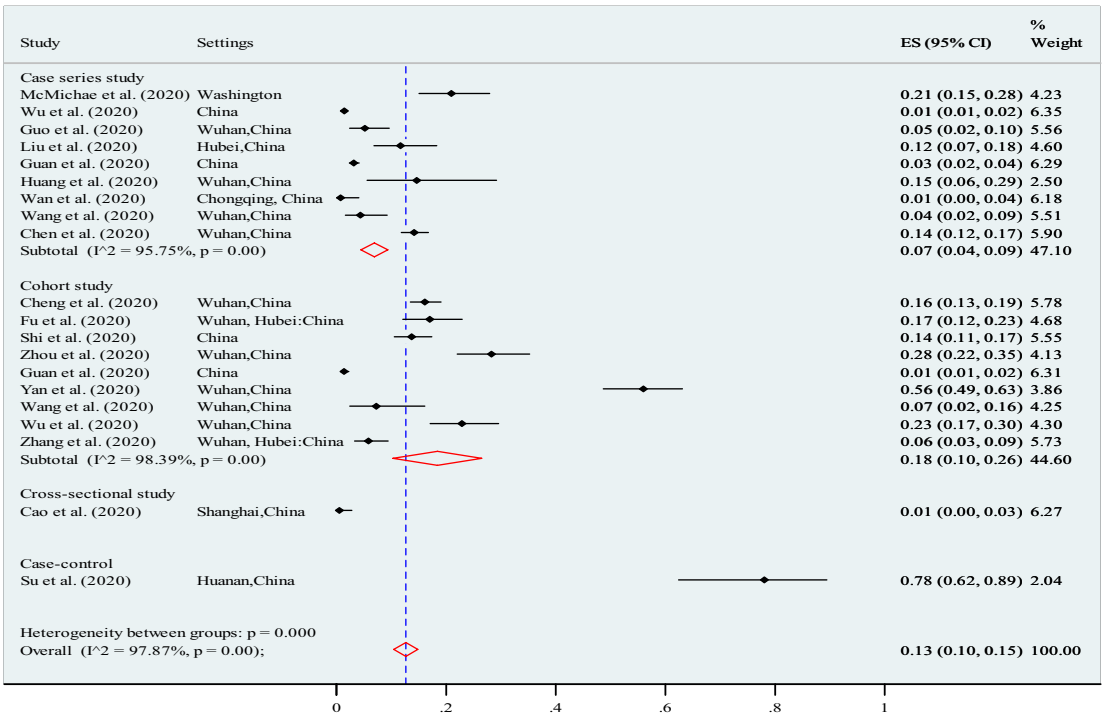
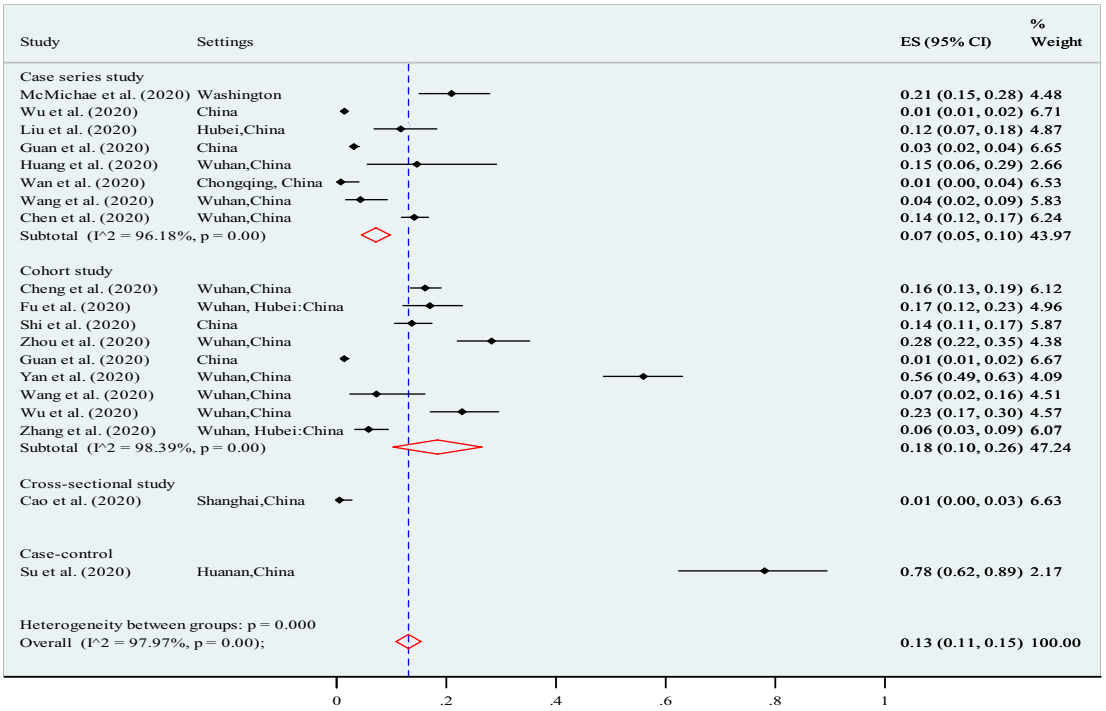


Fig. 3 Association between case fatality ratio (CFR) and number of chronic comorbid conditions in COVID-19 infected populations. **a** CFR for any type of chronic disease. **b** CFR for 2 chronic comorbid conditions. **c** CFR for 3 chronic comorbid conditions. **d** CFR for 4 chronic comorbid conditions. **e** CFR for 5 chronic comorbid conditions. **f** CFR for 6 or more chronic comorbid conditions

(c) CFR for three chronic comorbid conditions



(d) CFR for four chronic comorbid conditions

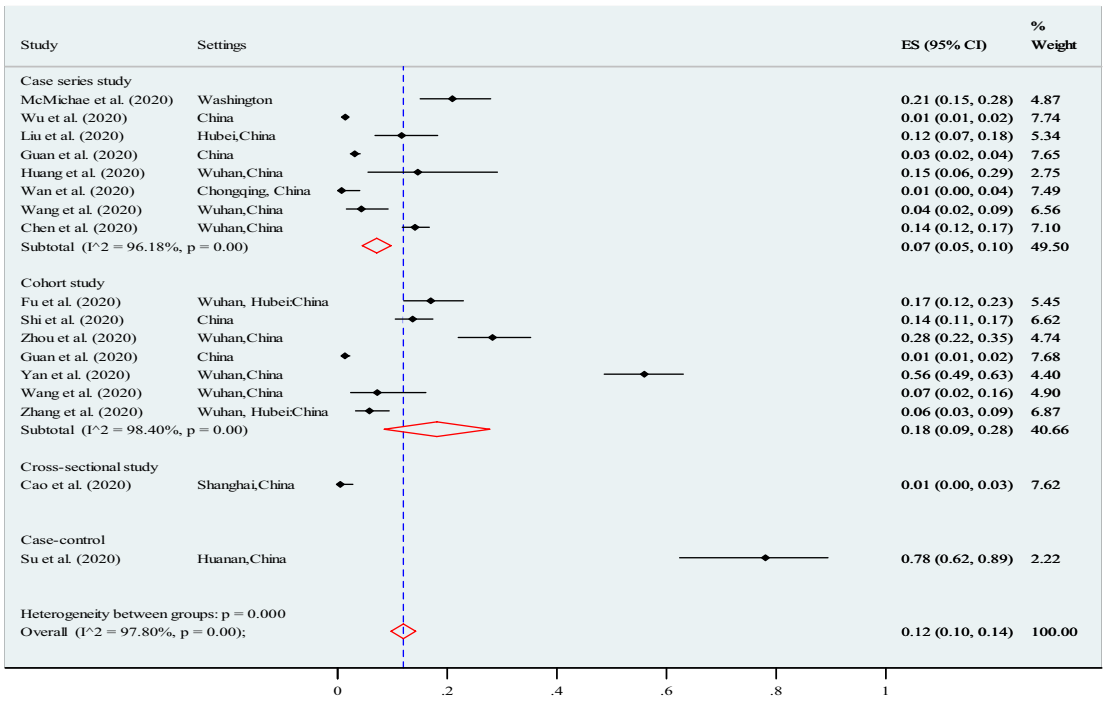
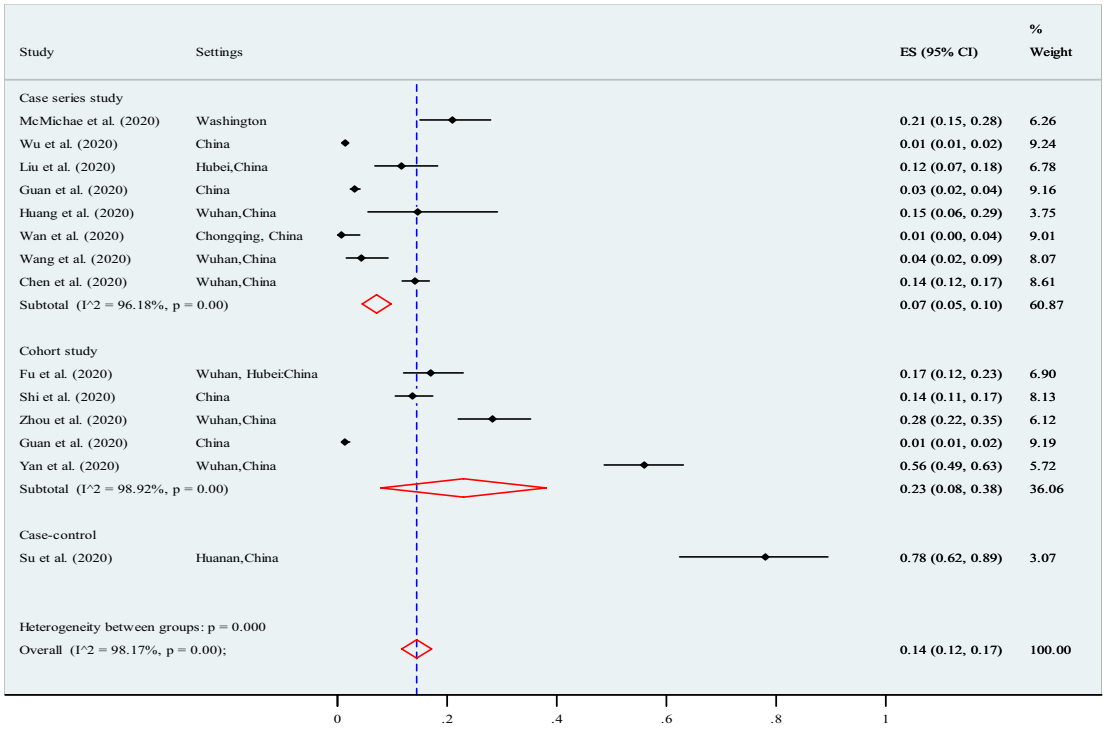


Fig. 3 (continued)

conditions had a lower CFR of 1.4% compared to patients with comorbid conditions [3]. Some studies suggest that COVID-19 which causes pneumonia may also damage organs [10, 14, 60, 61]. Consequently, patients eventually die of multiple organ failure, shock, acute respiratory distress syndrome, heart failure, arrhythmias, and renal failure

(e) CFR for five chronic comorbid conditions



(f) CFR for six or more chronic comorbid conditions

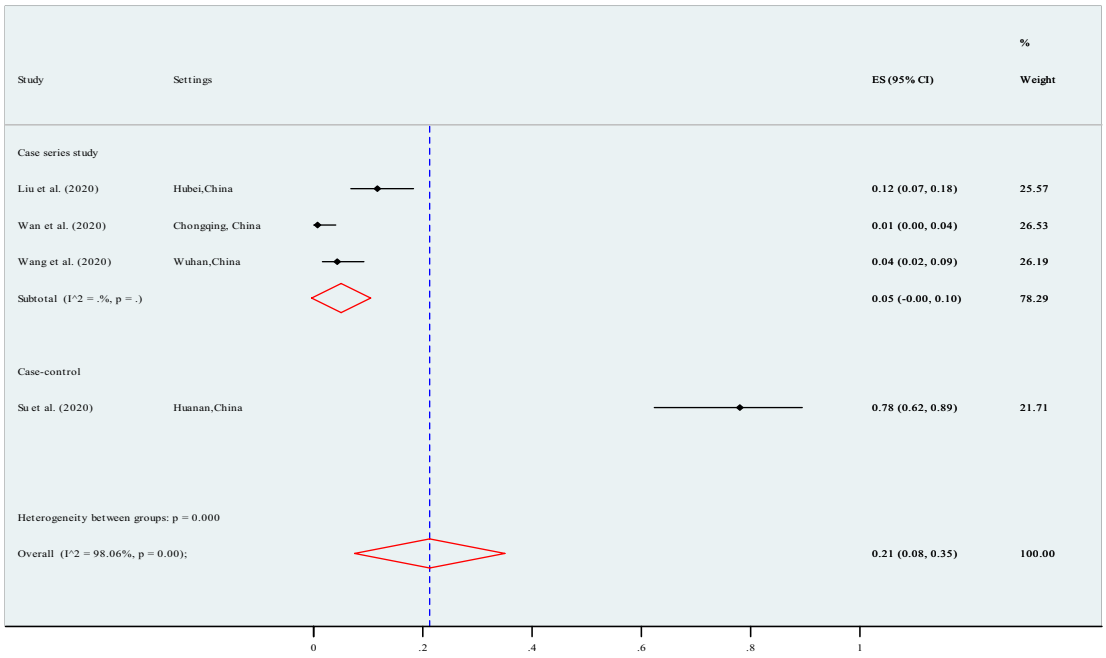
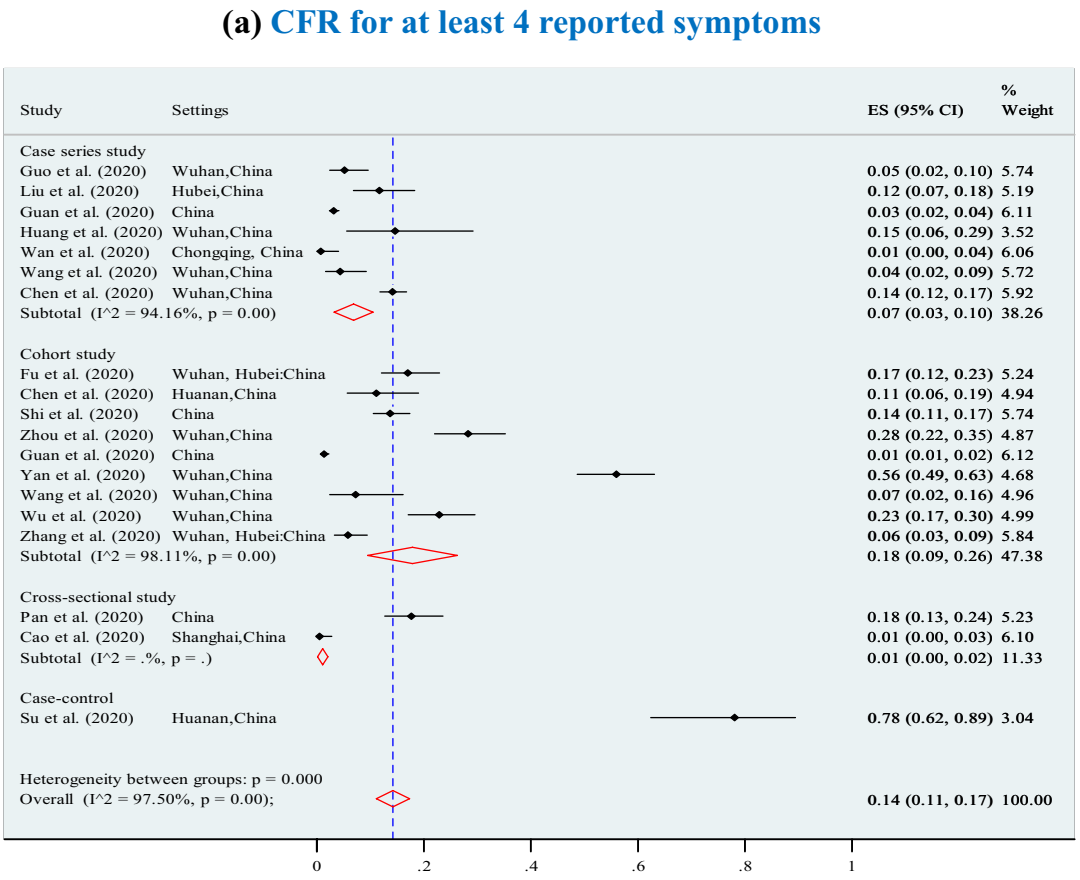


Fig. 3 (continued)

[11–13, 44, 62, 63]. Considering age-stratified data, the CFR of elderly patients (≥ aged 70 years) was estimated at 37.6% in Italy and only 11.9% in China [54]. It can be argued that the elderly patients suffered from more than one underlying chronic comorbid conditions than younger patients [12, 35, 59, 64, 65]. This is similar to findings of a 2013 study of



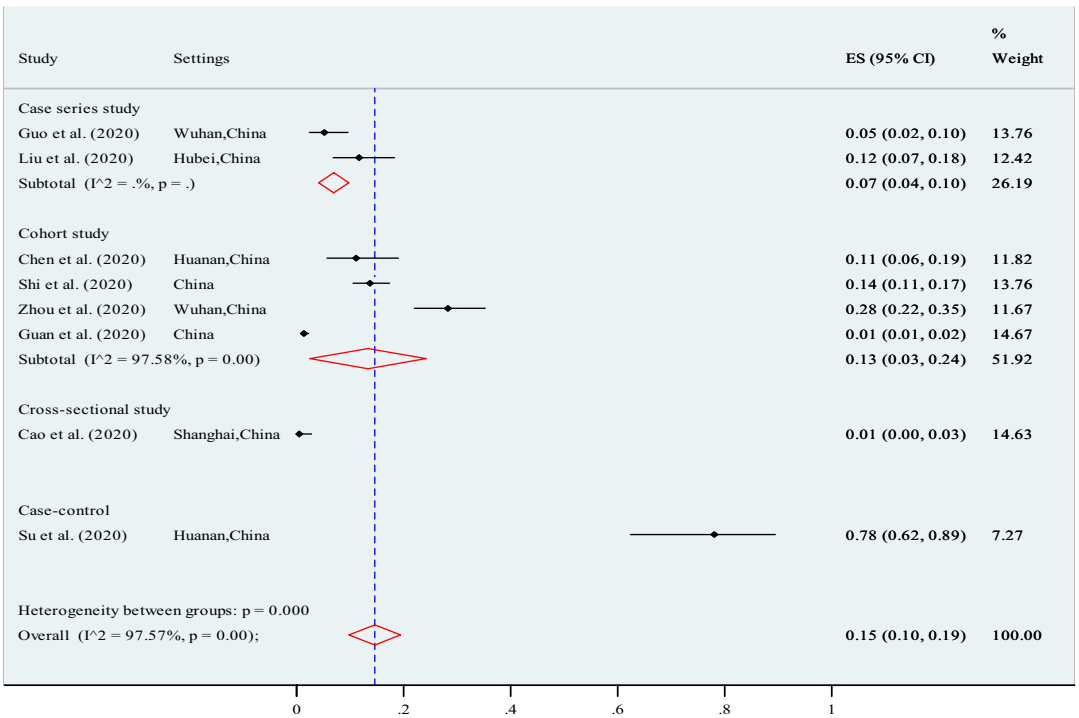
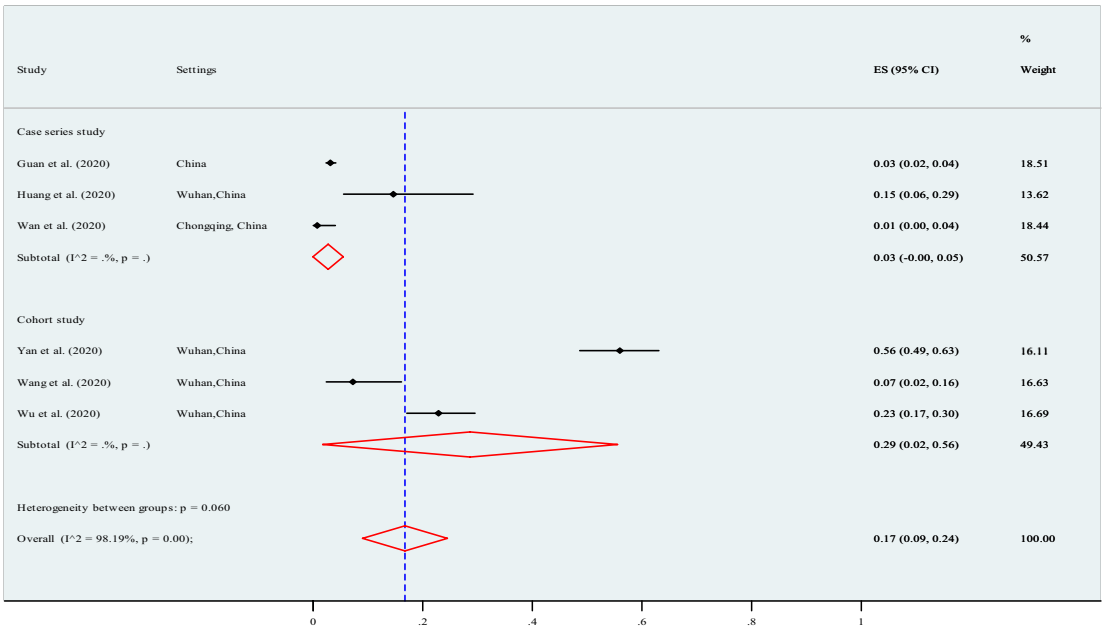


Fig. 4 Association between case fatality ratio (CFR) and reported symptoms in COVID-19 infected populations. **a** CFR for at least four reported symptoms. **b** CFR for 5 to 6 reported symptoms. **c** CFR for 7 to 8 reported symptoms. **d** CFR for more 8 reported symptoms

(c) CFR for 7-8 reported symptoms



(d) CFR for 9 or more reported symptoms

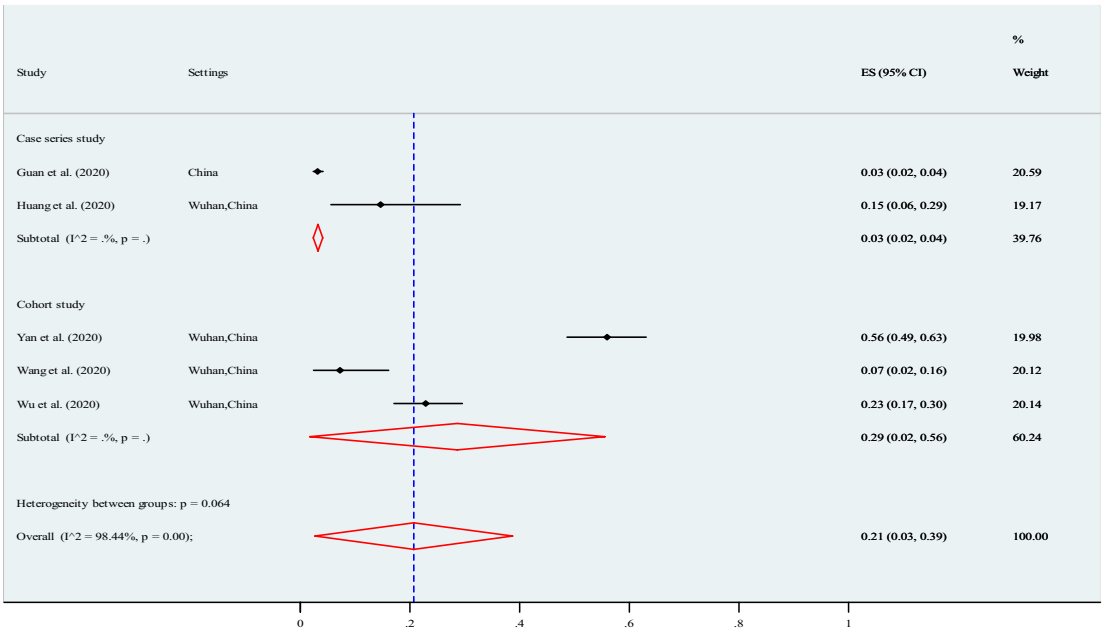


Fig. 4 (continued)

influenza (H7N9) that associated comorbidity among aged people with increased risk of dying [60]. Furthermore, the risk of death among the elderly was aggregated by the low immune system due to multiple medical illnesses [52, 59, 64, 66–68].

This meta-analysis has some limitations. First, the included studies were heterogeneous in designs, perspectives, and varied in terms of study participants (41 to 122,653). Second, included studies had different follow-up periods which may be responsible for significant heterogeneity especially because some participant were still hospitalised. Third, few of the included studies considered data on comorbidities of COVID-19 patients. Therefore, it

Table 3 Stratified analysis of the likelihood of death among COVID-19 infected population

Characteristics	Meta-regression		Monte Carlo permutation test for meta-regression[a]	
	Pooled coefficient (β) (95% confidence interval, CI)	Probability value (p value)	p values	
			Unadjusted	Adjusted
Mean age of total patients				
< 50 years	0.002 (− 0.015, 0.019)	0.828	0.802	1.000
≥ 50 years	0.151 (0.019, 0.321)	0.009	0.037	0.689
Incubation period in day	0.011 (0.004, 0.021)	0.043	0.025	0.037
Chronic comorbid conditions				
Any type of chronic disease	0.014 (0.005, 0.072)	0.007	0.026	0.017
Hypertension	0.055 (0.013, 0.238)	0.054	0.968	1.000
Diabetes	0.188 (0.130, 0.506)	0.023	0.017	0.033
Cardiovascular disease (CVD)	0.221 (− 0.071, 0.512)	0.129	0.062	0.764
Respiratory system disease	0.331 (0.219, 0.881)	0.022	0.020	0.036
Other chronic diseases	0.346 (− 0.105, 0.796)	0.124	0.028	0.012
Number of chronic comorbidity				
At least one chronic comorbid condition	0.014 (0.005, 0.072)	0.007	0.067	0.065
2 chronic comorbid conditions	0.006 (0.001, 0.017)	0.026	0.058	0.046
3 chronic comorbid conditions	0.007 (0.001, 0.017)	0.031	0.049	0.029
4 chronic comorbid conditions	0.009 (0.001, 0.017)	0.035	0.029	0.033
5 chronic comorbid conditions	0.013 (0.001, 0.025)	0.048	0.055	0.010
≥ 6 chronic comorbid conditions	0.012 (0.004, 0.025)	0.056	0.061	0.025
Study design				
Case series study	0.005 (− 0.012, 0.021)	0.687	0.780	0.920
Case–control study	0.771 (− 0.852, 2.394)	0.335	NA	NA
Cohort study	0.016 (− 0.012, 0.043)	0.286	0.429	0.899
Cross-sectional study	− 0.006 (− 0.025, 0.005)	0.318	0.501	0.972
Sample size				
≤ 200 patients	− 0.01 (− 0.029, 0.009)	0.266	0.319	0.493
> 200 patients	0.011 (0.009, 0.029)	0.013	0.031	0.026
Number of studies (n)	23		–	
tau-squared (τ^2)[d]	0.034		–	
Adjusted R-squared (R^2)[c]	45.23%		–	
I-squared (I^2)[b]	96.86%		–	
Permutations[e]	–		10,000	

[a]Moment-based estimate of between-study variance without Knapp & Hartung modification to standard errors

[b]Percentage (%) of residual variation due to heterogeneity

[c]Proportion of between-study variance explained with Knapp–Hartung modification

[d]Residual estimated maximum likelihood estimate of between-study variance

[e]Monte Carlo methods use random numbers, so results may differ between runs

is possible that overall pooled estimates represent an underestimation due inadequate data on comorbidity.

Our findings provide insight on how public health systems should consider chronic comorbid conditions in the COVID-19 response, the treatment and management of COVID-19 patients. There is an urgent need for protocols on care for patients with comorbid conditions. Symptoms of COVID-19 (e.g., fever, cough or fatigue) are almost similar to those of influenza infections, and to some extent some of the chronic conditions. This calls for urgent action to develop guidelines for differential diagnosis for COVID-19 symptoms and comorbidities to enable the public health systems to quickly differentiate the disease from other respiratory system diseases caused by influenza, respiratory syncytial virus, and other respiratory viruses. Considering the insufficient level of ongoing evidence, there is a need to further prioritise research to inform response and risk management decisions, particularly at household level and health

Table 4 Assessing publication bias

Parameters	Number of study	Egger's test[a]		Begg's test[b]	
		Slope	Bias	Adj. Kendall's score (P–Q)[c]	Continuity corrected test
Reported comorbidity					
Any type of chronic disease	23	0.03 ($p=0.004$)	14.88 ($p=0.002$)	− 95 ($z=$-2.51; $p=0.012$)	$z=2.48$ ($p=0.013$)
Hypertension	20	0.05 ($p<0.001$)	6.43 ($p<0.001$)	− 04 ($z=$-0.13; $p=0.897$)	$z=0.10$ ($p=0.922$)
Diabetes	21	0.01 ($p=0.042$)	8.98 ($p=0.015$)	− 54 ($z=$-1.63; $p=0.103$)	$z=1.60$ ($p=0.110$)
Cardiovascular disease (CVD)	21	0.01 ($p=0.132$)	8.64 ($p=0.050$)	08 ($z=0.24$; $p=0.809$)	$z=0.21$ ($p=0.833$)
Respiratory system disease	17	0.05 ($p=0.001$)	− 2.39 ($p=0.177$)	84 ($z=3.46$; $p=0.001$)	$z=3.42$ ($p=0.001$)
Other chronic diseases	18	0.01 ($p=0.001$)	6.09 ($p=0.120$)	73 ($z=2.77$; $p=0.006$)	$z=2.73$ ($p=0.006$)
Case fatality rate (CFR)					
At least one chronic comorbid condition	23	0.01 ($p=0.001$)	5.20 ($p=0.001$)	85 ($z=2.39$; $p=0.025$)	$z=2.22$ ($p=0.027$)
2 chronic comorbid conditions	20	0.01 ($p=0.001$)	5.21 ($p=0.001$)	76 ($z=2.47$; $p=0.014$)	$z=2.43$ ($p=0.015$)
3 chronic comorbid conditions	19	0.02 ($p=0.001$)	5.68 ($p=0.002$)	69 ($z=2.41$; $p=0.016$)	$z=2.38$ ($p=0.017$)
4 chronic comorbid conditions	17	0.01 ($p=0.001$)	5.25 ($p=0.001$)	64 ($z=2.64$; $p=0.008$)	$z=2.60$ ($p=0.009$)
5 chronic comorbid conditions	14	0.03 ($p=0.002$)	6.16 ($p=0.002$)	43 ($z=2.35$; $p=0.019$)	$z=2.30$ ($p=0.021$)
≥6 chronic comorbid conditions	5	0.02 ($p=0.001$)	5.68 ($p=0.002$)	69 ($z=2.41$; $p=0.016$)	$z=2.38$ ($p=0.017$)

[a]Egger's test for small-study effects was performed in terms of regress standard normal deviate of effect estimate against its standard error

[b]Begg's test was performed to detect publication bias for small-study effects

[c]Rank correlation between standardized effect estimate and its standard error

care facilities. Furthermore, there is a need to investigate the association of household and health facilities care among COVID-19 patients to reduce stigmatisation. Anecdotal evidence suggest that people discharged from government quarantine or after recovering in hospitals are subjected to communal violence and chased away from their homes by their neighbours. Enhancing the systematic and real-time sharing of epidemiologic data, clinical outcomes and experience is critical to inform the global response.

Conclusions

Chronic comorbid conditions (e.g., hypertension, diabetes mellitus, cardiovascular disease, respiratory disease, and other chronic diseases) were identified as high risk factors. Considering the insufficient level of evidence, there is need to further prioritise research to inform response and risk management decisions, particularly at household level and health care facilities. Furthermore, there is need to investigate the association of household and health facilities care among COVID-19 patients. We call on countries with the greatest knowledge on COVID-19 to further enhance the systematic and real-time sharing of epidemiologic data, clinical outcomes and experience to inform the global response. Therefore, targeted public health vaccination interventions might be adopted by developing herd immune system to save people with chronic conditions from COVID-19 and other associated respiratory infections.

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Author contributions RAM and AMNR conceptualised the study. RAM led the literature review with contributions from AMNR and JKK. RAM led the data analysis with contributions from AMNR. RAM, AMNR and JKK led the data interpretation. RAM wrote the first draft of the manuscript with input from AMNR and JKK. All named authors contributed to development of the analysis plan, collection and analysis of primary data, data interpretation, and critically reviewed the revised initial draft of the manuscript. All authors read and approved the final draft.

Funding This study was conducted without financial support from any funding body.

Compliance with ethical standards

Conflict of interest The authors declared no conflicts of interest in this work.

Ethical approval The study does not require ethical approval, because the meta-analysis is based on published research and the original data are anonymous. All of the patient information was de-identified.

Appendix

See Tables 5, 6, 7 and 8.

Table 5 Quality score assessment for cohort study

Studies	Quality assessment indicators											Overall score	Overall appraisal
	Q_1	Q_2	Q_3	Q_4	Q_5	Q_6	Q_7	Q_8	Q_9	Q_{10}	Q_{11}		
Wang et al. [5, 41]	✓	✓	✓	✓	✓	×	✓	✓	×	×	✓	8 (medium)	Included
Guan et al. [39, 44]	✓	✓	✓	✓	✓	×	✓	×	×	®	✓	7.5 (medium)	Included
Zhang et al. [12]	✓	✓	✓	✓	✓	×	✓	✓	✓	×	✓	9 (high)	Included
Chen et al. [6, 45]	✓	✓	✓	✓	×	×	✓	×	×	®	✓	6.5 (medium)	Included
Zhou et al. [34]	✓	✓	✓	✓	×	×	✓	✓	×	×	✓	7 (medium)	Included
Cheng et al. [36]	✓	✓	✓	✓	×	×	✓	×	×	®	✓	6.5 (medium)	Included
Fu et al. [37]	✓	✓	✓	✓	✓	×	✓	×	×	®	✓	7.5 (medium)	Included
Wu et al. [35, 47]	✓	✓	✓	✓	✓	×	✓	✓	×	×	✓	8.5 (medium)	Included
Yan et al. [40]	✓	✓	✓	✓	×	×	✓	®	×	×	✓	6.5 (medium)	Included
Shi et al. [38]	✓	✓	✓	✓	×	×	✓	✓	✓	®	✓	8.5 (medium)	Included

Note ✓ = yes (= 1), × = no (= 0), ® = unclear (= 0.5); quality assessment decision rules for 11 scales [(i) poor if the overall score ≤ 5, (ii) medium if overall scores is 6 to 9, and (iii) high if the overall score > 9], Q_1.Were the two groups similar and recruited from the same population? Q_2. Were the exposures measured similarly to assign people to both exposed and unexposed groups? Q_3. Was the exposure measured in a valid and reliable way? Q_4. Were confounding factors identified? Q_5. Were strategies to deal with confounding factors stated? Q_6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? Q_7. Were the outcomes measured in a valid and reliable way? Q_8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur? Q_9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored? Q_{10}. Were strategies to address incomplete follow-up utilized? Q_{11}. Was appropriate statistical analysis used?

Table 6 Quality score assessment for cross-sectional study

Quality assessment indicators	Selected studies	
	Cao et al. [43]	Pan et al. [42]
Q1. Were the criteria for inclusion in the sample clearly defined?	✓	✓
Q2. Were the study subjects and the setting described in detail?	✓	✓
Q3. Was the exposure measured in a valid and reliable way?	✓	✓
Q4. Were objective, standard criteria used for measurement of the condition?	✓	✓
Q5. Were confounding factors identified?	✓	✓
Q6. Were strategies to deal with confounding factors stated?	×	×
Q7. Were the outcomes measured in a valid and reliable way?	✓	✓
Q8. Was appropriate statistical analysis used?	✓	✓
Overall quality score	7 (high)	7 (high)
Overall appraisal	Included	Included

Note ✓ = yes (= 1), × = no (= 0), ® = unclear (= 0.5); quality assessment decision rules for 8 scales: (i) poor if the overall score < 5, (ii) medium if overall scores is 5 to 6, and (iii) high if the overall scores > 6

Table 7 Quality score assessment for case-series study

Study	Quality assessment indicators										Overall scores	Overall appraisal
	Q_1	Q_2	Q_3	Q_4	Q_5	Q_6	Q_7	Q_8	Q_9	Q_{10}		
Chen et al. [6, 45]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10 (high)	Included
Guan et al. [39, 44]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10 (high)	Included
Guo et al. [48]	✓	✓	®	✓	✓	✓	✓	✓	✓	×	8.5 (high)	Included
Huang et al. [7]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10 (high)	Included
McMichael et al. [2]	✓	✓	✓	✓	✓	✓	✓	✓	×	×	8 (medium)	Included
Wu et al. [35, 47]	✓	✓	✓	×	×	✓	×	✓	✓	×	6 (medium)	Included
Wan et al. [49]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10 (high)	Included
Wang et al. [5, 41]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10 (high)	Included
CDC [8]	✓	✓	✓	✓	✓	✓	✓	✓	®	×	8.5 (high)	Included
Liu et al. [46]	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	9 (high)	Included

Note ✓ = yes (= 1), × = no (= 0), ® = unclear (= 0.5); quality assessment decision rules for 10 scales: (i) poor if the overall scores < 6, (ii) medium if overall scores is 6 to 8, and (iii) high if the overall scores > 8. Q_1. Were there clear criteria for inclusion in the case series? Q_2. Was the condition measured in a standard, reliable way for all participants included in the case series? Q_3. Were valid methods used for identification of the condition for all participants included in the case series? Q_4. Did the case series have consecutive inclusion of participants? Q_5. Did the case series have complete inclusion of participants? Q_6. Was there clear reporting of the demographics of the participants in the study? Q_7. Was there clear reporting of clinical information of the participants? Q_8. Were the outcomes or follow-up results of cases clearly reported? Q_9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Q_{10}. Was statistical analysis appropriate?

Table 8 Quality score assessment for case–control study

Quality assessment indicators	Su et al. [50]
Q1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	✓
Q2. Were cases and controls matched appropriately?	×
Q3. Were the same criteria used for identification of cases and controls?	✓
Q4. Was exposure measured in a standard, valid and reliable way?	✓
Q5. Was exposure measured in the same way for cases and controls?	✓
Q6. Were confounding factors identified?	✓
Q7. Were strategies to deal with confounding factors stated?	✓
Q8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	✓
Q9. Was the exposure period of interest long enough to be meaningful?	×
Q10. Was appropriate statistical analysis used?	✓
Overall quality score	8 (medium)
Overall appraisal	Included

Note ✓ = yes (= 1), × = no (= 0), ® = unclear (= 0.5); quality assessment decision rules for 10 scales: (i) poor if the overall scores < 6, (ii) medium if the overall scores is 6 to 8, and (iii) high if the overall scores > 8

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