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The effect of cardiovascular disease and acute cardiac injury on fatal COVID-19: a meta-analysis

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ARTICLE INFO

Article history:

Received 7 July 2020

Received in revised form 4 April 2021

Accepted 6 April 2021

Keywords:

Cardiovascular diseases

Cardiac injury

COVID-19

Mortality

Meta analysis

ABSTRACT

Background: With the continuance of the global COVID-19 pandemic, cardiovascular disease (CVD) and cardiac injury have been suggested to be risk factors for severe COVID-19.

Objective: The aim is to evaluate the mortality risks associated with CVD and cardiac injury among hospitalized COVID-19 patients, especially in subgroups of populations in different countries.

Methods: A comprehensive systematic literature search was performed using 9 databases from November 1, 2019 to November 9, 2020. Meta-analyses were performed for CVD and cardiac injury between non-survivors and survivors of COVID-19.

Results: Although the prevalence of CVD in different populations was different, hospitalized COVID-19 patients with CVD were at a higher risk of fatal outcomes (OR = 2.72; 95% CI 2.35–3.16) than those without CVD. Separate meta-analyses of populations in four different countries also reached a similar conclusion that CVD was associated with an increase in mortality. Cardiac injury was common among hospitalized COVID-19 patients. Patients with cardiac injury had a significantly higher mortality risk than those without cardiac injury (OR = 13.25; 95% CI: 8.56–20.52).

Conclusions: Patients' CVD history and biomarkers of cardiac injury should be taken into consideration during the hospital stay and incorporated into the routine laboratory panel for COVID-19.

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1. Introduction

Coronavirus disease 2019 (COVID-19), a recently discovered disease, has broken through the limits of national borders and circulated rapidly worldwide. Considering the speed of its spread and disease outcomes on an international scale, it was announced as a pandemic by the World Health Organization (WHO) on March 11, 2020. As of March 19, 2021, 223 countries or regions were involved, more than 120.9 million confirmed cases were diagnosed, and these numbers have continued to increase [1]. The global mortality rate of COVID-19 is approximately 2.2% [1], while the mortality rate of hospitalized COVID-19 cases is commonly over 10.0% [2–4]. This is because hospitalized patients tend to have a more serious condition and generally require more effective and special therapies than those in isolation at home. Facing the current severe epidemic situation with limited medical resources, it is urgent to identify significant risk factors leading to death and then

take targeted measures to reduce the fatal risk of hospitalized patients, which can also improve the utilization of medical resources.

The Society of Cardiology [5] and the American College of Cardiology [6] strongly recommend careful cardiac assessment of symptomatic COVID-19 cases. Some primary studies also mentioned two potentially major cardiac risk factors that might be related to the severity of COVID-19 infection [2–4]. One risk factor is baseline cardiovascular disease (CVD), which is defined as a group of disorders of the heart and blood vessels, such as coronary heart disease, peripheral arterial disease, and congenital heart disease [7], occurring before COVID-19 infection and causing more serious clinical outcomes. The other risk factor is acute cardiac injury, as assessed by increased serum levels of high-sensitivity cardiac troponin I (hs-cTnI) or troponin T (hs-cTnT) [8]. Acute cardiac injury has been observed as a common complication of COVID-19 infection and could lead to an increase in severe cardiac events among critically ill patients with COVID-19, including cardiac arrest, arrhythmia, and acute myocardial infarction [9]. Furthermore, several meta-analyses also attempted to assess the combined prognostic effect of CVD or acute cardiac injury on COVID-19, but these estimates varied [10,11]. This might be due to the difference in data sources, sample size and definitions of keywords. For example, the study population was mainly from China, the number of articles included in the meta-analysis was small, or hypertension was regarded

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as a kind of CVD, which is inconsistent with the WHO's definition of CVD [7].

Therefore, we wanted to more comprehensively assess and compare the pooled effect of two risk factors (baseline CVD and acute cardiac injury) on the fatal outcomes of hospitalized COVID-19 patients worldwide. We were also interested in analysis of populations in different countries separately, the analysis of which is lacking. In this study, we selected hospitalized COVID-19 patients as the target group, chose a one-year time span and retrieved 3651 articles from 9 databases to perform meta-analysis. In particular, our study further assessed and compared the association of baseline CVD and COVID-19 mortality in populations from four countries.

2. Methods

2.1. Inclusion criteria

Research articles fulfilling the following criteria were included: (1) the published original research studies used quantitative methods to report the number of confirmed cases of COVID-19 with baseline CVD or acute cardiac injury among survivors and non-survivors from 2019 to 2020, or studies reported the mortality rate of these cases when the total number of survival and death cases was known; (2) according to the WHO, CVD is defined as a group of disorders of the heart and blood vessels, including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, and deep vein thrombosis and pulmonary embolism[7], (3) acute cardiac injury is assessed by increased serum levels of high-sensitivity cardiac troponin I (hs-cTnI) or troponin T (hs-cTnT)[8], (4) randomized controlled trials (RCTs), cohort studies, case-control studies, and cross-sectional studies were included.

2.2. Exclusion criteria

Research articles fulfilling the following criteria were excluded: (1) data that were duplicated in more than one study, and the least recent or the one with a smaller number of cases would be excluded; (2) articles that investigated factors related to cardiac-related infection and other factors (e.g., diabetes) but did not report them separately; (3) cases that were enrolled in studies without a diagnosis of COVID-19 confirmed by real-time reverse-transcriptase polymerase chain reaction (RT-PCR); (4) the research object of the articles was a special population that may affect the meta-analysis results, such as pregnant women or recipients of kidney transplants; (5) the study enrolled cases with unnecessary limitation, for example, patients who presented to the emergency department (ED) with COVID-19 infection were excluded; (6) patients that were not admitted to hospitals.

2.3. Search strategy

The meta-analysis was conducted based on the preferred reporting items for systematic reviews and PRISMA checklist [12] (Supplementary Fig. 1). A comprehensive systematic literature search was performed in various online databases, including PubMed, Scopus, Web of Science, Cochrane Library databases, WanFang Data, WeiPu Data, CNKI, China CDC and USA CDC, from November 1, 2019 to November 9, 2020. The key words are described in Table 1. All references of the included articles were hand-searched and browsed to identify more potentially eligible studies. No ethics committee approval was mandatory.

2.4. Research selection and meta-analysis

The articles that fulfilled the search criteria were carefully assessed by title, abstract and full text independently by two investigators (Jiali

Table 1
The key words used in the meta-analysis

Section	Key words
Disease	"COVID-19" OR "2019-nCoV" OR "2019 novel coronavirus" OR "coronavirus 2019" OR "SARS-CoV-2"
Risk factor	"cardiovascular disease" OR "CVD" OR "cardiac injury" OR "coronary heart disease" OR "cardiomyopathy" OR "heart failure"
Outcome	"fatal" OR "mortality" OR "death"

Long and Yefei Luo) to select eligible ones for meta-analysis. The articles written in Chinese were translated to English by a medical professional fluent in both Chinese and English. Two investigators collected and sorted characteristics of eligible articles into tables, including authors, published year, country, study type, sample size, mortality rate, age, and prevalence of CVD/cardiac injury. Disagreement between the investigators was solved through discussion and consensus of all authors. Later, meta-analyses were performed using Review Manager 5.3 with odds ratio (OR) as a principal effect measure. I^2 acted as a measure of heterogeneity for each meta-analysis. In meta-analysis, if $P < 0.05$ or $I^2 \text{ value} > 50\%$, the studies are considered heterogeneous, and a random effects model is used; if $P > 0.05$ and $I^2 \text{ value} < 50\%$, there is no significant evidence to consider the studies as heterogeneous, and a random effects model is used. Subgroup analyses will be performed if more than 2 countries have 3 or more articles.

2.5. Bias assessment

Firstly, we used Newcastle-Ottawa Scale (NOS) to assess the methodological quality of the included articles. NOS judges individual articles on three broad perspectives: "Selection of study groups", "Comparability of study groups", and "Ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively". Therefore, NOS can quantitatively assess bias of articles such as selection bias and information bias. The quality assessment of articles ranges from low scores (0–4) to moderate scores (5–6) to high scores (7–9), representing three different levels of study quality. When the score is higher, the article is less likely to be biased. Later, we performed a symmetrical shape and regression-based Harbord's test for all outcomes to assess whether there was publication bias or small-study effect. We also conducted a sensitivity analysis in which we tried to remove one study at a time in a meta-analysis, re-estimated the combined effect size, and compared it with the results of the meta-analysis before this exclusion. If the results before and after do not change substantially, it suggests that a single study has no obvious effect on heterogeneity.

3. Results

The search process yielded a total of 3651 articles (Fig. 1). 493 articles were excluded because of duplication, and 2910 articles were further excluded after a preliminary review of titles and abstracts, resulting in 248 studies. Among these articles, 7 articles overlapped study data with other articles, and 185 articles met the other exclusion criteria. Finally, 56 articles remained [2–4,9,13–64].

3.1. Basic characteristics of included studies

3.1.1. General information

Fifty-six articles were included in the analysis, with available data on 52,301 hospitalized COVID-19 patients from 13 countries, 17.8% of whom died. Among these articles, 3 articles provided data on both CVD and cardiac injury, while the other 44 articles and 9 articles only mentioned information on CVD and cardiac injury, respectively (Fig. 2).

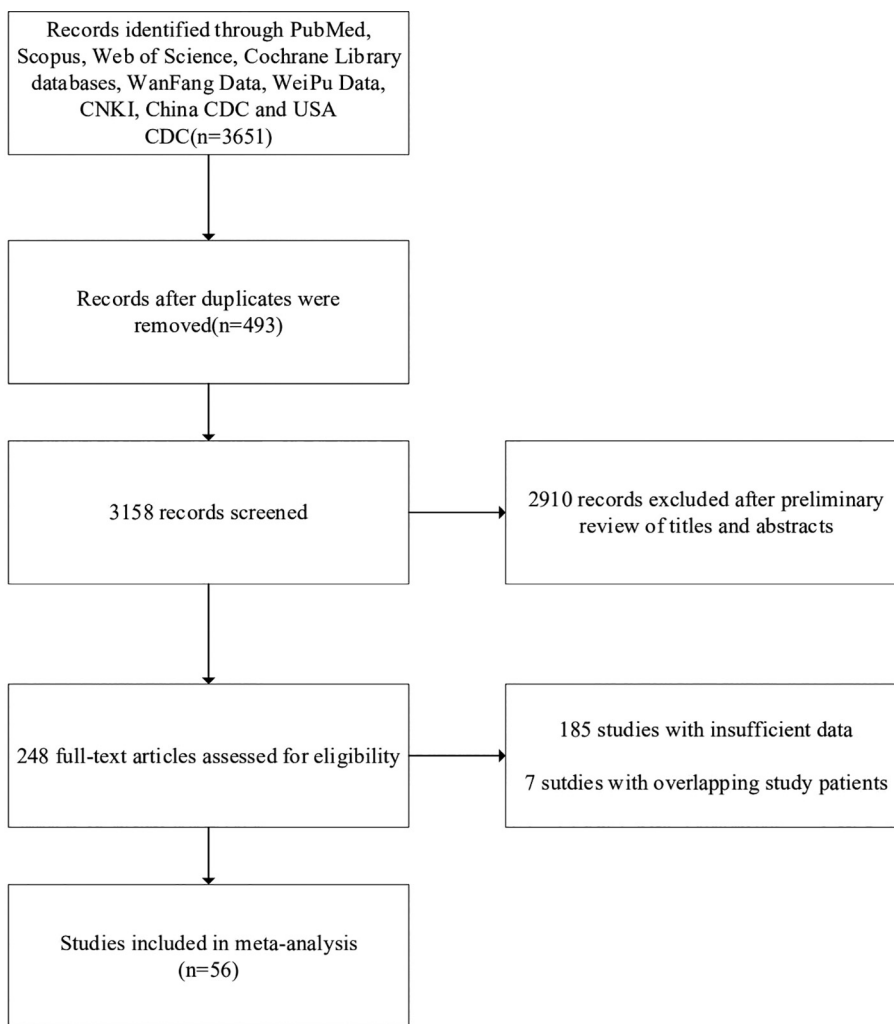


Fig. 1. Flow diagram for selection of articles for inclusion in later analysis.

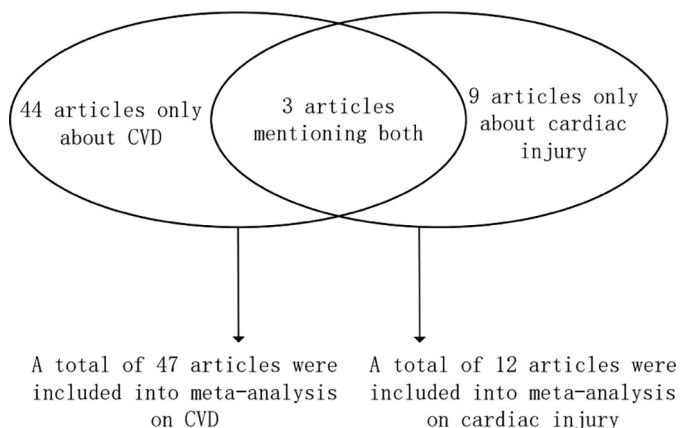


Fig. 2. The number and distribution of articles used for meta-analysis on CVD and cardiac injury.

3.1.2. CVD

Forty-seven studies [2–4,9,13–15,17,19,21–23,25–28,30–33,35–41,43–48,50–57,59–64] reported data about CVD involving research populations from 12 countries, of which China, Italy, the USA, and Iran had 3 or more articles (Table 2, Fig. 3). A total of 49,285 cases were

included in the analysis, with a 18.5% (9137/49,285) mortality rate. The overall prevalence of baseline CVD in survivors was 7.1% (2836/40,148), while the rate in non-survivors was 18.4% (1684/9137). Furthermore, the prevalence of CVD in China, Italy, the USA, and Iran was 10.2%, 15.8%, 9.0% and 9.5%, respectively.

3.1.3. Cardiac injury

The relationship between cardiac injury and mortality was described in 12 studies involving 6 countries (Table 3, Fig. 4, 16, 18, 20, 24, 29, 34, 36, 40, 42, 49, 58, 64). Cardiac injury was a common condition among hospitalized COVID-19 patients, ranging from 17.3% to 60.7%. Due to the limited number of articles included, there was no subgroup analysis on populations in different countries.

3.2. Methodological quality of included studies

The quality of the searched articles was assessed using NOS, and the scoring was performed as described in Table 2 and Table 3. Because the searched articles were not of bad quality, these studies were all used for subsequent meta-analysis. (1) CVD: The searched articles about CVD were assessed ranging from moderate quality (5–6 scores) to high quality (7–8 scores), and none of the studies scored less than 5. The average score of the included studies was 6.2, with a standard deviation (SD) of 1.1. Some studies scored lower on the “Comparability of study groups” part of the scale because these studies mainly focused on the

Table 2
The information of 47 studies included in the meta-analysis of CVD to fatal COVID-19

No.	Author (year studied)	Country	Study type	Sample size (N)	Mortality rate	Age (yrs)	Non-survivors		Survivors		NOS score
							N	CVDs	N	CVDs	
1	Abbasi, B. (2020)	Iran	A retrospective cohort study	262	21.4%	58 (43–67#)	56	34 (60.7%)	206	44 (21.4%)	6
2	Aladağ, N. (2020)	Turkey	A retrospective cohort study	50	30.0%	64.80 (50.3–79.3)	15	7 (46.67%)	35	25 (71.43%)	6
3	Alamdari, N. M. (2020)	Iran	A large-scale retrospective cross-sectional study	459	13.7%	61.8 (49.9–73.7)	63	29 (46.0%)	396	156 (39.4%)	5
4	Alvarez-Garcia, J. (2020)	USA	A retrospective cohort study	6439	25.8%	63.5 (45.9–81.1)	1664	169 (10.2%)	4775	253 (5.3%)	8
5	An, W. (2020)	China	A retrospective cohort study	110	10.0%	–	11	1 (9.1%)	99	4 (4.0%)	7
6	Bursi, F. (2020)	Italy	A retrospective cohort study	49	32.7%	65.7 (53.1–78.3)	16	6 (37.5%)	33	5 (15.2%)	7
7	Cao, Y. (2020)	China	A two-centre retrospective case control study	101	34.7%	56.6 (41.5–71.7)	35	11 (31.4%)	66	10 (15.2%)	7
8	Carrillo-Vega, M. F. (2020)	Mexico	A descriptive cohort study	9946	9.7%	48.2 (33.8–62.5)	963	64 (6.6%)	8983	246 (6.3%)	6
9	Carter, B. (2020)	UK and Italy	A multi-centre international observational cohort study	1559	27.1%	74.0 (61.0–83.0)	422	132 (31.3%)	1137	213 (18.7%)	7
10	Chen, F. F. (2020)	China	A retrospective cohort study	681	15.3%	65.0 (54.0–72.0)	104	25 (24.0%)	577	55 (9.5%)	5
11	Chen, R. (2020)	China	A retrospective cohort study	1590	3.1%	69 (51–86)	50	8 (16.0%)	1540	51 (3.3%)	5
12	Chilimuri, S. (2020)	USA	A retrospective cohort study	375	42.7%	63.0 (52.0–72.0)	160	38 (23.8%)	215	24 (11.2%)	5
13	Ciardullo, S. (2020)	Italy	A single-centre retrospective cohort study	373	38.1%	72 (58–86)	142	65 (45.8%)	231	75 (32.5%)	5
14	Ciceri, F. (2020)	Italy	An observational cohort study	410	23.2%	65 (56–75)	95	25 (26.3%)	315	26 (8.3%)	7
15	Cipriani, A. (2020)	Italy	A single-centre observational cohort study	109	18.3%	71 (60–81)	20	9 (45.0%)	89	9 (10.1%)	6
16	Di Castelnuovo, A. (2020)	Italy	A national retrospective observational cohort study	3762	17.5%	–	665	165 (24.8%)	3097	266 (8.6%)	7
17	Eslami, V. (2020)	Iran	A single-centre prospective cohort study	87	14.9%	54.6 (39.3–69.9)	13	4 (30.8%)	74	11 (14.9%)	7
18	Farré, N. (2020)	Spain	A single-centre cohort study	623	11.9%	–	74	15 (20.3%)	549	18 (3.3%)	7
19	Ferrando, C. (2020)	Spain and Andorra	A multi-centre prospective observational and cohort study	663	30.6%	64 (56–72)	203	6 (3.0%)	460	3 (0.7%)	7
20	Grasselli, G. (2020)	Italy	A retrospective observational cohort study	1715	53.4%	64 (56–70)	915	224 (24.5%)	800	88 (11.0%)	7
21	Guo, T. (2020)	China	A single-centre retrospective observational cohort study	187	23.0%	58.5 (43.8–73.2)	43	29 (67.4%)	144	37 (86.0%)	7
22	Gupta, S. (2020)	USA	A multi-centre cohort study	2215	35.4%	62 (51–71)	784	158 (20.2%)	1431	130 (9.1%)	7
23	Halvatsiotis, P. (2020)	Greece	A multi-centre retrospective cross-sectional study	86	28.9%	65.5 (56–73)	26	4 (15.4%)	60	14 (23.3%)	7
24	Harmouch, F. (2020)	USA	A retrospective cohort study	560	14.5%	63 (39–87)	81	19 (23.5%)	479	35 (7.3%)	5
25	He, X. W. (2020)	China	A single-centre retrospective cohort study	54	48.1%	68.0 (59.8–74.3)	26	5 (19.2%)	28	3 (10.7%)	8
26	He, Y. (2020)	China	A cohort study	336	39.6%	65 (50–77)	133	36 (27.1%)	203	23 (11.3%)	6
27	Homayounieh, F. (2020)	Iran	A retrospective cohort study	75	20.0%	–	15	5 (33.3%)	60	13 (21.7%)	6
28	Hwang, J. M. (2020)	Korea	A retrospective cohort study	103	25.2%	67.6 (52.3–82.9)	26	6 (23.1%)	77	6 (7.8%)	6
29	Inciardi, R. M. (2020)	Italy	A cohort study	99	26.3%	67 (55–79)	26	19 (73.1%)	73	34 (46.6%)	8
30	Lanza, G. A. (2020)	Italy	A retrospective cohort study	324	13.6%	65.9 (50.7–81.1)	44	17 (38.6%)	280	50 (17.9%)	5
31	Li, C. (2020)	China	A retrospective cohort study	2068	8.8%	63 (51–70)	183	28 (15.3%)	1885	154 (8.2%)	5
32	Li, J. (2020)	China	A retrospective cohort study	74	18.9%	66 (55–72)	14	4 (28.6%)	60	2 (3.3%)	6
33	Lu, J. (2020)	China	A retrospective cohort study	20	50.0%	69.8 (57.8–81.8)	10	2 (20.0%)	10	2 (20.0%)	6
34	McCullough, S. A. (2020)	USA	A retrospective observational cohort study	756	11.9%	63.3 (47.3–79.3)	90	16 (17.8%)	666	39 (5.9%)	5
35	Nikpouraghdam, M. (2020)	Iran	A retrospective cohort study	2964	8.1%	55.50 (40.4–70.7)	239	4 (1.7%)	2725	33 (1.2%)	6
36	Pan, F. (2020)	China	A case-control study	124	71.8%	68 (61–75)	89	13 (14.6%)	35	6 (17.1%)	5
37	Peterson, E. (2020)	USA	A single-centre retrospective cohort study	355	22.5%	–	80	24	275	53	8

(continued on next page)

Table 2 (continued)

No.	Author (year studied)	Country	Study type	Sample size (N)	Mortality rate	Age (yrs)	Non-survivors		Survivors		NOS score
							N	CVDs	N	CVDs	
38	Rastad, H. (2020)	Iran	A retrospective cohort study	2957	10.2%	54.8 (37.9–71.7)	301 (30.0%)	54 (17.9%)	2656 (19.3%)	260 (9.8%)	5
39	Rath, D. (2020)	Germany	A consecutive prospective cohort study	123	13.0%	68 (53–83)	16 (13.0%)	6 (37.5%)	107 (20.6%)	22 (9.8%)	7
40	Rey, J. R. (2020)	Spain	A retrospective cohort study	3080	20.3%	62.3 (42.0–82.6)	626 (20.3%)	74 (11.8%)	2454 (11.8%)	78 (3.2%)	7
41	Shi, S. (2020)	China	A retrospective cohort study	671	9.2%	63 (50–72)	62 (9.2%)	21 (33.9%)	609 (14.3%)	39 (6.4%)	5
42	Sun, J. H. (2020)	China	A retrospective cohort study	939	11.7%	62 (51–70)	110 (11.7%)	8 (7.3%)	829 (15.2%)	57 (6.9%)	6
43	Twigg, H. L. (2020)	USA	A cohort study	242	19.8%	59.6 (44.1–75.1)	48 (19.8%)	9 (18.8%)	194 (23.0%)	19 (9.8%)	6
44	Xu, J. (2020)	China	A multicenter retrospective cohort study	239	61.5%	62.5 (49.2–75.8)	147 (62.5%)	21 (14.3%)	92 (15.2%)	14 (15.2%)	6
45	Zhang, J. (2020)	China	A retrospective cohort study	541	9.8%	–	53 (9.8%)	32 (60.4%)	488 (23.0%)	112 (23.0%)	6
46	Zhao, Y. (2020)	China	A single-centre retrospective case control study	539	23.2%	58 (43–69)	125 (23.2%)	20 (16.0%)	414 (16.0%)	17 (4.1%)	6
47	Zhou, F. (2020)	China	A multi-centre retrospective cohort study	191	28.3%	56.0 (46.0–67.0)	54 (28.3%)	13 (24.1%)	137 (24.1%)	2 (1.5%)	5

#The numbers in our study were accurate to one digit after the decimal point, but some of the numbers were only displayed as integers in a few primary articles included.

analysis of research results without sufficient description of the characteristics of the cohort. (2) Cardiac injury: Most articles regarding cardiac injury were of high quality, with an average score of 7.1 and an SD of 1.1. None of the studies scored less than 5. Two studies received full scores.

3.3. Meta-analysis

3.3.1. CVD

The main individual studies included in the analysis revealed that patients who died had a higher ratio of baseline CVD, with quite a few studies showing a neutral effect. The pooled meta-analysis showed that baseline CVD increased the fatal risk of hospitalized COVID-19 patients (OR = 2.72; 95% CI 2.35–3.16; I² = 66%, P < 0.00001) (Fig. 5). An I² value of 66% suggested that the included studies might be heterogeneous. For this reason, we used a random effect model for the meta-analysis. we conducted a sensitivity analysis, and the results before

and after did not change substantially, which excluded the influence of the inclusion of a single study on heterogeneity, indicating that the meta-analysis results were relatively robust. Furthermore, we used a random effect model for the meta-analysis, which is considered more robust for studies with possible heterogeneity. Furthermore, we considered whether the heterogeneity was due to the differences in the research subjects in different countries and conducted a subgroup analysis as shown below.

We further analysed the risk of CVD on fatal outcomes in populations of different countries. A total of four countries had three or more articles included in the analysis, namely, China, the USA, Italy and Iran (Fig. 6). The OR values of these four countries were all significant, fluctuating up and down the global OR value. The risks of CVD in China (OR = 3.09; 95% CI 2.13–4.46; I² = 70%, P < 0.00001) and Italy (OR = 2.88; 95% CI 2.49–3.34; I² = 48%, P < 0.00001) were higher than the global value, while those of the USA (OR = 2.29;

CVD

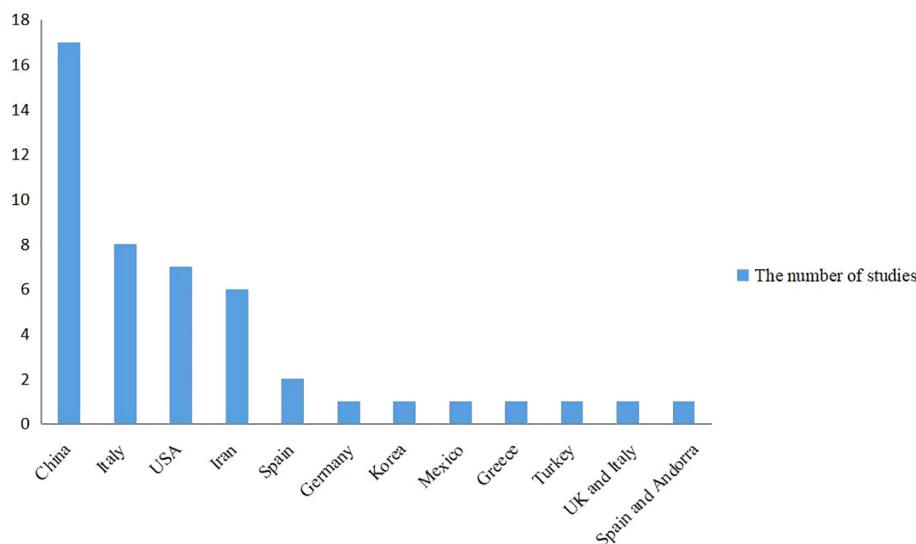


Fig. 3. National distribution of the study population included in the meta-analysis of CVD.

Table 3
The information of 12 studies included in the meta-analysis of acute cardiac injury to fatal COVID-19

No.	Author (year studied)	Country	Study type	Sample size (N)	Mortality rate	Age (yrs)	Non-survivors		Survivors		NOS score
							N	Cardiac injury	N	Cardiac injury	
1	Al-Wahaibi, K. (2020)	Oman	A retrospective cohort study	143	16.8%	49.4 (34.0–64.7)	24	16 (66.7%)	119	15 (12.6%)	6
2	Barman, H. A. (2020)	Turkey	A multi-centre retrospective cohort study	607	17.0%	–	103	64 (17.0%)	504	86 (17.1%)	7
3	Calvo-Fernández, A. (2020)	Spain	A cohort study	872	9.2%	62.3 (44.2–80.4)	80	66 (82.5%)	792	159 (20.1%)	9
4	Chen, L. (2020)	China	A single-centre observational cohort study	63	27.0%	53 (43–65)	17	12 (70.6%)	46	11 (23.9%)	8
5	Deng, Y. (2020)	China	A retrospective case control study	225	48.4%	–	109	65 (59.6%)	116	1 (0.9%)	6
6	Ferrante, G. (2020)	Italy	A single-centre cohort study	332	20.5%	66.9 (55.4–75.5)	68	50 (73.5%)	264	73 (27.7%)	8
7	Guo, T. (2020)	China	A single-centre retrospective observational cohort study	187	23.0%	58.5 (43.8–73.2)	43	31 (72.1%)	144	21 (14.6%)	7
8	He, X. W. (2020)	China	A single-centre retrospective cohort study	54	48.1%	68.0 (59.8–74.3)	26	18 (69.2%)	28	6 (21.4%)	8
9	Heberto, A. B. (2020)	Mexico	A multi-centre prospective observational cohort study	254	35.0%	53.8 (41.1–66.5)	89	46 (51.7%)	165	27 (16.4%)	9
10	Lu, Q. (2020)	China	A retrospective cohort study	56	39.3%	71.5 (56.3–85.8)	22	20 (90.1%)	34	14 (41.2%)	7
11	Shi, S. (2020)	China	A single-centre retrospective cohort study	416	13.7%	64 (21–95)	57	42 (73.4%)	359	40 (11.1%)	5
12	Zhou, F. (2020)	China	A multi-centre retrospective cohort study	191	28.3%	56.0 (46.0–67.0)	54	32 (59.3%)	137	1 (0.7%)	5

95% CI 2.00–2.63; $I^2 = 18\%$, $P < 0.00001$) and Iran (OR = 2.17; 95% CI 1.35–3.49; $I^2 = 63\%$, $P < 0.00001$) were lower than the global value. In addition, the heterogeneity of the meta-analysis in Italy, the USA and Iran was smaller than the total heterogeneity. Finally, based on the I^2 value, we used a fixed effect model for the population of the USA and Italy, and a random effect model for the population in the other two countries.

3.3.2. Cardiac injury

A random-effect model was used in the analysis of cardiac injury. Cardiac injury was found to be strongly associated with an increased risk of a fatal outcome (OR = 13.25; 95% CI: 8.56–20.52; $I^2 = 68\%$, $P < 0.00001$) (Fig. 7). All included articles pointed to the strengthening effect of cardiac injury with fatal results. We conducted a sensitivity analysis again, and a similar conclusion was reached. The influence of the inclusion of a single study on heterogeneity was excluded, implying that the results of the meta-analysis were relatively reliable.

3.3.3. Publication Bias

The funnel-plot analysis showed a symmetrical shape for all outcomes (CVD (8A), cardiac injury (8B), and CVD in China (8C), the USA (8D), Iran (8E) and Italy (8F)), indicating no possible publication bias (Fig. 8). Regression-based Harbord’s test showed no indication of small-study effects (Table 4), which ruled out the possible heterogeneity to a certain extent. Therefore, we believe that the differences in the inclusion and data collection of research subjects in different countries may be a potential source of heterogeneity, and the results could be considered credible.

4. Discussion

So far, many countries including Italy, Spain, Germany, the USA and the UK have reported that they are in trouble. On one hand, their hospitals are facing an overload of ICU and a shortage of ICU nurses and protective equipment. On the other hand, there are a large number of COVID-19 patients in these countries who need emergency

Cardiac injury

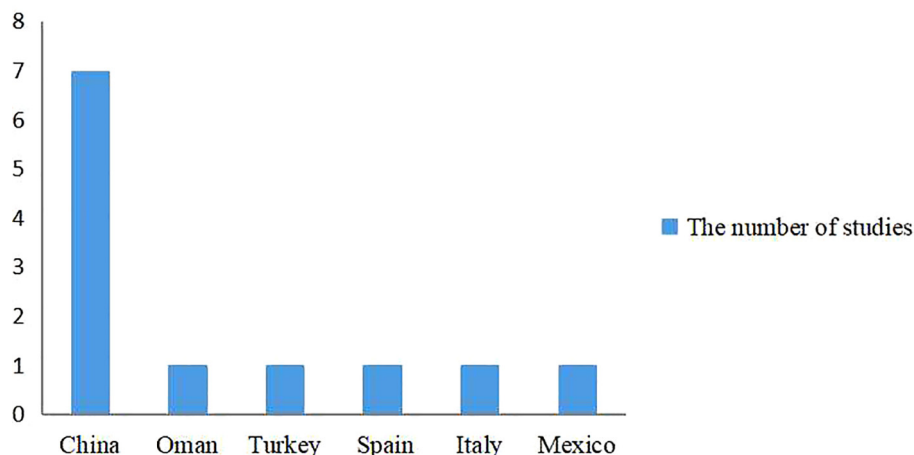


Fig. 4. National distribution of the study population included in the meta-analysis of cardiac injury.

CVD

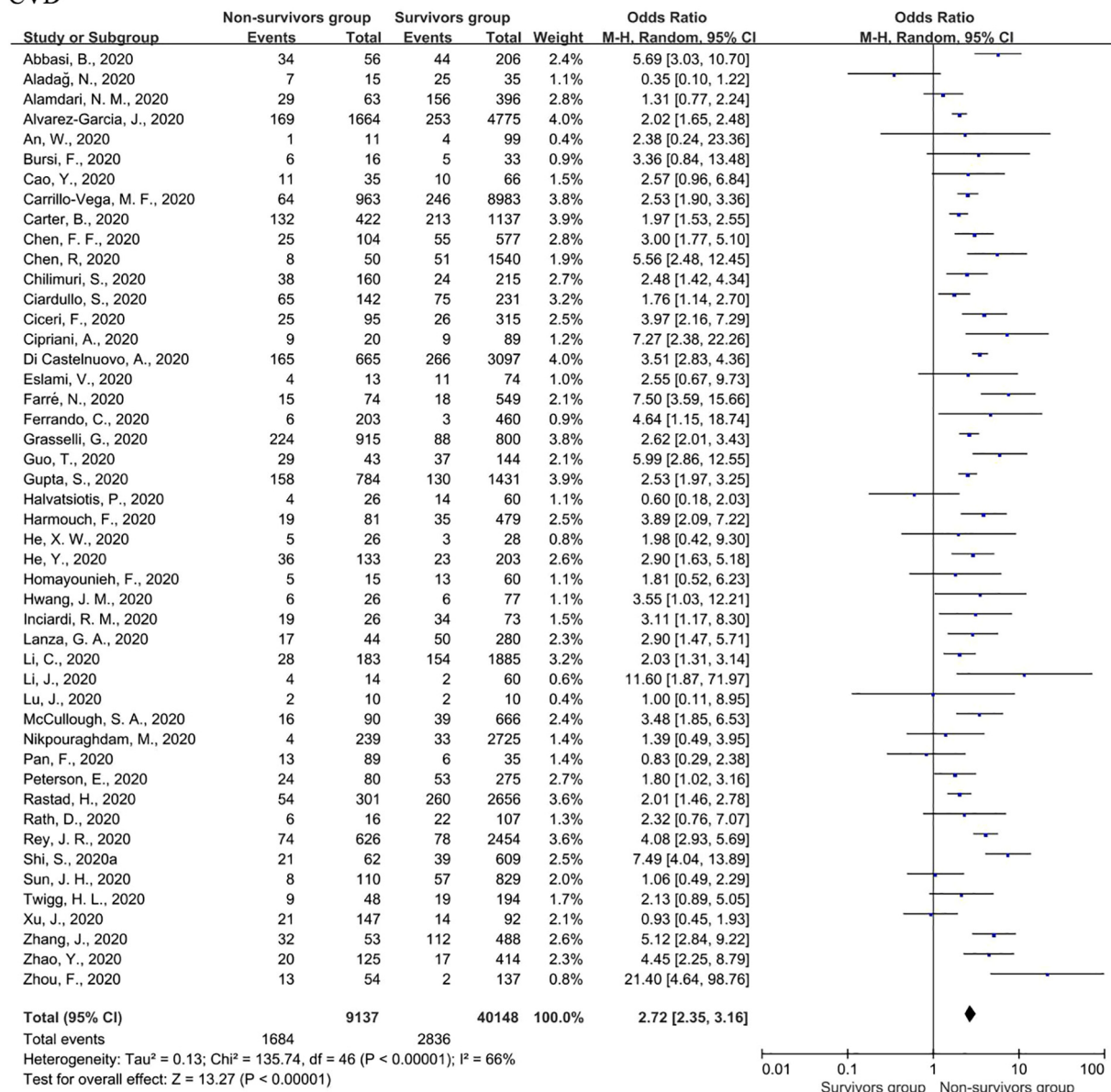


Fig. 5. Forest plots of the association of CVD with fatal COVID-19.

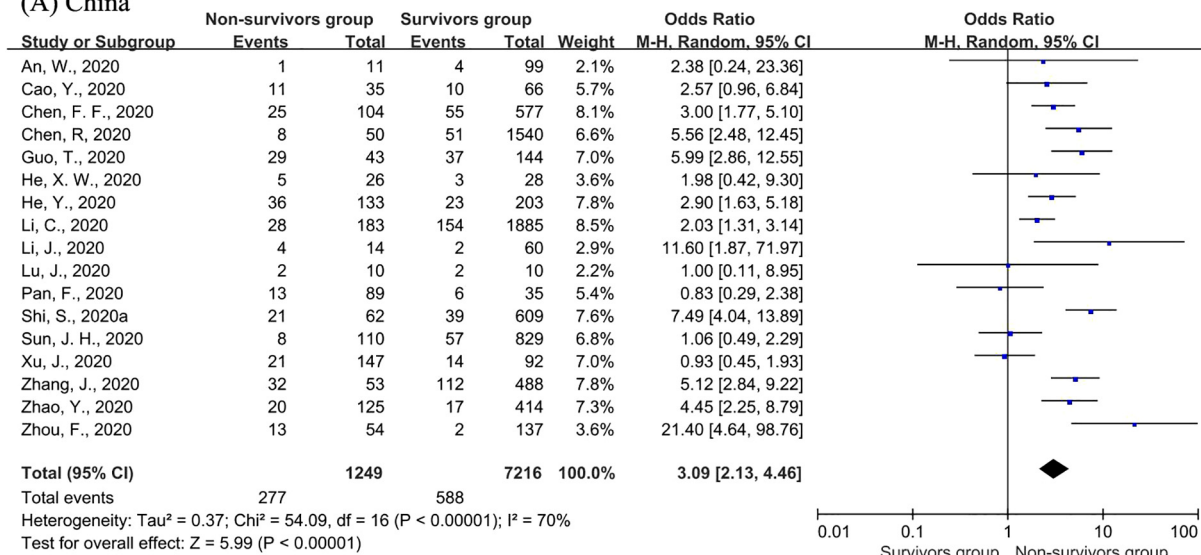
treatment. Due to the rapid deterioration of COVID-19, these patients will face death threats if they cannot get emergency treatment in time such as being admitted to ICU for continuous monitoring and respiratory assistance. This contradiction has greatly affected the normal operation of the hospitals and the treatment of COVID-19 patients. By identifying the risk factors associated with mortality, and then intervening in time, the proportion of patients who get worse and then die will decrease, thereby reducing the need for first aid and saving limited medical resources.

4.1. Main findings

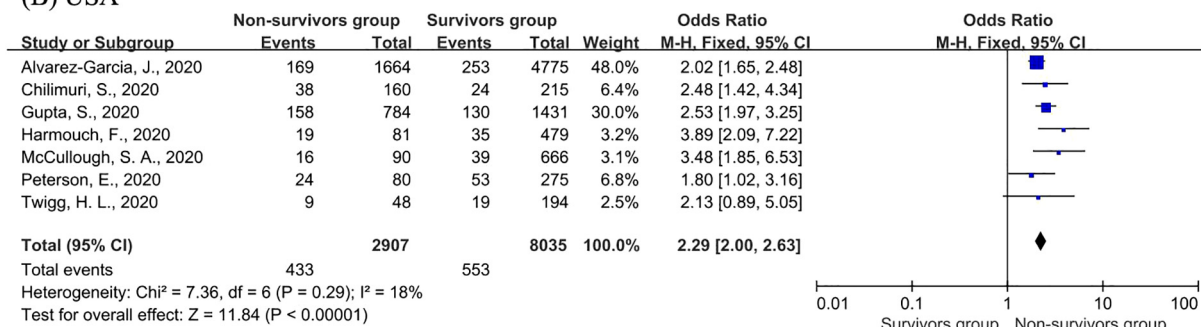
This meta-analysis of 56 studies systematically assessed the impact of baseline CVD and acute cardiac injury on the fatal risk of hospitalized COVID-19 patients. This analysis included more global data with a clear definition of the research objects, carefully compared the duplication of study data and then deleted the repetitive studies as

appropriate to reduce bias. In particular, our study further assessed and compared the risk value of CVD in populations from four countries. In this study, we found that (1) CVD: from a global perspective, the overall mortality of hospitalized COVID-19 patients was high, and patients with baseline CVD were at a higher risk of fatal outcomes than those without CVD. In addition, further analysis of the population in four countries reached a similar conclusion as above, again highlighting the importance of CVD. In addition, the CIs of OR values in different countries on fatal outcomes overlapped; thus, there was no significant evidence to prove that the risk of CVD on adverse outcomes in a single country was significantly higher than those in other countries. (2) Cardiac injury: cardiac injury was obviously common among hospitalized COVID-19 patients, ranging from 17.3% to 60.7%. Patients with cardiac injury had a thirteen-fold higher mortality risk than those without cardiac injury, suggesting that cardiac injury can act as a more powerful prognostic predictor of COVID-19 than CVD.

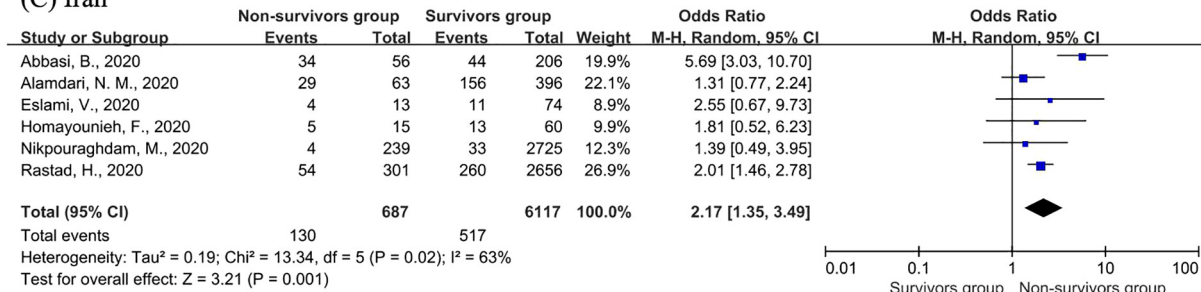
(A) China



(B) USA



(C) Iran



(D) Italy

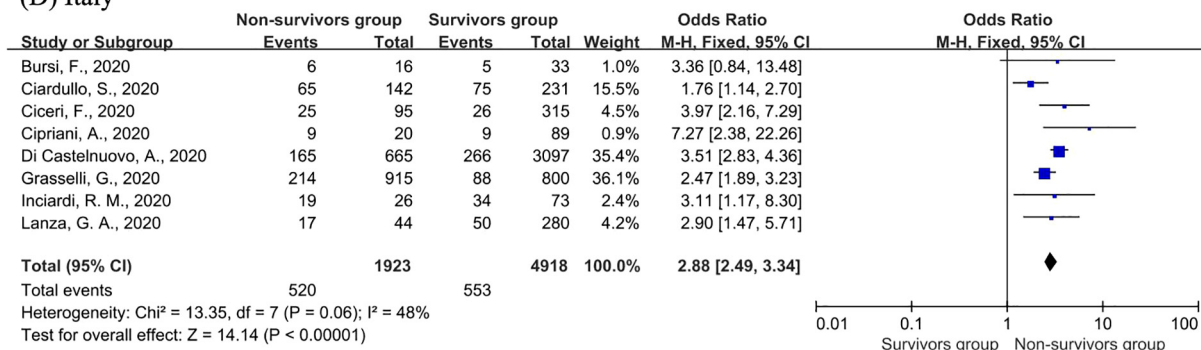


Fig. 6. Forest plots of the association of CVD in China (A), the USA (B), Iran (C) and Italy (D) with fatal COVID-19.

4.2. Pathogenic mechanism of study results

The adverse effect of CVD and acute cardiac injury on COVID-19 mortality may be due to the pathogenic mechanism of diseases.

Inflammation plays important roles in diseases; that is, inflammatory activation mediates the vulnerability of patients with CVD to COVID-19 infection, and the systemic inflammatory response syndrome caused by COVID-19 promotes the development of cardiac injury,

Cardiac injury

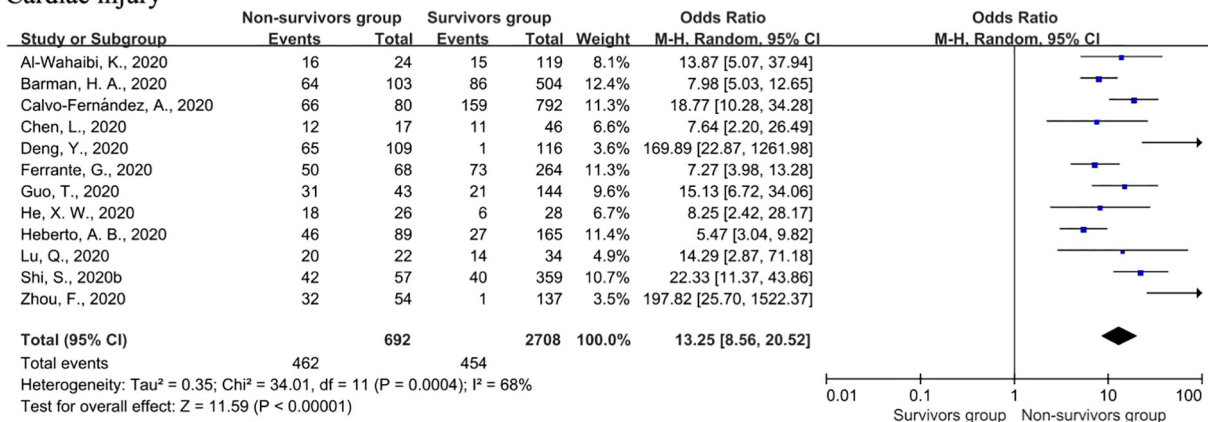


Fig. 7. Forest plots of the association of cardiac injury with fatal COVID-19.

which may worsen the condition of COVID-19 patients and even aggravate mortality. CVD is defined as a group of disorders of the heart and blood vessels [7]. Patients with CVD often have chronic inflammation since inflammatory activation acts as an essential contributor to CVD development and progression. For example, the elevated serum inflammatory factors tumour necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β) might induce a decrease in myocardial contractility and cause left heart dysfunction and dilation [65], while an increased co-expression of interleukin-9 (IL-9) and interleukin-17 (IL-17) showed a putative pro-inflammatory role in tissue inflammation and chronicity of tissue damage in giant cell arteritis and atherosclerosis [66,67]. On the other hand, inflammation is a common characteristic of COVID-19 infection and is important for its development. Increased serum inflammatory factors (e.g., IL-9, IL-1 β , TNF- α) and decreased lymphocytes were detected in COVID-19 patients, especially in critically ill patients [62]. The changes in serum inflammatory factors in COVID-19 infection and CVD overlap. Besides, decreased lymphocytes were implicated in the progression and destabilization of atherosclerosis [68]. The virus itself also seemed to mediate myocardial damage [69]. This evidence explains why the cardiovascular system and heart are involved in this respiratory disease, and patients who have a group of disorders of the heart and blood vessels seem to be more vulnerable to COVID-19 and to have a more severe clinical course and prognosis. On the other hand, an increasing number of studies have shown that systemic inflammatory response syndrome (including cytokine storm, immune cell imbalance and uncontrolled inflammation) caused by COVID-19 plays an important role in the development of cardiac injury. For example, cardiac injury markers were elevated simultaneously with inflammatory factors (amino-terminal B-type natriuretic peptide, D-dimers, procalcitonin, IL-6) in patients with cardiac injury, and the inflammatory factors were higher than those of patients without cardiac injury, suggesting that patients suffering from cardiac injury had more severe systemic inflammation [45,49]. Furthermore, severe cardiac events (e.g., myocardial failure) induced by cardiac injury were correlated with COVID-19-induced pulmonary distress and elevation of pulmonary artery pressure, which promoted the occurrence of acute respiratory distress syndrome (ARDS), a common cause of deterioration and mortality in COVID-19 patients [55]. This was supported by evidence that patients with ARDS had a high incidence of elevated cardiac injury biomarkers, which was also independently associated with an increase in 60-day mortality and organ failure [70]. Therefore, cardiac injury is common in COVID-19 infection and increases the risk of deterioration and even mortality.

4.3. Recommendations for clinical practice

Our study indicated that CVD and acute cardiac injury were associated with an increase in mortality of hospitalized COVID-19 patients. Deterioration of the condition will increase the need for emergency rescue in hospitalized patients, such as Intensive Care Unit (ICU) admission. In order to better treat patients and save limited medical resources, we suggest that inquiry of CVD history and monitoring of biochemical predictors of cardiac injury could be taken into consideration during the hospital stay, especially within the first week of admission for critically ill patients. Li et al. [9] described that the median levels of cardiac markers and inflammatory markers peaked on the 3rd day and then gradually decreased between the 4th and 7th days of hospitalization in critically ill survivors, while the levels of these markers continued to rise among non-survivors. In the case of rapid development of the disease, the test results can remind medical staff of the risks faced by COVID-19 patients and provide evidence-based support for the optimal use of therapies, such as risk stratification or consideration of the use of drugs and/or cooperation with other examinations, ultimately delaying the deterioration of the disease and promoting the recovery of COVID-19 patients. For example, Fried, J.A. et al. described that if the patient had cardiomyopathy and prolonged baseline QT, the use of hydroxychloroquine and azithromycin might be affected [71]. Besides, the susceptibility of people with CVD to COVID-19 infection requires people to pay special attention to personal protection to prevent COVID-19.

4.4. Limitations

Although we performed the above studies, which specifically analysed the data of different countries and made some suggestions for clinical practice based on the results, further discussion was limited by some weaknesses. (1) RCTs that met the inclusion criteria but not the exclusion criteria were not searched. If there are RCT data, the persuasiveness of the meta-analysis results will be further improved. However, we have fully discussed the 56 articles searched and included in the analysis above based on attention to article quality. NOS assessed the methodological quality of all 56 articles and proved that their quality was sufficient for meta-analysis. The results of sensitivity analysis, funnel-plot analysis, and regression-based Harbord's test indicated the credibility of the meta-analysis results. In addition, the meta-analysis results were biologically reasonable without conflict with known biological knowledge on pathogenic mechanism, which further proved the credibility of the results of this article. (2) Some people wondered

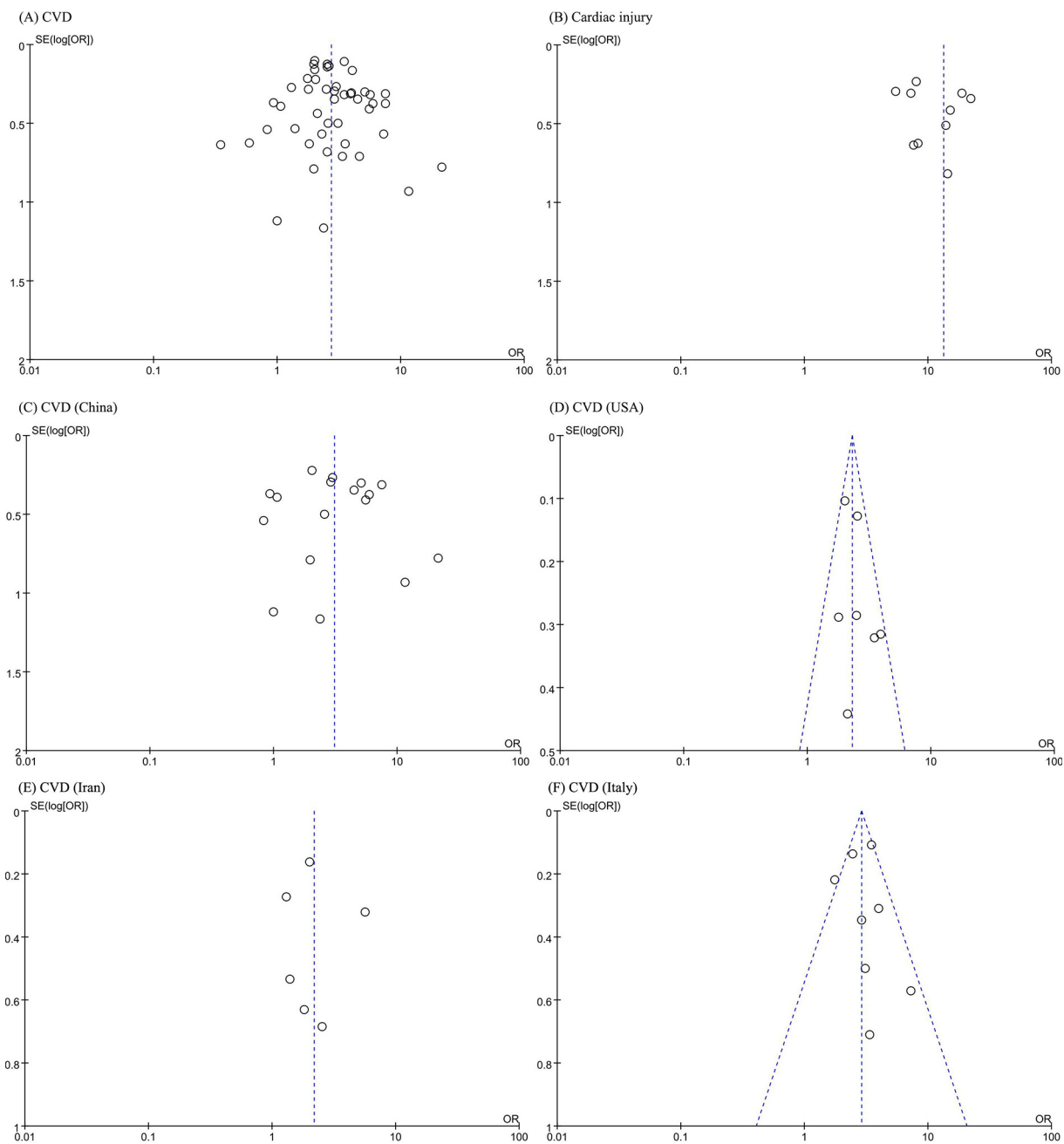


Fig. 8. Funnel-plot analysis of CVD (A), cardiac injury (B), and CVD in China (C), the USA (D), Iran (E) and Italy (F).

Table 4
Regression-based Harbord's test for all associations analysed

	Number of studies included	P value for small-study effects
CVD	47	0.176
Cardiac injury	12	0.812
CVD (China)	17	0.244
CVD (USA)	7	0.218
CVD (Italy)	8	0.85
CVD (Iran)	6	0.98

whether cardiac injury might be secondary to baseline CVD but occur before COVID-19 infection and whether the development of cardiac injury may be prompted by the stronger inflammation induced by the interaction between CVD and COVID-19 infection. However, Heberto,

A. B. et al. once indirectly rejected this speculation since they found no statistically significant difference in the prevalence of baseline CVD among COVID-19 cases with and without cardiac injury [42]. The current data still fails to explain the relationship between the two risk factors. It will be interesting to compare cardiac biomarkers before and after COVID-19 infection to determine the context of the two risk factors in future studies.

5. Conclusion

In brief, both CVD and cardiac injury are associated with increasing mortality among hospitalized COVID-19 patients. Therefore, inquiry of patients' CVD history should be taken into consideration, and biomarkers of cardiac injury could be incorporated into the routine laboratory panel for COVID-19 during the hospital stay.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajem.2021.04.013>.

Data availability

All data analysed during this study are included within the manuscript and its additional file.

Funding

This work was supported by National Natural Science Foundation of China (Grant No. 81473034), General Guidance Project of Guangzhou Health and Family Planning Technology (Grant No. 20181A011050).

Authors' contributions

All authors met PRISMA guidelines for authorship and provided analysis interpretation, critical review, revision, and final approval of the article. Jiali Long, Yefei Luo and Yuehong Wei contributed to the concept/design, data collection, analysis and writing manuscript of the study. Chaojun Xie and Jun Yuan aided in the revision and publication management. The first three authors, two corresponding authors contributed equally to this manuscript, separately.

Declaration of Competing Interest

All authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

This work was supported by National Natural Science Foundation of China (Grant No. 81473034), General Guidance Project of Guangzhou Health and Family Planning Technology (Grant No. 20181A011050).

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