Original Article

Risk factors for mortality of coronavirus disease 2019 (COVID-19) patients during the early outbreak of COVID-19: a systematic review and meta-analysis

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Background: Identification of risk factors for poor prognosis of patients with coronavirus disease 2019 (COVID-19) is necessary to enable the risk stratification and modify the patient's management. Thus, we performed a systematic review and meta-analysis to evaluate the in-hospital mortality and risk factors of death in COVID-19 patients.

Methods: All studies were searched via the PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), VIP, and Wanfang databases. The in-hospital mortality of COVID-19 patients was pooled. Odds ratios (ORs) or mean difference (MD) with 95% confidence intervals (CIs) were calculated for evaluation of risk factors.

Results: A total of 80 studies were included with a pooled in-hospital mortality of 14% (95% CI: 12.2–15.9%). Older age (MD =13.32, 95% CI: 10.87–15.77; P<0.00001), male (OR =1.66, 95% CI: 1.37–2.01; P<0.00001), hypertension (OR =2.67, 95% CI: 2.08–3.43; P<0.00001), diabetes (OR =2.14, 95% CI: 1.76–2.6; P<0.00001), chronic respiratory disease (OR =3.55, 95% CI: 2.65–4.76; P<0.00001), chronic heart disease/cardiovascular disease (OR =3.15, 95% CI: 2.43–4.09; P<0.00001), elevated levels of high-sensitive cardiac troponin I (MD =66.65, 95% CI: 16.94–116.36; P=0.009), D-dimer (MD =4.33, 95% CI: 2.97–5.68; P<0.00001), C-reactive protein (MD =48.03, 95% CI: 27.79–68.27; P<0.00001), and a decreased level of albumin at admission (MD =−3.98, 95% CI: −5.75 to −2.22; P<0.0001) are associated with higher risk of death. Patients who developed acute respiratory distress syndrome (OR =62.85, 95% CI: 29.45–134.15; P<0.00001), acute cardiac injury (OR =25.16, 95% CI: 6.56–96.44; P<0.00001), acute kidney injury (OR =22.86, 95% CI: 4.60–113.66; P=0.0001), and septic shock (OR =24.09, 95% CI: 4.26–136.35; P=0.0003) might have a higher in-hospital mortality.

Conclusions: Advanced age, male, comorbidities, increased levels of acute inflammation or organ damage indicators, and complications are associated with the risk of mortality in COVID-19 patients, and should be integrated into the risk stratification system.

Keywords: Coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-

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CoV-2); meta-analysis; mortality; risk factors

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Introduction

According to the World Health Organization, a novel pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously known as 2019-nCoV) is designated as coronavirus disease 2019 (COVID-19) (1). SARS-CoV-2 belongs to the coronavirus family together with SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), but has more rapid transmission than SARS-CoV and MERS-CoV (2-4), which leads to a dramatic increase in the number of confirmed cases during a short period, thereby posing a serious threat for health systems worldwide. Till August 4, 2020, a cumulative total of 18,142,718 confirmed COVID-19 cases and 691,013 deaths have been reported in 216 countries (5).

Fever and cough are main clinical manifestations of COVID-19 patients (6). Most of COVID-19 patients have a favorable outcome, but a minority of them may develop severe pneumonia, dyspnea and hypoxemia, and progress into respiratory or multi-organ failure and even death (7). Based on 55,924 laboratory confirmed cases in China, the overall national mortality rate is 3.8%, but the fatality rate of patients over 80 years old is up to 22% (8). Besides, male, pre-existing comorbidities, elevated inflammatory markers, and complications [i.e., acute respiratory distress syndrome (ARDS), acute cardiac injury, acute kidney injury and sepsis] were associated with an increased risk of death (9-15).

In the early stages of COVID-19 outbreak, because effective vaccines and antiviral drugs for SARS-CoV-2 are lacking, the management of critically ill patients is often challenging. Thus, it is very essential to identify the risk factors associated with poor outcome of COVID-19 patients and perform early interventions for high-risk patients. The present study aimed to systematically review the evidence on the in-hospital mortality of COVID-19 patients and elucidate the risk factors of mortality in COVID-19 patients.

Methods

This meta-analysis was conducted based on Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines and results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (available at http://dx.doi.org/10.21037/apm-20-2557).

Registration

This study was registered at PROSPERO (registration number: CRD42020169921).

Search strategy

All relevant studies regarding mortality of COVID-19 patients were retrieved via the PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), VIP, and Wanfang databases. The search terms were ("2019-nCoV" OR "SARS-CoV-2" OR "COVID-19" OR "new coronary pneumonia" OR "corona virus" OR "novel coronavirus" OR "nCoV" OR "severe acute respiratory syndrome coronavirus 2") AND ("death" OR "died" OR "die" OR "mortality" OR "survival" OR "survivor" OR "fatal" OR "outcome" OR "decease" OR "deadly" OR "lethal" OR "fatality"). The last search was performed on May 26, 2020.

Study selection

There was neither publication language nor publication status restriction. All eligible studies should report the mortality and/or risk factors for death in COVID-19 patients. Exclusion criteria were as follows: (I) duplicates; (II) case reports, reviews or meta-analyses, guidelines, consensus, experimental or animal studies, comments, notes, and correspondences; (III) irrelevant papers; (IV) data regarding the mortality and/or risk factors cannot

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be extracted; and (V) duplicate study population. As for duplicate studies, we selected only one original study with more comprehensive clinical and laboratory data. Case-control studies were excluded from the proportion meta-analyses regarding mortality of COVID-19 patients due to their potential patient selection bias.

Data extraction

The following data were extracted from the included studies: the first author, publication year, region, source of cases, enrollment period, follow-up periods, number of COVID-19 patients, number of COVID-19 patients with severe disease, number of non-survivors and survivors, age, gender, and other potential risk factors for death.

Study quality

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included studies. It includes study selection (four items), comparability (two items), and exposure/outcome (three items). The highest NOS score was 9, and studies with a NOS score of >6 were considered as high quality.

Statistical analysis

All meta-analyses were performed using STATA version 12.0 (Stata Corp., College Station, Texas, USA) and Review Manager software version 5.4 (Cochrane collaboration, the Nordic Cochrane Centre, Copenhagen, Denmark). The meta-analyses were conducted by using a random-effect model. We pooled the in-hospital mortality in COVID-19 patients, and then calculated the pooled proportion with 95% confidence interval (CI). We collected the risk factors for death in COVID-19 patients, and then calculated the odds ratios (ORs) or mean difference (MD) with 95% CIs. The heterogeneity among studies was evaluated by Cochrane Q test and the I^2 statistics, and I^2 >50% and/or P<0.1 were considered to have statistically significant heterogeneity. Publication bias was assessed with Egger test. P<0.1 was considered as a statistically significant publication bias. Subgroup analyses, meta-regression analyses, and sensitivity analyses would be performed to explore the sources of heterogeneity among studies. Subgroup analyses were conducted according to the sample size (>100 versus ≤100), source of cases (single-center versus multiple-center), NOS (>6 versus ≤6), region (Asia versus Europe versus North America), study design (retrospective versus prospective), longest follow-up duration (>30 days versus ≤30 days), and proportion of patients with severe disease (>50% versus ≤50%). Meta-regression analyses were also grouped in terms of the variables mentioned above. Scattered plots were drawn to show the trend in overall in-hospital mortality according to the proportion of severe COVID-19 patients included. The correlation between them was evaluated using Spearman correlation analysis in the IBM SPSS 22.0 (IBM Corp, Armonk, NY, USA). Coefficients were calculated. A two-sided P<0.05 indicates a statistical significance.

Results

Study selection

A total of 7,003 studies were identified via the 6 databases, and 6 studies were identified via a manual search. Finally, 80 studies with 25,385 COVID-19 patients were included (*Figure 1*). All included studies are listed in the Appendix.

Study characteristics

Characteristics of the included studies were listed in *Table 1*. Forty-three studies were published as full texts, 32 was published in press (i.e., available online ahead of print), and 5 studies were preprinted. The sample size ranged from 8 to 2,964. Sixty-one studies were performed in Asia, 11 in Europe, and 8 in North America; 72 of them were retrospective and 8 were prospective; 56 and 24 studies were single-center and multi-center studies, respectively.

Study quality

The NOS score ranged between 3 and 8. Twenty-two studies were considered to be of high quality and 3 were of low quality (Table S1).

Mortality

The results of the meta-analyses regarding in-hospital mortality of COVID-19 patients are summarized in *Table 2*.

Overall analyses

Eighty studies reported the in-hospital mortality of COVID-19 patients, and the pooled in-hospital mortality of COVID-19 patients was 14% (95% CI: 12.2–15.9%). The heterogeneity was statistically significant (I^2 =97.8%;

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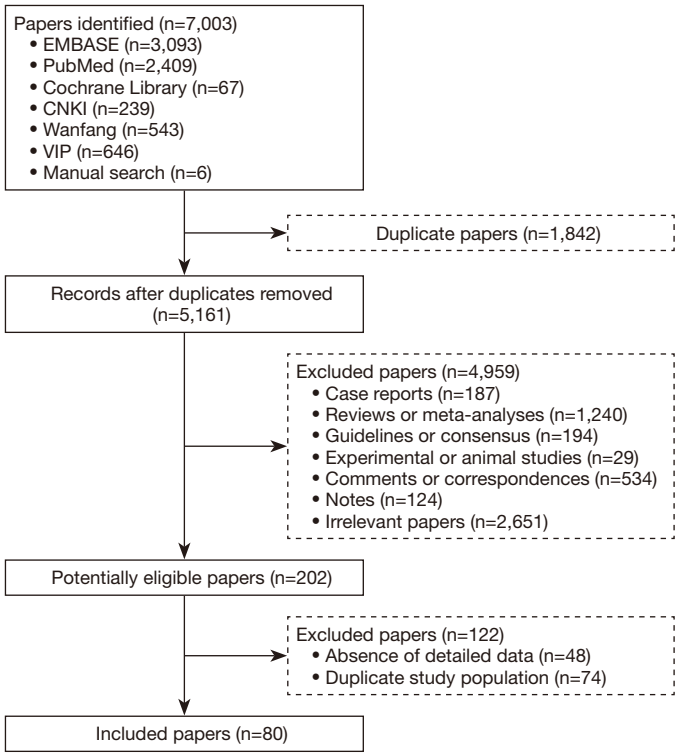

Figure 1 Flow chart of study selection.

P<0.001). Fifty studies reported the number of severe COVID-19 patients, and the pooled incidence of severe COVID-19 patients was 49.6% (95% CI: 43.6–55.6%). The heterogeneity was statistically significant (I^2 =99.9%; P<0.001).

Subgroup analyses

The pooled in-hospital mortality of COVID-19 patients was 10.1%, 23.7%, and 25.4% in Asia, Europe, and North America, respectively. The pooled in-hospital mortality of COVID-19 patients was 13.7% and 15.2% in studies with a sample size of >100 and ≤100, respectively. The pooled in-hospital mortality of COVID-19 patients was 14.2% and 13.6% in single-center and multiple-center studies, respectively. The pooled in-hospital mortality of COVID-19 patients was 13.6% and 18% in retrospective and prospective studies, respectively. The pooled in-hospital mortality of COVID-19 patients was the same between the studies with NOS >6 and NOS ≤6 (both 14%). The pooled in-hospital mortality of COVID-19 patients was 15.1% and 17.3% in studies with the longest follow-up duration of >30 days and ≤30 days, respectively. The pooled in-hospital mortality of COVID-19 patients was 22.5% and 7.7% in studies with the proportion of patients with severe disease of >50% and ≤50%, respectively. The heterogeneity was statistically significant in all subgroup analyses.

Meta-regression analyses

The results of meta-regression analyses are shown in Table S2. Meta-regression analyses indicated that region (Asia versus Europe versus North America) (P=0.0001), proportion of patients with severe disease (>50% versus ≤50%) (P<0.001), rather than sample size (>100 versus ≤100) (P=0.456), source of cases (single-center versus multiple-center) (P=0.756), NOS (>6 versus ≤6) (P=0.956), study design (retrospective versus prospective) (P=0.403), and longest follow-up duration (>30 versus ≤30 days) (P=0.624), might be related to the heterogeneity.

Sensitivity analyses

The sensitivity analysis showed that none of these included studies could significantly influence the results of the meta-analysis.

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Table 1 Characteristics of studies included in the meta-analysis

First author (year)	Country	Source of cases	Enrollment period	Longest follow-up periods	No. of severe patients (%)	Sample size	Non-survivors			Survivors		
							N (%)	Age, years[a]	Male (%)	N (%)	Age, years[a]	Male (%)
Aggarwal S [2020]	United States	UnityPoint Clinic	2020.03.01–2020.04.04	NA	NA	16	3 (18.8)	NA	NA	13 (81.3)	NA	NA
Barrasa H [2020]	Spain	University Hospital Araba	2020.03.04–2020.03.31	33 days	48 (100.0)	48	14 (29.2)	NA	NA	34 (70.8)	NA	NA
Benussi A [2020]	Italy	ASST Spedali Civili di Brescia Hospital	2020.02.21–2020.04.05	NA	NA	56	21 (37.5)	NA	NA	35 (62.5)	NA	NA
Bhatraju PK [2020]	United States	Nine hospital in the Seattle	2020.02.24–2020.03.09	28 days	24 (100.0)	24	12 (50.0)	NA	NA	12 (50.0)	NA	NA
Bianchetti A [2020]	Italy	Acute Hospital in Brescia Province, Northern Italy	NA	NA	NA	627	194 (30.9)	NA	NA	433 (69.1)	NA	NA
Borghesi A [2020]	Italy	Radiological Sciences and Public Health, University of Brescia	2020.03.04–2020.03.24	NA	NA	302	65 (21.5)	77 [70.5–81]	50 (76.9)	237 (78.5)	64 [54–73.3]	144 (60.8)
Buckner FS [2020]	United States	Three University of Washington affiliated hospitals	2020.03.02–2020.03.26	67 days	51 (48.6)	105	35 (33.3)	NA	NA	70 (66.7)	NA	NA
Cai Q [2020]	China	Third People's Hospital of Shenzhen	2020.01.11–2020.02.06	55 days	58 (19.5)	298	3 (1.0)	NA	NA	295 (99.0)	NA	NA
Cecconi M [2020]	Italy	Humanitas Research Hospital	2020.02.22–2020.03.22	32 days	27 (11.3)	239	36 (15.1)	NA	NA	203 (84.9)	NA	NA
Chen R [2020]	China	575 hospitals in China	As of January 31, 2020	NA	NA	1590	50 (3.1)	68 [51–86]	39/50 (78.0)	1,540 (96.9)	48[1–94]	865/1,528 (56.6)
Andrea C [2020]	Italy	San Raffaele Hospital	2020.02.27–2020.03.17	42 days	NA	191	42 (22.0)	75.3±12.9	31 (73.8)	149 (78.0)	60.4±13.7	100 (67.1)
Cummings MJ [2020]	United States	Milstein Hospital and Allen Hospital	2020.03.02–2020.04.01	57 days	257 (100.0)	257	101 (39.3)	NA	NA	156 (60.7)	NA	NA
Deng Y [2020]	China	Hankou and Caidian branch of Tongji Hospital, and Hankou branch of Central Hospital of Wuhan	2020.01.01–2020.02.21	NA	104 (10.8)	964	109 (11.3)	69 [62–74]	73 (67.0)	855 (88.7)	NA	NA
Dong XC [2020]	China	Designated hospitals in Tianjin	NA	NA	62 (45.9)	135	3 (2.2)	NA	NA	132 (97.8)	NA	NA
Du RH [2020]	China	Wuhan Pulmonary Hospital	2019.12.25–2020.02.07	90 days	NA	179	21 (11.7)	70.2±7.7	10 (47.6)	158 (88.3)	56.0±13.5	87 (55.1)
Gao L [2020]	China	Hubei General Hospital	NA	15 days	54 (100.0)	54	18 (33.3)	NA	NA	36 (66.7)	NA	NA
Giacomelli A [2020]	Italy	Luigi Sacco Hospital in Milan	2020.02.21–2020.03.19	28 days	88 (37.8)	233	48 (20.6)	NA	39 (81.3)	185 (79.4)	NA	122 (65.9)
Guo T [2020]	China	Seventh Hospital of Wuhan	2020.01.23–2020.02.23	33 days	NA	187	43 (23.0)	NA	NA	144 (77)	NA	NA
Hong KS [2020]	South Korea	Yeungnam University Medical Center	As of March 29, 2020	NA	NA	98	5 (5.1)	NA	NA	93 (94.9)	NA	NA
Hou W [2020]	China	Beijing YouAn Hospital	2020.01.21–2020.03.09	NA	22 (21.8)	101	5 (5.0)	NA	NA	96 (95.0)	NA	NA
Hu H [2020]	China	Renmin Hospital of Wuhan University (Sichuan Medical Team)	2020.02.07–2020.03.07	NA	105 (100.0)	105	19 (18.1)	75.05±12.94	14 (73.7)	86 (81.9)	57.71±15.34	48 (55.8)
Hu L [2020]	China	Tianyou Hospital in Wuhan	2020.01.08–2020.02.20	62 days	172 (53.3)	323	35 (10.8)	NA	NA	288 (89.2)	NA	NA
Huang J [2020]	China	Third People's Hospital of Yichang	2020.01.25–2020.03.24	NA	NA	299	16 (5.4)	69.2±9.7	11 (68.8)	283 (94.6)	52.5±16.6	149 (52.7)
Inciardi RM [2020]	Italy	Civil Hospitals of Brescia	2020.03.04–2020.03.25	14 days	NA	99	26 (26.3)	NA	NA	73 (73.7)	NA	NA
Israelsen SB [2020]	Denmark	Hvidovre Hospital	2020.03.10–2020.04.23	41 days	NA	175	43 (24.6)	NA	NA	132 (75.4)	NA	NA
Itelman E [2020]	Israel	Sheba Medical Center	2020.02.01–2020.04.10	NA	26 (16.0)	162	5 (3.1)	NA	NA	157 (96.9)	NA	NA
Javanian M [2020]	Iran	Ayatollah Rohani, Shahid Beheshti and Yahyanejad hospitals	2020.02.25–2020.03.12	21 days	NA	100	19 (19.0)	69.26±11.10	12 (63.2)	81 (81.0)	57.74±13.58	39 (48.1)
Ji D [2020]	China	Fuyang Second People's Hospital and Fifth Medical Center of Chinese PLA General Hospital	2020.01.20–2020.02.22	58 days	0 (0)	208	2 (1.0)	NA	NA	206 (99.0)	NA	NA
Klang E cohort1 [2020]	United States	Mount Sinai Hospital, Mount Sinai Brooklyn, Mount Sinai Queens, Mount Sinai Morningside and Mount Sinai West	2020.03.01–2020.05.17	NA	NA	572	60 (10.5)	46.5 [42.8–49]	45 (75.0)	512 (89.5)	40 [34–46]	352 (68.8)
Klang E cohort2 [2020]	United States	Mount Sinai Hospital, Mount Sinai Brooklyn, Mount Sinai Queens, Mount Sinai Morningside and Mount Sinai West	2020.03.01–2020.05.17	NA	NA	2,834	1,076 (38.0)	76 [67–84]	615 (57.2)	1,758 (62.0)	68 [60–77]	949 (54.0)
Li J [2020]	China	Central Hospital of Wuhan	2020.01.15–2020.03.15	NA	173 (47.8)	362	77 (21.3)	72 [64.5–82]	50 (64.9)	285 (78.7)	65 [57.5–71]	139 (48.7)
Li R [2020]	China	Hanchuan City People's Hospital	2020.01.20–2020.02.14	40 days	37 (16.4)	225	2 (0.9)	NA	NA	223 (99.1)	NA	NA
Li X [2020]	China	Designated hospitals in Guizhou	2020.01.20–2020.02.12	NA	NA	135	1 (0.7)	NA	NA	134 (99.3)	NA	NA

Table 1 (*continued*)

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Table 1 (*continued*)

First author (year)	Country	Source of cases	Enrollment period	Longest follow-up periods	No. of severe patients (%)	Sample size	Non-survivors			Survivors		
							N (%)	Age, years[a]	Male (%)	N (%)	Age, years[a]	Male (%)
Ling L [2020]	China	Prince of Wales Hospital's	2020.01.22–2020.02.11	28 days	8 (100.0)	8	1 (12.5)	NA	NA	7 (87.5)	NA	NA
Liu J [2020]	China	Two COVID-19 designated hospitals in Hunan	As of February 16, 2020	NA	0 (0)	24	1 (4.2)	NA	NA	23 (95.8)	NA	NA
Liu K [2020]	China	Hainan General Hospital	2020.01.01–2020.02.15	NA	NA	56	3 (5.4)	NA	NA	53 (94.6)	NA	NA
Liu K [2020]	China	Nine tertiary hospitals in Hubei	2019.12.30–2020.01.24	NA	NA	137	16 (11.7)	NA	NA	121 (88.3)	NA	NA
Long L [2020]	China	First People's Hospital of Jingzhou and Xiangyang Central Hospital	2020.01.16–2020.02.24	45 days	48 (15.9)	301	17 (5.6)	NA	NA	284 (94.4)	NA	NA
Luo X [2020]	China	Eastern Campus of Renmin Hospital of Wuhan University	2020.01.30–2020.02.20	21 days	157 (52.7)	298	84 (28.2)	71 [64–80]	51 (60.7)	214 (71.8)	51 [37–63]	99 (46.3)
Mehta V [2020]	United States	Montefiore Medical Center and Albert Einstein College of Medicine	2020.03.18–2020.04.08	25 days	NA	218	61 (28.0)	76 [10–92]	36 (59.0)	157 (72.0)	66 [10–92]	91 (58.0)
Nikpouraghdam M [2020]	Iran	Baqiyatallah hospital in Tehran	2020.02.19–2020.04.15	NA	NA	2,964	239 (8.1)	NA	NA	2,725 (91.9)	NA	NA
Nowak B [2020]	Poland	Central Clinical Hospital of the Ministry of the Interior and Administration	2020.03.16–2020.04.07	22 days	41 (24.3)	169	46 (27.2)	75.3±11.9	30 (65.2)	123 (72.8)	59.3±20.1	57 (46.3)
Qi X [2020]	China	16 designated hospitals in China	2019.12.31–2020.03.24	84 days	NA	21	5 (23.8)	68 [50–75]	4 (80.0)	16 (76.2)	69 [52–75]	7 (43.8)
Renieris G [2020]	Greece	Eight departments participating in the Hellenic Sepsis Study Group	NA	28 days	NA	74	10 (13.5)	NA	9 (90.0)	64 (86.5)	NA	45 (70.3)
Shekerdemian LS [2020]	United States	NA	2020.03.14–2020.04.03	27 days	33 (68.8)	48	2 (4.2)	NA	NA	46 (95.8)	NA	NA
Sun H [2020]	China	Sino-French New City Branch of Tongji Hospital	2020.01.29–2020.03.05	36 days	NA	244	121 (49.6)	72 [66–78]	82 (67.8)	123 (50.4)	67 [64–72]	51 (41.5)
Tan ND [2020]	China	West Campus of Wuhan Union Hospital (First Affiliated Hospital of Sun Yat-sen University Medical Team)	2020.01.28–2020.04.08	30 days	87 (87.0)	100	11 (11.0)	NA	NA	89 (89.0)	NA	NA
Tang N [2020]	China	Tongji Hospital in Wuhan	2020.01.01–2020.02.13	72 days	449 (100.0)	449	134 (29.8)	68.7±11.4	90 (67.2)	315 (70.2)	63.7±12.2	178 (56.5)
Tian S [2020]	China	Designated hospitals in Beijing	2020.01.20–2020.02.10	21 days	46 (17.6)	262	3 (1.1)	NA	NA	259 (98.9)	NA	NA
Wan S [2020]	China	Chongqing University Three Gorges Hospital	2020.01.23–2020.02.08	16 days	40 (29.6)	135	1 (0.7)	NA	NA	134 (99.3)	NA	NA
Wang D [2020]	China	Zhongnan Hospital of Wuhan University and Xishui People's Hospital	As of February 10, 2020	NA	NA	544	19 (3.5)	73 [64–81]	16 (84.2)	525 (96.5)	NA	NA
Wang K [2020]	China	First People's Hospital of Jiangxia District in Wuhan	2020.01.07–2020.02.11	35 days	NA	296	19 (6.4)	65.6±12.6	11 (57.9)	277 (93.6)	46.0±14.4	129 (46.6)
Wang Z [2020]	China	Main campus of Union Hospital in Wuhan	2020.01.16–2020.01.29	19 days	NA	69	5/67 (7.5)	NA	NA	62/67 (92.5)	NA	NA
Wei JF [2020]	China	Public Health Clinical Centre of Chengdu and West China Hospital, Sichuan University	2020.01.16–2020.03.10	NA	37 (36.6)	101	3 (3.0)	NA	NA	98 (97.0)	NA	NA
Wu J [2020]	China	Tongren Hospital of Wuhan University	2020.01.30–2020.03.10	49 days	NA	101	9 (8.9)	NA	NA	92 (91.1)	NA	NA
Xie J [2020]	China	Wuhan Union Hospital (Beijing Medical Team)	2020.01.28–2020.02.28	45 days	97 (69.3)	140	36 (25.7)	NA	25 (69.4)	104 (74.3)	NA	NA
Xu B [2020]	China	Hubei Provincial Hospital of traditional Chinese and Western medicine	2019.12.26–2020.03.01	NA	107 (57.2)	187	28 (15.0)	73 [68–77.3]	17 (60.7)	159 (85.0)	NA	NA
Yang Q [2020]	China	Wuhan Third Hospital	2020.01.28–2020.02.12	NA	33 (24.3)	136	23 (16.9)	NA	NA	113 (83.1)	NA	NA
Yu Y [2020]	China	16 designated hospitals in Wuhan	2020.02.26–2020.02.27	43 days	226 (100.0)	226	87 (38.5)	NA	NA	139 (61.5)	NA	NA
Zhang H [2020]	China	Huanggang Central Hospital and The Second Affiliated Hospital of Shandong First Medical University	2020.01.22–2020.02.28	41 days	37 (19.1)	194	9 (4.6)	NA	NA	185 (95.4)	NA	NA
Zhang J [2020]	China	Liyuan Hospital	2020.01.16–2020.02.20	NA	19 (100.0)	19	8 (42.1)	77 [66–91]	5 (62.5)	11 (57.9)	68 [38–87]	6 (54.5)
Zhang J [2020]	China	Renmin Hospital of Wuhan University	2020.01.11–2020.02.06	29 days	409 (61.7)	663	25 (3.8)	67.1 [61–78]	15 (60.0)	638 (96.2)	59.1 [43–68]	306 (48.0)
Zhang L [2020]	China	Wuhan Asia General Hospital	2020.01.12–2020.03.15	NA	NA	343	13 (3.8)	NA	NA	330 (96.2)	NA	NA
Zhang Y [2020]	China	West Court of Union Hospital in Wuhan	2020.01.29–2020.02.12	43 days	171 (66.3)	258	15 (5.8)	NA	NA	243 (94.2)	NA	NA

Table 1 (*continued*)

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Table 1 (*continued*)

First author (year)	Country	Source of cases	Enrollment period	Longest follow-up periods	No. of severe patients (%)	Sample size	Non-survivors			Survivors		
							N (%)	Age, years[a]	Male (%)	N (%)	Age, years[a]	Male (%)
Zhang YT [2020]	China	Designated hospitals in Guangdong	2020.01.15–2020.03.04	69 days	222 (16.4)	1,350	8 (0.6)	NA	NA	1,342 (99.4)	NA	NA
Zhao XY [2020]	China	Jingzhou Central Hospital	2020.01.16–2020.02.10	25 days	30 (33.0)	91	2 (2.2)	NA	NA	89 (97.8)	NA	NA
Zhou F [2020]	China	Jinyintan Hospital and Wuhan Pulmonary Hospital	2019.12.29–2020.01.31	33 days	119 (62.3)	191	54 (28.3)	69 [63–76]	38 (70.4)	137 (71.7)	52 [45–58]	81 (59.1)
Zhou X [2020]	China	Wuhan Fourth Hospital	2020.01.25–2020.02.20	NA	NA	110	9 (8.2)	NA	NA	101 (91.8)	NA	NA
An W [2020]	China	Hubei No. 3 People's Hospital	2020.01.24–2020.02.19	NA	15 (13.6)	110	11 (10.0)	72.4±7.1	6 (54.5)	99 (90.0)	54.6±15.6	38 (38.4)
Chang Z [2020]	China	Wuhan Puren Hospital	2020.01–2020.02	NA	57 (38.0)	150	20 (13.3)	NA	NA	130 (86.7)	NA	NA
Foy BH [2020]	United States	Massachusetts General Hospital, Brigham and Women's Hospital, North Shore Medical Center and Newton-Wellesley Hospital	2020.03.04–2020.04.28	55 days	NA	1,198	155 (12.9)	75±13.2	98 (63.2)	1,043 (87.1)	59.6±17.5	563 (54.0)
Guo F [2020]	China	First Affiliated Hospital of Bengbu Medical College	2020.01.22–2020.03.08	NA	31 (39.2)	79	5 (6.3)	NA	NA	72 (91.1)	NA	NA
Li JW [2020]	China	Wuhan Red Cross Hospital in Wuhan	2020.01.21–2020.02.14	24 days	NA	161	65 (40.4)	67 [31–87]	42 (64.6)	96 (59.6)	46 [22–87]	38 (39.6)
Luo M [2020]	China	Wuhan Tongren Hospital of Wuhan University (Wuhan Third Hospital)	2020.01.17–2020.02.25	NA	152 (11.6)	1,305	69 (5.3)	NA	46 (66.7)	1,236 (94.7)	NA	NA
Fang XW [2020]	China	Infectious Hospital of Anhui Provincial Hospital	2020.01.22–2020.02.18	27 days	24 (30.4)	79	1 (1.3)	NA	NA	78 (98.7)	NA	NA
Yang H [2020]	China	Sino-French Eco-City section of Tongji Hospital (Peking University Supporting Medical Team)	2020.01.29–2020.03.10	68 days	19 (20.2)	94	13 (13.8)	77 [67.5–83]	8 (61.5)	81 (86.2)	66 [59.0–72.5]	37 (45.7)
Yang JK [2020]	China	Wuhan Union Hospital (Beijing Tongren Hospital Medical Team)	2020.01.29–2020.03.20	55 days	46 (66.7)	69	16 (23.2)	64 [57–68]	13 (81.3)	53 (76.8)	60 [51–67]	21 (39.6)
Zhang CS [2020]	China	Dabieshan Medical Center	2020.01.30–2020.02.14	NA	32 (100.0)	32	6 (18.8)	59.3±11.1	3 (50.0)	26 (81.3)	57.9±12.4	17 (65.4)
Zhang F [2020]	China	Wuhan No.1 Hospital	2019.12.25–2020.01.15	NA	22 (45.8)	48	17 (35.4)	78.65±8.31	12 (70.6)	31 (64.6)	66.16±13.66	21 (67.7)
Zhang G [2020]	China	Wuhan Xinzhou District People's Hospital	2020.01.16–2020.02.25	46 days	32 (33.7)	95	6 (6.3)	66 [38.3–76.8]	6 (100.0)	89 (93.7)	49 [39.5–57]	47 (52.8)
Zhang JG [2020]	China	The First People's Hospital of Jiangxia District (The Affiliated Hospital of Jiangsu University Medical Team)	2020.02.01–2020.03.15	NA	30 (22.2)	135	18 (13.3)	65 [56.8–76.8]	9 (50.0)	117 (86.7)	NA	NA

[a], age data presented as median (interquartile range), mean (standard deviation) or median (range).

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Table 2 Mortality of COVID-19 patients: results of meta-analyses

Groups	No. studies	Range	Pooled proportion using random-effects model	Heterogeneity		Publication bias: 95% CI; $P_{egger: bias}$
				I^2	P	
Overall mortality	79	0.6–50%	0.140 (95% CI: 0.122–0.159)	97.80%	<0.001	3.896–7.253; <0.001
Sample size						
>100	54	0.6–40.4%	0.137 (95% CI: 0.115–0.158)	98.40%	<0.001	5.011–9.934; <0.001
≤100	25	0.6–40.5%	0.153 (95% CI: 0.114–0.192)	86.80%	<0.001	3.255–5.424; <0.001
Region						
Asia	61	0.6–50%	0.101 (95% CI: 0.086–0.115)	95.60%	<0.001	3.477–5.847; <0.001
Europe	11	13.5–37.5%	0.237 (95% CI: 0.197–0.276)	77.80%	<0.001	–4.227 to 4.729; 0.902
North America	7	4.2–39.3%	0.254 (95% CI: 0.150–0.359)	98.60%	<0.001	–15.421 to 14.102; 0.917
Source of cases						
Single-center	55	0.7–42.1%	0.142 (95% CI: 0.121–0.163)	95.70%	<0.001	3.585–6.639; <0.001
Multiple-center	24	0.6–50%	0.136 (95% CI: 0.099–0.173)	98.90%	<0.001	2.029–11.399; 0.007
Study quality						
NOS >6	21	0.7–35.4%	0.140 (95% CI: 0.106–0.174)	93.70%	<0.001	2.264–6.298; <0.001
NOS ≤6	58	0.6–50%	0.140 (95% CI: 0.118–0.162)	98.30%	<0.001	3.866–8.353; <0.001
Study design						
Retrospective	71	0.6–50%	0.136 (95% CI: 0.117–0.156)	97.90%	<0.001	3.594–7.186; <0.001
Prospective	8	0.7–39.3%	0.180 (95% CI: 0.093–0.267)	97.80%	<0.001	3.937–15.797; 0.007
Longest follow-up						
>30 days	24	0.9–38%	0.151 (95% CI: 0.118–0.184)	96.80%	<0.001	4.754–9.401; <0.001
≤30 days	21	0.7–50%	0.173 (95% CI: 0.127–0.220)	96.70%	<0.001	4.347–9.276; <0.001
Proportion of patients with severe disease						
>50%	20	3.8–50%	0.225 (95% CI: 0.165–0.284)	96.10%	<0.001	2.808–8.163; <0.001
≤50%	30	0.7–35.4%	0.077 (95% CI: 0.061–0.094)	94.70%	<0.001	2.934–6.010; <0.001

NOS, Newcastle-Ottawa scale.

Risk factors

A total of 31 studies reported the detailed data regarding the association of demographic and clinical characteristics, laboratory data, imaging features, and complications with mortality of COVID-19 patients, of which 25 performed both univariate and multivariate analyses (Table S3).

The detailed results of meta-analyses are presented in *Table 3* and forest plots in the Supplementary Materials.

Demographics

Meta-analyses indicated that male (OR =1.66, 95% CI: 1.37–2.01; P<0.00001) and older age (MD =13.32, 95% CI: 10.87–15.77; P<0.00001) were significant risk factors for death of COVID-19 patients.

Comorbidities

Meta-analyses indicated that hypertension (OR =2.67, 95% CI: 2.08–3.43; P<0.00001), diabetes (OR =2.14, 95% CI: 1.76–2.6; P<0.00001), chronic respiratory disease (OR =3.55, 95% CI: 2.65–4.76; P<0.00001), chronic heart disease/cardiovascular disease (OR =3.15, 95% CI: 2.43–4.09; P<0.00001), cerebrovascular disease (OR =5.92, 95% CI: 4.16–8.42; P<0.00001), chronic kidney disease (OR =3.04, 95% CI: 2.12–4.36; P<0.00001), cancer (OR =3.05,

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Table 3 Comparison of demographic characteristics, comorbidities, clinical symptoms, laboratory data, imaging features, and complications between non-survivors and survivors of COVID-19

Parameter	No. studies	Pooled MD (95% CI)	Pooled OR (95% CI)	P value	Heterogeneity	
					I^2	Cochran's Q P value
Demographics and clinical characteristics						
Male	31	–	1.66 (1.37, 2.01)	<0.00001	57%	<0.0001
Older age	30	13.32 (10.87, 15.77)	–	<0.00001	94%	<0.00001
Time from illness onset to hospital admission, days	11	0.49 (–0.34, 1.33)	–	0.25	56%	0.01
Comorbidities						
Hypertension	24	–	2.67 (2.08, 3.43)	<0.00001	68%	<0.00001
Diabetes	24	–	2.14 (1.76, 2.6)	<0.00001	37%	0.04
Chronic respiratory disease	21	–	3.55 (2.65, 4.76)	<0.00001	25%	0.14
CHD/cardiovascular disease	24	–	3.15 (2.43, 4.09)	<0.00001	58%	0.0001
Cerebrovascular disease	10	–	5.92 (4.16, 8.42)	<0.00001	0%	0.63
Chronic kidney disease	15	–	3.04 (2.12, 4.36)	<0.00001	62%	0.0005
Smoking	8	–	1.32 (1.07, 1.62)	0.01	5%	0.40
Cancer	17	–	3.05 (1.92, 4.85)	<0.00001	62%	0.0002
Clinical symptoms						
Fever	19	–	1.12 (0.82, 1.53)	0.48	25%	0.16
Cough	17	–	1.02 (0.75, 1.39)	0.90	42%	0.03
Dyspnea	13	–	5.31 (2.74, 10.28)	<0.00001	81%	<0.00001
Myalgia	9	–	0.91 (0.64, 1.31)	0.62	0%	0.52
Fatigue	11	–	1.47 (0.93, 2.34)	0.10	61%	0.004
Hemoptysis	3	–	1.25 (0.38, 4.14)	0.72	0%	0.37
Sputum production	11	–	1.88 (1.39, 2.55)	<0.0001	22%	0.24
Diarrhea	12	–	1.14 (0.83, 1.56)	0.43	0%	0.51
Laboratory tests						
White blood cell count, $\times10^9$/L	18	3.23 (2.63, 3.83)	–	<0.00001	52%	0.005
Lymphocyte count, $\times10^9$/L	15	–0.41 (–0.52, –0.30)	–	<0.00001	82%	<0.00001
Neutrophil count, $\times10^9$/L	10	2.47 (0.06, 4.88)	–	0.04	95%	<0.00001
Platelet count, $\times10^9$/L	11	–44.37 (–53.01, –35.74)	–	<0.00001	0%	0.68
Hemoglobin, g/L	7	–5.59 (–10.64, –0.54)	–	0.03	69%	0.004
Albumin, g/L	7	–3.98 (–5.75, –2.22)	–	<0.0001	81%	<0.0001
ALT, U/L	13	6.72 (1.80, 11.64)	–	0.007	72%	<0.0001
AST, U/L	13	16.78 (11.78, 21.78)	–	<0.00001	60%	0.003
TBIL, μmol/L	6	1.59 (0.06, 3.11)	–	0.04	0%	0.52

Table 3 (*continued*)

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Table 3 (*continued*)

Parameter	No. studies	Pooled MD (95% CI)	Pooled OR (95% CI)	P value	Heterogeneity	
					I^2	Cochran's Q P value
LDH, U/L	10	288.29 (225.73, 350.85)	–	<0.00001	59%	0.009
High-sensitive cardiac troponin I, pg/mL	4	66.65 (16.94, 116.36)	–	0.09	78%	0.04
Hypersensitive troponin I, >26.2 pg/mL	3	–	26.80 (8.99, 79.94)	<0.00001	3%	0.36
NT-proBNP, μg/L	3	1.08 (0.79, 1.36)	–	<0.00001	0%	0.82
CK, U/L	9	96.64 (47.87, 145.41)	–	0.0001	76%	<0.0001
CK-MB, U/L	5	6.37 (3.72, 9.03)	–	<0.00001	0%	0.58
PT, s	8	0.73 (0.20, 1.25)	–	0.006	45%	0.08
APTT, s	6	1.17 (–3.68, 6.02)	–	0.64	92%	<0.00001
D-dimer, mg/L	13	4.33 (2.97, 5.68)	–	<0.00001	92%	<0.00001
CRP, mg/L	11	48.03 (27.79, 68.27)	–	<0.00001	83%	<0.00001
ESR, mm/h	5	7.87 (2.53, 13.21)	–	0.004	51%	0.09
IL-6, pg/mL	3	47.98 (–8.34, 104.29)	–	0.09	97%	<0.00001
Procalcitonin, ng/mL	6	0.23 (0.06, 040)	–	0.007	89%	<0.00001
Serum ferritin, mg/L	3	0.92 (0.67, 1.17)	–	<0.00001	48%	0.15
Fasting blood glucose, mmol/L	4	1.42 (0.68, 2,16)	–	0.0002	0%	0.81
Serum creatinine, μmol/L	15	26.11 (12.61, 39.61)	–	0.0002	93%	<0.00001
SpO_2, %	6	–8.32 (–11.49, –5.15)	–	<0.00001	80%	<0.00001
Imaging features						
Bilateral involvement	5	–	3.33 (1.57, 7.05)	0.002	46%	0.11
Ground-glass opacity	3	–	3.67 (0.85, 15.79)	0.08	63%	0.07
Complications						
ARDS	8	–	62.85 (29.45, 134.15)	<0.00001	47%	0.06
Acute cardiac injury	6	–	25.16 (6.56, 96.44)	<0.00001	73%	0.002
Acute kidney injury	7	–	22.86 (4.60, 113.66)	0.0001	68%	0.005
Septic shock	7	–	24.09 (4.26, 136.35)	0.0003	76%	0.0003

OR, odds ratio; WMD, weighted mean difference; COPD, chronic obstructive pulmonary disease; CHD, chronic heart disease; ALT, alanine aminotransferase; AST, aspartate transaminase; LDH, lactate dehydrogenase; NT-proBNP, amino-terminal pro-brain natriuretic peptide; CK, creatine kinase; CK-MB, creatine kinase-MB; PT, prothrombin time; APTT, activated partial thromboplastin time; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SpO_2, peripheral oxygen saturation; ARDS, acute respiratory distress syndrome.

95% CI: 1.92–4.85; P<0.00001), and smoking (OR =1.32, 95% CI: 1.07–1.62; P=0.01) were significant risk factors for death of COVID-19 patients.

Clinical symptoms

Meta-analysis indicated that dyspnea (OR =5.31, 95% CI: 2.74–10.28; P<0.00001) and expectoration (OR =1.88, 95% CI: 1.39–2.55; P<0.0001) at admission were significant risk factor for death of COVID-19 patients, but fever (OR =1.12, 95% CI: 0.82–1.53; P=0.48), cough (OR =1.02, 95% CI: 0.75–1.39; P=0.90), myalgia (OR =0.91, 95% CI: 0.64–1.31; P=0.62), fatigue (OR =1.47, 95% CI: 0.93–2.34;

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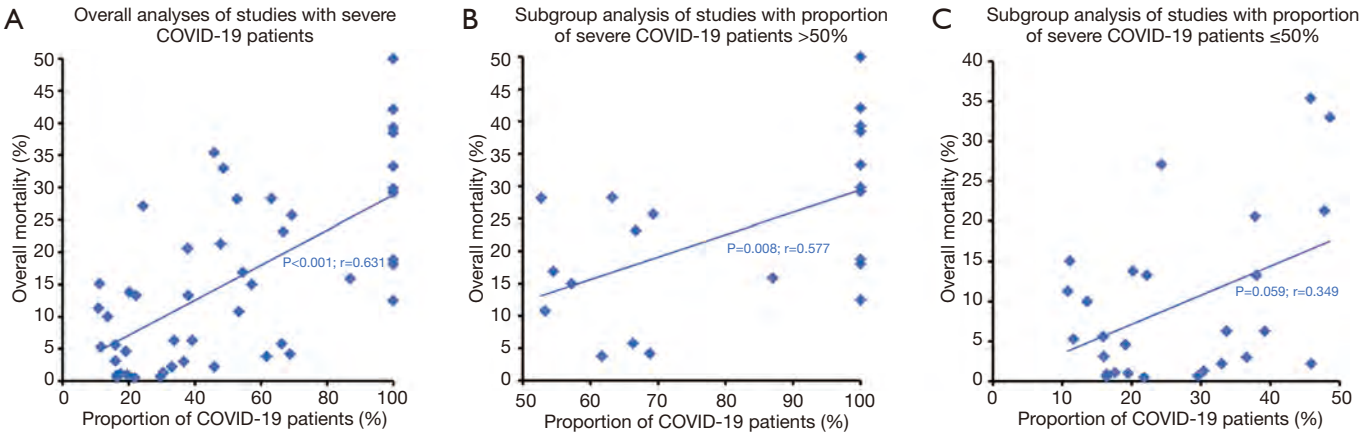

Figure 2 Scattered plots of association of mortality with the proportion of severe COVID-19 patients. (A) Scattered plots showing an increased trend of overall mortality with the proportion of severe COVID-19 patients included. (B) In studies with the proportion of severe patients >50%, an increased trend of mortality with the proportion of severe COVID-19 patients included. (C) In studies with the proportion of severe patients >50%, an increased trend of mortality with the proportion of severe COVID-19 patients included.

P=0.10), hemoptysis (OR =1.25, 95% CI: 0.38–4.14; P=0.72), and diarrhea (OR =1.14, 95% CI: 0.83–1.56; P=0.43) at admission were not significantly associated with mortality.

Laboratory tests

Meta-analysis indicated that increased levels of white blood cells (WBC) (MD =3.23, 95% CI: 2.63–3.83; P<0.00001), alanine aminotransferase (ALT) (MD =6.72, 95% CI: 1.80–11.64; P=0.007), aspartate aminotransferase (AST) (MD =16.78, 95% CI: 11.78–21.78; P<0.00001), total bilirubin (TBIL) (MD =1.59, 95% CI: 0.06–3.11; P=0.04), lactate dehydrogenase (LDH) (MD =288.29, 95% CI: 225.73–350.85; P<0.00001), high-sensitive cardiac troponin I (hs-cTnI) (MD =66.65, 95% CI: 16.94–116.36; P=0.009), D-dimer (MD =4.33, 95% CI: 2.97–5.68; P<0.00001), C-reactive protein (MD =48.03, 95% CI: 27.79–68.27; P<0.00001), and serum creatinine (MD =26.11, 95% CI: 12.61–39.61; P=0.0002) at admission were significant risk factors for death of COVID-19 patients; and decreased levels of albumin (MD =–3.98, 95% CI: –5.75 to –2.22; P<0.0001), lymphocytes (MD =–0.41, 95% CI: –0.52 to –0.30; P<0.00001), hemoglobin (MD =–5.59, 95% CI: –10.64 to –0.54; P=0.03), platelet (MD =–44.37, 95% CI: –53.01 to –37.74; P<0.00001), and peripheral oxygen saturation (SpO_2) (MD =–8.32, 95% CI: –11.49 to –5.15; P<0.00001) at admission were significant risk factors for death of COVID-19 patients. Additionally, hs-cTnI >26.2 pg/mL as a categorical variable (OR =26.80, 95% CI: 8.99–79.94; P<0.00001) at admission was significantly associated with an increased risk of COVID-19 mortality.

Imaging features

Meta-analysis indicated that bilateral involvement was a significant risk factor for death of COVID-19 patients (OR =3.33, 95% CI: 1.57–7.05; P=0.002), but ground-glass opacity was not significantly associated with mortality (OR =3.67, 95% CI: 0.85–15.79; P=0.08).

Complications

Meta-analysis indicated that ARDS (OR =62.85, 95% CI: 29.45–134.15; P<0.00001), acute cardiac injury (OR =25.16, 95% CI: 6.56–96.44; P<0.00001), acute kidney injury (OR =22.86, 95% CI: 4.60–113.66; P=0.0001), and septic shock (OR =24.09, 95% CI: 4.26–136.35; P=0.0003) were significant risk factors for death of COVID-19 patients.

Scattered plots demonstrated an increased trend of overall mortality with the proportion of severe COVID-19 patients included (P<0.001, r=0.631) (*Figure 2A*). In studies with the proportion of severe patients >50%, the trend remained statistically significant (P=0.008; r=0.577) (*Figure 2B*). In studies with the proportion of severe patients ≤50%, the trend remained not statistically significant (P=0.059, r=0.349) (*Figure 2C*).

Discussion

The present meta-analysis suggested that the pooled in-

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hospital mortality of COVID-19 patients was 14%. By comparison, previous meta-analyses reported that the mortality of COVID-19 patients was relatively lower [i.e., 3.2% in the Hu' meta-analysis (16) or 7.7% in our previous meta-analysis (6)]. This discrepancy can be explained by the difference in the severity of COVID-19 patients included among them. Indeed, the proportion of severe COVID-19 patients was higher in the present meta-analysis than the previous meta-analysis [49.6% versus 18% (16)], which might overestimate the overall mortality.

Severe disease status was an independent risk factor for death in COVID-19 patients (17,18). Our subgroup analyses also found that the in-hospital mortality of COVID-19 patients in studies with the proportion of patients with severe disease of >50% was higher than those ≤50% (22.5% versus 7.7%). Severe patients had more prominent laboratory abnormalities [i.e., leukopenia, lymphopenia, elevated levels of C-reactive protein and interleukin 6 (IL-6)] as compared to non-severe patients. Increased levels of C-reactive protein and inflammatory cytokines, such as IL-6, may induce "cytokines storm", thereby aggravating systemic inflammatory response syndrome in patients with severe disease, which may be a driving factor of acute lung injury and ARDS and even death (19-21). The mortality in COVID-19 patients with ARDS was up to 39% (22). We also confirmed that ARDS was associated with a 62.85-fold increase in the risk of death in COVID-19 patients.

The mortality of COVID-19 patients greatly varies among regions. It seems to be the lowest in China (3.1%) and the highest in the United Kingdom (20.8%) and New York State (20.99%) (23). Our subgroup analysis also demonstrated that the in-hospital mortality of COVID-19 patients in Europe and North America were higher than Asia (23.7% and 25.4% versus 10.1%). This might be explained by the aging of patients in Europe and North America. It has been reported that 37.6% of COVID-19 patients are beyond 70 years old in Italy, but only 11.9% in China (24). As shown by our meta-analysis and others (23), age is a significant risk factor of death in COVID-19 patients. In other words, a higher proportion of elderly patients is often in parallel with an increased mortality. This phenomenon could be attributed to the relationship of aging with immune response impairment and chronic inflammation (25) and a high prevalence of comorbidities, such as hypertension, diabetes, and cardiovascular disease, in elderly patients. Obesity is common in Western countries with an increasing prevalence of obesity, and associated with poor prognosis of COVID-19 patients (26,27). Angiotensin-converting enzyme 2 (ACE2) is the receptor of SARS-CoV-2 infection target cells, and ACE2 expression level in adipocytes is higher than that in lung tissue. Obese people have more adipose tissue and therefore higher ACE2 levels. Among the obese population, the renin-angiotensin-aldosterone system is overactive, increasing the production of angiotensin II (26). Elevated angiotensin II levels in COVID-19 patients are related to the severity of lung injury (28), which will increase the risk of death. Additionally, it has been confirmed that obesity increases the risk of cardiovascular disease and its mortality (29). Besides, the difference in public prevention and control strategies of COVID-19 among countries is another major explanation for this variation (30).

Pre-existing comorbidities correlated with an increased risk of mortality in COVID-19 patients, probably because patients with hypertension and diabetes have higher circulating ACE2 levels (31,32). A wider distribution of ACE2 in cardiac epithelial cells as well as respiratory, kidney, and liver is associated with organ failure in patients with SARS (33-35). Therefore, it is postulated that patients with cardiovascular disease are more prone to use angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs), thereby elevating the ACE2 expression and then increasing the risk of SARS-CoV-2 infection and disease progression (36).

Acute cardiac injury was also associated with poor outcomes in COVID-19 patients. Similarly, previous studies suggested that COVID-19 patients with abnormal troponin I, which is a marker of acute myocardial injury, had worse prognosis (37,38). Underlying mechanisms for explaining this phenomenon are as follows. First, the release of proinflammatory cytokines, endothelial dysfunction, and increased oxidative stress can lead to a hypercoagulable state, which is prone to coronary arterial thrombosis and triggers acute coronary syndrome (25). Second, SARS-CoV-2 binds to ACE2 receptor, which is widely expressed in cardiomyocytes, thereby attacking cardiac epithelial cells and inducing cardiac injury (39-41).

Lung pathology of critically ill patients showed occlusion and micro-thrombosis in pulmonary vessels (42). Additionally, severe COVID-19 patients, especially those with sepsis, are often at a hypercoagulable state (20,43). Our study confirmed that D-dimer level, a convenient biomarker of thrombotic events (44), was associated with the mortality of COVID-19 patients.

Of note, non-survival group had a significantly higher

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proportion of male than survival group. This may be attributed to the difference in the levels and types of sex hormones between males and females. Estrogen can modulate the responses of adaptive and innate immunity, which can reduce the susceptibility of females to viral infections (45). On the contrary, males are more susceptible to SARS-CoV-2 infection (46).

Major limitations of the present work should be that all studies included in this meta-analysis were observational with different patient characteristics and follow-up periods, a majority of studies were retrospective, and some of them were of low quality, which might produce the potential selection bias and recall bias. Additionally, the heterogeneity in most of meta-analyses was significant. Although we performed subgroup, meta-regression, and sensitivity analyses, the source of heterogeneity was not clearly identified.

In conclusion, based on the systematic review and meta-analysis, the in-hospital mortality of COVID-19 patients was up to 14%. Older age, male, comorbidities (i.e., hypertension, diabetes, cardiovascular diseases, and respiratory diseases), clinical presentations with dyspnea and expectoration, and laboratory abnormalities (i.e., WBC, AST, ALT, serum creatinine, C-reactive protein, LDH, hs-cTnI, and D-dimer), should be important predictors for mortality of COVID-19 patients. Moreover, patients who develop ARDS, acute cardiac injury, acute kidney injury, and septic shock are at higher risk of death.

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Supplementary

Appendix: References of all included studies

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Table S1 Quality of included studies

References	Quality Score	Selection (☆☆☆☆)				Comparability (☆☆)		Outcome (☆☆☆)		
Aggarwal S (2020)	7	☆	☆	☆	/	☆	☆	☆	/	☆
Barrasa H (2020)	6	☆	–	☆	☆	/	/	☆	☆	☆
Benussi A (2020)	5	☆	☆	☆	/	/	☆	☆	/	/
Bhatraju P (2020)	5	☆	/	☆	/	/	/	☆	☆	☆
Bianchetti A (2020)	4	☆	☆	☆	/	/	/	☆	/	/
Borghesi A (2020)	5	☆	☆	☆	/	/	/	☆	/	/
Buckner F (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Cai Q (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Cecconi M (2020)	5	☆	/	☆	/	/	/	☆	☆	☆
Chen R (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Andrea C (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Cummings M (2020)	6	☆	/	☆	☆	/	/	☆	☆	☆
Deng Y (2020)	4	☆	☆	☆	/	/	/	☆	/	/
Dong X (2020)	5	☆	☆	☆	/	/	/	☆	/	☆
Du R (2020)	7	☆	☆	☆	☆	/	/	☆	☆	☆
Gao L (2020)	7	☆	☆	☆	/	/	☆	☆	☆	☆
Giacomelli A (2020)	7	☆	☆	☆	☆	/	/	☆	☆	☆
Guo T (2020)	4	☆	☆	☆	/	/	/	☆	/	/
Hong K (2020)	7	☆	☆	☆	/	/	☆	☆	☆	☆
Hou W (2020)	5	☆	☆	☆	/	/	☆	☆	/	/
Hu H (2020)	4	☆	☆	☆	/	/	/	☆	/	/
Hu L (2020)	7	☆	☆	☆	/	☆	/	☆	☆	☆
Huang J (2020)	4	☆	☆	☆	/	/	/	☆	/	/
Inciardi R (2020)	7	☆	☆	☆	/	☆	/	☆	☆	☆
Israelsen S (2020)	8	☆	☆	☆	/	☆	☆	☆	☆	☆
Itelman E (2020)	4	☆	☆	☆	/	/	/	☆	/	/
Javanian M (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Ji D (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Klang E cohort1 (2020)	4	☆	☆	☆	/	/	/	☆	/	/
Klang E cohort2 (2020)	4	☆	☆	☆	/	/	/	☆	/	/
Li J (2020)	5	☆	☆	☆	/	☆	/	☆	/	/
Li R (2020)	5	☆	/	☆	/	/	/	☆	☆	☆
Li X (2020)	3	☆	/	☆	/	/	/	☆	/	/
Ling L (2020)	5	☆	/	☆	/	/	/	☆	☆	☆
Liu J (2020)	5	☆	/	☆	/	/	/	☆	☆	☆
Liu K (2020)	6	☆	☆	☆	/	☆	☆	☆	/	/
Liu K (2020)	3	☆	/	☆	/	/	/	☆	/	/
Long L (2020)	7	☆	☆	☆	☆	/	/	☆	☆	☆
Luo X (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Mehta V (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Nikpouraghdam M (2020)	3	☆	/	☆	/	/	/	☆	/	/
Nowak B (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Qi X (2020)	8	☆	☆	☆	/	☆	☆	☆	☆	☆
Renieris G (2020)	7	☆	☆	☆	/	/	☆	☆	☆	☆
Shekerdemian L (2020)	5	☆	/	☆	/	/	/	☆	☆	☆
Sun H (2020)	7	☆	☆	☆	☆	/	/	☆	☆	☆
Tan N (2020)	8	☆	☆	☆	/	☆	☆	☆	☆	☆
Tang N (2020)	7	☆	☆	☆	/	/	☆	☆	☆	☆
Tian S (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Wan S (2020)	7	☆	☆	☆	☆	/	/	☆	☆	☆
Wang D (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Wang K (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Wang Z (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Wei J (2020)	5	☆	☆	☆	☆	/	/	☆	/	/
Wu J (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Xie J (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Xu B (2020)	4	☆	☆	☆	/	/	/	☆	/	/
Yang Q (2020)	4	☆	☆	☆	/	/	/	☆	/	/
Yu Y (2020)	6	☆	/	☆	☆	/	/	☆	☆	☆
Zhang H (2020)	5	☆	/	☆	/	/	/	☆	☆	☆
Zhang J (2020)	4	☆	☆	☆	/	/	/	☆	/	/
Zhang J (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Zhang L (2020)	4	☆	☆	☆	/	/	/	☆	/	/
Zhang Y (2020)	7	☆	☆	☆	/	☆	/	☆	☆	☆
Zhang Y (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Zhao X (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Zhou F (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Zhou X (2020)	4	☆	☆	☆	/	/	/	☆	/	/
An W (2020)	5	☆	☆	☆	/	/	☆	☆	/	/
Chang Z (2020)	7	☆	☆	/	☆	☆	/	☆	☆	☆
Foy B (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Guo F (2020)	7	☆	☆	☆	/	☆	☆	☆	/	☆
Li J (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Luo M (2020)	7	☆	☆	☆	/	☆	/	☆	☆	☆
Fang X (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Yang H (2020)	7	☆	☆	☆	/	☆	/	☆	☆	☆
Yang J (2020)	6	☆	☆	☆	/	/	/	☆	☆	☆
Zhang C (2020)	7	☆	☆	☆	/	☆	/	☆	☆	☆
Zhang F (2020)	7	☆	☆	☆	/	/	/	☆	☆	☆
Zhang G (2020)	7	☆	☆	☆	/	☆	/	☆	☆	☆
Zhang J (2020)	6	☆	☆	☆	/	☆	☆	☆	/	/

/ indicates no star.

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Table S2 Results of meta-regression analyses

Covariates	P value
Sample size (≥100 versus <100)	0.456
Region (Asia versus Europe versus North America)	0.0001
Source of cases (single-center versus multiple-center)	0.756
NOS (>6 versus ≤6)	0.956
Study design (retrospective versus prospective)	0.403
Longest follow-up (>30 versus ≤30 days)	0.624
Proportion of patients with severe disease (>50% versus ≤50%)	<0.001

NOS, Newcastle-Ottawa Scale.

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Table S3 Risk of factors in COVID-19 patients

First author (year)	Risk factors of death in the univariate analysis	Risk factors of death in the multivariate analysis
Benussi A (2020)	Older age, hypertension, qSOFA score, thrombocytopenia, elevated C-reactive protein, and lactate dehydrogenase	qSOFA score, thrombocytopenia, elevated lactate dehydrogenase
Borghesi A (2020)	Older age, male, Brixia score, hypertension, cardiovascular disease, diabetes, oncologic history within the past 5 years, immunosuppressive conditions	Older age, Brixia score, immunosuppressive conditions
Chen R (2020)	Age ≥75, Male, CHD, CVD, COPD, diabetes, hypertension, malignancy, chronic renal diseases, abnormal chest X-ray, Dyspnea, PCT >0.5 ng/mL, LDH ≥250 U/L, AST >40 U/L, ALT >40 U/L, TBIL ≥17.1, creatinine kinase ≥200, creatinine ≥133, D-dimer ≥0.5	Age ≥75, CHD, CVD, dyspnea, PCT >0.5 ng/mL, AST >40 U/L
Andrea C (2020)	Older age, hypertension, heart failure, diabetes, COPD, cancer, CKD, ACEI/ARBs and B-blocker	Older age, heart failure and CKD
Cummings M (2020)	Older age, hypertension, chronic cardiac disease, chronic pulmonary disease, diabetes, higher concentrations of IL-6 and D-dimer	Older age, chronic cardiac disease, chronic pulmonary disease, higher concentrations of IL-6 and D-dimer
Du R (2020)	Age ≥65 years, hypertension, cardiovascular or cerebrovascular diseases, dyspnea, fatigue, sputum production, headache, WBC >10×10^9/L, neutrophil counts >6.3×10^9/L, $CD3^+CD8^+$ T cells ≤75 cell/mL, cardiac troponin I ≥0.05 ng/mL, myoglobin>100 ng/mL, creatinine ≥133 μmol/L, D-dimer ≥0.5 mg/L, PaO_2 ≥80 or <60 mmHg	Age ≥65 years, cardiovascular or cerebrovascular diseases, $CD3^+CD8^+$ T cells ≤75 cell/μL, cardiac troponin I ≥0.05 ng/mL
Gao L (2020)	Older age, male, hypertension, leukocytosis, lymphopenia, elevated NT-proBNP, Myoglobin, creatine kinase-MB, hs-TnI, urea, creatinine, CRP and procalcitonin	Elevated NT-proBNP and procalcitonin, leukocytosis, lymphopenia
Giacomelli A (2020)	Older age, comorbidity, obesity, treated with at least one anti-hypertensive, severe disease, critical disease, anemia, lymphopenia, elevated D-dimer, CRP, creatinine, and creatine kinase	Older age, obesity, critical disease, elevated CRP, creatine kinase
Huang J (2020)	Older age, any comorbidity, lymphopenia, hypoalbuminemia	Any comorbidity, lymphopenia, hypoalbuminemia
Klang E cohort 1 (2020)	BMI ≥40 kg/m^2	Age, BMI ≥40 kg/m^2, congestive heart failure, chronic kidney disease, intubation and mechanical ventilation
Klang E cohort 2 (2020)	Coronary artery disease, congestive heart failure, hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease	Older age, male sex, BMI ≥40 kg/m^2, coronary artery disease, diabetes mellitus, chronic kidney disease, intubation and mechanical ventilation
Mehta V (2020)	Age >65 years, ICU admission, hypertension, chronic lung disease, CAD, CHF, reduced baseline hemoglobin and nadir hemoglobin, leukocytosis, lymphopenia, elevated D-dimer, lactate and LDH	Age >65 years, higher composite comorbidity score, ICU admission, elevated D-dimer, lactate and LDH
Renieris G (2020)	Age ≥64 years, Charlson's comorbidity index ≥3, APACHE II score ≥10, pneumonia severity index ≥11, SOFA ≥4, serum H_2S on day 1 ≥150.44 μM, severe respiratory failure	Serum H2S on day 1 ≥150.44 μM, severe respiratory failure
Sun H (2020)	Older age, Male, SpO_2, increased heart rate and respiratory rate, consciousness disorders, hypertension, previous respiratory diseases, leukocytosis, lymphopenia, elevated NT-proBNP, PCT, hs-TnI, D-dimer, AST, ALT, creatinine, eGFR, and hs-CRP	Older age, leukocytosis, lymphopenia
Tang N (2020)	Older age, male, higher PT, lower platelet count, higher D-dimer, more sepsis-induced coagulopathy	Older age, higher PT, lower platelet count, higher D-dimer
Wang D (2020)	Older age, male, hypertension, diabetes, cardiovascular disease, leukocytosis, thrombocytopenia, elevated neutrophil counts, CK-MB, lactate dehydrogenase, ALT, AST, and creatinine	Older age, male
Wang K (2020)	Older age, hypertension, CHD, elevated neutrophil, hs-CRP, D-dimer, AST, and GFR, decreased SpO_2, lymphopenia	Older age, decreased SpO_2, elevated neutrophil, hs-CRP, and GFR
Xie J (2020)	Age ≥60 years, male, hypertension, dyspnea, SpO_2 ≤90%, leukocytosis, thrombocytopenia, elevated CRP, D-dimer, and neutrophil count	Dyspnea, SpO_2 ≤90%, leukocytosis, elevated neutrophil count, and CRP
Xu B (2020)	Lower T lymphocyte subsets levels (lower T lymphocyte subsets lymphocyte <500/μL, $CD3^+$ T-cell <200/μL, $CD4^+$ T cell <100/μL, $CD8^+$ T cell <100/μL, NK-cell <50/μL, and B-cell <50/μL counts)	Lower T lymphocyte subsets levels (lower T lymphocyte subsets lymphocyte <500/μL, $CD3^+$ T cell <200/μL, $CD4^+$ T cell <100/μL, $CD8^+$ T cell <100/μL, NK-cell <50/μL, and B-cell <50/μL counts)
Zhou F (2020)	Older age, coronary heart disease, diabetes, hypertension, respiratory rate >24/min, lymphopenia, leukocytosis, and elevated ALT, lactate dehydrogenase, hs-TnI, creatine kinase, D-dimer, serum ferritin, IL-6, prothrombin time, creatinine, and procalcitonin, SOFA score, qSOFA score	Age, SOFA score, D-dimer >1
Foy B (2020)	Older age, elevated RDW, lymphopenia, D-dimer	Elevated RDW (>14.5%)
Luo M (2020)	Male, age ≥70 years, use traditional Chinese medicine, clinical classification (severe/critical), hypertension, coronary heart disease, diabetes, tumors, uremia, nucleic acid test (+)	Use traditional Chinese medicine, clinical classification (severe/critical), hypertension, coronary heart disease, diabetes, tumors, uremia
Yang H (2020)	Older age, SpO_2, lymphocyte, myocardial injury, IL-2R >710 U/mL, IL-6 >35 ng/L, IL-10 >9.1 ng/L	Older age, SpO_2, IL-10 >9.1 ng/L
Yang J (2020)	Male, fasting blood glucose ≥7 mmol/L, Elevated lactate dehydrogenase, creatinine, and hydroxybutyrate dehydrogenase	Fasting blood glucose ≥7 mmol/L.
Zhang F (2020)	Decreased SpO_2, elevated creatinine, D-dimer, and hs-TnI	Decreased SpO_2, elevated D-dimer and hs-TnI

qSOFA, quick Sequential Organ Failure Assessment; CHD, coronary heart disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CHF, chronic heart failure; ICU, intensive care unit; ACEI, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CKD, chronic kidney disease; RDW, red blood cell distribution width; IL-6, interleukin-6; NT-proBNP, N-terminal pro-brain natriuretic peptide; CK-MB, creatine kinase-MB; HsTnI, high-sensitivity troponin-I; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; AST, aspartate aminotransferase; TBIL, total bilirubin; Brixia score, chest X-ray scoring system; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure; SpO_2, peripheral capillary oxygen saturation.

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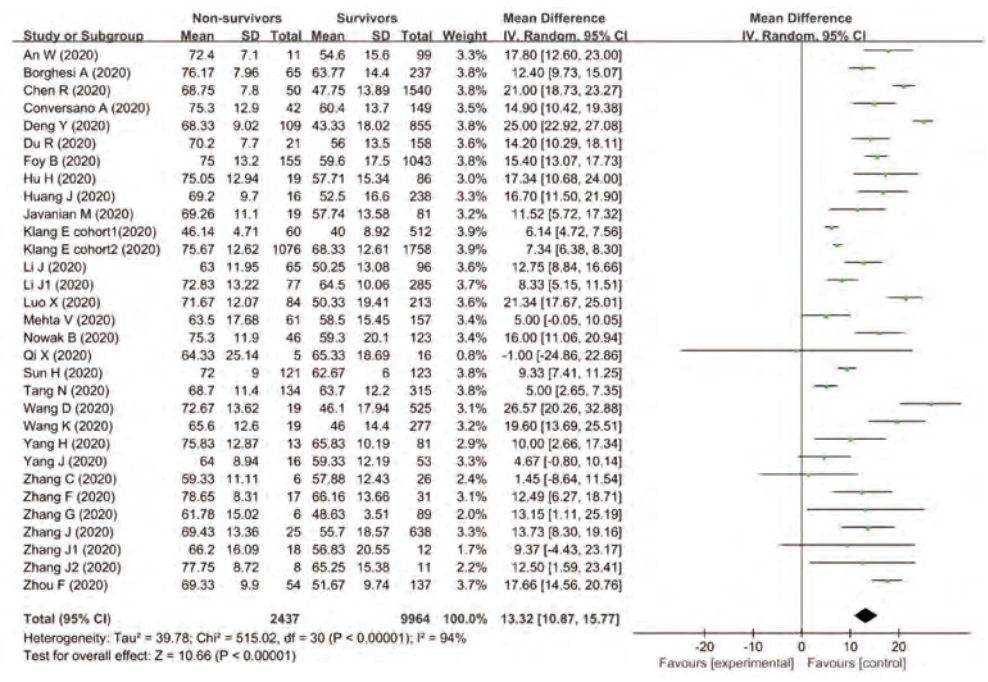
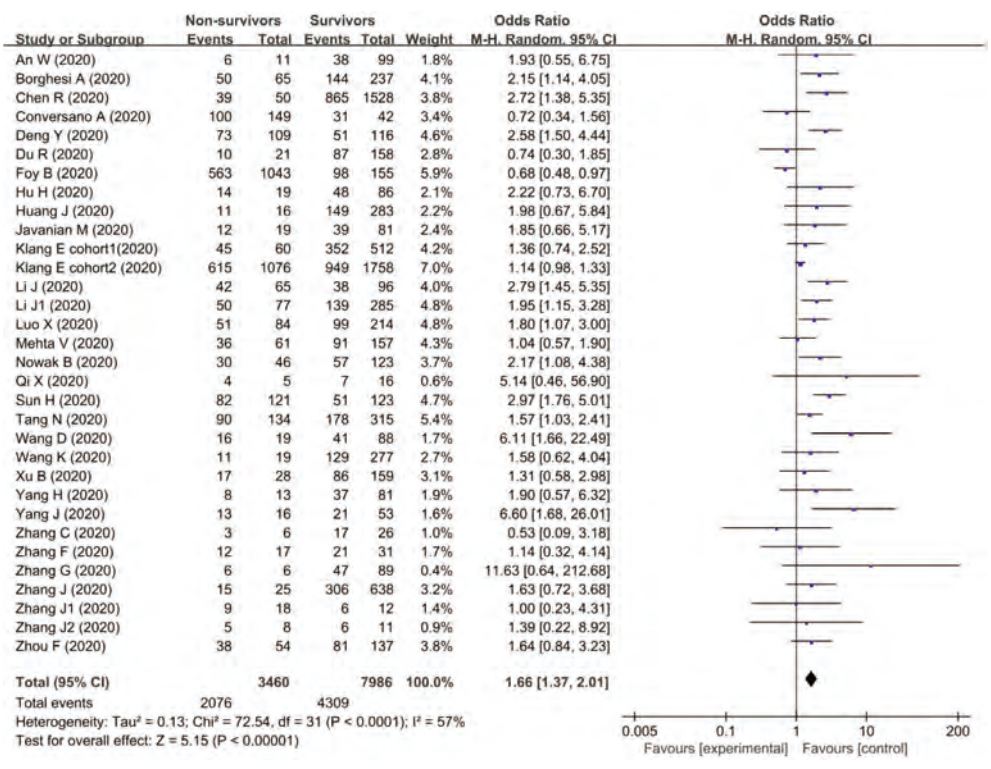
Supplementary material

1. Demographics and clinical characteristics

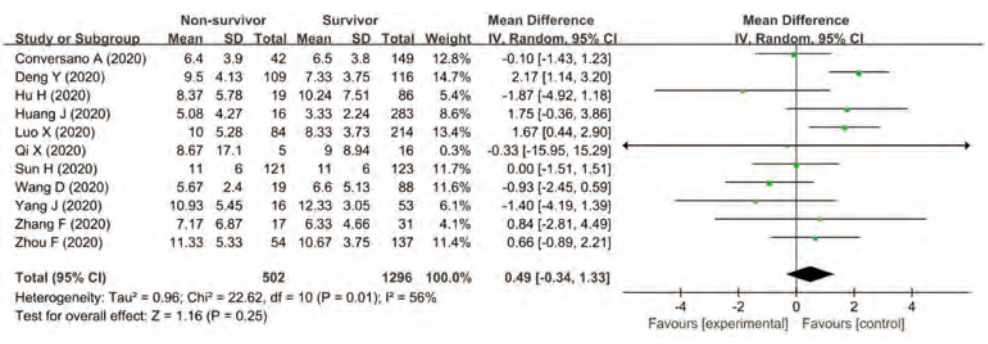
1.1 Old age



1.2 Male

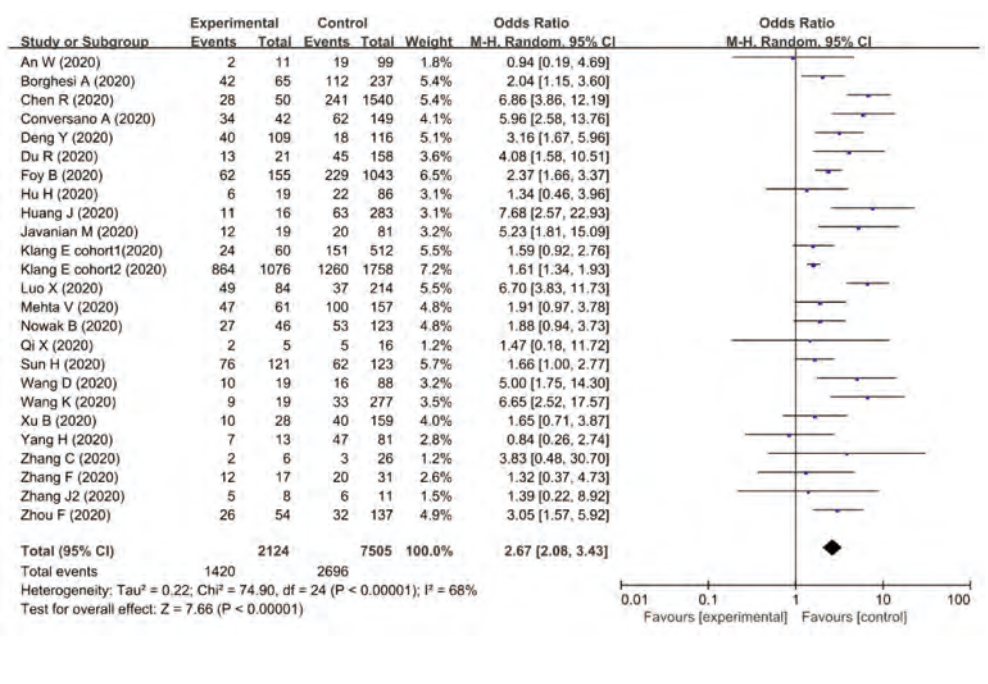


1.3 Time from illness onset to hospital admission, days

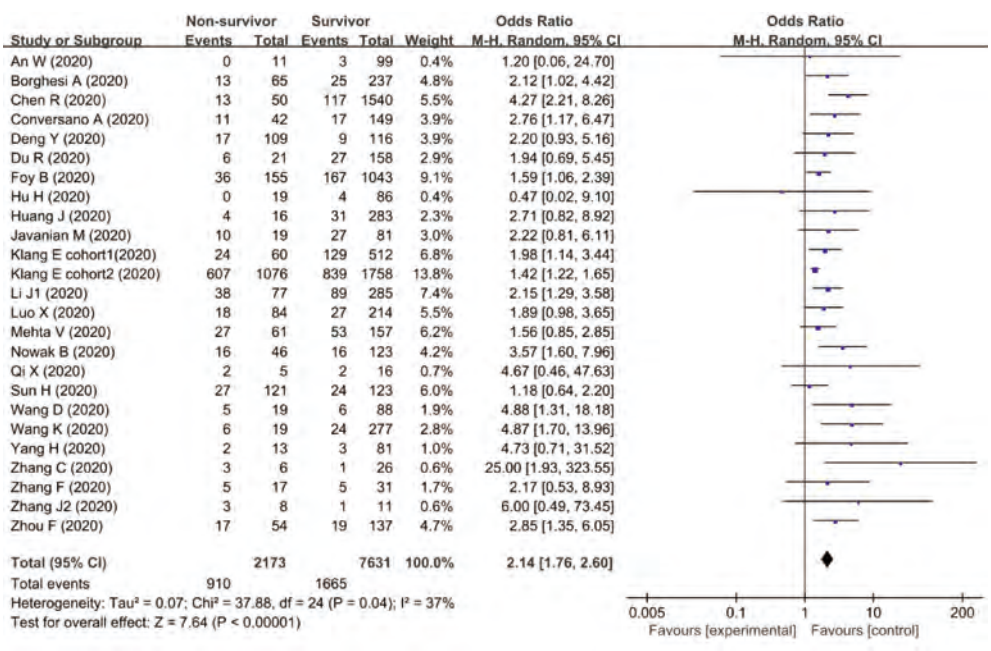


1.4 Comorbidities

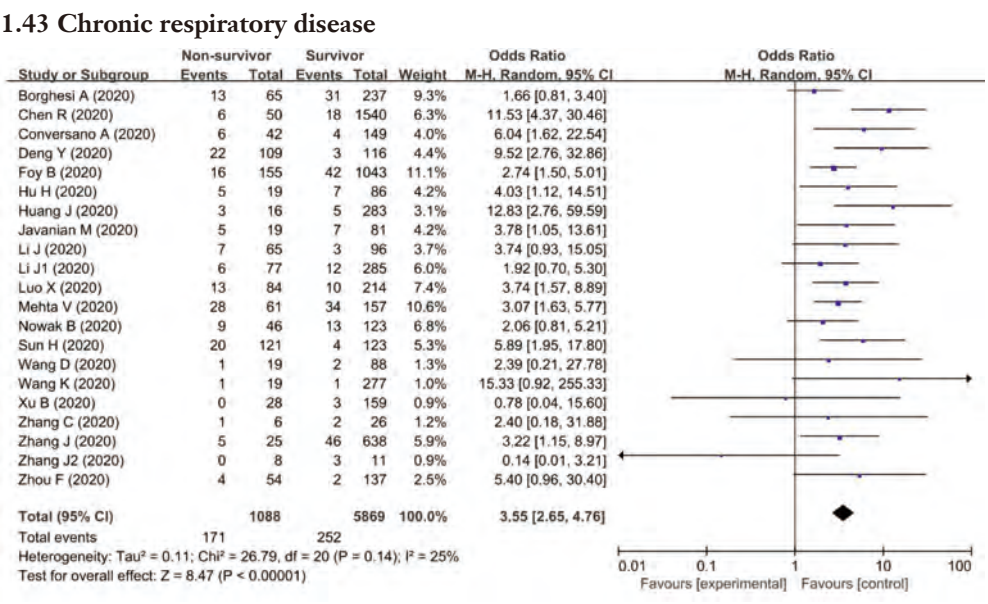
1.41 Hypertension



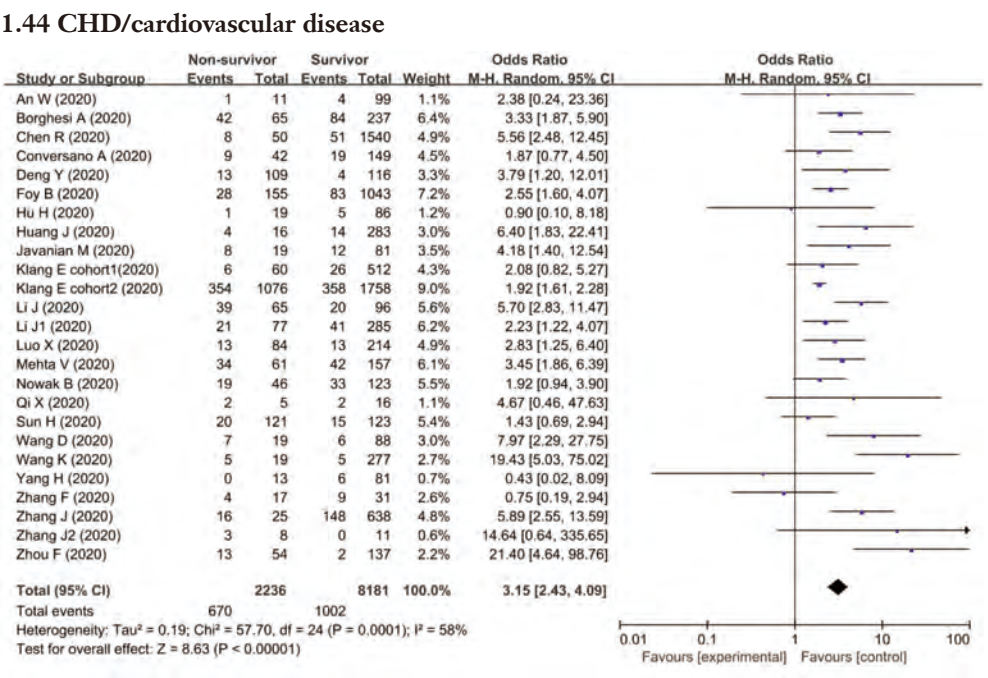
1.42 Diabetes



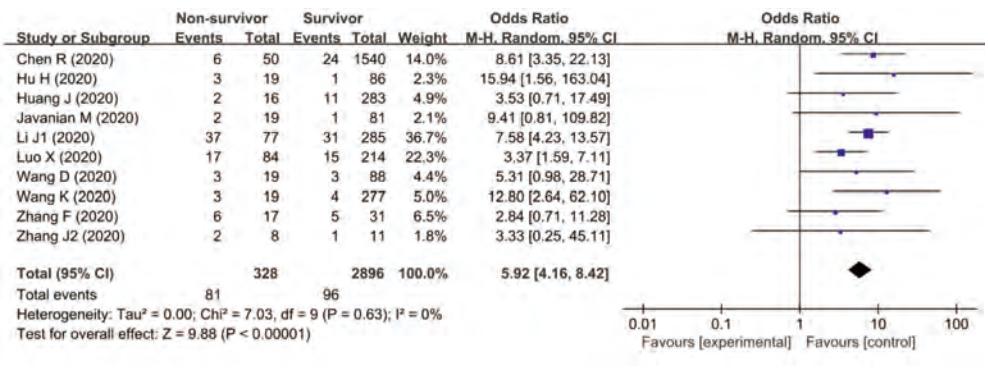
1.43 Chronic respiratory disease



1.44 CHD/cardiovascular disease



1.45 Cerebrovascular disease



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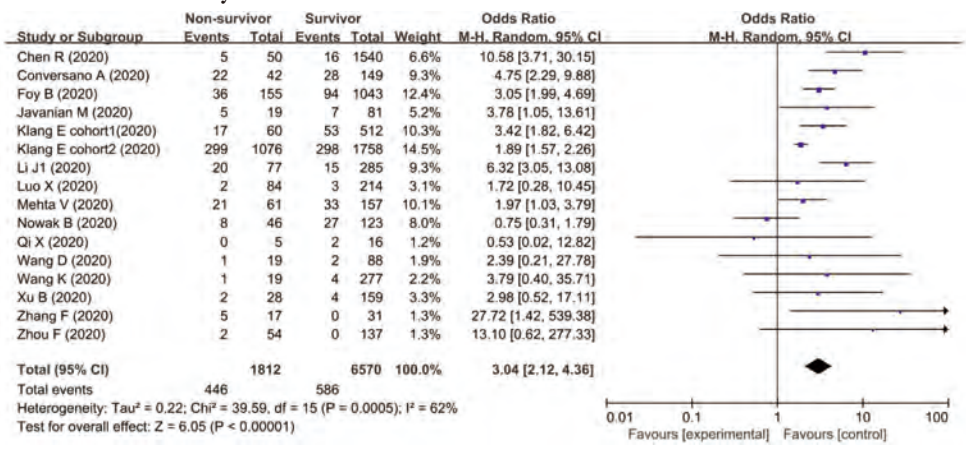
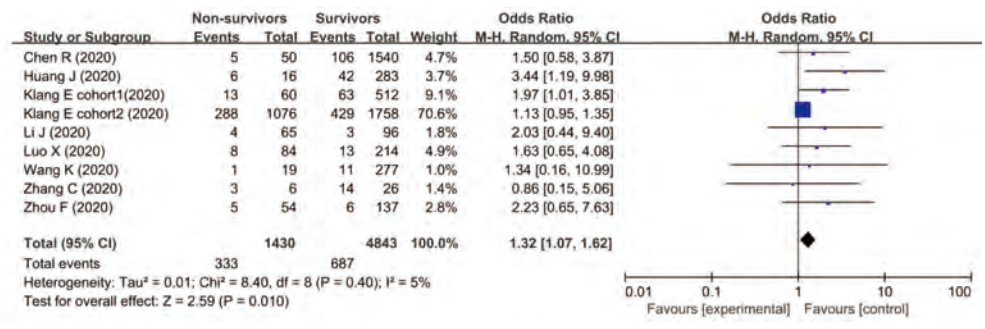
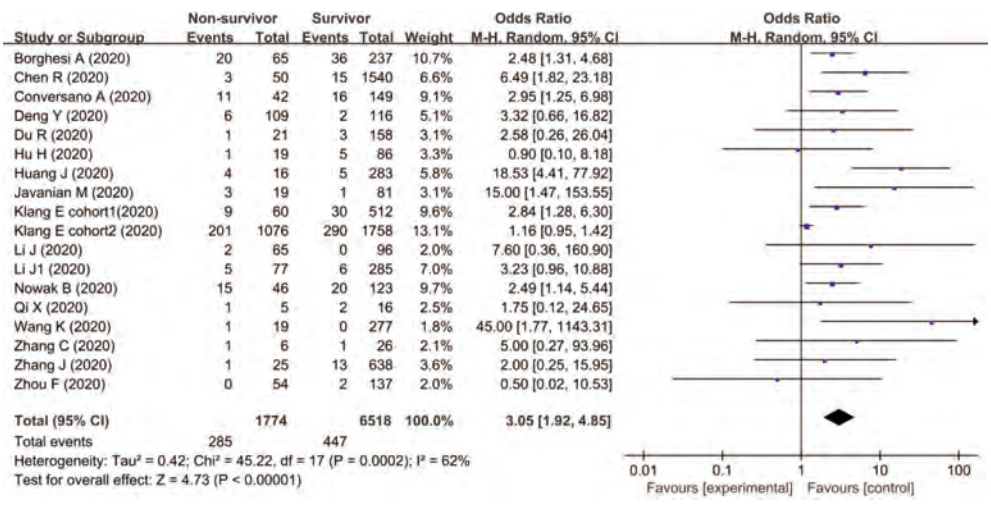
1.46 Chronic kidney disease



1.47 Smoking

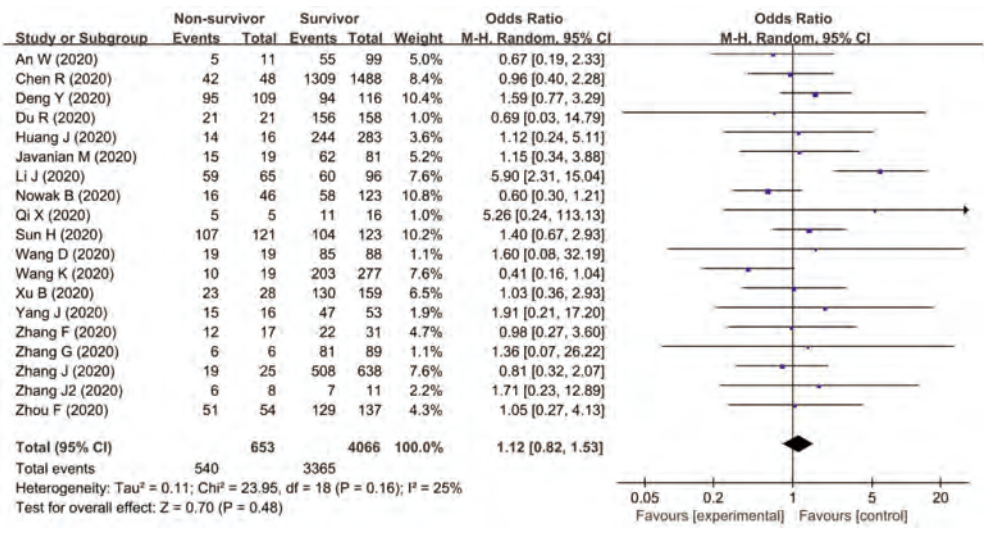


1.48 Cancer

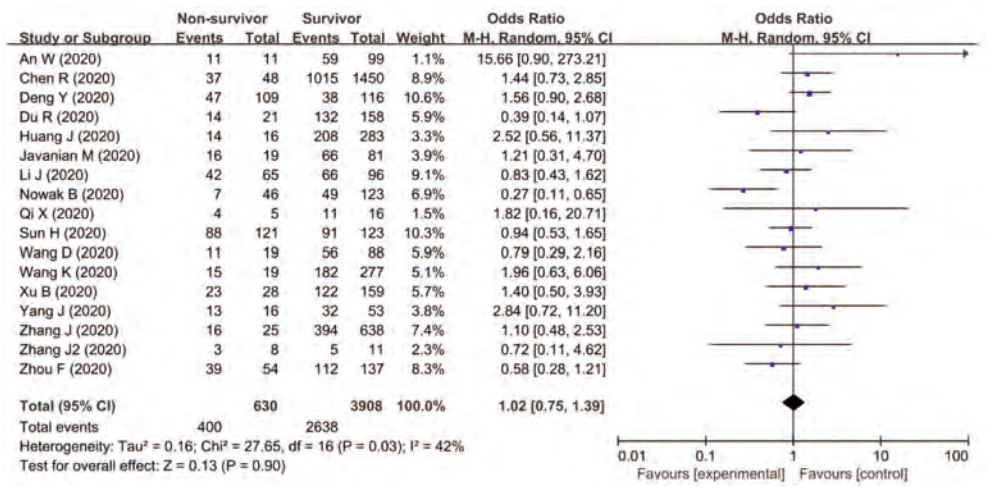


1.5 Clinical symptoms

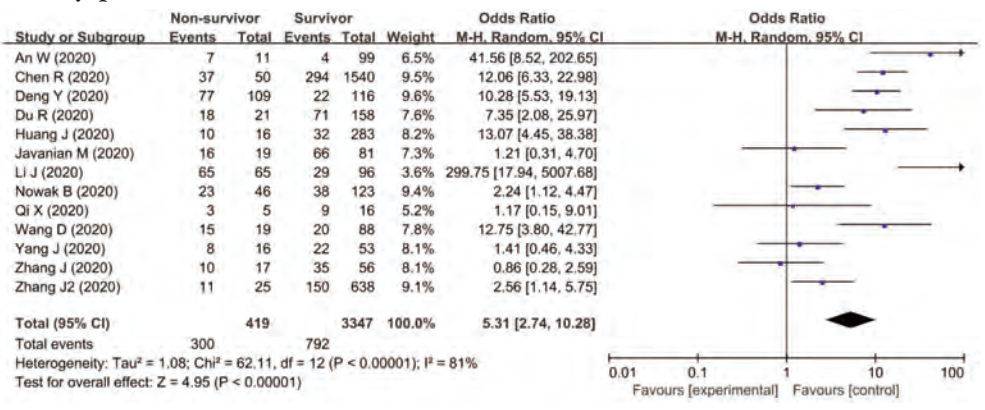
1.51 Fever



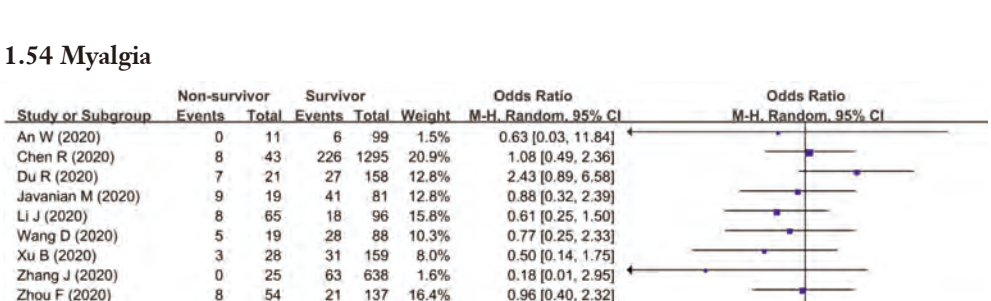
1.52 Cough



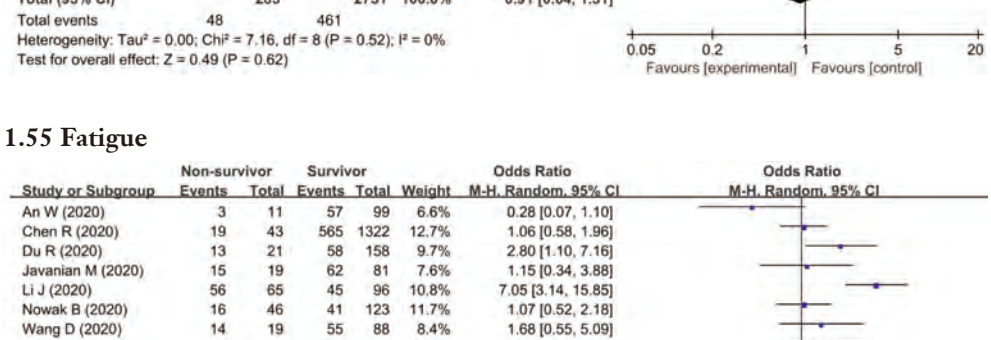
1.53 Dyspnea



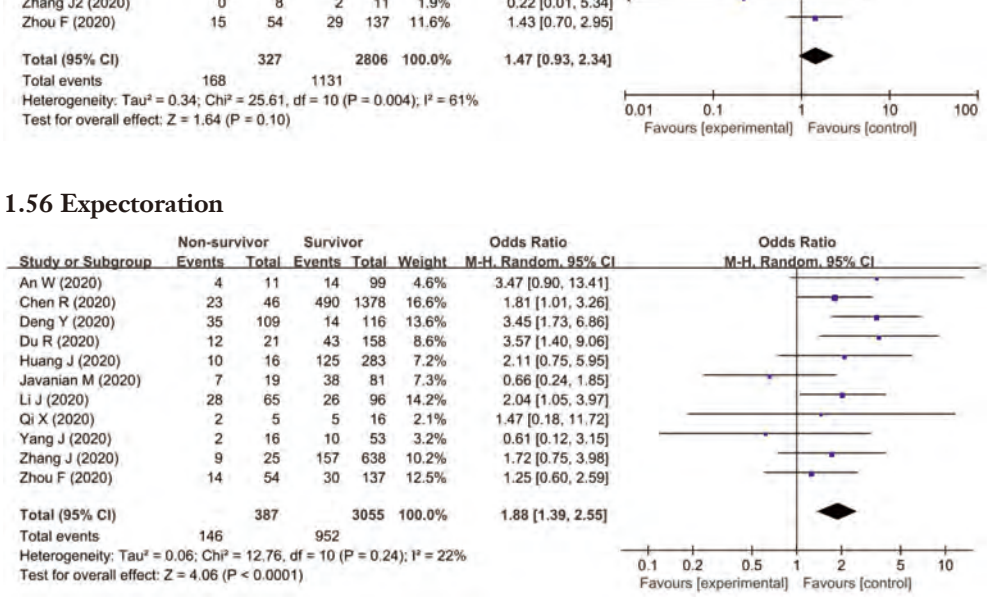
1.54 Myalgia



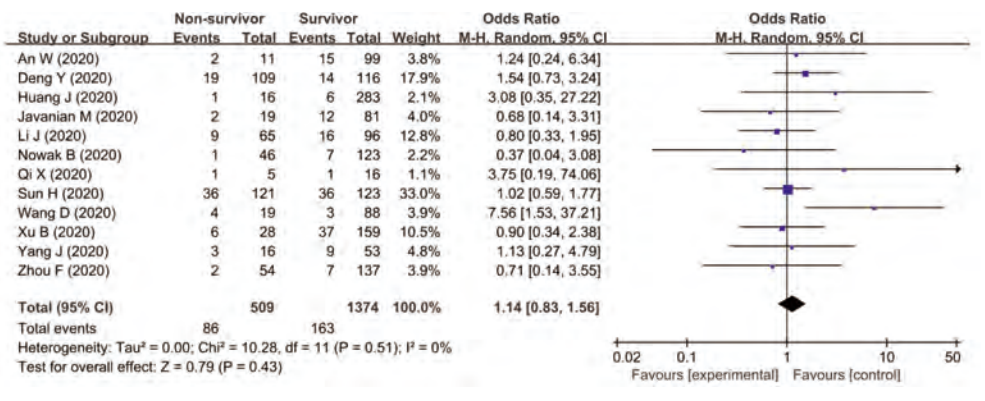
1.55 Fatigue



1.56 Expectoration

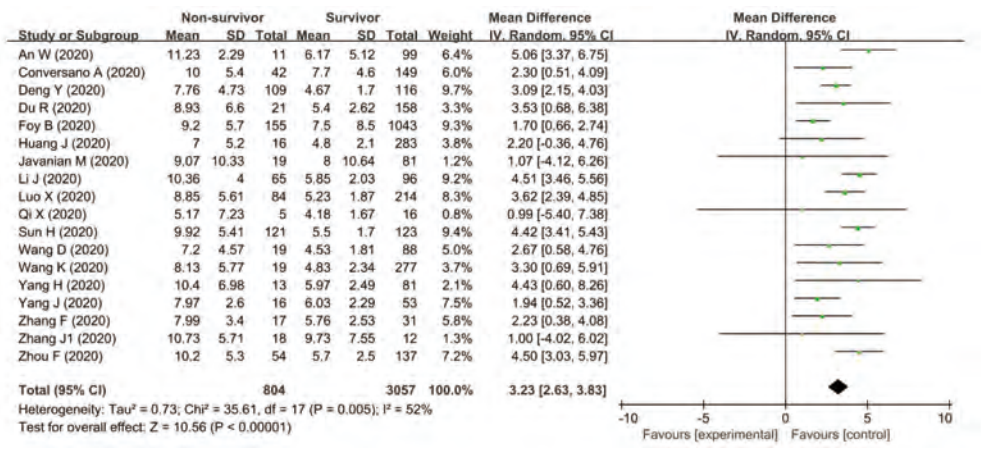


1.57 Diarrhea



2. Laboratory tests

2.1 White blood cell count, $\times 10^9$/L



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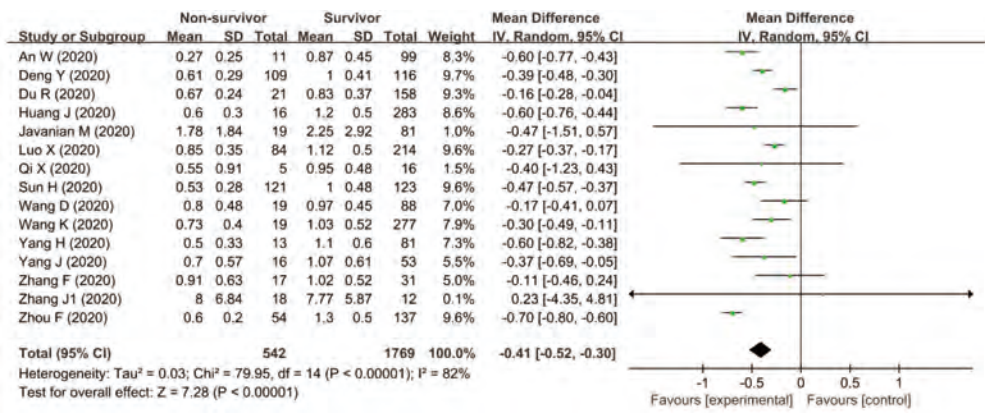
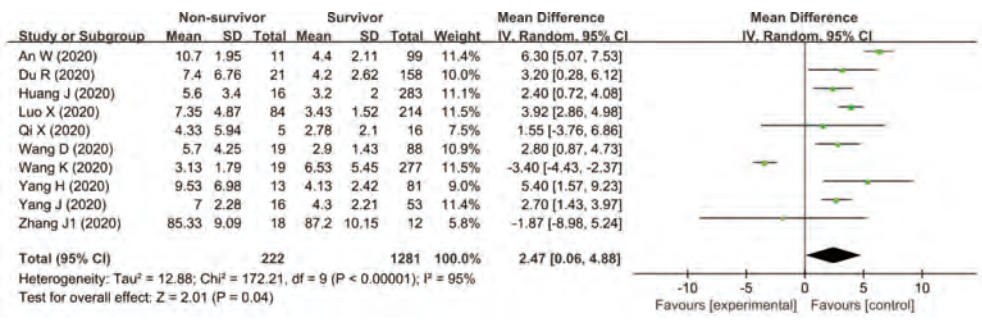
2.2 Lymphocyte count, $\times 10^9$/L

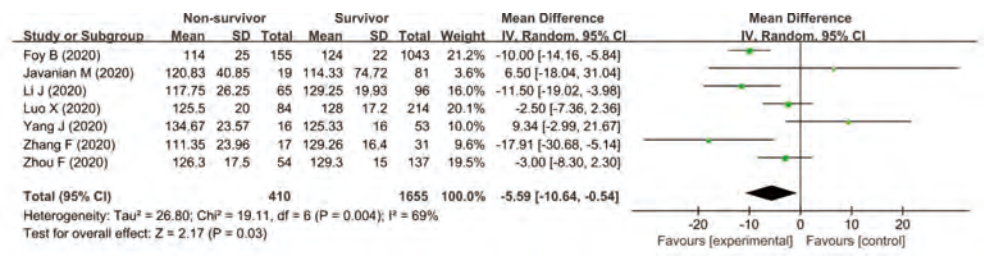


2.3 Neutrophil count, $\times 10^9$/L

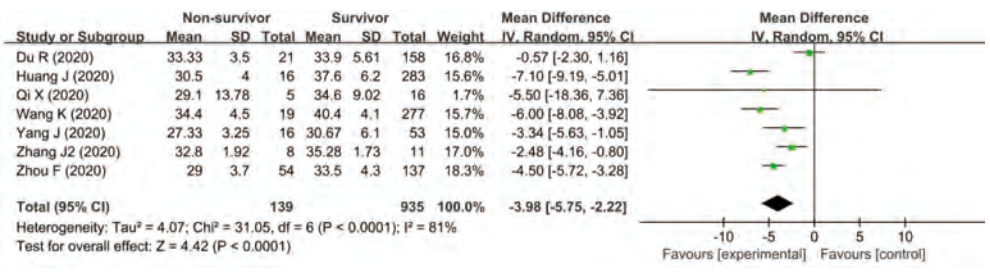


2.4 Platelet count, $\times 10^9$/L

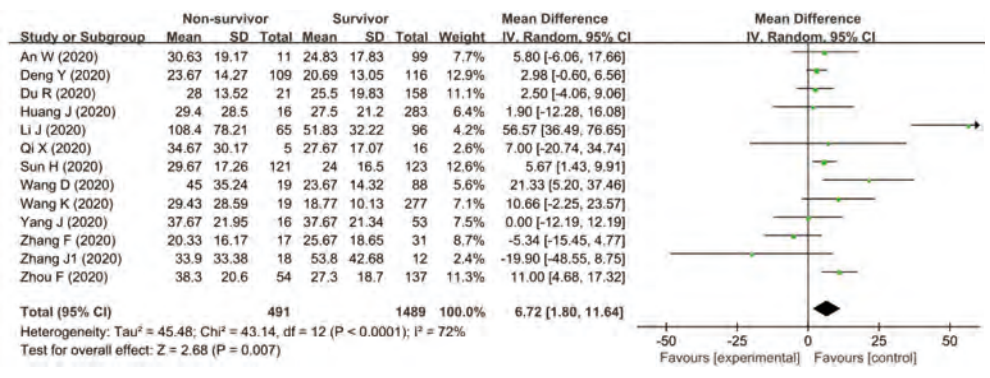
2.5 Hemoglobin, g/L



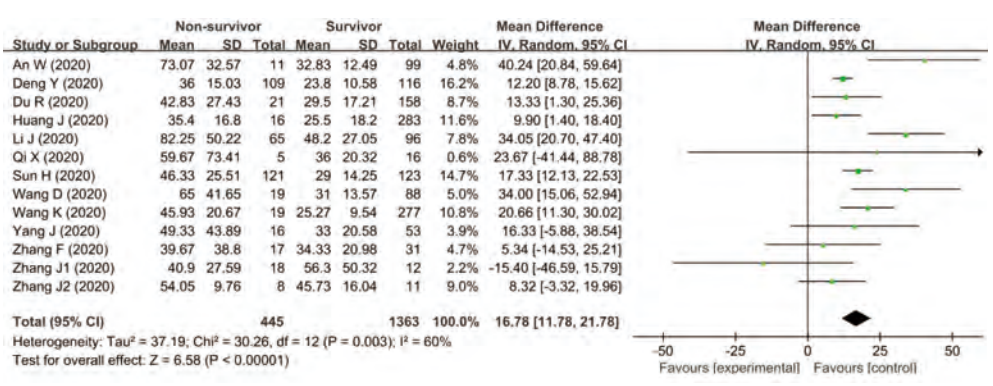
2.6 Albumin, g/L



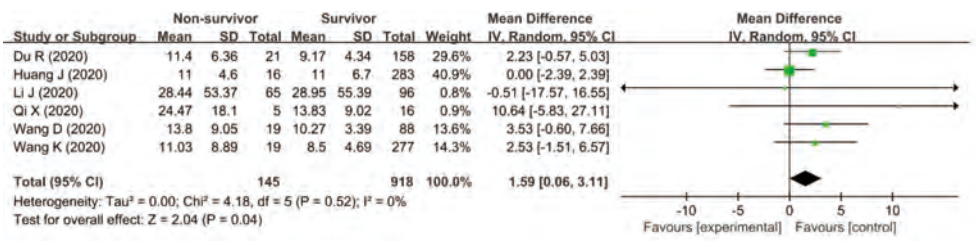
2.7 ALT, U/L



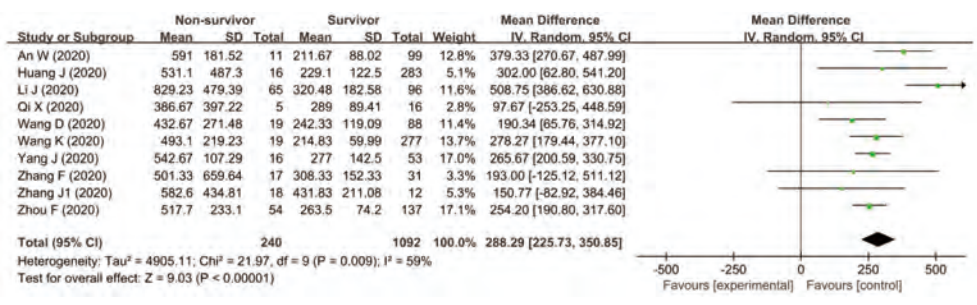
2.8 AST, U/L



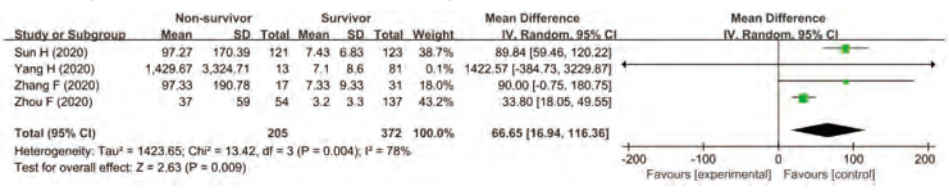
2.9 TBIL, μmol/L



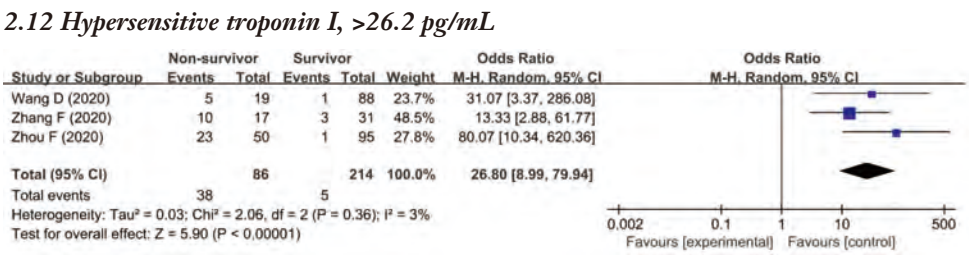
2.10 LDH, U/L



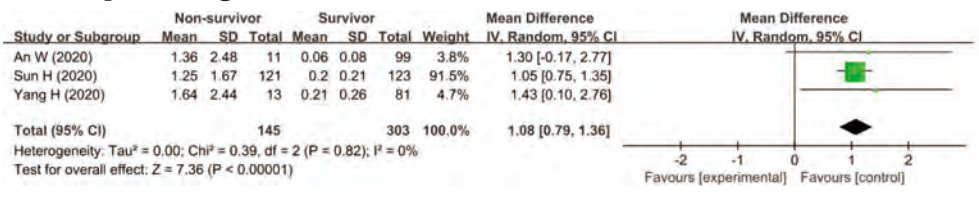
2.11 High-sensitive cardiac troponin I, pg/mL



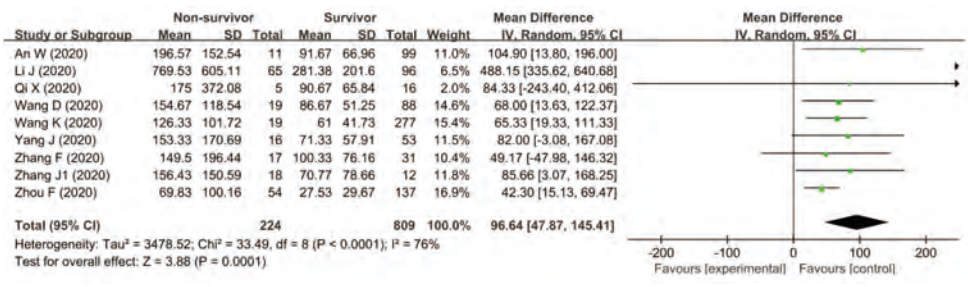
2.12 Hypersensitive troponin I, >26.2 pg/mL



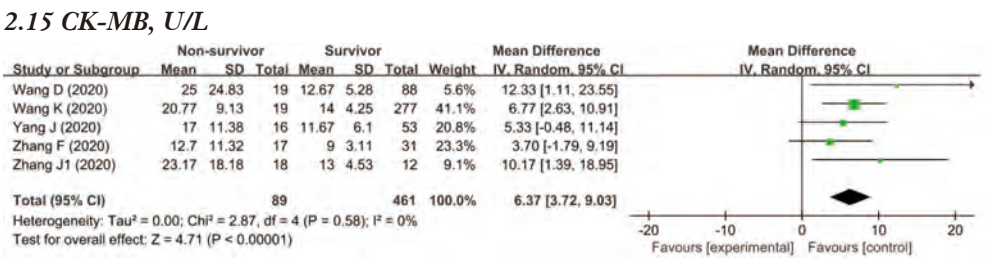
2.13 NT-proBNP, μg/L



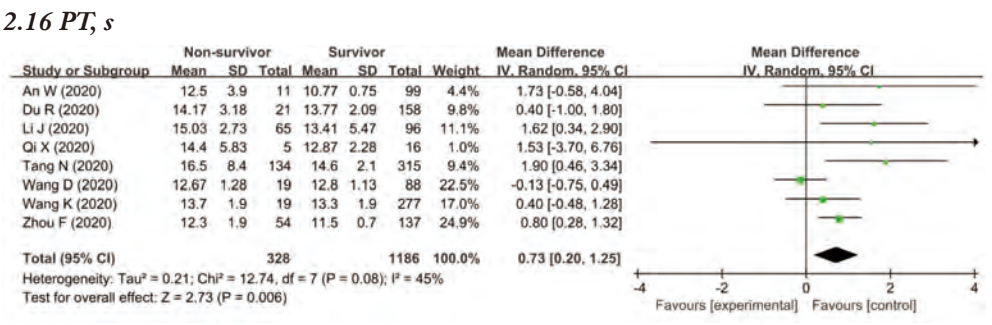
2.14 Creatine kinase



2.15 CK-MB, U/L



2.16 PT, s



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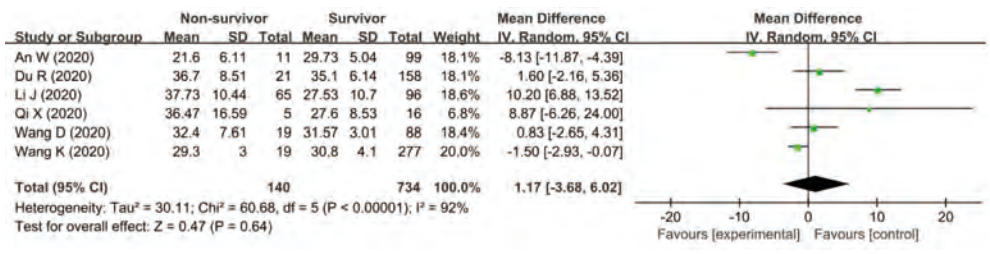
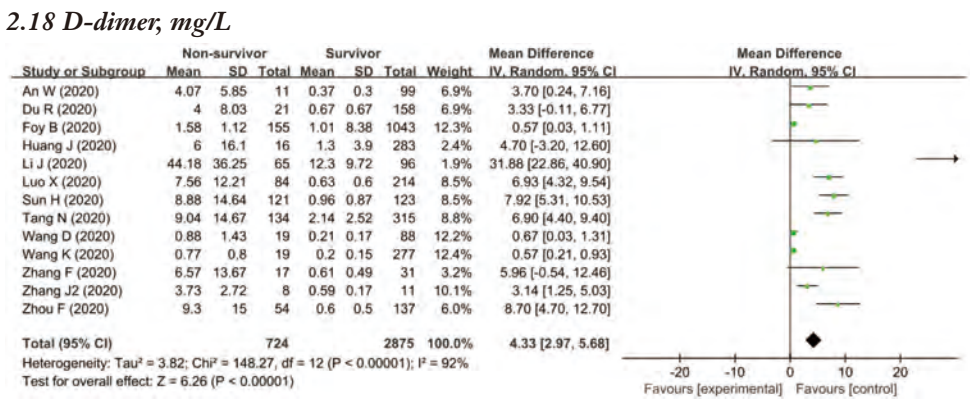
http://dx.doi.org/10.21037/apm-20-2557

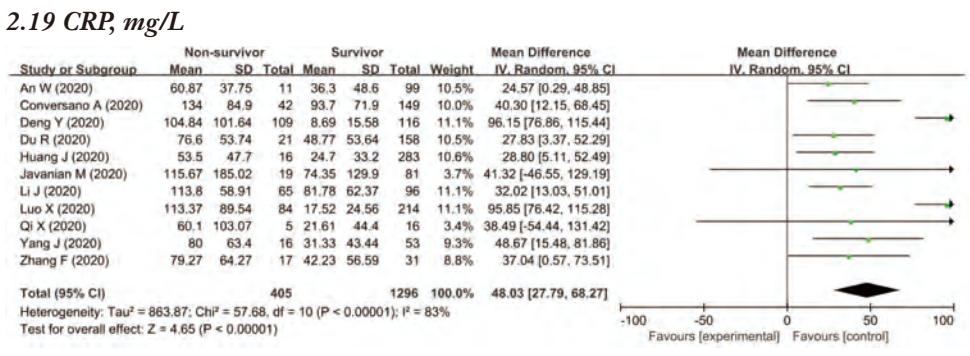
2.17 APTT, s



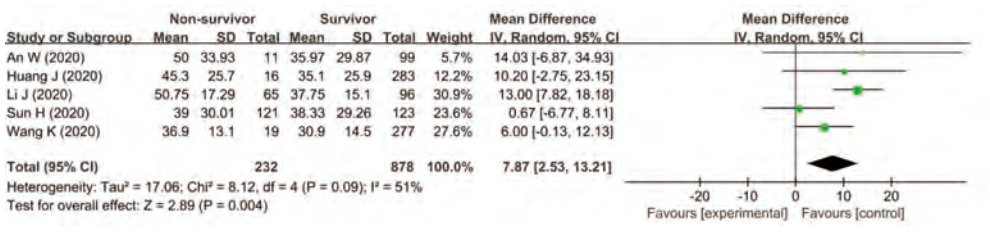
2.18 D-dimer, mg/L



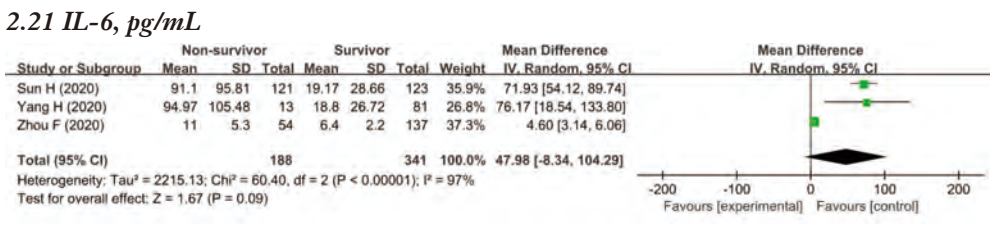
2.19 CRP, mg/L



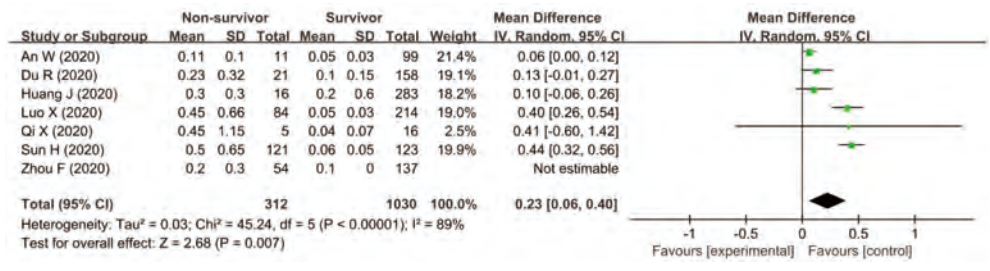
2.20 ESR, mm/h



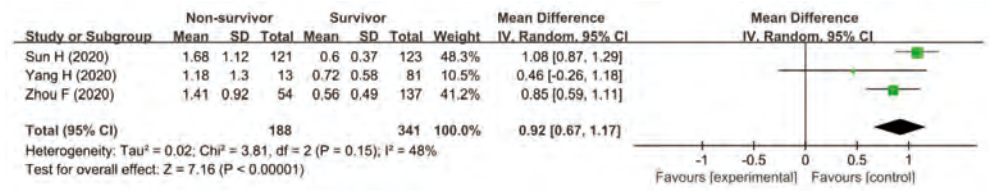
2.21 IL-6, pg/mL



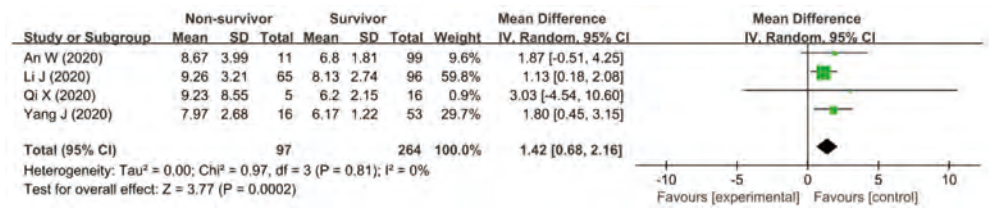
2.22 Procalcitonin, ng/mL



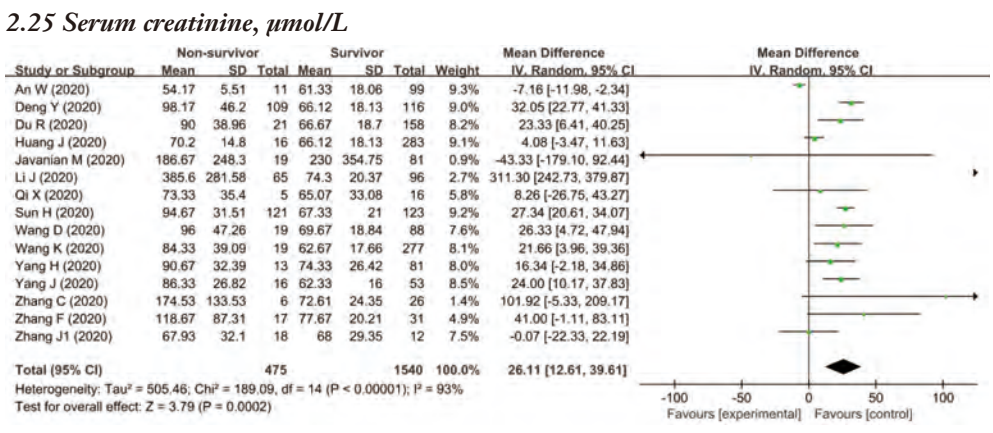
2.23 Serum ferritin, mg/L



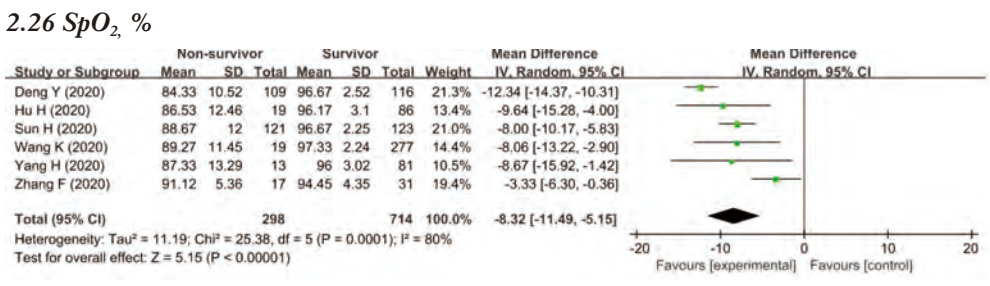
2.24 Fasting blood glucose, mmol/L



2.25 Serum creatinine, μmol/L

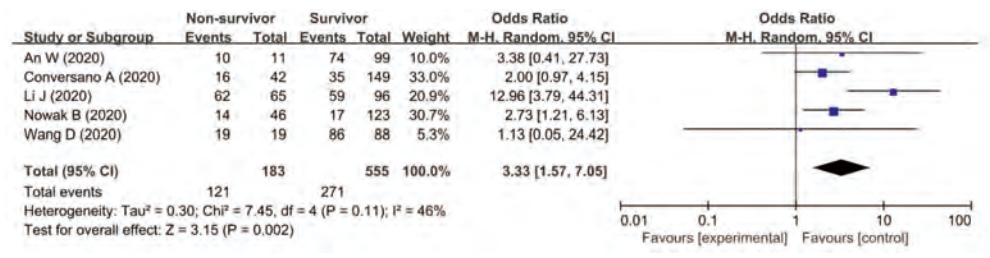


2.26 SpO_2, %

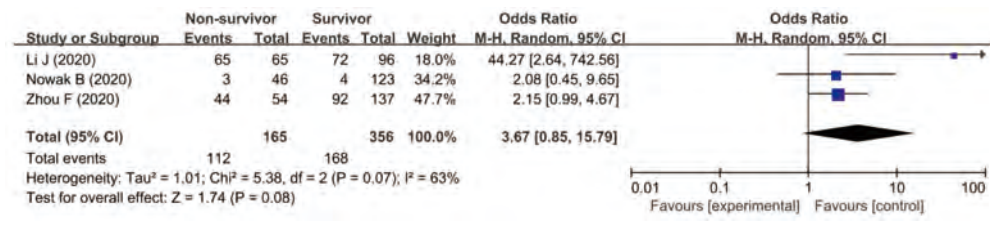


3. Imaging features

3.1 Bilateral involvement

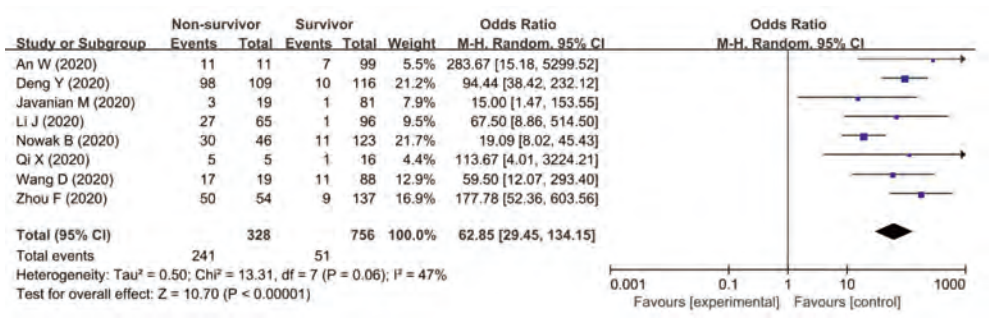


3.2 Ground-glass opacity

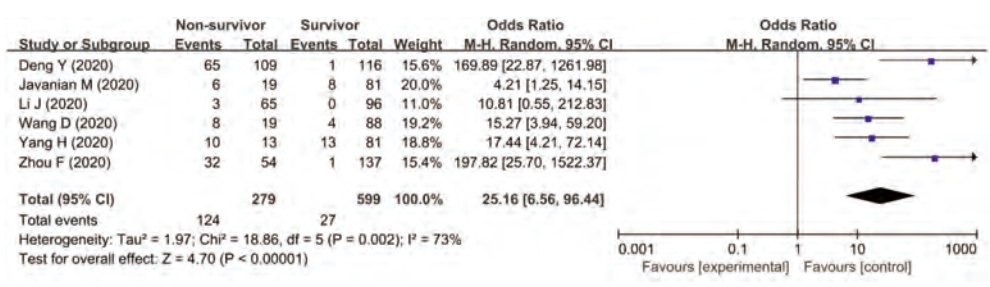


4. Complications

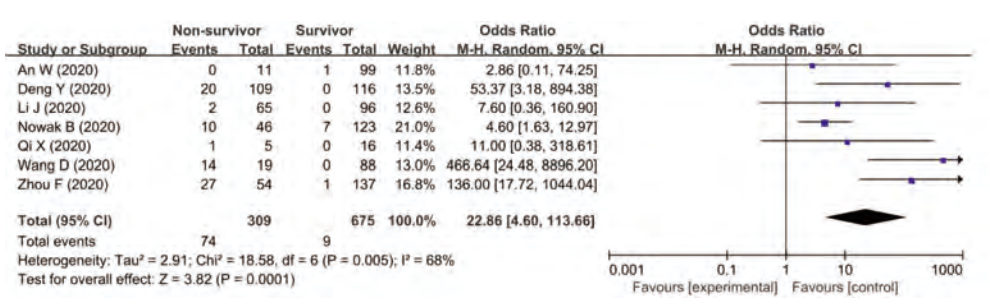
4.1 ARDS



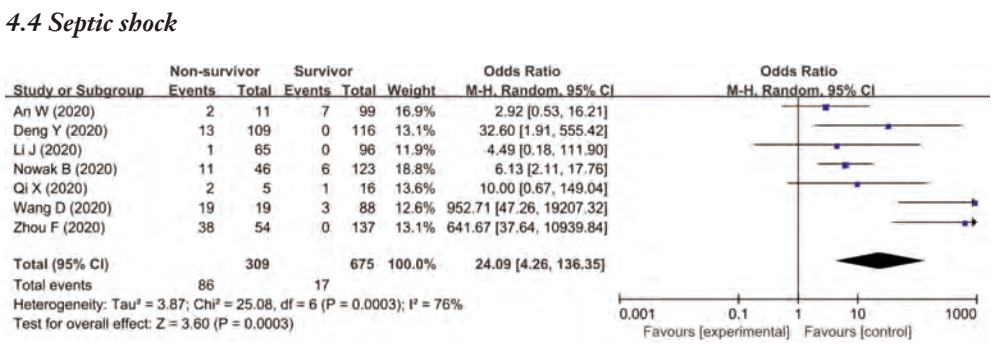
4.2 Acute cardiac injury



4.3 Acute kidney injury



4.4 Septic shock



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