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Risk factors and prognosis for COVID-19-induced acute kidney injury: a meta-analysis

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ABSTRACT

Objective To analyse the incidence, risk factors and impact of acute kidney injury (AKI) on the prognosis of patients with COVID-19.

Design Meta-analysis.

Data sources PubMed, Embase, CNKI and MedRxiv of Systematic Reviews from 1 January 2020 to 15 May 2020.

Study selection Studies examining the following demographics and outcomes were included: patients' age; sex; incidence of and risk factors for AKI and their impact on prognosis; COVID-19 disease type and incidence of continuous renal replacement therapy (CRRT) administration during COVID-19 infection.

Results A total of 79 research articles, including 49 692 patients with COVID-19, met the systemic evaluation criteria. The mortality rate and incidence of AKI in patients with COVID-19 in China were significantly lower than those in patients with COVID-19 outside China. A significantly higher proportion of patients with COVID-19 from North America were aged ≥65 years and also developed AKI. European patients with COVID-19 had significantly higher mortality and a higher CRRT rate than patients from other regions. Further analysis of the risk factors for COVID-19 combined with AKI showed that age ≥60 years and severe COVID-19 were independent risk factors for AKI, with an OR of 3.53, 95% CI (2.92–4.25) and an OR of 6.07, 95% CI (2.53–14.58), respectively. The CRRT rate in patients with severe COVID-19 was significantly higher than in patients with non-severe COVID-19, with an OR of 6.60, 95% CI (2.83–15.39). The risk of death in patients with COVID-19 and AKI was significantly increased, with an OR of 11.05, 95% CI (9.13–13.36).

Conclusion AKI was a common and serious complication of COVID-19. Older age and having severe COVID-19 were independent risk factors for AKI. The risk of in-hospital death was significantly increased in patients with COVID-19 complicated by AKI.

Strengths and limitations of this study

- This study presents the first systematic analysis of the COVID-19 risk factors that lead to acute kidney injury (AKI).
- This study was the first meta-analysis of in-hospital mortality of patients with both COVID-19 and AKI.
- This study included patients with AKI who had been diagnosed according to the Kidney Disease Improving Global Outcomes guidelines to analyse AKI incidence, which may have led to missed diagnoses.
- Since the clinical data collection was based on publications with limited availability, many important risk factors could not be included, such as infection duration and medications used for treatment.

INTRODUCTION

An unexplained acute respiratory disease was detected in Wuhan, Hubei Province, China in December of 2019. On 12 February 2020, the International Committee on Taxonomy of Viruses announced that this new coronavirus was officially classified as SARS-CoV-2. The WHO also announced that the disease caused by SARS-CoV-2 had been officially named COVID-19.[1] As of 15 May 2020, more than 4.4 million COVID-19 cases have been reported in 215 countries and regions worldwide, with a cumulative death toll of more than 300 000. COVID-19 has become a major infectious disease that seriously endangers human health.

COVID-19 is primarily transmitted through respiratory droplets and direct contact.[2 3] Most patients with COVID-19 have dyspnoea as the main clinical manifestation, and some cases may be complicated by heart, kidney, circulatory, liver, nerve and other multisystem injuries.[4–8] These patients may eventually die of diffuse alveolar injury and progressive respiratory failure. The cytokine storm syndrome involved in the pathogenesis of acute respiratory distress syndrome and organ failure during SARS-CoV infection seems to be related to a massive inflammatory reaction. Viral replication in targeted organs, including the kidneys, induces systemic viral sepsis and systemic inflammatory responses, as well as subsequent cell damage in multiple organs. In addition, renal failure in patients with COVID-19 may occur due to rhabdomyolysis, hypoxemia, dehydration, presence of

Table 1 Search strategy

	Search strategy
Databases	Pubmed, Embase, CNKI, MedRxiv
Criteria	Language (in English or Chinese), species (studies on humans)
Data	1 January 2020 to 15 May 2020
#1 (MeSH)	"COVID 19 virus" OR "COVID-19 virus" OR "coronavirus disease 2019 virus" OR "SARS-CoV-2"OR "SARS 2" OR "2019-nCoV" OR "2019 novel coronavirus" OR "Wuhan coronavirus" OR "Wuhan seafood market pneumonia virus"
#2 (Entry terms)	"kidney" OR "renal"
Search	#1 and #2

MeSH, Medical Subject Headings.

underlying diseases and improper administration of non-steroidal anti-inflammatory drugs.[9]

Widely distributed across humans, other mammals and birds, SARS-CoV and SARS-CoV-2 are enveloped RNA viruses that rely on ACE2 as the receptor to infect normal tissues and cells.[10] One study showed that the affinity of the SARS-CoV-2 S protein to ACE2 was 10–20-fold of that of SARS-CoV to ACE2.[11] In 2003, 6.7% of SARS cases were complicated by acute renal impairment, and 91.7% of patients who died from SARS suffered from acute kidney injury (AKI) as a complication.[12] Studies also have shown that patients infected with SARS-CoV-2 had significantly increased serum creatinine (SCr) and hospital mortality after AKI.[13–15] However, another study showed that COVID-19 did not cause AKI, and did not aggravate kidney damage in patients with complication of chronic kidney disease.[16] To understand the incidence of COVID-19 in conjunction with AKI and its impact on prognosis, we systematically analysed the relationships between AKI incidence, demographic characteristics, clinical characteristics and prognosis in patients with COVID-19 to provide references for the diagnosis, treatment and prognosis of patients with COVID-19 complicated by AKI in clinical practice.

METHODS

Search strategy

Articles for this review were identified by comprehensive search in the PubMed, Embase, CNKI and MedRxiv online databases. The search strategy is provided in table 1. The following Medical Subject Heading terms and free words were used: "COVID 19 virus," "COVID-19 virus," "coronavirus disease 2019 virus," "SARS-CoV-2," "SARS 2," "2019-nCoV," "2019 novel coronavirus," "Wuhan coronavirus," "Wuhan seafood market pneumonia virus," "kidney" and "renal." Articles published in English and Chinese between 1 January 2020 and 15 May 2020 were included. The initial search yielded 4232 articles, and after exclusion by two independent reviewers on the basis of screening criteria (language, age range, relevance and non-human studies), the number of articles was reduced to 3316. Seventy-nine articles met all screening criteria (figure 1). We carried out sensitivity analyses to identify possible studies explaining the heterogeneity. The exclusion of each study one at a time did not significantly

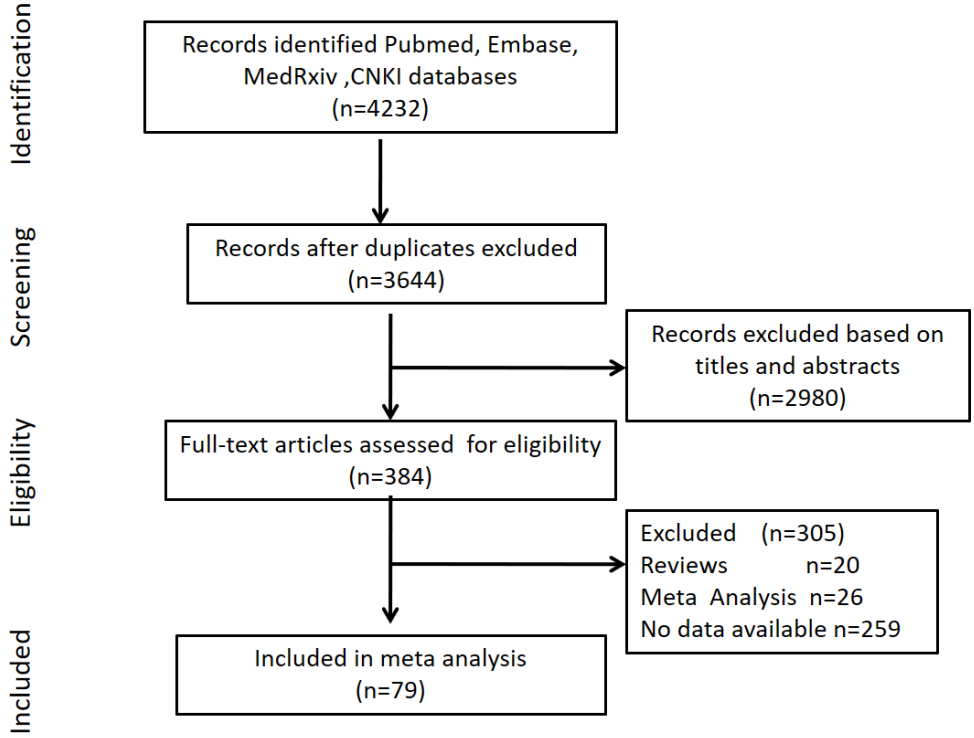

Figure 1 Flow diagram for selection of studies.

Table 2 Demographic and clinical characteristics of patients from 79 COVID-19 studies

ID	Country	Study author(s)	Year	SS (N)	Age in years n (%)	(n/n)	AKI n (%)	CRRT n (%)	Severe disease n (%)	Deaths n (%)
1	China	Bicheng Zhang	2020	82	<60, 16 (19.5) ≥60, 66 (81.5)	54/28	26 (31.7)	NA	NA	82 (100.0)
2	China	Xiaomin Luo	2020	403	<60, 232 (57.6) ≥60, 171 (42.4)	193/210	57 (14.1)	NA	205 (50.9)	100 (24.8)
3	China	Wen Zhao	2020	77	<65, 55 (71.4) ≥65, 22 (28.6)	34/43	2 (2.6)	NA	20 (26.0)	5 (6.5)
4	China	Hua Fan	2020	101	<60, 22 (21.8) ≥60, 89 (78.2)	64/37	8 (7.9)	8 (7.9)	NA	101 (100.0)
5	China	Qiao Shi	2020	101	<60, 26 (25.7) ≥60, 75 (74.3)	41/60	23 (22.8)	5 (5.0)	NA	101 (100.0)
6	China	Jiaqiang Liao	2020	46	<60, 46 (100.0)	24/21	3 (6.5)	NA	1 (2.2)	NA
7	China	Guqin Zhang	2020	221	<65, 159 (71.9) ≥65, 62 (29.1)	108/113	10 (4.5)	5 (2.3)	55 (24.9)	NA
8	China	Yichun Cheng	2020	710	NA	374/336	22 (3.1)	NA	252 (35.5)	89 (12.5)
9	China	Qingxian Cai	2020	298	NA	149/149	17 (5.7)	4 (0.2)	58 (19.5)	NA
10	China	Lin Fu	2020	200	<60, 102 (53.8) ≥60, 98 (46.2)	99/101	45 (22.5)	NA	NA	34 (17.0)
11	China	Yi Yang	2020	36	NA	30/6	8 (22.2)	22 (61.1)	NA	NA
12	China	Wang Wenjun	2020	11	NA	1/10	8 (72.7)	0 (0.0)	11 (100.0)	NA
13	China	Luwen Wang	2020	116	NA	67/49	12 (10.8)	NA	52 (46.8)	67 (60.4)
14	China	Huayan Xu	2020	53	NA	28/25	5 (9.4)	4 (7.5)	NA	NA
15	China	Bo Diao	2020	85	<60, 55 (64.7) ≥60, 30 (36.3)	48/37	23 (27.1)	NA	NA	NA
16	China	Shijiao Yan	2020	168	<65, 135 (80.4) ≥65, 33 (19.6)	81/87	6 (3.6)	NA	36 (21.4)	6 (3.6)
17	China	Di Qi	2020	267	<50, 138 (51.7) ≥50, 129 (48.3)	149/118	4 (1.5)	0 (0.0)	50 (18.7)	4 (1.5)
18	China	Chengfeng Qiu	2020	104	<60, 90 (86.5) ≥60, 14 (13.5)	49/55	2 (1.9)	NA	16 (15.4)	1 (1.0)
19	China	Yang Tao	2020	167	<60, 140 (83.8) ≥60, 27 (16.2)	NA	0	NA	22 (13.2)	NA

Continued

Table 2 Continued

ID	Country	Study author(s)	Year	SS (N)	Age in years n (%)	(n/n)	AKI n (%)	CRRT n (%)	Severe disease n (%)	Deaths n (%)
20	China	Zonghao Zhao	2020	75	<60, 62 (82.7) ≥60, 13 (17.3)	42/33	15 (20.0)	NA	NA	NA
21	China	Yang Xu	2020	69	<60, 42 (60.9) ≥60, 27 (39.1)	35/34	0 (0)	NA	25 (36.2)	1 (1.4)
22	China	Guang Chen	2020	21	<50, 6 (28.6) ≥50, 15 (71.4)	17/4	1 (4.8)	NA	11 (52.4)	NA
23	China	Yonghao Xu	2020	45	NA	29/16	7 (15.6)	4 (8.9)	25 (55.6)	NA
24	China	Xiaofan Lu	2020	244	NA	128/116	51 (20.9)	NA	87 (35.7)	NA
25	China	Zhen Li	2020	193	NA	95/98	55 (28.5)	7 (3.6)	65 (33.7)	32 (16.6)
26	China	Yi Zheng	2020	34	NA	23/11	7 (20.6)	5 (14.7)	15 (44.1)	0
27	China	Ao-Xiang Guo	2020	159	<60, 26 (16.4) ≥60, 133 (83.6)	99/60	9 (5.3)	NA	NA	121 (76.1)
28	China	Xiufeng Jiang	2020	55	NA	27/28	3 (5.5)	NA	8 (14.5)	NA
29	China	Ling Hu	2020	323	<65, 212 (65.6) ≥65, 111 (34.4)	166/157	17 (5.3)	72 (22.3)	146 (45.2)	26 (8.0)
30	China	Guanhua Xiao	2020	287	NA	160/127	55 (19.2)	NA	124 (43.2)	19 (6.6)
31	China	Xuelian Liao	2020	81	<65, 58 (71.6) ≥65, 23 (28.4)	51/30	6 (7.4)	5 (6.2)	NA	NA
32	China	Yan Zhang	2020	258	NA	135/123	7 (2.7)	NA	NA	15 (5.8)
33	China	Xiaobo Yang	2020	52	<60, 25 (48.1) ≥60, 27 (51.9)	35/17	15 (28.8)	9 (17.3)	NA	20 (38.5)
34	China	Chaolin Huang	2020	41	NA	30/11	3 (7.3)	3 (7.3)	NA	6 (14.6)
35	China	Dawei Wang	2020	138	NA	75/63	5 (3.6)	2 (1.4)	NA	NA
36	China	Yingxia Liu	2020	12	<60, 5 (41.7) ≥60, 7 (58.3)	8/4	2 (16.7)	NA	NA	NA
37	China	Xiao Wei Xu	2020	63	<65, 60 (96.8) ≥65, 2 (3.2)	36/27	3 (4.5)	NA	NA	NA
38	China	Nanshan Chen	2020	99	<60, 62 (62.6) ≥60, 37 (37.4)	67/32	9 (9.1)	9 (9.1)	NA	11 (11.0)
39	China	Xu S	2020	355	NA	193/162	56 (15.8)	NA	32 (24.2)	32 (24.2)
40	China	Tie Long Chen	2020	203	NA	108/95	22 (12.3)	NA	NA	19 (9.4)
41	China	Tao Chen	2020	274	<60, 121 (44.2) ≥60, 153 (55.8)	171/103	29 (10.5)	3 (1.1)	NA	113 (41.2)
42	China	Yichun Cheng	2020	701	NA	367/334	36 (5.1)	NA	NA	113 (16.1)
43	China	Yan Deng	2020	225	NA	124/101	20 (8.9)	NA	95 (42.2)	109 (48.4)

Continued

Table 2 Continued

ID	Country	Study author(s)	Year	SS (N)	Age in years n (%)	(n/n)	AKI n (%)	CRRT n (%)	Severe disease n (%)	Deaths n (%)
44	China	Shaoqing Lei	2020	34	NA	14/20	2 (5.9)	1 (2.9)	15 (44.1)	7 (20.6)
45	China	Xun Li	2020	25	NA	NA	12 (48.0)	NA	NA	25 (100.0)
46	China	Tao Chen	2020	54	NA	34/20	29 (53.7)	NA	54 (100)	NA
47	China	Pei G	2020	333	NA	182/151	22 (6.6)	NA	189 (56.8)	29 (8.7)
48	China	Shaobo Shi	2020	416	NA	205/211	8 (1.9)	2 (0.5)	NA	57 (13.7)
49	China	Su H	2020	26	NA	7/19	9 (34.6)	5 (19.2)	NA	26 (100.0)
50	China	Wang D	2020	107	<60, 71 (66.4) ≥60, 36 (33.6)	57/50	14 (13.1)	NA	NA	19 (17.8)
51	China	Yang R	2020	212	<65, 150 (70.8) ≥65, 62 (29.2)	107/105	28 (13.2)	NA	NA	25 (11.8)
52	China	Zhang X	2020	645	NA	328/317	2 (0.3)	0 (0.0)	64 (9.9)	NA
53	China	Xiaobo Feng	2020	114	<65, 52 (45.6) ≥65, 62 (54.4)	71/43	35 (30.7)	2 (1.8)	NA	9 (7.9)
54	China	Rong Yin	2020	106	<65, 20 (18.9) ≥65, 86 (81.1)	64/42	7 (6.6)	3 (2.8)	59 (55.7)	8 (7.5)
55	China	Puyu Shi	2020	134	<65, 114 (85.1) ≥65, 20 (14.9)	65/69	3 (2.2)	1 (0.7)	46 (34.3)	1 (0.7)
56	China	Xiaolong Qi	2020	21	NA	11/10	1 (4.8)	2 (9.5)	NA	5 (23.8)
57	China	Jie Chen	2020	1087	NA	452/635	104 (9.5)	NA	NA	20 (1.8)
58	China	Jianguo Zhang	2020	135	NA	67/68	11 (8.1)	NA	30 (22.2)	12 (8.9)
59	China	Jia Huang	2020	414	<55, 268 (64.7) ≥55, 146 (35.3)	167/247	6 (1.4)	5 (1.2)	92 (22.2)	3 (0.7)
60	Spain	Alberto M Borobia	2020	2226	NA	1074/1152	173 (7.7)	NA	75 (3.3)	460 (20.7)
61	USA	Lili Chan	2020	3235	NA	1868/1367	1406 (43.5)	280 (8.7)	NA	638 (19.7)
62	France	Sébastien Rubin	2020	71	NA	55/16	57 (80.3)	6 (8.5)	71 (100.0)	4 (5.6)
63	Kuwait	Sulaiman Almazeedi	2020	1096	<65, 1016 (92.7) ≥65, 80 (7.3)	888/208	14 (1.3)	5 (0.5)	19 (1.7)	19 (1.7)
64	USA	Sachin J Shah	2020	26	NA	NA	10 (38.5)	1 (3.8)	NA	1 (3.8)
65	USA	Ahmad Khan	2020	6056	<65, 1617 (26.7) ≥65, 4439 (73.3)	2383/3671	528 (8.7)	71 (11.7)	598 (9.9)	367 (9.9)
66	Mexico	Rahul Shekhar	2020	50	NA	NA	13 (26.0)	12 (24.0)	13 (26.0)	10 (20.0)
67	England	Simon Brill	2020	450	<60, 137 (30.4) ≥60, 313 (69.6)	272/178	85 (18.9)	NA	56 (12.4)	173 (38.4)
68	Germany	Gagiannis D	2020	22	NA	12/10	3 (13.6)	NA	11 (50.0)	4 (18.2)

Continued

Table 2 Continued

ID	Country	Study author(s)	Year	SS (N)	Age in years n (%)	(n/n)	AKI n (%)	CRRT n (%)	Severe disease n (%)	Deaths n (%)
69	Spain	Adrián Sánchez-Montalvá	2020	82	NA	52/30	9 (10.0)	0 (0)	14 (17.1)	22 (26.8)
70	USA	Raef Fadel	2020	213	NA	109/114	101 (47.4)	NA	26 (12.2)	39 (18.3)
71	Switzerland	Jean Regina	2020	200	<65, 86 (43.0) ≥65, 114 (57.0)	120/80	30 (15.0)	NA	36 (18.0)	25 (12.5)
72	USA	Leonidas Palaiodimos	2020	200	<65, 104 (52.0) ≥65, 96 (48.0)	98/102	70 (3.50)	16 (8.0)	32 (16.0)	48 (24.0)
73	Iran	Ghasem Janbabaei	2020	18754	<60, 7104 (37.9) ≥60, 11650 (62.1)	NA	300 (16.0)	131 (0.7)	1444 (7.7)	2738 (14.6)
74	Global	Rand Alattar	2020	25	NA	23/2	2 (8.0)	NA	21 (84.0)	3 (12.0)
75	Italy	Spinello Antinori	2020	35	NA	26/9	8 (22.9)	NA	18 (51.4)	4 (11.4)
76	Germany	E M Junga	2020	5	NA	5/0	5 (100.0)	3 (60.0)	5 (100.0)	NA
77	Hong Kong China	Lowell Ling	2020	8	NA	4/4	2 (25.0)	2 (25.0)	8 (100.0)	1 (12.5)
78	Portugal	Madanelo M	2020	122	NA	NA	4 (3.3)	NA	NA	NA
79	USA	Safiya Richardson	2020	5700	NA	3437/2263	1370 (24.0)	225 (3.9)	1281 (22.5)	553 (9.7)

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; NA, not available.

alter the results or the heterogeneity for every factor (online supplemental figure S1–5).

Two experienced physician reviewers performed independent and blinded data abstraction on outcome measures using a standardised approach. The reviewers conducted quality ratings based on the Cochrane risk-of-bias criteria for each study. Figure 1 shows the flow chart for the selection of studies. The selected articles and summaries of their findings were submitted to a professionally trained researcher, En Liu, for review.

Data extraction and data analyses

Retrospective analyses, cross-sectional studies and case reports related to confirmed COVID-19 cases were included, and patients' demographic data, clinical characteristics, comorbidities and epidemiological findings were collected. We excluded articles lacking full text, a clear diagnosis or incidence of AKI, as well as articles that did not meet the requirements (ie, reviews, meta-analyses, guideline recommendations, comments and basic research). The summary data, including authors' names, year of publication, and the age, sex, clinical characteristics and epidemiological findings of included patients, are recorded in the form of tables and figures.

MATLAB_R2016 software was used for meta-analysis. The effects from count data were presented as ORs and their 95% CIs. The Q test was used (the default test level was set at α=0.1) to determine the size of heterogeneity. If Q test results were p>0.1, there was no heterogeneity between studies and a fixed-effects model was used for meta-analysis. If Q test results were p<0.1, there was heterogeneity between studies, and a random-effects model was used for meta-analysis. The test level of the combined effect of meta-analysis was α=0.05.

Definition and interpretation

The disease type, or stage of COVID-19 disease severity, was determined according to the Guidelines for Diagnosis and Treatment of COVID-19 published by NHC China on 18 February 2020 (6th edition). A severe case was defined as having either: (1) a respiratory rate >30/min, (2) an oxygen saturation ≤93% or (3) an arterial oxygen pressure/fractional inspired oxygen ratio ≤300mm Hg. Lung imaging showed that the lesions progressed more than 50% within 24–48 hours.[17]

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

As of 15 May 2020, 79 studies on COVID-19-related AKI from around the world were selected, including 62 studies from Asia, 9 studies from Europe and 7 studies

Table 3 Summary of clinical characteristics of patients with COVID-19

Variable	All patients (n=49 692)
Sex	30 555
Male	16 071 (52.6%)
Female	14 484 (47.4%)
Age	
50 years as the cut-off	288
<50 years	144 (50.0%)
≥50 years	144 (50.0%)
55 years as the cut-off	414
<55 years	268 (64.7%)
≥55 years	146 (35.3%)
60 years as the cut-off	21 340
<60 years	8384 (39.3%)
≥60 years	12 966 (60.7%)
65 years as the cut-off	9050
<65 years	3838 (42.4%)
≥65 years	5212 (57.6%)
Country	49 692
China	11 124 (22.4%)
Non-China	38 568 (77.6%)
Disease type	41 417
Non-severe	35 794 (86.4%)
Severe	5623 (14.6%)
Death	6259/47 078 (13.3%)
Acute kidney injury	
Incidence	5249/49 692 (10.6%)
Non-severe	94/1732 (5.4%)
Severe	177/802 (22.1%)
Death	1403/6357 (22.1%)
CRRT	940/39 561 (2.4%)

CRRT, continuous renal replacement therapy; .

from North America. Table 2 shows the demographic and clinical characteristics of these 79 COVID-19 studies.

Demographic and clinical characteristics

Table 3 shows the demographic and clinical characteristics of 49 692 patients with COVID-19. Among these patients, 52.6% were men, with a 1.11:1 male-to-female ratio. A total of 414 cases were regrouped using the age of 55 years as a cut-off, with 146 (35.3%) of these cases involving patients ≥55 years old. A total of 21 340 cases were regrouped using the age of 60 years as a cut-off, with 12 966 (60.7%) of these cases involving patients ≥60 years old. A total of 9050 cases were regrouped using the age of 65 years as a cut-off, with 5212 (57.6%) of these cases involving patients ≥65 years old. A total of 41 417 patients with COVID-19 were classified based on the severity of COVID-19, of which 14.6% (5623/41 417) were severe cases. Among all 49 692 patients with COVID-19 included in this meta-analysis, the overall incidence of AKI was 10.6% (5249/49 692). The incidences of AKI in non-severe, severe and deceased cases of COVID-19 were 5.4% (94/1732), 22.1% (177/802) and 22.1% (1403/6357), respectively. Additionally, 2.4% (940/39 561) of patients received continuous renal replacement therapy (CRRT).

Comparison of demographic and clinical characteristics of patients with COVID-19 between different regions

This study included 11 124 patients with COVID-19 described in 60 articles from China and 38 568 patients with COVID-19 described in 20 articles from outside China. Table 4 shows the demographic and clinical characteristics of all included patients. The group of patients with COVID-19 from outside China had significantly higher proportions of patients aged ≥60 (62.3% vs 46.5%, p<0.05) and 65 years (62.6% vs 32.3%, p<0.05), and the proportion of those who died was higher than that of the Chinese patients (13.3% vs 12.4%, p<0.05). The incidences of AKI in all patients with COVID-19 and in those with severe COVID-19 were significantly higher outside of China than in China (10.9% vs 9.5%, 41.5% vs 20.4%, respectively, p<0.05). No significant difference was found in the incidence of AKI in patients with mild COVID-19 infection. The incidence of AKI in patients who died from COVID-19 and the rate of CRRT in China were significantly higher than those outside China (35.7% vs 20.7% and 4.4% vs 2.1%, respectively, p<0.05).

This study included 30 974 Asian patients with COVID-19 from 62 articles; 3213 European patients with COVID-19 from 9 articles; and 15 480 North American patients with COVID-19 from 7 articles. Table 5 shows the demographic and clinical characteristics of patients with COVID-19 among different regions. No difference in sex was found among all patients. The population of patients with COVID-19 from North America had significantly higher proportions of patients aged ≥65 years and a higher incidence of AKI (p<0.05) than the Asian patient population. European patients with COVID-19 in Europe had a significantly higher rate of both CRRT and mortality than patients with COVID-19 from the other regions.

Analysis of risk factors for COVID-19 in conjunction with AKI

Eight studies investigated the risk factors for AKI in COVID-19, and no heterogeneity was found among the studies. The use of a fixed-effects model to combine the data showed that age ≥60 years old and having severe infection were independent risk factors for AKI during COVID-19 infection, with ORs of 3.53 (95% CI (2.92–4.25), p<0.001) and 6.07 (95% CI (2.53–14.58), p<0.001), respectively. The use of a random-effects model to combine the studies showed no correlation between male sex and incidence of AKI in patients with COVID-19, with an OR of 1.36 (95% CI (0.84–2.20), p=0.21). However, the probability of AKI complications in male patients with

Table 4 Comparison of clinical characteristics between Chinese and non-Chinese patients with COVID-19

Variable	Patients from China (n=11 124)	Patients from non-Chinese countries (n=38 568)	X^2	P value
Sex	10 932	19 624		
Male	5649	10 422	5.790	0.016
Female	5283	9202		
Age				
50 years as the cut-off	288	NA		
<50 years	144	NA	NA	NA
≥50 years	144	NA		
60 years as the cut-off	2136	19 204		
<60 years	1143	7241	201.320	<0.001
≥60 years	993	11 963		
65 years as the cut-off	1499	7552		
<65 years	1015	2823	471.130	<0.001
≥65 years	484	4729		
Death	1056/8527	5108/38 441	5.000	0.025
Acute kidney injury				
Incidence	1052/11 124	4188/38 568	17.980	<0.001
Non-severe	80/1540	14/192	1.460	0.227
Severe	150/737	27/65	15.590	<0.001
Death	206/577	1197/5780	68.560	<0.001
CRRT	190/4286	750/35 275	87.680	<0.001

CRRT, continuous renal replacement therapy; NA, not available.

Table 5 Comparison of clinical characteristics among different regions

Variable	Asia (n=30 974)	Europe (n=3213)	North America (n=15 480)	P value
Sex	11 998	3091	15437	
Male	6507	1616	7918	0.148
Female	5491	1475	7519	
Age				
60 years as the cut-off	20 900	489	NA	
<60 years	8247	137	NA	<0.001
≥60 years	12 653	313	NA	
65 years as the cut-off	2676	200	7347	
<65 years	2047	86	1721	<0.001
≥65 years	629	114	4534	
Death	4392/28 624 (15.3%)	692/3086 (22.4%)	1656/15 480 (10.6%)	<0.001
Acute kidney injury				
Incidence	1323/30 974 (4.3%)	374/3213 (11.6%)	3498/15 480 (22.6%)	<0.001
Non-severe	84/1572 (5.3%)	8/146 (5.5%)	2/14 (14.0%)	0.338
Severe	154/745 (20.7%)	13/26 (50.0%)	10/31 (32.3%)	<0.001
Death	226/678 (33.3%)	97/330 (29.4%)	395/5349 (7.4%)	<0.001
CRRT	326/24 136 (1.4%)	9/158 (5.7%)	605/15 276 (4.0%)	<0.001

CRRT, continuous renal replacement therapy; NA, not available.

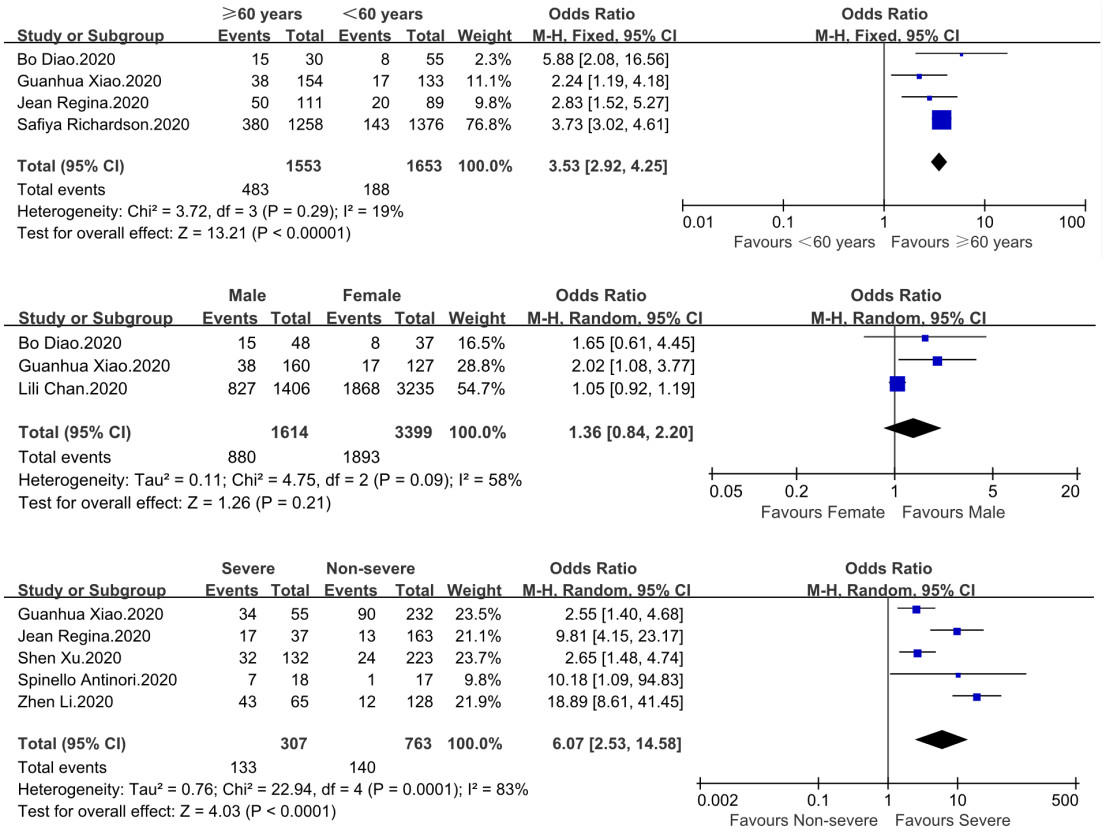

Figure 2 Forest plot showing the subgroup analysis of AKI risk factors. (A) The Q test showed p>0.1, indicating no heterogeneity existed between studies. The fixed-effects model was used to combine the data, with an OR of 3.53 (95% CI (2.92–4.25), p<0.001), suggesting that age was a risk factor for AKI; the older the patient, the higher the risk of AKI. (B) The Q test showed p<0.1, indicating heterogeneity existed between studies. The random-effects model was used to combine the data, with an OR of 1.36 (95% CI (0.84–2.20), p=0.21) and no statistical significance, suggesting that being man had no significant correlation with the incidence of AKI in patients with COVID-19, but the probability of AKI in male patients with COVID-19 was higher than that of female patients with COVID-19. (C) The Q test showed p>0.1, indicating no heterogeneity existed between studies. The fixed-effects model was used to combine the data, with an OR of 6.07 (95% CI (2.53–14.58), p<0.001), suggesting that severe COVID-19 was a risk factor for AKI. Patients with severe COVID-19 had a higher risk of developing AKI than patients with non-severe COVID-19. AKI, acute kidney injury.

COVID-19 was higher than that in female patients with COVID-19 (figure 2).

Incidence of need for CRRT during COVID-19 infection

Thirty-eight studies reported the administration of CRRT to 39 561 patients, but there was no statistical heterogeneity among these studies (p>0.1). Nine studies reported administration of CRRT to 6795 patients. The rate of CRRT in severe COVID-19 cases was significantly higher than the rate in non-severe COVID-19 cases, with an OR of 6.60, 95% CI (2.83–15.39) (figure 3). Only one

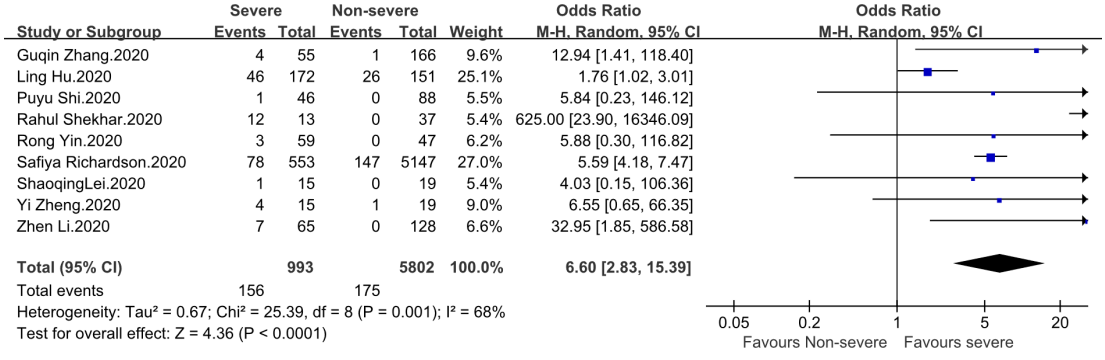

Figure 3 Forest plot showing the subgroup analysis of patients requiring CRRT during COVID-19 infection. The Q test showed p>0.1, indicating no heterogeneity existed between studies. The fixed-effects model was used to combine the data, with an OR of 6.60 (95% CI (2.83–15.39), p<0.001), suggesting that the rate of CRRT required by patients with severe COVID-19 was significantly higher than that of patients with non-severe COVID-19. CRRT, continuous renal replacement therapy.

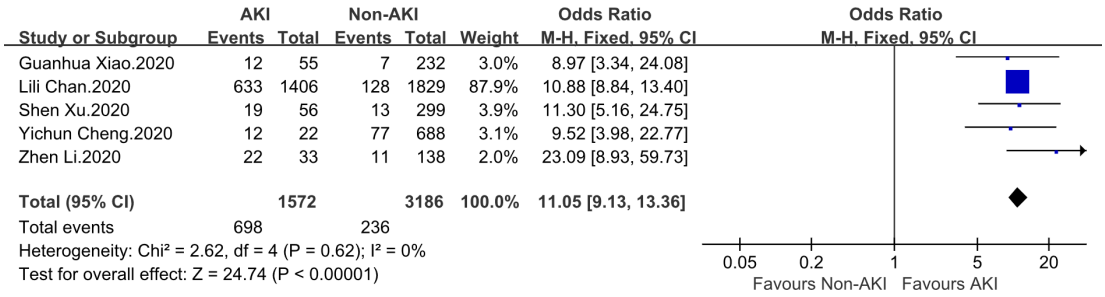

Figure 4 Forest plot showing the subgroup analysis of risk of death. The Q test showed p>0.1, indicating no heterogeneity existed between studies. The fixed-effects model was used to combine the data, with an OR of 11.05 (95% CI (9.13–13.36), p<0.001), suggesting that AKI incidence was a risk factor for death. The risk of death in patients with COVID-19 complicated by AKI was higher than that in patients with COVID-19 not complicated by AKI. AKI, acute kidney injury.

study analysed the effect of receiving CRRT on in-hospital mortality, but there was no statistical heterogeneity.

Prognostic analysis of COVID-19 combined with AKI

A total of five studies investigated the risk of death in patients with COVID-19 after development of AKI. The Q test showed p>0.1, indicating no heterogeneity between studies. The fixed-effects model was used to combine the data, with an OR of 11.05 (95% CI (9.13–13.36), p<0.001), suggesting that patients with COVID-19 complicated by AKI had a higher risk of in-hospital death (figure 4).

DISCUSSION

The retrospective analysis of our system showed that the incidence of kidney injury in patients with COVID-19 was 10.6%, which was higher than the incidence of AKI (8%) in hospitalised patients without COVID-19.[18] Currently, the mechanism of kidney injury in patients with COVID-19 is believed to involve SARS-CoV-2 directly attacking intrinsic renal cells. SARS-CoV-2 is a cytopathic virus that passes through the membrane protein ACE2 to enter host cells.[10] High ACE2 expression in proximal tubular epithelial cells may be a potential target for kidney injury. Cellular transmembrane serine proteases (TMPRSSs) act as co-receptors and activate the spike protein on the SARS-CoV-2 viral surface, enabling membrane fusion into host cells. Single-cell RNA sequencing analysis of kidney cells has revealed that ACE2 is expressed along with TMPRSSs in proximal straight tubule cells and podocytes, indicating that the kidney cells are exposed to SARS-CoV-2 infection.[9] One study has shown that the main pathological changes in the kidneys of patients with COVID-19 are swelling, vacuolar degeneration, shedding of renal tubular epithelial cells, and showing visible protein casts and pigmented casts in the lumen.[19] In addition, SARS-CoV-2 inclusion bodies have been found in renal tubular epithelial cells.[6] These findings suggest that SARS-CoV-2 may directly attack renal tubular epithelial cells and cause AKI. In addition, SARS-CoV-2 can directly infect glomerular endothelia, podocytes and renal tubules, causing acute tubular injury, and occasionally collapsing focal segmental glomerulopathy in the kidney tissue. Renal biopsies of patients with COVID-19 have revealed global collapse of the glomerular capillary loops, accompanied by hyperplasia of overlying glomerular epithelial cells, many of which contain abundant eosinophilic intracytoplasmic protein droplets. Collapsing glomerulopathy (CG) is increasingly reported in African American patients with COVID-19 infection. It is possible that CG following COVID-19 infection in this population may be linked to underlying APOL1 kidney risk alleles, which are not uncommon in this ethnic group. This lesion should be considered in the differential diagnosis of rapidly declining renal function in association with heavy proteinuria in patients with COVID-19 disease, especially in patients of African ancestry.[20 21]

High-load SARS-CoV-2 infection induces cytokine storm, in which various inflammatory mediators are released, such as interleukin (IL)-6, IL-1β, tumour necrosis factor-alpha, inducible protein-10, monocyte chemotactic protein 1, granulocyte-colony stimulating factor and macrophage inflammatory protein-1α, leading to ischaemia, hypoxia, fibrosis and kidney injury.[22–24] Furthermore, COVID-19 that is accompanied by high fever, shock, dehydration and hypoxemia, and treated with non-steroidal anti-inflammatory drugs, antiviral drugs, antibiotics and other potentially nephrotoxic drugs, may cause AKI. In addition, advanced age, diabetes and hypertension also induce or aggravate the incidence and progression of AKI.[25]

To our knowledge, this study presents the first systematic analysis of the risk factors of COVID-19 that lead to AKI. A recent report suggested that the incidence of AKI in patients with severe COVID-19 was significantly higher than in patients with non-severe COVID-19, with an OR of 11.02,[26] which was consistent with our conclusion. In addition, our study showed that advanced age was an independent risk factor for AKI, with an OR of 3.53. After SARS-CoV-2 infected elderly patients, the morbidity and mortality rates increased significantly, possibly implicating that the weakened immune system function of elderly patients and the ageing of tissues lead to greater susceptibility to viral replication.[27 28] Another study found that advanced age was an independent risk factor for AKI in hospitalised patients without COVID-19.[29] The viral clearance ability of male patients with SARS-CoV-2

infection is significantly lower than that of female patients with SARS-CoV-2 infection, which may represent one potential reason for the increased severity of symptoms and incidence of complications observed in male patients with SARS-CoV-2 infection.[30] Higher rates of smoking and alcohol consumption, as well as biological differences in the immune system between the sexes, could make men more vulnerable to AKI during SARS-CoV-2 infection. The role of androgen-responsive elements (AREs) of the TMPRSS type II (TMPRSS2) gene has been underappreciated as one of the major players of male dominance in the severe COVID-19 category. AREs of the TMPRSS2 gene are responsible for higher expression of the TMPRSS2 enzyme on the epithelial cell membranes of the respiratory system, which facilitates the non-endosomal entry of SARS-CoV-2 into the lung tissue.[31]

Our study found that the incidence of CRRT in patients with severe COVID-19 was significantly greater than that in patients with non-severe COVID-19. A recent report using increased SCr and urea nitrogen as the diagnostic standard for AKI had results consistent with our conclusion.[32] Unfortunately, only one study used in this meta-analysis reported the relationship between CRRT and in-hospital death in patients with COVID-19 in China; therefore, strong evidence for COVID-19 treatment in these patients is lacking.

Also, this study was the first meta-analysis to assess the in-hospital mortality in patients with both COVID-19 and AKI. Our results showed that the mortality rate of patients with COVID-19 and AKI was 22.1%, and the risk of death in patients with COVID-19 and AKI was 11.05 times that of patients with COVID-19 not complicated by AKI. In hospitalised patients without COVID-19, the mortality rate of AKI was 1.0%–14.4%, and the mortality rate of severely ill patients in the intensive care unit with AKI as a complication was 21.8%,[33] both of which were lower than the mortality rate of patients with COVID-19 in conjunction with AKI, suggesting that patients with both COVID-19 and AKI had a higher risk of death than patients with COVID-19 who did not have AKI.

In brief, this systematic analysis suggests that patients with COVID-19 were at risk for kidney injury, which was closely related to age, sex and disease type. Patients with COVID-19 in conjunction with AKI had a high risk of death. Thus, it is necessary to prevent the controllable factors related to AKI through diagnostic and treatment strategies. This includes providing full volume support, alleviation of hypoxemia and avoidance of nephrotoxic drug administration in patients with COVID-19 who are elderly and men, or in those who have severe COVID-19. In addition, early serum and urine tests to assess kidney function and early detection and treatment of AKI have been conducive to reducing the occurrence of AKI in patients with COVID-19 and to improving treatment success rates.

This study had several limitations related to the inclusion of patients with AKI who had been diagnosed according to the Kidney Disease Improving Global Outcomes guidelines in our analysis of AKI incidence. First, the baseline creatinine level was unknown in some patients, which may have led to missed AKI diagnoses. In some studies, the absolute level of increased SCr in patients as a standard for kidney injury may have overestimated the incidence of AKI.[26] Second, due to the limitation of examining only objective conditions, the long-term prognosis of SARS-CoV-2 infection, which might directly attack the kidneys and cause AKI in patients with COVID-19, is not clear. This topic must be investigated further.

Contributors JR and LL conceived the study, performed literature searches, extracted the data, assessed the quality of the studies and drafted the manuscript. XW and RJW performed literature searches. YS and KL performed the statistical analysis and drafted the manuscript. JY and LZ drafted the manuscript. All authors read and approved the final manuscript.

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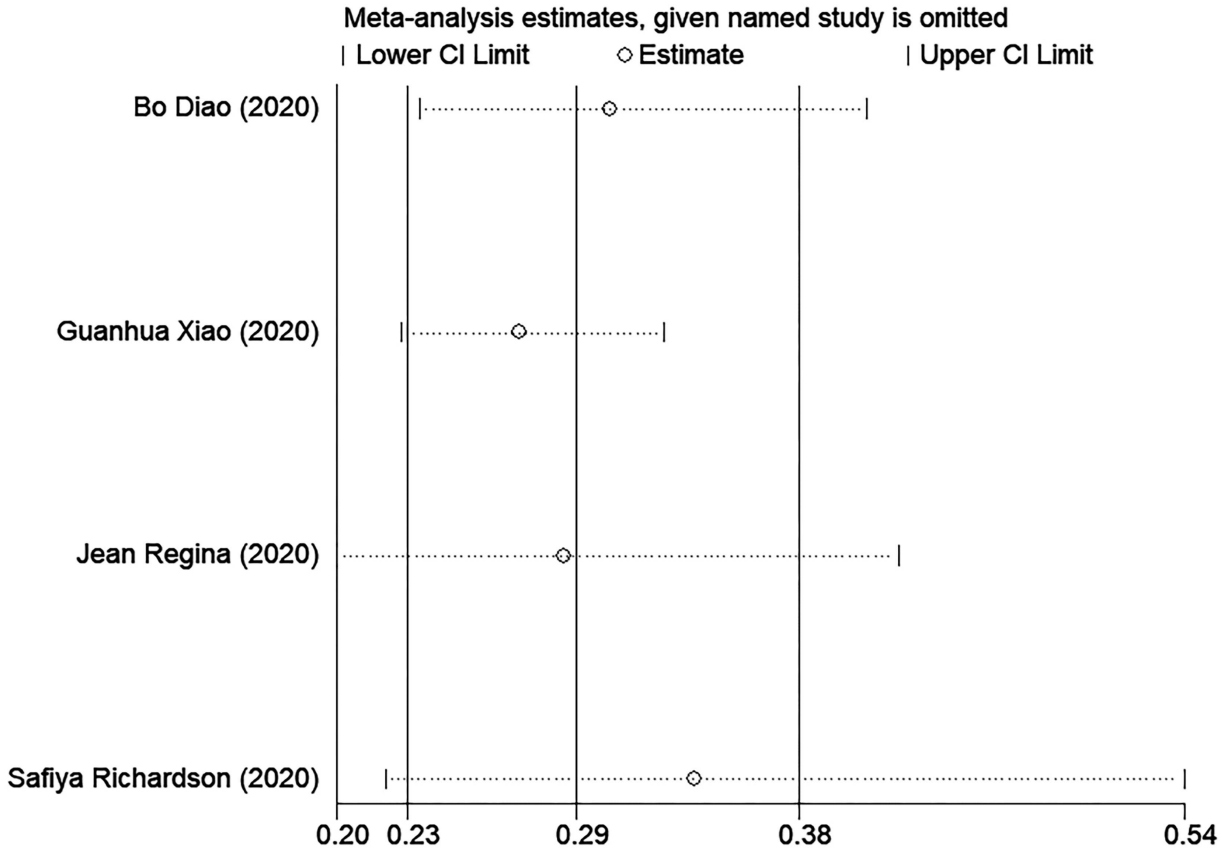
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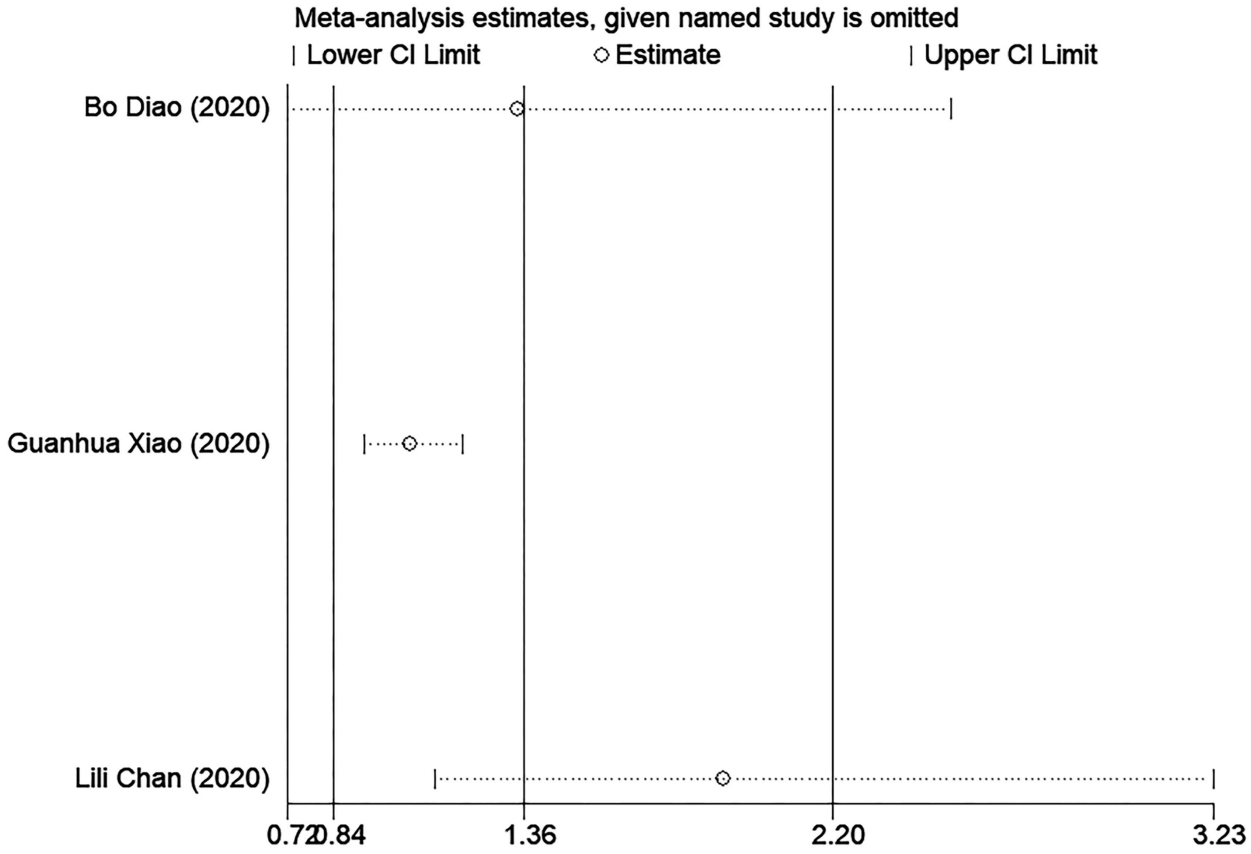
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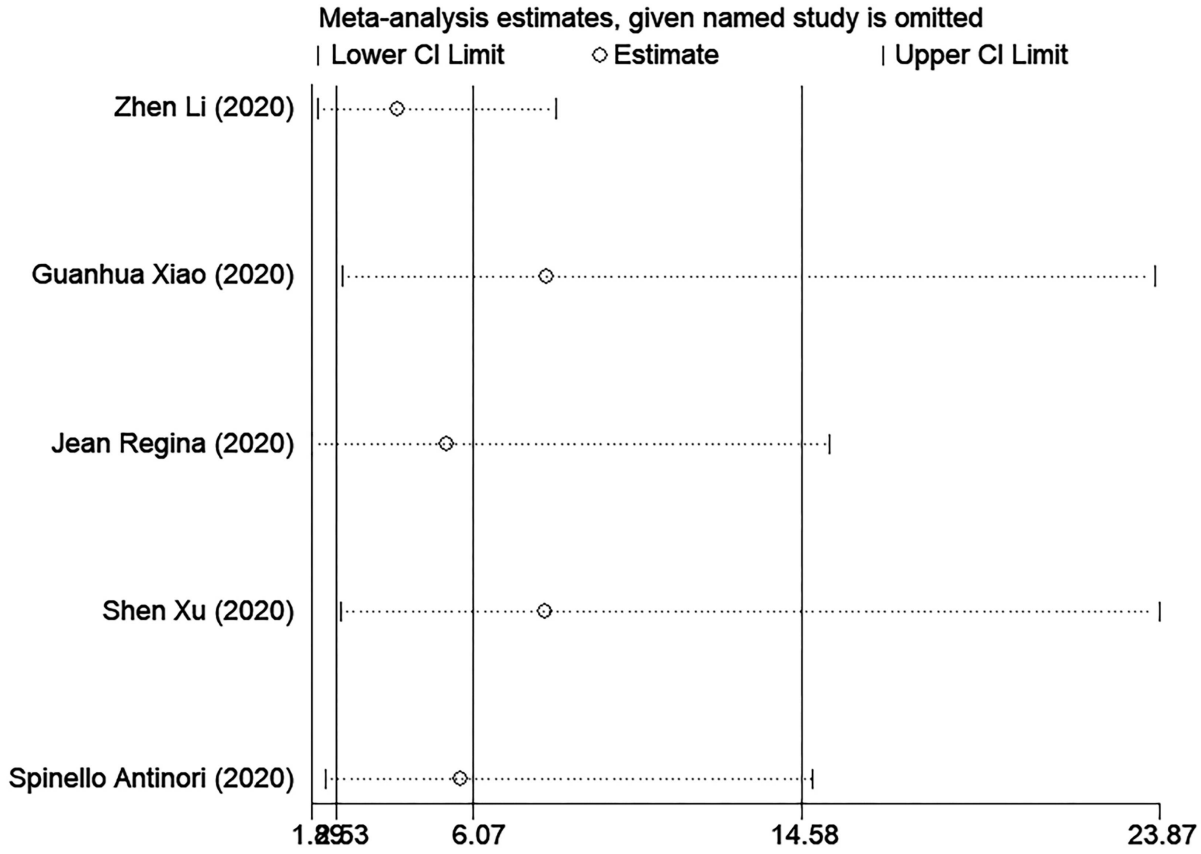
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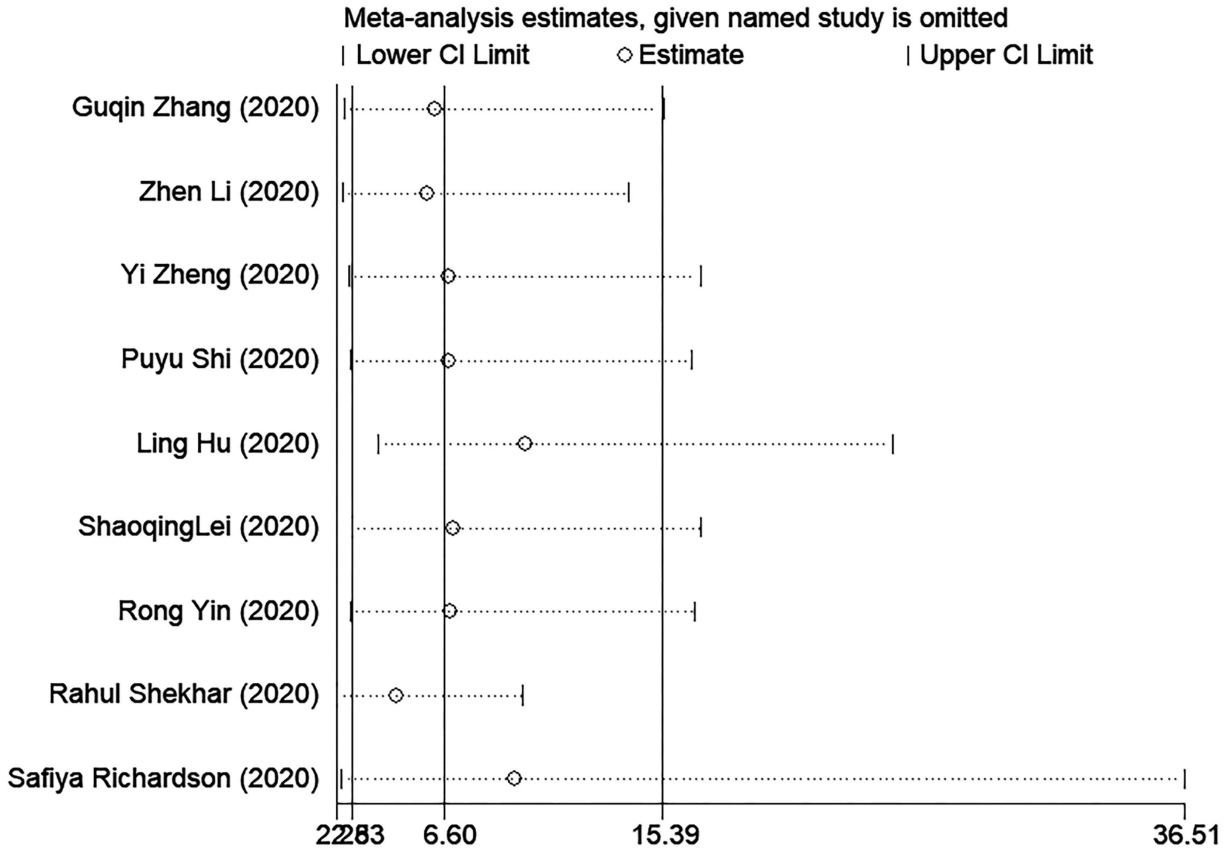
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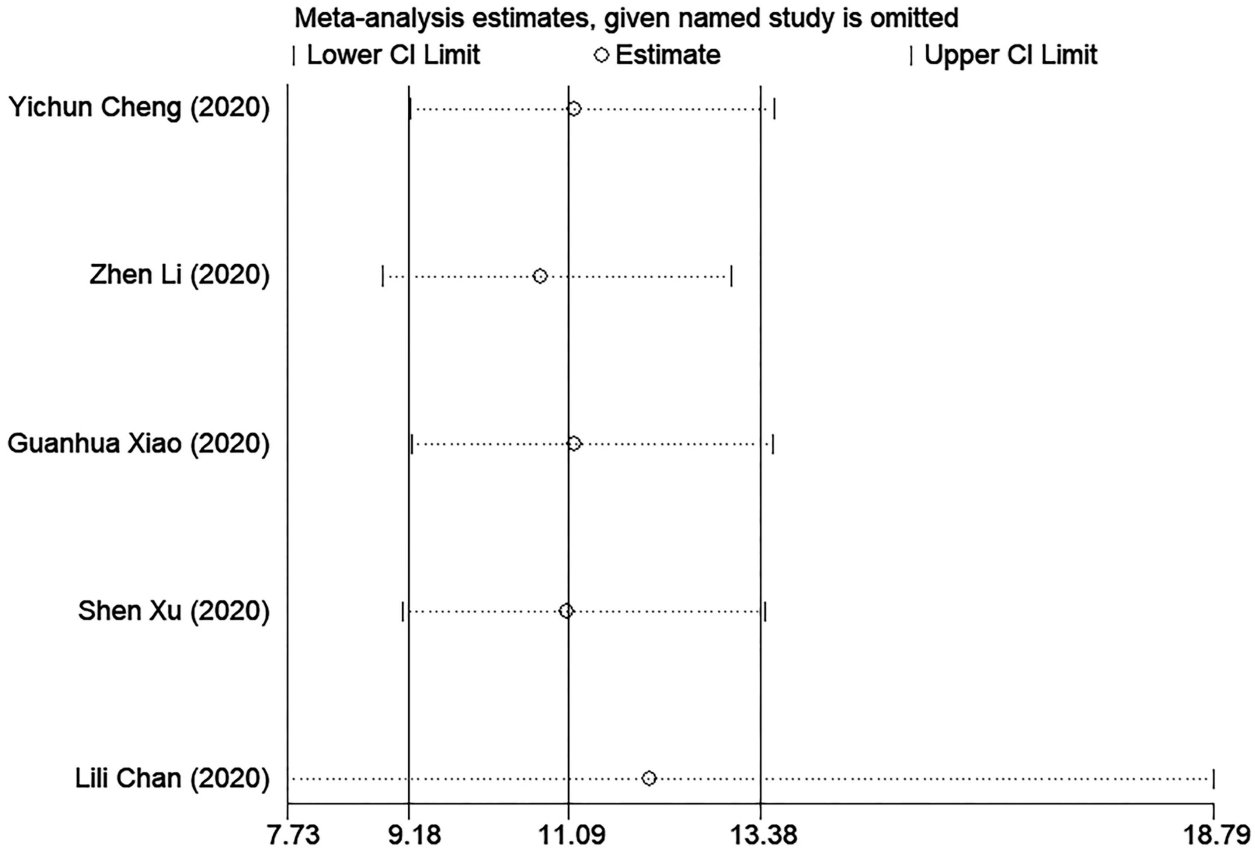
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