

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

# American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

# Association of acute kidney injury with the severity and mortality of SARS-CoV-2 infection: A meta-analysis



# Lichen Ouyang, PhD<sup>a,1</sup>, Yeli Gong, PhD<sup>a,1</sup>, Yan Zhu, MD<sup>d</sup>, Jie Gong, PhD<sup>b,c,\*</sup>

<sup>a</sup> Department of Immunology, School of Medicine, Jianghan University, Wuhan 430022, China

<sup>b</sup> Department of Anesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

<sup>c</sup> The First Clinical College, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

<sup>d</sup> Reproductive Medicine Center, Union Hospital, Tongji Medical Colleage, Huazhong University of Science and Technology, Wuhan 430022, China

#### ARTICLE INFO

Article history: Received 7 July 2020 Received in revised form 11 August 2020 Accepted 26 August 2020

Keywords: SARS-CoV-2 COVID-19 Severity Mortality Renal impairment Acute kidney injury

## ABSTRACT

*Background*: we aimed to explore the relationship of acute kidney injury (AKI) with the severity and mortality of coronavirus disease 2019 (COVID-19).

*Methods:* A systematic literature search was conducted in PubMed, EMBASE, Scopus, Web of Science, MedRxiv Database. We compared the laboratory indicators of renal impairment and incidences of AKI in the severe versus non-severe cases, and survival versus non-survival cases, respectively.

*Results*: In 41 studies with 10,335 COVID-19 patients, the serum creatinine (sCr) in severe cases was much higher than that in non-severe cases (SMD = 0.34, 95% CI: 0.29–0.39), with a similar trend for blood urea nitrogen (BUN) (SMD = 0.66, 95%CI: 0.51–0.81), hematuria (OR = 1.59, 95% CI: 1.15–2.19), and proteinuria (OR = 2.92, 95% CI: 1.58–5.38). The estimated glomerular filtration rate decreased significantly in severe cases compared with non-severe cases (SMD = -0.45, 95% CI: -0.67 - -0.23). Moreover, the pooled OR of continuous renal replacement therapy (CRRT) and AKI prevalence for severe vs. non-severe cases was 12.99 (95%CI: 4.03–41.89) and 13.16 (95%CI: 10.16–17.05), respectively. Additionally, 11 studies with 3759 COVID-19 patients were included for analysis of disease mortality. The results showed the levels of sCr and BUN in non-survival cases remarkably elevated compared with survival patients, respectively (SMD = 0.97, SMD = 1.49). The pooled OR of CRRT and AKI prevalence for saws 31.51 (95%CI: 6.55–151.59) and 77.48 (95% CI: 24.52–244.85), respectively.

*Conclusions:* AKI is closely related with severity and mortality of COVID-19, which gives awareness for doctors to pay more attention for risk screening, early identification and timely treatment of AKI.

© 2020 Elsevier Inc. All rights reserved.

#### 1. Introduction

Coronavirus disease 2019 (COVID-19), a newly emerging acute respiratory disease, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and causes substantial morbidity and mortality [1]. As of 12 June 2020, 7,519,566 COVID-19 cases have been confirmed and 419,447 people died from COVID-19 in more than 200 countries around the world. Most patients with COVID-19 are considered as non-severe patients and recover from this infection. However, the symptoms in about 10% of COVID-19 patients are severe and progress rapidly to critical conditions, including organ dysfunctions, such as acute respiratory distress syndrome (ARDS), acute cardiac injury, acute kidney injury (AKI) and even death [2].

Recently, several clinical studies have demonstrated that AKI was one of the most common complications in patients with SARS-CoV-2 infection. For example, in one retrospective study of 193 patients from Wuhan in China, Li et al. reported that proteinuria, hematuria, and elevated levels of blood urea nitrogen (BUN), as well as serum creatinine (sCr) were significantly associated with the death of COVID-19 patients [3]. In addition, an analysis of 355 inpatients in Wuhan showed that prevalence of AKI was 15.8% in admitted patients and 33.9% COVID-19 patients with AKI were died on mean 10.9 day after hospitalization [4]. However, the study of 116 hospitalized COVID-19 patients in Wuhan demonstrated that SARS-CoV-2 infection did not result in AKI [5]. A meta-analysis with large clinical samples is warranted to draw a

Abbreviations: COVID-19, coronavirus disease 2019; sCr, serum creatinine; BUN, blood urea nitrogen; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; SD, standard deviation; NOS, Newcastle-Ottawa scale; ACE2, angiotensinconverting enzyme 2; CRRT, continuous renal replacement therapy; PRISMA, preferred reporting items for systematic reviews and meta-analysis.

<sup>\*</sup> Corresponding author at: Department of Anesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology; The First Clinical College, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China.

E-mail address: gong\_jie2019@163.com (J. Gong).

<sup>&</sup>lt;sup>1</sup> Lichen Ouyang and Yeli Gong contributed equally to this work.

reliable conclusion. Therefore, we performed the present meta-analysis to investigate the association of AKI with the severity and mortality of SARS-CoV-2 infection.

## 2. Methods

The systematic review and meta-analysis were performed according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and reported based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [6,7]. This meta-analysis has no protocol.

## 2.1. Search strategy

Articles published from December 2019 to 8 June 2020 in Pubmed, EMBASE, Web of Science, Scopes, and MedRxiv Database were searched. To identify all the articles displaying the renal impairment in COVID-19, we used the following terms alone or in combination for literature search: "SARS-CoV-2", "COVID-19", "2019-nCoV", "nCoV", "COVID-19", "coronavirus", "severe acute respiratory syndrome coronavirus 2", "renal", "kidney", "acute kidney\*", "acute renal\*", "urology", "urogential system", "urea", "urinalysis", "creatinine", "proteinuria", "hematuria", "blood urea nitrogen" and "serum creatinine".

## 2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) subjects: adult inpatients diagnosed with COVID-19 according to the guidelines for the diagnosis and treatment of novel coronavirus disease; (2) clinical features: definite disease severity or mortality according to the guidelines for the diagnosis and treatment of novel coronavirus disease; (3) outcomes: COVID-19 patients with exact values of renal impairment indicators including BUN, sCr or estimated glomerular filtration rate (eGFR), and the incidences of hematuria, proteinuria, continuous renal replacement therapy (CRRT) and AKI.

Exclusion criteria included: (1) studies with special populations, such as children, elderly, pregnant women, transplant recipients and cancer patients; (2) case reports, reviews, letters, meta-analysis, guide-lines, editorials and comments; (3) studies without the data of renal impairment indicators (eg.BUN, sCr or eGFR) or incidence of hematuria, proteinuria, CRRT and AKI for comparison between severe versus non-severe cases or survival versus non-survival cases; (4) sample size less than 20 patients. The flow chat of the study selection was drafted in accordance to the PRISMA principle.

## 2.3. Definitions

The degrees of COVID-19 severity were evaluated according to the the guidelines for the diagnosis and treatment of novel coronavirus disease. The clinical subgroups of disease severity were described as follows: (1) non-severe group: the clinical symptoms were mild, and there was no or mild imaging signs of pneumonia [8]; (2) severe group (any of the following conditions): I, shortness of breath with respiratory rate  $\geq$ 30 bpm; II, finger SpO<sub>2</sub>  $\leq$  93% at rest; III, ARDS or arterial partial pressure of oxygen/fraction of inspired oxygen  $\leq$ 300 mmHg; IV, respiratory failure (requiring mechanical ventilation); V, shock; VI, other organ failure (requiring ICU monitoring and treatment) [9].



Fig. 1. Flowchart of study selection.

## *2.4.* Data extraction and quality assessment

Two investigators worked independently to decide which studies should be included, and the disagreement was resolved by a third investigator. Data was extracted from selected studies including the first author's name, publication data, sex, average age, numbers of patients and study type. In addition, laboratory examinations of renal impairments including BUN, sCr, eGFR, proteinuria and hematuria, and incidence of AKI and CRRT were also extracted. The data shown as median and interquartile range was transformed into mean and standard deviation (SD) according to the formula below (http://www. math.hkbu.edu.hk/tongt/papers/median2mean.html). The prevalence of proteinuria, hematuria, CRRT and AKI as well as average means of BUN, sCr and eGFR were evaluated between severe and non-severe group or survival and non-survival group, respectively.

The quality of studies was evaluated according to the Newcastle-Ottawa scale (NOS) containing three aspects (selection, comparability

#### Table 1

Characteristics of included studies.

and outcomes). Scores ranging from 0 to 9, and studies with the score  $\geq$ 6 were considered as high quality studies.

## 2.5. Statistical analysis

All data was analyzed by the Review Manager meta-analysis software (version 5.4). The standardized mean differences (SMDs) and 95% confidence intervals (CIs) were calculated for continuous data. The odds ratios (ORs) and 95% CIs were calculated for dichotomous data. The magnitude of heterogeneity between different studies was tested using  $I^2$  statistics. If there was no evidence of between studies heterogeneity ( $I^2 \le 50\%$ ), a fixed-effects model was used to calculate. Otherwise, a random-effects model was selected [10]. The Z score was tested for overall effect, with significance considered as P < .05. Publication bias was evaluated by funnel plot if the number of included studies >10.

Study	Country	City	Type of study	Sample size, n	Male N.(%)	Age, years (mean (SD)/median(IQR))	NOS score
Antinori S [11]	Italy	Milan	/	35	26(74.3)	63(51-69)	6
Argenziano MG [12]	US	New York	Retrospective	850	511(60)	63(50-75)	6
Bi QF [13]	China	Shenzhen	Retrospective	420	200(47.6)	/	7
Cai QX [14]	China	Shenzhen	Retrospective	298	145(48.66)	47.5(33-61)	7
Cao M [16]	China	Shanghai	Cohort	198	101(51.0)	50.1(16.3)	6
Cao WL [17]	China	Xiangyang	Retrospective	128	60(46.9)	/	6
Chen G [18]	China	Wuhan	Retrospective	21	17(81)	56.3(14.3)	5
Duan [ [23]	China	Chongqin	Retrospective	348	184(52.9)		6
Gong [ [26]	China	Guangzhou, Wuhan	Retrospective	189	88(46.6)	49(35, 63)	5
Guan W [27]	China	Guangzhou	/	1099	637(58)	47(35-58)	6
Hong KS [28]	Korea	Daegu	Retrospective	98	38(38.8)	55.4(17.1)	6
Huang CL [30]	China	Wuhan	/	41	30(73)	49(41-58)	6
Huang H [31]	China	Guangzhou	Retrospective	125	63(50.4)	44.87(18.55)	6
Huang SP [32]	China	Shanghai	/	415	217(52.3)	44(30-61)	5
Huang YS [2]	China	Wuhan	Cohort	223	126(56.5)	62(49-70)	6
Hu L [29]	China	Wuhan	Retrospective	323	166(51.4)	61(23-91)	7
[iang XF [33]	China	Wuxi	Retrospective	55	27(49.1)	45(27-60)	7
Liu R [37]	China	Wuhan	/	119	40(33.61)		8
Li Z [3]	China	Wuhan, Chongqing	Retrospective	193	95(49)	57(46-67)	7
Pei GC [41]	China	Wuhan	Retrospective	333	182(54.7)	56.3(13.4)	7
PengYD [42]	China	Wuhan	Retrospective	112	53(47.32)	62(55-67)	6
Petrilli CM[43]	US	New York	Cross-sectional	1999	1251(62.6)	62(50-74)	7
Yan SJ [51]	China	Hainan	Retrospective	168	81(48.2)	51(36-62)	5
Rica R [21]	Spain	/	Cohort	48	32(67)	65.98(13.91)	5
Xu Y [50]	China	Wuhan	Retrospective	69	35(50.7)	57(43-69)	6
Wang DW [47]	China	Wuhan	Retrospective	138	75(54.3)	56(42-68)	6
Wan SX [46]	China	Chonggin	/	135	72(53.3)	47(36-55)	5
Wu CM [49]	China	Wuhan	Retrospective	201	128(63.7)	51(43-60)	6
Xu S [4]	China	Wuhan, Fuyang	Retrospective	355	193(54.4)		6
Regina I [44]	Swiss	/	Retrospective	200	120(60.0)	70(55–81)	6
Shi PY [45]	China	, Outside Wuhan	Retrospective	134	65(48.5)	46(34-58)	6
Yang OX [9]	China	Wuhan	Retrospective	136	66(48.5)	56(44-64)	7
Zhang GO [54]	China	Wuhan	Retrospective	221	108(48.9)	55(39-66.5)	6
Zhang HZ [55]	China	Chonggin	Retrospective	43	22(51.2)	/	6
Zhao XY [56]	China	lingzhou	Retrospective	91	49(53.8)	/	6
Zhou HF [57]	China	Wuhan	Retrospective	178	72(40.4)	47(35-61)	6
Chen X [20]	China	Hunan	/	291	145(49.8)	46(34, 59)	6
Ma KL [39]	China	Chongging	Cohort	84	48(57.1)	48(42.3-62.5)	5
Liu IY [36]	China	Beijing	Prospective	61	31(50.8)	40(1-86)	6
Liu YL [38]	China	Wuhan	/	109	59 (54.1)	55(43-66)	6
Liu L [34]	China	Chongain	Retrospective	51	32(62.7)	45(34-51)	6
Giacomelli A [25]	Italy	Milan	Cohort	233	161(69.1)	61(50-72)	6
Yang IK [52]	China	Wuhan	Cohort	69	34(493)	61(52-67)	7
Zhang F [53]	China	Wuhan	Retrospective	48	33(68.8)	70 58(13 38)	6
Chen T [19]	China	Wuhan	Retrospective	274	171(62)	62(44-70)	7
Deng Y [22]	China	Wuhan	Retrospective	225	125(55.1)	/	6
Paranipe I [40]	USA	New York	Retrospective	2199	1293(58.8)	65(54-76)	6
Zhou F [1]	China	Wuhan	Cohort	191	119(62)	56(46-67)	6
Cao II. [15]	China	Wuhan	Cohort	102	53(52)	54(37-67)	6
Fu I [24]	China	Wuhan	Cohort	200	99(493)	/	6
Li KV [35]	China	Wuhan	Retrospective	102	59(58)	, 57(45_70)	6
Wang 7H [49]	Chipa	Wuhan	Case_control	116	65(56)	61 1(51_69)	8
vvalig Zri [40]	Clilld	v V UIIdII	Case-COIILIOI	110	(00)	01.1(01-00)	0

SD, Mean difference; IQR, Interquartile range; NOS, Newcastle-Ottawa scale.

## American Journal of Emergency Medicine 43 (2021) 149-157

the titles and abstracts, case reports, reviews, letters, meta-analysis, editorials, guidelines, comments, not relevant studies and sample size less

than 20 (n = 2150) were ruled out. 94 articles were excluded after thoroughly reviewing the full texts due to the following reasons: studies focused on special populations (n = 35); studies without available data

(n = 47), studies with sample less than 20 (n = 12). Finally, 52 articles

## 3. Results

#### 3.1. Study selections

We searched a total of 2893 articles according to the search terms. Firstly, duplicated articles (n = 597) were excluded. After reviewing

# A. sCr

	Non-survival		Survival				Std. Mean Difference		Std. Mean	Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% Cl	
Chen T 2020	89.4136	36.05	113	68.1122	22.44	161	16.0%	0.74 [0.49, 0.99]				
Deng Y 2020	98.6746	46.2	109	66.1818	18.13	116	14.9%	0.93 [0.66, 1.21]				
Fu L 2020	88.374	40.24	34	67.2822	22.06	166	11.0%	0.81 [0.43, 1.19]				
Giacomelli A 2020	111.0148	48.64	48	82.222	22.42	185	12.7%	0.97 [0.64, 1.30]				
Li KY 2020	108.16	82.61	15	69.82	19.6	87	6.5%	1.06 [0.49, 1.63]				
Paranjpe I 2020	130.4285	85.59	310	82.6832	32.83	768	21.1%	0.89 [0.75, 1.03]				
Wang ZH 2020	117.14	34.35	15	74.69	18.05	101	5.9%	2.03 [1.43, 2.64]				
Yang JK 2020	86.02	26.82	16	62.35	16	53	6.0%	1.23 [0.64, 1.83]				
Zhang F 2020	120.5887	87.31	17	77.572	20.21	31	5.8%	0.78 [0.17, 1.40]				-
Total (95% CI)			677			1668	100.0%	0.97 [0.80, 1.14]			•	
Heterogeneity: Tau <sup>2</sup> =	0.03; Chi² =	17.18,	df = 8 (	P = 0.03);	l² = 539	%				+		
Test for overall effect:	Z = 11.21 (F	P < 0.00	001)						-2 Favou	irs [Survival]	Favours [Non-s	z survival]

## B. BUN

	Non-survival Survival					;	Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chen T 2020	8.93	5.18	113	4.041	1.57	161	27.6%	1.38 [1.11, 1.65]	
Fu L 2020	8.18	4.02	34	4.35	1.87	166	22.7%	1.61 [1.21, 2.01]	-
Li KY 2020	9.45	6.79	15	4.34	1.73	87	16.5%	1.69 [1.09, 2.28]	
Wang ZH 2020	10.03	3.6	15	5.35	1.96	101	16.2%	2.09 [1.48, 2.69]	
Yang JK 2020	6.62	3.9	16	4.58	2.06	53	17.1%	0.78 [0.20, 1.35]	
Total (95% CI)			193			568	100.0%	1.49 [1.15, 1.84]	· · · · · · · · · · · · · · · · · · ·
Heterogeneity: Tau <sup>2</sup> =	0.09; Cł	$hi^2 = 10$	).94, df	-	-4 -2 0 2 4				
Test for overall effect:	Z = 8.58	(P < 0	0.00001		Favours [Survival] Favours [Non-survival]				

## C. AKI

U. ANI								
••••	Non-sur	vival	Surviv	/al		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fixed, 95% Cl
Cao JL 2020	15	17	5	85	13.1%	120.00 [21.27, 676.92]		
Chen T 2020	28	113	1	161	41.5%	52.71 [7.05, 394.12]		<b>_</b>
Deng Y 2020	20	109	0	116	26.4%	53.37 [3.18, 894.38]		
Zhou F 2020	27	54	1	137	18.9%	136.00 [17.72, 1044.04]		
Total (95% CI)		293		499	100.0%	77.48 [24.52, 244.85]		•
Total events	90		7					
Heterogeneity: Chi <sup>2</sup> = 0	).75, df = 3	(P = 0.	86); l² = 0	%				
Test for overall effect: 2	Z = 7.41 (F	o < 0.000	001)				0.001	Favours [Survival] Favours [Non-survival]

## D. CRRT

	Non-sur	vival	Surviv	/al		Odds Ratio		Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixe	ed, 95% CI	
Cao JL 2020	5	17	1	85	27.2%	35.00 [3.76, 325.69]				
Chen T 2020	3	113	0	161	46.2%	10.23 [0.52, 200.03]				$\rightarrow$
Zhou F 2020	10	54	0	137	26.6%	64.89 [3.73, 1129.76]				<b></b>
Total (95% CI)		184		383	100.0%	31.51 [6.55, 151.59]				
Total events	18		1							
Heterogeneity: Chi <sup>2</sup> = 0	).80, df = 2	2 (P = 0.0	67); l² = 0	%					10	100
Test for overall effect: 2	Z = 4.30 (F	o < 0.000	01)				0.01	U.1 Favours [Survival]	Favours [Non-sur	/ival]

**Fig. 2.** Meta-analysis of prevalence of AKI and CRRT as well as two laboratory indexes of kidney injury. Forest plots represent the comparisons of the prevalence of AKI and CRRT and standard mean differences (SMD) in two laboratory indicators between non-survival and survival cases. A, sCr (serum creatinine, µmol/L); B, BUN (blood urea nitrogen, mmol/L); C, AKI (acute kidney injury); D, CRRT (continuous renal replacement therapy).

[1-4,9,11-57] with 14,094 patients were included in our meta-analysis. Fig. 1 showed the flow diagram of the studies selections.

## 3.2. Study characteristics

°Cr

As shown in Table 1, most of studies were from China, and six studies were published from other countries [11,12,25,28,40,43]. Among of them, 41 studies with 10,335 patients were analyzed for the association of renal impairment with severity of COVID-19 [2-4,9,11-14,16-18,20,21,23,26-34,36-39,41-47,49-51,54-57]. In additions, 11 studies with 3759 patients reported the association of renal impairment with mortality of COVID-19 [1,15,19,22,24,25,35,40,48,52,53]. The incidence of AKI and CRRT during SARS-CoV-2 infections was evaluated between the severe versus non-severe cases or survival versus non-survival cases, respectively.

## 3.3. Association between AKI and mortality of COVID-19

As shown in Fig. 2A, sCr was measured in nine studies among 2345 patients. The heterogeneity test of sCr was shown as  $l^2 = 53\%$ , thus we applied the random-effects model for further investigation. The following results elucidated that sCr was significantly higher in non-survival group than that in survival group [SMD = 0.97, 95%CI (0.80,

1.14), Z = 11.21, P < 0.00001]. There was moderate statistical heterogeneity between the studies to evaluate BUN ( $l^2 = 63\%$ ). In Fig. 2B, the levels of BUN in five studies were remarkably elevated in non-survival group compared with survival group [SMD = 1.49, 95%CI (1.15, 1.84), Z = 8.58, P < 0.00001]. Furthermore, we compared the incidence of AKI between survival and non-survival group (Fig. 2C). The heterogeneity test of AKI was shown as  $l^2 = 0$ . Pooled analysis of four studies among 792 COVID-19 patients revealed that the incidence of AKI was statistically higher in non-survival group (30.72%) compared with survival group (1.4%) [OR 77.48, 95%CI (24.52, 244.85), Z = 7.41, P < 0.00001]. Additionally, 3 studies reported the application rate of CRRT in non-survival group Without heterogeneity ( $l^2 = 0$ ). As shown in Fig. 2D, non-survival group had higher application rate of CRRT than survival group [OR = 31.51, 95% CI: 6.55 to 151.59, P < 0.0001].

## 3.4. Correlation between AKI and severity of COVID-19

As illustrated in Fig. 3, sCr was evaluated in 35 studies among 6949 patients, with no statistical heterogeneity ( $I^2 = 37\%$ ). 35 studies reported that the level of sCr was significantly increased in severe group compared with non-severe group [SMD = 0.34, 95%CI (0.29–0.39), Z = 12.21, P < 0.00001]. In Fig. 4A, the heterogeneity test of BUN in

301	S	evere		No	n-sever	e		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Antinori S 2020	90.99	59.73	18	88	24.29	17	0.7%	0.06 [-0.60, 0.73]	
Cai QX 2020	75	32.69	58	61.7	17.9	240	3.5%	0.62 [0.32, 0.91]	
Cao M 2020	71.56	22.1	19	62.89	18.68	179	1.3%	0.45 [-0.02, 0.93]	
Cao WL 2020	79.35	78.9	21	51.8	73.51	107	1.4%	0.37 [-0.10, 0.84]	
Chen G 2020	90.7	38.5	11	73.3	11.6	10	0.4%	0.58 [-0.30, 1.45]	
Chen X 2020	54.56	18.09	50	53.15	19.01	241	3.2%	0.07 [-0.23, 0.38]	
Duan J 2020	81	27	20	67	18	328	1.4%	0.75 [0.30, 1.21]	
Gong J 2020	60.28	29.84	28	61.15	21.77	161	1.9%	-0.04 [-0.44, 0.36]	
Hong KS 2020	88.4	26.52	13	70.72	44.2	85	0.9%	0.41 [-0.17, 1.00]	
Huang CL 2020	74.55	32.89	13	71.73	21.25	28	0.7%	0.11 [-0.55, 0.77]	
Huang H 2020	77.56	42.19	32	64.02	26.95	93	1.8%	0.43 [0.02, 0.83]	
Huang SP 2020	68.12	19.28	27	63.47	16.85	321	1.9%	0.27 [-0.12, 0.67]	
Huang YS 2020	80.45	28.31	98	65.04	18.27	125	4.0%	0.66 [0.39, 0.93]	
Jiang XF 2020	64.13	34.85	8	53.35	17.59	47	0.5%	0.51 [-0.24, 1.27]	
Li Z 2020	72.29	25.78	65	65.81	19.49	128	3.3%	0.30 [-0.00, 0.60]	
Liu JY 2020	65.45	24.25	17	57.17	17.09	44	0.9%	0.42 [-0.14, 0.99]	
Liu L 2020	60.95	16.53	7	69.06	14.56	44	0.5%	-0.54 [-1.34, 0.27]	
Liu YL 2020	68.41	21.34	53	65.41	21.31	56	2.1%	0.14 [-0.24, 0.52]	
Ma KL 2020	63.3	21.3	20	65.19	16.84	64	1.2%	-0.10 [-0.61, 0.40]	
Pei GC 2020	71.58	20.87	189	67.9	18.72	144	6.3%	0.18 [-0.03, 0.40]	
Peng YD 2020	76.6	28.37	16	67.74	13.21	96	1.0%	0.55 [0.01, 1.08]	
Petrilli CM 2020	100.22	43.98	650	85.63	28.21	932	29.2%	0.41 [0.31, 0.51]	
Regina J 2020	102.33	34.71	37	90.52	31.98	163	2.3%	0.36 [0.00, 0.72]	
Rica R 2020	98.12	89.28	21	96.36	60.11	27	0.9%	0.02 [-0.55, 0.59]	
Shi PY 2020	63.55	17.75	46	60.11	16.58	88	2.3%	0.20 [-0.16, 0.56]	
Wan SX 2020	63.07	17.53	40	66.7	18.07	95	2.2%	-0.20 [-0.57, 0.17]	
Wang DW 2020	84.27	30.88	36	71	19.55	102	2.0%	0.57 [0.19, 0.96]	
Wu CM 2020	74.97	25.99	84	69.09	17.71	117	3.8%	0.27 [-0.01, 0.55]	
Xu S 2020	78.06	38.67	131	69.1	31.8	224	6.4%	0.26 [0.04, 0.48]	
Xu Y 2020	64.83	22.17	25	57.63	16.94	44	1.2%	0.38 [-0.12, 0.87]	
Yan SJ 2020	64.82	29.97	36	61.25	16.73	132	2.2%	0.18 [-0.19, 0.54]	
Yang QX 2020	75.72	36.19	33	64.9	15.34	103	1.9%	0.49 [0.09, 0.88]	
Zhang GQ 2020	82.78	33.5	55	67	17.95	166	3.1%	0.69 [0.38, 1.00]	
Zhang HZ 2020	66.6	17.05	14	68.91	17.58	29	0.7%	-0.13 [-0.77, 0.51]	
Zhou HF 2020	72.13	25.62	52	65.37	13.35	126	2.8%	0.38 [0.05, 0.70]	
Total (95% Cl)			2043			4906	100.0%	0.34 [0.29, 0.39]	•
Heterogeneity: Chi <sup>2</sup> =	54.16, df	= 34 (P	= 0.02	); I <sup>2</sup> = 37	7%			-	
Test for overall effect:	Z = 12.21	(P < 0.	.00001)						Favours [Non-severe] Favours [Severe]

Fig. 3. Forest plot represents the comparisons of standard mean differences (SMD) in sCr between severe and non-severe cases.

23 studies was shown as  $I^2 = 71\%$ , thus we applied the random-effects model for further investigation. Sensitivity analysis by removing one study each time suggested the results were robust. Subgroup analysis

by the country of study, sample size, age, male percentage and quality score of the studies failed to resolve the obvious heterogeneity. The level of BUN in severe group was remarkably higher than that in non-

Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Mean         SD         Total         Weight         IV. Random. 95% Cl         IV. Random. 95% Cl           Cai QX 2020         5.2         1.94         5.8         3.91         1.22         240         5.4%         0.93 [0.63, 1.22]         IV. Random. 95% Cl         IV. Random. 95% Cl           Cao M 2020         5.51         3.76         19         4.53         1.52         179         4.0%         0.63 [0.05, 1.01]         IV. Random. 95% Cl           Cao M 2020         6.06         13.03         21         5.4         9.83         107         4.1%         0.06 [0.40, 0.53]         IV. Fandom. 95% Cl           Chen G 2020         7.7         3.7         11         4.2         1.3         1.0         1.9%         0.45 [0.44, 0.75]           Duan J 2020         4.1         2.8         8.9         0.07 [0.38, 0.52]         IV.10 [0.78, 1.42]         IV.11 [0.74, 1.66]         IV.11 [0.74, 1.63]         IV.11 [0.74, 1.64]         IV.10 [0.78, 1.42]         IV.11 [0.	A BUN									
Study or Subgroup         Mean         SD         Total         Wean         SD         Total         Weight         IV. Random. 95% CI         IV. Random. 95% CI           Cai QX 2020         5.2         1.94         58         3.91         1.22         240         5.4%         0.93 [0.63, 1.22]           Cao M 2020         5.51         3.76         19         4.53         1.52         179         4.0%         0.53 [0.05, 1.01]           Cao M 2020         6.06         13.03         21         5.4         9.83         107         4.1%         0.06 [-0.40, 0.53]           Chen X 2020         4.55         1.79         50         3.94         1.26         24         5.3%         0.045 [0.14, 0.75]           Duan J 2020         4.1         2.6         20         4         1.48         328         4.2%         0.07 [-0.38, 0.52]           Gong J 2020         7.47         3.46         98         4.04         1.35         125         5.4%         1.36 [1.07, 1.66]           Jiang XF 2020         6.61         5.99         8         4.01         0.59         1.52         1.49         1.58           Li Z 2020         6.54         2.36         5.3         3.75         1.26 <td></td> <td>S</td> <td>Severe</td> <td></td> <td>Nor</td> <td>1-seve</td> <td>re</td> <td></td> <td>Std. Mean Difference</td> <td>Std. Mean Difference</td>		S	Severe		Nor	1-seve	re		Std. Mean Difference	Std. Mean Difference
Cai QX 2020 5.2 1.94 58 3.91 1.22 240 5.4% 0.93 $[0.63, 1.22]$ Cao M 2020 5.51 3.76 19 4.53 1.52 179 4.0% 0.53 $[0.05, 1.01]$ Cao WL 2020 6.06 13.03 21 5.4 9.83 107 4.1% 0.06 $[-0.40, 0.53]$ Chen G 2020 7.7 3.7 11 4.2 1.3 10 1.9% 1.19 $[0.24, 2.13]$ Chen X 2020 4.55 1.79 50 3.94 1.26 241 5.3% 0.45 $[0.14, 0.75]$ Duan J 2020 4.1 2.6 20 4 1.4 328 4.2% 0.07 $[-0.38, 0.52]$ Gong J 2020 5.02 3.2 28 3.9 1.05 161 4.5% 0.72 $[0.31, 1.12]$ Hong KS 2020 7.12 4.06 13 5.2 3.2 85 3.3% 0.57 $[-0.02, 1.16]$ Huang YS 2020 7.47 3.46 98 4.04 1.35 125 5.4% 1.36 $[1.07, 1.66]$ Jiang XF 2020 6.61 5.99 8 4.01 0.99 47 2.4% 1.08 $[0.31, 1.86]$ Li Z 2020 6.61 5.99 8 4.01 1.57 128 5.2% 1.10 $[0.78, 1.42]$ Liu J 2020 4.95 2.57 7 4.28 1.92 44 2.3% 0.33 $[-0.47, 1.13]$ Liu V 2020 5.06 2.02 17 4.2 1.23 44 3.4% 0.57 $[0.00, 1.14]$ Liu L 2020 4.95 2.57 7 4.28 1.92 44 2.3% 0.33 $[-0.47, 1.13]$ Liu V 2020 5.4 2.36 53 3.75 1.45 56 4.6% 0.99 $[0.52, 1.31]$ Ma KL 2020 4.99 2.71 20 4.04 1.14 64 3.8% 0.51 $[0.00, 1.02]$ Pei G 2020 4.96 2.38 189 4.01 1.42 144 5.9% 0.47 $[0.25, 0.69]$ Peng YD 2020 6.62 4.94 54 16 5.07 2.93 96 3.7% 0.42 $[-0.11, 0.95]$ Shi PY 2020 4.15 2.14 46 3.61 0.98 88 4.9% 0.36 $[0.00, 0.72]$ Wang DW 2020 6.65 4.09 36 4.07 1.5 102 4.6% 1.05 $[0.26, 1.01]$ Zhang GQ 2020 6.22 3.2 55 4.11 1.27 166 5.2% 1.09 $[0.77, 1.41]$ Zhou HF 2020 4.09 1.14 52 3.68 1.36 126 5.1% 0.31 $[-0.01, 0.64]$ Total (95% Cl) 1049 2937 100.0% 0.66 $[0.51, 0.81]$ Heterogeneity: Tau <sup>2</sup> = 0.09; Ch <sup>2</sup> = 75.56, df = 22 (P < 0.0001); P = 71%	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Cao M 2020       5.51       3.76       19       4.53       1.52       179       4.0%       0.53 [0.05, 1.01]         Cao WL 2020       6.06       13.03       21       5.4       9.83       107       4.1%       0.06 [-0.40, 0.53]         Chen G 2020       7.7       3.7       11       4.2       1.3       10       1.9%       1.19 [0.24, 2.13]         Chen X 2020       4.55       1.79       50       3.94       1.26       241       5.3%       0.45 [0.14, 0.75]         Duan J 2020       5.02       3.2       28       3.9       1.05       161       4.5%       0.07 [-0.38, 0.52]         Huang YS 2020       7.47       3.46       98       4.04       1.35       125       5.4%       1.36 [1.07, 1.66]         Jiang XF 2020       6.61       5.99       8       4.01       0.99       47       2.4%       1.08 [0.31, 1.86]         Li Z 2020       6.37       2.96       65       3.75       1.45       56       4.6%       0.91 [0.52, 1.31]         Li Z 2020       5.54       2.36       53       3.75       1.45       56       4.6%       0.91 [0.52, 1.62]	Cai QX 2020	5.2	1.94	58	3.91	1.22	240	5.4%	0.93 [0.63, 1.22]	
Cao WL 2020       6.06       13.03       21       5.4       9.83       107       4.1%       0.06       [-0.40, 0.53]         Chen G 2020       7.7       3.7       11       4.2       1.3       10       1.9%       1.19       [0.24, 2.13]         Chen X 2020       4.55       1.79       50       3.94       1.26       241       5.3%       0.45       [0.41, 0.75]         Duan J 2020       5.02       3.2       28       3.9       1.05       161       4.5%       0.07       [0.38, 0.52]         Gong J 2020       5.02       3.2       28       3.3%       0.57       0.02, 1.16]         Huarg YS 2020       7.47       3.46       98       4.01       0.99       47       2.4%       1.08       [0.31, 1.86]         Liz 2020       6.61       5.99       8       4.01       1.99       4.2       2.3%       0.33       [0.47, 1.13]         Liu L 2020       4.95       2.57       7       4.28       1.92       4.4       3.8%       0.57       [0.00, 1.14]         Liu L 2020       4.96       2.38       88       4.01       1.42       1.44       6.58       0.91       0.51       0.025       0.69	Cao M 2020	5.51	3.76	19	4.53	1.52	179	4.0%	0.53 [0.05, 1.01]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Cao WL 2020	6.06	13.03	21	5.4	9.83	107	4.1%	0.06 [-0.40, 0.53]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Chen G 2020	7.7	3.7	11	4.2	1.3	10	1.9%	1.19 [0.24, 2.13]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Chen X 2020	4.55	1.79	50	3.94	1.26	241	5.3%	0.45 [0.14, 0.75]	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Duan J 2020	4.1	2.6	20	4	1.4	328	4.2%	0.07 [-0.38, 0.52]	
Hong KS 2020 7.12 4.06 13 5.2 3.2 85 3.3% 0.57 [-0.02, 1.16] Huang YS 2020 7.47 3.46 98 4.04 1.35 125 5.4% 1.36 [1.07, 1.66] Jiang XF 2020 6.61 5.99 8 4.01 0.99 47 2.4% 1.08 [0.31, 1.86] Li Z 2020 6.37 2.96 65 4.01 1.57 128 5.2% 1.10 [0.78, 1.42] Liu JY 2020 5.06 2.02 17 4.2 1.23 44 3.4% 0.57 [0.00, 1.14] Liu L 2020 4.95 2.57 7 4.28 1.92 44 2.3% 0.33 [-0.47, 1.13] Liu YL 2020 5.54 2.36 53 3.75 1.45 56 4.6% 0.91 [0.52, 1.31] Ma KL 2020 4.96 2.38 189 4.01 1.42 144 5.9% 0.47 [0.25, 0.69] Pei GC 2020 4.96 2.38 189 4.01 1.42 144 5.9% 0.47 [0.25, 0.69] Pei GC 2020 4.96 2.38 189 4.01 1.42 144 5.9% 0.47 [0.25, 0.69] Peng YD 2020 6.42 4.54 16 5.07 2.93 96 3.7% 0.42 [-0.11, 0.95] Shi PY 2020 4.15 2.14 46 3.61 0.98 88 4.9% 0.36 [0.00, 0.72] Wang DW 2020 6.65 4.09 36 4.07 1.5 102 4.6% 1.05 [0.65, 1.45] Xu S 2020 5.93 4.29 131 4.3 2.3 224 5.9% 0.51 [0.29, 0.73] Yan SJ 2020 4.71 3.2 36 3.6 1.05 132 4.8% 0.63 [0.26, 1.01] Zhang GQ 2020 6.22 3.2 55 4.11 1.27 166 5.2% 1.09 [0.77, 1.41] Zhou HF 2020 4.09 1.14 52 3.68 1.36 126 5.1% 0.31 [-0.01, 0.64] Total (95% CI) 1049 2937 100.0% 0.66 [0.51, 0.81] Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup> = 71% Test for overall effect: $Z = 8.58 (P < 0.00001)$	Gong J 2020	5.02	3.2	28	3.9	1.05	161	4.5%	0.72 [0.31, 1.12]	
Huang YS 2020       7.47       3.46       98       4.04       1.35       125       5.4%       1.36 [1.07, 1.66]         Jiang XF 2020       6.61       5.99       8       4.01       0.99       47       2.4%       1.08 [0.31, 1.86]         Li Z 2020       6.37       2.96       65       4.01       1.57       128       5.2%       1.10 [0.78, 1.42]         Liu J 2020       5.06       2.02       17       4.2       1.23       44       3.4%       0.57 [0.00, 1.14]         Liu L 2020       4.95       2.57       7       4.28       1.92       44       2.3%       0.33 [-0.47, 1.13]         Liu V 2020       5.54       2.36       53       3.75       1.45       56       4.6%       0.91 [0.52, 1.31]         Ma KL 2020       4.89       2.71       20       4.04       1.14       64       3.8%       0.51 [0.00, 1.02]         Pei GC 2020       4.96       2.38       189       4.01       1.42       144       5.9%       0.42 [-0.11, 0.95]         Shi PY 2020       4.15       2.14       46       3.61       0.98       8.8       4.9%       0.36 [0.00, 0.72]         Wang DW 2020       6.65       4.09       3.6	Hong KS 2020	7.12	4.06	13	5.2	3.2	85	3.3%	0.57 [-0.02, 1.16]	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Huang YS 2020	7.47	3.46	98	4.04	1.35	125	5.4%	1.36 [1.07, 1.66]	
Li Z 2020 6.37 2.96 65 4.01 1.57 128 5.2% 1.10 [0.78, 1.42] Liu JY 2020 5.06 2.02 17 4.2 1.23 44 3.4% 0.57 [0.00, 1.14] Liu L 2020 4.95 2.57 7 4.28 1.92 44 2.3% 0.33 [-0.47, 1.13] Liu YL 2020 5.54 2.36 53 3.75 1.45 56 4.6% 0.91 [0.52, 1.31] Ma KL 2020 4.89 2.71 20 4.04 1.14 64 3.8% 0.51 [0.00, 1.02] Pei GC 2020 4.96 2.38 189 4.01 1.42 144 5.9% 0.47 [0.25, 0.69] Peng YD 2020 6.42 4.54 16 5.07 2.93 96 3.7% 0.42 [-0.11, 0.95] Shi PY 2020 4.15 2.14 46 3.61 0.98 88 4.9% 0.36 [0.00, 0.72] Wang DW 2020 6.65 4.09 36 4.07 1.5 102 4.6% 1.05 [0.65, 1.45] Xu S 2020 5.93 4.29 131 4.3 2.3 224 5.9% 0.51 [0.29, 0.73] Yan SJ 2020 4.71 3.2 36 3.6 1.05 132 4.8% 0.63 [0.26, 1.01] Zhang GQ 2020 6.22 3.2 55 4.11 1.27 166 5.2% 1.09 [0.77, 1.41] Zhou HF 2020 4.09 1.14 52 3.68 1.36 126 5.1% 0.31 [-0.01, 0.64] Total (95% CI) 1049 2937 100.0% 0.66 [0.51, 0.81] Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); I <sup>2</sup> = 71% Test for overall effect; $Z = 8.58 (P < 0.00001)$	Jiang XF 2020	6.61	5.99	8	4.01	0.99	47	2.4%	1.08 [0.31, 1.86]	
Liu JY 2020 5.06 2.02 17 4.2 1.23 44 3.4% 0.57 [0.00, 1.14] Liu L 2020 4.95 2.57 7 4.28 1.92 44 2.3% 0.33 [-0.47, 1.13] Liu YL 2020 5.54 2.36 53 3.75 1.45 56 4.6% 0.91 [0.52, 1.31] Ma KL 2020 4.89 2.71 20 4.04 1.14 64 3.8% 0.51 [0.00, 1.02] Pei GC 2020 4.96 2.38 189 4.01 1.42 144 5.9% 0.47 [0.25, 0.69] Peng YD 2020 6.42 4.54 16 5.07 2.93 96 3.7% 0.42 [-0.11, 0.95] Shi PY 2020 4.15 2.14 46 3.61 0.98 88 4.9% 0.36 [0.00, 0.72] Wang DW 2020 6.65 4.09 36 4.07 1.5 102 4.6% 1.05 [0.65, 1.45] Xu S 2020 5.93 4.29 131 4.3 2.3 224 5.9% 0.51 [0.29, 0.73] Yan SJ 2020 4.71 3.2 36 3.6 1.05 132 4.8% 0.63 [0.26, 1.01] Zhang GQ 2020 6.22 3.2 55 4.11 1.27 166 5.2% 1.09 [0.77, 1.41] Zhou HF 2020 4.09 1.14 52 3.68 1.36 126 5.1% 0.31 [-0.01, 0.64] Total (95% CI) 1049 2937 100.0% 0.66 [0.51, 0.81] Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup> = 71% Test for overall effect: $Z = 8.58$ (P < 0.00001)	Li Z 2020	6.37	2.96	65	4.01	1.57	128	5.2%	1.10 [0.78, 1.42]	
Liu L 2020 4.95 2.57 7 4.28 1.92 44 2.3% 0.33 [-0.47, 1.13] Liu YL 2020 5.54 2.36 53 3.75 1.45 56 4.6% 0.91 [0.52, 1.31] Ma KL 2020 4.89 2.71 20 4.04 1.14 64 3.8% 0.51 [0.00, 1.02] Pei GC 2020 4.96 2.38 189 4.01 1.42 144 5.9% 0.47 [0.25, 0.69] Peng YD 2020 6.42 4.54 16 5.07 2.93 96 3.7% 0.42 [-0.11, 0.95] Shi PY 2020 4.15 2.14 46 3.61 0.98 88 4.9% 0.36 [0.00, 0.72] Wang DW 2020 6.65 4.09 36 4.07 1.5 102 4.6% 1.05 [0.65, 1.45] Xu S 2020 5.93 4.29 131 4.3 2.3 224 5.9% 0.51 [0.29, 0.73] Yan SJ 2020 4.71 3.2 36 3.6 1.05 132 4.8% 0.63 [0.26, 1.01] Zhang GQ 2020 6.22 3.2 55 4.11 1.27 166 5.2% 1.09 [0.77, 1.41] Zhou HF 2020 4.09 1.14 52 3.68 1.36 126 5.1% 0.31 [-0.01, 0.64] Total (95% CI) 1049 2937 100.0% 0.66 [0.51, 0.81] Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup> = 71% Test for overall effect: $Z = 8.58$ (P < 0.00001)	Liu JY 2020	5.06	2.02	17	4.2	1.23	44	3.4%	0.57 [0.00, 1.14]	
Liu YL 2020 5.54 2.36 53 3.75 1.45 56 4.6% 0.91 [0.52, 1.31] Ma KL 2020 4.89 2.71 20 4.04 1.14 64 3.8% 0.51 [0.00, 1.02] Pei GC 2020 4.96 2.38 189 4.01 1.42 144 5.9% 0.47 [0.25, 0.69] Peng YD 2020 6.42 4.54 16 5.07 2.93 96 3.7% 0.42 [-0.11, 0.95] Shi PY 2020 4.15 2.14 46 3.61 0.98 88 4.9% 0.36 [0.00, 0.72] Wang DW 2020 6.65 4.09 36 4.07 1.5 102 4.6% 1.05 [0.65, 1.45] Xu S 2020 5.93 4.29 131 4.3 2.3 224 5.9% 0.51 [0.29, 0.73] Yan SJ 2020 4.71 3.2 36 3.6 1.05 132 4.8% 0.63 [0.26, 1.01] Zhang GQ 2020 6.22 3.2 55 4.11 1.27 166 5.2% 1.09 [0.77, 1.41] Zhou HF 2020 4.09 1.14 52 3.68 1.36 126 5.1% 0.31 [-0.01, 0.64] Total (95% Cl) 1049 2937 100.0% 0.66 [0.51, 0.81] Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup> = 71% Test for overall effect: $Z = 8.58$ (P < 0.00001)	Liu L 2020	4.95	2.57	7	4.28	1.92	44	2.3%	0.33 [-0.47, 1.13]	
Ma KL 2020       4.89       2.71       20       4.04       1.14       64       3.8%       0.51 [0.00, 1.02]         Pei GC 2020       4.96       2.38       189       4.01       1.42       144       5.9%       0.47 [0.25, 0.69]         Peng YD 2020       6.42       4.54       16       5.07       2.93       96       3.7%       0.42 [-0.11, 0.95]         Shi PY 2020       4.15       2.14       46       3.61       0.98       88       4.9%       0.36 [0.00, 0.72]         Wang DW 2020       6.65       4.09       36       4.07       1.5       102       4.6%       1.05 [0.65, 1.45]         Xu S 2020       5.93       4.29       131       4.3       2.3       224       5.9%       0.51 [0.29, 0.73]         Yan SJ 2020       4.71       3.2       36       3.6       1.05       132       4.8%       0.63 [0.26, 1.01]         Zhang GQ 2020       6.22       3.2       55       4.11       1.27       166       5.2%       1.09 [0.77, 1.41]         Zhou HF 2020       4.09       1.14       52       3.68       1.36       126       5.1%       0.31 [-0.01, 0.64]         Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup>	Liu YL 2020	5.54	2.36	53	3.75	1.45	56	4.6%	0.91 [0.52, 1.31]	
Pei GC 2020 $4.96$ $2.38$ $189$ $4.01$ $1.42$ $144$ $5.9\%$ $0.47$ [ $0.25$ , $0.69$ ]         Peng YD 2020 $6.42$ $4.54$ $16$ $5.07$ $2.93$ $96$ $3.7\%$ $0.42$ [ $-0.11$ , $0.95$ ]         Shi PY 2020 $4.15$ $2.14$ $46$ $3.61$ $0.98$ $88$ $4.9\%$ $0.36$ [ $0.00, 0.72$ ]         Wang DW 2020 $6.65$ $4.09$ $36$ $4.07$ $1.5$ $102$ $4.6\%$ $1.05$ [ $0.65, 1.45$ ]         Xu S 2020 $5.93$ $4.29$ $131$ $4.3$ $2.3$ $224$ $5.9\%$ $0.51$ [ $0.29, 0.73$ ]         Yan SJ 2020 $4.71$ $3.2$ $36$ $3.6$ $1.05$ $132$ $4.8\%$ $0.63$ [ $0.26, 1.01$ ]         Zhang GQ 2020 $6.22$ $3.2$ $55$ $4.11$ $1.27$ $166$ $5.2\%$ $1.09$ [ $0.77, 1.41$ ]         Zhou HF 2020 $4.09$ $1.14$ $52$ $3.68$ $1.36$ $126$ $5.1\%$ $0.31$ [ $-0.10, 0.64$ ]         Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); $P = 71\%$ $-0.5$ $0$ <td>Ma KL 2020</td> <td>4.89</td> <td>2.71</td> <td>20</td> <td>4.04</td> <td>1.14</td> <td>64</td> <td>3.8%</td> <td>0.51 [0.00, 1.02]</td> <td></td>	Ma KL 2020	4.89	2.71	20	4.04	1.14	64	3.8%	0.51 [0.00, 1.02]	
Peng YD 2020 $6.42$ $4.54$ $16$ $5.07$ $2.93$ $96$ $3.7\%$ $0.42$ [-0.11, 0.95]         Shi PY 2020 $4.15$ $2.14$ $46$ $3.61$ $0.98$ $88$ $4.9\%$ $0.36$ [0.00, 0.72]         Wang DW 2020 $6.65$ $4.09$ $36$ $4.07$ $1.5$ $102$ $4.6\%$ $1.05$ [0.65, 1.45]         Xu S 2020 $5.93$ $4.29$ $131$ $4.3$ $2.3$ $224$ $5.9\%$ $0.51$ [0.29, 0.73]         Yan SJ 2020 $4.71$ $3.2$ $36$ $3.6$ $1.05$ $132$ $4.8\%$ $0.63$ [0.26, 1.01]         Zhang GQ 2020 $6.22$ $3.2$ $55$ $4.11$ $1.27$ $166$ $5.2\%$ $1.09$ [0.77, 1.41]         Zhou HF 2020 $4.09$ $1.14$ $52$ $3.68$ $1.36$ $126$ $5.1\%$ $0.31$ [-0.01, 0.64]         Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup> = 71\% $0.66$ [0.51, 0.81] $-1$ $-0.5$ $0$ $0.5$ $1$ Test for overall effect: $7 = 8.58$ (P < 0.00001) $20.00001$ ) $10.000001$ $0.55$	Pei GC 2020	4.96	2.38	189	4.01	1.42	144	5.9%	0.47 [0.25, 0.69]	
Shi PY 2020 $4.15$ $2.14$ $46$ $3.61$ $0.98$ $88$ $4.9\%$ $0.36$ $[0.00, 0.72]$ Wang DW 2020 $6.65$ $4.09$ $36$ $4.07$ $1.5$ $102$ $4.6\%$ $1.05$ $[0.65, 1.45]$ Xu S 2020 $5.93$ $4.29$ $131$ $4.3$ $2.3$ $224$ $5.9\%$ $0.51$ $[0.29, 0.73]$ Yan SJ 2020 $4.71$ $3.2$ $36$ $3.6$ $1.05$ $132$ $4.8\%$ $0.63$ $[0.26, 1.01]$ Zhang GQ 2020 $6.22$ $3.2$ $55$ $4.11$ $1.27$ $166$ $5.2\%$ $1.09$ $[0.77, 1.41]$ Zhou HF 2020 $4.09$ $1.14$ $52$ $3.68$ $1.36$ $126$ $5.1\%$ $0.31$ $[-0.1, 0.64]$ Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup> = 71\% $0.66$ $[0.51, 0.81]$ $-1$ $-0.5$ $0$ $0.5$ $1$ Test for overall effect: $7 = 8.58$ (P < 0.00001) $0.00001$ ) $10.9$ $0.0001$ ) $0.5$ $1$	Peng YD 2020	6.42	4.54	16	5.07	2.93	96	3.7%	0.42 [-0.11, 0.95]	
Wang DW 2020 $6.65$ $4.09$ $36$ $4.07$ $1.5$ $102$ $4.6\%$ $1.05$ $[0.65, 1.45]$ Xu S 2020 $5.93$ $4.29$ $131$ $4.3$ $2.3$ $224$ $5.9\%$ $0.51$ $[0.29, 0.73]$ Yan SJ 2020 $4.71$ $3.2$ $36$ $3.6$ $1.05$ $132$ $4.8\%$ $0.63$ $[0.26, 1.01]$ Zhang GQ 2020 $6.22$ $3.2$ $55$ $4.11$ $1.27$ $166$ $5.2\%$ $1.09$ $[0.77, 1.41]$ Zhou HF 2020 $4.09$ $1.14$ $52$ $3.68$ $1.36$ $126$ $5.1\%$ $0.31$ $[-0.01, 0.64]$ Total (95% CI)       1049       2937 $100.0\%$ $0.66$ $[0.51, 0.81]$ $-1$ $-0.5$ $0$ $0.5$ $1$ Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup> = 71\% $-1$ $-0.5$ $0$ $0.5$ $1$	Shi PY 2020	4.15	2.14	46	3.61	0.98	88	4.9%	0.36 [0.00, 0.72]	
Xu S 2020       5.93       4.29       131       4.3       2.3       224       5.9% $0.51 [0.29, 0.73]$ Yan SJ 2020       4.71       3.2       36       3.6       1.05       132       4.8% $0.63 [0.26, 1.01]$ Zhang GQ 2020       6.22       3.2       55       4.11       1.27       166       5.2%       1.09 [0.77, 1.41]         Zhou HF 2020       4.09       1.14       52       3.68       1.36       126       5.1% $0.31 [-0.01, 0.64]$ Total (95% Cl)       1049       2937       100.0%       0.66 [0.51, 0.81]         Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup> = 71% $-1$ $-0.5$ $0$ $0.5$ $1$	Wang DW 2020	6.65	4.09	36	4.07	1.5	102	4.6%	1.05 [0.65, 1.45]	
Yan SJ 2020 $4.71$ $3.2$ $36$ $3.6$ $1.05$ $132$ $4.8\%$ $0.63$ [0.26, 1.01]         Zhang GQ 2020 $6.22$ $3.2$ $55$ $4.11$ $1.27$ $166$ $5.2\%$ $1.09$ [0.77, 1.41]         Zhou HF 2020 $4.09$ $1.14$ $52$ $3.68$ $1.36$ $126$ $5.1\%$ $0.31$ [-0.01, 0.64]         Total (95% Cl)       1049       2937 $100.0\%$ $0.66$ [0.51, 0.81] $-1$ $-0.5$ $0$ $0.5$ $1$ Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup> = 71\% $-1$ $-0.5$ $0$ $0.5$ $1$	Xu S 2020	5.93	4.29	131	4.3	2.3	224	5.9%	0.51 [0.29, 0.73]	
Zhang GQ 2020 $6.22$ $3.2$ $55$ $4.11$ $1.27$ $166$ $5.2\%$ $1.09$ [0.77, 1.41]         Zhou HF 2020 $4.09$ $1.14$ $52$ $3.68$ $1.36$ $126$ $5.1\%$ $0.31$ [-0.01, 0.64]         Total (95% Cl)       1049       2937       100.0% $0.66$ [0.51, 0.81]         Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup> = 71% $-1$ $-0.5$ $0$ $0.5$ $1$	Yan SJ 2020	4.71	3.2	36	3.6	1.05	132	4.8%	0.63 [0.26, 1.01]	
Zhou HF 2020       4.09       1.14       52       3.68       1.36       126       5.1%       0.31 [-0.01, 0.64]         Total (95% Cl)       1049       2937       100.0%       0.66 [0.51, 0.81]         Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup> = 71%       -1       -0.5       0       0.5       1         Test for overall effect: Z = 8.58 (P < 0.00001)	Zhang GQ 2020	6.22	3.2	55	4.11	1.27	166	5.2%	1.09 [0.77, 1.41]	
Total (95% Cl)       1049       2937       100.0%       0.66 [0.51, 0.81]         Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup> = 71%       -1       -0.5       0       0.5       1         Test for overall effect: Z = 8.58 (P < 0.00001)	Zhou HF 2020	4.09	1.14	52	3.68	1.36	126	5.1%	0.31 [-0.01, 0.64]	
Total (95% Cl)       1049       2937       100.0%       0.66 [0.51, 0.81]         Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < 0.00001); l <sup>2</sup> = 71% $-1$ $-0.5$ 0       0.5       1         Test for overall effect: Z = 8.58 (P < 0.00001)										
Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 75.56, df = 22 (P < $0.00001$ ); l <sup>2</sup> = 71% Test for overall effect: Z = 8.58 (P < $0.00001$ )	Total (95% CI)			1049			2937	100.0%	0.66 [0.51, 0.81]	
Test for overall effect: Z = 8.58 (P < 0.00001)	Heterogeneity: Tau <sup>2</sup> =	0.09; Cł	ni² = 75.	56, df =	= 22 (P ·	< 0.00	001); l²	= 71%	_	-1 -0.5 0 0.5 1
Favours [Non-severe] Favours [Severe]	Test for overall effect:	Z = 8.58	(P < 0.	00001)						Favours [Non-severe] Favours [Severe]

## B. eGFR

	Severe		Non-severe				Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Huang SP 2020	99.34	28	27	113.2	26.67	321	30.4%	-0.52 [-0.91, -0.12]	I
Rica R 2020	78.48	25.28	21	76.15	25.99	27	14.6%	0.09 [-0.48, 0.66]	
Zhang HZ 2020	89.82	16.47	14	103.07	13.26	29	10.6%	-0.91 [-1.57, -0.24]	
Zhou HF 2020	93.24	22.79	52	102.1	16.8	126	44.4%	-0.47 [-0.80, -0.14]	
Total (95% CI)			114			503	100.0%	-0.45 [-0.67, -0.23]	•
Heterogeneity: Chi <sup>2</sup> =	5.34, df	= 3 (P =	0.15);	l² = 44%					
Test for overall effect:	Z = 4.04	(P < 0.	Favours [Severe] Favours [Non-severe]						

# C.CRRT

.

	Sever	re	Non-sev	vere		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl		
Guan W 2020	9	173	0	926	9.0%	107.01 [6.20, 1847.50]			
Hong KS 2020	3	13	0	85	8.4%	57.00 [2.75, 1181.76]			
Hu L 2020	46	172	26	151	18.3%	1.76 [1.02, 3.01]			
Huang CL 2020	3	13	0	28	8.3%	19.00 [0.90, 399.79]			
Li Z 2020	7	65	0	128	8.9%	32.95 [1.85, 586.58]			
Shi PY 2020	1	46	0	88	7.8%	5.84 [0.23, 146.12]			
Wan SX 2020	4	40	1	95	11.3%	10.44 [1.13, 96.62]			
Wang DW 2020	2	36	0	102	8.3%	14.86 [0.70, 317.07]	· · · · · · · · · · · · · · · · · · ·		
Zhang GQ 2020	4	55	1	166	11.3%	12.94 [1.41, 118.40]	│ —— <b>—</b> →		
Zhao XY 2020	3	30	0	61	8.5%	15.65 [0.78, 313.52]			
Total (95% CI)		643		1830	100.0%	12.99 [4.03, 41.89]	-		
Total events	82		28						
Heterogeneity: Tau <sup>2</sup> =	1.87; Chi²	= 23.5	6, df = 9 (	P = 0.00	05); l² = 62	2%			
Test for overall effect:	Z = 4.29 (	P < 0.0	001)						
							Favours [Non-severe] Favours [Severe]		

Fig. 4. Forest plots represent the comparisons of standard mean differences (SMD) in BUN and eGFR as well as the prevalence of CRRT between severe and non-severe cases. A, BUN (blood urea nitrogen, mmol/L); B, eGFR (estimated glomerular filtration rate, ml/min); C, CRRT (continuous renal replacement therapy).

severe group [SMD = 0.66, 95%CI (0.51–0.81), Z = 8.58, P < 0.00001]. As indicated in Fig. 4B, 4 studies reported the eGFR with no remarkable heterogeneity ( $I^2 = 44\%$ ). The eGFR decreased significantly in severe cases compared with non-severe cases [SMD = -0.45, 95% CI (-0.67 - -0.23), Z = 4.04, P < 0.0001]. Additionally, 10 studies reported the application rate of CRRT with moderate heterogeneity ( $I^2 = 62\%$ ). As shown in Fig. 4C, the application rate of CRRT in severe group was

...

significantly higher than that in non-severe group [OR = 12.99, 95% CI: 4.03 to 41.89, P < 0.0001].

As severity of illness was related with complication in COVID-19, we also evaluated the incidence of AKI in severe and non-severe group (Fig. 5A). The heterogeneity test of AKI was shown as  $l^2 = 20\%$ . 19 studies among 4968 COVID-19 patients reported that the incidence of AKI was shown to be 26.74% in severe group, which was significant higher

Α ΑΚΙ							
/ /	Sever	е	Non-sev	vere		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% Cl
Antinori S 2020	7	18	1	17	1.9%	10.18 [1.09, 94.83]	
Argenziano MG 2020	184	236	104	614	37.6%	17.35 [11.95, 25.20]	
Bi QF 2020	9	93	2	327	2.4%	17.41 [3.69, 82.10]	
Cai QX 2020	13	58	4	240	3.6%	17.04 [5.32, 54.65]	
Guan W 2020	5	173	1	926	0.9%	27.53 [3.20, 237.12]	· · · · · · · · · · · · · · · · · · ·
Hong KS 2020	8	13	1	85	0.3%	134.40 [13.94, 1295.98]	
Hu L 2020	15	172	2	151	5.7%	7.12 [1.60, 31.66]	
Huang CL 2020	3	13	0	28	0.7%	19.00 [0.90, 399.79]	
Jiang XF 2020	2	8	1	47	0.6%	15.33 [1.20, 195.74]	<b></b>
Li Z 2020	43	65	12	128	8.1%	18.89 [8.61, 41.45]	
Pei GC 2020	30	189	5	144	14.1%	5.25 [1.98, 13.89]	
Regina J 2020	17	36	13	164	7.3%	10.39 [4.37, 24.70]	
Shi PY 2020	2	46	1	88	1.9%	3.95 [0.35, 44.82]	
Wan SX 2020	1	40	4	95	6.8%	0.58 [0.06, 5.39]	
Wang DW 2020	3	36	2	102	2.8%	4.55 [0.73, 28.39]	
Yan SJ 2020	3	36	0	132	0.6%	27.69 [1.40, 549.10]	│ ————→
Yang QX 2020	3	33	1	103	1.3%	10.20 [1.02, 101.68]	
Zhang GQ 2020	8	55	2	166	2.5%	13.96 [2.87, 67.97]	
Zhao XY 2020	5	30	0	61	0.8%	26.53 [1.41, 497.65]	
Total (95% CI)		1350		3618	100.0%	13.16 [10.16, 17.05]	•
Total events	361		156				
Heterogeneity: Chi <sup>2</sup> = 22	2.51, df =	18 (P =	: 0.21); l <sup>2</sup>	= 20%			
Test for overall effect: Z	= 19.54 (	P < 0.0	0001)				0.01 0.1 1 10 100
	. (		,				Favours INON-Severel Favours ISeverel

## B. Proteinuria

	Sever	е	Non-sev	/ere		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
Cao M 2020	8	18	51	144	17.1%	1.46 [0.54, 3.93]			
Li Z 2020	31	47	45	82	21.3%	1.59 [0.76, 3.35]	+		
Liu R 2020	22	52	12	67	19.7%	3.36 [1.46, 7.73]			
Pei GC 2020	156	189	63	144	25.8%	6.08 [3.69, 10.02]			
Zhou HF 2020	11	19	18	64	16.1%	3.51 [1.22, 10.16]			
Total (95% CI)		325		501	100.0%	2.92 [1.58, 5.38]	◆		
Total events	228		189						
Heterogeneity: Tau <sup>2</sup> = 0	0.31; Chi <sup>2</sup>	= 11.9	9, df = 4 (	P = 0.02	2); l² = 67%	6			
Test for overall effect: 2	Z = 3.43 (I	P = 0.0	006)				Favours [Non-severe] Favours [Severe]		

## C. Hematuria

	Seve	re	Non-sev	/ere		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Li Z 2020	21	47	36	82	24.4%	1.03 [0.50, 2.12]	_ <b>_</b>
Liu R 2020	22	52	27	67	22.9%	1.09 [0.52, 2.27]	
Pei GC 2020	91	189	48	144	47.6%	1.86 [1.19, 2.91]	
Zhou HF 2020	10	19	14	64	5.1%	3.97 [1.35, 11.66]	
Total (95% CI)		307		357	100.0%	1.59 [1.15, 2.19]	◆
Total events	144		125				
Heterogeneity: Chi <sup>2</sup> = 5	.63, df =	3 (P = 0	0.13); l² =	47%			
Test for overall effect: Z	Z = 2.83 (	P = 0.0	05)				Favours [Non-severe] Favours [Severe]

Fig. 5. Forest plots represent the comparisons of incidence of AKI and two clinical characteristics of kidney injury between severe and non-severe cases. A, AKI; B, Proteinuria; C, Hematuria.

than that in non-severe group (4.31%) [OR = 13.16, 95%CI (10.16–17.05), Z = 19.54, P < 0.00001].

As shown in Fig. 5B, based on the 5 studies with significant heterogeneity to evaluate proteinuria ( $I^2 = 67\%$ ), COVID-19 patients in severe cases had higher ratio of proteinuria than non-severe cases [OR = 2.92, 95% CI (1.58–5.38), Z = 3.43, P = 0.0006]. In addition, we also performed meta-analysis on the incidence of hematuria of 664 COVID-19 patients with no statistical heterogeneity among 4 studies ( $I^2 = 47\%$ ). The incidence of hematuria in severe group was statistically higher compared with non-severe group [OR = 1.59, 95% CI (1.15–2.19), Z = 2.83, P = 0.005] (Fig. 5C).

## 4. Discussion

Our meta-analysis including 14,094 subjects from 52 studies explored the potential relationship between renal impairment as well as AKI and the clinical outcome (severity and mortality) of COVID-19 patients. To our knowledge, this is the first systemic review and metaanalysis which evaluated the kidney function and prevalence of AKI between survival and non-survival cases. We found that the prevalence of AKI in non-survival cases was 30.72%, which was approximately 77.48fold higher than that in survival cases. Furthermore, patients who died of COVID-19 displayed higher baseline of sCr and BUN as well as higher application rate of CRRT than the survival cases. Meanwhile, our results including severe and non-severe cases (41 studies, 10,335 patients) demonstrated that the overall rate of AKI in severe cases was 13.16fold higher compared with non-severe cases. The levels of sCr and BUN were shown elevated, while eGFR was decreased in severe cases compared with non-severe cases. In addition, the average ratio of proteinuria, hematuria and CRRT were 2.92-fold, 1.59-fold and 12.99-fold in severe cases compared with those in non-severe cases, respectively.

Currently, the exact mechanism of renal impairment involved in COVID-19 remains unclear. One potential explanation is direct virus attack mediated via angiotensin-converting enzyme 2 (ACE2). RNA sequencing studies found that ACE2, the novel protein of coronavirus receptor, was highly expressed in proximal renal tubules, which could explain that the urinary analysis was obviously abnormal in COVID-19 patients [58]. Hence, early detection of urinary analysis is important for preventing the occurrence of AKI. In addition, hyper-activated immune response may be partly responsible for the development of kidney damage. Clinical studies have shown that the levels of inflammatory cytokines in severe patients are significantly increased compared with mild patients [30]. A recent biopsy pathology result of a COVID-19 patient with ARDS demonstrated that the numbers of CD4<sup>+</sup> and CD8<sup>+</sup> T cells in peripheral blood were greatly reduced, while T cells were excessively activated [59]. These above findings indicated that pathological waterfall-like cytokines storm caused by immune dysregulation may be involved in the occurrence and development of AKI and multiple organ dysfunctions. Additionally, patients with COVID-19, especially severe and critical cases, are prone to complications such as sepsis, shock, and hypovolemia, which could cause the occurrence or aggravation of AKI through excessive inflammatory responses, apoptosis, and mitochondrial stress [60]. Therefore, optimizing fluid volume and maintaining hemodynamic stability are crucial for severe COVID patients to ensure adequate and effective perfusion pressure of the kidney, which could prevent the occurrence or progression of AKI.

There are strengths of this meta-analysis. To the best of our knowledge, this is the first large meta-analysis which performed a pairwise comparison of kidney function indicators and prevalence of AKI in severe vs. non-severe or non-survival vs. survival cases, respectively. Secondly, we have included a large number of studies covering six countries, with patient population above fourteen thousand. Finally, our meta-analysis provides the awareness for clinicians to pay more attention for risk screening, early identification and timely treatment of AKI. Our study also has several limitations. Firstly, although we firstly investigated the renal impairments in survival and non-survival cases, we did not analyze the laboratory changes in hematuria, proteinuria, and eGFR due to the lack of literatures. Secondly, we found moderate statistical heterogeneity in BUN levels. However, the heterogeneity could not be removed through subgroup analysis. Thirdly, another limitation of our analysis is that some articles provided median and interquartile ranges of values in sCr, BUN and eGFR. The mean and SD for these data were required for conversion based on the median and interquartile range, which might result in inaccuracy of values. Lastly, lots of drugs are nephrotoxic to cause the drug-related AKI, such as antibiotics, ACE inhibitors and nonsteroidal anti-inflammatory drugs. We were not sure whether clinical data were affected by drug side-effects.

In conclusions, our meta-analysis provides the further evidence that kidney impairment and AKI are susceptible to occur in COVID-19 patients with worse clinical outcome. The risk of AKI dramatically increased in severe COVID-19. Therefore, it is necessary to establish the early identification for AKI, such as dynamic monitoring urine analysis, renal function, and biomarker detections of renal injury, which should be helpful for improvement for prognosis of COVID-19 patients.

## Funding

This work was supported by the National Natural Science Foundation of China (Grant number: 81500064).

## **Declaration of Competing Interest**

The authors declare no conflict of interest.

#### References

- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229):1054–62.
- [2] Huang Y, Lyu X, Li D, et al. A cohort study of 223 patients explores the clinical risk factors for the severity diagnosis of COVID-19. medRxiv. 2020 [preprint].
- [3] Li Z, Wu M, Yao J, et al. Caution on kidney dysfunctions of COVID-19 patients. medRxiv. 2020 [preprint].
- [4] Xu S, Fu L, Fei J, et al. Acute kidney injury at early stage as a negative prognostic indicator of patients with COVID-19: a hospital-based retrospective analysis. medRxiv. 2020 [preprint].
- [5] Wang L, Li X, Chen H, et al. Coronavirus disease 19 infection does not result in acute kidney injury: an analysis of 116 hospitalized patients from Wuhan, China. Am J Nephrol. 2020;51(5):343–8.
- [6] JPT Higgins, Thomas J, Chandler J, LT Cumpston M, Page MJ, Welch VA, editors. Cochrane handbook for systematic reviews of interventions version 6.0. London, UK: The Cochrane Collaboration; July 2019. p. 2019 Available from: http:// handbook.cochrane.org. (Accessed June 2020).
- [7] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clin Res Ed). 2009;339:b2700.
- [8] Liu W, Tao ZW, Wang L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl). 2020; 133(9):1032–8.
- [9] Yang Q, Xie L, Zhang W, et al. Analysis of the clinical characteristics, drug treatments and prognoses of 136 patients with coronavirus disease 2019. J Clin Pharm Ther. 2020;45(4):606–9.
- [10] Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev. 1987;9:1–30.
- [11] Antinori S, Cossu MV, Ridolfo AL, et al. Compassionate remdesivir treatment of severe COVID-19 pneumonia in intensive care unit (ICU) and non-ICU patients: clinical outcome and differences in post-treatment hospitalisation status. Pharmacol Res. 2020;158:104899.
- [12] Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 Patients with COVID-19 in New York: retrospective case series. medRxiv. 2020 [preprint].
- [13] Bi Q, Hong C, Meng J, et al. Characterizing clinical progression of COVID-19 among patients in Shenzhen, China: an observational cohort study. medRxiv. 2020 [preprint].
- [14] Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy Eur J Allergy Clin Immunol. 2020 [preprint].
- [15] Cao J, Tu WJ, Cheng W, et al. Clinical features and short-term outcomes of 102 patients with Corona virus disease 2019 in Wuhan, China. Clin Infect Dis. 2020;71 (15):748–55 [preprint].

- [16] Cao M, Zhang D, Wang Y, et al. Clinical features of patients infected with the 2019 Novel Coronavirus (COVID-19) in Shanghai, China. medRxiv. 2020 [preprint].
- [17] Cao W, Shi L, Chen L, Xu X, Wu Z. Clinical features and laboratory inspection of novel coronavirus pneumonia (COVID-19) in Xiangyang, Hubei. medRxiv. 2020 [preprint].
   [18] Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and mod-
- erate forms of Coronavirus Disease 2019. medRxiv. 2020 [preprint]. [19] Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with co-
- ronavirus disease 2019: retrospective study. BMJ (Clin Res Ed). 2020;368:m1091. [20] Chen X, Zheng F, Qing Y, et al. Epidemiological and clinical features of 291 cases with
- coronavirus disease 2019 in areas adjacent to Hubei, China: a double-center observational study. medRxiv. 2020 [preprint].
- [21] de la Rica R, Borges M, Aranda M, et al. Low albumin levels are associated with poorer outcomes in a case series of COVID-19 patients in Spain: a retrospective cohort study. medRxiv. 2020 [preprint].
- [22] Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J (Engl). 2020;133(11):1261–7.
- [23] Duan J, Wang X, Chi J, et al. Correlation between the variables collected at admission and progression to severe cases during hospitalization among COVID-19 patients in Chongqing. J Med Virol. 2020 [ahead of online].
- [24] Fu L, Fei J, Xiang H, et al. Influence factors of death risk among COVID-19 patients in Wuhan, China: a hospital-based case-cohort study. medRxiv. 2020 [preprint].
- [25] Giacomelli A, Ridolfo AL, Milazzo L, et al. 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: a prospective cohort study. Pharmacol Res. 2020;104931.
- [26] Gong J, Ou J, Qiu X, et al. A tool to early predict severe Corona Virus Disease 2019 (COVID-19): a multicenter study using the risk nomogram in Wuhan and Guangdong, China. Clin Infect Dis. 2020;71(15):833–40.
- [27] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.
- [28] Hong KS, Lee KH, Chung JH, et al. Clinical features and outcomes of 98 patients hospitalized with SARS-CoV-2 infection in Daegu, South Korea: a brief descriptive study. Yonsei Med J. 2020;61(5):431–7.
- [29] Hu L, Chen S, Fu Y, et al. Risk factors associated with clinical outcomes in 323 COVID-
- 19 hospitalized patients in Wuhan, China. Clin Infect Dis. 2020 [ahead of online].
   [30] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
- [31] Huang H, Cai S, Li Y, et al. Prognostic factors for COVID-19 pneumonia progression to severe symptom based on the earlier clinical features: a retrospective analysis. medRxiv. 2020 [preprint].
- [32] Huang S, Huang M, Li X, Zhang T, Lu H. Significance of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio for predicting clinical outcomes in COVID-19. medRxiv. 2020 [preprint].
- [33] Jiang X, Tao J, Wu H, et al. Clinical features and management of severe COVID-19: a retrospective study in Wuxi, Jiangsu Province, China. medRxiv. 2020 [preprint].
- [34] Liu L, Gao J, Hu W, et al. Clinical characteristics of 51 patients discharged from hospital with COVID-19 in Chongqing, China. medRxiv. 2020 [preprint].
- [35] Li K, Chen D, Chen S, et al. Radiographic findings and other predictors in adults with COVID-19. medRxiv. 2020 [preprint].
- [36] Liu J, Liu Y, Xiang P, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med. 2020;18(1): 206.
- [37] Liu R, Ma Q, Han H, et al. The value of urine biochemical parameters in the prediction of the severity of coronavirus disease. Clin Chem Lab Med. 2019:2020.
- [38] Liu Y, Sun W, Li J, et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. medRxiv. 2020 [preprint].

- [39] Ma K, Liu Z, Cao C, et al. COVID-19 myocarditis and severity factors: an adult cohort study. medRxiv. 2020 [preprint].
- [40] Paranjpe I, Russak A, De Freitas JK, et al. Clinical characteristics of hospitalized COVID-19 patients in New York City. medRxiv. 2020 [preprint].
- [41] Pei G, Zhang Z, Peng J, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. J Am Soc Nephrol. 2020;31(6):1157–65.
- [42] Peng YD, Meng K, Guan HQ, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. Zhonghua Xin Xue Guan Bing Za Zhi. 2020;48(0):E004.
- [43] Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ (Clin Res Ed). 2020;369:m1966.
- [44] Regina J, Papadimitriou-Olivgeris M, Burger R, et al. Epidemiology, risk factors and clinical course of SARS-CoV-2 infected patients in a Swiss university hospital: an observational retrospective study. medRxiv. 2020 [preprint].
- [45] Shi P, Ren G, Yang J, et al. Clinical characteristics of imported and second-generation COVID-19 cases outside Wuhan, China: a multicenter retrospective study. medRxiv. 2020 [preprint].
- [46] Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in Northeast Chongqing. J Med Virol. 2020;92(7):797–806.
- [47] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323 (11):1061–9.
- [48] Wang Z, Li H, Li J, et al. Elevated serum IgM levels indicate poor outcome in patients with coronavirus disease 2019 pneumonia: a retrospective case-control study. medRxiv. 2020 [preprint].
- [49] Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Int Med. 2020 [preprint].
- [50] Xu Y, Li Y, Zeng Q, et al. Clinical characteristics of SARS-CoV-2 pneumonia compared to controls in Chinese Han population. medRxiv. 2020 [preprint].
- [51] Yan S, Song X, Lin F, et al. Clinical characteristics of coronavirus disease 2019 in Hainan, China. medRxiv. 2020 [preprint].
- [52] Yang J, Jin J, Liu S, et al. Blood glucose is a representative of the clustered indicators of multi-organ injury for predicting mortality of COVID-19 in Wuhan, China. medRxiv. 2020 [preprint].
- [53] Zhang F, Yang D, Li J, et al. Myocardial injury is associated with in-hospital mortality of confirmed or suspected COVID-19 in Wuhan, China: a single center retrospective cohort study. medRxiv. 2020 [preprint].
- [54] Zhang G, Hu C, Luo L, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol. 2020;127 [preprint].
- [55] Zhang H, Wang X, Fu Z, et al. Potential factors for prediction of disease severity of COVID-19 patients. medRxiv. 2020 [preprint].
- [56] Zhao X, Xu X, Yin H, et al. Clinical characteristics of patients with 2019 coronavirus disease in a non-Wuhan area of Hubei Province, China: a retrospective study. BMC Infect Dis. 2020;20(1).
- [57] Zhou H, Zhang Z, Fan H, et al. Urinalysis, but not blood biochemistry, detects the early renal-impairment in patients with COVID-19. medRxiv. 2020 [preprint].
- [58] Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260–3.
- [59] Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420–2.
- [60] Bellomo R, Kellum JA, Ronco C, et al. Acute kidney injury in sepsis. Intensive Care Med. 2017;43(6):816–28.