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Review

Corona Virus Disease 2019 (COVID-19) and Its Effect on Renal System, A Systematic Review and Meta-analysis

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Keywords. acute kidney injury, blood urea nitrogen, creatinine, COVID-19, SARS-CoV-2

Coronavirus disease 2019 (COVID-19) has been recently emerged with various manifestations, mainly on respiratory system. However, other organs might also be involved. Acute kidney injury has been reported as a complication with high variability and controversial results. We aimed to define the frequency of AKI as well as two specific renal biomarkers including BUN and serum Cr among individuals suffering from COVID-19 infection. We investigated Medline/PubMed, Scopus, and Google Scholar databases until 16th April 2020 and included all relevant peer-reviewed published studies without any language limitations. We further categorized patients according to their clinical status into severe, non-severe, and death groups. 18 records on 4528 individuals were assessed. The mean age of individuals were 52.5 ± 24.4 years (males: 55.6%). Prevalence of AKI was 4% (95% CI: 2% to 8%) and was significantly lower among non-severe patients in comparison to deceased ones (1%, 95% CI: 0% to 4%, vs. 31%, 95% CI: 19% to 47%). BUN mean was 5.14 mmol/L (95% CI: 4.60 to 5.69). Non-severe patients had remarkably lower means of BUN compared to deceased or those with severe infection (4.25 mmol/L, 95% Cl: 3.70 to 4.79, vs. 8.9 mmol/L, 95% CI: 7.94 to 9.86, vs. 6.63 mmol/L, 95% Cl: 5.62 to 7.65; respectively). The mean serum Cr was 71.60 mmol/L (95% Cl: 67.56 to 75.64). Our findings suggest that COVID-19 does not seem to involve renal system extensively and other possible mechanisms might be further investigated in this regard.

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INTRODUCTION

After two prior epidemics of Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) in 2002-2003 and 2012, respectively, a new pathogen related to this family was first emerged in Wuhan, China in late December 2019 with the reporting of multiple cases of pneumonia with unknown etiology.[1,2] Further analysis of respiratory samples revealed this virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), coronavirus disease 2019 (COVID-19), and 2019 novel coronavirus (2019-nCoV) were official interchangeable names introduced afterward to this positively charged enveloped single-stranded RNA virus. Due to its high spreading rate in all over the world,[3] world

health organization (WHO) declared the term "pandemic" in March 2020.[4] This infection usually presents with various nonspecific symptoms, including fever, cough, sore throat, fatigue, headache, and myalgia. Moreover, several studies report the occurrence of respiratory associated symptoms, including dyspnea and acute respiratory distress syndrome (ARDS).[5,6] Although the exact pathophysiological mechanism remains to be investigated, the probable issue is suggested to be related to the angiotensin-converting enzyme (ACE) receptor.[7] Despite this receptor is present in lung tissues resulted in severe pulmonary symptoms, other body organs including heart, kidneys, liver, gastrointestinal as well as nervous system have been reported to pose this kind of receptor.[8] Therefore, it seems this contagious virus might involve a variety of body tissues. Kidneys are one of the organs which are involved in this regard. Some studies reported the acute kidney injury[1] as a probable complication among patients suffering from COVID-19 infection.[9-11] On the other hand, it has been reported that patients with prior history of chronic kidney diseases (CKD) or those received renal replacement therapy are more susceptible in case of COVID-19 infection and specialized diagnostic guidelines as well as drug treatment strategies must be implemented in this regard.[1,12,13] Due to high variability and controversial results, implementation of a review seems to be necessary in this regard. In this review, we sought to define the proportion of AKI as well as two specific renal biomarkers including blood urea nitrogen (BUN) and serum creatinine (Cr) among individuals suffering from COVID-19 infection.

MATERIALS AND METHODS

Protocol and Registration

We implemented current study in the context of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[14] We further registered this manuscript protocol in the International Prospective Register of Systematic Reviews (PROSPERO) database registry (CRD42020179094).

Eligibility Criteria

We aimed to estimate proportions of AKI and mean levels of renal functional biochemistry indices, including BUN and serum Cr in patients with laboratory-confirmed COVID-19 infection. All peer-reviewed published case series, cross-sectional, review, cohort, and case-control studies without any language limitations were included. We excluded animal studies, case reports, or case series with less than 20 individuals, letters, or any kinds of studies without complete data.

Information Source and Search Strategies

Two individual authors extracted data from full-text articles. Medline/PubMed, Scopus, and Google Scholar databases were searched until 16th April 2020. We added time limitation for google scholar database searching from 1st Jan. 2020. We searched the following terms related to AKI in various combinations: "acute kidney injury", "acute renal injury", "acute kidney damage", "acute renal damage", "renal insufficiency", "kidney insufficiency", "kidney injury", "renal injury", "kidney damage", "renal damage", "renal failure", "kidney failure", "SARS-CoV-2", "coronavirus", "covid-19", "2019-nCoV", and "coronavirus covid-19". The following terms in the databases mentioned above were used in combinations for investigating renal functional laboratory enzymes indices: "blood urea nitrogen", "BUN", "urea nitrogen", "serum creatinine", "creatinine", "Cr", "SARS-CoV-2", "coronavirus", "covid-19", "2019-nCoV", and "coronavirus covid-19".

Data Management and Selection Process

The flow diagram of the study, according to AKI, BUN, and Cr, is represented in Figure 1 (A, B, and C; respectively). Two independent reviewers first screened the titles and abstracts of manuscripts. In terms of relevancy, full texts were obtained and assessed additionally based on our pre-defined inclusion and exclusion criteria. If there was any duplicate publications, we counted only the single one. In the presence of any terms indicating kidney injury or BUN as well as Cr, the articles were selected and classified in their specific groups.

Data Collection Process and Data Items

After the selection of eligible studies, data including authors' names, location of study conduction, date of study implementation, sample size, age (median and interquartile range (IQR) or mean ± standard deviation (SD), as reported), sex

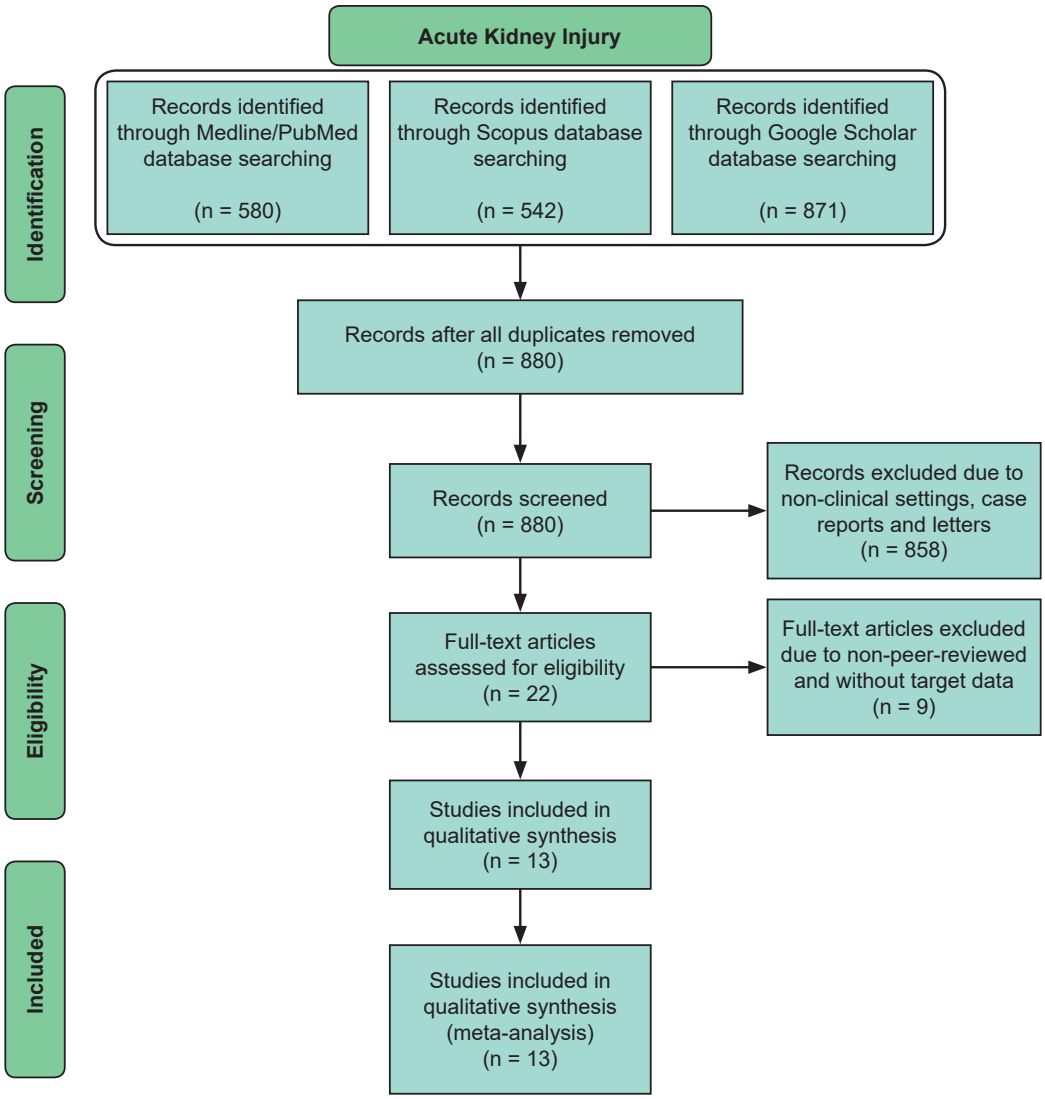


Figure 1A. Flow diagram of studies (A: AKI)

(male/female), the proportion of AKI and laboratory information related to kidney performance (including BUN and Cr) were obtained by two independent investigators. The third researcher checked if there were any discrepancies between data extraction files, and disagreements were finally resolved by consensus.

Risk of Bias Assessment, Data Synthesis, and Statistical Approach

We used a critical appraisal tool (AXIS tool) to assess the quality of cross-sectional studies.[15] "Assessment of multiple systematic reviews" (AMSTAR) or "strengthening the reporting of observational studies in epidemiology" (STROBE) tools were utilized for quality assessment of systematic review and other observational studies, respectively.[16,17] For investigating pooled prevalence with their specific 95% CI, we used the binary random-effects model. Inverse-variance with the random-effects model was used for pooled results of proportions and means with their respective 95% CIs. We used Wan and colleagues' statistical method for calculation of means and SDs in studies in which medians and IQRs were reported for continuous variables.[18] Funnel plots were depicted for assessment of publication bias and symmetrical distribution of our predefined variables including AKI, BUN, and Cr over each side of the pooled estimate. We utilized forest plots for demonstration of the impact of COVID-19 on AKI, BUN, and Cr. We converted all unit variables to the standard units for better

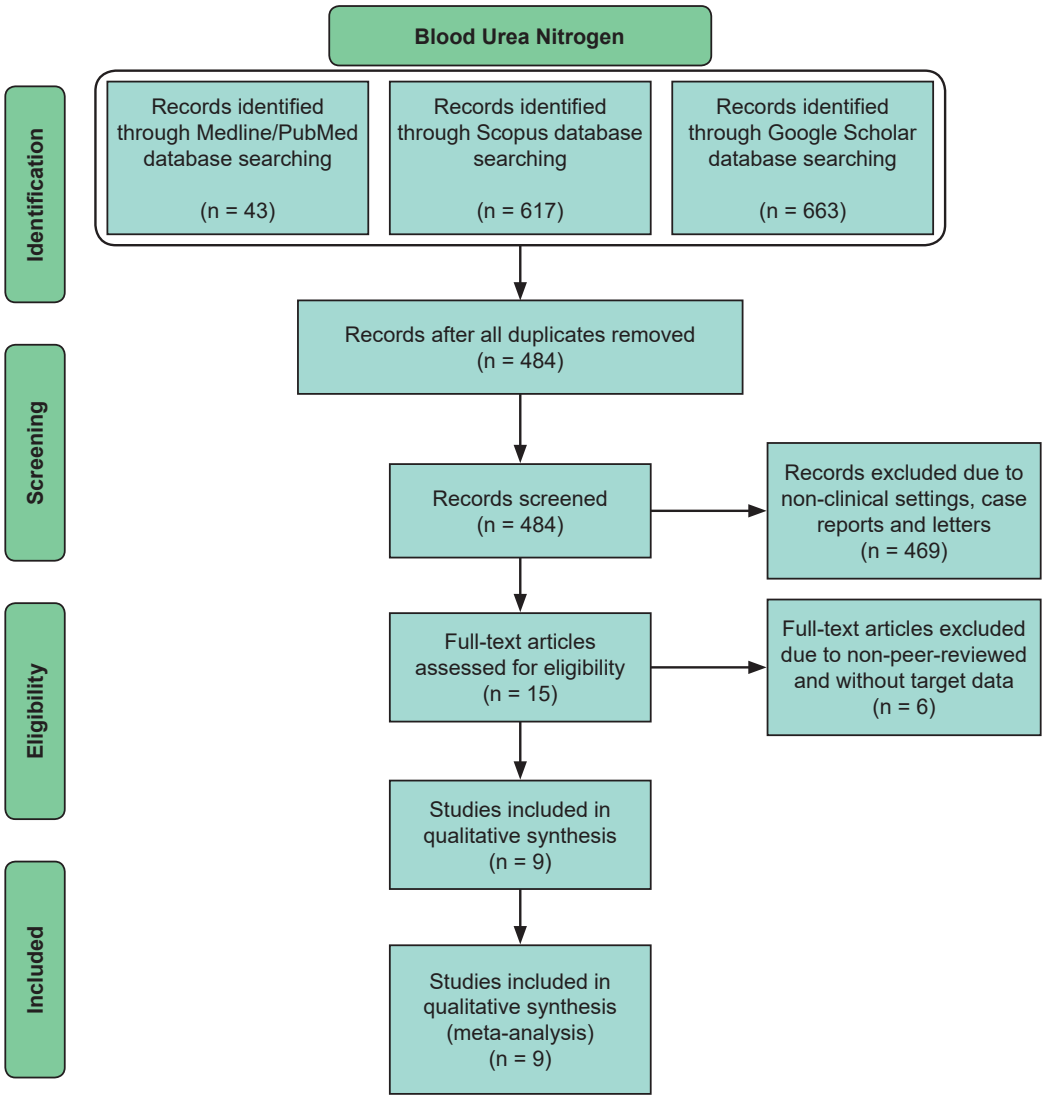


Figure 1B. Flow diagram of studies (B: BUN)

analysis. Heterogeneity measurement was done using Cochran's Q statistic, $I^{2,}$ and the tau-squared (τ^2). We categorized the study population based on the severity of the infection reported by each record as the followings: severe group (including intensive care unit (ICU), critical and severe), non-severe group (including non-ICU, general and non-severe) and death group (including non-survivor and death). We used comprehensive meta-analysis software (version 2) for performing all analyses.

RESULTS

Study Selection and Characteristics

The study was designed to assess the impact of COVID-19 infection on renal systems according to three predefined variables, including AKI, BUN, and Cr. In terms of the former variable, we found 1993 records in all databases with the removal of 1980 records because of duplications and not achieving inclusion criteria. Finally, data of 13 full-texts were extracted (Figure 1A). AKI was defined as an increase in serum Cr level by ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours according to kidney disease improving global outcomes (KIDGO) guideline.[19] For BUN, databases were searched, and 484 records were screened. After all, duplicated records were eliminated, 459 records were excluded due to non-clinical settings, case reports, letters, non-peer-reviewed or without target data, and full-texts of 9 studies were obtained for further analysis (Figure 1B). We found 2535 records in databases in terms of Cr. After the removal of

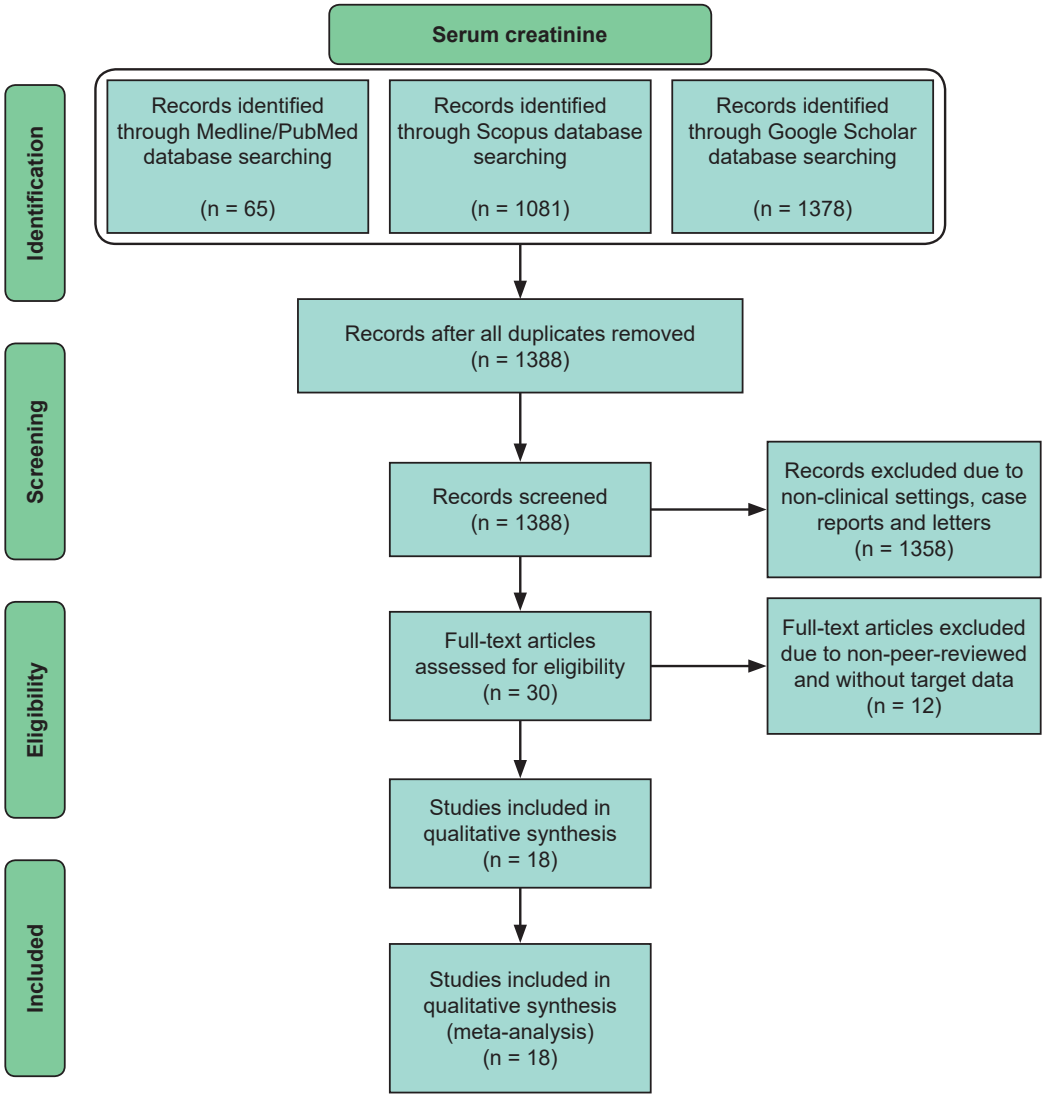


Figure 1C. Flow diagram of studies (C: Cr)

duplicated records either within each database or between databases, 1388 records were screened, and 18 full-text articles were included after the elimination of non-eligible studies (Figure 1C). Summary characteristics and analysis of included studies are summarized in Tables 1 and 2. All studies were conducted in China and had cross-sectional designs. The total number of participants in AKI, BUN, and Cr groups were 4031, 2197, and 4528; respectively. Table S1 represented the risk of bias assessment of included studies. In all included studies, the objectives were clearly defined. Moreover, they all had appropriate study designs without any sample size justification. The target study sample was clearly characterized in all records and each study had recruited subjects who had been appropriately represented the target population with proper explanation of selection process. There was not any non-respondent in any studies and consequently no measures were taken in this regard. In all recruited studies, the desired variables were correctly measured according to study aims. Methodological description and determination of statistical significance were clearly announced in all records. In terms of their results, all basic data and statistical analysis previously mentioned in methods section were consistent and sufficiently described. The discussion and conclusion of all studies were appropriately written based on their reported outcomes. All records had ethical approval codes and there was not any observed conflict of interest in any included studies. With an exception

Table 1. Summary of Studies Reporting Kidney Function in Patients Infected with COVID-19

Authors	Country	Date	Population	N	Age (years)					Sex	Kidney Function Indices*
					Median	IQR		Mean	SD	Male (%)	
Chen C et al. [20]	China	Jan. 2019 - Feb. 2020	Total	150	NA	NA	NA	59	16	84 (56)	Cr: 70.03 ± 25.98
			ICU (critical)	24	NA	NA	NA	68.5	13.6	18 (75)	Cr: 82.5 (67, 119)
			Non-ICU (General)	126	NA	NA	NA	57.1	15.6	66 (52.3)	Cr: 66 (53, 80)
Chen N et al. [11]	China	1st Jan. 2020 - 20th Jan. 2020	Total	99	NA	NA	NA	55.5	13.1	67 (68)	Cr: 75.6 (25) Elevated Cr: 3 (3%) BUN: 5.9 ± 2.6 Elevated BUN: 6 (6%) AKI: 3 (3%)
Chen T et al. [9]	china	13th Jan. 2020 - 12 Feb. 2020	Total	274	62	44	70	NA	NA	171 (62)	Cr: 76 (58, 94) BUN: 4.9 (3.5, 5.7) AKI: 29 (11%)
			Survivors	161	51	37	66	NA	NA	88 (55)	Cr: 66 (54, 84) BUN: 4 (3, 5.1) AKI: 1 (1 %)
			Death	113	68	62	77	NA	NA	83 (73)	Cr: 88 (66, 114) BUN : 8.4 (5.7, 12.6) AKI: 28 (25%)
Chen X et al. [5]	China	26th Jan. 2020 - 31th Jan. 2020	Total	78	45	15	79	NA	NA	39 (50)	Cr: 62.74 Elevated Cr: 11 (14.1%) BUN: 3.95 Elevated BUN: 1 (1.3%)
Cheng et al. [31]	china	28th Jan. 2020 - 11th Feb. 2020	Total	701	63	50	71		NA	367 (52.4)	Cr: 77 (31) Elevated Cr: 101 (14.1%) BUN : 5.7 ± 3.9 Elevated BUN: 92 (13.1%) AKI: 36 (5.1%)
Deng et al. [10]	china	1st Jan. 2020 - 21th Feb. 2020	Total	225	NA	NA	NA	NA	NA	124 (55.1)	AKI: 20 (8.9%)
			Death	109	69	62	74	NA	NA	73 (67)	Cr: 89 (72, 103.5) AKI: 20 (18.3%)
			Survivors	116	40	33	57	NA	NA	51 (44)	Cr: 65 (54.6, 78.75) AKI: 0 (0%)
Guan W et al. [32]	China	11th Dec. 2019 - 29th Jan. 2020	Total	1099	47	35	58	NA	NA	640 (58.1)	Elevated Cr: 12/752 (1.6%) AKI: 6 (0.5%)
			ICU	173	52	40	65	NA	NA	100 (57.8)	Elevated Cr: 6/138 (4.3%) AKI: 5 (2.9%)
			Non-ICU	926	45	34	57	NA	NA	540 (58.2)	Elevated Cr: 6/614 (1%) AKI: 1 (0.1%))

Table 1. Continued

Authors	Country	Date	Population	N	Age (years)					Sex	Kidney Function Indices*
					Median	IQR		Mean	SD	Male (%)	
Huang et al. [5]	China	16th Dec. 2019 - 2nd Jan. 2020	Total	41	49	41	58	NA	NA	30 (73)	Cr: 74.2 (57.5, 85.7) Elevated Cr: 4 (10%) AKI: 3 (7%)
			ICU	13	49	41	61	NA	NA	11 (85)	Cr: 79 (53.1, 92.7) Elevated Cr: 2 (15%) AKI: 3 (23%)
			Non-ICU	28	49	41	57.5	NA	NA	19 (68)	Cr: 73.3 (57.5, 84.7) Elevated Cr: 2 (7%) AKI: 0 (0%)
Lei et al. [27]	China	1st Jan- 5th Feb 2020	Total	34	55	43	63	NA	NA	14 (41.2)	Cr: 57.4 (46.6, 64) BUN: 4.5 (3.8, 7.5) AKI: 2 (5.9%)
			ICU	15	55	44	74	NA	NA	5 (33.3)	Cr: 63 (60, 76) BUN: 5.8 (4.9, 10.3) AKI: 2 (13.3%)
			Non-ICU	19	47	29	58	NA	NA	9 (47.4)	Cr: 46.8 (42, 57) BUN: 4 (3.3, 4.2) AKI: 0 (0%)
Shi S et al. [33]	china	20th Jan. 2020 - 10 Feb. 2020	Total	416	64	21	95	NA	NA	205 (49.3)	Cr: 59.22 (48.62, 71.6) BUN: 4.5 (3.8, 7.5) AKI: 8 (1.9%)
Wang D et al. [10]	China	1st Jan. 2020 - 28th Jan. 2020	Total	138	56	42	68	NA	NA	75 (54.3)	Cr: 72 (60, 78) BUN: 4.4 (3.4, 5.8) Elevated BUN: 15 (14.7%) AKI: 5 (3.6%)
			ICU	36	66	57	78	NA	NA	22 (61.1)	Cr: 80 (66, 106) BUN: 5.9 (4.3, 9.6) AKI: 3 (8.3%)
			Non-ICU	102	51	37	62	NA	NA	53 (52)	Cr: 71 (58, 84) BUN: 4 (3.1, 5.1) AKI: 2 (2%)
Wang L et al. [22]	China	14th Jan. 2020 - 13th Feb. 2020	Total	116	54	38	69	NA	NA	67 (57.8)	Acute kidney injury: 0 (0%) Cr: 115.3 ± 178.28 BUN: 6.38 ± 5.94
Xu et al. [34]	China	10th Jan. 2020 - 26th Jan. 2020	Total	62	41	32	52	NA	NA	35 (56)	Cr: 72 (61, 84) Elevated Cr: 3 (5%)
Yang et al. [11]	China	24th Dec. 2019 - 26 Jan. 2020	Total	52	NA	NA	NA	59.7	13.3	35 (67)	Cr: 79 ± 30.03 AKI: 15 (29%)
			Survivors	20	NA	NA	NA	51.9	12.9	14 (70)	Cr: 76.3 ± 27.4 AKI: 3 (15%)
			Non-survivors	32	NA	NA	NA	64.6	11.2	21 (66)	Cr: 80.7 ± 32.3 AKI: 12 (37.5%)

Table 1. Continued

Authors	Country	Date	Population	N	Age (years)				Sex	Kidney Function Indices*
					Median	IQR	Mean	SD	Male (%)	
Yudong et al. [21]	china	20th Jan. 2020 - 15th Feb. 2020	Total	112	62	55	67	NA	53 (47.32)	Cr: 68.85 ± 16.32 BUN : 5.22 ± 3.2
			Critical	16	57.5	54	63	NA	9 (56.25)	Cr: 69.65 (61.8, 96.7) BUN: 5.83 (3.86, 9.44)
			General	96	62	55	67.5	NA	44 (45.83)	Cr: 66.35 (59.55, 77.1) BUN: 4.5 (3.36, 7.25)
Zhang G et al. [35]	China	16th Jan. 2020 - 25th Feb. 2020	Total	95	49	39	58	NA	53 (55.8)	Elevated Cr: 22 (23.3%)
			Non-severe	63	49	41	57	NA	32 (50.8)	Elevated Cr: 14 (22.2%)
			Severe	32	50.5	38.3	58.8	NA	21 (65.6)	Elevated Cr: 8 (25%)
Zhang X et al. [36]	China	17th Jan. 2020 - 8th Feb. 2020	Total	645	NA	NA	NA	NA	328 (50.9)	Cr: 68.76 ± 23.54 BUN: 4.024 ± 1.63 AKI: 2 (0.3%)
Zhou et al. [37]	China	29th Dec 2019- 31th Jan 2020	Total	191	56	46	67	NA	119 (62)	Elevated Cr: 8/186 (4%) AKI: 28 (15%)
			Death	54	69	63	76	NA	38 (70)	Elevated Cr: 5 (9%) AKI: 27 (50%)
			Survivors	137	52	45	58	NA	81 (59)	Elevated Cr: 3/132 (2%) AKI: 1 (1%)

BUN, blood urea nitrogen; Cr, creatinine; ICU, intensive care unit; IQR, interquartile range; NA, not available.
*BUN unit: mmol/L, Cr unit: µmol/L

of three articles [20-22], the limitation section had been explained completely in all others.

Acute Kidney Injury

The mean age of individuals were 52.5 ± 24.4 years and more than half of them were males (55.6%). Figure 2 showed the forest plot of AKI in COVID-19 infected individuals. Our findings revealed that the frequency of renal injury was 4% (95% CI: 2% to 8%; Figure 2A). Further analysis based on the severity of disease indicated that AKI was significantly less common among non-severe patients in comparison with deceased ones (1%, 95% CI: 0% to 4%; vs. 31%, 95% CI: 19% to 47%; respectively). In comparison to survivors, those who died because of this infection had 19.98 (95% CI: 3 to 133.12) times higher likelihood of having AKI (Figure 3). The funnel plot for this outcome is represented in Figure 4.

BUN

Patients had mean age of 54.5 ± 19.4 years and 53.7% of them were contained male subjects. The mean of BUN in all studies was 5.14 mmol/L (95% CI: 4.60 to 5.69; Figure 5A). Further subgroup analysis revealed that non-severe patients had remarkably lower means of BUN compared to deceased or severe ones (4.25 mmol/L, 95% Cl: 3.70 to 4.79; vs. 8.9 mmol/L, 95% CI: 7.94 to 9.86; vs. 6.63 mmol/L, 95% Cl: 5.62 to 7.65; respectively. Figure 5B). The proportion of elevated BUN was 7% (95% Cl: 2% to 17%; Figure 6). Due to the absence of reported elevated BUN according to disease severity, we were unable to perform analysis between groups. Funnel plot for serum BUN is shown in Figure 7.

Cr

The mean age of patients was 52.6 ± 24.3 years with the dominance of male gender (53.3%). The mean serum Cr was 71.60 mmol/L (95% Cl: 67.56 to 75.64, Figure 8A). Further subgroup analysis showed that patients with milder forms of the infection had lower serum Cr means in comparison to death group (65.07 mmol/L, 95% Cl: 58.59 to 71.56; vs. 87.75 mmol/L, 95% Cl: 84.25 to 91.26; Figure 8B). 7% of infected individuals had elevated Cr levels (95% Cl: 4% to 14%, Figure 9A); however, the difference according to the severity of the infection was not significantly different between

Table 2. Summary Analysis Result of Included Studies According to AKI, BUN, and Cr

Kidney Function Indices	Population	Q*	I^{2**}	τ^{2***}	*P*	Proportions	95% CI
AKI	Total	140.796	91.47%	1.070	< .01	0.04	0.02 to 0.08
	Subgroups	106.755	89.69%	1.582	< .01	0.17	0.11 to 0.25
Elevated BUN	Total	9.422	78.77%	0.600	< .01	0.07	0.02 to 0.17
	Subgroups	-	-	-	-	-	-
Elevated Cr	Total	86.574	91.91%	0.940	< .01	0.07	0.04 to 0.14
	Subgroups	56.838	89.44%	1.703	< .01	0.10	0.05 to 0.18
Kidney Function Indices	**Population**	**Q***	**I^{2**}**	**τ^{2***}**	***P***	**MRAW**	**95% CI**
BUN	Total	173.929	95.97%	0.538	< .01	5.14	4.60 to 5.69
	Subgroups	125.514	95.22%	1.809	< .01	5.61	5.18 to 6.04
Cr	Total	268.541	95.15%	51.390	< .01	71.60	67.56 to 75.64
	Subgroups	182.211	93.41%	113.478	< .01	82.10	79.17 to 85.04

*Cochran's Q statistic for heterogeneity
**Index for the degree of heterogeneity
***Tau-squared measure of heterogeneity.
BUN, blood urea nitrogen; Cr, creatinine; MRAW, mean raw.

groups (Figure 9B). The funnel plot for serum Cr based on total studies is represented in Figure 10.

DISCUSSION

This review presents the frequency of AKI as well as two specific renal biomarkers, including BUN and Cr among individuals suffering from COVID-19 infection. After inclusion of 18 articles with data of 4528 patients, we found that the prevalence of AKI was 4% (95% CI: 2% to 8%). Although AKI was infrequent among COVID-19 infected patients and most of them experienced a subclinical course, severe patients had higher percentages of renal injury. Therefore, this issue should be considered more frequently. Despite the exact pathophysiological mechanisms still remains unknown, several theories have been postulated in this regard. This virus affects immune system leading to production of a tremendous amount of cytokines and this cytokine storm as well as immune cell dysregulation might be responsible for induction of AKI.[23,24] Moreover, hypercoagulable state due to production of tissue factor probably resulted from specific cytokine production as well as pathogen-associated molecular proteins (PAMP) secretion could play pivotal roles in micro-thrombi and micro-emboli occurrence and subsequent organ dysfunction.[23,25] Also, this virus has been reported to find in urine specimens.[26,27] Thus, some assumptions have been made for direct involvement of renal system with this virus. ACE2 protein has been recognized as one of the major binding location of COVID-19 on renal tissues and found in both apical membrane of proximal convoluted tubules (PCT) and podocytes. Therefore, direct attachment of this virus should be considered more. However, this protein could not solely cause proper entrance to the renal cells and other priming mechanisms might also be required. COVID-19 fusion activated peptides are produced by cleavage of S protein.[28] Presence of both ACE2 and renal cells proteases, named trans-membrane protease serine 2 (TMPRSS2), are necessary for proper entrance and induction of cellular infectivity.[23] On the other hand, the presence of these two proteins differs among different races in a way that ACE2 has been reported to express more frequently among occidental individuals in comparison with Asian patients. Consequently, the former descent infected with COVID-19 might experience a higher proportion rate of AKI.[29] Other secondary causes of AKI might be angiotensin over activity, rhabdomyolysis, renal hypoperfusion caused by cardiovascular comorbidities, sepsis and nephrotoxic agents.[23,25]

With respect to our findings in terms of low AKI frequency, COVID-19 infected patients did not show any remarkable elevation in terms of BUN and Cr. However, individuals experienced a severe from of the infection had higher BUN means rather than non-severe ones (8.9 mmol/L, 95% CI: 7.94 to 9.86, vs. 4.25 mmol/L, 95% Cl: 3.70 to 4.79). Although BUN elevation would mostly resulted from renal damage, other possible etiologies should be taken

Table S1. Risk of Bias Assessment

Components	Chen C et al.	Chen N et al.	Chen T et al.	Chen X et al.	Cheng et al.	Deng et al.	Guan W et al.	Huang et al.	Lei et al.	Shi S et al.	Wang D et al.	Wang L et al.	Xu et al.	Yang et al.	Yudong et al.	Zhang G et al.	Zhang X et al.	Zhou et al.
1. Were the aims/objectives of the study clear?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study design appropriate for the stated aim (s)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the sample size justified?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
4. Was the target/reference population clearly defined? (Is it clear who the research was about?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was the sample frame taken from an appropriate population base so that it closely represented the target/ reference population under investigation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Was the selection process likely to select subjects/ participants that were representative of the target/reference population under investigation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Were measures undertaken to address and categorize non-responders?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
8. Were the risk factor and outcome variables measured appropriate to the aims of the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the risk factor and outcome variables measured correctly using instruments/ measurements that had been trialed, piloted or published previously?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table S1. Continued

Components	Chen C et al.	Chen N et al.	Chen T et al.	Chen X et al.	Cheng et al.	Deng et al.	Guan W et al.	Huang et al.	Lei et al.	Shi S et al.	Wang D et al.	Wang L et al.	Xu et al.	Yang et al.	Yudong et al.	Zhang G et al.	Zhang X et al.	Zhou et al.
10. Is it clear what was used to determined statistical significance and/or precision estimates? (eg, p values, CIs)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the basic data adequately described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Does the response rate raise concerns about non-response bias?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
14. If appropriate, was information about non-responders described?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
15. Were the results internally consistent?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. Were the results for the analyses described in the methods, presented?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17. Were the authors' discussions and conclusions justified by the results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18. Were the limitations of the study discussed?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
19. Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
20. Was ethical approval or consent of participants attained?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

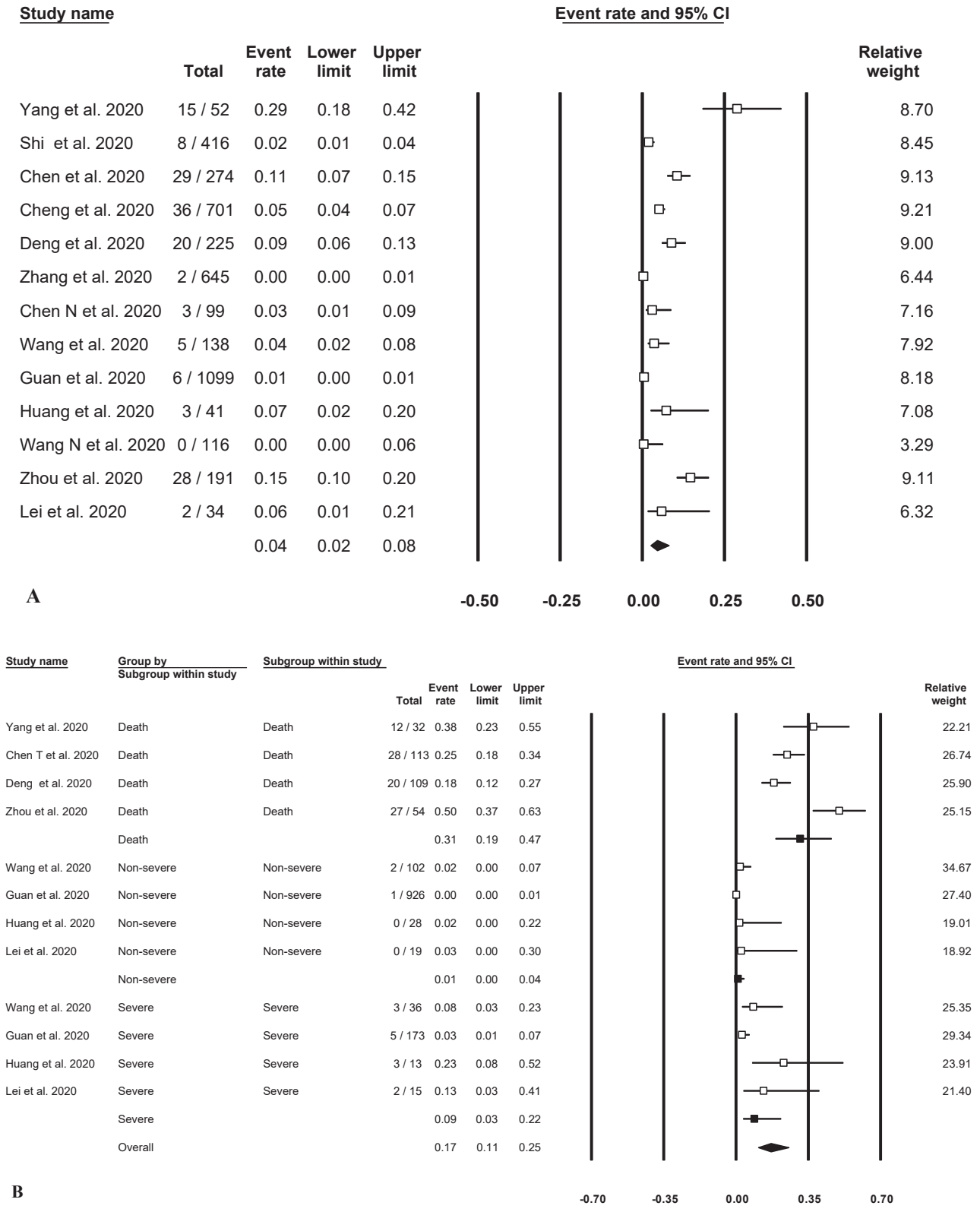


Figure 2. Forest plots for proportions of AKI based on total (A) and subgroups (B) of studies

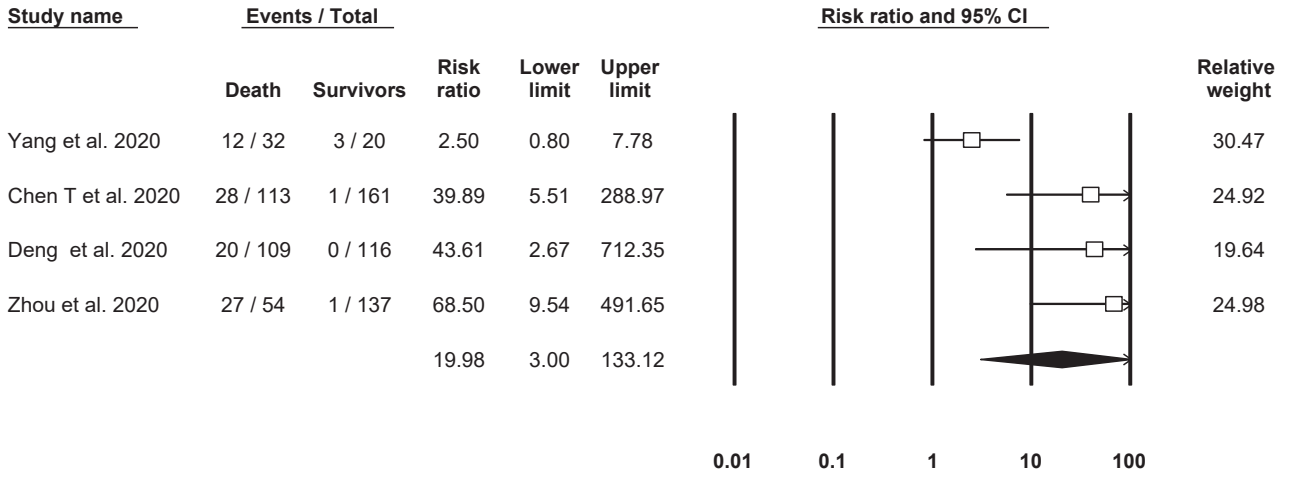


Figure 3. Forest plot for a risk ratio of AKI according to severe and non-severe groups

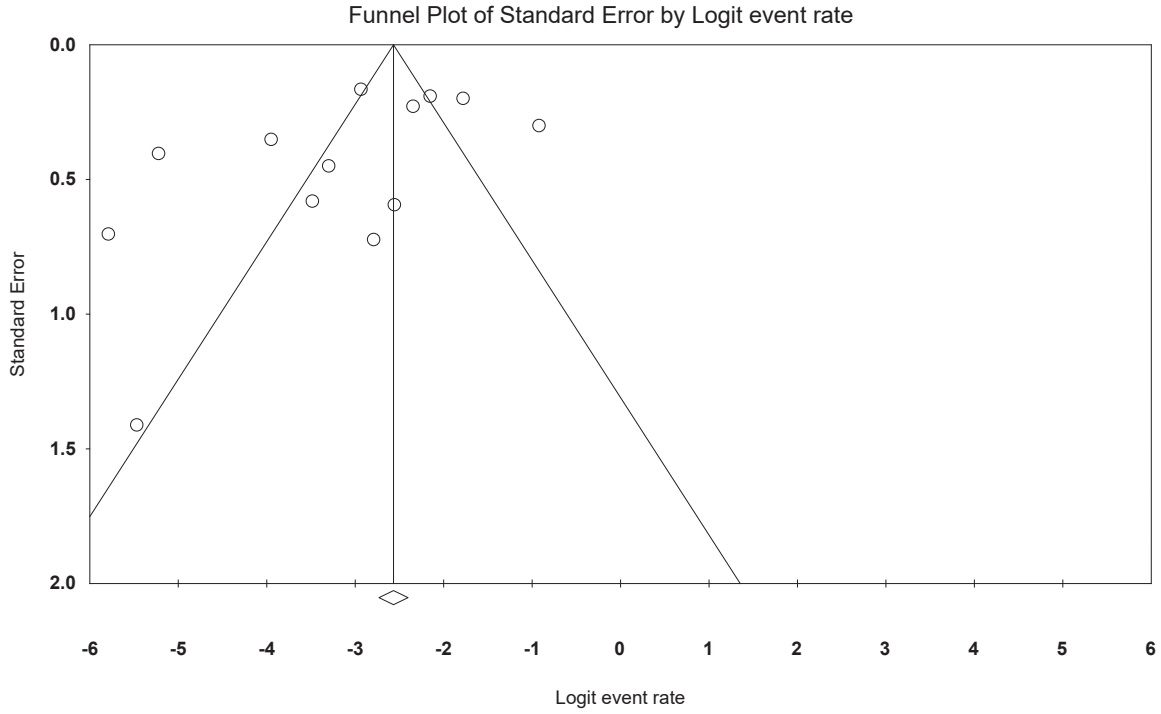


Figure 4. Funnel plot for AKI based on total studies

into account. Hyper-catabolism status mostly observed in severe patients as well as high protein intake given to admitted ICU patients might all be responsible for this heightened BUN levels.[30] Also, it has been suggested that anti-diuretic hormone (ADH) would be produced more frequently led to higher renal medullary absorption of urea nitrogen.[4,30]

To best of our knowledge, this review is the first investigating simultaneous frequency of AKI as well as levels of renal biomarkers among individuals suffering from COVID-19 infection. Although we tried our best in order to include all relevant studies, several limitation might be considered. With respect to daily data publication of COVID-19 infection, we gathered and analyzed all relevant studies by 16th April 2020 and we were not able to include other relevant records afterwards. Each included study might pose some limitations in terms of study design, sample size, definition of AKI or data collection,

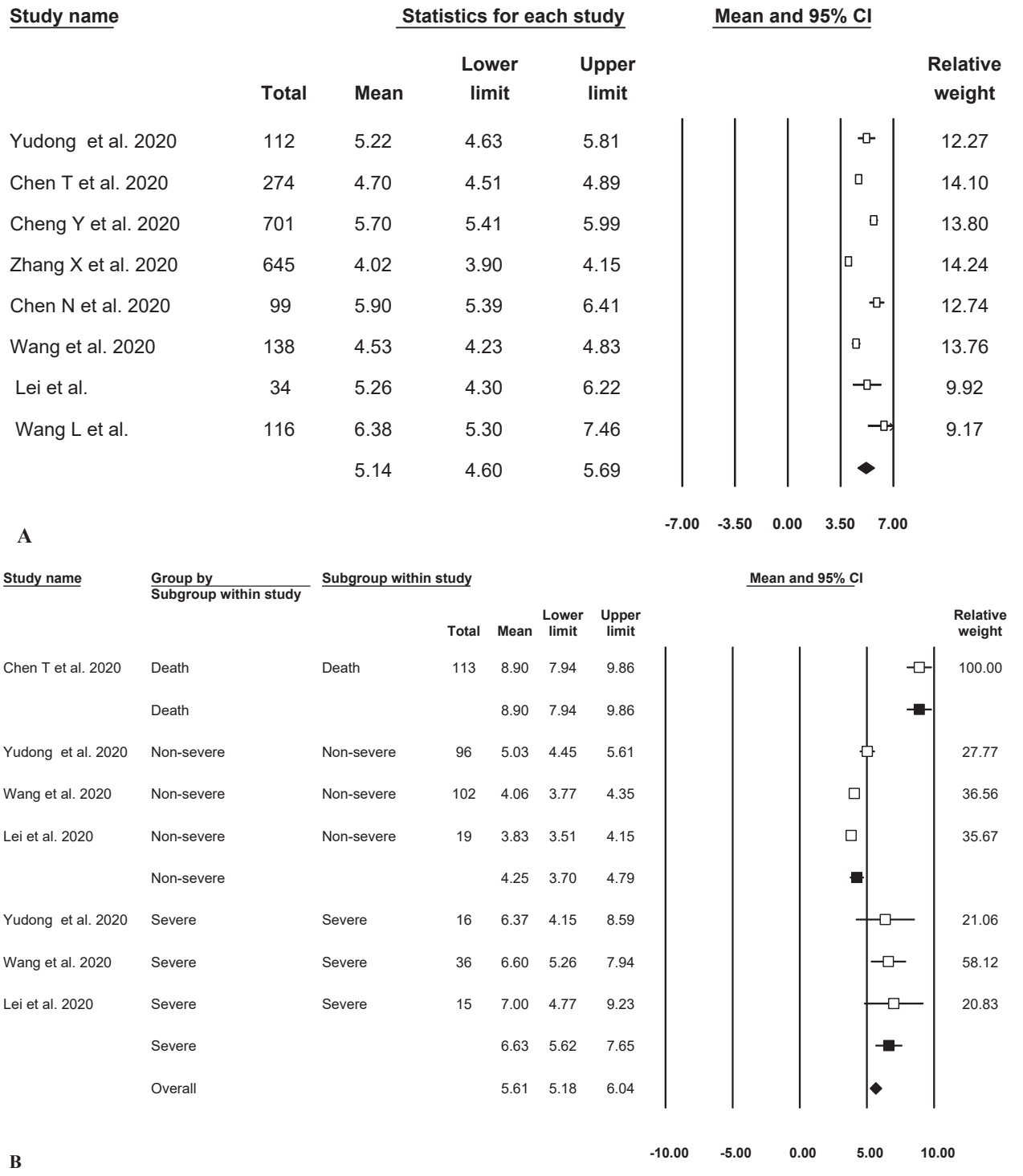


Figure 5. Forest plots for proportions of BUN based on total (A) and subgroups (B) of studies

which would subsequently affect our outcomes. Although we implemented random effect model for data analysis, higher $I^{2,}$ percentages of included studies revealed a high heterogeneity level and the outcomes must be interpreted cautiously. China was the country in which all investigations were done. Therefore, generalization of findings to other nations must be done with caution. Publication bias, as depicted by funnel plots, might considerably affect the reproducibility of the findings. With

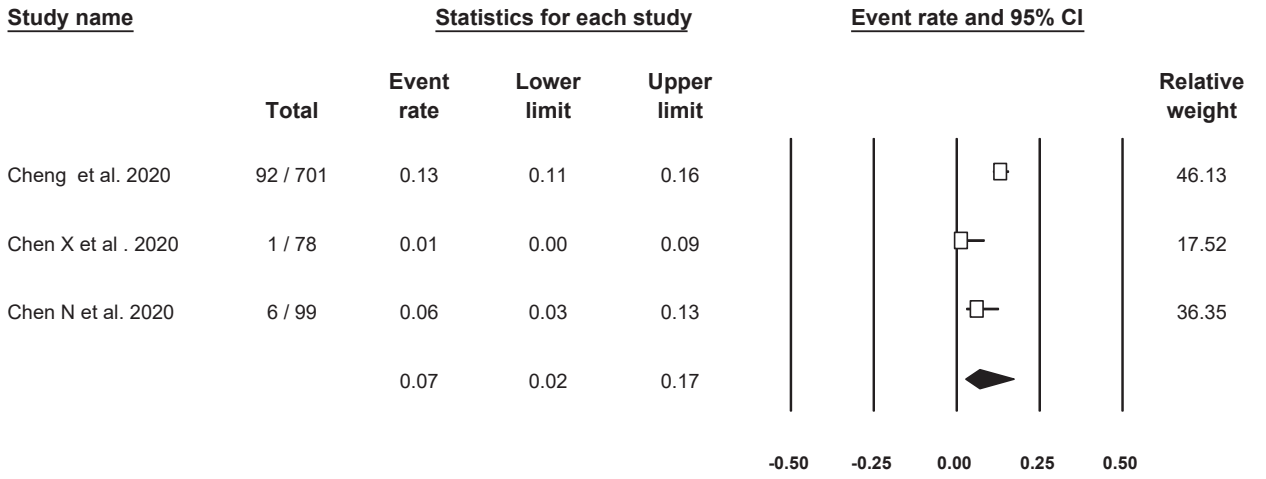


Figure 6. Forest plots for proportions of elevated BUN

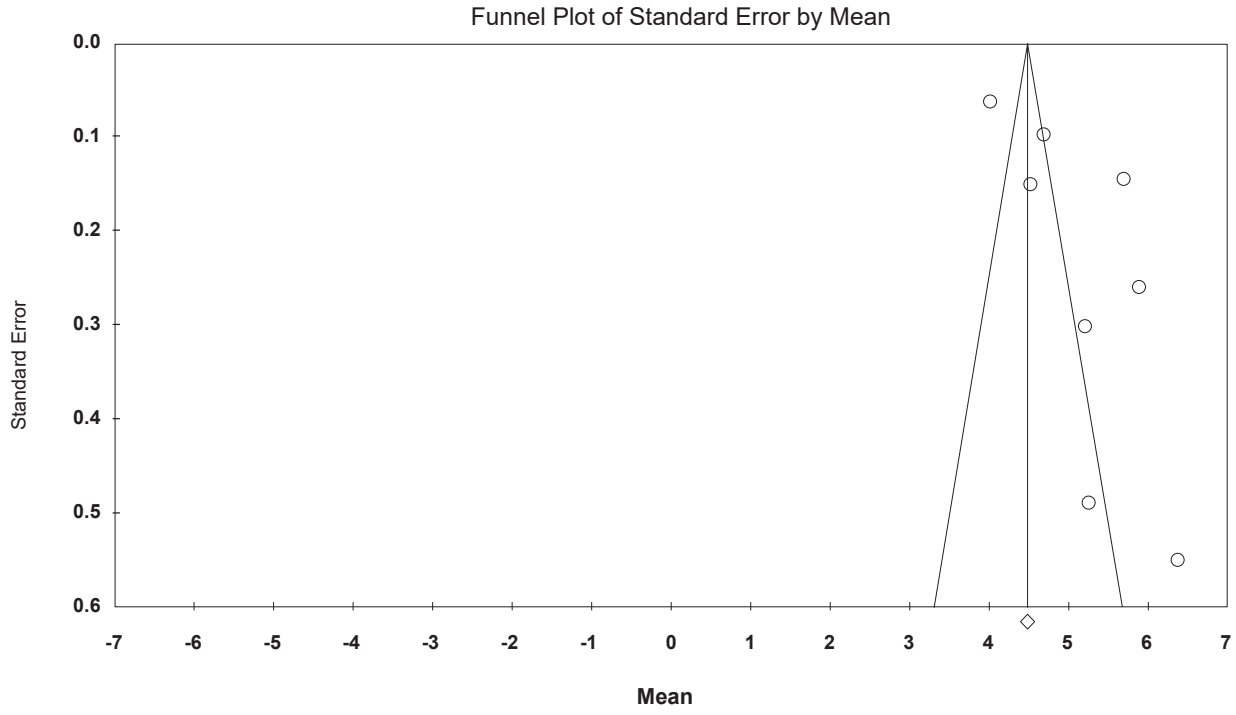


Figure 7. Funnel plot for serum BUN based on total studies

exception of very few studies, most records did not categorize recruited subjects according to probable previous CKD history or other previously proved renal disease risk factors. Therefore, we could not divide patients in this regard for investigation of the probable effect of the risk factors on the occurrence as well as severity of renal injury.

CONCLUSION

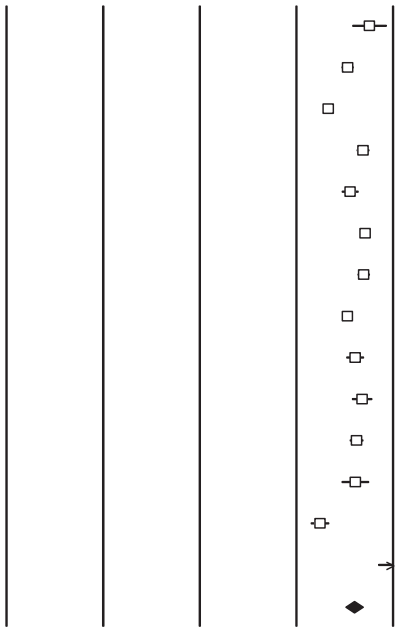
In conclusion, this review indicates that AKI as well as abnormal BUN and Cr levels are less frequent findings among COVID-19 infected patients and this virus might not seem to affect the renal system extensively. Other pathophysiological mechanisms should be assessed with higher priority in order to find the exact etiology in this regard.

DECLARATIONS

Ethical approval and consent to participate

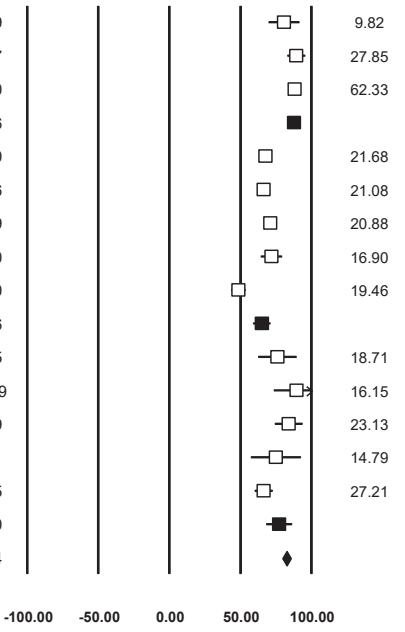
Not applicable

Study name	Total	Mean	Lower limit	Upper limit	Relative weight
Yang et al. 2020	52	79.00	70.76	87.24	6.15
Yudong et al. 2020	112	68.85	65.83	71.87	7.90
Shi et al. 2020	416	59.81	58.17	61.45	8.15
Chen T et al. 2020	274	76.00	72.82	79.18	7.86
Chen C et al. 2020	150	70.03	65.87	74.19	7.60
Cheng et al. 2020	701	77.00	74.71	79.29	8.05
Deng et al. 2020	225	76.33	73.25	79.41	7.89
Zhang X et al. 2020	645	68.76	66.94	70.58	8.13
Xu et al. 2020	62	72.33	67.99	76.67	7.54
Chen N et al. 2020	99	75.60	70.68	80.52	7.36
Wang et al. 2020	138	73.00	69.63	76.37	7.81
Huang et al. 2020	41	72.46	65.83	79.09	6.76
Lei et al. 2020	34	56.00	51.48	60.52	7.49
Wang L et al 2020	116	115.30	82.86	147.74	1.31
		71.60	67.56	75.64	



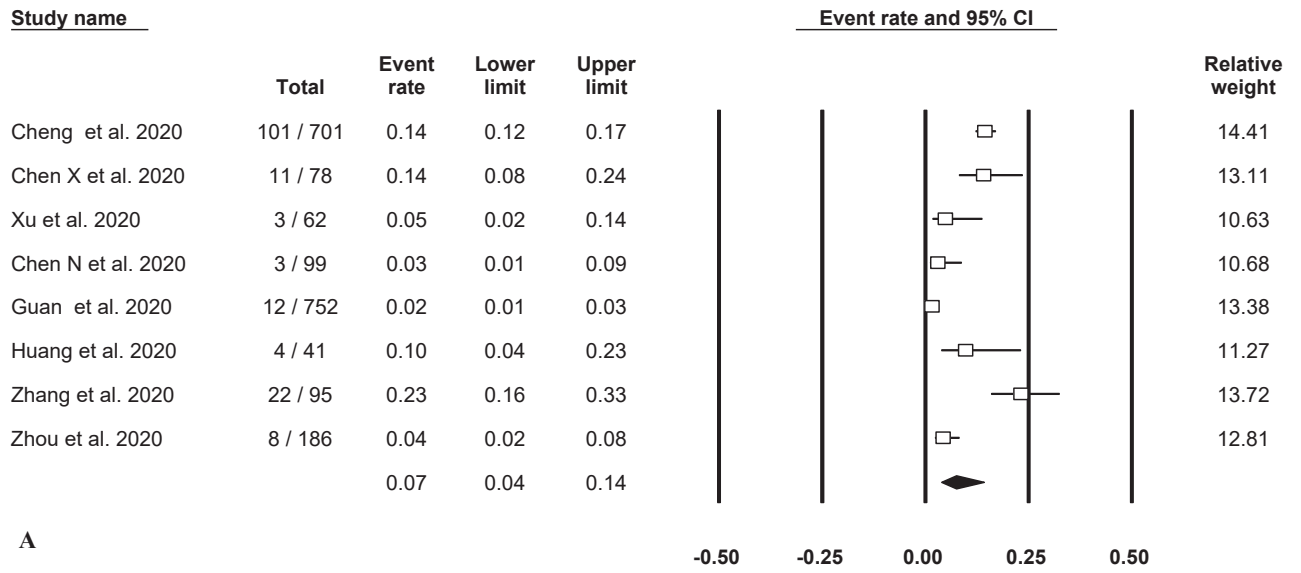
A

Study name	Group by Subgroup within study	Subgroup within study	Total	Mean	Lower limit	Upper limit	Relative weight
Yang et al. 2020	Death	Death	32	80.70	69.51	91.89	9.82
Chen T et al. 2020	Death	Death	113	89.33	82.69	95.97	27.85
Deng et al. 2020	Death	Death	109	88.16	83.72	92.60	62.33
	Death			87.75	84.25	91.26	
Yudong et al. 2020	Non-severe	Non-severe	96	67.66	65.02	70.30	21.68
Chen C et al. 2020	Non-severe	Non-severe	126	66.33	62.80	69.86	21.08
Wang et al. 2020	Non-severe	Non-severe	102	71.00	67.21	74.79	20.88
Huang et al. 2020	Non-severe	Non-severe	28	71.83	63.96	79.70	16.90
Lei et al. 2020	Non-severe	Non-severe	19	48.60	43.20	54.00	19.46
	Non-severe			65.07	58.59	71.56	
Yudong et al. 2020	Severe	Severe	16	76.05	62.15	89.95	18.71
Chen C et al. 2020	Severe	Severe	24	89.50	73.11	105.89	16.15
Wang et al. 2020	Severe	Severe	36	84.00	73.91	94.09	23.13
Huang et al. 2020	Severe	Severe	13	74.93	57.05	92.81	14.79
Lei et al. 2020	Severe	Severe	15	66.33	59.71	72.95	27.21
	Severe			77.25	67.80	86.70	
	Overall			82.10	79.17	85.04	



B

Figure 8. Forest plots for proportions of serum Cr based on total (A) and subgroups (B) of studies



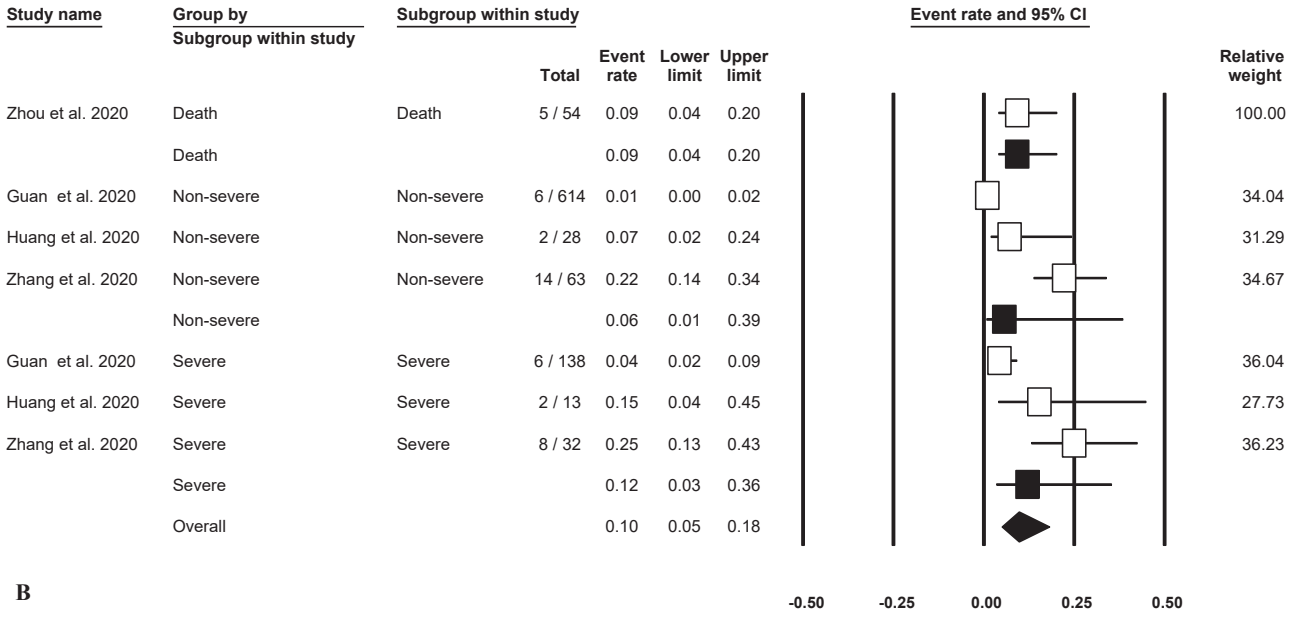


Figure 9. Forest plots for proportions of elevated serum Cr based on total (A) and subgroups (B) of studies

Consent for publication

Not applicable

Availability of data and materials

The datasets generated during and/or analyzed during the current study are not publicly available due to confidential issues but are available from the corresponding author on reasonable request.

Competing interests

None of the authors had any personal or financial conflicts of interest.

Funding

No funding has been attributed to this study

Authors contribution:

1. Study concept and design: M. V., SA. E., M. H, D. S.
2. Acquisition of data: SA. E, M. V.
3. Analysis and interpretation of data: M. V., SA. E.

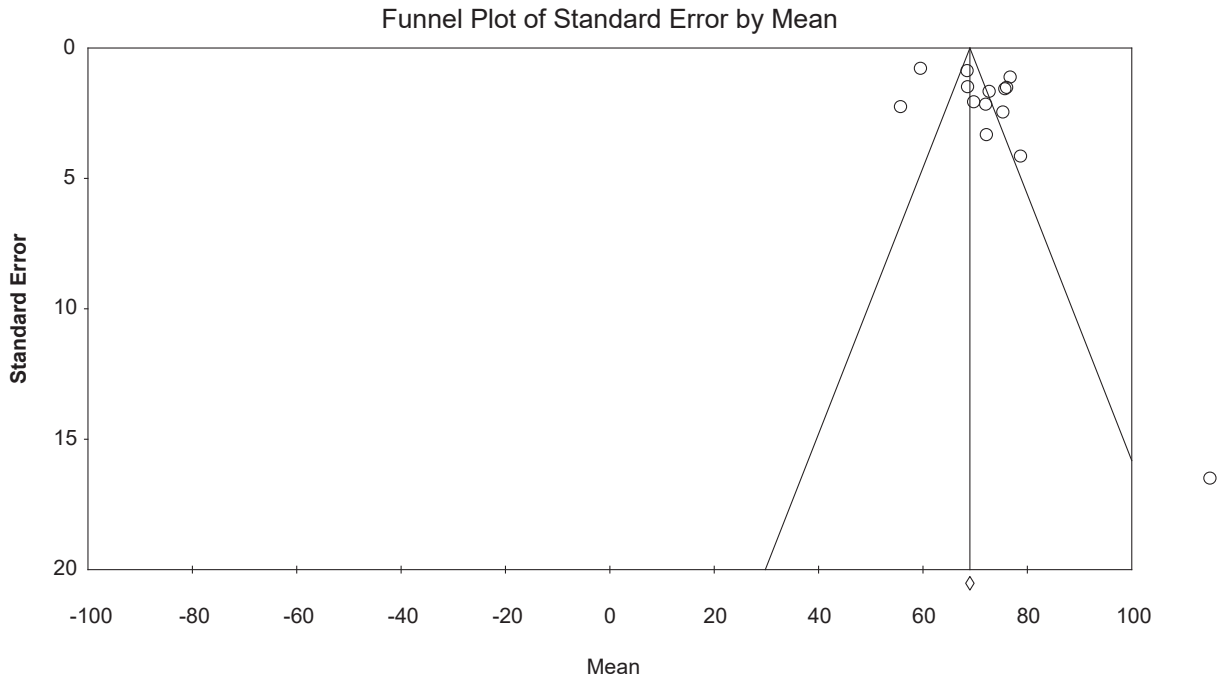


Figure 10. Funnel plot for serum Cr based on total studies

4. Drafting of the manuscript: SA. E., M. V, D. S, M. M
5. Critical revision of the manuscript for valuable intellectual content: M. V., D. S., M. H., M. M, SA. E.
6. Statistical analysis: M. V.
7. Administrative, technical, and material support: M. H., D. S., M. M.
8. Supervision: D. S., M. H., M. M.

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Abbrevitions:

2019-nCoV: 2019 novel coronavirus
ACE: angiotensin-converting enzyme
AKI: acute kidney injury
ARDS: acute respiratory distress syndrome
AMSTAR: assessment of multiple systematic reviews
AXIS tool: appraisal tool for cross-sectional studies
BUN: blood urea nitrogen
CI: confidence interval
CKD: chronic kidney diseases
COVID-19: coronavirus disease 2019
Cr: creatinine
ICU: intensive care unit
IQR: interquartile range
KIDGO: kidney disease improving global outcomes
MERS: the Middle East respiratory syndrome
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
RNA: ribonucleic acid
SARS-CoV-2: severe acute respiratory syndrome- coronavirus 2
SD: standard deviation
STROBE: strengthening the reporting of observational studies in

epidemiology
TMPRSS2: trans-membrane protease serine 2
WHO: world health organization

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