Incidence of acute kidney injury and its association with mortality in patients with COVID-19: a meta-analysis

Panupong Hansrivijit ,[1] Chenchen Qian,[1] Boonphiphop Boonpheng,[2] Charat Thongprayoon ,[3] Saraschandra Vallabhajosyula,[4] Wisit Cheungpasitporn,[5] Nasrollah Ghahramani[6]

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[1]Department of Internal Medicine, UPMC Pinnacle Harrisburg, Harrisburg, Pennsylvania, USA
[2]Division of Nephrology, University of California Los Angeles David Geffen School of Medicine, Los Angeles, California, USA
[3]Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA
[4]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA
[5]Division of Nephrology, University of Mississippi Medical Center, Jackson, Mississippi, USA
[6]Division of Nephrology, Pennsylvania State University College of Medicine, Hershey, Pennsylvania, USA

Correspondence to
Dr Panupong Hansrivijit, Department of Internal Medicine, UPMC Pinnacle Harrisburg, Harrisburg, PA 17101-2010, USA; hansrivijitp@upmc.edu

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ABSTRACT

Acute kidney injury (AKI) is a complication of COVID-19. However, the incidence of AKI in COVID-19 varies among studies. Thus, we aimed to evaluate the pooled incidence of AKI and its association with mortality in patients with COVID-19 using a meta-analysis. We search Ovid MEDLINE, EMBASE, and the Cochrane Library for eligible publications reporting the clinical characteristics of patients with COVID-19 without language restriction. Incidence of AKI and mortality were reported. Meta-regression was used to describe the association between outcomes. From 26 studies (n=5497), the pooled incidence of AKI in patients with COVID-19 was 8.4% (95% CI 6.0% to 11.7%) with a pooled incidence of renal replacement therapy of 3.6% (95% CI 1.8% to 7.1%). The incidence of AKI was higher in critically ill patients (19.9%) compared with hospitalized patients (7.3%). The pooled estimated odds ratio for mortality from AKI was 13.33 (95% CI 4.05 to 43.91). No potential publication bias was detected. By using meta-regression analyses, the incidence of AKI was positively associated with mortality after adjusted for age and sex (Q=26.18; p=0.02). Moreover, age (p<0.01), diabetes (p=0.02), hypertension (p<0.01) and baseline serum creatinine levels (p=0.04) were positively associated with AKI incidence in adjusted models. In conclusion, AKI is present in 8.3% of overall patients with COVID-19 and in 19.9% of critically ill patients with COVID-19. Presence of AKI is associated with 13-fold increased risk of mortality. Age, diabetes, hypertension, and baseline serum creatinine levels are associated with increased AKI incidence.

Significance of this study

What is already known about this subject?
- ► COVID-19 is a newly assigned disease entity caused by severe acute respiratory syndrome coronavirus 2.
- ► The incidence of acute kidney injury (AKI) in COVID-19 is unknown.

What are the new findings?
- ► The pooled incidence of AKI among patients with COVID-19 was 8.4% with a pooled incidence of renal replacement therapy of 3.6%.
- ► Critically ill patients with COVID-19 had higher incidence of AKI compared with hospitalized patients.
- ► AKI was associated with increased mortality by 13-fold (OR 13.33, 95% CI 4.05 to 43.91).
- ► Increasing age, history of diabetes, history of hypertension and higher baseline serum creatinine levels were associated with AKI based on adjusted meta-regression analysis.

How might these results change the focus of research or clinical practice?
- ► AKI may be uncommon in patients with COVID-19. However, if present, AKI was associated with increased mortality. Avoiding AKI especially in patients who have predisposing risk factors may improve the outcome of COVID-19.

INTRODUCTION

COVID-19 is a disease entity caused by a new coronavirus, named by the WHO as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is a positive-sense single-stranded RNA virus which can be spread by droplets from person to person.[1] Since the first case was identified in Wuhan, Hubei, China, SARS-CoV-2 rapidly spread from a single city to the entire country in just 30 days.[2] On March 11, 2020, the WHO has declared the novel coronavirus outbreak a global pandemic.[3] As of May 20, 2020, there have been 4,789,205 confirmed cases of COVID-19, causing 318,789 deaths in 216 countries worldwide with more than 1.5 million confirmed cases in the USA.[4]

Acute kidney injury (AKI) is a common complication in both medical and surgical patients. The incidence of AKI was reported between 8% and 18% of hospitalized patients based on the Grampian Laboratory Outcomes Morbidity and Mortality Study II.[5] In this

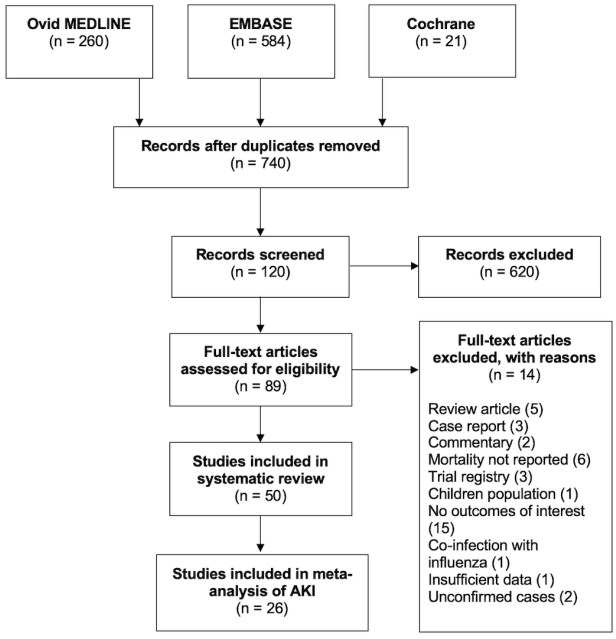

Figure 1 Flowchart of systematic literature search from all databases. AKI, acute kidney injury.

study, Sawhney *et al* have shown that AKI is associated with increased mortality within 1 year and after 10 years of follow-up.[5] From a multinational database, the incidence of AKI in mechanically ventilated patients was reported at 22%, slightly higher than general inpatients.[6] Most of these patients developed AKI within 48 hours after intensive care unit (ICU) admission.[6] Several factors, such as use of vasopressors, intra-aortic balloon pump, chronic kidney disease (CKD), and high Acute Physiologic Assessment and Chronic Health Evaluation II score, are the risk factors for severe AKI requiring renal replacement therapy (RRT) in the ICU.[7]

Although it has been well established that AKI is linked to elevated mortality in hospitalized patients,[8] whether this knowledge would extend to patients with COVID-19 remained unanswered. Several studies have provided front-line data about the mortality risks in patients with confirmed COVID-19. Zhou *et al*[9] conducted a multicenter, retrospective cohort study of 191 patients with confirmed COVID-19 in Wuhan and identified several risk factors for mortality. However, evidence is lacking on studies reporting the association between mortality risk and AKI in patients with COVID-19. Herein, we performed a systematic review with meta-analysis aiming to provide more information about the incidence of AKI and the association between AKI and mortality in patients with COVID-19.

MATERIALS AND METHODS

Information sources and search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology statements.[10 11] We conducted a systematic literature search of Ovid MEDLINE, EMBASE, and the Cochrane Library from database inception through April 24, 2020 without language restriction. The literature search was conducted by 2 independent authors (PH and WC). The search strategy for each database is elaborated in online supplementary document 1. To avoid potential publication bias and replication of study samples, we did not search through *medrxiv.org* due to lack of peer review process. Studies published in Chinese language were translated by CQ and a medical translator.

Study selection

Because COVID-19 is an emerging pandemic, a large number of studies were published within a short period of time. Thus, we cautiously screened all citations to avoid duplication of the patient populations among studies. Valid Institutional Review Board number or approval by the National Health Commission of that country was screened. Inclusion criteria included observational studies of patients infected with SARS-CoV-2 and reported the mortality as one of the outcomes of interest. SARS-CoV-2 infection was confirmed by positive real-time reverse transcription PCR test. Eligible studies needed to provide the following information: age, sex, diagnosis, patients' comorbidities, incidence of AKI, need of RRT and mortality. Retrieved articles were independently examined for eligibility by 2 authors (PH and CQ). Conflicts were resolved by consensus among the authors. All references were managed through EndNote X9.2 software (Clarivate Analytics, Philadelphia, PA, USA).

Data collection process

A structured data collection form was developed to gather the following data from each included study: title, author name, publication year, country where the study was conducted, location where data were collected, type of study, patients' diagnoses, sample size, age, sex, comorbidities, incidence of AKI, incidence of RRT, mortality and definition of AKI. The risk of bias was assessed using ROBINS-I (risk of bias in non-randomized study - of interventions) tool for non-randomized studies of interventions.[12] The quality of studies that fulfilled the inclusion criteria was rated as low, moderate or high risk of bias.

Measurements

The incidence of AKI, RRT and mortality were reported in percentage with 95% CI. The OR for mortality from AKI was also reported with 95% CI.

Statistical analysis

We used the Comprehensive Meta-Analysis software V.3.3.070 (Biostat, Englewood, NJ, USA) to conduct meta-analyses and SPSS V.23.0 (IBM) for descriptive analyses. Statistical heterogeneity of studies was assessed using Cochran's Q test and I^2 index.[13] I^2 was analyzed by using fixed effects model. We analyzed the results by using the random effects model to minimize the heterogeneity or between-study variance.

Sensitivity analysis, subgroup analysis, meta-regression and publication bias

Sensitivity analyses were performed in order to minimize the heterogeneity among studies by subtracting 1 study at a time. Subgroup analysis was performed based on the disease severity (critically ill patients vs hospitalized patients). Meta-regression analysis was performed to elaborate the

Table 1 Characteristics of studies reporting the incidence of acute kidney injury in patients infected with SARS-CoV-2

Study	Country	Location	n	Subject	Age* (y)	Male (%)	DM (%)	HTN (%)	Heart disease† (%)	Lung disease‡ (%)	Cancer (%)	CKD (%)	AKI (%)	Mortality (%)	OR of AKI for mortality (95% CI)
Arentz *et al*[27]	USA	Washington state	21	Confirmed COVID-19, critically ill	70	52	33.3	–	42.9	33.3	–	48	19.1 RRT: 0%	52.4	–
Barrasa *et al*[28]	Spain	Victoria	48	Confirmed COVID-19, critically ill	63.2	56	19	–	10	37	–	–	0	12.5	–
Cao *et al*[29]	China	Wuhan	102	Confirmed COVID-19, hospitalized	54	52	10.8	27.5	4.9	9.8	3.9	3.9	19.6 Death with AKI: 15/17 Survived with AKI: 5/85	16.7	–
Chen *et al*[30]	China	Tongji Hospital	113	Confirmed COVID-19, hospitalized	62	62	17	34	8	7	3	1	11 Death with AKI: 28/115 Survived with AKI: 1/161	41.2	–
Du *et al*[31]	China	Wuhan	179	Confirmed COVID-19, hospitalized	57.6	54.2	18.4	32.4	16.2	4.5	2.2	–	9.5	11.7	4.706 (0.786 to 28.178)
Du *et al*[32]	China	Hannan and Wuhan Union Hospital	85	Deceased COVID-19, fatal cases, hospitalized	65.8	72.9	22.4	37.6	11.8	2.4	7.1	3.5	18.8 (RRT 9.4%)	100	–
Chen *et al*[33]	China	Jinyintan Hospital	99	Confirmed COVID-19, hospitalized	55.5	68	13	–	40	1	1	–	3.1 RRT: 9%	11	–
Cheng *et al*[34]	China	Tongji Hospital	701	Confirmed COVID-19, hospitalized	63	52.4	14.3	33.4	–	1.9	4.6	2	5 CRRT: 0%	16.1	6.34 (3.47 to 11.58)
Deng *et al*[35]	China	Wuhan	225	Confirmed COVID-19, hospitalized	54.5	55.5	11.7	26.1	7.7	11.4	3.6	–	8.9 (deceased with AKI 20/109, survived with AKI 0/116)	48.4	–
Du *et al*[36]	China	Wuhan	109	Confirmed COVID-19, hospitalized	70.7	67.9	31.2	59.6	33.9	15.6	7.3	7.3	11 (RRT 11%)	100	–
Guan *et al*[37]	China	Multicenter	1099	Confirmed COVID-19, hospitalized	47.0	58.1	7.4	15.0	2.5	1.1	0.9	0.7	0.5 RRT: 0.8%	1.4	–
Guo *et al*[38]	China	Seventh Hospital	187	Confirmed COVID-19, hospitalized	58.5	48.7	15	32.6	4.3	–	7	3.2	14.6	23	–

Continued

Table 1 Continued

Study	Country	Location	n	Subject	Age* (y)	Male (%)	DM (%)	HTN (%)	Heart disease† (%)	Lung disease‡ (%)	Cancer (%)	CKD (%)	AKI (%)	Mortality (%)	OR of AKI for mortality (95% CI)
Huang *et al*[39]	China	Wuhan	41	Confirmed COVID-19, hospitalized	49.0	73	20.0	15.0	15.0	2.0	2.0	–	7 (RRT 7%)	15	–
Lei *et al*[40]	China	Sun Yet-Sen University	20	Confirmed COVID-19, hospitalized	43.2	50	5	–	25	5	0	–	0 (RRT 0%)	0	–
Lian *et al*[41]	China	Zhejiang province	788	Confirmed COVID-19, hospitalized	45.8	51.6	7.2	16	1.4	0.4	0.8	0.9	1.53 (RRT 0%)	8.8	–
Ling *et al*[42]	Hong Kong	Multicenter	8	Confirmed COVID-19, critically ill	64.5	50	25	38	0	0	0	25	25 (RRT 25%)	12.5	–
Liu *et al*[43]	China	Shenzhen	12	Confirmed COVID-19, hospitalized	53.7	67	16.7	25.0	33.3	8.3	0	16.7	16.7 RRT: –	8.3	–
Wang *et al*[44]	China	Zhongnan Hospital	138	Confirmed COVID-19, hospitalized	56.0	54.3	10.1	31.2	14.5	2.9	7.2	2.9	3.6 RRT: 1.45%	4.3	–
Yang *et al*[45]	China	Jinyintan Hospital	52	Confirmed COVID-19, critically ill	59.7	67	17.0	–	10.0	8.0	4.0	–	29 (RRT 5%) Death with AKI: 12/32 Survived with AKI: 3/20	61.5	–
Zhou *et al*[9]	China	Jinyintan Hospital and Wuhan Pulmonary Hospital	191	Confirmed COVID-19, hospitalized	56.0	62	19	30	8	3	1	1	15 (RRT 5%) In deceased cases: 27/54 In survived cases: 1/137	28.3	–
Shi *et al*[46]	China	Wuhan	416	Confirmed COVID-19, hospitalized	64	49.3	14.4	30.5	48.1	2.9	2.2	3.4	1.9	13.7	1.22 (0.6 to 2.5)
Tang *et al*[47]	China	Wuhan	73	Confirmed COVID-19, critically ill	67	61.5	27.4	52.1	31.5	1.4	–	4.1	17.8	28.8	–
Tu *et al*[48]	China	Wuhan	174	Confirmed COVID-19, hospitalized	70	45.4	9.8	21.2	9.2	6.9	–	–	15.5	14.4	–
Wang *et al*[49]	China	Wuhan	339	Confirmed COVID-19, hospitalized	71	49	16	40.8	15.7	–	–	3.8	8.1	19.2	–

Continued

Table 1 Continued

Study	Country	Location	n	Subject	Age* (y)	Male (%)	DM (%)	HTN (%)	Heart disease† (%)	Lung disease‡ (%)	Cancer (%)	CKD (%)	AKI (%)	Mortality (%)	OR of AKI for mortality (95% CI)
Liu *et al*[50]	China	Hainan	56	Confirmed COVID-19, hospitalized	53.8	55.3	7.1	17.8	3.6	–	–	–	17.8	5.4	–
Zhang *et al*[51]	China	Wuhan	221	Confirmed COVID-19, hospitalized	55	48.9	10	24.4	10	2.7	4.1	2.7	4.5	5.4	–

*Mean or median.
†Including cardiovascular disease, heart failure, valvular heart disease or atrial fibrillation.
‡Including chronic obstructive lung disease, asthma or interstitial lung disease.
AKI, acute kidney injury; CKD, chronic kidney disease; CRRT, continuous renal replacement therapy; DM, diabetes mellitus; HTN, hypertension; RRT, renal replacement therapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

association between (1) incidence of AKI and mortality, and (2) clinical characteristics and incidence of AKI using the random effects model. Scatterplots were also presented. Publication bias was analyzed using Egger's regression intercept and funnel plot if the number of included studies was greater than 10.[14]

RESULTS

Study characteristics

Figure 1 illustrates the PRISMA flowchart of the literature search and selection. Of 740 citations, we found 26 studies that reported the incidence of AKI as well as mortality in 5497 confirmed cases of SARS-CoV-2 infection (table 1). Studies which reported the mortality of patients with COVID-19 but without the incidence of AKI are depicted in online supplementary table S1. All studies were in retrospective observational design. Studies were conducted in China (n=21), the USA (n=1), Spain (n=1), and Hong Kong (n=1). The mean age was 56.3±8.6 years with 54.6% male. Reported comorbidities include hypertension (26.3%), diabetes (12.5%), heart disease (12.1%), lung disease (3.5%), cancer (2.7%) and CKD (2.3%). The mean serum creatinine levels were 0.79±0.16 mg/dL. AKI is defined by the Kidney Disease Improving Global Outcomes criteria in most reporting studies.

Incidence of AKI

A total of 5497 patients from 26 studies were included in the meta-analysis of AKI incidence following COVID-19. By using random effects model, we found that the pooled incidence of AKI in patients with confirmed SARS-CoV-2 infection was 8.4% (95% CI 6.0% to 11.7%; I^2 by fixed effects=88.9%; figure 2A).

Mortality

A total of 5497 patients from 26 studies were included in the meta-analysis of mortality from COVID-19. We found that the pooled estimated mortality was 18.7% (95% CI 13.2% to 25.8%; I^2 by fixed effects model=95.0%; figure 2B).

Incidence of RRT

Of 14 studies included with a total of 3364 patients, the pooled incidence of RRT use was 3.6% (95% CI 1.8% to 7.1%; I^2 by fixed effects model=82.2%; figure 2C).

OR for mortality from AKI

The OR of mortality from AKI was analyzed based on the data available from 8 studies. The pooled estimated OR for mortality in patients with AKI was 13.33 (95% CI 4.05 to 43.91; I^2 by fixed effects=85.0%; figure 2D). This finding remained significant through sensitivity analyses.

The incidence of AKI and mortality were also evaluated separately. Of the 8 studies (n=1971) that reported the OR for mortality from AKI, the pooled incidence of AKI and mortality was 10.1% (95% CI 6.0% to 16.4%; I^2 by fixed effects model=90.8%) and 26.8% (95% CI 16.9% to 39.7%; I^2 by fixed effects model=96.1%), respectively (online supplementary document 3). Egger's regression intercept for AKI incidence and mortality was 0.752 and 0.549, respectively, suggesting no publication bias.

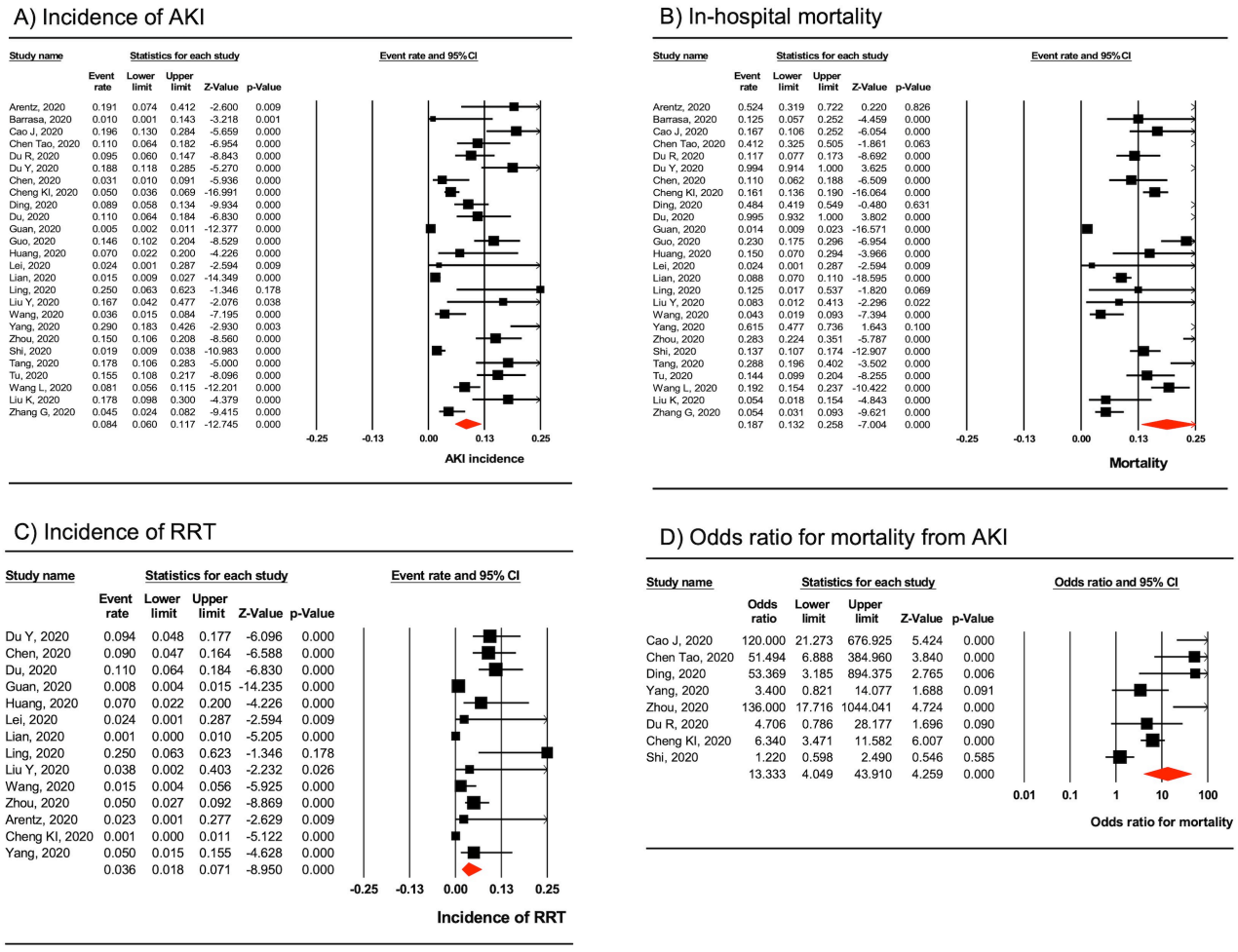

Figure 2 Forest plot demonstrating a meta-analysis of (A) incidence of acute kidney injury, (B) in-hospital mortality, (C) incidence of renal replacement therapy, and (D) OR for mortality from acute kidney injury. AKI, acute kidney injury; RRT, renal replacement therapy.

Meta-regression analysis: AKI and mortality

We performed a meta-regression analysis to evaluate the association between AKI and mortality by using random effects model. Interestingly, we found that the incidence of AKI was positively associated with increased mortality in patients with COVID-19 from both unadjusted and adjusted models. The coefficients were 9.6311 (Q=17.47; p<0.001; unadjusted; figure 3) and 6.1815 (Q=26.18; p=0.02; adjusted for age and sex), respectively. However, AKI was not an independent risk factor for mortality after the following variables were held constant: age, sex, diabetes, hypertension and baseline serum creatinine level (Q=15.88, p=0.37). The results of meta-regression analyses are detailed in online supplementary document 2.

Meta-regression analysis: clinical characteristics and AKI

Table 2 elaborates the results of meta-regression analysis for each covariate. In brief, age, history of diabetes, history of hypertension and baseline serum creatinine levels were predictive of increased AKI in both unadjusted model and model 1. Scatterplots of each significant covariate are illustrated in figure 4. However, only baseline serum creatinine levels were associated with increased incidence of AKI in model 2.

Subgroup analysis

Table 3 depicts the results from subgroup analysis comparing studies with critically ill patients versus studies with hospitalized patients. Critically ill patients had significantly higher incidence of AKI compared with hospitalized patients (19.9% vs 7.3%; p=0.002). However, although critically ill patients had a trend toward higher mortality compared with hospitalized patients, this difference did not reach statistical significance (33% vs 16.1%; p=0.076).

Publication bias

The funnel plots for the analysis of AKI incidence and mortality are illustrated in online supplementary figure S1. Egger's regression intercept for the incidence of AKI, mortality, and incidence of RRT was 0.392, 0.628 and 0.273, respectively, indicating no potential publication bias.

DISCUSSION

We identified the incidence of AKI in patients with COVID-19 to be approximately 8.4% with the incidence of RRT of 3.6%. This is surprisingly less than general hospitalized patients in which the incidence of AKI was reported at 22%.[8] Compared with Middle East respiratory

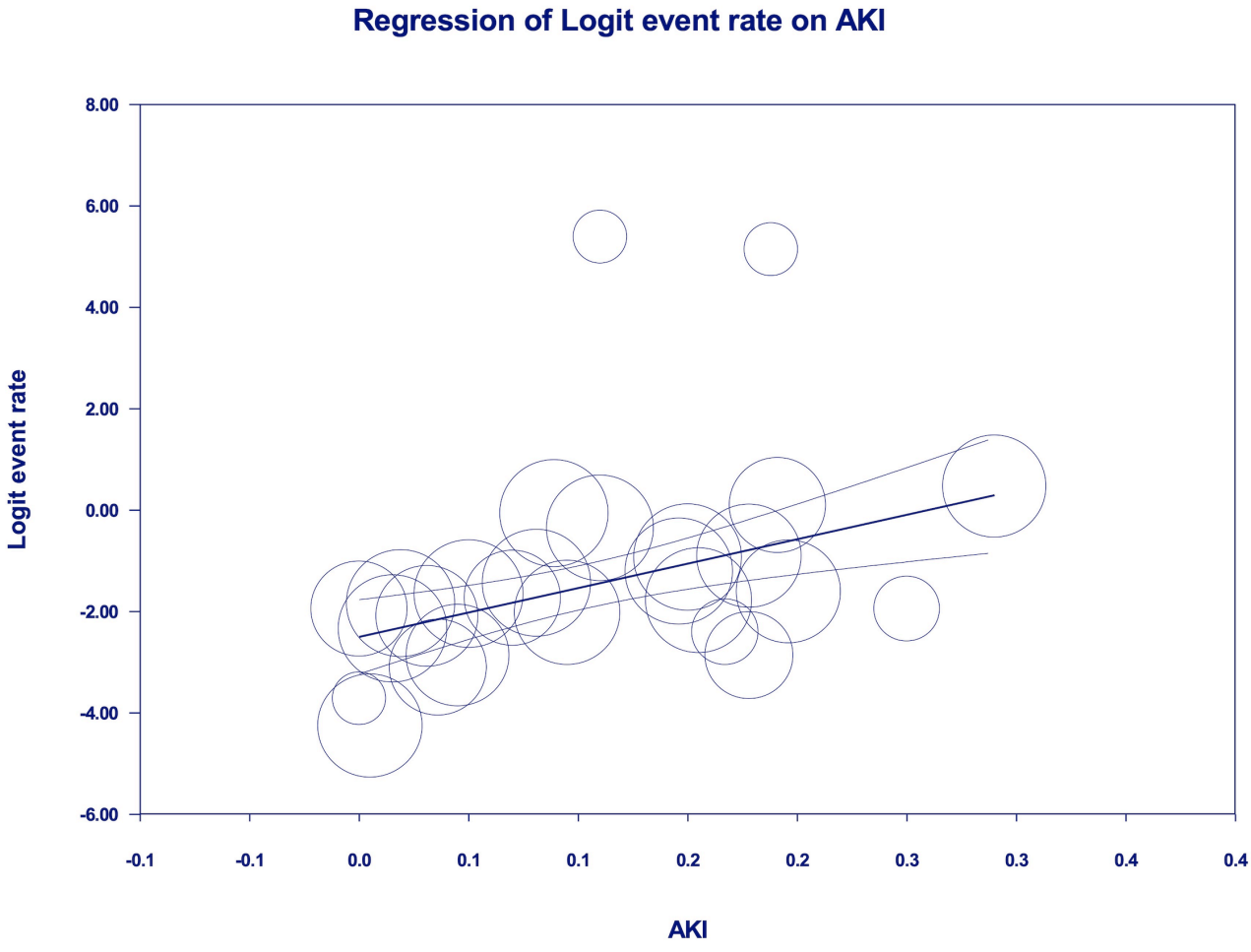

Figure 3 Scatterplot of the association between incidence of acute kidney injury and mortality rate. AKI, acute kidney injury.

syndrome coronavirus (MERS-CoV) outbreaks, patients infected with SARS-CoV-2 had a lower incidence of kidney involvement. Available evidence reported that the incidence of AKI ranged from 17.2% to 26.7% in MERS-CoV-infected patients.[15 16] This virus carried over 34.4% of case fatality since 2012.[17] Earlier in 2005, Chu *et al* conducted a retrospective cohort study of 536 patients with confirmed SARS-CoV infection and identified 36 (6.7%) patients with acute renal impairment.[18] Although our findings are similar to the data from patients with SARS-CoV, it is premature to conclude the incidence of AKI in patients with COVID-19 during the ongoing pandemic. Clinical data from other

Table 2 Results of meta-regression analysis of each covariate toward incidence of acute kidney injury

	Model 1 (unadjusted)		Model 2 (adjusted)†		Model 2 (adjusted)‡	
Variable	Coefficient		Coefficient		Coefficient	
Age	0.0635	Q=6.63, p=0.01*	0.0743	Q=10.79, p=0.02*	−0.0136	Q=12.45, p=0.84
Male	−0.0208	Q=3.81, p=0.05				
Asian	2.1833	Q=1.71, p=0.19				
DM	7.4784	Q=6.74, p=0.01*	9.3515	Q=19.16, p<0.01*	7.6582	Q=12.45, p=0.14
HTN	3.5684	Q=4.22, p=0.04*	4.3811	Q=11.65, p=0.02*	0.5704	Q=12.45, p=0.90
Heart disease	−0.4261	Q=0.06, p=0.80				
Lung disease	9.1485	Q=2.56, p=0.11				
Cancer	9.5281	Q=0.67, p=0.41				
CKD	9.3508	Q=3.90, p=0.09				
Baseline SCr	3.4821	Q=4.19, p=0.04*	3.6041	Q=15.43, p<0.01*	1.7025	Q=12.45, p=0.01*

*Statistically significant.
†Adjusted for sex and chronic kidney disease.
‡Adjusted for age, diabetes, hypertension, and baseline serum creatinine level.
CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; SCr, serum creatinine.

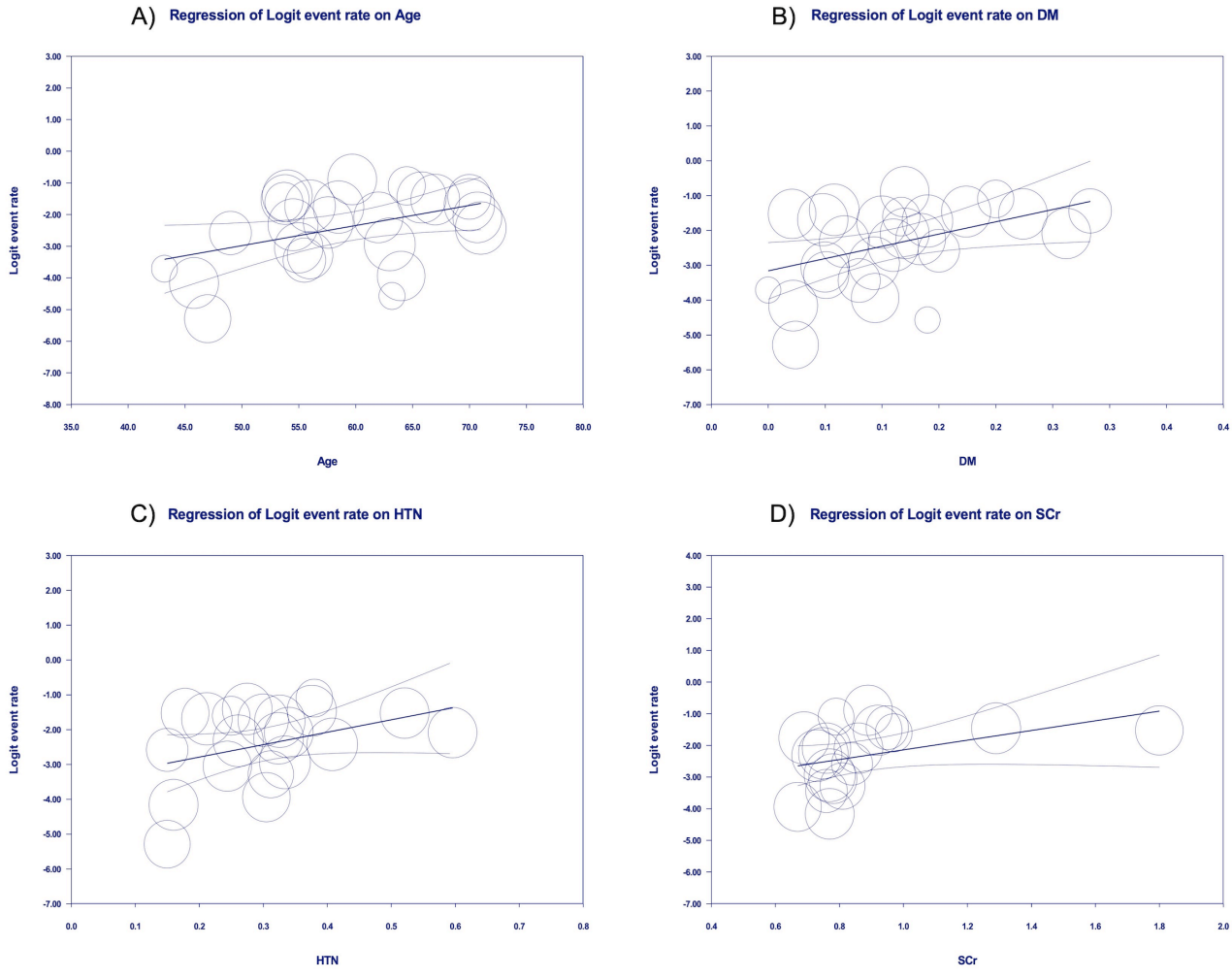

Figure 4 Scatterplot of the association between (A) age, (B) diabetes mellitus (DM), (C) hypertension (HTN), (D) baseline serum creatinine (SCr) levels and incidence of acute kidney injury.

nations including the USA, the UK, Italy, France, Germany and Iran are being collected and would impact the overall incidence of AKI in patients with COVID-19.

We identified that increasing age, diabetes, hypertension and elevated baseline serum creatinine levels are possible predisposing factors for AKI in patients infected with SARS-CoV-2. Consistent with our backbone knowledge, advanced age and diabetes are well-known risk factors for AKI.[19] Similar to SARS-CoV, Chu *et al* demonstrated that age, history hypertension and hypoalbuminemia are potential risk factors for AKI in these patients.[18] However, we added that patients with elevated baseline serum creatinine levels were associated with higher incidence of AKI even after adjusted for other covariates. These patients might include, but not limited to, patients with CKD or patients with some degrees of renal impairment that did not fulfill the criteria for AKI. Physicians should pay close attention to these patients as they are at significant risk of developing AKI.

We have demonstrated that AKI is significantly more common in critically ill patients compared with hospitalized patients (19.9% vs 7.3%). This finding corresponds

Table 3 Subgroup analyses comparing studies with critically ill patients versus studies with hospitalized patients

Subgroup analyses					
Subgroup	**n**	**Incidence (%)**	**95% CI**	**I^2 statistic (%)**	
Incidence of AKI					
Critically ill	5	19.9	11.8 to 31.5	48.4	
Hospitalized	21	7.3	5.0 to 10.4	89.5	Q=9.540, p=0.002*
Mortality					
Critically ill	5	33.0	16.2 to 55.6	86.0	
Hospitalized	21	16.1	11.0 to 23.1	95.4	Q=3.157, p=0.076

*Statistically significant.
AKI, acute kidney injury.

with the data from other cohorts. The overall incidence of AKI in ICU patients ranged from 20% to 50%, higher than those of non-ICU patients.[20] Depending on the diagnoses and comorbidities, lower incidence of AKI was seen in elective surgical patients while patients with sepsis had the highest incidence of AKI.[20] In our study, although critically ill patients had higher mortality than hospitalized patients, the difference, however, was not statistically significant. This could be resulted from an important limitation. Studies that included hospitalized patients with COVID-19 did not report the mortality in general inpatients and critically ill patients separately. Thus, one could argue that the true mortality in non-critically ill patients should be lower than what we reported here.

The underlying etiology of AKI is likely multifactorial. Systemic inflammation, sepsis, hemodynamic instability or concurrent use of diuretics may lead to pre-renal azotemia or acute tubular necrosis (ATN). In critically ill patients, it may be necessary to do radiographic studies with iodinated contrast which could lead to contrast-induced AKI. Additionally, thrombotic microangiopathy leading to ATN is also possible, particularly given that recent evidence suggests that patients with COVID-19 are at greater risk of experiencing thromboembolic events.[21] The use of broad-spectrum empirical antibiotics especially in high doses may also lead to ATN and interstitial nephritis. Initial treatment regimens, such as lopinavir-ritonavir, high-dose oseltamivir or high-dose hydroxychloroquine may contribute to the development of AKI as well.[22 23] However, newer therapeutic breakthroughs, such as remdesivir (NCT04292730, NCT04323761), tocilizumab (NCT04317092), favipiravir (NCT04310228), sarilumab (NCT04327388), sirolimus (NCT04341675) and combined hydroxychloroquine and azithromycin (NCT04329832) are being investigated and we are optimistic to see how these treatments improve the clinical outcomes of patients with COVID-19 and the incidence of AKI. Furthermore, it is possible that the virus itself can infect podocytes and renal tubular cells leading to nephrotoxicity and AKI based on a human cell study model.[24] Some studies also reported that viral RNA was detectable in urine of the infected patients.[25 26] However, whether these findings correlate with the pathogenesis remains unproven.

Our meta-regression analyses demonstrated that the incidence of AKI was associated with increased mortality in patients with COVID-19 after adjustment for age and sex but not with adjustment for additional variables, such as hypertension, diabetes and baseline serum creatinine level. This implies that the overall mortality from COVID-19 could be confounded by other factors other than AKI. However, our findings are comparable to what was previously described during SARS-CoV outbreak. Up to 91.7% of SARS-CoV-infected patients with acute renal impairment died and the relative risk for mortality from acute renal impairment was 16.91 (95% CI 8.37 to 34.16; $p<0.001$).[18] However, although we reported an OR of 13.3-fold for mortality from AKI, this crude OR was unadjusted for other variables due to statistical limitation. Large multinational studies comparing the clinical characteristics of survivors and non-survivors using multivariate analysis are ideal to describe the odds for mortality from AKI.

Herein, we are the first to report the pooled incidence of AKI and its association with mortality in patients with COVID-19. However, our study is subjected to certain limitations. First, all studies were retrospective, making them susceptible to selection bias. However, given the current situation of SARS-CoV-2 outbreak, available data from clinical trials are limited. Second, the pooled mortality in our study was higher than what previously reported by the WHO. This could be secondary to selection bias as AKI was mainly described in critically ill patients. Third, stages and etiologies of AKI were not identified in all studies. One could argue that worsening stages of AKI are likely to be associated with higher mortality. Additionally, the included studies provided limited data on the characteristics of patients with AKI, such as urine output status, and the need for dialysis. This information is crucial to determine the severity and recoverability of AKI. Fourth, the majority of included patients were Asian race as these studies were originated from China. Certainly, there are some concerns that the data obtained from these studies may be incomplete due to ethical issues or lack of adequate follow-up duration especially in the early phase of the pandemic. Fifth, the definition for AKI was not uniformly described in every study. Sixth, there were insufficient data to conduct the survival analysis since most studies did not provide the data on the time to death. Moreover, the incidence of RRT may be under-represented at some facilities due to medical staff and/or equipment shortage. Finally, the clinical information about COVID-19 is dynamic as the current practice varies based on evolving clinical evidence or similarly, the behavior of virus may revolve throughout the different phases in the pandemic.

In conclusion, at least to this point, AKI is an uncommon complication of COVID-19. The incidence of AKI is high in critically ill patients with COVID-19. Our study suggests an association between AKI and increased mortality. Age, diabetes, hypertension, and elevated baseline serum creatinine levels were associated with increased AKI. More studies, including the ones from multinational databases, are encouraged to confirm our findings.

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ORCID iDs
Panupong Hansrivijit http://orcid.org/0000-0002-5041-4290
Charat Thongprayoon http://orcid.org/0000-0002-8313-3604

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