Acute Kidney Injury in COVID-19 is Associated with Mortality: A Meta-Analysis

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ABSTRACT

Background: By March 2020, The World Health Organization (WHO) has declared Coronavirus disease-19 (COVID-19) as a global pandemic. Further investigations found that COVID-19 may lead to acute kidney injury (AKI). Some studies have been done, but the incidence and outcome of AKI in COVID-19 are variable between studies. Moreover, given the high number of COVID-19 cases in our country, we aimed to perform a systematic review and meta-analysis regarding the detailed outcome of AKI in COVID-19 patients as reported in the available literature.

Methods: We performed a comprehensive literature search from several databases, such as EuropePMC, PubMed, ProQuest, Directory of Open Access Journal (DOAJ), and related references between December 1, 2019, and December 5, 2020. The primary outcome was mortality, and the secondary outcomes were the need for Intensive Care Unit (ICU) care, severe and critical COVID-19 infection, and Acute Respiratory Distress Syndrome (ARDS).

Results: There were a total of 25,990 patients from 21 studies. Acute kidney injury was associated with increased odds of mortality (OR 13.43 [8.35, 21.60], $p < 0.00001$; I^2: 82%, $p < 0.00001$), need for ICU care (OR 14.57 [8.51, 24.94], $p < 0.00001$; I^2: 84%; $p < 0.0001$), critical COVID-19 (OR 10.41 [3.88, 27.90], $p < 0.00001$; I^2: 67%; p = 0.02), and ARDS (OR 2.84 [1.30, 6.22], $p = 0.009$; I^2: 91%; $p = 0.001$).

Conclusion: Acute kidney injury is associated with mortality, need for ICU care, critical COVID-19 patients, and ARDS.

Keywords: AKI, COVID-19, Coronavirus, mortality, outcomes

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused a cluster of severe pneumonia in Wuhan in December 2019.[1] The viral infection was later called Coronavirus disease-19 (COVID-19) and has quickly expanded all over the world.[2] By March 2020, The World Health Organization (WHO) has declared this new Coronavirus infection as a global pandemic. As of December 2020, data has recorded a total of 65.8 million cases worldwide and 1.5 million death cases.[3]

The symptoms of COVID-19 may be different in each person, ranging from asymptomatic, mild respiratory disease to critical illness.[4] However, COVID-19 is reported to mainly affects the respiratory tract.[5] In some cases, COVID-19 cases would be unpredictable and more severe which often leads to multiple organ failure. Eventually, COVID-19 patients may have died from respiratory failure.[6]

Further investigations found that the kidney is one of the main COVID-19 infection sites[7] due to the expression of ACE2 which may lead to renal dysfunction.[8] Additionally, cytokine storm as the underlying pathogenesis in COVID-19 severe infection was thought to be the other cause of organ failure including in acute kidney injury (AKI).[8–10] Risk of AKI in COVID-19 patients is alarming to a physician. Some studies have been done, but the incidence of AKI in COVID-19 is also variable between studies.[11] Furthermore, recent studies regarding the outcome of AKI in COVID-19 are unsettled. Some studies concluded that COVID-19-related AKI tends to have a significantly higher risk of progression to end-stage renal disease (ESRD) which could lead to higher mortality.[11] Cheng et al stated that AKI in COVID-19 patients is associated with high in-hospital mortality.[14] Nonetheless, another study showed that COVID-19 did not cause AKI or aggravate AKI in CKD patients.[15] There are reports of viral particles in kidney tissue specimens in COVID-19 patients but definitive proof that these inclusions are SARS-CoV-2 has not been demonstrated.[16] Thus, the specific information about the association of AKI in COVID-19 is still unknown. Knowing this information will contribute towards clinicians, particularly preventive

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measures during this pandemic. Therefore, the study regarding this matter is still very much needed.

Also, given the high number of COVID-19 cases in our country, we aimed to perform a systematic review and meta-analysis regarding the detailed outcomes of AKI in COVID-19 patients including mortality, the need for ICU care, acute respiratory distress syndrome (ARDS), severe and critical COVID-19 infection as reported in the available literature.

METHODS

Eligibility Criteria. We included all research articles in adult patients (> 18 years old) diagnosed with COVID-19 with AKI based on Kidney Disease Improving Global Outcome (KDIGO) 2012 reporting one or more of the disease's outcomes, including mortality, the need for ICU care, acute respiratory distress syndrome (ARDS), or severe and critical COVID-19 infection. The following types of articles were excluded: articles other than original research (e.g., case report or series, review articles, letters to the editor, editorials, or commentaries), duplicate publication, and non-English articles.

Search Strategy and Study Selection. This meta-analysis was accomplished according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[17] We systematically searched EuropePMC, PubMed, ProQuest, Directory of Open Access Journal (DOAJ) and references screening with the following search terms: ("Coronavirus Disease 2019" OR "COVID-19" OR "novel coronavirus pneumonia" OR "2019-nCoV" OR "SARS-CoV-2") AND ("kidney" OR "renal" OR "acute kidney injury" OR "AKI" or "renal injury" or "acute renal failure") AND ("ARDS" OR "critically ill COVID-19" OR "Mortality" OR "outcome" OR "ICU"). Search results were limited to studies between December 1, 2019 and December 5, 2020. Duplicate results were removed initially. The remaining articles were independently screened for relevance by their abstracts with three authors. These articles were thoroughly read and those that fulfilled our criteria were included in the study. The final inclusion of studies was merely based on the agreements of all authors. Any disagreement was resolved by consensus. The full text of residual articles was assessed according to the inclusion and exclusion criteria. The search was performed from November 29, 2020, to December 5, 2020.

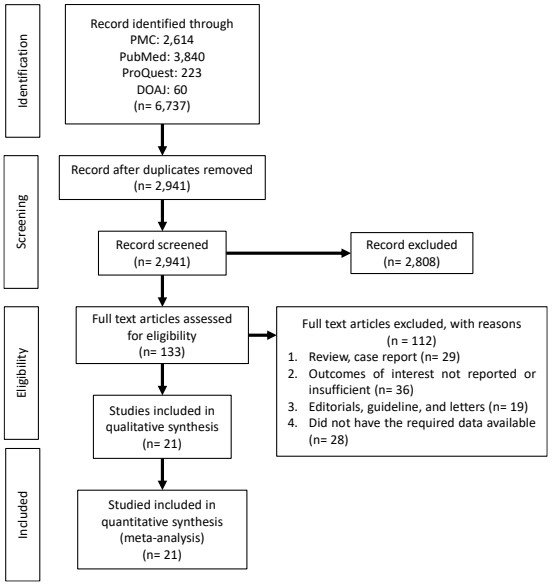

Figure 1. Prisma Flow Diagram

Data Extraction. Data extraction was performed independently by three authors and we used standardized forms that include authors, year of study, period of study, location of study, study design, number of samples, number of AKI patients, blood urea nitrogen (BUN), and serum creatinine of patients, sex, age, comorbidity (hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disease (CVD), cancer, chronic obstructive pulmonary disease (COPD), cerebrovascular disease) and outcomes. The primary outcome was mortality, and the secondary outcomes were the need for ICU care, severe and critical COVID-19 infection, and ARDS.

Definition. Acute kidney injury was defined based on KDIGO classification.[18] ARDS was defined according to the Berlin criteria.[19] Severe and critical COVID-19 infection definition was based on Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment 7th Edition.[20] Severe COVID-19 infection was defined if at least one of the following items was satisfied: (a) breathing rate $\geq$ 30/min, (b) pulse oximeter oxygen saturation (SpO2) $\leq$ 93% at rest, (c) ratio of the partial pressure of arterial oxygen (PaO2) to a fraction of inspired oxygen (FiO2) $\leq$ 300 mmHg. The critical case was defined if at least one of the following items was satisfied: (a) respiratory failure requiring mechanical ventilation, (b) shock, or (c) patients combined with other organ failure needed ICU monitoring and treatment.

Statistical Analysis. To perform a meta-analysis, *Review Manager 5.4.1* (Copenhagen: The Cochrane Collaboration, 2020) and *Stata version 16* (StataCorp LP, Texas 77845, USA) were used. The effects of the data were presented as Odds Ratio (OR). Dichotomous variables were calculated using the Mantel-Haenszel formula. The OR was reported with a 95% Confidence Interval (CI) for dichotomous variables. The *p*-value was two-tailed, and statistical significance was set at $\leq$ 0.05.

Heterogeneity was assessed with the Q-statistic test and I^2 test. The I^2 statistic measured the percentage of total variation across the studies due to clinical or methodological heterogeneity instead of chance. If the significant Q statistics ($p < 0.1$) indicated heterogeneity across the studies, a random-effect model was utilized. Otherwise, a fixed-effect model was utilized. Substantial heterogeneity was represented by I^2 for >50%.[21]

Table 1. Demographic and Clinical Characteristics of Included Studies

Authors	Period	Location	Study Design	Samples (AKI/N)	BUN (mmol/L)	Peak Serum Creatinine (μmol/L)	Male (AKI vs Non-AKI; n, %)	Age (AKI vs Non-AKI)	Comorbidity (n, %)							Outcome
									HT	DM	CKD	CVD	Malignancy	COPD	Cerebrovascular disease	
Yan Q	Jan 27-Mar 18, 2020	Wuhan, China	observational, retrospective	882 (115/767)	N/A	N/A	86(74.8) vs 354(46.2)	75 (69–81) vs 70 (68–76)	N/A	46(40.0) vs 231(30.1)	37(32.2) vs 46(6.0)	79 (68.7) vs 436(56.8)	7(6.1) vs 34(4.4)	17(14.8) vs 69(9.0)	7(6.1) vs 31(4.0)	Mortality, ICU care, ARDS
Lim JH	Feb 17-May 15, 2020	Daegu, South Korea	observational, retrospective	160 (30/130)	23.7 (15.7–32.0)	97.26(70.74–141.47)	20 (66.7) vs 66 (50.8)	75 (60–98) vs 67(24.0–92)	18 (60.0) vs 59 (45.4)	14 (46.7) vs 36 (27.7)	N/A	5 (16.7) vs 16 (12.3)	7 (23.3) vs 19 (14.6)	4 (13.3) vs 12 (9.2)	N/A	Mortality, ICU care, ARDS
Tan LS	Jan 11-Apr 24, 2020	Shenzhen, China	observational, retrospective	417 (40/377)	5.43 (3.69-6.51)	68.5 (54.5-96.5)	26 (65.0) vs 172 (45.6)	60.1 ± 12.5 vs 43.7 ± 17.4	15 (37.5) vs 40 (10.6)	5 (12.5) vs 14 (3.7)	N/A	10 (25.0) vs 16 (4.2)	0 (0.0) vs 6 (1.6)	19 (47.5) vs 81 (21.5)	1 (2.5) vs 2 (0.5)	Severe COVID-19, critical COVID-19
Kolhe N	Mar 5-May 13, 2020	Derby, UK	observational, retrospective	1161 (304/857)	N/A	N/A	179 (58.9) vs 478 (55.8)	74.9 ± 12.8 vs 71.1 ± 17.0	N/A	75 (24.7) vs 180 (21)	104 (34.2) vs 120 (14.0)	42 (13.8) vs 77(9.0)	32 (10.5) vs 70(8.2)	85 (28) vs 226(26.4)	36(11.8) vs 81(9.5)	ICU care
Li Q	Feb 4-Apr 16, 2020	Wuhan, China	observational, retrospective	107 (48/59)	9.4 (6.2-13.4) vs 6.1 (4.5-8.1)	183.6 (126.1–279.5) vs 67.6 (57.6–77.1)	32 (66.7) vs 37 (62.7)	73 (67-81) vs 68 (63-75)	36 (75.0) vs 37 (62.7)	12 (25.0) vs 10 (16.9)	5 (10.4) vs 0	21 (43.8) vs 12 (20.3)	N/A	11 (22.9) vs 12 (20.3)	13 (27.1) vs 6 (10.2)	Mortality, ICU care, ARDS
Hirsch J	Mar1-Apr 5, 2020	New York, USA	observational, retrospective	5449 (1993/3456)	N/A	197.18 (123.79-364.29) vs 86.65 (70.74-106.1)	1270 (63.7) vs 2047 (59.2)	69.0 (58.0, 78.0) vs 61.0 (50.0, 72.0)	1292 (64.8) vs 1745 (50.5)	830 (41.6) vs 967 (28.0)	N/A	289 (14.5) vs 311 (9.0)	65 (3.3) vs 99 (2.9)	147 (7.4) vs 149 (4.3)		ICU care, severe COVID-19
Nimkar A	Mar 10-May 13, 2020,	New York, USA	observational, retrospective	327 (179/148)	N/A	N/A	101 (56.4) vs 81 (54.7)	75 (63–85) vs 67 (53.5–78)	126 (70.4) vs 83 (56.1)	87 (48.6) vs 52 (35.1)	33 (18.4) vs 7 (4.7)	59 (32.9) vs 39 (26.4)	36 (20.1) vs 30 (20.3)	24 (13.4) vs 20 (13.5)	59 (32.9) vs 32 (21.6)	Mortality
Taher A	Apr 1-May 31,2020	Bahrain	observational, retrospective	73 (29/44)	5.99	134.86	21 (72.4) vs 23 (52.3)	57.5 ± 13.7 vs 52.2 ± 13.1	15 (51.7) vs 16 (36.4)	17 (58.6) vs 16 (36.4)	6 (20.7) vs 0 (0)	N/A	3 (10.3) vs 2 (4.5)	N/A	N/A	Mortality, ICU care, severe COVID-19, critical COVID-19
Cui	Jan 5-Mar 21, 2020	Wuhan, China	observational, retrospective	116 (21/95)	N/A	N/A	12 (57.1) vs 54 (56.8)	61.05 ± 12.9 vs 58.58 ± 14.6	9 (42.9) vs 29 (30.5)	2 (9.5) vs 26 (27.4)	1 (4.8) vs 4 (4.2)	10 (47.6) vs 38 (40)	N/A	4 (19) vs 10 (10.5)	N/A	Mortality, severe COVID-19, critical COVID-19
Wang	up to Feb 10, 2020	Wuhan, China	observational, retrospective	107 (14/93)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Mortality
Bahl	Mar 1-Mar 31, 2020	USA	observational, retrospective	1461 (382/1079)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Mortality
Chen	N/A	Wuhan, China	observational, retrospective	1859 (99/1760)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Mortality
Xia	Feb 5-Mar 20, 2020	Wuhan, China	observational, retrospective	81 (41/40)	12.5(8.6-27.8) vs 96(79.8-107.8)	104 (74-188.5) vs 65.5(48-80)	30 (73.2) vs 24 (60)	69.6± 9.3 vs 63.6 ±12.7	23 (56.1) vs 20 (50)	11 (26.8) vs 8(20)	1 (2.4) vs 2(5)	8 (19.5) vs 9(22.5)	N/A	N/A	2 (4.9) vs 9 (22.5)	Mortality
Sang	Jan 23-April 6, 2020	Wuhan, China	observational, retrospective	210 (92/118)	N/A	N/A	62 (67.4) vs 69 (58.5)	65 (59-73) vs 62 (54-70)	45 (48.9) vs 53 (44.9)	23 (25) vs 21 (17.8)		9 (9.8) vs 14 (11.9)	10 (10.9) vs 4 (3.4)	2 (2.2) vs 3 (2.5)	6 (6.52) vs 6 (5.1)	Mortality, critical COVID-19
Chaibi K	Mar 1-Mar 31 2020	France and Spain	observational, retrospective	211 (55/156)	N/A	78 ± 28	45 (82) vs 118 (76)	63 ± 10 vs 60 ± 11	32 (58) vs 75 (48)	23 (42) vs 55 (35)	11 (20) vs 7 (4)	8 (14) vs 11 (7)				Mortality
Cheng Y	Jan 28-Mar 29, 2020	Wuhan, China	observational, retrospective	119 (51/68)	N/A	69 (54-85)	51 vs 61	N/A	51 vs 61	51 vs 61	N/A	N/A	51 vs 61	51 vs 61	N/A	Mortality, severe COVID-19, critical COVID-19
Xu J	Jan 12-Feb 3, 2020	Wuhan, China	observational, retrospective	239 (119/120)	N/A	72.1 (58–85.3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Mortality
Liu Ym	Dec 30, 2019-Apr 17, 2020	Hubei, China	observational, retrospective	12,413 (317/11,096)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	ARDS
Gao S	Jan 23-Feb 29, 2020	Wuhan, China	observational, retrospective	210 (4/206)	4.7 (3.4 – 6.1)	67.1 (56.5 – 84.1)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Mortality, ICU care, ARDS
Hou W	Jan 21-Mar 9, 2020	Beijing, China	observational, retrospective	101 (12/89)	N/A	64.3 (53.5-77.8)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Mortality
Xiao G	Jan 5-Mar 8, 2020	Wuhan, China	observational, retrospective	287(55/232)	N/A	N/A	38 (69.1) vs 122 (52.6)	66 (57-74) vs 60 (49-69)	23 (42) vs 64 (28)	12 (22) vs 33 (14)	N/A	10 (18) vs 23 (10)	3 (5) vs 5 (2)	N/A	9 (16) vs 14 (6)	Mortality, severe COVID-19

Abbreviations: AKI, acute kidney disease; COVID-19, Coronavirus disease-19; BUN, Blood Urea Nitrogen; HT, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; CVD, cardiovascular disease; N/A, not available.

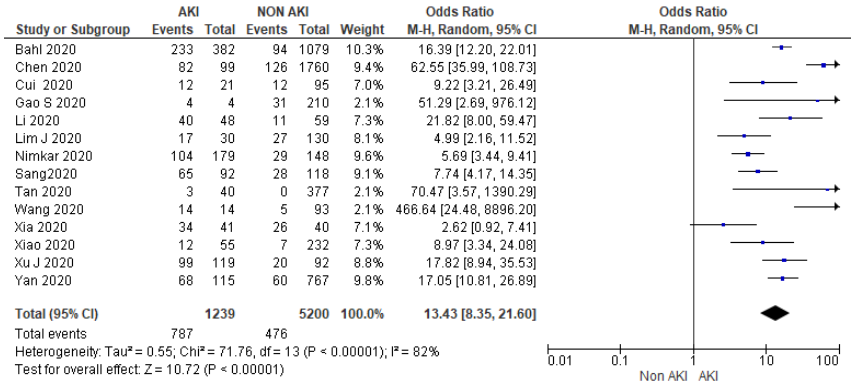

Figure 2. Acute Kidney Injury and Mortality. Forest plot shows that acute kidney injury was associated with increased mortality. (Abbreviations: AKI, Acute Kidney Injury; CI, Confidence Interval; M-H, Mantel-Haenszel)

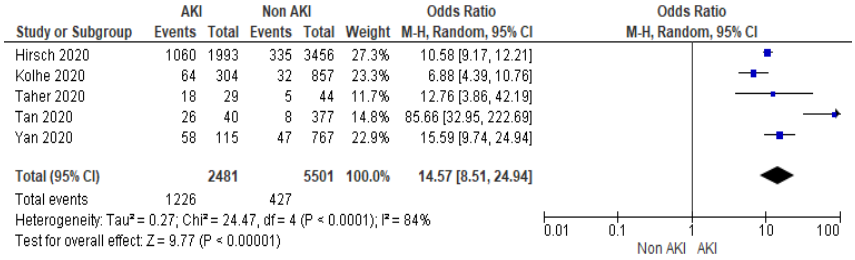

Figure 3. Acute kidney injury and need for ICU care. Forest plot shows that AKI was associated with an increased need for ICU care. (Abbreviations: AKI, Acute Kidney Injury; CI, Confidence Interval; M-H, Mantel-Haenszel)

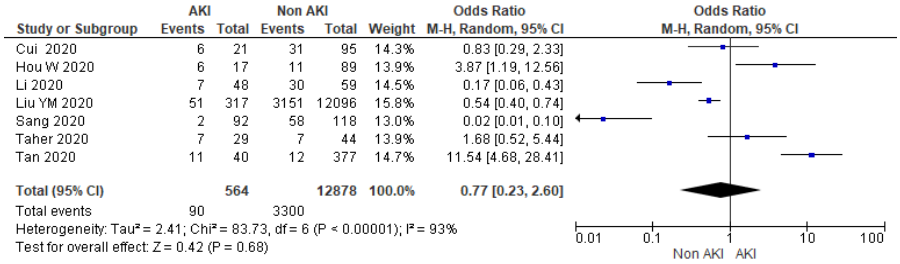

Figure 4. Acute Kidney Injury and Severe COVID-19. Forest plot shows that acute kidney injury was not significant for an increased risk of severe COVID-19. (Abbreviations: AKI, Acute Kidney Injury; CI, Confidence Interval; M-H, Mantel-Haenszel)

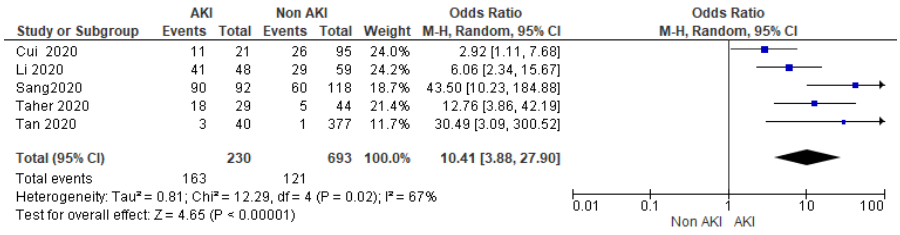

Figure 5. Odds Ratios of Acute Kidney Injury and Critical COVID-19. Forest plot shows that acute kidney injury was associated with increased critical COVID-19. (Abbreviations: AKI, Acute Kidney Injury; CI, Confidence Interval; M-H, Mantel-Haenszel)

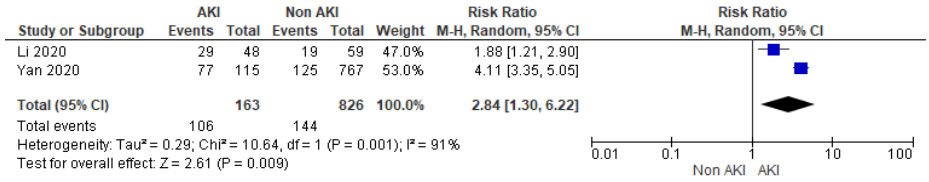

Figure 6. Odds ratios of Acute Kidney Injury and ARDS. Funnel plot shows that AKI was associated with ARDS. (Abbreviations: AKI, Acute Kidney Injury; CI, Confidence Interval; M-H, Mantel-Haenszel)

performed the regression-based Harbord's test. We also performed a qualitative assessment for publication bias by using funnel plot analysis, an asymmetrical shape indicates publication bias.

RESULTS

Baseline Characteristics and Study Selection. We found a total of 6,737 records, and 21 studies are included in qualitative and quantitative synthesis (meta-analysis) (*Fig. 1*).[22-42]

The baseline characteristics of the included studies are presented in *Table 1*. The location of the studies was variable. Of the 21 included studies, 14 studies were from China, three studies were from the USA, two studies were conducted in a European country, one study was from South Korea, and one study was from Bahrain. The included studies from various regions will help our analysis to represent COVID-19 patients worldwide. Our study encompasses a total of 25,990 patients with 4,000 identified as AKI patients (14%). Approximately 64.62% of AKI patients were male. Most patients are elderly with the highest median age was the study by Yan Q et al (75 (69–81) vs 70 (68–76)). Comorbidities in our study were variable, including hypertension (63.97%), DM (36.09%), and CVD (25.24%).

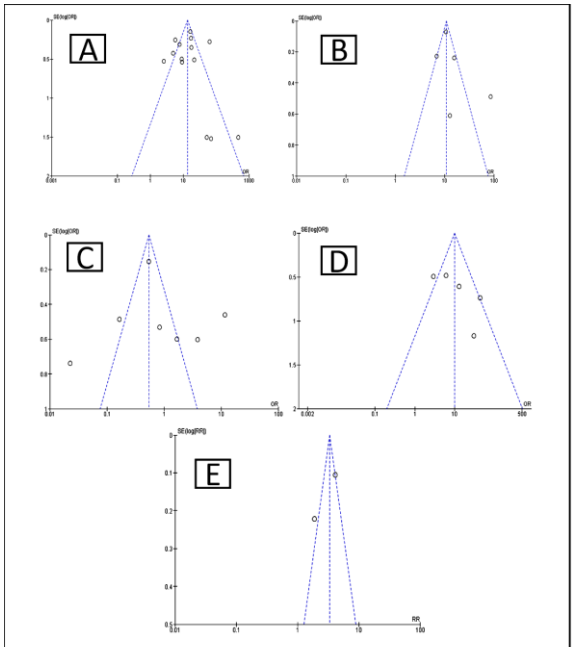

Figure 7. Funnel-plot analysis for publication bias, A: funnel plot of acute kidney injury and mortality, B: funnel plot acute kidney injury and need for ICU care, C: funnel plot acute kidney injury and severe COVID-19, D: funnel plot acute kidney injury and critical COVID-19, and E: funnel plot acute kidney injury and ARDS.

Publication Bias. The funnel-plot analysis showed an asymmetrical shape for all outcomes (*Fig. 7A, B, C, D, E*), indicating possible publication bias. Regression-based Harbord's test showed indication of small-study effects for mortality (p=0.004) and severe COVID-19 (p=0.015).

DISCUSSION

This meta-analysis demonstrated that AKI in COVID-19 was associated with increased mortality, the need for ICU care, critical COVID-19, and ARDS. This finding is consistent with the previous study which found the AKI was associated with worse outcome.[12] By previous studies, the beta coronaviruses SARS-CoV and the most recent SARS-CoV-2 use angiotensin-converting enzyme 2 (ACE-2) as a receptor to facilitate viral entry into target cells; ACE-2 is also located on the surface of kidney tubular cells, and their infection may worsen the local inflammatory response and consequently the incidence and the duration of AKI episodes.[43,44]

In addition to directly attacking renal cells, to the best of our knowledge, the association of AKI and critical COVID-19 are due to cytokine storm or hyper-inflammation with increased levels of IL-6, IL-8, and interferon-gamma which leads to increased vascular permeability and diffuse alveolar damage. A higher viral load of SARS-CoV-2 even has a higher chance to induce a cytokine storm.[45] The release of inflammatory mediators and effects of angiotensin II is also responsible for the activation of the coagulation cascade which leads to a hypercoagulable state. Thrombosis event which is associated with the severity of COVID-19, plays a vital role in developing AKI. As fibrin deposits present in the glomerular loop causing dysregulation of coagulation homeostasis, the disruption of renal microcirculatory could take place and lead to AKI eventually.[46] Other condition accompanying critical COVID-19 also aggravates kidney injuries, such as hypotension or dehydration, hypoxemia, and sepsis.[43,47,48] The mechanism of "organ crosstalk" explains the association

between AKI and ARDS. Impaired function of an organ is communicated to the dysfunction of other organs and subsequently inflicted damage among organs via complex mechanisms in critical illness, including in COVID-19 infection.[49] As mentioned earlier, other ARDS-related critical conditions such as shock, mechanical ventilation, and/or high PEEP might contribute to AKI as well.[36] Mechanical ventilation was speculated to cause several dysfunctions, such as cardiovascular and hemodynamic disturbances, (central venous pressure elevation and increased intra-thoracic pressure) and renal vasoconstriction which also deteriorates renal function.[50,51] Both ARDS and critical COVID-19 contribute to the need of ICU care and mortality.

In terms of severe COVID-19, the association between acute kidney injury and severe COVID-19 did not show statistical significance. Criteria for severe COVID-19 are mainly respiratory abnormalities, when organ failure happened, the patient was determined as critical COVID-19. Hence, the association between severe COVID-19 and AKI might not be clear. We believe it is still essential from a clinical standpoint to differentiate the severity of the disease.

Given the results of our study, AKI may be the early warnings for the physicians for poor prognosis. Early detection and more aggressive strategies may reduce the mortality rate in AKI with COVID-19. Future endeavors regarding this field should include other factors and certain marker parameters (such as IL-6) contributing to poor outcomes, specific populations with larger sample sizes, and interventions in AKI with COVID-19. Also, more studies about the long-term complication of AKI such as progression to chronic kidney disease should be investigated.

Limitations

There are some limitations of the study. First, the presence of publication bias; this is possibly due to the limited number of studies regarding the pertinent issues. Most studies are from China in which the patients might overlap across the reports. Second, some studies in our meta-analysis only included ICU patients which probably cause a high mortality rate. Third, heterogeneity was noticeably high in our study. This may happen due to a significant variation of sample sizes and included study design.

CONCLUSION

In conclusion, acute kidney injury is associated with mortality, need for ICU care, critical COVID-19 patients and ARDS. AKI should be considered as poor outcome in clinical management, prevention, and management of COVID-19 in the hospital setting in global pandemic.

Authorship contribution statement

Ni Made Putri Lastiana: Conceptualization, methodology, formal analysis, data curation, investigation, writing review and editing.

Marianto: conceptualization, methodology, data curation, formal analysis, investigation, writing-original draft, writing review and editing.

Dian Daniella: conceptualization, methodology, data curation, formal analysis, investigation, writing-original draft, writing review and editing.

Declaration of Conflict of Interest

The authors certify that there are no existing relevant conflicts of interest to declare. The authors certify that there were no funding sources supporting this work and output.

References

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. N Engl J Med. 2020 Mar 26;382(13):1199–207.
2. Heymann DL, Shindo N. COVID-19: what is next for public health? The Lancet. 2020 Feb;395(10224):542–5.
3. World Health Organization. COVID-19 Weekly Epidemiological Update. World Health Organization; 2020.
4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323(11):1061.
5. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med. 2020 May 5;172(9):577–82.
6. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020 Feb;395(10223):507–13.
7. Lillie PJ, Samson A, Li A, Adams K, Capstick R, Barlow GD, et al. Novel coronavirus disease (Covid-19): The first two patients in the UK with person-to-person transmission. J Infect. 2020 May;80(5):578–606.
8. Yalameha B, Roshan B, VKS Bhaskar L, Mohmoodnia L. Perspectives on the relationship of renal disease and coronavirus disease 2019. J Nephropharmacology. 2020 Apr 27;9(2):e22–e22.
9. Kellum JA, van Till JWO, Mulligan G. Targeting acute kidney injury in COVID-19. Nephrol Dial Transplant. 2020 Oct 1;35(10):1652–62.
10. Sepehr Ebrahimi-Dehkordi, Hasan Banitalebi, Ali Hasanpour-Dehkordi. Acute kidney injury due to cytokine storm in patients with COVID-19 infection. J Nephropathol [Internet]. [cited 2020 Dec 16];10(4). Available from: http://www.nephropathol.com/Files/Inpress/jnp-17133.pdf
11. Chen Y-T, Shao S-C, Hsu C-K, Wu I-W, Hung M-J, Chen Y-C. Incidence of acute kidney injury in COVID-19 infection: a systematic review and meta-analysis. Crit Care. 2020 Dec;24(1):346.
12. Robbins-Juarez SY, Qian L, King KL, Stevens JS, Husain SA, Radhakrishnan J, et al. Outcomes for Patients With COVID-19 and Acute Kidney Injury: A Systematic Review and Meta-Analysis. Kidney Int Rep. 2020 Aug;5(8):1149–60.
13. Ali H, Daoud A, Mohamed MM, Salim SA, Yessayan L, Baharani J, et al. Survival rate in acute kidney injury

superimposed COVID-19 patients: a systematic review and meta-analysis. Ren Fail. 2020 Jan 1;42(1):393–7.
14. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020 May;97(5):829–38.
15. Wang L, Li X, Chen H, Yan S, Li D, Li Y, 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.
16. Rudnick MR, Hilburg R. Acute Kidney Injury in COVID-19: Another Challenge for Nephrology. Am J Nephrol. 2020;51(10):761–3.
17. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015 Jun 2;162(11):777.
18. Khwaja A. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. Nephron. 2012 Aug 7;120(4):c179–84.
19. Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA [Internet]. 2012 Jun 20 [cited 2020 Dec 15];307(23). Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2012.5669
20. China National Health Commission. Chinese CLinical Guidance for COVID019 Pneumonia Diagnosis and Treatment. 2020.
21. Deek J, Higgins J, Altman D. Analysing data and undertaking meta-analysis. In: Cochrane handbook for systematic reviews of interventions. England: John Wiley & Sons Ltd; 2008. p. 244–96.
22. Yan Q, Zuo P, Cheng L, Li Y, Song K, Chen Y, et al. Acute Kidney Injury Is Associated with In-hospital Mortality in Older Patients With COVID-19. Newman AB, editor. J Gerontol Ser A. 2020 Jul 16;glaa181.
23. Lim J-H, Park S-H, Jeon Y, Cho J-H, Jung H-Y, Choi J-Y, et al. Fatal Outcomes of COVID-19 in Patients with Severe Acute Kidney Injury. J Clin Med. 2020 Jun 3;9(6):1718.
24. Tan L-S, Huang X-Y, Wang Y-F, Jia Y, Pang Q-L, Zhang W-X, et al. Association of acute kidney injury and clinical outcomes in patients with COVID-19 in Shenzhen, China: a retrospective cohort study. Am J Transl Res. 2020;12(10):6931–40.
25. Kolhe NV, Fluck RJ, Selby NM, Taal MW. Acute kidney injury associated with COVID-19: A retrospective cohort study. Remuzzi G, editor. PLOS Med. 2020 Oct 30;17(10):e1003406.
26. Li Q, Zhang T, Li F, Mao Z, Kang H, Tao L, et al. Acute Kidney Injury Can Predict In-Hospital Mortality in Elderly Patients with COVID-19 in the ICU: A Single-Center Study. Clin Interv Aging. 2020 Nov; Volume 15:2095–107.
27. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020 Jul;98(1):209–18.
28. Taher A, Alalwan AA, Naser N, Alsegai O, Alaradi A. Acute Kidney Injury in COVID-19 Pneumonia: A Single-Center Experience in Bahrain. Cureus [Internet]. 2020 Aug 12 [cited 2020 Dec 25]; Available from: https://www.cureus.com/articles/37442-acute-kidney-injury-in-covid-19-pneumonia-a-single-center-experience-in-bahrain
29. Nimkar A, Naaraayan A, Hasan A, Pant S, Durdevic M, Suarez CN, et al. Incidence and Risk Factors for Acute Kidney Injury and Its Effect on Mortality in Patients Hospitalized From COVID-19. Mayo Clin Proc Innov Qual Outcomes. 2020 Dec;4(6):687–95.
30. Cui X, Yu X, Wu X, Huang L, Tian Y, Huang X, et al. Acute Kidney Injury in Patients with the Coronavirus Disease 2019: A Multicenter Study. Kidney Blood Press Res. 2020;45(4):612–22.
31. Wang D, Yin Y, Hu C, Liu X, Zhang X, Zhou S, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Crit Care. 2020 Dec;24(1):188.
32. Bahl A, Van Baalen MN, Ortiz L, Chen N-W, Todd C, Milad M, et al. Early predictors of in-hospital mortality in patients with COVID-19 in a large American cohort. Intern Emerg Med. 2020 Nov;15(8):1485–99.
33. Chen L, Yu J, He W, Chen L, Yuan G, Dong F, et al. Risk factors for death in 1859 subjects with COVID-19. Leukemia. 2020 Aug;34(8):2173–83.
34. Xia P, Wen Y, Duan Y, Su H, Cao W, Xiao M, et al. Clinicopathological Features and Outcomes of Acute Kidney Injury in Critically Ill COVID-19 with Prolonged Disease Course: A Retrospective Cohort. J Am Soc Nephrol. 2020 Sep;31(9):2205–21.
35. Sang L, Chen S, Zheng X, Guan W, Zhang Z, Liang W, et al. The incidence, risk factors and prognosis of acute kidney injury in severe and critically ill patients with COVID-19 in mainland China: a retrospective study. BMC Pulm Med. 2020 Dec;20(1):290.
36. Chaibi K, Dao M, Pham T, Gumucio-Sanguino VD, Di Paolo FA, Pavot A, et al. Severe Acute Kidney Injury in Patients with COVID-19 and Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2020 Nov 1;202(9):1299–301.
37. Cheng Y, Zhang N, Luo R, Zhang M, Wang Z, Dong L, et al. Risk Factors and Outcomes of Acute Kidney Injury in Critically Ill Patients with Coronavirus Disease 2019. Kidney Dis. 2020 Oct 26;1–9.
38. Xu J, Yang X, Yang L, Zou X, Wang Y, Wu Y, et al. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan, China. Crit Care. 2020 Dec;24(1):394.
39. Liu Y-M, Xie J, Chen M-M, Zhang X, Cheng X, Li H, et al. Kidney Function Indicators Predict Adverse Outcomes of COVID-19. Med. 2020 Oct;S2666634020300179.
40. Gao S, Jiang F, Jin W, Shi Y, Yang L, Xia Y, et al. Risk factors influencing the prognosis of elderly patients infected with COVID-19: a clinical retrospective study in Wuhan, China. Aging. 2020 Jul 15;12(13):12504–16.
41. Hou W, Zhang W, Jin R, Liang L, Xu B, Hu Z. Risk factors for disease progression in hospitalized patients with COVID-19: a retrospective cohort study. Infect Dis. 2020 Jul 2;52(7):498–505.
42. Xiao G, Hu H, Wu F, Sha T, Huang Q, Li H, et al. Acute kidney injury in patients hospitalized with COVID-19 in Wuhan, China: A single-center retrospective observational study [Internet]. Intensive Care and Critical Care Medicine; 2020 Apr [cited 2020 Dec 25]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.06.20055194
43. Hassanein M, Radhakrishnan Y, Sedor J, Vachharajani T, Vachharajani VT, Augustine J, et al. COVID-19 and the kidney. Cleve Clin J Med. 2020 Oct;87(10):619–31.
44. Fanelli V, Fiorentino M, Cantaluppi V, Gesualdo L, Stallone G, Ronco C, et al. Acute kidney injury in SARS-CoV-2 infected patients. Crit Care. 2020 Dec;24(1):155.
45. Lin L, Wang X, Ren J, Sun Y, Yu R, Li K, et al. Risk factors and prognosis for COVID-19-induced acute kidney injury: a meta-analysis. BMJ Open. 2020 Nov;10(11):e042573.
46. Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. Acute kidney injury in critically ill patients with COVID-19. Intensive Care Med. 2020 Jul;46(7):1339–48.
47. Qian J-Y, Wang B, Liu B-C. Acute Kidney Injury in the 2019 Novel Coronavirus Disease. Kidney Dis. 2020;6(5):318–23.

48. Nadim MK, Forni LG, Mehta RL, Connor MJ, Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol [Internet]. 2020 Oct 15 [cited 2020 Dec 23]; Available from: http://www.nature.com/articles/s41581-020-00356-5
49. Husain-Syed F, Ricci Z, Brodie D, Vincent J-L, Ranieri VM, Slutsky AS, et al. Extracorporeal organ support (ECOS) in critical illness and acute kidney injury: from native to artificial organ crosstalk. Intensive Care Med. 2018 Sep;44(9):1447–59.
50. van den Akker JP, Egal M, Groeneveld JA. Invasive mechanical ventilation as a risk factor for acute kidney injury in the critically ill: a systematic review and meta-analysis. Crit Care. 2013;17(3):R98.
51. Joannidis M, Forni LG, Klein SJ, Honore PM, Kashani K, Ostermann M, et al. Lung–kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup. Intensive Care Med. 2020 Apr;46(4):654–72.