

Acute kidney injury is associated with worse prognosis in COVID-19 patients: a systematic review and meta-analysis

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Abstract. *Background:* The association between acute kidney injury (AKI) and outcome of coronavirus disease 2019 (COVID-19) has not yet been conclusively established. Therefore, we conducted a meta-analysis of recent scientific literature to assess whether AKI may be associated with worse prognosis and increased mortality in COVID-19 patients. *Methods:* A systematic search of literature was conducted between 1st November 2019 and 15th May 2020 on Medline (PubMed interface) and China National Knowledge Infrastructure (CNKI) to identify potentially eligible studies. Cohort or case-control studies reporting data on AKI in patients with or without severe COVID-19 were included. Studies were divided into separate cohorts for analysis based on two endpoints (severity [severe vs non-severe] and mortality [non-survivors vs survivors]). Data were pooled into a meta-analysis to estimate pooled odds ratio (OR) with 95% confidence interval (95% CI) for either outcome. *Results:* A total of 15 studies (n= 5,832 patients) were included in the analysis. Overall, AKI was found to be associated with significantly increased odds of COVID-19 severity (OR= 18.5; 95% CI 8.99-38.08) and mortality (OR= 23.9; 95% CI 18.84-30.31). No heterogeneity was observed for both outcomes (Cochran's Q= 6.21, p=0.52, I²=0% and Cochran's Q= 4.56, p=0.47, I²=0% respectively). *Conclusion:* According to current data, AKI seems to be associated with worse prognosis in COVID-19 patients. Further investigation of the underlying mechanism of renal disease in COVID-19 would be needed to clarify possible therapeutic targets. AKI could be used as a clinical characteristic in severity classification and risk stratification.

Key words: Acute Kidney Injury, COVID-19, Mortality

Introduction

Coronavirus disease 2019 (COVID 19) is a novel zoonotic disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. Since the outbreak began in December 2019, the disease has rapidly spread all over the world persuading the World Health Organization (WHO) to declare it a global pandemic in March, 2020 [3]. Currently, transmission of SARS-CoV-2 is through person-to-person contact

with infected COVID-19 patients either directly or via droplets [4]. This has resulted in major travel restrictions and lockdowns in many countries with concomitant untoward economic and social repercussions.

The infectivity of SARS-CoV-2 is via its attachment to the angiotensin-converting enzyme 2 (ACE2) receptor, which is widely found in many immune and non-immune cells including epithelial cells of intestinal and respiratory mucosa, endothelial cells and renal tubules [5]. This has resulted to the seeding of

the virus to many organs as evidenced by its isolation not only from respiratory samples but also from other body fluids, including conjunctival secretions [6], semen [7], stool [8] and even occasionally urine [9], thus supporting active renal involvement. Consequently, the clinical course of COVID 19 is highly variable. Although initial reports indicated that it mainly caused respiratory disease with alveolar damage and acute respiratory distress [10], current understanding is that COVID-19 encompasses a broader spectrum ranging from asymptomatic disease to multiple organ failure (MOF) and death [11]. The severity of disease and likelihood of mortality has further been linked with many other factors including advanced age, male sex and pre-existing chronic medical conditions [11]. In severe cases of COVID-19, the development of acute organ injury, including acute kidney injury (AKI), has also been documented.

The occurrence of AKI in COVID-19 patients has been reported to range between 5% and 27% [12-14]. In a few instances, patients were known to present to the emergency department with AKI- related symptoms as the only presenting features [15,16]. Previous studies have also demonstrated that elevated creatinine levels at admission is associated with increased risk of severe disease [17]. This renal involvement has been directly linked to the severity of respiratory disease [18] and has been heightened by preponderance of ACE2 expression at the surface of renal tubular epithelial cells [19]. Although COVID-19 patients were shown to have higher risk of in-hospital mortality [13,18], this association has not been conclusively established. Furthermore, the relationship of AKI as a predictor to the severity of COVID-19 has largely not been defined. Therefore, this study aims at clarify the clinical association between AKI and COVID-19 severity and mortality.

Methods

Study protocol and registration

This systematic review and meta-analysis was conducted in strict conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) guidelines [20]. The study protocol has been reported in the International Prospective Register of Systematic Reviews (PROSPERO identifier: CRD42020184330).

Literature Search Strategy

A comprehensive and systematic search of scientific literature was conducted between November 1st, 2019 to May 15th, 2020 on PubMed and China National Knowledge Infrastructure (CNKI) to identify eligible studies. The electronic search was carried out using the following keywords: (1) (((COVID-19) OR SARS-CoV-2) OR 2019-nCoV (2) (((((Acute kidney injury) OR Acute renal injury) OR AKI) OR Creatinine) OR Urine output))) OR Laboratory characteristics (3) 1 AND 2. No language restriction was applied. When the articles were published by the same study group and an overlap was found, only the most recent article was included to avoid duplication of data. The PubMed function “related articles” was used to extend the search. We also searched major infectious disease, nephrology and general medicine journals reporting articles about COVID-19 infection to look for additional studies. We then performed hand-search of bibliography of included studies, to identify other potentially eligible investigations.

Eligibility Criteria

All studies were screened and assessed for eligibility by three independent reviewers (I.C, V.K, and B.N). Search results were screened by title and abstract, with those of potential relevance evaluated by full text. Studies were deemed eligible for inclusion if they fulfilled the following criteria: (1) observational cohort or case-control studies reporting AKI frequency data, (2) clearly defined AKI as per the KDIGO clinical practice guidelines [21], (3) used appropriate definition of severe disease or compared survivors to non-survivors in a general cohort or compared survival to non-survivors in a critically ill cohort, (4) disease severity was monitored over the course of study, (5) clearly outlined the definition of “severe disease” and (6) sample size >10. Severe disease was defined in this analysis as a composite of: (1) respiratory distress, respiratory rate ≥ 30 per

min; (2) oxygen saturation on room air at rest $\leq 93\%$; (3) partial pressure of oxygen in arterial blood / fraction of inspired oxygen ≤ 300 mmHg; (4) patients requiring mechanical ventilation/vital life support/intensive care unit admission (ICU); (5) death. Reviews and studies with incomplete or irrelevant data were excluded. Any disagreement between reviewers arising during the eligibility assessment was settled through consensus.

Data Extraction and Quality Assessment

Data extraction was conducted by three independent reviewers (I.C, V.K and B.N). For each study, the following information was extracted: surname of the first author and year of publication, country and city where the study was performed, type of study, sample size, baseline demographic characteristics, proportion of patients with severe and non-severe COVID-19, proportion of patients with AKI, and mortality from COVID-19. Any variances were resolved by consensus. Quality assessment and analysis of risk of bias of all selected full-text articles was performed using the methodological index for non randomized studies (MINORS) tool.

Outcomes of Interest

The primary outcome of interest was the association between AKI and COVID-19 severity, while the secondary outcome was the association between AKI and COVID-19 mortality. A tertiary outcome was the association between AKI and mortality in patients with severe COVID-19 disease. Thus, a total of three separate meta-analyses were performed.

Statistical Analysis

The statistical analysis was carried out using MetaXL (software Version 5.3, EpiGear International Pty Ltd., Sunrise Beach, Australia) and the Meta-Analyst (software version 5.26.14, Center for Evidence-Based Medicine, Brown University, Providence, USA). The strength of association between AKI and COVID-19 severity and mortality was estimated using odds ratio (OR). A random-effects model was applied. The magnitude of heterogeneity among the

included studies was assessed using the chi-squared test (Chi^2) and I-squared statistic (I^2). For the Chi^2 test, a Cochran's Q p value of <0.10 was considered significant. The values of the I^2 statistic were interpreted as follows at a 95% confidence interval: Thresholds of 25%, 50% and 75% to designate low, moderate, and high heterogeneity were applied [22]. Publication bias was assessed by funnel plot analysis. A random effects meta-regression using log OR was performed to evaluate the impact of baseline characteristics (age and sex) and co-morbidities (diabetes, cardiovascular disease, chronic lung disease, cancer, and hypertension) on association of AKI with disease severity in patients with COVID-19. Additionally, leave-one out sensitivity analysis was performed to assess the robustness of the results, and to further probe the sources of inter-study heterogeneity.

Results

Study Identification

The initial search generated 346 potentially relevant articles. Following duplicate removal and primary screening, 52 articles were assessed by full text for eligibility in the meta-analysis. Of these, 37 were excluded because the primary and secondary outcome of the study did not match the criteria set in this review. A total of 15 articles could hence be included in this systematic review and meta-analysis (Figure 1; Table 1 and 2).

Characteristics of the Included Studies and Quality Assessment

A total of 15 studies ($n= 5,832$ patients) were included. Of the included studies, 12 were from China, 2 from the United States (US) and 1 from South Korea. Seven studies reported AKI data in patients with and without severe COVID-19, seven studies reported data on mortality, while one study reported both. The essential characteristics of the included studies are outlined in tables 1 and 2. Summary of the methodological index for non randomized studies (MINORS) assessment for the included studies is provided in figure 2.

Meta-analysis on the association between AKI and COVID-19 severity

A total of 8 studies (n=1,730 patients) reported data on association between AKI and COVID-19 severity. In five out of these eight studies, AKI was associated with significantly enhanced odds of severe COVID-19 (Figure 3). In pooled analysis, AKI was found to be associated with significantly increased odds of severe COVID-19 (OR=18.5; 95% CI 8.99-38.08). No evidence of inter-study heterogeneity was observed for this outcome (Cochran's $Q=6.21$, $p=0.52$, $I^2=0\%$). No significant changes in the OR could be seen in the leave-one-out sensitivity analysis.

Meta-analysis on the association between CVD and overall COVID-19 mortality

A total of 6 studies (n=2,296 patients) reported data on association between AKI and COVID-19 mortality in all hospitalized patients (with both severe and non-severe form of the disease). In all these studies AKI was associated with significantly enhanced odds of mortality in COVID-19. In the pooled analysis, AKI was found to be associated with a significantly increased odds of mortality in COVID-19 patients (OR= 23.9; 95% CI 18.84-30.31). No evidence of inter-study heterogeneity was observed for this outcome (Cochran's $Q=4.56$, $p=0.47$, $I^2=0\%$). No significant changes in the OR were seen in the leave-one-out sensitivity analysis (Figure 4).

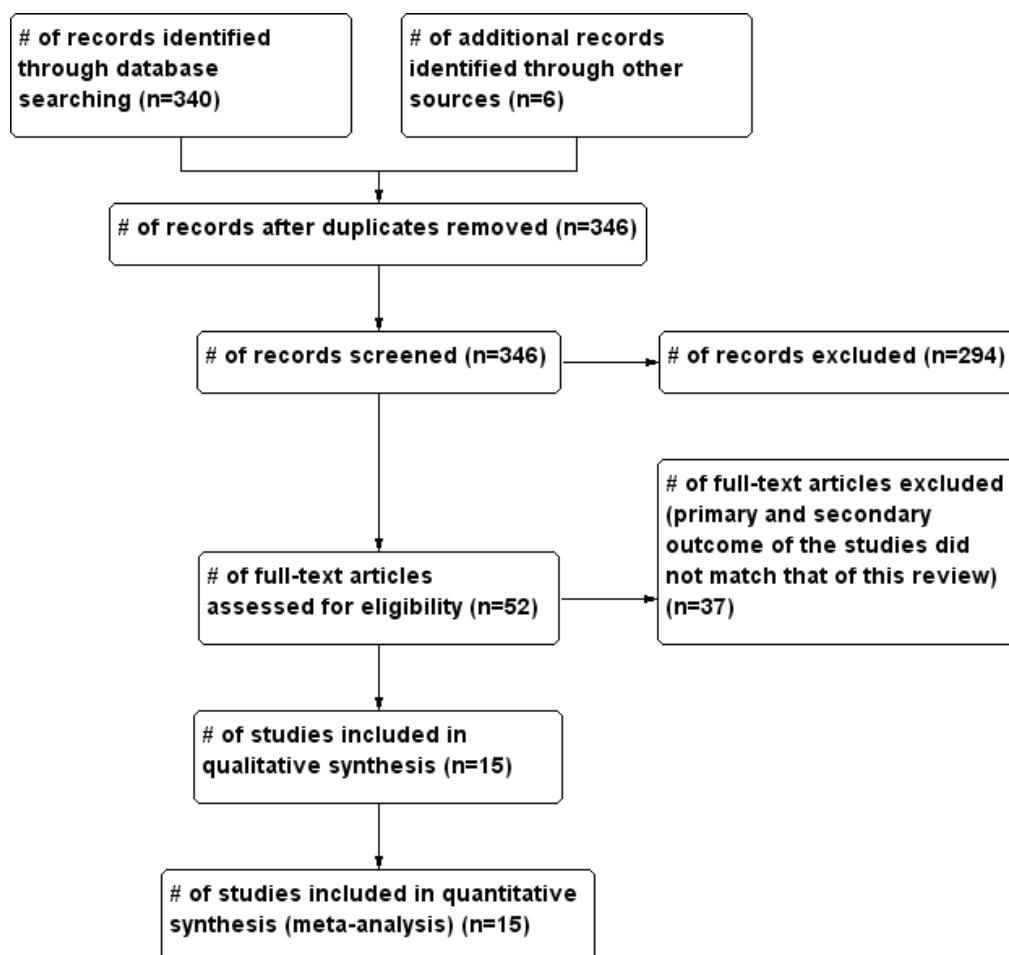


Figure 1. Flow of studies through the meta-analysis

Table 1. Characteristics of studies included in the severity cohort analysis

Study	Country & City	Sample Size	Severe patients			Non-severe patients				
			n (%)	Age (yrs)	Women (%)	AKI (%)	n (%)	Age (yrs)	Women (%)	AKI (%)
Guan et al. [4]	Outside Hubei, China	1099	173 (15.7%)	52 (40-65)	73 (42%)	5 (2.9%)	926 (84.3%)	45 (34-57)	386 (42%)	1 (0.1%)
Huang et al. [23]	Wuhan, China	41	13 (31.7%)	49 (41-61)	2 (15%)	3 (23.1%)	28 (68.3%)	49 (41-57.5)	15 (53.6%)	0 (0%)
Zhang Guqin et al., [24]	Wuhan, China	221	55 (24.9%)	62 (52-74)	20 (36.4%)	8 (14.5%)	166 (75.1%)	51 (36-64.3)	93 (56%)	2 (1.2%)
Yao et al., [25]	Dabieshan, China	108	25 (23.1%)	-	12 (48%)	9 (36%)	83 (76.9%)	50.0 (34.0-56.0)	53 (63.9%)	7 (8.4%)
Aggarwal et al., [26]	Iowa, USA	16	8 (50%)	67 (38-70)	3 (38%)	8 (100%)	8 (50%)	68.5 (41-95)	1 (13%)	3 (37.5%)
Wang D et al., [27]	Wuhan, China	138	36 (26.1%)	66 (57-78)	14 (38.9)	3 (8.3%)	102 (73.9%)	51 (37-62)	49 (48%)	2 (1.9%)
Chen G et al., [28]	Wuhan, China	21	11 (52.4%)	61 (56.5-66)	1 (9.1%)	2 (18.2%)	10 (47.6%)	52 (42.8-56)	3 (30%)	0 (0%)
Hong et al., [29]	Daegu, South Korea	98	13 (13.2%)	63.2±10.1	7 (53.8%)	8 (61.5%)	85 (86.8%)	54.2±17.7	53 (62.4%)	1 (1.2%)

Table 2. Characteristics of studies included in the mortality analysis cohort

Study	Country & City	Sample			Survivors			Non-survivors		
		Size	n (%)	Age (yrs)	Women (%)	AKI (%)	n (%)	Age (yrs)	Women (%)	AKI (%)
Zhou F et al., [10]	Wuhan, China	191	137 (71.7%)	52 (45-58)	56 (41%)	36 (26.3%)	54 (28.3%)	69 (63-76)	16 (30%)	41 (75.9%)
Chen T et al., [12]	Wuhan, Chins	274	161 (58.8%)	51 (37-66)	73 (45%)	8 (5%)	113 (41.2%)	68 (62-77)	30 (27%)	44 (40%)
Yao et al., [25]	Dabieshan, China	108	12 (11.1%)	-	-	5 (41.7%)	96 (88.9%)	65.0 (51.0,73.5)	5 (41%)	18 (18.75%)
Wang Y et al., [30]	Wuhan, China	344	211 (61.3%)	57 (47-69)	106 (50.2%)	6 (2.8%)	133 ((38.7%)	70 (62-77)	59 (44.4%)	80 (60.2%)
Yang et al., [11]	Wuhan, China	52	20 (38.5%)	51.9±12.9	6 (30%)	3 (15%)	32 (61.5%)	64.6±11.2	11 (34%)	12 (37.5%)
Deng et al., [31]	Wuhan, China	225	116 (51.6%)	40 (33-57)	65 (56%)	0 (0%)	109 (48.4%)	69 (62-74)	36 (33%)	20 (18.3%)
Ruan et al., [32]	Wuhan, China	150	82 (54.7%)	50 (44-81)	29 (35%)	2 (2.4%)	68 (45.3%)	67 (15-81)	19 (28%)	21 (30.9%)
Richardson et al., [33]	New York, USA	2358	1869 (79.3%)	-	-	176 (9.4%)	489 (20.7%)	-	-	347 (70.9%)

	Clearly stated aim	Inclusion of consecutive patients	Prospective data collection	Endpoints appropriate to study aim	Unbiased assessment of study endpoint	Follow-up period appropriate to study aim	<5% lost to follow-up	Prospective calculation of study size	Adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses
Aggarwal et al., 2020	+	+	-	+	-	+	+	-	+	+	+	+
Chen G et al., 2020	+	+	-	+	-	+	+	-	+	+	+	+
Chen T et al., 2020	+	+	-	+	-	+	+	-	+	+	+	+
Deng et al., 2020	+	+	-	+	-	+	+	-	+	+	-	+
Guan et al., 2020	+	+	-	+	-	+	+	-	+	+	+	+
Hong et al., 2020	+	+	-	+	?	+	+	-	+	+	-	+
Huang et al., 2020	+	+	-	+	+	+	+	-	+	+	+	+
Richardson et al., 2020	+	+	+	+	?	+	+	+	+	+	?	+
Ruan et al., 2020	+	?	-	+	?	+	+	-	+	+	-	+
Wang D et al., 2020	+	+	-	+	?	+	+	-	+	+	-	+
Wang Y et al., 2020	+	+	+	+	?	+	+	+	+	+	-	+
Yang et al., 2020	+	+	-	+	?	+	+	-	+	+	+	+
Yao et al., 2020	+	+	-	+	+	+	+	-	+	+	-	+
Zhang G et al., 2020	+	-	-	+	?	+	+	-	+	+	-	+
Zhou et al., 2020	+	+	-	+	+	+	+	-	+	+	-	+

Figure 2. Summary of the MINORS quality assessment of the included studies

Meta-analysis on the association between AKI and mortality in severe COVID-19 disease

A total of two studies (n= 396 patients) reported data on mortality in patients with severe COVID-19 disease. In the pooled analysis, we found a non-significant trend toward increased mortality in AKI patients with severe COVID-19 disease, with high

level of inter-study heterogeneity (OR=14.05; 95% CI: 0.98-201.33, $I^2=90\%$, Cochran's $Q=10.15$, $p=0.001$). The bulk of the confidence interval extended well beyond the null value of 1, indicating a substantial elevated probability of a clinically important effect of AKI on mortality in patients with severe form of COVID-19 (Figure 5).

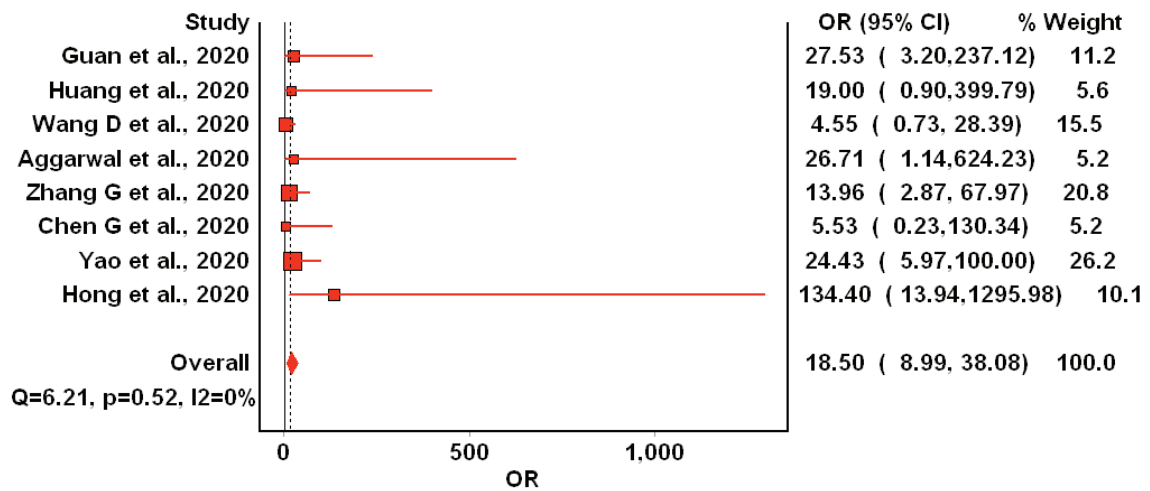


Figure 3. Forest plot for association between AKI and COVID-19 severity

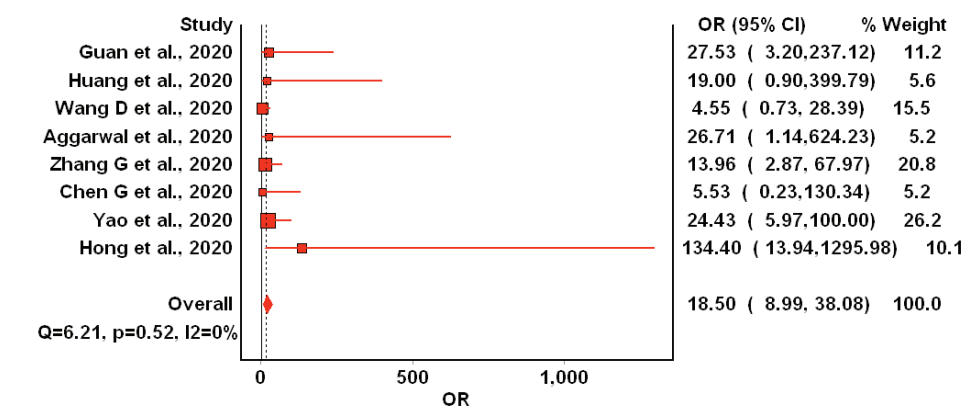


Figure 4. Forest plot for association between AKI and overall COVID-19 mortality

Publication Bias and Meta-Regression

The potential for publication bias was evaluated in funnel plots (supplementary material). No asymmetry was noted in funnel plot for AKI and COVID-19 severity, while mild asymmetry was noted in the funnel plot for AKI and overall COVID-19 mortality. In the meta-regression of odds of severe disease/mortality with AKI, the age, sex and co-morbidities (history of cardiovascular disease, hypertension or diabetes) in patients in the severe group had no significant influence on calculated pooled OR (supplementary material).

Discussion

The main findings of the current study demonstrate that development of AKI in COVID-19 patients seems to be a predictor of worse outcome in the course of illness, including disease severity and mortality.

AKI has been previously found to be an independent predictor of mortality throughout an ample array of critical illnesses [34]. Acute renal failure commonly complicates acute respiratory distress (ARDS) due to impaired oxygenation, fluid overload, cardiogenic shock, superimposed sepsis or injurious mechanical ventilation [21]. In COVID-19, the incidence of

AKI has been seen in up to 29% of patient cohorts [10,11]. Nevertheless, the pathophysiology of acute renal injury still remains a subject of current investigation in COVID-19. Several mechanisms have been postulated. It is known that SARS-CoV-2 spike protein binds to ACE2 receptor in host cells [5]. Puelles et al., [35] recently demonstrated that the RNA for angiotensin-converting enzyme 2 (ACE2), the receptor that is considered to facilitate SARS-CoV-2 infection is enriched in multiple kidney-cell types from fetal development through adulthood [35]. In the kidney, host cells have been identified as podocytes and proximal straight tubule cells [36]. Puelles et al., [35] in their study successfully identified SARS-CoV-2 in all kidney compartments examined, supporting the hypothesis of renal tropism. It is postulated that the cytopathic effects of the virus on these cells is responsible for the renal manifestations of COVID-19 [37]. Indeed, acute tubular necrosis with inflammatory cell infiltration has been demonstrated at autopsy [14,38]. In a case series 12 patients who died for COVID-19, Wichmann et al also found clear histopathologic evidence of cytopathic involvement and severe shock injury in renal tissue [39]. These findings have been recently confirmed in another case series of 11 autopsy of patients who have died for COVID-19, which showed dramatic cytopathic injuries of proximal tubules, nodular glomerulosclerosis and regenerating

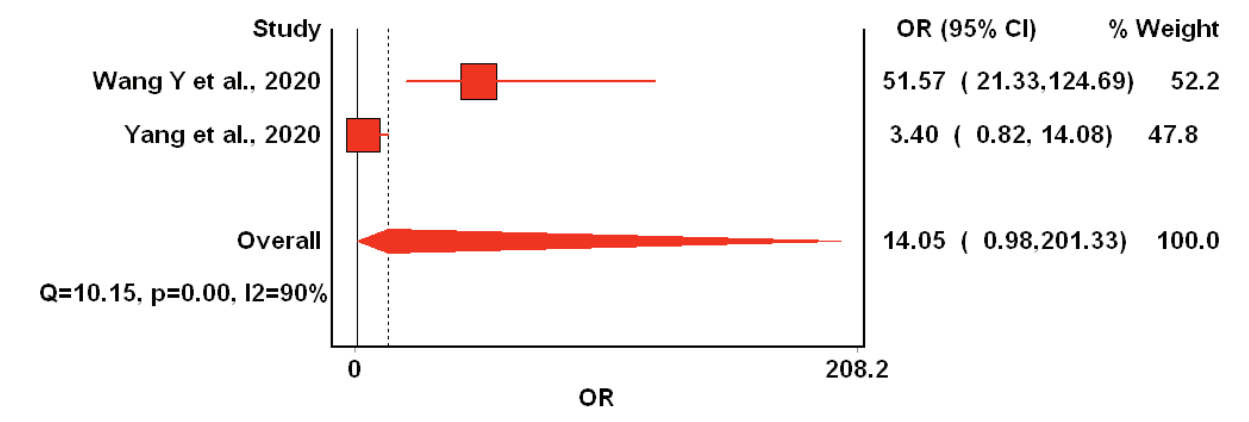


Figure 5. Forest plot for association between AKI and mortality in severe COVID-19

abnormalities with flattened tubular epithelium [40]. The clinical appearance of AKI in COVID-19 may also be a manifestation of microangiopathy and hypercoagulability which have been observed in the heart where they result in infarction [41] and inflammation [42]. Further, the hypercytokinemia that is a feature of this illness [43] and the resultant activation of the innate immune system can result in direct injury in the kidney. This is in the background of hypotension that attends this cytokine storm and superimposed sepsis which may itself cause AKI [44]. An interplay among these factors may therefore explain the clinical appearance of AKI in COVID-19. Regardless of the underlying pathophysiology, it seems unquestionable that occurrence of AKI in COVID-19 will be associated with worse clinical progression and/or mortality as seen in current data.

Taken together, the results of our meta-analysis would lead us to conclude that AKI is a relatively frequent manifestation in COVID-19 and, when it occurs in the clinical course of the disease, is a predisposing factor for development of worse clinical outcome (e.g., more severe illness) and/or death. Further investigation on the underlying mechanism of renal disease in COVID-19 would be needed to clarify possible therapeutic targets, whilst AKI could be used as clinical characteristic in severity classification and risk stratification for predicting unfavourable disease progression.

Author contributions

Conceptualization- IC, MM

Methodology- IC, VK, BMH

Data curation- IC, VK, BN

Software & Formal Analysis- IC

Investigation- All authors

Writing – Original Draft Preparation- IC, JM, MM

Writing – Review & Editing- All authors

Supervision- IC

Approval for submission- All authors

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Author contribution: All authors contributed to design and execution of the study. All authors participated in article drafting and critical revision.

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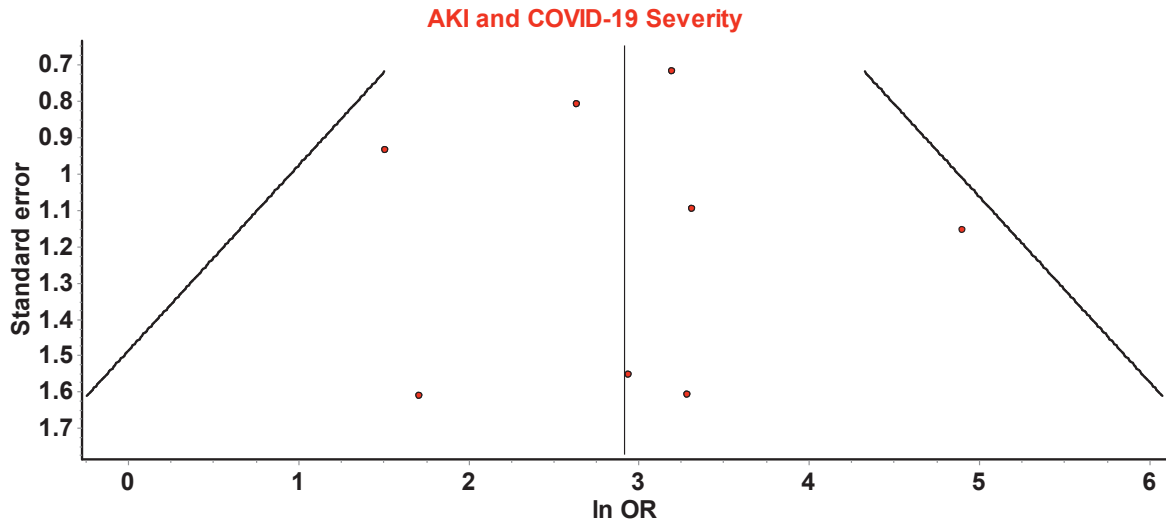
School of Medicine, University of Nairobi, Nairobi, Kenya.

Email: isaacbm@outlook.com

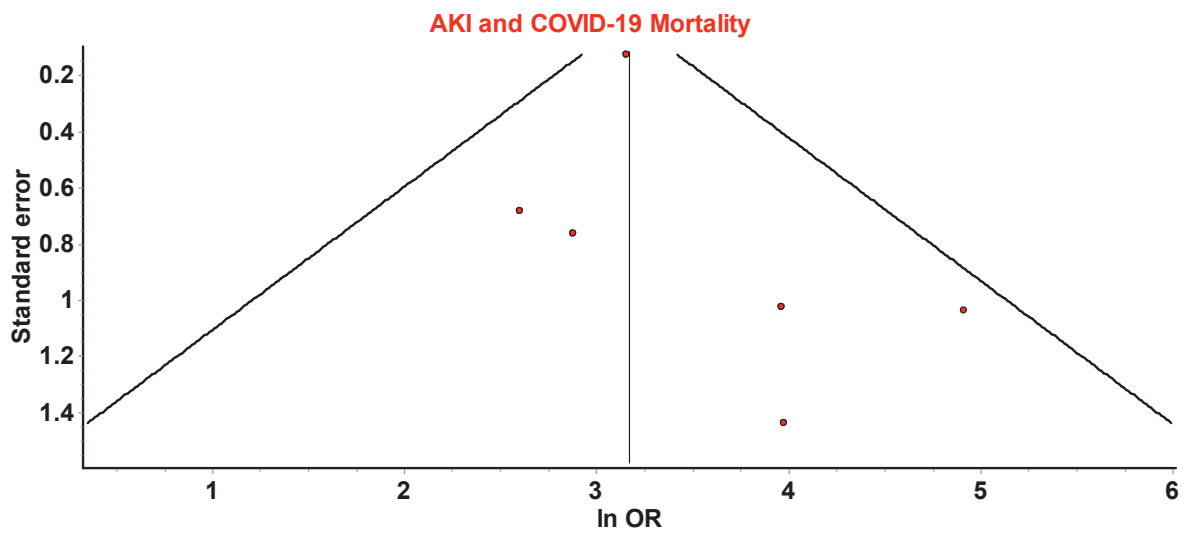
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SUPPLEMENTARY MATERIAL
(Publication Bias and Meta-Regression)

Funnel Plots: Severity



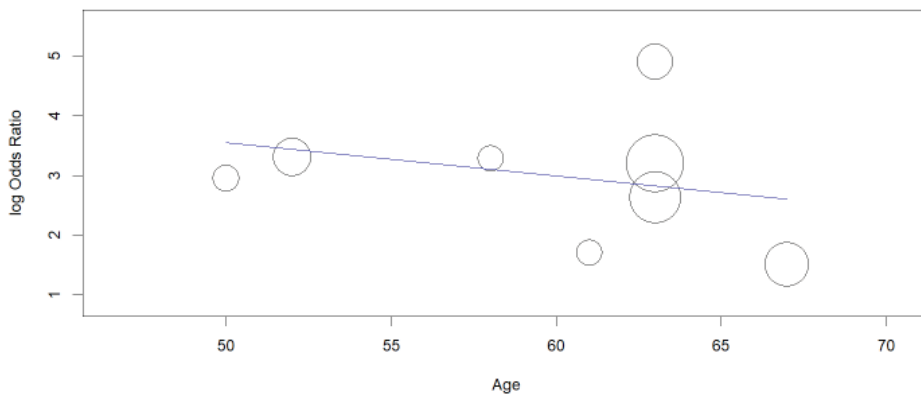
Funnel Plots: Mortality (general cohort)



Meta-regression (Severity)

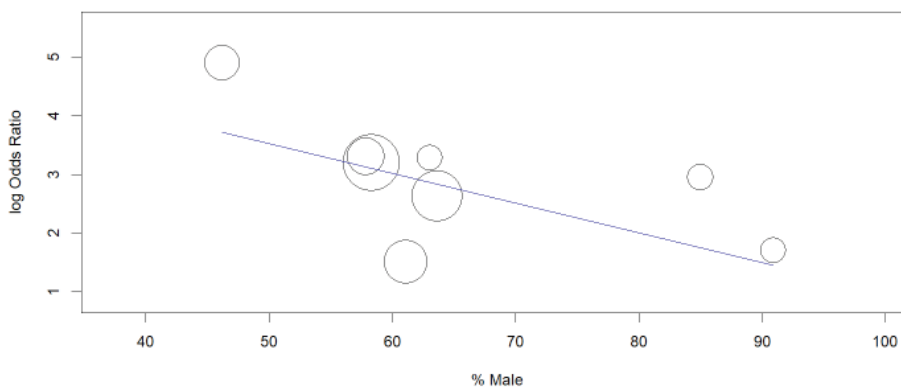
Model Results

Covariate	Coefficients	Lower bound	Upper bound	Std. error	p-Value
Intercept	6.350	-2.680	15.379	4.607	0.168
Age	-0.056	-0.203	0.091	0.075	0.455

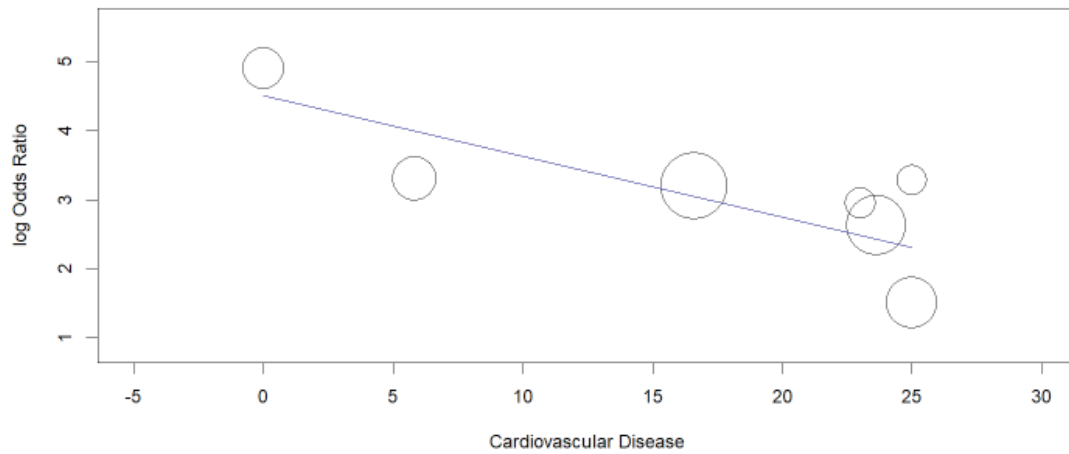


Model Results

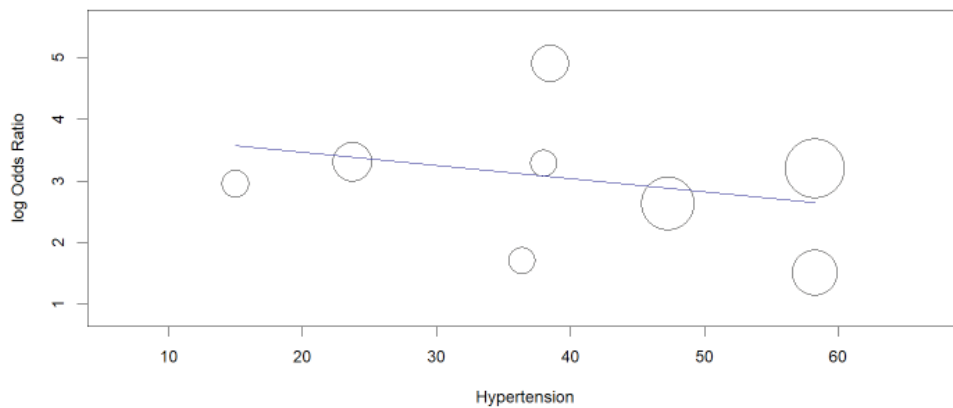
Covariate	Coefficients	Lower bound	Upper bound	Std. error	p-Value
Intercept	6.052	1.623	10.481	2.260	0.007
% Male	-0.051	-0.121	0.020	0.036	0.160



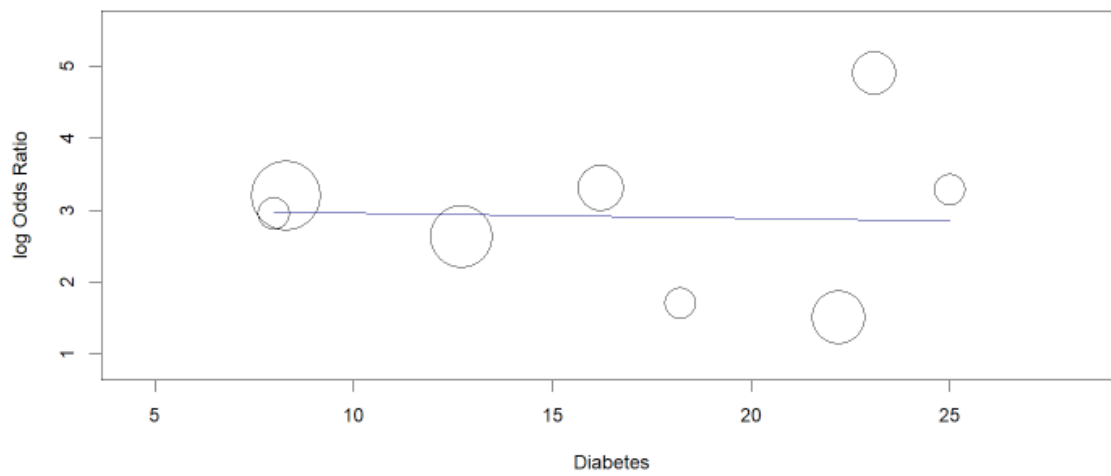
Covariate	Coefficients	Lower bound	Upper bound	Std. error	p-Value
Intercept	4.500	2.811	6.188	0.861	< 0.001
Cardiovascular Disease	-0.088	-0.175	0.000	0.045	0.050



Covariate	Coefficients	Lower bound	Upper bound	Std. error	p-Value
Intercept	3.881	1.374	6.388	1.279	0.002
Hypertension	-0.021	-0.074	0.032	0.027	0.432

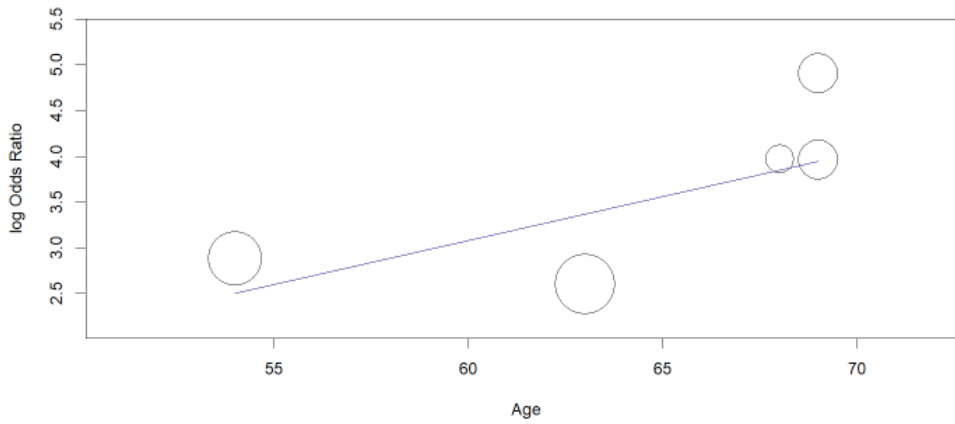


Covariate	Coefficients	Lower bound	Upper bound	Std. error	p-Value
Intercept	3.026	1.073	4.979	0.996	0.002
Diabetes	-0.007	-0.127	0.113	0.061	0.907

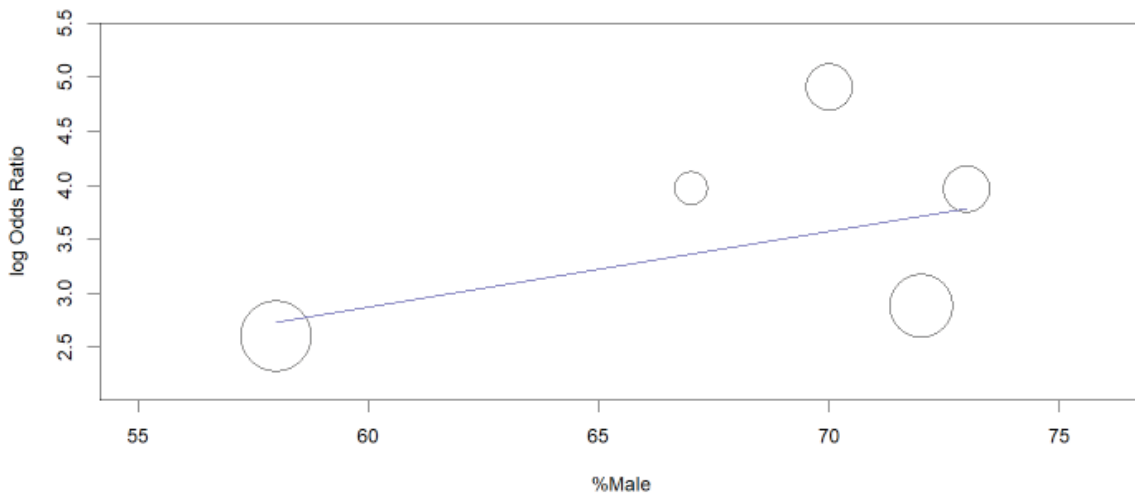


Meta-regression (Severity)

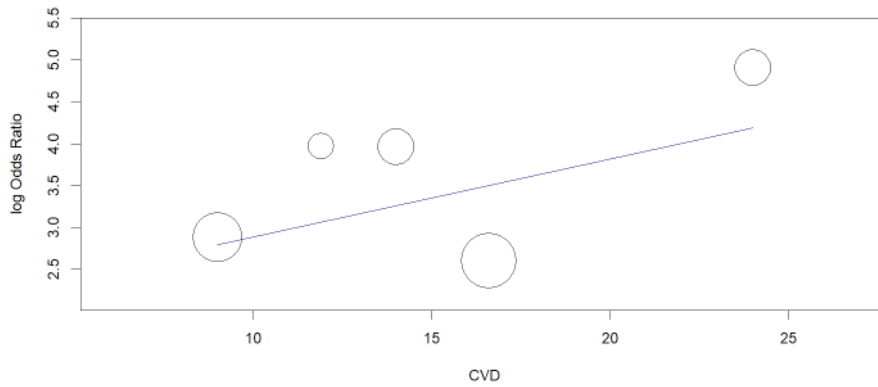
Covariate	Coefficients	Lower bound	Upper bound	Std. error	p-Value
Intercept	-2.662	-11.017	5.693	4.263	0.532
Age	0.096	-0.037	0.228	0.068	0.157



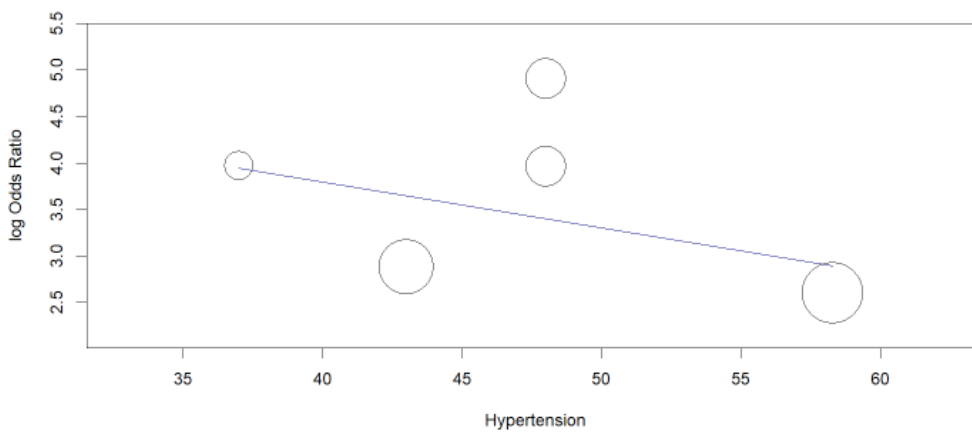
Covariate	Coefficients	Lower bound	Upper bound	Std. error	p-Value
Intercept	-1.349	-9.507	6.809	4.162	0.746
%Male	0.070	-0.052	0.192	0.062	0.258



Covariate	Coefficients	Lower bound	Upper bound	Std. error	p-Value
Intercept	1.960	-0.558	4.478	1.285	0.127
CVD	0.093	-0.068	0.254	0.082	0.259



Covariate	Coefficients	Lower bound	Upper bound	Std. error	p-Value
Intercept	5.770	0.298	11.243	2.792	0.039
Hypertension	-0.049	-0.159	0.060	0.056	0.379



Covariate	Coefficients	Lower bound	Upper bound	Std. error	p-Value
Intercept	1.713	-0.188	3.613	0.970	0.077
Diabetes	0.097	-0.006	0.200	0.053	0.066

