

Diabetes mellitus and hypertension as risk factors of acute kidney injury induced by COVID-19: A systematic review and meta-analysis

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ABSTRACT

INTRODUCTION Acute kidney injury (AKI) is one of the severe complications of COVID-19. The two distinct medical conditions sharing similar comorbidities are diabetes and hypertension. However, the correlation between AKI and COVID-19 patients with diabetes and/or hypertension, has not been extensively discussed. This study aims to assess the risk factors of AKI induced by COVID-19, using a meta-analysis approach.

METHODS A meta-analysis was carried out by reviewing the latest relevant studies on online databases such as PubMed, Google Scholar and Medline, up to 21 March 2022. The required information related to hypertension and diabetes as the potential risk factors of AKI induced by COVID-19, was extracted. The association was analyzed using pooled odds ratio (OR) and a 95% confidence interval (95% CI).

RESULTS We analyzed 29 studies consisting of 10698 AKI patients with COVID-19 and 20917 controls. Our results show that patients with diabetes (OR=1.5442; 95% CI: 1.3652–1.7467, $p < 0.0001$, p_{Het} (heterogeneity test)=0.0001, pE (Egger test)=0.8074) and hypertension (OR=1.7921; 95% CI: 1.5091–2.1281, $p < 0.0001$, $p_{Het} < 0.0001$, $pE = 0.2182$) had higher odds to develop AKI when infected with COVID-19.

CONCLUSIONS Diabetes and hypertension are prominent risk factors of acute kidney injury induced by COVID-19.

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a severe acute respiratory infection that first emerged in 2019 in Wuhan, China¹. With 343 million cases recorded in October 2020, COVID-19 has become a global pandemic². The clinical manifestation of COVID-19 infection tends to be broad, ranging from mild upper respiratory tract disease to severe lung infection with respiratory failure, and often death³. The symptoms are also frequently associated with the extrapulmonary organs, and the kidneys are vulnerable organs to this infection⁴.

One of the most severe complications of COVID-19 is acute kidney injury (AKI)⁵. A large number of acute kidney injury cases were found among patients with confirmed COVID-19. As stated in 'Kidney Disease: Improving Global Outcomes' guidelines, the incidence rate of AKI in hospitalized adults in China was 11.6%, but for inpatients in the intensive care unit (ICU), the incident rate increases to 50%⁶. However, those conditions could be worsened by other medical conditions accompanying the COVID-19 patients. Several medical conditions, such as hypertension and diabetes, have similar traits in affecting COVID-19 and AKI patients⁷.

In COVID-19 patients, the incidence of AKI becomes a

crucial prognostic factor. However, no sources specifically discussed the risk factors of AKI in COVID-19 patients. Diabetes and hypertension are several comorbidities of COVID-19 and the risk factors of AKI, which are easily observed and well documented in COVID-19 patients worldwide. As a result, this meta-analysis is intended to explore the correlation between hypertension and diabetes as the risk factors of AKI in COVID-19 patients.

METHODS

Study design

This study aimed to determine the association between diabetes and hypertension as the risk factors for AKI in COVID-19 patients. Therefore, we calculated the combined odds ratio (OR) and a 95% confidence interval (95% CI) using a random or fixed-effect model. To ensure the quality of our study, we created a meta-analysis using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist⁸.

Literature search strategy

The search string used in our present study was adapted from Medical Subject Heading (MeSH) comprising: [Acute Kidney Injury] AND [(SARS-CoV-2) OR (COVID-19)] AND

[(Hypertension) OR (Diabetes Mellitus)]. The search strategy was conducted in PubMed, Google Scholar, and Medline, up to 21 March 2022. Additionally, we searched the reference lists of pertinent literature for potentially relevant articles in English. We only included articles with the larger sample sizes, if several studies with similar study data were found. Three independent authors carried out the search strategy to meet the required standards (SS, IRS, BP).

Study eligibility

The articles included in our study met the following criteria: 1) articles with case-control, cross-sectional, and cohort designs; 2) articles identifying AKI progression risk variables in COVID-19 patients, and the prevalence of acute kidney injury in groups (with the 2012 Kidney Disease Improving Global Outcomes guidelines used to diagnose AKI during hospitalization); and 3) presenting the number of patients with hypertension or diabetes mellitus for estimating OR and 95% CI. On the other hand, articles were excluded if they: 1) had irrelevant titles or abstracts; 2) were reviews and case reports; 3) had insufficient and/or unspecific data; 4) were unpublished studies; 5) were low quality; and 6) did not define the diagnostic criteria for AKI.

Data extraction

The data extracted from each study were: 1) type of literature study; 2) total patients with AKI; 3) total patients without AKI; 4) total patients with DM for each group; and 5) total patients with HT for each group. Three investigators (SS, IRS, BP) worked together to collect the data. If there were differences, a discussion was carried out to reach an agreement.

Quality assessment

Three independent authors (SS, IRS, BP) evaluated the quality of the articles in our analysis using the Newcastle-Ottawa Scale (NOS), based on three factors consisting of patient selection (4 points), comparability (2 points), and exposure determination (3 points). The total score ranged from 0 (worst) to 9 (best). The study was considered good if the score was 7, moderate if the score was 5, and bad if the score was $<5^9$. We consulted a senior author if there were differences between the three independent authors (JKF, BD, AG).

Statistical analysis

We analyzed the risk factors of AKI in COVID-19 patients by calculating using the Z test, and the estimation effect was determined by calculating OR and 95% CI. Potential publication bias and heterogeneity were assessed before assessing the relationship and impact estimates. To validate publication bias, we performed the Egger test and a funnel plot. Publication bias was described as a $p < 0.05$. Additionally, the Q test was used to assess heterogeneity. If $p < 0.10$, the random effect model was applied, if the $p \geq 0.10$, the fixed-

effect model was applied. The statistical program R (R Core team, Vienna, Austria) version 4.0.4 was used for all our analyses¹⁰.

RESULTS

Eligible studies

Our literature search strategy collected 476 potentially relevant studies published from October 2020 to March 2022. From the identified studies, 68 duplicates and 224 studies with irrelevant title were excluded. The remaining 184 studies were screened; 96 studies were excluded due to irrelevance, and 8 studies were unavailable to be reviewed. As a result, there were 80 studies reviewed, but only 29 studies met our inclusion criteria¹¹⁻³⁹, and 51 studies were excluded. The reasons for the exclusion included insufficient data (32 studies), updated data (3 studies), review paper (39 studies), and case report (6 studies). The flowchart of the study selection process is shown in Figure 1, while the baseline characteristics of the included studies are provided in Table 1.

Data synthesis

Our study analysis shows that diabetes increased the risk of AKI in COVID-19 patients (OR=1.5442; 95% CI: 1.3652–1.7467, $p < 0.0001$, $p_{Het} = 0.0001$, $pE = 0.8074$). Our study also indicated an increased risk of AKI in COVID-19 patients with hypertension (OR=1.7921; 95% CI: 1.5091–2.1281, $p < 0.0001$, $p_{Het} < 0.0001$, $pE = 0.2182$). These results were obtained from 10698 AKI patients with COVID-19 and 20917 controls from 29 studies. The summary of the estimated effect of the risk factors AKI in COVID-19 is provided in Table 2.

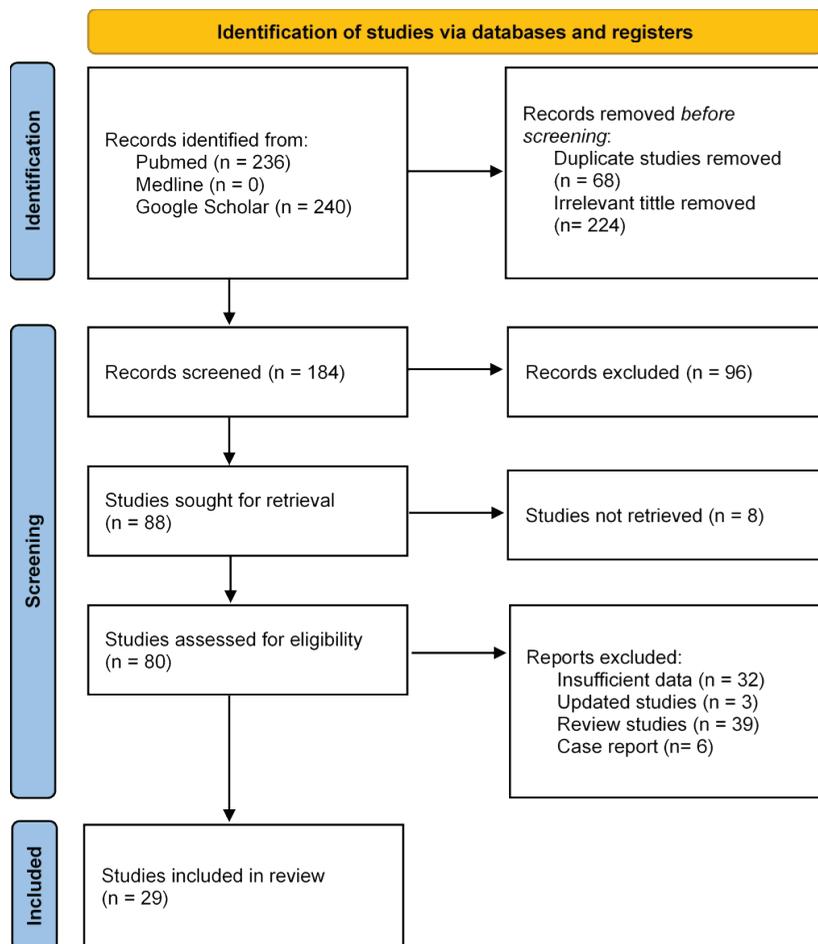
Heterogeneity among studies and publication bias

Overall, evidence of heterogeneity was found in all groups. Therefore, the included studies in each group were calculated using a random-effect model. However, the Egger test was not significant in the hypertension and diabetes groups, indicating no publication bias. The Egger test was found significant in the obesity groups, indicating publication bias. Detailed information of the heterogeneity and Egger tests is summarized in Table 2, and in Figures 2 and 3.

DISCUSSION

Our meta-analysis results emphasized that comorbidities, such as hypertension and diabetes, may give an early warning to physicians about AKI progression in patients with COVID-19. These two comorbidities are known to be associated with COVID-19 severity⁴⁰, but their relationship with AKI progression was still to be discussed. The previous meta-analysis conducted by Kaminska et al.⁴¹ exclusively discussed the outcome of COVID-19 patients with diabetes, and the result showed that AKI is one of the associated complications. Further, a previous meta-analysis by Fabrizi et al.⁴² observed the outcome of AKI in COVID-19 patients,

Figure 1. PRISMA flowchart of included studies



and their study also showed the association between hypertension and AKI in COVID-19 patients. Therefore, our meta-analysis supports the result of the previous meta-analyses in which diabetes and hypertension increase the risk of AKI in COVID-19 patients.

The condition accompanying COVID-19 patients has a pivotal role when the physician starts prognosing and managing COVID-19. Our studies focused on how the comorbidities affect the progression of COVID-19 into kidney injury. SARS-CoV-2, the virus causing COVID-19, infects the lung cells through the angiotensin-converting enzyme 2 (ACE2) receptor⁴³. The expression of ACE2 receptor is not only observed in the lung cells, but also in the renal cells at the proximal tubular cells and podocytes; thus, making it possible to involve them directly⁴⁴. Moreover, tubular necrosis resulting from indirect causation is the most common pathogenesis of AKI, as in 60% of COVID-19 patients²⁶. It may occur either from ischemic tubular injury or toxic tubular injury as an impact of various mechanisms, such as hypovolemia, cytokine release, and medication-induced ramifications from the underlying COVID-19 infection⁴⁵. Of the mechanisms, the gap for explanation may exist to link

the comorbidities and the deterioration of renal functions in COVID-19 patients.

The interesting part of SARS-CoV-2 infection is how it combines diabetes and hypertension as two distinct medical conditions that may affect the renal cells in the same way. Diabetes and hypertension interrupt ACE2 expression in patients without COVID-19⁴⁶. Instead of protecting by reducing the viral entry receptor in podocytes and tubular cells, the high affinity of the SARS-CoV-2 virus to the ACE2 receptor further worsens ACE2 deficiency^{7,47}. This condition leads to the activation of angiotensin II that fails to be converted into inactive peptides by ACE2⁴⁸. Angiotensin II will induce the pro-inflammatory cytokine and cause the inflammatory response to damage the protein, lipid, and DNA in the renal structure, and this condition leads to glomerular filtration rate reduction⁷. The pro-inflammatory cytokines, such as IL-1, IL-6, and TNF- α , are responsible for this mechanism, and among COVID-19 patients, they are considered to play a key role in ischemic acute kidney injury pathophysiology⁴⁹.

Our results, thus, stress the complexity of the AKI management in COVID-19 patients with diabetes and

Table 1. Baseline characteristics of included studies

Author Year	Study type	Country	City	Hospital	COVID-19 severity	N	Sample size		Risk factors				NOS
							AKI+	AKI-	Age (years), mean (SD)	DM n	HT n	Obesity n	
Alfano et al. ¹¹ 2020	Cohort retrospective	Italy	Modena	University Hospital of Modena	All cases	307	69	238	65.2 (14.01)	54	138	28	9
Bowe et al. ¹² 2021	Cohort retrospective	USA	St Louis	VA St. Louis Health Care System	All cases	5216	1655	3561	69 (11.12)	2537	3985	-	8
Casas-Aparicio et al. ¹³ 2021	Cohort retrospective	Mexico	Mexico City	Instituto Nacional de Enfermedades Respiratorias	Severe cases	99	58	41	52.9 (13.2)	27	30	56	9
Chan et al. ¹⁴ 2021	Cohort retrospective	USA	Multi-center	Mount Sinai Health system	All cases	3993	1835	2158	66 (16.31)	1019	1527	-	9
Cheng et al. ¹⁵ 2020	Cohort retrospective	China	Wuhan	Tongji Hospital	All cases	1392	99	1293	65.33 (20.78)	241	499	-	9
Costa et al. ¹⁶ 2021	Cohort retrospective	Brazil	Rio de Janeiro	Hospital Unimed-Rio	All cases	102	57	45	66.35 (15.75)	32	55	-	8
Doherty et al. ¹⁷ 2020	Cohort retrospective	Brazil	Sao Paulo	Hospital Israelita Albert Einstein (HIAE)	Severe cases	201	101	100	65.33 (11.94)	64	98	-	8
Fominskiy et al. ¹⁸ 2020	Cohort retrospective	Italy	Milan	San Raffaele scientific institute	Severe cases	96	72	24	57.85 (8.00)	16	42	-	8
Hamilton et al. ¹⁹ 2020	Cohort retrospective	UK	Manchester	Multi-center	All cases	1032	210	822	70 (20.04)	335	-	-	9
Hansrivijit et al. ²⁰ 2021	Cohort retrospective	USA	Multi-center	Multi-center	All cases	283	115	168	64.1 (15.9)	108	189	132	9
Hectors et al. ²¹ 2021	Cohort retrospective	USA	New York	Weill Cornell Medicine	All cases	45	16	29	62 (55.90)	13	26	-	8
Jewell et al. ²² 2021	Cohort retrospective	UK	London	King's College Hospital	All cases	1248	487	761	69 (17.1)	406	681	-	9
Joseph et al. ²³ 2020	Cohort retrospective	France	Paris	Saint Louis Hospital	All cases	100	81	19	59.66 (10.53)	30	56	21	8
Lee et al. ²⁴ 2020	Cohort retrospective	USA	New York	Multi-center	All cases	1002	294	708	65 (17.07)	378	597	184	8

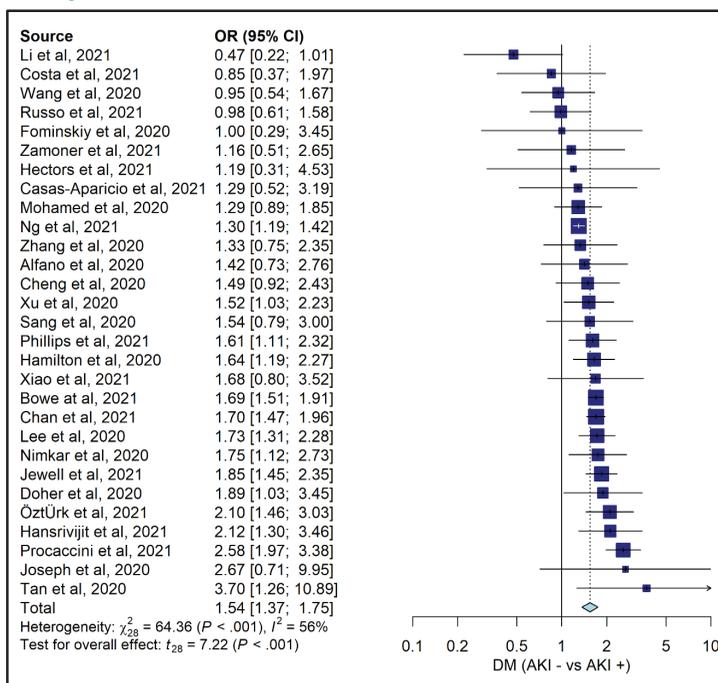
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Table 1. Continued

Author Year	Study type	Country	City	Hospital	COVID-19 severity	N	Sample size		Risk factors				NOS
							AKI+	AKI-	Age (years), mean (SD)	DM n	HT n	Obesity n	
Li et al. ²⁵ 2021	Cohort retrospective	China	Shanghai	Shanghai Public Health Clinical center	All cases	1249	91	1158	37.66 (17.07)	63	142	353	8
Mohamed et al. ²⁶ 2020	Cohort retrospective	USA	New Orleans	Ochsner Medical center	All cases	575	161	414	63 (12.5)	281	242	-	8
Ng et al. ²⁷ 2021	Cohort retrospective	USA	New York	Multicenter	All cases	9019	3216	5803	65.92 (2.8)	3469	5730	3323	9
Nimkar et al. ²⁸ 2020	Case series	USA	New York	Montefiore New Rochelle Hospital	All cases	327	179	148	70.66 (17.12)	139	209	-	9
Öztürk et al. ²⁹ 2021	Cohort retrospective	Turkey	Multi-center	Multicenter	All cases	621	202	419	60 (19.3)	172	332	-	9
Phillips et al. ³⁰ 2021	Cohort retrospective	UK	Southampton	University Hospital Southampton	All cases	632	216	416	-	142	321	179	9
Procaccini et al. ³¹ 2021	Case control	Spain	Madrid	Hospital Universitario Infanta Leonor	All cases	1096	548	548	75.09 (13.7)	328	701	56	9
Russo et al. ³² 2021	Cohort retrospective	Italy	Genoa	Hospital Policlinico San Martino	All cases	777	176	601	70 (16.0)	16	49	-	9
Sang et al. ³³ 2020	Cohort retrospective	China	Wuhan	Multicenter	All cases	210	92	118	63 (11.0)	44	98	-	9
Tan et al. ³⁴ 2020	Cohort retrospective	China	Shenzhen	Third People's Hospital of Shenzhen	All cases	377	40	337	45.2 (17.7)	19	65	-	8
Wang et al. ³⁵ 2020	Case control	China	Wuhan	Multicenter	All cases	275	136	139	69.33 (11.17)	62	150	-	9
Xiao et al. ³⁶ 2021	Cohort retrospective	China	Wuhan	Hankou Hospital	All cases	287	55	232	61 (14.2)	45	87	-	9
Xu et al. ³⁷ 2020	Cohort retrospective	China	Multi-center	Jin Yin Tan Hospital	All cases	671	263	408	64.66 (12.62)	131	287	-	9
Zamoner et al. ³⁸ 2021	Cohort retrospective	Brazil	Sao Paulo	University Hospital Sao Paulo	All cases	101	51	50	55 (54.4)	34	22	22	8
Zhang et al. ³⁹ 2020	Cohort retrospective	China	Wuhan	Multi-center	All cases	282	123	159	69 (13.41)	61	146	-	9

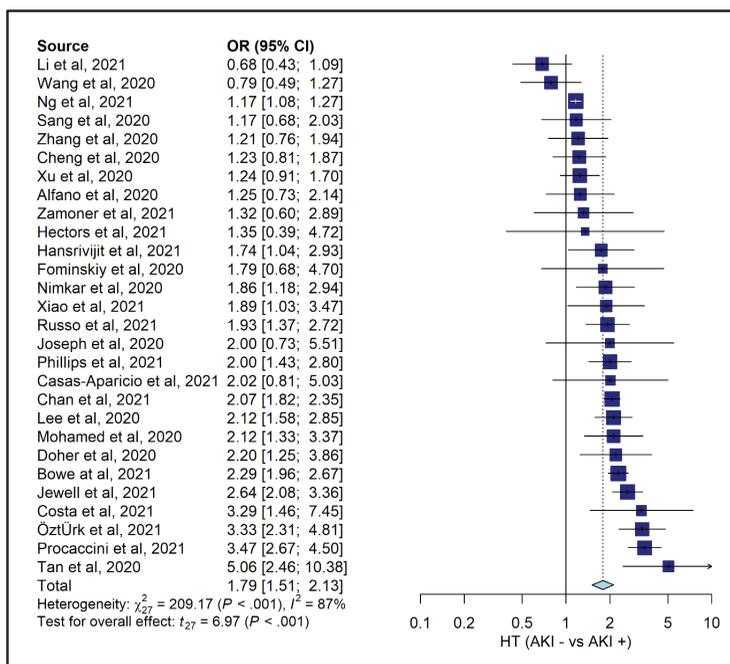
AKI: acute kidney injury. DM: diabetes mellitus. HT: hypertension. SD: standard deviation. NOS: Newcastle-Ottawa Scale.

Figure 2. Forest plot of diabetes as the risk factor of AKI in COVID-19 patients*



*OR=1.5442; 95% CI: 1.3652-1.7467; p<0.0001; pHet=0.0001; pE=0.8074.

Figure 3. Forest plot of hypertension as the risk factor of AKI in COVID-19 patients*



*OR=1.7921; 95% CI: 1.5091-2.1281; p<0.0001; pHet<0.0001; pE=0.2182.

hypertension to the clinicians. In COVID-19 patients, the goal of diabetes and hypertension treatments is to manage those conditions and to prevent AKI. Patients with diabetes must be aware of the benefits and risks of sodium-glucose co-transporter-2 (SGLT2) conflicting

issues. SGLT2 has an anti-inflammatory effect, but its involvement in kidney secretion function renders the patients prone to AKI due to ketoacidosis⁵⁰. In addition, long-term diabetic patients have pathological lesions in the nephron, including arteriosclerosis, thickening of

Table 2. Summary of the risk factors of COVID-19 induced AKI

Risk factor	NS	Model	AKI+ (%)	AKI- (%)	pE	pHet	p	OR	95% CI
Diabetes	29	Random	4296 (37.63)	5749 (28.18)	0.8074	0.0001	<0.0001	1.5442	1.3652–1.7467
Hypertension	28	Random	6773 (61.10)	9729 (49.21)	0.2182	<0.0001	<0.0001	1.7921	1.5091–2.1281
Obesity	13	Random	2507 (34.42)	4544 (35.27)	0.0389	<0.0001	0.0152	1.4463	1.0886–1.9215

NS: number of studies. pE: Egger test p-value. pHet: heterogeneity test p-value. AKI: acute kidney injury.

the glomerular basement membrane, accumulation of extracellular matrix, and interstitial fibrosis⁵¹. Both direct and indirect damages caused by the COVID-19 virus to the nephron worsen acute kidney injury. Therefore, insulin treatment is much favorable, notably in COVID-19 patients with critical conditions⁵². Moreover, COVID-19 patients with hypertension are facing the safety issue of angiotensin receptor blockers (ARB) and angiotensin-converting enzyme inhibitor (ACEI) medication. A study conducted by Oussalah et al.⁵³ concluded that ARB and ACEI increased the risk of AKI and respiratory failure in 149 COVID-19 patients due to lung and kidney organ-crosstalk. Furthermore, an increase in intraglomerular capillary pressure often occurs in patients with long-standing hypertension. Thus, arterionephrosclerosis is often present⁵⁴. Decreased renal perfusion associated with hemodynamic disturbances also causes a decrease in glomerular filtration rate⁵⁵. Hemodynamic disturbances found in COVID-19 patients possibly increase the risk of decreasing perfusion and filtration in hypertensive patients with COVID-19. However, the cornerstone of AKI treatment in patients with and without COVID-19 is fluid management. However, in severe COVID-19 patients, the clinicians need a robust effort to inhibit the AKI progression. At the moment, continuous renal replacement therapy is generally used, but different treatment strategies, such as monoclonal antibody and plasma convalescent therapy, are popular as the last alternative⁵⁶.

Limitations

Our meta-analysis has some limitations. This study did not include other related comorbidities, such as age and cardiovascular disease, and other risk factors, such as medication, disease severity, the use of mechanical ventilation, and treatment related to COVID-19 or AKI. Although there is a link to AKI progression in COVID-19 patients, only a handful of studies discuss those factors. Additionally, a bigger population is needed to evaluate the true effect of each variable. Further research that includes more high-quality studies are required to provide better evidence.

CONCLUSIONS

Our meta-analysis shows that diabetes and hypertension increase the risk of acute kidney injury (AKI) induced by COVID-19. The reason behind this result is still not well

explained, but the inflammation process has a major role in the pathophysiology of AKI progression in COVID-19 patients. However, future studies are needed to reveal the reasons behind this pathophysiology.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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There was no source of funding for this research.

ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent were not required for this study.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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