ARTÍCULO DE REVISIÓN

Gac Méd Caracas 2023;131(Supl 2):S137-S143
DOI: 10.47307/GMC.2023.131.s2.7

Characteristics of COVID-19 Patients who Developed Acute Kidney Injury and Its Association with Mortality: A Systematic Review

Características de los pacientes con COVID-19 que desarrollaron lesión renal aguda y su asociación con la mortalidad: una revisión sistemática

Evan Kurniawan Gianto[1*]

SUMMARY

Introduction: *AKI incidence reported in COVID-19 patients is increasing with contradictory study results about AKI development with increased mortality. This study was conducted to assess a possible correlation between risk factors that led to AKI and increased mortality.*
Methods: *A total of eight articles found through an online database published between 2020 and 2021 were used. A total of 9 455 patients with COVID-19 were divided into AKI and non-AKI.*
Results: *There are 2 754 AKI patients with a mean age of 67, 1 781 (64.7 %) are male, 1 161 (42.1 %) are diabetic, 1 823 (66.2 %) hypertensive, and 1 508 (54.7 %) use mechanical ventilation, with 39.2 % (1 052) mortality rate. In non-AKI patients, there are 6 701 patients with a mean age of 60, 3 595 (53.6 %) are male, 1 759 (26.2 %) are diabetic, 3 133 (46.7 %) hypertensive, and 490 (7.3 %) use mechanical ventilation, with a 7.6 % (508) mortality rate. Several studies suggest various mechanisms of AKI development, including multi-organ dysfunction syndrome, direct kidney infection, acute respiratory distress syndrome, infection-related mitochondrial failure, cytokine storm, SARS-CoV-2 renal tropism, and even mechanical ventilation usage.*
Conclusion: *AKI contributes to and or correlates with severity, prognosis, and mortality in COVID-19 patients. It develops more often in older males with Diabetes and or Hypertension and those with mechanical ventilation compared to non-AKI patients. Mortality in COVID-19 with AKI population is significantly higher than in those without AKI.*

Keywords: *COVID-19, acute kidney injury, diabetes mellitus, hypertension, mechanical ventilation, mortality rate.*

RESUMEN

Introducción: *La incidencia de lesión renal aguda (LRA) en pacientes con COVID-19 está aumentando con resultados de estudios contradictorios sobre el desarrollo de LRA con mayor mortalidad. Este estudio se realizó para obtener una imagen de una posible correlación entre los factores de riesgo que llevaron a la LRA y el aumento de la mortalidad.*

DOI: https://doi.org/10.47307/GMC.2023.131.s2.7

ORCID: 0000-0003-0594-6172[1]

[1]General Practitioner at Army Hospital Doctor Soepraoen, Malang, 65141, Indonesia.

*Corresponding Author: Evan Kurniawan Gianto, MD
General Practitioner at Army Hospital Doctor Soepraoen, Malang, 65141, Indonesia Jalan Bunga Cengkeh No.6, Kelurahan Tulusrejo, Kecamatan Lowokwaru, RT 001 / RW 012, Kota Malang, Jawa Timur, Indonesia, 65141
Phone: +6282334051787
E-mail: evankgianto@gmail.com

Recibido: 22 de noviembre 2022
Aceptado: 11 de enero 2023

Métodos: *Se utilizan un total de ocho artículos encontrados a través de una base de datos en línea publicados entre 2020 y 2021. Un total de 9 455 pacientes con COVID-19 se dividieron en LRA y no LRA.*
Resultados: *Hay 2754 pacientes con LRA con una edad media de 67 años, 1 781 (64,7 %) son del sexo masculino, 1 161 (42,1 %) diabéticos, 1 823 (66,2 %) hipertensos y 1 508 (54,7 %) utilizan ventilación mecánica, con una tasa de mortalidad del 39,2 % (1 052). En pacientes sin LRA hay 6 701 pacientes con una edad media de 60 años, 3 595 (53,6 %) son del sexo masculino, 1 759 (26.2 %) diabéticos, 3 133 (46,7 %) hipertensos y 490 (7,3 %) utilizan ventilación mecánica, con una tasa de mortalidad del 7,6 % (508). Varios estudios sugieren varios mecanismos de desarrollo de LRA, incluido el síndrome de disfunción multiorgánica, la infección renal directa, el síndrome de dificultad respiratoria aguda, la falla mitocondrial relacionada con la infección, la tormenta de citoquinas, el tropismo renal por SARS-CoV-2 e incluso el uso de ventilación mecánica.*
Conclusión: *LRA contribuye y se correlaciona con la gravedad, el pronóstico y la mortalidad en pacientes con COVID-19. Se desarrolla con mayor frecuencia en hombres mayores con diabetes o hipertensión y también en aquellos con ventilación mecánica en comparación con pacientes sin LRA. La mortalidad en la población de COVID-19 con LRA es significativamente mayor que en aquellos sin LRA.*

Palabras clave: *COVID-19, daño renal agudo, diabetes mellitus, hipertensión arterial, ventilación mecánica, tasa de mortalidad.*

INTRODUCTION

Coronavirus disease (COVID-19) first emerged in 2019. As this paper was written, the latest WHO Epidemiological Update reported over 278 million cases and 5.4 million deaths worldwide (1,2). Indonesia reported 4 259 644 cases and 143 969 deaths (3). Most infected people developed a mild to moderate respiratory illness and would recover without special treatment or medical attention. Although most patients present with mild symptoms, older people and those with comorbidities are highly prone to develop serious illnesses (1). Some studies focused on pulmonary complications more than other complications, although Acute Kidney Injury (AKI) is common among critically ill patients infected with COVID-19, AKI data are few or they simply report incidence (4-7). AKI is a recognized factor of poor prognosis and is also associated with high mortality rates in ICU (6,8-10). Most patients with AKI are older and have concomitant conditions like Hypertension or Diabetes Mellitus (4,6,11). Therefore, AKI is another notable non-respiratory clinical sign of COVID-19 infection (4). Several studies report variable results for COVID-19-induced AKI, which varies from 3 %-50 % depending on the severity and the setting of the studies, with a mortality rate ranging from 60 %-90 % (6-8,11,12).

Some cells are more vulnerable to SARS-CoV-2 infection, including Artery Smooth Muscle cells, Cardiac Epithelial cells, Gastrointestinal system, Intestinal Epithelial cells, Kidney Tubular Epithelial cells, Liver Endothelial cells, and Pulmonary Alveolar cells type II (10). The kidney is a target for SARS-CoV-2 infection, resulting in virus-induced direct cytotropic effect and cytokine-induced systemic inflammatory response (5,8). Glomerular filtration and urine production may be affected by subsequent stressors such as cytokine storm, hypoxia, drug-associated nephrotoxicity, secondary infection with various viruses, bacteria, and fungi, and the use of high intra-thoracic pressure and PEEP (6,12). Thus, this study was conducted to assess a possible correlation between risk factors that led to AKI and increased mortality.

METHODS

Eligibility Criteria

The following research manuscripts and studies were cited: research papers where the study sample is adults who got infected with COVID-19 that have data on numbers of AKI and non-AKI patients, gender, mean age, comorbidities such as hypertension, and diabetes mellitus, use of mechanical ventilation, and in-hospital mortality rate.

Search Strategies and Study Selection

This study was made in December 2021 by a comprehensive literature search using Google Scholar for articles published between 2020 and

2021, with keywords COVID-19, Acute Kidney Injury, and AKI. A total of 30 articles were collected and screened by the author 5 articles were removed due to duplication, 6 articles were removed after screening the abstract, and 11 articles were excluded due to lack of data of interest. Finally, 8 articles that met all the Inclusion criteria are eligible for use in this study.

Data Extraction

Data extraction was conducted using a standardized extraction table that includes the author's name, location, year, age, sex, hypertension, diabetes mellitus, usage of mechanical ventilation, and mortality rate.

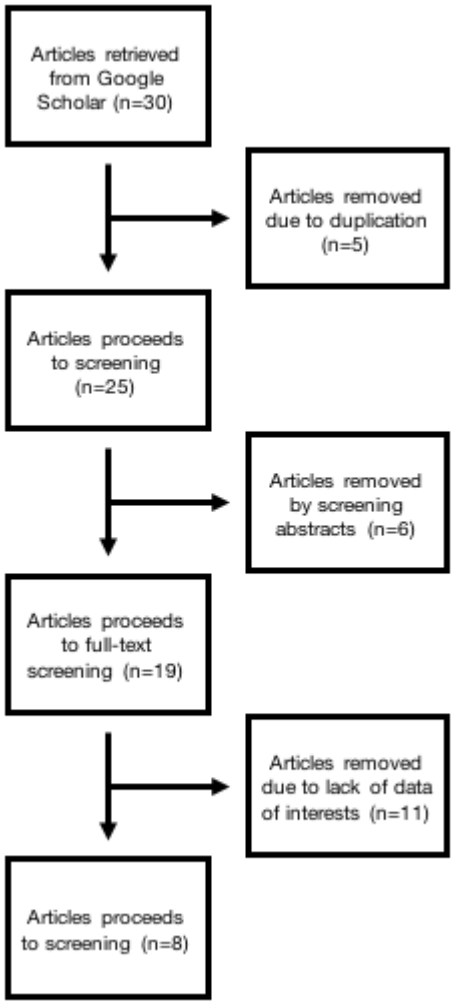

Figure 1. PRISMA flow chart.

RESULTS

Characteristics of the studies

Eight articles used in this systematic review were published between 2020 and 2021. A total of 9 455 patients with COVID-19 from 8 studies were collected. There are 2 754 (29.1 %) patients with COVID-19 who developed AKI and 6 701 (70.9 %) patients who did not develop AKI along the way. All studies report the characteristics of interest such as mean age, gender, diabetes, hypertension, use of mechanical ventilation, and mortality rate.

Characteristics of COVID-19 patients with AKI and without AKI (non-AKI)

Zahid et al. (13) observed 128 patients with AKI, with a mean age of 67, among them 89 (69.5 %) are male, with 67 (52.3 %) diabetic and 97 (75.8 %) hypertensive. 68 (53.1 %) end up with mechanical ventilation and a 52.7 % (109) mortality rate. As for non-AKI patients, there are 341 patients observed with a mean age of 65, among them 179 (52.5 %) are male, with 152 (44.6 %) diabetic and 226 (66.3 %) hypertensives. 32 (9.4 %) ended up with mechanical ventilation and a 28.4 % (97) mortality rate. It was concluded that AKI in COVID-19 is common and carried high mortality.

Hirsch et al. (14) observed 1993 patients with a mean age of 69, among them 1270 (63.7 %) are male, with 830 (41.6 %) diabetic and 1 292 (64.8 %) hypertensive. With 1068 (53.6 %) ending up with mechanical ventilation and a 34.8 % (694) mortality rate. As for non-AKI patients, there are 3 456 patients observed with a mean age of 61, among them 2 047 (59.2 %) are male, with 967 (28 %) diabetic and 1 745 (50.5 %) hypertensive. 122 (3.5 %) ended up with mechanical ventilation and a 5.6 % (194) mortality rate. This study concludes that AKI occurs frequently among COVID-19 patients and is associated with a poor prognosis.

Pelayo et al. (15) observed 110 patients with a mean age of 70, among them 60 (54.5 %) are male, with 58 (53 %) diabetic and 104 (80 %) hypertensive. 37 (34 %) ended up with mechanical

ventilation and a 31 % (34) mortality rate. As for non-AKI patients, there are 113 patients observed with a mean age of 61, among them 55 (48.7 %) are male, with 46 (41 %) diabetic and 76 (64 %) hypertensive. 11 (10 %) ended up with mechanical ventilation and a 9 % (10) mortality rate. It is concluded that there is a high burden of AKI among COVID-19 patients with multiple comorbidities.

Joseph et al. (16) observed 81 patients with a mean age of 60, among them 59 (73 %) are male, with 27 (34 %) diabetic and 48 (60 %) hypertensive. 49 (61 %) ended up with mechanical ventilation and a 28 (35 %) mortality rate. As for non-AKI patients, there are 19 patients observed with a mean age of 54, among them 11 (58 %) are male, with 3 (16 %) diabetic and 8 (42 %) hypertensive. 6 (32 %) ended up with mechanical ventilation and a 5 % (1) mortality rate. This study concludes that the proportion of patients with AKI during severe COVID-19 infection is higher.

Cui et al. (17) observed 21 patients with a mean age of 61, among them 12 (57.1 %) are male, with 2 (9.5 %) diabetic and 9 (42.9 %) hypertensive. 14 (66.7 %) ended up with mechanical ventilation and a 57.1 % (12) mortality rate. As for non-AKI patients, there are 95 patients observed with a mean age of 58, among them 54 (56.8 %) are male, with 26 (27.4 %) diabetic and 29 (30.5 %) hypertensive. 25 (26.3 %) ended up with mechanical ventilation and a 12 (12.6 %) mortality rate. Cui et al. found that patients with AKI had higher in-hospital mortality.

Cheng et al. (18) observed 99 patients with a mean age of 66, among them 67 (67.7 %) are male, with 23 (23.2 %) diabetic and 40 (40.4 %) hypertensive. 80 (80.8 %) ended up with mechanical ventilation and a 71.7 % (71) mortality rate. As for non-AKI patients, there are 1 293 patients observed with a mean age of 63, among them 644 (50 %) are male, with 218 (17 %) diabetic and 459 (35 hypertensives). With 204 (16 %) ending up with mechanical ventilation and a 10 % (129) mortality rate. In contrast with other studies, Cheng et al. found that AKI is uncommon but still carries high in-hospital mortality.

Paek et al. (19) observed 28 patients with a mean age of 74, among them 16 (57 %) are male, with 16 (57 %) diabetic and 22 (78.6 %) hypertensive. 13 (46.4 %) ending up with mechanical ventilation and a 46.4 % (13) mortality rate. As for non-AKI patients, there are 676 patients observed with a mean age of 57, among them 194 (28.7 %) are male, with 107 (15.8 %) diabetic and 204 (30.2 %) hypertensives. With 8 (1.2 %) ending up with mechanical ventilation and a 1.6 % (11) mortality rate. This study concluded that AKI incidence is low, but severe AKI was associated with in-hospital death.

Lee et al. (20) observed 294 patients with a mean age of 69, among them 208 (71 %) are male, with 138 (47 %) diabetic and 211 (72 %) hypertensive. 179 (61 %) ended up with mechanical ventilation and a 40 % (118) mortality rate. As for non-AKI patients, there are 708 patients observed with a mean age of 63, among them 411 (58 %) are male, with 240 (34 %) diabetic and 386 (55 %) hypertensive. 82 (12 %) ended up with mechanical ventilation and an 8 % (54) mortality rate. This study identified a high incidence of AKI in hospitalized patients with COVID-19.

With all studies combined, there are 2 754 AKI patients with a mean age of 67, among them, 1 781 (64.7 %) are male, with 1161 (42.1 %) diabetic patients and 1 823 (66.2 %) hypertensive patients. With 1 508 (54.7 %) ending up with mechanical ventilation and a 39.2 % (1 052) mortality rate. As for non-AKI patients, there are 6 701 patients with a mean age of 60, among them, 3 596 (53.6 %) are male, with 1759 (26.2 %) diabetic patients and 3 133 (46.7 %) hypertensive patients. With 490 (7.3 %) ending up with mechanical ventilation and a 7.6 % (508) mortality rate (13-20).

DISCUSSION

The comparison data of this systematic review showed that patients with AKI present in older patients, an even greater male percentage, a greater percentage of patients with diabetes and hypertension as comorbidities, a significantly higher percentage of mechanical ventilation usage, and a significantly higher mortality rate. Although SARS-CoV-2 mainly targets the respiratory system, as the primary binding site, ACE2 receptor expression determines

Table 1. Study characteristics of AKI patients

Author	Year	Country	Sample	Mean Age	Male, n (%)	Diabetes, n (%)	Hypertension, n (%)	Mechanical Ventilation, n (%)	Mortality, n (%)
Zahid et al.	2020	USA	128	67	89 (69.5)	67 (52.3)	97 (75.8)	68 (53.1)	109 (52.7)
JS Hirsch et al.	2020	USA	1993	69	1270 (63.7)	830 (41.6)	1292 (64.8)	1068 (53.6)	694 (34.8)
Pelayo et al.	2020	USA	110	70	60 (54.5)	58 (53)	104 (80)	37 (34)	34 (31)
Joseph et al.	2020	France	81	60	59 (73)	27 (34)	48 (60)	49 (61)	28 (35)
Cui et al.	2020	China	21	61	12 (57.1)	2 (9.5)	9 (4.9)	14 (66.7)	12 (57.1)
Cheng et al.	2020	China	99	66	67 (67.7)	23 (23.2)	40 (40.4)	80 (80.8)	71 (71.7)
Paek JH et al.	2020	Korea	28	74	16 (57)	16 (57)	22 (78.6)	13 (46.4)	13 (46.4)
Lee et al.	2021	USA	294	69	208 (71)	138 (47)	211 (72)	179 (61)	118 (40)
	Total		2754	67	1781 (64.7)	1161 (42.1)	1823 (66.2)	1508 (54.7)	1052 (39.2)

Table 2. Study characteristics of non-AKI patients

Author	Year	Country	Sample	Mean Age	Male, n (%)	Diabetes, n (%)	Hypertension, n (%)	Mechanical Ventilation, n (%)	Mortality, n (%)
Zahid et al.	2020	USA	341	65	179 (52.5)	152 (44.6)	226 (66.3)	32 (9.4)	97 (28.4)
JS Hirsch et al.	2020	USA	3456	61	2047 (59.2)	967 (28)	1745 (50.5)	122 (3.5)	194 (5.6)
Pelayo et al.	2020	USA	113	61	55 (48.7)	46 (41)	76 (64)	11 (10)	10 (9)
Joseph et al.	2020	France	19	54	11 (58)	3 (16)	8 (42)	6 (32)	1 (5)
Cui et al.	2020	China	95	58	54 (56.8)	26 (27.4)	29 (30.5)	25 (26.3)	12 (12.6)
Cheng et al.	2020	China	1293	63	644 (50)	218 (17)	459 (35)	204 (16)	129 (10)
Paek JH et al.	2020	Korea	676	57	194 (28.7)	107 (15.8)	204 (30.2)	8 (1,2)	11 (1.6)
Lee et al.	2021	USA	708	63	411 (58)	240 (34)	386 (55)	82 (12)	54 (8)
	Total		6701	60	3595 (53.6)	1759 (26.2)	3133 (46.7)	490 (7.3)	508 (7.6)

Table 3. Study characteristics comparison

	AKI (n = 2754)	non-AKI (n = 6701)
Mean Age	67	60
Male, n (%)	1781 (64.7)	3595 (53.6)
Diabetes, n (%)	1161 (42.1)	1759 (26.2)
Hypertension, n (%)	1823 (66.2)	3133 (46.7)
Mechanical Ventilation, n (%)	1508 (54.7)	490 (7.3)
Mortality, n (%)	1052 (39.2)	508 (7.6)

its tropism (5). Several organs that express ACE2 receptors are alveolar type II cells, colon colonocytes, esophagus keratinocytes, ileum, kidney proximal tubules, liver cholangiocytes, rectum, and stomach epithelial cells (12). Men also have a higher ACE2 level compared to women, and to make it worse, SARS-CoV-2 has a selective tropism for the kidneys, this might be due to ACE2 expression in the kidney that is much more than in the lung tissue (5,7,8). In

the kidney specifically, ACE2 is expressed in the brush borders apical membrane of the proximal tubules and podocytes (6,12). As such, SARS-CoV-2 renal tropism is associated with disease severity and finally the development of AKI (21).

Ahmadian et al. found viral components in the urine may be an indicator of renal tubule direct infection (12). A prominent acute proximal tubular injury, peritubular erythrocyte aggregation, glomerular fibrin thrombi, and ischemic collapse due to increased clotting, disseminated intravascular coagulation, and small vessel thrombosis is reported as findings from a kidney biopsy of an AKI patient with COVID-19 (5,12).

Several studies suggest various mechanisms of AKI development, including multi-organ dysfunction syndrome, direct kidney infection, acute respiratory distress syndrome, infection-related mitochondrial failure, and cytokine storm (9). While various mechanisms, including the release of pathogen-associated molecular patterns, COVID-19-associated macrophage activation, hyperferritinemia, cytokine storms, and damage-associated molecular proteins, which can trigger the release of tissue factors and the activation of coagulation factors, can lead to hyper-coagulability (5). Cytokine storm is one of the proposed mechanisms of COVID-19-induced organ damage, therefore, the ideal course of treatment to lower or eliminate inflammatory cytokines would be efficient to avoid cytokine-induced organ damage (12). SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a receptor to facilitate viral entry (11). ACE2 also converts angiotensin II into angiotensin 1-7, which mitigates renin-angiotensin system-related vasoconstriction (6). It is believed that the virus might infiltrate the kidney by invading podocytes and obtaining access to the proximal tubule (5). ACE2 is highly expressed in the kidney's proximal tubule, causing RAAS imbalance (6). In SARS-CoV-2 patients with various characteristics like hypertension, cardiovascular disorders, diabetes, and advanced age, it has been observed that ACE2 deficiency suppresses its protective roles, diminishes anti-inflammatory benefits, and increases the effects of angiotensin II (12). When invasive mechanical ventilation is utilized in combination with a non-protective approach, the inflammatory effects are one mechanism that is being proposed (6).

The proportion of patients developing AKI is significantly higher with severe COVID-19 infection (8). In terms of mortality, Gabarre et al. studied that only AKI stage 2 or above was linked to a higher risk of mortality. This association may reflect the severity of the disease itself or the underlying patient condition (6).

The limitation of this study is that it didn't compare the degree of AKI and also not using data from specific Asian populations which may further elaborate on the correlation between AKI incidence, its severity, and mortality.

CONCLUSION

Acute Kidney Injury needs to be put into consideration when managing COVID-19 patients as it contributes and or correlates with disease severity, prognosis, and mortality of patients. In this systematic review, we found that AKI develops more often in older males, with Diabetes and Hypertension as comorbidities compared to non-AKI patients. The use of mechanical ventilation in AKI patients can translate to current disease severity but also can contribute as aggravating factors for AKI development. With overall mortality in COVID-19 with an AKI population significantly higher than those without AKI, management of COVID-19 that usually focused heavily on the respiratory system needs to put the renal system into consideration.

Acknowledgment

I would thank AIM-ICME 3 editorial board and the organizing committee for the thorough review and suggestions for this paper.

Conflict of Interests

The author has no conflicts of interest to declare.

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