PREDICTORS OF MORTALITY OF COVID-19 INFECTED PATIENTS WITH ACUTE KIDNEY INJURY

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) is a condition brought on by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) where this virus is highly contagious. In several studies, acute kidney injury was associated with the cause of death. This study aimed to analyze what factors played a role as predictors of mortality in COVID-19 patients who experienced acute kidney injury.

Method: This study used a one-center retrospective cohort method where the study was conducted at Dr. Soetomo General Academic Teaching Hospital, Surabaya, Indonesia. Statistical analysis of multivariate logistic regression was performed, and the results were presented in the form of an odds ratio (OR), with a p-value considered significant < 0.05 and a 95% confidence interval.

Results: A total of 498 COVID-19 patients with acute kidney injury were included in this study. Our research found that 153 subjects (30.7%) died. The results of multivariate logistic regression analysis showed that the largest OR value was the D-dimer value variable, namely 2.102 (95% CI: 1.361-3.247), which means that COVID-19 patients with acute kidney injury who have a D-dimer value of ≥ 1.2 mg/L have the possibility of experiencing mortality within 30 days was 2.1 times greater than in patients with D-dimer values < 1.2 mg/L. The next variables were albumin value < 3.5 g/dL (OR 2.015, 95% CI: 0.992-4.091), history of hypertension (OR 2.003, 95% CI: 1.343-2.988).

Conclusion: Our study found that a history of hypertension, higher than normal D-dimer levels, and hypoalbuminemia were predictors of mortality in patients with acute kidney injury who were infected with COVID-19.

Keywords: Covid-19, Mortality, Acute Kidney Injury

Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus which is extremely contagious is the one that causes coronavirus disease 2019 (COVID-19). There is no doubt that the COVID-19 pandemic has had a detrimental impact on the physical and mental wellbeing of healthcare personnel. Additionally, because of the budgetary constraints caused by this pandemic, the healthcare systems were unable to supply the necessary beds, medications, vaccines, and intensive care units. It is obvious that the COVID-19 pandemic has not yet completely healed the healthcare systems. An extremely contagious virus causing more than six million deaths, COVID-19 is the most serious worldwide health disaster since the 1918 influenza pandemic (1, 2). The SARS-CoV-2 virus spread quickly across the globe in a brief period of time shortly after its initial incidence of this Covid-19 disease was first discovered in China's Wuhan Province, Hubei Province, at the end of December 2019. On March 11, 2020, the World Health Organization (WHO) subsequently declared a worldwide pandemic. Globally, the pandemic caused a significant number of fatalities and severe morbidities. Fortunately, as of 22nd October 2022, there were more than 632 million cases and 6.6 million deaths, with more than 12.8 billion vaccination doses given (2).

In several studies, prior acute kidney injury (AKI) has been associated with severe and critical COVID-19 infection. This association has resulted in an increased risk of death (3). The cause of AKI is still debated whether it predicts mortality in COVID-19 patients with AKI. Numerous factors are thought to play a role in the emergence of AKI in COVID-19 carriers. These variables could include endothelial dysfunction,

disturbance of the renin-angiotensin-aldosterone system, systemic inflammation, direct viral invasion of kidney cells, cytokine storm, immune-mediated damage, and systemic inflammation (4). Demographic and epidemiological characteristics may influence this. CKD predictor factors for predicting mortality in COVID-19 patients are still debated to date, perhaps because of the difficulty in differentiating CKD from AKI in patients hospitalized during the COVID-19 pandemic outbreak (5).

Several laboratory results were also investigated to have a relationship with AKI-associated mortality in COVID-19 patients. In COVID-19 individuals with AKI, direct renal involvement in the inflammatory process, complement activation, and coagulopathy all play a part. AKI is significantly influenced by a number of factors, including inflammatory response linked to immunologic injury, cardio-renal dysfunction, cell invasion, and hypovolemia. Numerous other factors are also being studied (6, 7).

This study aimed to analyze what factors played a role as predictors of mortality in COVID-19 patients who experienced AKI. Hopefully, this study can provide information so that interventions can be carried out and reduce mortality rates in COVID-19 patients who experience AKI.

Materials and methods

Study design

This study used a single center retrospective cohort method where the research was conducted at Dr. Soetomo General Academic Teaching Hospital, Surabaya, Indonesia. Consecutive sampling method was used in this study. The study was approved by the research ethics committee of Airlangga University (1618/101/4/VIII/2022). All procedures were carried out in accordance with the Declaration of Helsinki and pertinent rules and laws. Research data was taken from medical records from 1st June 2020, to 31st January 2021. Confirmatory diagnosis of COVID-19 was carried out utilizing a Real-Time-Polymerase-Chain-Reaction (RT-PCR) examination.

Inclusion and exclusion criteria

The inclusion criteria of research subjects were hospitalized patients diagnosed with COVID-19, aged > 18 years, mild to severe COVID-19 infection and experienced AKI. Exclusion criteria were incomplete medical record data and were treated in the intensive care unit (ICU). AKI was defined as a trend of increasing/decreasing serum creatinine above the normal range or returning to normal during hospitalization and/or decreasing urine output < 0.5 ml/kg/hour (8).

Sample collection

Data such as age, gender, history of type 2 diabetes mellitus, history of history of chronic obstructive lung disease (COPD), history of the human immunodeficiency virus (HIV), history of cancer, patients with CKD with history of regular hemodialysis (HD) and non-HD, fever, shortness of breath, radiological features of pneumonia and results from laboratory data (NLR, D-dimer, albumin, and CRP) were collected from medical records. Patients on regular dialysis or with HIV frequently have weak immune systems or underlying medical issues that make them more vulnerable to life-threatening infections. Laboratory cut-off values such as Neutrophil-to-Lymphocyte Ratio (NLR) (5.5), D-dimer (1.2 mg/L), albumin (3.5 g/dL), and c-reactive protein (CRP) (40 mg/L) were used (8-12).

Definition of research variables

The severity of COVID-19 illness was defined using the fourth edition of the National Guidelines for COVID-19 Management (12). Mild COVID-19 infection was defined as a COVID-19 patient with symptoms of an upper respiratory tract infection without pneumonia and oxygen saturation (SpO_2) > 95%, so no additional oxygen supplementation was required (12). A moderate degree of COVID-19 infection was defined as a patient without indications of severe pneumonia, such as SpO_2 > 93% with room air, but with clinical indicators of pneumonia (rapid breathing, shortness of breath, cough, fever). Severe COVID-19 infection was defined as severe pneumonia characterized by cough, fever, shortness of breath, respiratory rate of above 30 breaths/minute, severe respiration distress, and SpO_2 < 93% (12).

Data analysis

All data were assessed using the Statistical Package for the Social Sciences (SPSS) version 26 program. Demographic data and clinical characteristics were presented descriptively, namely frequency and percentage. Analysis of mortality predictor factors was carried out by bivariate test using the Chi-square test for nominal data. The results are presented in the form of an odds ratio (OR), with a p-value considered significant < 0.05 and a 95% confidence interval, then a prediction model was made.

Results

Demographic characteristics of respondents

A total of 498 subjects met the inclusion criteria. The number of male subjects was more than female, with a comparison of 267 (53.6%) and 231 (46.4%). Most of the subjects were < 60 years old (65.9%).

In this study, we looked at research variables from medical records in the form of history taking results, physical examinations, and laboratory tests. It was found that more than half of the participants (53.8%) had a history of diabetes mellitus, indicating a high prevalence of this condition among the population. Similarly, a substantial number of participants (51.0%) had a history of hypertension, highlighting its significant presence within the study group. Additionally, a substantial proportion of participants (70.1%) had an NLR (Neutrophil-to-Lymphocyte Ratio) of 5.5 or higher, suggesting possible inflammation or infection.

Most participants (74.1%) showed elevated D-dimer levels of 1.2 mg/L or higher, indicating potential issues with fibrin degradation and blood clotting. Hypoalbuminemia was prevalent among the participants, with only a small percentage (12.2%) having albumin levels equal to or higher than 3.5 g/dL, while the majority (87.8%) exhibited lower levels. Finally, a very small number of participants (2.0%) had CRP (C-reactive protein) levels equal to or higher than 40 mg/L, indicating a low prevalence of significant inflammation (Table 1 and Table 2).

Table 1: Clinical and laboratory characteristics of research subjects

Clinical characteristics	Results (n = 498)
Gender	
Male	267 (53.6%)
Female	231 (46.4%)
Age	
< 60 years old	328 (65.9%)
> 60 years old	170 (34.1%)
History of diabetes mellitus	
Yes	268 (53.8%)
No	230 (46.2%)
History of hypertension	
Yes	254 (51.0%)
No	244 (49.0%)
History of chronic obstructive lung disease	
Yes	7 (1.4%)
No	491 (98.6%)
History of regular hemodialysis	
Yes	99 (19.9%)
No	399 (80.1%)
History of HIV infection	
Yes	15 (3.0%)
No	483 (97.0%)
History of cancer	
Yes	32 (6.4%)
No	466 (93.6%)
Fever	
Yes	2 (0.1%)
No	496 (99.9%)
Dyspnea	
Yes	22 (4.4%)
No	476 (96.2%)
Pneumonia filtrate on chest x-ray	
Yes	272 (54.6%)
No	226 (45.4%)

Table 2: Laboratory results of research subjects

Laboratory results	Results (n = 498)
Anemia	
Yes	357 (71.7%)
No	141 (28.3%)
NLR	
≥ 5.5	349 (70.1%)
< 5.5	149 (29.9%)
D-dimer	
≥ 1.2 mg/L	369 (74.1%)
< 1.2 mg/L	129 (25.9%)
Albumin	
≥ 3.5 g/dL	61 (12.2%)
< 3.5 g/dL	437 (87.8%)
CRP	
≥ 40 mg/L	10 (2.0%)
< 40 mg/L	488 (98.0%)

HIV: Human Immunodeficiency Virus
NLR: Neutrophil-to-Lymphocyte Ratio

Mortality of COVID-19 patients with AKI

Of the 498 COVID-19 patients who experienced AKI, 153 subjects (30.7%) died. Age was found to be significantly associated with mortality (p = 0.045), with participants aged 60 years or older exhibiting a higher mortality rate compared to those below 60 years old. Additionally, mortality was significantly associated with a history of hypertension (p = 0.001), with participants having hypertension experiencing a higher mortality rate compared to those without hypertension. A history of cancer also showed a significant association with mortality (p = 0.041), as participants with a history of cancer had a higher mortality rate compared to those without.

Moreover, mortality was significantly associated with NLR (p < 0.001), with participants having an NLR of 5.5 or higher demonstrating a higher mortality rate compared to those with an NLR below 5.5. Finally, albumin levels showed a significant association with mortality (p = 0.022), as participants with albumin levels below 3.5 g/dL exhibited a higher mortality rate compared to those with albumin levels equal to or higher than 3.5 g/dL. These findings highlight the impact of age, hypertension, cancer history, NLR, and albumin levels on mortality in the study population.

From the results of bivariate analysis using the Chi-square test it was found that the variables were age 60 years, history of hypertension, history of cancer, NLR value 5.5, D-dimer value 1.2 mg/L, and albumin value < 3.5 g/ dL was significantly associated with mortality in COVID-19 patients with AKI (Table 3).

Table 3: Comparison of the characteristics of research subjects based on the outcome

Variable	Survive (n = 153)	Not Survive (n = 345)	p value
Gender			0.701
Male	84	184	
Female	69	162	
Age			0.045*
≥ 60 years old	62	108	
< 60 years old	91	237	
History of diabetes mellitus			0.948
Yes	82	185	
No	71	159	
History of hypertension			0.001*
Yes	61	193	
No	92	152	
History of chronic lung disease			0.342
Yes	1	6	
No	152	339	
History of regular hemodialysis			0.187
Yes	25	74	
No	128	271	
History of HIV infection			0.824
Yes	5	10	
No	148	335	
History of cancer			0.041*
Yes	15	17	
No	138	328	
Fever			0.860
Yes	0	2	
No	153	343	
Dyspnea			0.192
Yes	4	18	
No	149	327	
Pneumonia filtrate on chest X-ray			0.780
Yes	85	187	
No	68	158	
Anemia			0.883
Yes	109	248	
No	44	97	
NLR			0.000*
≥ 5.5	124	225	
< 5.5	29	120	
D-dimer			0.001*
≥ 1.2 mg/L	99	270	
< 1.2 mg/L	54	75	
Albumin			0.022*
≥ 3.5 g/dL	11	50	
< 3.5 g/dL	142	295	
CRP			0.767
≥ 40 mg/L	4	6	
< 40 mg/L	149	339	

* Statistically significant

Analysis of the correlation between clinical and laboratory characteristics with mortality of COVID-19 patients with AKI

D-dimer levels, hypoalbuminemia, and hypertension were identified as three variables that significantly influenced mortality. The results of multivariate logistic regression analysis showed that the largest OR value was the D-dimer value variable, namely 2.102 (95% CI: 1.361-3.247), which means that COVID-19 patients with AKI who have a D-dimer value ≥ 1.2 mg/L have the possibility of experiencing mortality within 30 days was 2.1 times greater than in patients with D-dimer values < 1.2 mg/L. The next variables were albumin value < 3.5 g/dL (OR 2.015, 95% CI: 0.992-4.091), history of hypertension (OR 2.003, 95% CI: 1.343-2.988) (Table 4).

Table 4: Results of multivariate analysis of clinical and laboratory characteristics on 30-day mortality

Predictor variable	p value	Odds Ratio (CI 95%)
History of hypertension	< 0.001	2.003 (1.343 – 2.988)
D-dimer (≥ 1.2 mg/L)	< 0.001	2.102 (1.361 – 3.247)
Albumin (< 3.5 g/dL)	< 0.001	2.015 (1.361 – 3.247)

Discussion

In this study, it was found that hypertension, D-dimer, and albumin, can predict the incidence of mortality within 30 days in patients with AKI infected with COVID-19. Even though COVID-19 may impact healthy people of all ages, studies have demonstrated that the probability of death is greater in older people and those with chronic diseases like hypertension. The study also stated that complications and hospitalization rates were higher in COVID-19 patients with hypertension. In our study, 254 (51%) COVID-19 patients had a history of hypertension. The incidence of mortality in patients with hypertension in our study was statistically

significant (p < 0.001) (OR 2003, 95% CI: 1.343-2.988). The main reasons for the higher mortality rate and ICU stay in this group of patients with hypertension are unknown (12).

However, several studies have hypothesized the presence of the angiotensin-converting enzyme 2 (ACE2) in the body as a possible cause of higher mortality and ICU admission rates. The cellular receptor known as ACE-2 enables the virus to enter host cells and begin infection. Higher levels of ACE-2 expression may increase susceptibility to SARS-CoV-2 infection and perhaps exacerbate COVID-19 symptoms, according to previous studies (13). Angiotensin 2 is converted to angiotensin 1-7 by a substance that can be discovered in the epithelium cells of the lungs, liver, and heart. Angiotensin 1-7 then plays an enhanced anti-inflammatory and antioxidant function, causing vasodilation and reducing blood pressure (14). The ACE2 gene is expressed more frequently as a result of coronaviruses using it as a binding site to attach to and penetrate their host's body, raising the chance of COVID-19 infection (15, 16). ACE2 enzyme increases in hypertensive patients due to angiotensin II receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs), which in turn increase the risk of COVID-19 infection (17).

D-dimer is a byproduct of fibrin breakdown that is produced when plasmin cleaves fibrin linkages (18). D-dimers are frequently used in clinical practice to diagnose pulmonary embolism (PE), deep vein thrombosis (DVT), and disseminated intravascular coagulation (DIC) (19). Among the most frequent test results in COVID-19 individuals who need to be hospitalized is a high D-dimer (20). The most adverse long-lasting effects are linked with increased D-dimer levels during hospital stay, according to studies (21). The levels of D-dimer were below 1.2 mg/dL in 369 (74.1%) of the participants in our research, and there proved relationship among D-dimer amounts and mortality (p = 0.001) (OR = 2.102, 95% CI: 1.361-3.247). Study by Hilda et al. (22) found that in 82.69% of cases, D-dimer levels in non-survivors were higher than 1.49 mg/L.

In comparison to females, males showed a lower cut-off (> 1.49 mg/L vs. > 2.2 mg/L). The level of D-dimer was shown to be significantly correlated with coronavirus illness mortality in 2019 (p = 0.001) (22, 23). D-dimer amount was found to be > 2.14 g/ml by Yao et al. (24). When being admitted, with a specificity of 71.3% and sensitivity of 88.2%, as a predictor of death. The recognized hypercoagulable state that COVID-19 induces increases the risk of blood clot formation in a number of organs (24). Elevated D-dimer levels represent the disintegration of fibrin clots and may signify continuous activation of the coagulation process. Microvascular thrombosis, such as pulmonary embolism, deep vein thrombosis, and disseminated intravascular coagulation, are frequently present in severe COVID-19 patients and can cause organ failure and mortality (23).

Our study also found that hypoalbuminemia (< 3.5 g/dL) could predict mortality in COVID-19 patients with AKI (p < 0.001) (OR 2.015, 95% CI: 0.992-4.091). Uncertainty exists regarding the root cause process linking hypoalbuminemia to unfavorable COVID-19 outcomes. Endothelial failure is significant from a pathogenetic perspective in COVID-19 (24). Endothelial dysfunction is caused by a number of variables, such as the SARS-CoV-2 response, lack of oxygen, immune cell activation and recruitment, and the generation of inflammation-related substances. This procedure causes the epithelial-endothelial barrier to lose its structural strength, allowing peptides and liquids, including hypoalbuminemia, to move from the intra-vascular to the extra-vascular segment and cause hypoalbuminemia. Thus, in COVID-19 individuals, hypoalbuminemia may be a sign of epithelial-endothelial injury (25).

In inflammatory diseases and COVID-19, neutrophil extracellular traps (NETs) play a significant role in mediating tissue injury (26). Patients with hypoalbuminemia are more likely to experience serious breathing problems and pass away, which may be due to the fact that hypoalbuminemia has been shown to hinder the development of NETs. Deoxyribonucleic acid (DNA), histones (H1, H2A, H2B, H3, and H4), oxidizing enzymes, microbicidal proteins, and cytoplasmic proteins make up extracellular webs known as NETs, which are made up of decondensed chromatin. Neutrophils create NETs to contain pathogens during a number of thrombo-inflammatory diseases, including sepsis, thrombosis, and respiratory failure. Transcriptome investigation of COVID-19 patients revealed a relationship between 16 NET-associated genes, including metabolic enzymes, structural proteins, anti-microbial related peptides, peroxisomal peptide, and others, and neutrophil authentication. All of this involved T, NK, and B cells and was connected to innate immunity (via IFN signaling). However, the consequences included lowered antiviral immunity and direct lung injury due to the negative regulation of T cell and NK cell immune activity via LGAS9 and CEACAM1, respectively (27-31).

The clinical implications of our study's findings highlight the importance of early recognition and targeted interventions in COVID-19 patients with acute kidney injury (AKI). The predictors of mortality, including hypertension, elevated D-dimer levels, and hypoalbuminemia, provide valuable insights for improving patient outcomes. Strategies such as optimizing blood pressure control, monitoring D-dimer levels, addressing hypoalbuminemia through nutritional support, and individualized care based on risk stratification can aid in the management of these patients. A collaborative and multidisciplinary approach involving various healthcare professionals is essential for optimizing outcomes.

The limitation of our study is that this study is a single center so the study results cannot be fully generalized to the broader population. Second, we conduct laboratory tests when patients come to the emergency department without considering the onset of COVID-19 symptoms. The analysis's retroactive nature imposes inherent restrictions on the gathering and analysis of data. Reliance on already-existing medical records and databases may result in missing data, erroneous or incomplete information, or

both. The representativeness and generalizability of our findings may be impacted by this.

Conclusion

Our study found that a history of hypertension, higher than normal D-dimer levels, and hypoalbuminemia were predictors of mortality in patients with AKI who were infected with COVID-19. Incorporating hypoalbuminemia, D-dimer levels, and hypertension into risk stratification models might help identify high-risk individuals who may benefit from more frequent monitoring, intense management, or early interventions. Such prediction model validation and improvement can improve clinical judgment and maximize resource use.

Acknowledgement

Not applicable

Competing interests

The authors declare that they have no competing interests.

Ethical Clearance

This study has been approved by the committee ethics of Airlangga University with registered number: (1618/101/4/VIII/2022).

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