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Analysis of Kidney Function Tests as Predictor of Mortality in COVID-19

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ABSTRACT

Cytokine release syndrome and Acute Respiratory Distress Syndrome (ARDS) increase the incidence of Acute Kidney Injury (AKI) in COVID-19 patients, which is associated with a poor prognosis and risk of death. The purpose of this study was to analyze urea, creatinine, and eGFR values as predictors of mortality in COVID-19 patients. A retrospective cohort study was carried out using secondary data from medical records of 311 COVID-19 patients who were treated at the Hasanuddin University State Higher Education Hospital from August 2020 to August 2021. Data were analyzed using the Mann-Whitney test, Chi-Square, and Logistic Regression. The risk of mortality for COVID-19 patients with urea levels > 53 mg/dL was 5.128 times higher than that of urea levels ≤ 53 mg/dL (OR=5.128; CI = 2.530 – 10.391, p<0.001). The risk of mortality for COVID-19 patients with creatinine levels > 1.3 mg/dL was 2.696 times higher than that of creatinine levels ≤ 1.3 mg/dL (OR= 2.696; CI = 1.330 – 5.463, p<0.001). The risk of mortality in COVID-19 patients with an eGFR < 90 mL/min/1.73 m^2 was 3.692 times higher than that of an eGFR ≥ 90 mL/min/1.73 m^2 (OR=3.692; CI=2.134 – 6.389, p<0.001). Multiple logistic regression analysis showed that urea and eGFR were better predictors of mortality than creatinine (OR=0.374, p=0.002 vs OR 0.344, p=0.007 vs. OR 1.192, p=0.694). The COVID-19 patient group with high serum urea and creatinine levels and low eGFR values had a greater risk of mortality compared to the group of patients who had normal results. Urea levels and eGFR values were better predictors of mortality than serum creatinine.

Keywords: Urea, creatinine, glomerular filtration rate, a predictor of COVID-19

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Human-to-human transmission leads to a more aggressive spread of SARS-CoV-2. Transmission of SARS-CoV-2 from symptomatic patients occurs through droplets, which come out when coughing or sneezing. Severe cases of COVID-19 can cause acute respiratory syndrome and even death.[1-4]

Based on the severity of cases, COVID-19 is divided into several groups, namely asymptomatic, mild, moderate, severe, and critical. An asymptomatic condition is the mildest condition because there are no symptoms. Patients whose mild/uncomplicated symptoms have non-specific symptoms. Moderate symptomatic patients are those with pneumonia but have no signs of severe pneumonia and do not require oxygen supplementation. Severe symptoms/severe pneumonia in patients are characterized by fever and one of the following manifestations: respiratory rate > 30 breaths/minute, severe respiratory distress, or oxygen saturation (SpO2) < 93 on room air. The critical situation is characterized by a state of respiratory failure, Acute Respiratory Distress Syndrome (ARDS), septic shock, and/or multiple organ failure.[3,5]

COVID-19 cases increased rapidly and spread to various countries in a short time. As of 20 June 2021, the World Health Organization (WHO) reported 177, 892,195 cases with 3,859,461 deaths (CFR 2.2%) worldwide. Indonesia reported its first case on March 2, 2020. Cases were increasing and spreading rapidly throughout Indonesia since then. As of July 7, 2021, there were 2,379,397 confirmed cases of COVID-19 with 1,973,388 recovered cases and 62,908 (CFR: 2.8%) deaths, while there were 32,345 positive confirmed cases in Makassar with a death rate reaching 563 case.[6-8]

The COVID-19 disease causes a global crisis across dimensions of health, economy, and education. The disease has spread rapidly and can result in a severe state with markedly high mortality in certain groups. Mortality is very high if there are no

proven effective preventive measures. Poor prognostic prediction correlates with high mortality in patients with COVID-19. Clinical studies show that changes in the levels of several laboratory parameters affect the mortality rate of COVID-19 patients. The development and use of accurate predictors for COVID-19 prognosis will benefit the clinical management of COVID-19 patients and will help reduce mortality.[9-11]

Hospitalizations related to COVID-19 are generally needed for acute respiratory failure, thereby only focusing on pulmonary involvement and complications in these patients. The frequency of extrapulmonary system involvement remains to increase. Kidney involvement in COVID-19 can be indicated based on the results of abnormal urine analysis in Acute Kidney Injury (AKI) associated with COVID-19, which is initially considered low and can be ignored. A recent meta-analysis showed that the incidence of AKI varied from 1.9% to 70.7% based on the severity of COVID-19. Depending on the pathophysiology of AKI and the duration of COVID-19 illness, the incidence of AKI may vary. Cytokine release syndrome and ARDS increase the frequency of AKI in COVID-19 patients. AKI is associated with a poor prognosis and increases the risk of death. Early prediction of kidney dysfunction related to COVID-19 can affect the prognosis of COVID-19 and reduce the risk of AKI.[12,13]

Several studies show that elevated urea and creatinine levels that are not due to chronic kidney disease are associated with severe COVID-19, indicating the possibility of acute inflammation caused by SARS-CoV-2 infection. Urea and creatinine are indicators of kidney function and can be considered important markers that change significantly in COVID-19 patients. Urea is the end product of protein and amino acid catabolism produced by the liver and distributed through the intracellular and extracellular fluids into the blood to be filtered by the glomerulus and partly reabsorbed in circumstances where urine is impaired. Creatinine is the end product of creatinine phosphate (protein), synthesized in the liver, and found in skeletal muscle and blood, which is excreted by the kidneys in the urine.[13]

Based on this background, authors were interested to perform a study to analyze urea, creatinine, and estimated Glomerular Filtration Rate (eGFR) as indicators of kidney function. It was expected that these parameters can be used as predictors of mortality in COVID-19 patients to enable clinicians to predict worsening and even mortality in COVID-19 patients to provide comprehensive management of COVID-19 patients with kidney complications.

METHODS

This study used a retrospective cohort study design by collecting secondary data from 311 COVID-19 patients based on the results of the Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) test who were treated at the Hasanuddin University Hospital in Makassar from August 2020 to August 2021. The research subjects were an accessible population, which met the inclusion criteria, namely COVID-19 patients who were ≥ 18 years old and had urea, creatinine, and eGFR test results at the time of admission to the hospital. COVID-19 patients who had a history of kidney problems before suffering from COVID-19 were excluded. Patients were then classified based on their outcome into recovery and non-recovery groups.

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 22. The statistical analysis method used was descriptive statistical calculations, Mann-Whitney tests, Chi-Square test, and Logistic Regression statistical tests to analyze the potential of kidney function tests as a predictor of COVID-19 mortality. The test results were considered significant with $p < 0.05$. The data were also analyzed using the Receiver Operating Characteristics (ROC) curve to obtain cut-off values for urea, creatinine, and eGFR values. Ethical eligibility approval was obtained from the Health Research Ethics Commission, Hasanuddin University Medical Faculty, Hasanuddin University Hospital, and Makassar Sayang Rakyat Hospital with number 584/UN4.6.4.5.31/ PP36/ 2A21.

RESULTS AND DISCUSSIONS

The results showed that out of 311 samples of COVID-19 patients, there were 154 (49%) males and 157 (50.5%) females with an age range of 19-84 years with the age 18-65 years as the most dominant age, which was found in 255 (82%) subjects. COVID-19 patients in this study consisted of 233 (74.9%) with moderate disease and 78 (25.1%) with severe disease. A total of 236 (75.8%) subjects had no comorbidities, while those whose comorbidities (24.12%) consisted of 34 (10.93%) diabetes mellitus, 26 (8.36%) hypertension, 8 (2.6%) malignancy, and 7 (2.3%) Cardiovascular Disease (CVD) (Table 1).

Table 1. Characteristics of research subjects

Criteria	n (%)
Gender	
Male	154 (49%)
Female	157 (50.5%)
Age	
18–65	255 (82%)
66–79	51 (16.4%)
80–99	5 (1.6%)
Comorbid	
None	236 (75.8%)
Diabetes mellitus	34 (10.93%)
Cardiovascular disease	7 (2.3%)
Hypertension	26 (8.36%)
Malignancy	8 (2.6%)
COVID-19 severity	
Moderate	233 (74.9%)
Severe	78 (25.1%)
Outcome	
Recovery	234 (75.2%)
Death	77 (24.8%)

A total of 234 (75.2%) subjects recovered from COVID-19 and 77 (24.8%) subjects died. Based on Table 2, a comparison of the median levels of urea, creatinine, and eGFR according to mortality through the Mann-Whitney test showed that there was a significant difference with a p-value of <0.001; < 0.001; and < 0.001, respectively ($p < 0.05$).

The distribution of urea and creatinine levels was based on the normal range of Pentra C 400 devices at the UNHAS RPTN and Sayang Rakyat Hospital: 0-53 mg/dL for urea and 0.6-1.3 mg/dL for creatinine, while the distribution of eGFR values were based on eLFG normal values. Based on Table 3, it was found that COVID-19 patients with urea levels > 53 mg/dL had a risk of death 5.128 times higher compared to patients with urea levels ≤ 53 mg/dL. Patients with creatinine levels > 1.3 mg/dL had a risk of death 2.696 times higher compared to patients with creatinine levels < 1.3 mg/dL. Patients with eGFR values < 90.43 mL/min/1.73 m^2 had a risk of death 3.692 times higher compared to patients with eGFR values ≥ 90 mL/min/1.73 m^2.

Table 4. Multiple logistic regression of urea, creatinine, and eLFG to mortality of COVID-19 patients

Variable	B	OR	p
Urea	-1.067	0.344	0.007
Creatinine	0.175	1.192	0.694
eLFG	-0.982	0.374	0.002

Data in Table 4 showed that based on multiple logistic regression analysis, it was found that the eGFR and urea levels had more influence on mortality that they could be used as predictors of mortality compared to creatinine levels (OR = 0.374,

Table 2. The difference in kidney function marker levels based on COVID-19 mortality

Variable	Recovery	Death	P
Urea (mg/dL)			
Median (min-max)	23 (10-192)	39 (15–214)	< 0.001
Creatinine (mg/dL)			
Median (min-max)	0.8 (0.4–7.3)	1.0 (0.7–9.4)	< 0.001
eLFG (mL/min/1.73 m^2)			< 0.001
Median (min-max)	105.51 (5.63–250.91)	74.76 (7.62–266.58)	

Table 3. Risk of mortality of COVID-19 patients based on kidney function marker levels

Variable	Mortality n (%)		p	OR (CI 95%)
	Yes	No		
Urea (mg/dL)				
>53	21 (28.38%)	17 (7.17%)	< 0.001	5.128
≤ 53	53 (71.62%)	220 (92.83%)		
Creatinine (mg/dL)				
>1.3	16 (21.62%)	22 (9.28%)	0.005	2.696
≤ 1.3	58 (78.38%)	215 (90.72%)		
eLFG (mL/min/1.73 m^2)				
< 90	48 (64.86%)	79 (33.33%)	< 0.001	3.692
≥ 90	26 (35.14%)	158 (66.67%)		

p=0.002 vs. OR=0.344, p=0.007 vs. OR=1.192, p=0.694).

The characteristics of research subjects in this study showed that there was a similar proportion of male and female COVID-19 patients. Subjects in this study consisted of 157 (50.5%) females and 154 (49.5%) males with the largest age range being in the age group of 18-65 years, which was found in 255 patients (82%). This was following the study of Mukherjee et al. suggesting that there was no significant difference between males and females based on their susceptibility to COVID-19 infection. Research by Guan *et al.* in 30 provinces in China with a total sample of 1099 reported that the average age of COVID-19 patients was 47 years and 41.9% were females.[14] A retrospective cohort study by Surendra *et al.* in 55 hospitals in Jakarta found that the median age of COVID-19 patients was 46 years (IQR 32-57) and the risk of death in hospitals increased with increasing age and the presence of more than one comorbid was reported in 31% of 4265 adult and pediatric patients.[15]

Based on the results of the study in Table 1, it was also found that the most research subjects in this study were patients who had no history of comorbidities compared to patients who had comorbidities, patients with moderate severity were compared to patients with severity, and patients who recovered were more than patients who died. This was following a study by Kangdra *et al*., which found that 55.2% of patients had no history of comorbidities and 44.8% had comorbidities, and 45.5% of patients with mild symptoms, 42.7% with moderate symptoms, and 11.8% with severe symptoms. These results were also following national data from the South Sulawesi COVID-19 Handling Task Force in October 2021, which reported 97.6% cases with recovery and 2.0% death.[16,17]

The results of the study found significant differences in urea levels, creatinine levels, and eGFR values between COVID-19 patients who recovered and patients who died. The mean urea and creatinine levels were found to be higher in COVID-19 patients who died compared to COVID-19 patients who recovered, while the eGFR value was lower in COVID-19 patients who died compared to patients who recovered. This was in line with a study by Liu *et al*. on 305 COVID-19 patients, which found that the median urea and creatinine levels were higher in non-surviving patients than in survivors, while the eGFR value was lower in non-surviving patients than in surviving patients.[17] Research by Cheng *et al.* on 710 COVID-19 patients reported that the prevalence of an increase in serum creatinine was 15.5% and an increase in Blood Urea Nitrogen (BUN) of 14.1% and a decrease in eGFR < 60 ml/min per 1.73 m^2 of 13.1%.[18,19]

Patients with urea levels > 53 mg/dL had a risk of death 5.128 times higher compared to those with urea levels ≤ 53 mg/dL. Patients with creatinine levels > 1.3 mg/dL had a risk of death 2.696 times higher compared to patients with creatinine levels ≤ 1.3 mg/dL. Patients with eGFR values < 90 mL/min/ 1.73 m^2 have a risk of death 3.692 times higher compared to patients with eGFR values ≥ 90 mL/min/1.73 m^2. This study was in line with research conducted by Cheng *et al*., which found an increase in urea led to a risk of death 7.15 times higher compared to normal urea, an increase in serum creatinine led to a risk of death 2.99 times higher compared to normal creatinine. These findings were in contrast to research by Ramesh *et al.* on 175 COVID-19 patients, which found that subjects with DM whose an eGFR ≤ 61.5 had a risk of death of only 0.965 times.[19] A study by Liu *et al*. found that increased urea levels and decreased eGFR were associated with an increased risk of mortality in COVID-199 patients. This was associated with the involvement of impaired kidney function in COVID-19 patients which can lead to AKI, which is associated with a highly increased risk of death in COVID-1921 patients.[17]

Acute kidney injury is a syndrome characterized by sudden and rapidly impaired kidney function in regulating the body's fluid and electrolyte composition, as well as the removal of metabolic waste products. The definition of AKI is based on serum creatinine (Cr) levels and Urine Output (UO). According to Kidney Disease Improving Global Outcomes (KDGIO), AKI in adults is characterized by one of the following: an increase in serum creatinine (SCr) of ≥ 26 μmol/L (0.3 mg/dL) in 48 hours, or an increase in SCr to > 1.5 times in previous 7 days, or urine volume < 0.5 mL/kg/hour for > 6 hours.[20,21]

Anatomical studies have reported significant kidney inflammation in patients with severe COVID-19. There are two presumed mechanisms by which SARS-CoV-2 induces kidney inflammation. First, SARS-CoV-2 can directly infect epithelial cells and renal tubular podocytes via the ACE2 receptor, which facilitates cell-targeted infection by the virus. Consequently, acute tubular necrosis, podocytopathy, microangiopathy, and collapse glomerulopathy can occur due to massive inflammation in the renal tubular epithelial cells and podocytes. Second, the binding between SARS-CoV-2 and the ACE2 receptor activates

angiotensin II and induces cytokine production, which can lead to hyper coagulopathy and microangiopathy, and ultimately lead to renal hypoxia.[22-24] The study by Cheng *et al*. found that patients with elevated baseline serum creatinine were more likely to be admitted to the intensive care unit, undergoing mechanical ventilation, and had a higher risk of death.[19]

The use of a retrospective cohort study, which required complete secondary data remained one of the limitations of this study, hence, incomplete secondary data were not taken with the result of reducing the number of research samples. Predictor research requires a lot of variables because to determine the prognosis of a disease, it is necessary to pay attention to many factors; however, this study only examined kidney function tests as a predictor of mortality.

CONCLUSIONS AND SUGGESTIONS

Serum urea and serum creatinine levels in COVID-19 patients who died were higher than in patients who recovered, while the eGFR values of COVID-19 patients who died were lower than those who recovered. COVID-19 patients with high serum urea and serum creatinine levels and low eGFR values had a higher risk of death than patients with normal levels. eGFR and urea levels can be used as predictors of mortality.

Further studies were needed using better designs, for example, prospective cohorts, a higher number of variables, and subjects to analyze the mortality of COVID-19 patients.

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