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The aggregate index of systemic inflammation may predict mortality in COVID-19 patients with chronic renal failure

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Abstract. – OBJECTIVE: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first detected in December 2019 and then spread globally, resulting in a pandemic. Initially, it was unknown if chronic kidney disease (CKD) contributed to the mortality caused by COVID-19. The immunosuppression associated with this disease may minimize the COVID-19-described hyper-inflammatory state or immunological dysfunction, and a high prevalence of comorbidities may lead to a poorer clinical prognosis.

Patients with COVID-19 have abnormal circulating blood cells associated with inflammation. Risk stratification, diagnosis, and prognosis primarily rely on hematological features, such as white blood cells and their subpopulations, red cell distribution width, mean platelet volume, and platelet count, in addition to their combined ratios.

In non-small-cell lung cancer, the aggregate index of systemic inflammation (AISI), (neutrophils x monocytes x platelets/lymphocytes) is evaluated. In light of the relevance of inflammation in mortality, the objective of this study is to determine the impact of AISI on the hospital mortality of CKD patients.

PATIENTS AND METHODS: This study is an observational retrospective study. Data and test outcomes of all CKD patients, stages 3-5, hospitalized for COVID-19 and followed between April and October 2021 were analyzed.

RESULTS: Patients were divided into two groups according to death (Group 1-Alive, Group 2-Died). Neutrophil count, AISI and C-reactive protein (CRP) levels were increased in Group-2 [10.3±4.6 *vs.* 7.65±4.22; *p*=0.001, 2,084.1 (364.8-2,577.5) *vs.* 628.9 (53.1-2,275); *p*=0.00 and 141.9 (20.5-318) *vs.* 84.75 (0.92-195); *p*=0.00; respectively]. Receiver operating characteristic (ROC) analysis demonstrated 621.1 as a cut-off value for AISI to predict hospital mortality with 81% sensitivity and 69.1% specificity [area under ROC curve 0.820 (95% CI: 0.733-0.907), *p*<.005].

Cox regression analysis was used to analyze the effect of risk variables on survival. In survival analysis, AISI and CRP were identified as important survival predictors [hazard ratio (HR): 1.001, 95% CI: 1-1.001; *p*=0.00 and HR: 1.009, 95% CI: 1.004-1.013; *p*=0.00].

CONCLUSIONS: This study demonstrated the discriminative effectiveness of AISI in predicting disease mortality in COVID-19 patients with CKD. Quantification of AISI upon admission might assist in the early detection and treatment of individuals with a bad prognosis.

Key Words:
COVID-19, Chronic kidney disease, Aggregate index of systemic inflammation, Inflammation, Mortality.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was diagnosed for the first time in December 2019 and subsequently spread internationally, resulting in a pandemic. By June 2022, this disease had resulted in the deaths of over 6 million people globally[1].

Initially, it was unclear if chronic kidney disease (CKD) played a role in COVID-19 mortality. Immunosuppression associated with this illness might diminish the hyper-inflammatory state described in COVID-19. On the other hand, immune dysfunction and a high incidence of comorbidities (such as cardiovascular disease and diabetes) may lead to a poorer clinical course[2]. Recent studies[3,4] have linked CKD to severe COVID-19, an increased risk of hospitalization, and increased mortality.

The incidence of CKD among COVID-19 patients has been estimated[5] to be between 1% and 2%. CKD is linked to an increased incidence of inpatient and outpatient pneumonia[6]. Moreover, lung infection mortality in individuals with CKD is nearly tenfold greater than in the average population[7].

It has been found[8] that COVID-19-positive individuals have abnormalities in their circulating blood

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cells associated with inflammation and immunological state. Hematological parameters, such as white blood cells and their subpopulations, red cell distribution width, mean platelet volume, and platelet, as well as combined ratios of these parameters, such as neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), are widely used for risk stratification, diagnosis, and prognosis[8,9].

The aggregate index of systemic inflammation (AISI), (neutrophils x monocytes x platelets/lymphocytes) is an index studied in non-small-cell lung cancer[10]. Considering the role of inflammation on mortality, this study aims to determine the impact of AISI on CKD patients' hospital mortality.

Patients and Methods

A study protocol was submitted and approved by the Ethics Committee of Zonguldak Bulent Ecevit University (26.01.2022-/2). This study is an observational retrospective study. The data and test findings of all CKD patients hospitalized for COVID-19 and followed between April 2021 and October 2021 were obtained and examined.

The inclusion criteria were as follows: a) 18 years old or older, b) SARS-CoV-2 positive by real-time PCR, c) all enrolled positive patients admitted to the hospital exclusively for COVID-19, d) CKD stages 3-5. The exclusion criteria were a) age <18 and b) a history of immunodeficiency diseases and the use of immune suppressive medications.

All laboratory, clinical, and demographic data were extracted from electronic medical records using a data collecting technique. Hypertension (HT), diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD) were reported as comorbidities. Neutrophil count, albumin, white blood cell count (WBC), lymphocyte count, monocyte count, creatinine, glucose, hemoglobin, platelet, sodium, potassium, blood urea nitrogen (BUN), D-dimer, and ferritin were extracted from the hospital admission data. Neutrophils x monocytes x platelets/lymphocytes were used to calculate the aggregate index of systemic inflammation (AISI).

Statistical Analysis

SPSS for Windows 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA) was used for statistical analysis. Unless otherwise specified, continuous variable data are given as mean and standard deviation. Student's *t*-test (for data with a normal distribution) or the Mann-Whitney U test was used to compare groups (in data without normal distribution). Using the Chi-square test, categorical variables were compared. In addition, a cox regression analysis was conducted to identify factors influencing hospital mortality. Using a receiver operating characteristic (ROC) analysis, the optimal AISI threshold for predicting hospital mortality was identified. As the ideal cutoff value, the value corresponding to the maximum sensitivity and specificity values in the ROC analysis was selected. p=0.05 on both sides was judged significant

Results

Of the 85 patients included in the study, 39 (45.9%) were male. The mean age was 72.1±11.2 years. Sixty-five patients had diabetes (76.5%), 32 had hypertension (37.6%), and 8 had COPD (9.4%). The mean creatinine level was 3.59 (01.79-13.8) mg/dl, and C-reactive protein (CRP) was 113.68 (0.91-318.1). Mean AISI was found to be 1,360.1 (53.04-14,529.7). The mortality rate was 50.6% (43 patients). Laboratory findings of the patients can be seen in Table I.

Table I. General characteristics of the patients.

Age (years)	72±12 (36-99)
Gender (male, N, %)	39 (45.9%)
DM (N, %)	65 (76.5%)
HT (N, %)	32 (37.6%)
COPD (N, %)	8 (9.4%)
AKI (N, %)	30 (35.3%)
ICU hospitalization (days)	9 (0-97)
Glucose (mg/dl)	210±71 (138-800)
Urea (mg/dl)	125.1±12.1
Creatinine (mg/dl)	3.59 (1.79-13.8)
Uric acid (mg/dl)	7.59±3.01 (2.9-19.1)
Albumin (gr/dl)	3.08±0.58 (1.52-4.76)
LDH (U/L)	386 (148-3,142)
Hb (gr/dl)	10.99±2.23
Neutrophil (K/ml)	9.58±4.91 (3.5-25.4)
Lymphocyte (K/ml)	1.09±0.78 (0.2-4.1)
Platelet (K/ml)	201±88 (29-471)
Monocyte (K/ml)	0.5±0.3 (0.1-1.4)
Ferritin (µg/dl)	876.24 (15.71-3,786)
D-dimer (mg/L)	2.2 (0.1-71.8)
CRP (mg/L)	113.68 (0.91-318.1)
AISI	1,360.17 (53.04-14,529.7)
Mortality (N, %)	43 (50.6%)

DM: diabetes mellitus, HT: hypertension, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, ICU: intensive care unit, Na: sodium, K: potassium, Ca: calcium, Hb: hemoglobin, CRP: C-reactive protein, AISI: aggregate index of systemic inflammation.

Table II. Comparision of the patients survived (Group-1) and died (Group-2).

	Group-1 (N=42)	Group-2 (N=43)	*p*
Age (years)	73.1±14.2	74.4±11.3	0.334
Gender (male, N, %)	16 (38.1%)	23 (53.5%)	0.154
DM (N, %)	31 (73.8%)	34 (79.1%)	0.327
HT (N, %)	12 (28.6%)	20 (46.5%)	0.088
COPD (N, %)	2 (4.8%)	6 (14%)	0.147
AKI (N, %)	10 (23.8%)	20 (46.5%)	0.029
Dialysis (N, %)	29 (69%)	32 (74.4%)	0.582
Glucose (mg/dl)	226 (83-800)	193 (71-668)	0.343
U.acid (mg/dl)	6.96±2.49	8.21±3.36	0.09
Albumin (gr/dl)	3.22±0.53	2.94±0.61	***0.027***
LDH (U/L)	337 (148-1,797)	434 (153-3,142)	0.455
Hb (gr/dl)	11.28±2.17	10.71±2.29	0.276
Neutrophil (K/ml)	7.65±4.22	10.3±4.6	***0.001***
Lymphocyte (K/ml)	1.03 (0.33-5.3)	1.01 (0.2-1.4)	0.243
Platelet (K/ml)	203±87	198±89	0.165
Ferritin (µg/dl)	840.28 (44-3,799.1)	911.4 (15.7-2,967)	0.335
D-dimer (mg/L)	1.45 (0.1-7.3)	2.94 (0.01-72)	0.08
CRP (mg/L)	84.75 (0.92-195)	141.9 (20.5-318)	***0.00***
AISI	628.9 (53.1-2,275.2)	2,084.1 (364.8-2,577.5)	***0.00***

DM: diabetes mellitus, HT: hypertension, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, ICU: intensive care unit, Na: sodium, K: potassium, Ca: calcium, Hb: hemoglobin, CRP: C-reactive protein, AISI: aggregate index of systemic inflammation.

Patients were divided into two groups according to death (Group 1-Alive, Group 2-Died). There was no significant difference between groups in terms of age and gender (73.1±14.2 *vs.* 74.4±11.3; $p>0.05$ and 38.1% *vs.* 53.5; $p=0.154$, respectively). HT, COPD and DM incidence were similar between groups (28.6% *vs.* 46.5% $p=0.088$, 4.8% *vs.*14% $p=0.147$ and 73.8% *vs.* 79.1; $p=0.327$; respectively). Neutrophil count, AISI and CRP levels were increased in Group-2 [10.3±4.6 *vs.* 7.65±4.22; $p=0.001$, 2,084.1 (364.8-2,577.5) *vs.* 628.9 (53.1-2,275); $p=0.00$ and 141.9 (20.5-318) *vs.* 84.75 (0.92-195); $p=0.00$; respectively]. The albumin level was significantly higher in patients who survived (Table II). The incidence of acute renal failure was higher in patients who died (46.5% *vs.* 23.8%; $p=0.029$).

Receiver operating characteristic (ROC) analysis demonstrated 621.1 as a cut-off value for AISI to predict the hospital mortality with 81% sensitivity and 69.1% specificity [area under ROC curve 0.820 (95% CI: 0.733-0.907), $p<.005$]. (Figure 1).

Cox regression analysis was used to analyze the effect of risk variables on survival. In survival analysis, AISI and CRP were identified as important survival predictors (HR: 1.001, 95% CI: 1-1.001; $p=0.00$ and HR: 1.009, 95% CI: 1.004-1.013; $p=0.00$). In determining mortality,

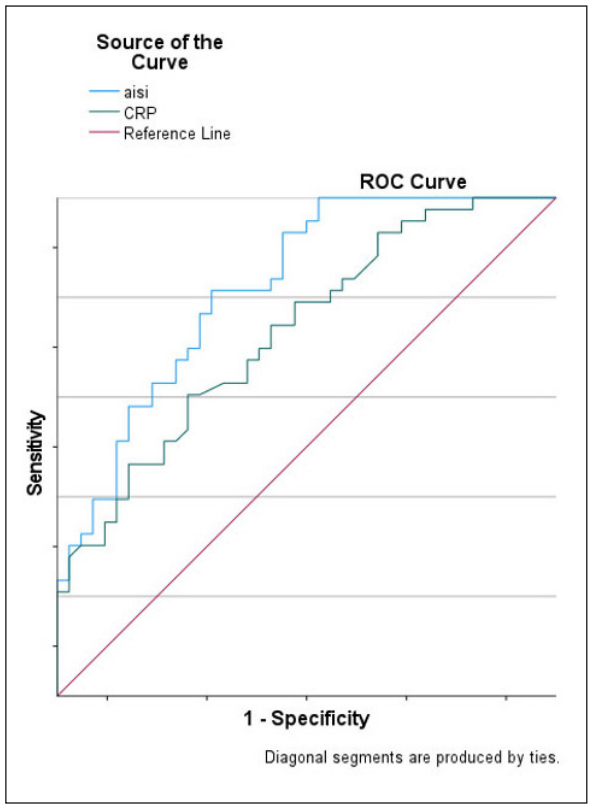

Figure 1. ROC analysis of AISI and CRP.

age (95% CI: 0.992-1.059; p=0.144) presence of HT (95% CI: 0.269-1.128; p=0.103), DM (95% CI: 0.828-4.751; p=0.165) and COPD (95% CI: 0.232-1.946; p=0.463) were unimportant.

Discussion

Recent evidence[11-13] suggests that AISI is a possible biomarker of survival in COVID-19, but our study is the first study to evaluate the connection between this index and mortality in CKD patients with SARS-CoV-2 infection, making it significant. We think that our research may extend the use of AISI to predict hospital mortality of COVID-19 in patients with CKD.

Several studies[14,15] have indicated poorer clinical outcomes and a higher death rate in CKD patients with COVID-19. The recent investigation revealed that the death rate among CKD patients was 50.6% and this is higher than normal population[16]. This may be explained by a pro-inflammatory condition accompanied with dysfunctional innate and adaptive immunity because of the uremic milieu in CKD patients. This situation may also cause an enhanced susceptibility to hyper-inflammation and cytokine storm during SARS-CoV-2 infection, ultimately leading to severe illness and mortality.

Evidence[17,18] from the worldwide epidemic demonstrated that patients with older age, male gender, and CKD-associated morbidities such as HT, DM, and coronary heart disease (CHD) are at a substantially higher risk of dying from COVID-19. In contrast, the distribution of COVID-19 mortality risk variables in patients with CKD differed from that of the general population. Prior research[19-20] indicated that certain widely reported comorbidities, such as hypertension, diabetes, chronic lung disease, and coronary artery disease, had no effect on mortality among CKD patients with COVID-19. In accordance with COVID-19 database analyses of the Turkish Society of Nephrology and the European Renal Association[19,21], it was discovered that male sex, HT, and diabetes do not increase the risk of death in CKD patients.

Cytokine storm has been associated with COVID-19 severity. The initial line of defense against viral infections consists of a quick and coordinated innate immune response. However, when the immune response is dysregulated, it can result in severe systemic inflammation and mortality[22]. Previous studies[23] on non-CKD patients with COVID-19 identified several biomarkers for severe disease, including lymphopenia and elevated levels of CRP, lactate dehydrogenase (LDH), procalcitonin (PCT), and cytokines (IL-6, IL-10, and tumor necrosis factor), highlighting the importance of immune-inflammatory responses in the pathogenesis and progression of COVID-19. Similarly, in our dataset, deceased CKD patients had a greater neutrophil count as well as a lower lymphocyte count.

Few studies have evaluated the predictive value of blood cell count-derived inflammatory indices in predicting death in CKD patients with COVID-19. The influence of neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), and peripheral lymphocyte ratio (PLR) on 37 CKD patients with SARS-CoV-2 infection was investigated and an increase in MLR was found[24] to be associated with higher mortality among CKD patients. Neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-C-reactive protein ratio (LCR) were related with the severe form and mortality rate of COVID-19 in a study[25] of 10 hemodialysis (HD) patients undergoing maintenance treatment. Another research[26] including 62 HD patients revealed an association between elevated NLR and the most severe type of COVID-19.

A greater AISI was related with mortality in our research group. To the best of our knowledge, no study has been conducted yet to examine the viability of AISI for determining COVID-19 disease mortality in CKD patients. As a novel systemic inflammatory indicator, the AISI based on counts of lymphocytes, neutrophils, platelets, and monocytes has been described[11] as a predictive factor in COVID. The distinct roles that lymphocytes, neutrophils, platelets, and monocytes play in immune response contribute to the ability of AISI to identify COVID-19 patients with a greater risk of mortality.

Neutrophils are the most significant cellular defense against infections; however, it is unclear if they play a role in anti-viral defense in viral pneumonia[27]. However, recruitment of neutrophils into the lungs has only been detected[27] in pneumonia patients with ARDS, suggesting that neutrophils play a role in protecting the airway epithelium in the presence of severe SARS-CoV-2 virus infection. It is recognized that lymphocytes are responsible for eliminating virus-infected cells[28]. Platelets contribute to hemostasis as well as the inflammatory response and host defense. Thrombocytopenia is hypothesized to develop as a result of decreased platelet production and increased consumption due to widespread alveolar injury[29].

Mononuclear phagocytes are a class of cells that contribute to innate and adaptive immunity and are broadly dispersed. Monocytes and macrophages in circulation are involved in all phases of SARS COVID-19. They contribute to comorbidities that predispose to clinical infection, viral resistance and spread, as well as host variables that define illness severity, recovery, and consequences. Blood monocytes provide a window into the systemic immune response, from production to tissue recruitment, showing the host's reaction to infection[30].

Taking these aspects into account, AISI may be better capable of representing the equilibrium of the host's inflammatory and immunological condition in COVID-19 CKD patients.

Limitations

This study has several limitations. As a single-center, retrospective, observational study, selection bias cannot be ruled out. In addition, AISI was computed at the time of hospital admission, and changes in duration of stay were not reported. Since only the data of hospitalized patients are studied and the age group comprises old individuals, it may be incorrect to generalize the population; thus, prospective multicenter studies should be done to corroborate these findings.

Conclusions

The current investigation demonstrated the discriminative efficacy of AISI in forecasting COVID-19 mortality in CKD patients. Due to the fact that AISI is based on the findings of a full blood count analysis, it is less costly, simpler, more easily applied, and more suited for general application. Quantification of AISI upon admission would aid the clinicians in early diagnosis and care of patients with a poor prognosis.

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Conflict of Interest
All authors declared that there is no potential conflict of interest relevant to this article.

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Authors' Contributions
Each Author has contributed substantially to the research, preparation and production of the paper and approves of its submission to the Journal.

Ethics Approval
A study protocol was submitted and approved by the Ethics Committee of Zonguldak Bulent Ecevit University (26.01.2022-/2).

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