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Research Article

Estimated glomerular filtration rate in identifying illness severity in newly admitted patients with COVID-19: A single-center study

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Abstract

Objectives: Early prediction of risk factors for serious illness and death in patients with coronavirus disease 2019 (COVID-19) appears to be a priority. This study aimed to examine whether a single estimated glomerular filtration rate (eGFR) at triage predicts the need for intensive care unit (ICU) admission of patients with COVID-19.

Methods: This retrospective study included data from patients with COVID-19 at the Bursa Yuksek Ihtisas Training and Research Hospital until October 2020. Patients were assigned to two groups according to their eGFR level at admission: group 1 (eGFR >60 mL/min/1.73 m^2) and group 2 (eGFR=30-60 mL/min/1.73 m^2).

Results: The results of 1447 consecutive patients diagnosed with COVID-19 were analyzed at hospital admissions. Of these, 1001 patients who met the study criteria were included in the study. The median age of group 2 was higher than group 1: 69 interquartile range (IQR 23) years versus 39 (IQR 23) years ($p<0.01$). Patients with an eGFR <60 mL/min/1.73 m^2 had lower lymphocyte counts while having higher C-reactive protein, d-dimer, lactate dehydrogenase, and fibrinogen levels. The ICU admissions were significantly higher in patients with a baseline eGFR <60 mL/min/1.73 m^2 (42.85%) compared with an eGFR >60 mL/min/1.73 m^2 (6.42%, $p<0.001$). There was a weak negative correlation between eGFR and ICU admission (rho=-0.291, $p<0.001$).

Conclusion: The eGFR at admission was strongly correlated with the severity of the disease. Therefore, measuring eGFR in all patients at admission may warrant appropriate triage.

Keywords: COVID-19, glomerular filtration rate, intensive care unit

Coronavirus disease 2019 (COVID-19) is an infectious disease, which can cause multiple symptoms, such as high fever, cough, shortness of breath, headache, sore throat, runny nose, loss of smell and taste, muscle and joint pain, weakness, and diarrhea. COVID-19 also affects the pulmonary, renal, cardiovascular, digestive, and nervous systems [1]. Moreover, clinical manifestations range from asymptomatic disease to severe viral pneumonia accompanied by respiratory failure which may result in death [2].

Early prediction of risk factors for serious illness and death in patients with COVID-19 is important. According to the current evidence, elderly people with underlying diseases, such as di-

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abetes, hypertension, and cardiovascular diseases, are at an increased risk of severe COVID-19 and an intensive care unit (ICU) admission [3, 4]. However, risk factors for severe disease may vary in different geographic areas due to ethnicity, genetic background, lifestyle, and demographic differences [5-8]. Depending on the studied population, the need for ICU might differ ranging from 5% to 32% [9].

An impaired kidney function negatively affects the maintenance of electrolyte and acid base balances of the human body by inhibiting the excretion of metabolites and toxins. Previous studies have shown an association between a low estimated glomerular filtration rate (eGFR) and increased hospitalization and mortality in patients with pneumonia [10, 11].

This study aimed to examine whether a single eGFR.

Materials and Methods

This retrospective study includes data from patients with COVID-19 at the Bursa Yuksek Ihtisas Training and Research Hospital until October 2020. Institutional Ethics Committee approved the study protocol (2020-10-31T19_02_55 and 2011-KAEK-25-2020/11-04).

The data were collected from hospital records. Patient demographics along with clinical and laboratory results at the time of admission were reviewed while protecting the anonymity and confidentiality of the data.

This study included patients with COVID-19, who were diagnosed as directed by the Department of Health. All patients were confirmed by reverse transcription-polymerase chain reaction detection of severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) RNA using nasal and pharyngeal swabs [3]. Patients directed from a pre-triage checkpoint to the triage unit with a clinical probability of COVID-19 were included. Individuals younger than 18 years of age, with GFR <30 mL/min/1.73 m^2 (n=17), without any laboratory test results at admission, and receiving maintenance hemodialysis or peritoneal dialysis were excluded from the study.

The triage protocol for patients with COVID-19 in our hospital included taking blood samples on admission and analyses within 1 h. The complete blood count was analyzed using an automatic blood counter (Mindray BC-5800, Mindray Biomedical Electronics Co., Ltd., Shenzhen, People's Republic of China). The C-reactive protein (CRP) levels were measured using a BN II system nephelometer (Siemens Healthcare Diagnostics, USA), d-dimer levels using a Sysmex CS-5100 (Siemens Healthcare Diagnostics, Erlangen, Germany), and ferritin using a Roche Cobas® e602 (Roche Diagnostics, Mannheim, Germany). Lactate dehydrogenase (LDH), serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, creatinine, sodium, potassium, and chloride were measured with a Roche Cobas® e702 (Roche Diagnostics, Mannheim, Germany).

eGFR was calculated based on the Modification of Diet in Renal Disease (MDRD) formula [12].

Patients were assigned to two groups according to their eGFR level at admission: group 1 (eGFR >60 mL/min/1.73 m^2) and group 2 (eGFR=30-60 mL/min/1.73 m^2).

Patients who were transferred to the ICU fulfilled one of the following criteria: they experienced dyspnea and respiratory distress, or they had a respiratory rate >30/min with PaO_2/FiO_2<100/min. Other possible criteria for an ICU admission included acute kidney injury, acute organ dysfunction, immunosuppression, acute bleeding diathesis, troponin increase, arrhythmia, lactate >2 mmol/L, capillary return disorder, and cutis marmorata [13].

Statistical analysis

The data were analyzed using the SPSS 23.0 statistics package (SPSS Inc., Chicago, IL, USA). In comparing the averages between groups, Student's t-tests were used for variables with a normal distribution and Mann-Whitney U tests were used for variables without a normal distribution. Categorical variables were compared with Chi-squared tests or Fisher's exact tests. Spearman correlation coefficient was used to calculate ICU admission and laboratory parameters at admission. The receiver operating characteristic curve (ROC) curve was used to evaluate the ability of the eGFR on ICU admission, and the optimal cut-off value was determined using Youden's index. Predicted probability for eGFR contribution to ICU admission was computed using a univariate logistic regression model. p-values <0.05 were considered significant.

Results

Baseline characteristics

The results of 1447 consecutive patients diagnosed with COVID-19 were analyzed at hospital admissions. Of these, 1001 patients who met the study criteria were included in the study. The median age of all patients was 42 (range 18-93) years. The clinical manifestations of severe cases with COVID-19 on admission included fever (49%), cough (46%), dyspnea/difficulty breathing (42%), sore throat (23%), runny nose/nasal congestion (17%), myalgia/arthralgia (11%), fatigue (15%), chest pain/discomfort (10%), anosmia (19%), headache (17%), nausea/vomiting (11%), and diarrhea (3%).

This study included 903 patients from group 1 (eGFR >60 mL/min/1.73 m^2) and 98 patients from group 2 (GFR=30-60 mL/min/1.73 m^2). Totally, 100 patients were admitted to the ICU: 58 from group 1 and 42 from group 2. The rate of ICU admissions was significantly higher in patients with a baseline eGFR <60 mL/min/1.73 m^2 (42.85%) compared to an eGFR >60 mL/min/1.73 m^2 (6.42%, p<0.001).

The median age of group 2 patients was higher than that of group 1 patients: 69 (IQR 23) years versus 39 (IQR 23) years (p<0.001). Patients with an eGFR <60 mL/min/1.73 m^2 had significantly higher CRP, d-dimer, LDH, and fibrinogen levels and a lower lymphocyte count (Table 1).

Table 1. Initial laboratory findings of the groups

	Group 1	Group 2	p
Number of patients	903	98	
Age; years (IQR)	39 (23)	69 (23)	<0.001
Gender (M/F)	454/449	53/45	
WBC; ×109/L	6.1 (3.0)	7.4 (5.8)	<0.001
Neutr ;%	63.9 (17.9)	71.3 (19.7)	<0.001
Lymphocyte; %	26.4 (16.8)	19.3 (18.0)	<0.001
Platelet; ×109/L	216 (75)	200 (120)	<0.001
CRP	5.8 (12.3)	28.7 (81.1)	<0.001
Ferritin	94 (149)	225 (301)	<0.001
D-dimer	0.34 (0.39)	1.05 (1.45)	<0.001
Fibrinojen	372 (142)	500 (217)	<0.001
LDH	211	309	<0.001
SGOT	23 (12)	29 (19)	<0.001
SGPT	20 (15)	18 (21)	<0.001
Na	139 (5)	137 (6)	0.002
K	4.2 (0.5)	4.4 (0.7)	0.003
Cl	101 (5)	101 (6)	0.054

Group 1: patients with eGFR >60 mL/min/1.73 m^2 ; Group2: patients with eGFR 30-60 mL/min/1.73 m^2; IQR: Interquartile range; M: Male; F: Female; WBC: White blood cell; Neutr: Neutrophile; CRP: C-reactive proteine; LDH: Llactate dehydrogenase; Na: Sodium; K: Potassium, Cl: Chloride.

Table 2. Initial laboratory findings of the patients admitted to intensive care unit compared with nonsevere patients

	Non ICU	ICU	p
BUN	11.7 (5.3)	18.0 (12.7)	<0.001
Creat	0.80 (0.29)	1.03 (0.52)	<0.001
GFR	103 (27)	69 (44)	<0.001
Na	139 (5)	137 (7)	0.001
K	4.2 (0.5)	4.3 (0.7)	0.621
Cl	102 (4.9)	99 (5.5)	<0.001

ICU: Intensive care unit; BUN: Blood urea nitrogen; Creat: Creatinine; GFR: Glomerular filtration rate; Na: Sodium; K: Potassium; Cl: Choride.

In group 1, 6.6% of the patients were ≥65 years of age, whereas in group 2, 54% of the patients were ≥65 years of age (p<0.01).

The blood urea nitrogen (BUN) level was higher in ICU patients [18.0 (IQR 12.7) vs. 11.7 (IQR: 5.3); p<0.001] in ICU patients (p<0.001) (Table 2).

There was a weak negative correlation between eGFR and ICU admission (rho=-0.291, p<0.001) (Table 3).

In the ROC analysis, the optimal cutoff for eGFR was 78 mL/min/1.73 m^2 (sensitivity, 0.602; specificity, 0.840). The area under the curve (AUC) was 0.778 (95% CI, 0.723-0.833) (Fig. 1). The ROC curve AUCs for BUN and creatinine levels were 0.817 (95% CI, 0.769-0.865) and 0.728 (95% CI, 0.666-0.790), respectively.

In the univariate linear regression analysis, eGFR was statistically significantly predicted ICU admission (r2=0.064, p<0.001).

Table 3. Spearman correlation analysis between ICU admission and blood parameters

Laboratory findings	ICU admission	
	rho	p
GFR	-0.291	<0.001
Lym	-0.252	<0.001
CRP	0.299	<0.001
Ferritin	0.279	<0.001
D dimer	0.261	<0.001
LDH	0.273	<0.001

ICU: Intensive care unit; eGFR: Estimated glomerular filtration rate; Lym: Lymphocyte; CRP: C-reactive protein; LDH: Lactate dehydrogenase.

Discussion

We found high ICU admission rates in patients with an eGFR below 60 mL/min/1.73 m^2. Accordingly, the eGFR can be an important abnormal laboratory finding reflecting the severe disease associated with a poor prognosis in COVID-19 [14]. High serum creatinine levels on admission also increase the likelihood of the patient being admitted to ICU [15]. The eGFR value at the time of admission was prognostic for mortality in patients with COVID-19, and this parameter should be considered when designing treatment algorithms [16]. Liu et al. [17] reported that baseline high BUN and creatinine levels were associated with COVID-19 disease severity, and these patients should be monitored more carefully for early intervention on admission. We also found that serum BUN and creatinine levels of our patients who

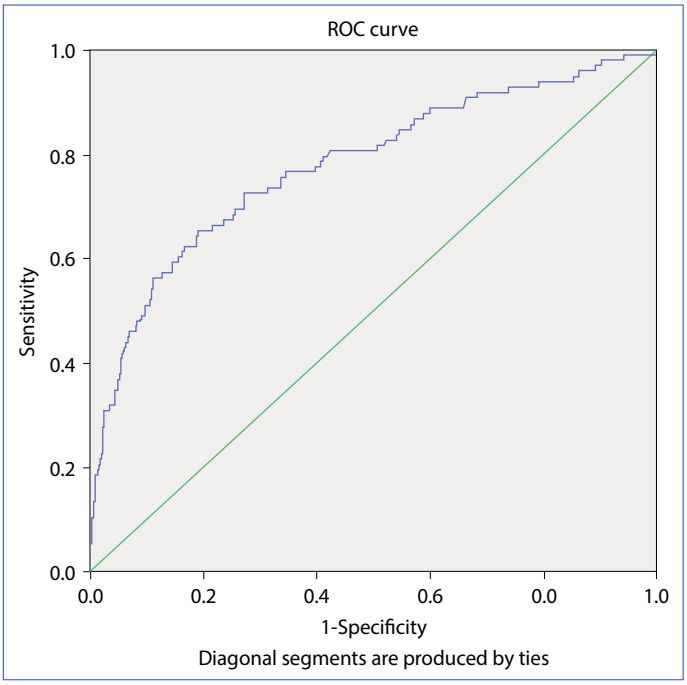

Figure 1. ROC curve of eGFR on admission to predict ICU.

ROC: Receiver operating characteristic curve; eGFR: Estimated glomerular filtration rate; ICU: Intensive care unit.

required ICU were higher than those who had a milder or moderate disease. It is important to identify patients who may become critical over time, to follow a more intense treatment protocol.

Since the beginning of the pandemic, older adults have consistently been reported to be at higher risk and vulnerable to the negative consequences of COVID-19 [18]. Typically, eGFR declines with age, even in people without kidney disease. Accordingly, the median age of the patient group with an eGFR <60 mL/min/1.73 m^2 was higher than the other COVID-19 patients.

Potentially useful blood biomarkers that support clinical decisions in patients with COVID-19 have been studied in hospitalized patients [19-21]. These include neutrophils, lymphocytes, CRP, LDH, d-dimer, ferritin, fibrinogen, and platelet, liver, and cardiac injury markers [20-24]. In this study, all COVID-19 severity markers were significantly different in those with an eGFR <60 mL/min/1.73 m^2 [19-24].

In this study, we demonstrated that patients with low eGFR had low lymphocyte counts on admission. Lymphopenia is the main characteristic of COVID-19 infections, which affects $CD4^+$T cells, $CD8^+$T cells, and B cells, and is more pronounced in critically ill patients [25, 26]. Previously, Winterberg et al. [27] showed that the number of naive circulating $CD4^+$T and $CD8^+$T cells is linked with serum urea and creatinine levels. This effect on urea and creatinine is important as $CD8^+$T cells appear to regulate the antibody response to a COVID-19 infection. Patients with chronic kidney disease are in an immunosuppressive state. Therefore, the capacity of antigen-presenting cells is defective, naive $CD4^+$T and $CD8^+$T lymphocytes are depleted, and cell-mediated immunity is impaired [28-31].

Serum sodium and chloride levels at admission were lower in patients whose disease became more severe and who were admitted to the ICU. Lippi's meta-analysis reported that patients who progressed to the severe form of COVID-19 were associated with lower concentrations of sodium, potassium, and calcium at admission and recommended that electrolytes be measured at admission [32]. However, in the meta-analysis by Nasiri et al. [33], sodium and potassium levels were within normal limits in patients with COVID-19. This is because different countries may have wide differences in age and comorbidities, and there may also be differences depending on the economic and social status of their citizens.

Limitations of the study

This study has a few limitations. It was a single-center retrospective study, with a limited number of patients. Other biomarkers of the functions of kidney, such as urine protein levels and hematuria, were not investigated due to data unavailability. We evaluated triage factors, but treatment methods were not included. Under emergency COVID-19 triage conditions, medical history may not be adequately collected. Unfortunately, we did not have the medical history, body mass index, and previous medications of the patients. Follow-up clinical and laboratory data to classify patients as lower or higher risk were beyond the scope of this study. Using a single eGFR might lead to a bias creatinine fluctuation due to measurement uncertainties. Our study was conducted in a leading training hospital; therefore, we would have recruited more serious patients. Finally, the generalizability of our results to other countries may be limited because countries have adopted different treatment guidelines according to local regulations and the availability of health resources.

Conclusion

The eGFR at admission is strongly correlated with the severity of the disease. Therefore, measuring eGFR in all patients at admission may warrant appropriate triage, pointing to a higher risk of kidney abnormalities, which may become more serious. We recommend that eGFR be measured at the time of application and used as an additional tool for risk classification.

Results in this study require validation with prospective studies and randomized controlled studies in cohorts from large geographic regions. These data may assist physicians in classifying patients who have higher and lower risks at triage assessment.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by the Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (No: 2011-KAEK-25-2020/11-04, Date: 25/11/2020).

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