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COVID-19 Infection in Kidney Transplant Recipients: A Single Center Experience

Tulin Akagun[a*], Ozdem Kavraz Tomar[a], Murat Usta[b], and Suleyman Baylan[c]

[a]Division of Nephrology, Department of Internal Medicine, Giresun Faculty of Medicine, Giresun University, Giresun, Turkey; [b]Department of Biochemistry, Department of Internal Medicine, Giresun Faculty of Medicine, Giresun University, Giresun, Turkey; and [c]Department of Internal Medicine, Giresun Faculty of Medicine, Giresun University, Giresun, Turkey

ABSTRACT

Background. Kidney transplant recipients appear to be particularly high risk for critical COVID-19 illness owing to chronic immunosuppression and coexisting conditions. The aim of this study is to present the clinical characteristics and outcomes of our hospital's kidney transplant recipients who were hospitalized due to COVID-19 infection.

Methods. In our retrospective observational study of COVID-19 PCR-positive patients, 31 of them were hospitalized with COVID-19 pneumonia and they were evaluated using demographics, laboratory data, treatment, and outcome. The prognostic nutritional index (PNI), which is calculated using the serum albumin concentration and total lymphocytic count, was also evaluated. The baseline immunosuppressive therapy of patients at the time of admission and the treatments they received during their hospitalization were recorded. All patients were treated with favipiravir.

Results. Of the 31 renal transplant patients with COVID-19 pneumonia, 20 were male and the mean age was 52.7 ± 13.4. Nine (29%) of the patients died. All patients were treated with favipiravir for 5 days; laboratory tests were recorded before and after treatment. The mean PNI of the patients who survived was higher than the patients who died.

Conclusions. The 9 patients who died had lower PNI and higher neutrophil-to-lymphocyte ratio (NLR), creatinine, l-lactate dehydrogenase (LDH), ferritin, and C-reactive protein (CRP) levels. Hospitalized kidney transplant recipients with COVID-19 have higher rates of mortality. The PNI exhibited good predictive performance and may be a useful clinical marker that can be used for estimating survival in COVID-19 patients.

COVID-19 is caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV2) [1]. Kidney transplant recipients appear to be particularly high risk for critical COVID-19 illness due to chronic immunosuppression and coexisting conditions [2]. The clinical presentation of COVID-19 in kidney transplant recipients may be different from the general population with a higher rate of severe disease complications including renal failure and mortality [1]. The aim of this study is to present the clinical characteristics and outcomes in our hospital's kidney transplant recipients who were hospitalized due to COVID-19 infection.

MATERIALS AND METHODS

Patients

In our retrospective observational study of COVID-19 PCR-positive patients, 31 were hospitalized with COVID-19 pneumonia (between March and September 2020) and they were evaluated using demographics, laboratory data, treatment, and outcome. The prognostic nutritional index (PNI), which is calculated using the serum albumin concentration and total lymphocytic count, was also evaluated. The

*Address correspondence to Tulin Akagun, Giresun University Faculty of Medicine, Giresun, Turkey. Tel: (+090) 454 310 20 20; Fax: (+090) 454 215 51 46. E-mail: tulinozbay@yahoo.com

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baseline immunosuppressive therapy of patients at the time of admission and the treatments they received during their hospitalization were recorded.

Statistical Analysis

We performed statistical analyses with MedCalc (MedCalc Software Ltd, Ostend, Belgium). After investigating the conformity of continuous variables to normal distribution with the Shapiro-Wilk test, variables with Gaussian distribution were shown as mean ± SD while variables with non-Gaussian distribution were shown as median (25th percentile −75th percentile). Paired-samples *t* test or Wilcoxon signed-rank tests were used to compare dependent group means/medians. The Mann-Whitney *U* test was used for independent group comparisons. Pearson's χ^2 test or Yates' correction was used to compare group frequencies. The diagnostic tools of the clinical and laboratory parameters were evaluated by receiver operating characteristics (ROC) analysis. Sensitivity, specificity, positive predictive values, negative predictive values, and Youden's index (J) were determined with contingency tables for the associated criterions. Statistical significance was evaluated at the $P < .05$ (two-tailed) level.

RESULTS

Demographic and Clinical Features

Of the 31 renal transplant patients with COVID-19 pneumonia, 20 were male and the mean age was 52.7 ± 13.4. A total of 9/31 (29%) patients dead. The patients who survived were younger. Administration of an anti-metabolite drug (mycophenolate mofetil or mycophenolate sodium) was discontinued in all patients. Calcineurin inhibitors (cyclosporine or tacrolimus) were discontinued in 7 patients whose clinical condition deteriorated. Favipiravir, the recommended drug by the Republic of Turkey Ministry of Health, was uniformly administered to all patients. Favipiravir treatment was initiated with 2 loading doses of 1600 mg each on day 1, followed by 600 mg twice daily for 5 to 10 days. Steroids were either continued at the maintenance dose or converted to intravenous dexamethasone/methylprednisolone depending on the disease severity. Intravenous steroid treatment was administered to 16 patients. Tocilizumab and convalescent plasma were also administered to patients who experienced the disease progressing in them despite favipiravir treatment. Low-molecular-weight heparin was administered to all patients. Laboratory tests were recorded before and after the administration of the treatment. Baseline immunosuppression and treatments given for COVID-19 patients are shown in Table 1.

Laboratory Data

The clinical and laboratory parameters of patients at the time of hospital admission are shown in Table 2. The mean PNI of the patients who survived was higher than patients who died. In the group of patients who died, the following were reported: the length of their hospital stay was longer ($P = .033$); NLR ($P = .078$), creatinine ($\boldsymbol{P = .033}$), and C-reactive protein (CRP) ($P = .105$) were higher; and hemoglobin ($\boldsymbol{P < .001}$) and albumin ($\boldsymbol{P = .047}$) were lower. The clinical parameters of patients after treatment are shown in Table 3. The mean PNI of the patients who survived was higher than patients who died. Lymphocyte and hemoglobin counts were lower in patients who died. NLR, CRP, creatinine, LDH, and ferritin results were higher in patients who died.

Table 1. Treatments of the Patients (N = 31)

	Discharged (n = 22)	Dead (n = 9)
Baseline immunosuppression		
CSA+MMF/MYF+CS	14	5
FK+MMF/MYF+CS	8	4
Withdrawal of antimetabolite	22	9
Withdrawal of CSA/FK	0	7
Favipiravir	22	9
Tocilizumab	2	0
Glucocorticoids	14	2
Convalescent plasma	1	1

CSA, cyclosporin; FK, tacrolimus; MMF, mycofenolat mofetil; MYF, mycofenolat sodium; CS, corticosteroid.

The diagnostic evaluations of PNI and hemoglobin before and after treatment are shown in Table 4. The ROC analysis of PNI (A) and hemoglobin (B) are shown in Fig. 1. The determined area under curves (AUCs) of PNI and hemoglobin were higher before and after treatment. The optimal decision thresholds for sensitivity and specificity were lower after treatment for PNI and hemoglobin (≤35.6 and ≤11.9 g/dL, respectively).

DISCUSSION

Mortality was 32% to 36% among patients in COVID-19 positive renal transplant patients [3,4]. Mortality was 29% (9 of the 31patients) in our patient group. Similar to our study's results, Akalın et al reported 28% mortality in kidney transplant patients

Table 2. Clinical and Laboratory Findings of Patients at the Time of Hospital Admission

	Discharged (n = 22)	Dead (n = 9)	*P*
Age	48.2 ± 12.9	57.2 ± 14.0	0.096
Sex (Male/Female)	16/6	4/5	0.140
PNI	46.1 (41.1-47.9)	37.2 (34.8-44.3)	0.065
Creatinine, mg/dL	1.51 (1.06-2.11)	2.55 (1.77-4.45)	0.033
eGFR, mL/dk	44.0 (27.7-80.2)	21.9 (15.1-34.2)	0.019
Urea, mg/dL	67.0 (49.8-89.0)	119.0 (85.0-190.0)	0.014
Albumin, g/dL	39.9 ± 5.3	35.6 ± 4.2	0.047
WBC, x10^9/L	6.57 ± 4.02	7.22 ± 5.06	0.593
Neutrophil, x10^9/L	3.73 (2.78-6.77)	5.02 (3.19-12.87)	0.403
Lymphocyte, x10^9/L	0.93 (0.65-1.34)	0.54 (0.25-1.15)	0.174
NLR	4.68 (1.85-8.31)	9.30 (4.43-49.67)	0.078
RBC, x10^12/L	4.72 ± 0.84	3.80 ± 0.67	0.003
Hemoglobin, g/dL	13.9 ± 1.87	11.2 ± 1.14	< .001
PLT, x10^9/L	195.2 ± 71.4	136.6 ± 38.5	0.033
LDH, U/L	241.3 ± 63.8	359.6 ± 217.3	0.320
Ferritin, ng/mL	336 (184-1079)	997 (285-2000)	0.166
CRP, mg/L	25.7 (6.6-84.7)	55.0 (36.5-108.0)	0.105

CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LDH, l-lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; PNI, prognostic nutritional index; RBC, red blood cells; WBC, white blood cells.

Table 3. Laboratory Findings of Patients after Treatment

	Discharged (n = 22)	Dead (n = 9)	*P*
PNI	42.5 (35.3-48.9)	27.8 (23.3-33.2)	<0.001
Creatinine, mg/dL	1.15 (1.00-1.64)	3.27 (1.88-4.89)	0.006
eGFR, mL/dk	71.0 (44.1-88.2)	16.4 (11.7-40.4)	0.002
Urea, mg/dL	64.0 (49.8-95.5)	204.0 (109.5-223.5)	0.020
Albumin, mg/dL	35.8 ± 6.2	25.7 ± 4.5	<0.0001
WBC, x10^9/L	6.98 ± 2.59	13.22 ± 9.54	0.026
Neutrophil, x10^9/L	4.89 (3.40-6.01)	11.03 (5.47-19.55)	0.012
Lymphocyte, x10^9/L	1.11 (0.77-2.09)	0.44 (0.21-0.80)	<0.001
NLR	4.40 (2.43-6.15)	26.54 (10.31-49.99)	<0.0001
RBC, x10^12/L	4.64 ± 0.76	3.56 ± 0.54	<0.001
Hemoglobin, g/dL	13.2 ± 2.04	10.0 ± 1.47	<0.0001
LDH, U/L	262.2 ± 73	550.4 ± 244.7	<0.001
Ferritin, ng/mL	340 (184-987)	2000 (963-2000)	0.005
CRP, mg/L	10.4 (5.2-19.8)	114.0 (65.0-252.5)	<0.0001
Length of stay (day)	8 (4-12)	16 (9-23)	0.033

CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LDH, l-lactate dehydrogenase; PNI, prognostic nutritional index; WBC, white blood cells; NLR, neutrophil-to-lymphocyte ratio; RBC, red blood cells.

[5]. The clinical outcomes for the transplant patients were poor, with 25% mortality mainly due to complications from pneumonia [6]. The mortality rate of the previous study from Turkey was 11.1% [7]. This difference might be attributable to the heterogeneity of the included patients and the differences in medical treatment level and medical resources. Although it did not reach statistical significance in our study, exitus patients were older.

The PNI, which is calculated from the serum albumin concentration and total lymphocyte count in peripheral blood, is an index that reflects chronic inflammation, immune system, and nutritional status and indicates prognostic significance in different patients [8]. PNI has been described as a simple and objective indicator of adverse outcomes not only for chronic conditions but also for acute illnesses, including acute coronary syndrome, acute heart failure, and stroke [9]. In our study, the mean PNI of the patients who survived was higher than patients who died (PNI = 10xserum albumin (g/dL)+0.005xtotal lymphocyte count). A low PNI was significantly associated with postoperative complications and survival in patients undergoing cardiovascular surgery [10]. Similarly, in another study PNI values ≤ 34 were associated with a two-fold higher risk of overall mortality and three-fold higher risk of in-hospital mortality in elderly patients hospitalized for acute heart failure [11]. In our study, we found the mean PNI value of 27.8 in the patient group who died. In another study with a larger number of COVID-19 patients (n = 450), mortality was reported to be 17.3% (78 of 450 patients). Comparison of baseline characteristics showed non-survivors had a higher age ($P < .001$) and lower PNI ($P < .001$) [12]. Although it did not reach statistical significance in our study, PNI values were found to be lower in the non-survivor group at the time of hospital admission. This may be due to a smaller number of our patient group.

NLR is a common and quick index of inflammation detection in laboratory examination. It is used in the diagnosis, treatment, and prognosis evaluation of pneumonia [13]. In addition, NLR constitutes a novel prognostic marker for oncologic,

Table 4. Diagnostic Evaluation of PNI and Hemoglobin Before and After Treatment

		AUC(95% CI)	*P* value for AUC	Decision threshold	Youden's index (J)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PNI	Before treatment	0.750 (0.528-0.905)	= 0.0544	≤ 37.6	0.59	71.4	87.5	71.4	87.5
	After treatment	0.929 (0.741-0.994)	< .0001	≤ 35.6	0.75	100	75.0	60.0	100
Hemoglobin	Before treatment	0.857 (0.681-0.957)	< .0001	≤ 12.9 g/dL	0.71	100	71.4	63.6	100
	After treatment	0.892 (0.724-0.975)	< .0001	≤ 11.9 g/dL	0.81	100	81.0	69.2	100

Area under curve (AUC) values were determined by receiver operating characteristics (ROC) analysis. Youden's index (J) formula = Sensitivity - (1 - Specificity).
AUC, area under curve; CI, confidence interval; PNI, prognostic nutritional index; PPV, positive predictive value; NNV, negative predictive value.

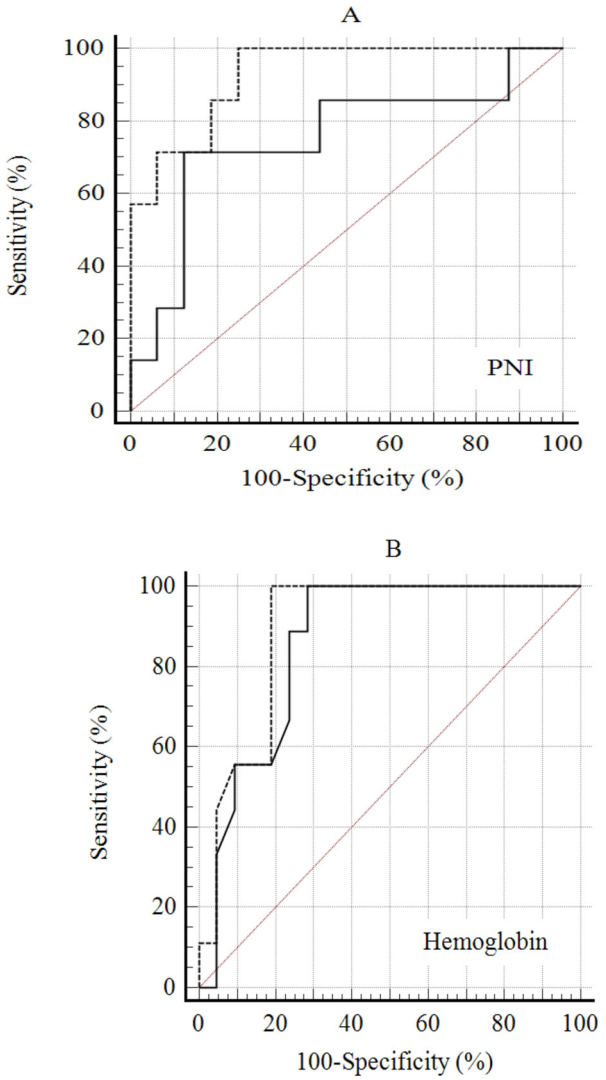

Fig 1. (A) The receiver operating characteristics (ROC) analysis of prognostic nutritional index (PNI) and (B) of hemoglobin. The solid lines indicate before treatment and the dashed lines indicate after treatment.

cardiovascular, and infectious diseases. Based on this, studies were conducted to investigate the prognostic value of NLR in COVID-19 infection [14−16]. In a study by Busbus et al, NLR = 3 presented a significant association with mortality [14]. In another study, the critical value of initial NLR and peak NLR (7.28 and 27.55, respectively) in prognosticate of intubation was the prognostic factor for COVID-19 patients' death [15]. Although it was higher in the exitus group baseline NLR values did not reach statistical significance in our study. The NLR value was found to be statistically significantly higher in the exitus patient group after the treatment (NLR 4.40 vs 26.54, $P < .0001$). In another study, elevated age and NLR were found to be independent biomarkers for indicating poor clinical outcomes [16]. In the Liu et al study, it was predicted that critical illness could develop in patients aged ≥ 50 years with an NLR ≥ 3.13 [17]. Similar to our results, Peçanha-Pietrobom et al found that patients with deteriorating clinical courses presented elevated and similar NLRs during first week of hospitalization. However, they were dramatically different at hospital discharge, with a decrease in survivors (NLR was around 5.5) and sustained elevation in non-survivors (NLR was around 21) [18].

We found that non-survivors had higher levels of white blood cells (WBC), neutrophil, LDH, urea, serum creatinine, CRP, and ferritin. Whereas the levels of lymphocyte, albumin, and hemoglobin were significantly lower in non-survivors. Similar to our results, Wang et al reported similar biochemical test results in patients with COVID-19 pneumonia [12]. In another study, lower lymphocytes and estimated Glomerular Filtration Rate (eGFR) were reported whereas higher CRP results were found in non-survivor kidney transplant patients [19]. In addition, in a study in which the data of 10 kidney transplant patients were presented, the ferritin values of the patients were found to be between 101-2871 ng/mL. Ferritin levels were found to be higher in 3 patients who died [20]. In our study, ferritin levels were found to be significantly higher in the non-survivor patient group.

There are studies conducted with the treatment of COVID-19 in kidney transplant recipients [21−23]. Cismaru et al reported the overall mortality rate of 33.3% in kidney transplant patients receiving favipiravir treatment [23]. Similarly, the mortality rate in our patient group was 29%. The efficacy of favipiravir treatment is still unclear [22,23]. The small sample size and retrospective nature are the major limitations of this study.

In conclusion, the 9 patients who died had lower PNI and higher NLR, creatinine, LDH, ferritin, and CRP levels. Hospitalized kidney transplant recipients with COVID-19 have higher rates of mortality. The PNI exhibited good predictive performance and may be a useful clinical marker that can be used for estimating survival in COVID-19 patients. Further studies are required to confirm these findings and evaluate the efficacy of PNI for predicting prognosis.

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