Turk J Intensive Care 2022;20(Suppl 1):71-80
DOI: 10.4274/tybd.galenos.2022.05025

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Can the Development of AKI be Predicted in COVID-19 Patients with Severe Pneumonia?

Ağır Pnömonili COVİD-19 Hastalarında ABH Gelişimi Tahmin Edilebilir mi?

Received/Geliş Tarihi : 27.01.2022
Accepted/Kabul Tarihi : 20.04.2022

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ABSTRACT *Objective:* Coronavirus disease-2019 (COVID-19) may cause severe respiratory disease, glomerular dysfunction and acute tubular necrosis. Lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, lymphopenia and increased neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) associated with poor prognosis. We investigated the effects of these mediators on the development of acute kidney injury (AKI).
Materials and Methods: Patients with severe pneumonia with the diagnosis COVID-19 were included in the retrospective study. Three subgroups were created: Group 1: patients who developed AKI at admission or at follow-up to the intensive care unit (ICU), group 2: those without AKI, group 3: Patients who developed AKI on the basis of chronic kidney disease. Demographic data, comorbidities, lactate, D-dimer, CRP, LDH, NLR, PLR, mortality were recorded and compared.
Results: Two hundred fifty six patients were evaluated. Group 2 D-dimer levels before ICU were significantly lower than those in group 3. Group 2 last day D-dimer levels were significantly lower than those of group 3 and group 1. Admission LDH values were higher in the group 1 than in groups 2 and 3. Last day LDH values were higher in the group 1 than in group 2. NLR values were higher in group 3 than in group 2 on the 6th day. Last day PLR values were lower in the group 1 than in group 2. No significant difference was present between the groups in terms of D-dimer, LDH, NLR, PLR levels at the other time points.
Conclusion: The contribution of laboratory findings in determining the risk of AKI has not been clarified.
Keywords: COVID-19, severe pneumonia, acute kidney injury

ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVİD-19) ciddi solunum yolu hastalığı, glomerüler disfonksiyon ve akut tübüler nekroza neden olabilir. Laktat dehidrogenaz (LDH), C-reaktif protein (CRP), D-dimer, lenfopeni ve artmış nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranının (PLO) kötü prognoz ile ilişkili olduğu bilinmektedir. Bu çalışmada bu mediyatörlerin akut böbrek hasarı (ABH) gelişimi üzerindeki etkilerini araştırmayı amaçladık.
Gereç ve Yöntem: Bu retrospektif çalışmaya COVİD-19 tanısı almış, şiddetli pnömoni gelişen hastalar dahil edildi. Üç alt grup oluşturuldu: Grup 1- yoğun bakım ünitesine (YBÜ) yatışta veya takipte ABH gelişen hastalar, grup 2- ABH olmayanlar, grup 3- kronik böbrek yetmezliği zemininde ABH gelişen hastalar. Demografik veriler, komorbiditeler, laktat, LDH, CRP, D-dimer, NLO, PLO değerleri ve mortalite kaydedildi ve karşılaştırıldı.
Bulgular: İki yüz elli altı hasta değerlendirildi. YBÜ öncesi grup 2'de D-dimer seviyeleri grup 3'ten anlamlı derecede düşüktü. Grup 2'de son gün D-dimer seviyeleri grup 3 ve grup 1'den anlamlı derecede düşüktü. Giriş LDH değerleri grup 1'de grup 2 ve grup 3'e göre daha yüksekti. Son gün LDH değerleri grup 1'de grup 2'ye göre daha yüksekti. Altıncı günde NLR değerleri grup 3'te grup 2'ye göre daha yüksekti. Grup 1'de son gün PLR değerleri grup 2'ye göre daha düşüktü. Diğer zamanlarda D-dimer, LDH, NLO ve PLO seviyeleri açısından gruplar arasında anlamlı bir fark yoktu.
Sonuç: ABH riskini belirlemede laboratuvar bulgularının katkısı açıklığa kavuşturulmamıştır.
Anahtar Kelimeler: COVİD-19, ağır pnömoni, akut böbrek hasarı

Introduction

Coronavirus disease-2019 (COVID-19) is a condition that is caused by the virus termed as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) from Coronaviridae family and that courses with respiratory tract disease and respiratory failure. A critical disease that requires intensive care unit (ICU) monitoring in approximately 5% of the patients emerges accompanied with severe respiratory failure and organ failures including primarily kidney failure. The prevalence rate of acute kidney injury (AKI) was reported to be 4.5-46% in the hospitalized patients with diagnosis of COVID-19 however that rate may rise up between 36.4-76% in the critically ill patients (1,2).

In the autopsy examinations performed in the individuals infected with SARS-CoV-2 virus, the inclusion bodies caused by the virus have been shown also in the glomerular podocytes and proximal tubules including ACE-2 receptors. Nevertheless, non-detection of an immune deposit formation or an evidence of haemorrhage in the renal interstitial field that will cause vasculitis and inflammation suggests that SARS-CoV-2 virus causes AKI and proteinuria by directly entering the glomerular and proximal tubular epithelia by the means of ACE-2 receptor (3).

AKI due to SARS-CoV-2 develops by the entry of the virus into the cell using the ACE-2 and CD147 receptors located on the renal proximal tubules and the ACE-2 receptors located on the glomerular podocytes. It induces glomerular damage such as focal segmental glomerulosclerosis or proximal tubular damage leading to acute tubular necrosis. It impairs renin angiotensin aldosterone system by binding to ACE-2 receptor. It causes the accumulation of angiotensin II by inhibiting the conversion of angiotensin II to angiotensin 1-7. The increased angiotensin II leads to inflammation, vasoconstriction, fibrosis and glomerular dysfunction. At the same time, it induces ischemia and necrosis via formation of fibrin deposits in the glomeruli by activating coagulation. The obstruction of the capillary lumen and diffuse proximal tubule injury occurs due to erythrocyte aggregation mostly without platelets or fibrinoid substances in the virus-infected kidneys. Also increasing cytokine (particularly IL-6) response depending on severe SARS-CoV-2 infection facilitates the glomerular and proximal tubule damage. In addition to all these factors, volume deficit, nephrotoxic treatments, mechanical ventilation and secondary infections also promote the development of AKI in the critically ill patients (4,5).

In the COVID-19 patients, increased neutrophil and decreased lymphocyte counts are associated with more severe disease course, ICU admission and mortality (6-8). Peak platelet value and platelet/lymphocyte ratio (PLR) are the independent risk factors for poor prognosis and prolonged hospital stay, respectively. Furthermore, peak platelet value has been associated with cytokine storm (9). Increased leukocyte count together with decreased platelet and lymphocyte counts are accompanied with myocardial damage and high troponin-T level in the COVID-19 patients (10). Increased lactate dehydrogenase (LDH), C-reactive protein (CRP) and ferritin counts are associated with higher risk for Acute respiratory distress syndrome (ARDS) development and poor prognosis in the COVID-19 patients. Also high D-dimer level is associated with poor prognosis, mortality, increased rate of ARDS development and myocardial damage (10,11).

In the light of all these evidence, we aimed in our study to investigate which inflammatory mediators that increase due to ACE-2 receptor involvement developing after infection with SARS-CoV-2 and subsequently occurring thrombosis tendency and cytokine storm have a higher impact on development of AKI and intensive care monitoring process.

Materials and Methods

Following obtaining the approval for the research from the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (decision no: 199, date: 16.06.2020), 350 patients diagnosed with confirmed COVID-19 who developed severe pneumonia and admitted to the tertiary stage ICU of University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital between the dates 18.03.2020-01.06.2020 were retrospectively examined. All the adult patients diagnosed with confirmed COVID-19 who had severe pneumonia and aged over 18 years were included in the study. The diagnosis of COVID-19 was made with clinical findings and ground glass opacities in thorax computed tomography. In addition, polimerase chain reaction (PCR) of SARS-CoV-2 was performed from all patients. The patients without diagnosis of COVID-19 were excluded from the study. The patients who met the inclusion criteria were included in the study.

The definition of severe respiratory tract infection (pneumonia): The presence of the followings in the patient with fever and signs of respiratory tract infection;

- Breathing rate >30/min and/or,
- Severe respiratory distress (dyspnea, use of extra respiratory muscles) and/or,
- Oxygen saturation in room air <90% (PaO_2/FiO_2<300 in the patient receiving oxygen support) (12).

The Definition AKI (13)

- An increase of 0.3 mg/dL or higher in serum creatinine level or,
- A 1.5 fold or higher elevation in the serum creatinine level compared with basal values known or estimated to occur in the last 7 days or,
- Urine output below 0.5 mL/kg/hour in the last 6 hours,

The patients were divided into 3 subgroups as the patients with developed AKI at baseline (group 1), those without AKI (group 2) and those with AKI on the ground of chronic kidney disease (CKD) (group 3). At the time of initial admission to the ICU; demographic data, comorbid diseases, time from disease onset to ICU admission, admission and discharge Sequential Organ Failure Assessment (SOFA) scores, diuresis amount in the first 6 and 24 hours of the patients as well as lactate, D-dimer, CRP, ferritin, fibrinogen, LDH, neutrophil/lymphocyte ratio (NLR) and PLR values of the patients who developed AKI in the ICU at the day of AKI development and during ICU monitoring were recorded from the patient files. The stage of AKI was assessed in the patients (Table 1) and the facts whether AKI stage increased in the intensive care monitoring process, whether increased AKI stage was associated with laboratory values (ferritin, fibrinogen, D-dimer, NLR, PLR) if it increased and how it was treated (by continuous renal replacement therapy) and whether concurrent multiorgan failure developed, and mortality analysis were recorded from the patient files compared. Differential diagnosis analysis was carried out for total mortality, mortality associated with AKI and non-AKI mortality causes. Invasive (IMV) and non-invasive mechanical ventilation treatments received by the patients, length of stay in the ICU and mechanical ventilation, discharge status (mortality or discharge to the ward) were recorded from the patient files and compared. In addition, the fact whether there was a difference between the patients who had CKD at entrance to the ICU and developed additional AKI in terms of acute phase reactants, oxidative stress and mortality.

Statistical Analysis

The statistical analysis was performed using SPSS 23.0 for Windows. The normality analysis of the continuous variables was carried out by Kolmogorov-Smirnov test accompanying skewness and kurtosis normality tests from the descriptive statistics. All the tests were conducted nonparametrically since the data were not normally distributed in at least one group regarding all study data. The descriptive statistics were expressed as numbers and percentages for categorical variables and given as median (minimum-maximum) for quantitative variables. The difference analysis of the quantitative variables was performed using Mann-Whitney U test in the independent two groups. The rates were compared with chi-square analysis in the independent groups. The statistical alpha significance level was accepted as $p<0.05$.

Results

The study included 256 patients constituted by 142 (55.5%) male and 114 (44.5%) female patients. The female patients had a similar mean age with male patients (p=0.135). AKI group (group 1), non-AKI group (group 2) and the group that developed AKI on the ground of CKD (group 3) included 169, 62 and 25 patients, respectively.

AKI developed in totally 72 patients after entrance to the ICU. AKI emerged due to use of nephrotoxic drugs in 5 of those patients. Aminoglycozide (AG) and colistin were administered alone in 2 and 1 patients, respectively, whereas AG and colistin were administered in combination in 2 patients.

Group 3 had a higher mean age than group 2 and group 1 (p<0.001) and (p=0.022), respectively. Mean age of group 1 was higher than group 2 (p=0.018).

The frequencies of coronary artery disease (CAD), hypertension (HT) and chronic obstructive pulmonary

Table 1. The stages of acute kidney injury (13)

Stage	Serum creatinine level	Urine amount
1	An increase of 1.5-1.9 fold basal value or >0.3 mg/dL	<0.5 mL/kg/hour for 6 hours
2	An increase of 2-2.9 fold basal value	<0.5 mL/kg/hour for 12 hours
3	An increase of 3-fold basal value or >0.4 mg/dL or >0.4 mg/dL or initiation of renal replacement therapy	<0.3 mL/kg/hour for longer than 24 hours or anuria for 12 hours and longer

Table 2. Demographic variables of the groups							
		Group			p		
		Group 1	Group 2	Group 3	Group 2 vs. Group 3	Group 2 vs. Group 1	Group 3 vs. Group 1
		n (%) / mean ± SD					
Sex	Female	75 (44.4%)	30 (48.4%)	9 (36%)	0.293	0.588	0.43
	Male	94 (55.6%)	32 (51.6%)	16 (64%)			
Age (year)		66.5±15.9	66.5±15.9	74.5±11.4	<0.001	0.018	0.02
Co-morbidities							
DM		42 (47.7%)	15 (44.1%)	11 (73.3%)	0.059	0.72	0.067
COPD		27 (38%)	9 (31%)	8 (72.7%)	0.017	0.509	0.03
HT		54 (59.3%)	22 (59.5%)	17 (89.5%)	0.021	0.99	0.013
CAD		29 (39.2%)	6 (23.1%)	10 (71.4%)	0.003	0.138	0.026
Arrhythmia		8 (14%)	3 (12%)	2 (25%)	0.372	0.803	0.421
AF		4 (7.4%)	1 (4.3%)	2 (25%)	0.089	0.618	0.116
CVD		10 (17.9%)	6 (24%)	2 (22.2%)	0.914	0.521	0.754
Alzheimer		11 (18.3%)	3 (12%)	1 (14.3%)	0.872	0.473	0.792
Malignity		18 (56.3%)	11 (45.8%)	4 (40%)	0.755	0.44	0.369
Lung cancer		10 (15.9%)	5 (17.9%)	1 (14.3%)	0.823	0.814	0.913
CKD		-	-	25 (100%)	<0.001	.	<0.001

*Chi-square test, **Mann-Whitney U test, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, AF: atrial fibrillation, CVD: cerebrovascular disease, CKD: chronic kidney disease, SD: standard deviation

disease (COPD) were higher in group 3 compared with group 1 (0.026, 0.013 and 0.030, respectively) and group 2 (0.003, 0.021 and 0.017, respectively) (Table 2).

Among AKI patients; the prevalence of AKI patients at entrance to the ICU was higher in group 3 whereas a higher rate of AKI developed in group 1 during ICU monitoring (p=0.014). No significant difference was present between the groups in terms of AKI stage.

The rate of exitus was significantly higher in group 3 and group 1 than group 2 (p=0.019, p=0.012, respectively). The patients of group 3 and group 2 needed ICU admission more lately than group 1 (p=0.011) and (p=0.022), respectively. SOFA values of group 2 at entrance to the ICU were significantly lower than group 3 (p=0.022). No significant difference was present between the groups in terms of entrance and discharge SOFA scores. Lactate values assessed before and on the first day of ICU admission were higher in group 1 than group 2 (p=0.019, p=0.005, respectively). No significant difference was found between the groups in terms of lactate values (Table 3).

PCR positivity was 50% in all patients. PCR positivity was higher in group 2 than group 1 (p=0.014).

Compared with group 2, group 3 and group 1 patients had a significantly higher frequency of oliguria within the first 6 hours of ICU admission (p<0.001, p<0.001, respectively).

Compared with group 2, group 3 and group 1 patients had a significantly higher frequency of oliguria within the first 24 hours of ICU admission (p<0.001, p<0.001, respectively).

Pre-ICU D-dimer levels of group 2 were significantly lower than group 3 (p=0.035). Group 2 showed significantly lower D-dimer levels on the last ICU day compared with group 3 and group 1 (p=0.025, p=0.002, respectively). No significant difference was present between the groups in terms of D-dimer levels on the other time points (Table 4).

LDH values of group 1 patients at entrance to the ICU were significantly higher than group 2 and group 3 patients (p=0.042, p=0.042). LDH values of group 1 patients on the last ICU day were higher than group 2 (p=0.001), (Table 4). No significant difference was present between the groups in terms of ferritin and CRP values.

NLR values of group 3 on the 6th ICU day were higher than group 2 (p=0.017) whereas no difference was found between the groups in terms of NLR values on the other time points (Table 4).

PLR values of group 1 on the last ICU day were lower than group 2 (p=0.017) whereas no difference was found between the groups in terms of PLR values on the other time points (Table 4).

Table 3. Lactate, SOFA, mortality of the groups						
	Group			p		
	Group 1	Group 2	Goup 3	Group 2 vs. Group 3	Group 2 vs. Group 1	Group 3 vs. Group 1
	n (%) / mean ± SD					
Lactate						
Onset	2.6±2.01	1.81±0.72	24.1±65.25	0.561	0.019	0.439
1st day	7.52±42.12	1.98±1.09	10.24±27.66	0.139	0.005	0.94
2nd day	3.5±9.54	1.77±0.34	40.81±85.45	0.151	0.497	0.254
Last day	6.62±17.6	5.97±18.34	17.79±53.16	0.746	0.073	0.246
SOFA						
First day	5.1±3	4.6±2.9	6.1±2.5	0.022	0.28	0.092
Last day	10	3	11	0.317	0.317	0.317
Mortality n (%)						
Exitus	126 (74.6%)	35 (57.4%)	21 (84%)	0.019	0.012	0.304
Alive	43 (25.4%)	26 (42.6%)	4 (16%)			
SOFA: Sequential Organ Failure Assesment, SD: standard deviation						

The administration of high-flow oxygen therapy was significantly higher in group 2 than group 3 patients (p=0.022) whereas no significant difference was determined between the patients in terms of administration of non-invasive ventilation (NIV) and IMV (Table 5).

A higher rate of patients from group 2 were discharged to the ward compared with group 1 (p=0.013) and group 3 (p=0.040) (35%, 19% and 12.5%, respectively) (Table 5).

Discussion

ARDS and mechanical ventilation are important risk factors with respect to development of AKI in the critically ill patients (14). Impaired gas exchange and hypoxia in ARDS causes development of AKI. Beside this, administration of nephrotoxic drugs and volume overload during ICU monitoring may facilitate the development AKI by both worsening ARDS and by also decreasing renal blood flow via increasing intra-abdominal pressure while mechanical ventilation may promote occurrence of AKI by altering renal blood flow (5,15). In addition, age, presence of CKD, diabetes mellitus (DM), HT, leukocytosis and lymphopenia have been accepted as risk factors with respect to development of AKI in COVID-19 patients (16). At the same time, severity of pneumonia is an independent risk factor (17). More elderly patients and higher comorbidity of HT, COPD and CAD in group 3 compared with other two groups in our study were consistent with these evidence, however, comorbidity rate of the patients who developed AKI without CKD on the ground was not higher than non-AKI patients. Although HT, DM and COPD are higher in group 3, the mortality rate is not different from group 1, suggesting that AKI alone significantly increases mortality in COVID-19 patients.

While SOFA score can be more effective than other predictors regarding prediction of mortality in AKI patients admitted in the ICU (18), it is effective as much as Acute Physiology and Chronic Health Evaluation-II and Simplified Acute Physiology score II also in the CKD patients (19). In our patients, SOFA values of AKI group was not significant compared with non-AKI patients, whereas only AKI patients on the ground of CKD had significantly higher SOFA values. However, higher mortality rates of both group 3 and group 1 compared with group 2 may suggest that SOFA indicates mortality in the AKI patients on the ground of CKD.

Even though, lactate value is not a direct indicator of tissue perfusion, any reason creating hypoxia increases lactate level and is associated with poor prognosis. It has been shown that postoperatively assessed serum lactate level particularly ≥4 mmol/L is a reliable indicator regarding development of AKI in low-risk cardiovascular surgery patients (20). Likewise, baseline lactate levels are a predictive indicator regarding development of AKI and mortality in the patients who admitted to the emergency department because of sepsis (21). In our patients, lactate values of group 1 at entrance to the emergency department and on first ICU day were higher than group 2. Mean lactate

Table 4. LDH, D-dimer, NLR, PLR variables of the groups						
	Group			p		
	Group 1	Group 2	Group 3	Group 2 vs. Group 3	Group 2 vs. Group 1	Group 3 vs. Group 1
	n (%)/mean ± SD					
LDH						
Admission	735.3±1466.7	518±329.6	500±234.4	0.733	0.721	0.581
1st day	1620.9±8000.9	625.8±463	560.9±373	0.475	0.042	0.042
2nd day	769.8±1232.9	617.9±660.7	754.1±1037.8	0.914	0.308	0.54
3rd-5th days	985.1±2042.9	487.4±206.2	541.6±321.6	0.944	0.695	0.855
7th-10th days	601.2±585.4	451.9±209.7	436.9±166.9	0.949	0.503	0.682
11th-20th days	1199.9±3823.2	544.4±471.5	587.1±447.4	0.962	0.859	0.667
21st-30th days	605.1±940.8	364.2±113	401	0.343	0.741	0.646
AKI 2	2391.1±12351.4	235	759.6±381	0.114	0.13	0.981
Last day	2651.5±5401.7	2397.1±12494.9	1017.7±1020.7	0.075	0.001	0.4
D-dimer						
Admission	4490.3±12106.5	2902.5±5765.9	5322.9±4118.9	0.035	0.428	0.079
1st day	13131.5±41409.8	8836±23364.1	5515.6±4221.3	0.313	0.103	0.717
2nd day	11148.7±30220.6	17239.7±37586.2	4564.9±4323.2	0.858	0.913	0.993
3rd-5th day	6224.2±13429.7	6766.1±11560.1	3496.5±3604.9	0.362	0.13	0.852
7th-10th day	6393.5±13260.4	4240.8±5309	2616±1689.9	0.652	0.997	0.596
11th-20th day	4095.1±4849.6	3397.1±3697.3	3143.5±3040.4	0.739	0.773	0.681
21st-30th day	5085.3±9380.7	1538.5±607.8	2550	0.121	0.521	0.529
AKI 2	8135.5±13716.8	-	5436.8±5017.8	-	-	0.669
Last day	9887.4±17983.3	5387.1±12970.7	6714.5±7216.7	0.025	0.002	0.826
NLR						
Emergency department	10.46±10.84	25.95±74.36	269.39±743.49	0.071	0.095	0.003
Admission	25.38±101.5	46.16±175.37	123.75±507.7	0.579	0.283	0.153
1st day	73.12±431.92	19.51±19.08	333.73±1006.44	0.198	0.991	0.134
2nd day	134.65±856.93	31.26±71.22	240.31±548.25	0.1	0.616	0.092
3rd-5th day	26.73±92.55	56.43±154.88	156.8±420.07	0.163	0.38	0.146
6th-7th day	36.86±103.15	56.2±236.23	253.57±614.11	0.017	0.089	0.092
7th-10th day	56.78±265.64	53.91±159.92	544±1066.68	0.151	0.139	0.211
11th-20th day	90.08±362.11	96.13±221.4	8.23	0.617	0.351	0.813
21st-30th day	77.2±331.29	46.15±25.24	170.74±458.84	0.157	0.088	0.307
AKI 2	54.92±291.21	31.01±74.2	232.26±834.16	0.218	0.823	0.086
PLR						
Emergency department	258.5±202.8	322±244.4	276.1±245.2	0.353	0.085	0.894
Admission	318.6±276.3	375.2±254.5	352.5±353.8	0.247	0.086	0.951
3rd day	7639.1±87238.4	357.7±238	446.7±285.5	0.21	0.742	0.146
5th day	6395.1±63436.5	381±245.6	441.4±363.9	0.874	0.812	0.709
7th day	356.5±292.2	312.1±216.8	391.4±237.3	0.34	0.657	0.448

Table 4. Continued

	Group				p		
	Group 1		Group 3		Group 2 vs. Group 3	Group 2 vs. Group 1	Group 3 vs. Group 1
	n (%)/mean ± SD						
10th day	301.5±246.1	269.2±204.8	464.7±278.9	0.059		0.58	0.099
20th day	273.3±218.3	198.5±86.9	249.3±62.6	0.296		0.511	0.746
30th day	256.9±201.5	199.5±120.1	182	0.617		0.484	0.651
AKI 2	368±353.7	64	340.6±328.6	0.206		0.184	0.926
Last day	224.9±234.8	287.3±220.3	289.5±289.1	0.745		0.017	0.171

AKI 2: The day when AKI devolops in the ICU. NLR: neurophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, SD: standard deviation, AKI: acute kidney injury, LDH: lactate dehydrogenase, ICU: intensive care unit

Table 5. NIV, HFNO, IMV, duration of ICU, duration of mechanical ventilation, discharge variables of the groups

		Group			p		
		Group 1	Group 2	Group 3	Group 2 vs. Group 3	Group 2 vs. Group 1	Group 3 vs. Group 1
		n (%)/mean ± SD					
NIV	Yes	31 (21.2%)	12 (26.7%)	3 (15.8%)	0.38	0.455	0.581
	No	115 (78.8%)	33 (73.3%)	16 (84.2%)			
HFNO	Yes	29 (19.9%)	15 (31.9%)	1 (5.3%)	0.022	0.087	0.121
	No	117 (80.1%)	32 (68.1%)	18 (94.7%)			
IMV	Yes	150 (90.4%)	48 (85.7%)	21 (87.5%)	0.832	0.333	0.662
	No	16 (9.6%)	8 (14.3%)	3 (12.5%)			
Duration of ICU (days)		15.1±17.6	12.7±14	8.7±8	0.505	0.167	0.048
Duration of mechanical ventilation (days)		12.2±15.6	10±11.6	7.1±8	0.563	0.236	0.068
Discharge	Yes	31 (19%)	20 (35.1%)	3 (12.5%)	0.04	0.013	0.44
	No	132 (81%)	37 (64.9%)	21 (87.5%)			

*Chi-square test, **Mann-Whitney U test, NIV: non-invasive ventilation, IMV: invasive mechanical ventilation, HFNO: high flow nasal oxygenation, ICU: intensive care unit, SD: standard deviation

value was 7.5 mmol/L on first ICU day in these patients who developed AKI during ICU monitoring process.

The absence of a difference between NLR and PLR values of the patients suggests that NLR and PLR are not differential parameters with respect to development of AKI. NLR value of group 3 on the 6th ICU day was higher than group 2, however, AKI developed in group 3 patients at entrance to ICU.

High values of D-dimer, LDH, NLR, PLR, ferritin and CRP have been associated with more severe disease progression, increased intensive care admission and mortality in COVID-19 patients (22-24). NLR and PLR progressed with higher values in the severe disease group that needed intubation and intensive care compared with those who had not severe disease (25). Therefore they may be differential hematological parameters in predicting development of pneumonia (26).

Similarly, it has been demonstrated that NLR and systemic immune inflammation index (platelet count x neutrophil count/lymphocyte count) progressed with higher values in COVID-19 patients with comorbidity of CKD and that they are effective in determination of the patients with high mortality (27). However, in our study patients, non-detection of a significant change in D-dimer, LDH, NLR, PLR, ferritin and CRP values in group 1 that developed a higher rate of AKI during ICU monitoring may be interpreted such that these monitoring parameters are not related with AKI. Even though D-dimer is a parameter that may increase in numerous medical circumstances, it is a monitoring

parameter that can provide information about thrombotic complications, cytokine storm and disease severity in COVID-19 patients (28-30). In a prospective study (n=41), higher LDH, D-dimer and CRP values were detected in the patients who developed AKI during hospital stay and more severe pulmonary involvement and intensive care admission were determined in these patients (31). In our study, no difference was found between D-dimer assessments between patient groups at entrance and monitoring. However, D-dimer levels were higher in group 3 and group 1 than group 2 on the last ICU day as correlated with disease severity.

Even though, higher LDH values at entrance to ICU in group 1 patients compared with group 2 and group 3 patients, and higher LDH values on the last ICU day in group 1 patients than group 2 points out the relationship between high LDH level and severity of COVID-19 as previously shown (32-34), the absence of a difference between patient groups during monitoring suggests that it has no diagnostic value regarding development of AKI.

Comorbid diseases such as DM, HT, CKD, atherosclerotic heart disease and COPD are risk factors for AKI (13,35). Similarly, HT, DM, obesity, dyslipidemia, cigarette smoking and advanced age are encountered as the most commonly known causes of AKI (36,37). In our study, no difference was observed between AKI patients and non-AKI group in terms of comorbidities whereas comorbid circumstances were frequently in group 3 patients. The length of ICU stay was shorter and mortality rate was high. No difference was identified between the groups regarding use of IMV and NIV. The longer duration of high-flow oxygen therapy and longer ICU stay in group 2 suggest that these patients may be treated with high-flow oxygen therapy for a longer time after being extubated and discharged to the ward.

Conclusion

AKI development courses with high mortality in COVID-19 patients. The nephrotoxicity of the medications should be avoided to prevent development of AKI as well as all critically patients in the ICU. Hypovolemia, hypoxia and hypotension should be managed meticulously. No diagnostic relationship was found between AKI development and intensive care severity parameters.

Ethics

Ethics Committee Approval: The approval for the research obtained from the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (decision no: 199, date: 16.06.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.S.K., Concept: R.S.K., A.A., N.T., Design: R.S.K., A.A., N.T., Data Collection and Process: R.S.K., A.A., E.D., R.G.A., Analysis or Interpretation: R.S.K., A.A., N.T., Literature Search: R.S.K., Writing: R.S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Yang X, Jin Y, Li R, Zhang Z, Sun R, Chen D. Prevalence and impact of acute renal impairment on COVID-19: a systematic review and meta-analysis. Crit Care 2020;24:356.
2. Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, et al. AKI in Hospitalized Patients with COVID-19. J Am Soc Nephrol 2021;32:151-60.
3. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020;98:219-27.
4. Ertuğlu LA, Kanbay A, Afşar B, Elsürer Afşar R, Kanbay M. COVID-19 and acute kidney injury. Tuberk Toraks 2020;68:407-18.
5. Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. Acute kidney injury in critically ill patients with COVID-19. Intensive Care Med 2020;46:1339-48.
6. Tjendra Y, Al Mana AF, Espejo AP, Akgun Y, Millan NC, Gomez-Fernandez C, et al. Predicting Disease Severity and Outcome in COVID-19 Patients: A Review of Multiple Biomarkers. Arch Pathol Lab Med 2020;144:1465-74.
7. Agbuduwe C, Basu S. Haematological manifestations of COVID-19: From cytopenia to coagulopathy. Eur J Haematol 2020;105:540-6.
8. Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. BMJ Evid Based Med 2021;26:107-8.
9. Qu R, Ling Y, Zhang YH, Wei LY, Chen X, Li XM, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol 2020;92:1533-41.
10. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol 2020;5:802-10.
11. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. Am J Hematol 2020;95:834-47.
12. Available from: URL: https://covid19bilgi.saglik.gov.tr/tr/covid-19-rehberi.html
13. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Official Journal of the International Society of Nephrology 2012;2. Available from: URL: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf.
14. Darmon M, Clec'h C, Adrie C, Argaud L, Allaouchiche B, Azoulay E, et al. Acute respiratory distress syndrome and risk of AKI among critically ill patients. Clin J Am Soc Nephrol 2014;9:1347-53.
15. Park BD, Faubel S. Acute Kidney Injury and Acute Respiratory Distress Syndrome. Crit Care Clin 2021;37:835-49.
16. Nadim MK, Forni LG, Mehta RL, Connor MJ Jr, Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol 2020;16:747-64.
17. Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. J Am Soc Nephrol 2020;31:1157-65.
18. Wang H, Kang X, Shi Y, Bai ZH, Lv JH, Sun JL, et al. SOFA score is superior to APACHE-II score in predicting the prognosis of critically ill patients with acute kidney injury undergoing continuous renal replacement therapy. Ren Fail 2020;42:638-45.
19. Goswami J, Balwani MR, Kute V, Gumber M, Patel M, Godhani U. Scoring systems and outcome of chronic kidney disease patients admitted in intensive care units. Saudi J Kidney Dis Transpl 2018;29:310-7.
20. Radovic M, Bojic S, Kotur-Stevuljevic J, Lezaic V, Milicic B, Velinovic M, et al. Serum Lactate As Reliable Biomarker of Acute Kidney Injury in Low-risk Cardiac Surgery Patients. J Med Biochem 2019;38:118-25.
21. Hsu YC, Hsu CW. Septic acute kidney injury patients in emergency department: The risk factors and its correlation to serum lactate. Am J Emerg Med 2019;37:204-8.
22. Bastug A, Bodur H, Erdogan S, Gokcinar D, Kazancioglu S, Kosovali BD, et al. Clinical and laboratory features of COVID-19: Predictors of severe prognosis. Int Immunopharmacol 2020;88:106950.
23. Hocanlı İ, Kabak M. Comparison of General Characteristics of Patients Diagnosed of Pcr Positive COVID- 19 Followed In Intensİve Care and Servıce. Van Tıp Derg 2021;28:258-64.
24. Düz ME, Balcı A, Menekşe E. D-dimer levels and COVID-19 severity: Systematic Review and Meta-Analysis. Tuberk Toraks 2020;68:353-60.
25. Erdogan A, Can FE, Gönüllü H. Evaluation of the prognostic role of NLR, LMR, PLR, and LCR ratio in COVID-19 patients. J Med Virol 2021;93:5555-9.
26. Damar Çakırca T, Torun A, Çakırca G, Portakal RD. Role of NLR, PLR, ELR and CLR in differentiating COVID-19 patients with and without pneumonia. Int J Clin Pract 2021;75:e14781.
27. Ozdemir A, Kocak SY, Karabela SN, Yılmaz M. Puede el índice de inflamación inmunitaria sistémica al ingreso predecir la mortalidad hospitalaria al ingreso de pacientes con enfermedad renal crónica e infección por SARS-CoV-2? [Can systemic immune inflammation index at admission predict in-hospital mortality in chronic kidney disease patients with SARS-CoV-2 infection]. Nefrologia (Engl Ed) 2021 Sep 15.
28. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert Rev Hematol 2020;13:1265-75.
29. Kazancıoğlu L, Erdivanlı B, Kazdal H, Özdemir A, Koyuncu T, Hızal A at al. Effectiveness of Laboratory Parameters as Morbidity and Mortality Indicators in Patients with Coronavirus Disease-2019 Admitted to the Intensive Care Unit. J Turk Soc Intens Care 2021;19:33-43.
30. Guo H, Sheng Y, Li W, Li F, Xie Z, Li J, et al. Coagulopathy as a Prodrome of Cytokine Storm in COVID-19-Infected Patients. Front Med (Lausanne) 2020;7:572989.
31. Tarragón B, Valdenebro M, Serrano ML, Maroto A, Llópez-Carratalá MR, Ramos A, et al. Acute kidney failure in patients admitted due to COVID-19. Nefrologia (Engl Ed) 2021;41:34-40.
32. Memikoğlu O. COVID-19: Tanı ve İzlemde Laboratuvar Testleri. Ankara: Ankara Üniversitesi Tıp Fakültesi. 2020.
33. Kiss S, Gede N, Hegyi P, Németh D, Földi M, Dembrovszky F, et al. Early changes in laboratory parameters are predictors of mortality and ICU admission in patients with COVID-19: a systematic review and meta-analysis. Med Microbiol Immunol 2021;210:33-47.
34. Tahtasakal CA, Oncul A, Sevgi DY, Celik E, Ocal M, Turkkan HM, et al. Could we predict the prognosis of the COVID-19 disease? J Med Virol 2021;93:2420-30.
35. Chen Z, McCulloch CE, Powe NR, Heung M, Saran R, Pavkov ME, et al. Exploring reasons for state-level variation in incidence of dialysis-requiring acute

kidney injury (AKI-D) in the United States. BMC Nephrol 2020;21:336.
36. Dada SA, Ajayi DD, Raimi TH, Thomas AA, Dele-Ojo B. Risk factors for kidney disease among civil servants: Report of annual screening and medical evaluation. Saudi J Kidney Dis Transpl 2020;31:440-7.
37. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. Lancet 2013;382:260-72.