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

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

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ABSTRACT *Objective:* COVID-19 may cause severe respiratory disease, glomerular dysfunction and acute tubular necrosis. LDH, 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 I: patients who developed AKI at admission or at follow-up to the intensive care unit (ICU), Group II: those without AKI, Group III: 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:* 256 patients were evaluated. Group II D-Dimer levels before ICU were significantly lower than those in Group III. Group II last day D-Dimer levels were significantly lower than those of Group III and Group I. Admission LDH values were higher in the Group I than in Groups II and III. Last day LDH values were higher in the Group I than in Group II. NLR values were higher in Group III than in Group II on the 6th day. Last day PLR values were lower in the Group I than in Group II. 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: COVID-19 ciddi solunum yolu hastalığı, glomerüler disfonksiyon ve akut tübüler nekroza neden olabilir. LDH, CRP, D-Dimer, lenfopeni ve artmış nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranının (PLO) kötü prognoz ile ilişkili olduğu bilinmektedir. Bu mediyatörlerin akut böbrek hasarı (ABH) gelişimi üzerindeki etkilerini araştırmayı amaçladık.

Gereç ve Yöntem: Retrospektif çalışmaya COVID-19 tanısı almış, şiddetli pnömoni gelişen hastalar dahil edildi. Üç alt grup oluşturuldu. Grup I: Yoğun Bakım Ünitesine (YBÜ) yatışta veya takipte ABH gelişen hastalar, Grup II: ABH olmayanlar, Grup III: Kronik böbrek yetmezliği zemininde ABH gelişen hastalar. Demografik veriler, komorbiditeler, laktat, LDH, CRP, D-Dimer, NLO, PLO, mortalite kaydedildi ve karşılaştırıldı.

Bulgular: 256 hasta değerlendirildi. YBÜ öncesi Grup II D-Dimer seviyeleri Grup III den anlamlı derecede düşüktü. Grup II son gün D-Dimer seviyeleri Grup III ve Grup I den anlamlı derecede düşüktü. Giriş LDH değerleri Grup I de Grup II ve Grup III e göre daha yüksekti. Son gün LDH değerleri Grup I de Grup II ye göre daha yüksekti. 6. günde NLR değerleri Grup III de Grup II ye göre daha yüksekti. Grup I de son gün PLR değerleri Grup II ye göre daha düşüktü. Diğer zamanlarda D-Dimer, LDH, NLO, PLO seviyeleri açısından gruplar arasında anlamlı fark yoktu.

Sonuç: ABH riskini belirlemede laboratuvar bulgularının katkısı açıklığa kavuşturulmamıştır.

Anahtar Kelimeler: COVID-19, ağır pnömoni, akut böbrek hasarı

Introduction

COVID-19 is a condition that is caused by the virus termed as SARS-CoV-2 from Coronaviridae family and that courses with respiratory tract disease and respiratory failure. A critical disease that requires intensive care unit 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 acute kidney injury and proteinuria by directly entering the glomerular and proximal tubular epithelia by the means of ACE-2 receptor. (3)

Acute kidney injury 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 (RAAS) 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, intensive care unit admission and mortality (6,7,8). 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 LDH, CRP and Ferritin counts are associated with higher risk for 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 acute kidney injury 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: 48670771-514.10, date: 16.06.2020), 350 patients diagnosed with confirmed COVID-19 who developed severe pneumonia and admitted to the tertiary stage intensive care unit of University of Health Sciences 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% (PaO₂/FiO₂<300 in the patient receiving oxygen support) (12).

The definition acute kidney injury (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 I), those without AKI (Group II) and those with AKI on the ground of chronic kidney disease (CKD) (Group III). At the time of initial admission to the ICU; demographic data, comorbid diseases, time from disease onset to intensive care unit admission, admission and discharge SOFA scores, diuresis amount in the first 6 and 24 hours of the patients as well as lactate, D-Dimer, C-Reactive protein (CRP), Ferritin, Fibrinogen, lactate dehydrogenase LDH, Neutrophil/Lymphocyte ratio and Platelet/Lymphocyte ratio values of the patients who developed AKI in the intensive care unit at the day of AKI development and during ICU monitoring were recorded from the patient files. The stage of acute kidney injury (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 acute kidney injury and non-AKI mortality causes. Invasive and noninvasive mechanical ventilation treatments received by the patients, length of stay in the intensive care unit 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 intensive care unit 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 I), non-AKI group (Group II) and the group that developed AKI on the ground of CKD (Group III) included 169, 62 and 25 patients, respectively.

AKI developed in totally 72 patients after entrance to the intensive care unit. AKI emerged due to use of nephrotoxic drugs in 5 of those patients. AG and colistin were administered alone in 2 and 1 patients, respectively, whereas AG and Colistin were administered in combination in 2 patients.

Group III had a higher mean age than Group II and Group I (p<0.001) and (p=0.022), respectively. Mean age of Group I was higher than Group II (p=0.018).

The frequencies of coronary artery disease (CAD), hypertension (HT) and COPD were higher in Group III

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

compared with Group I (0.026, 0.013 and 0.030, respectively) and Group II (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 III whereas a higher rate of AKI developed in Group I 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 III and Group I than Group II ($p=0.019$, $p=0.012$, respectively). The patients of Group III and Group II needed ICU admission more lately than Group I ($p=0.011$) and ($p=0.022$), respectively. SOFA values of Group II at entrance to the ICU were significantly lower than Group III ($p=0.022$). 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 I than Group II ($p=0.019$, $p=0.005$, 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 II than Group I ($p=0.014$).

Compared with Group II, Group III and Group I 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 II, Group III and Group I 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 II were significantly lower than Group III ($p=0.035$). Group II showed significantly lower D-Dimer levels on the last ICU day compared with Group III and Group I ($p=0.025$, $p=0.002$, 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 I patients at entrance to the ICU were significantly higher than Group II and Group III patients ($p=0.042$, $p=0.042$). LDH values of Group I patients on the last ICU day were higher than Group II ($p=0.001$), (Table 4). No significant difference was present between the groups in terms of ferritin and CRP values.

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

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

Table 2. Demographic variables of the groups

		Group			p		
		Group I	Group II	Group III	Group II vs. Group III	Group II vs. Group I	Group III vs. Group I
		n (%) / mean \pm 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 \pm 15,9	66,5 \pm 15,9	74,5 \pm 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 Diseases

Table 3. Lactate, SOFA, Mortality of the groups

	Group			p		
	Group I	Group II	Goup III	Group II vs. Group III	Group II vs. Group I	Group III vs. Group I
	n (%) / mean ± SD					
Lactate						
Onset	2,6±2,01	1,81±0,72	24,1±65,25	0,561	0,019	0,439
1th day	7,52±42,12	1,98±1,09	10,24±27,66	0,139	0,005	0,94
2th 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						

The administration of high-flow oxygen therapy was significantly higher in Group II than Group III patients ($p=0.022$) whereas no significant difference was determined between the patients in terms of administration of NIV and IMV (Table 5).

A higher rate of patients from Group II were discharged to the ward compared with Group I ($p=0.013$) and Group III ($p=0.040$) (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 (15,5). In addition, age, presence of CKD, 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 III 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 III, the mortality rate is not different from Group I, suggesting that AKI alone significantly increases mortality in COVI-19 patients.

While SOFA score can be more effective than other predictors regarding prediction of mortality in AKI patients admitted in the intensive care unit (18), it is effective as much as APACHE II and SAPS 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 III and Group I compared with Group II 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).

Table 4. LDH, D-DIMER, NLR, PLR variables of the groups

	Group			p		
	Group I	Group II	Group III	Group II vs. Group III	Group II vs. Group I	Group III vs. Group I
	n (%) / mean \pm SD					
LDH						
Admission	735,3 \pm 1466,7	518 \pm 329,6	500 \pm 234,4	0,733	0,721	0,581
1 th day	1620,9 \pm 8000,9	625,8 \pm 463	560,9 \pm 373	0,475	0,042	0,042
2 nd day	769,8 \pm 1232,9	617,9 \pm 660,7	754,1 \pm 1037,8	0,914	0,308	0,54
3 rd -5 th days	985,1 \pm 2042,9	487,4 \pm 206,2	541,6 \pm 321,6	0,944	0,695	0,855
7 th -10 th days	601,2 \pm 585,4	451,9 \pm 209,7	436,9 \pm 166,9	0,949	0,503	0,682
11 th -20 th days	1199,9 \pm 3823,2	544,4 \pm 471,5	587,1 \pm 447,4	0,962	0,859	0,667
21 st -30 th days	605,1 \pm 940,8	364,2 \pm 113	401	0,343	0,741	0,646
AKI 2	2391,1 \pm 12351,4	235	759,6 \pm 381	0,114	0,13	0,981
Last day	2651,5 \pm 5401,7	2397,1 \pm 12494,9	1017,7 \pm 1020,7	0,075	0,001	0,4
D-dimer						
Admission	4490,3 \pm 12106,5	2902,5 \pm 5765,9	5322,9 \pm 4118,9	0,035	0,428	0,079
1 st day	13131,5 \pm 41409,8	8836 \pm 23364,1	5515,6 \pm 4221,3	0,313	0,103	0,717
2 nd day	11148,7 \pm 30220,6	17239,7 \pm 37586,2	4564,9 \pm 4323,2	0,858	0,913	0,993
3 rd -5 th day	6224,2 \pm 13429,7	6766,1 \pm 11560,1	3496,5 \pm 3604,9	0,362	0,13	0,852
7 th -10 th day	6393,5 \pm 13260,4	4240,8 \pm 5309	2616 \pm 1689,9	0,652	0,997	0,596
11 th -20 th day	4095,1 \pm 4849,6	3397,1 \pm 3697,3	3143,5 \pm 3040,4	0,739	0,773	0,681
21 st -30 th day	5085,3 \pm 9380,7	1538,5 \pm 607,8	2550	0,121	0,521	0,529
AKI 2	8135,5 \pm 13716,8	-	5436,8 \pm 5017,8			0,669
Last day	9887,4 \pm 17983,3	5387,1 \pm 12970,7	6714,5 \pm 7216,7	0,025	0,002	0,826
NLR						
Emergency department	10,46 \pm 10,84	25,95 \pm 74,36	269,39 \pm 743,49	0,071	0,095	0,003
Admission	25,38 \pm 101,5	46,16 \pm 175,37	123,75 \pm 507,7	0,579	0,283	0,153
1 th day	73,12 \pm 431,92	19,51 \pm 19,08	333,73 \pm 1006,44	0,198	0,991	0,134
2 th day	134,65 \pm 856,93	31,26 \pm 71,22	240,31 \pm 548,25	0,1	0,616	0,092
3 th -5 th day	26,73 \pm 92,55	56,43 \pm 154,88	156,8 \pm 420,07	0,163	0,38	0,146
6 th -7 th day	36,86 \pm 103,15	56,2 \pm 236,23	253,57 \pm 614,11	0,017	0,089	0,092
7 th -10 th day	56,78 \pm 265,64	53,91 \pm 159,92	544 \pm 1066,68	0,151	0,139	0,211
11 th -20 th day	90,08 \pm 362,11	96,13 \pm 221,4	8,23	0,617	0,351	0,813
21 st -30 th day	77,2 \pm 331,29	46,15 \pm 25,24	170,74 \pm 458,84	0,157	0,088	0,307
AKI 2	54,92 \pm 291,21	31,01 \pm 74,2	232,26 \pm 834,16	0,218	0,823	0,086
PLR						
Emergency department	258,5 \pm 202,8	322 \pm 244,4	276,1 \pm 245,2	0,353	0,085	0,894
Admission	318,6 \pm 276,3	375,2 \pm 254,5	352,5 \pm 353,8	0,247	0,086	0,951
3 th day	7639,1 \pm 87238,4	357,7 \pm 238	446,7 \pm 285,5	0,21	0,742	0,146
5 th day	6395,1 \pm 63436,5	381 \pm 245,6	441,4 \pm 363,9	0,874	0,812	0,709
7 th day	356,5 \pm 292,2	312,1 \pm 216,8	391,4 \pm 237,3	0,34	0,657	0,448
10 th day	301,5 \pm 246,1	269,2 \pm 204,8	464,7 \pm 278,9	0,059	0,58	0,099
20 th day	273,3 \pm 218,3	198,5 \pm 86,9	249,3 \pm 62,6	0,296	0,511	0,746
30 th day	256,9 \pm 201,5	199,5 \pm 120,1	182	0,617	0,484	0,651
AKI 2	368 \pm 353,7	64	340,6 \pm 328,6	0,206	0,184	0,926
Last day	224,9 \pm 234,8	287,3 \pm 220,3	289,5 \pm 289,1	0,745	0,017	0,171
AKI 2: The day when AKI develops in the ICU. NLR: Neutrophil/lymphocyte ratio. PLR: Platelet/Lymphocyte ratio						

		Group			p		
		Group I	Group II	Group III	Group II vs. Group III	Group II vs. Group I	Group III vs. Group I
		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: Noninvasive ventilation, IMV: Invasive mechanical ventilation, HFNO: High flow nasal oksigenation

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 I at entrance to the emergency department and on first ICU day were higher than Group II. Mean lactate 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 III on the 6th ICU day was higher than Group II, however, AKI developed in Group III 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, 23, 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 I 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, 29, 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 III and Group I than Group II on the last ICU day as correlated with disease severity.

Even though, higher LDH values at entrance to ICU in Group I patients compared with Group II and Group III patients, and higher LDH values on the last ICU day in Group I patients than Group II points out the relationship between high LDH level and severity of COVID-19 as previously shown (32, 33, 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 diabetes mellitus, HT, CKD, atherosclerotic heart disease and COPD are risk factors for AKI (35, 13). 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 III 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 II 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 intensive care unit. 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: Following obtaining the approval for the research from the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (decision no: 48670771-514.10, date: 16.06.2020), 350 patients diagnosed with confirmed COVID-19 who developed severe pneumonia and admitted to the tertiary stage intensive care unit of University of Health Sciences Prof.Dr.Cemil Taşcıoğlu City Hospital between the dates 18.03.2020- 01.06.2020 were retrospectively examined.

Informed Consent: 350 patients diagnosed with confirmed COVID-19 who developed severe pneumonia and admitted to the tertiary stage intensive care unit of University of Health Sciences Prof.Dr.Cemil Taşcıoğlu City Hospital between the dates 18.03.2020- 01.06.2020 were retrospectively examined.

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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.

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