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ORIGINAL ARTICLE

COVID-19 Ricochets on Kidney Transplant and Hemodialysis Patients

Böbrek Nakli ve Hemodiyaliz Hastalarında COVID-19 Rikoşeleri

[1]Mevlut Hakan Goktepe, [1]Hilal Akay Cizmecioglu, [1]Ali Kursat Tuna, [2]Ahmet Cizmecioglu

[1]Necmettin Erbakan University, Faculty of Medicine, Department of Internal Medicine, Konya, Türkiye
[2]Selcuk University, Faculty of Medicine, Department of Internal Medicine, Konya, Türkiye

Correspondence

Ahmet Cizmecioglu, Department of General Internal Medicine, Selçuk University Faculty of Medicine, Akademi mh, Celal Bayar Cd. No:313, 42250, Selçuklu, Konya, Türkiye

E-Mail: mdahmet2002@gmail.com

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ABSTRACT

Background/Aims: An impaired immune response affects Coronavirus 2019 (COVID-19) disease progression. Immunities of both hemodialysis (HD) and Kidney Transplant (KTx) patients have already been suppressed. This study evaluated the prognostic laboratory results in HD and KTx patients with COVID-19.
Methods: This retrospective, case-control study was conducted with PCR (+) COVID-19 HD and KTx patients and a control group. All patients were divided into two subgroups according to disease severity. Patients' demographic records and laboratory results were obtained from the follow-up files.
Results: A total of 30 HD, 20 KTx patients, and 40 control groups were involved in the study. Gender and hospitalization duration did not differ between the groups. There was a 10% mortality rate in the KTx group and 27% in the HD group. Lung involvement in Computed Tomography (CT) was higher in HD patients (47%) than in KTx (25%). In subgroup evaluations, the most prominent laboratory values were fibrinogen in HD patients and LDH and Ferritin in KTx patients in determining disease severity.
Conclusions: Early hospitalization and treatment implementations will be associated with a good prognosis in HD and KTx patients since CT and laboratory results are not predictive in these groups of patients during the COVID-19 pandemic.

Keywords: COVID-19, Disease severity, Hemodialysis, Kidney transplantation

ÖZ

Arka Plan/Amaçlar: Bozulmuş bir bağışıklık cevabı, Coronavirüs 2019 (COVID-19) hastalığının prognozunu etkiler. Hem hemodiyaliz (HD) hem de Böbrek Nakli (BN) hastalarının bağışıklıkları zaten baskılıdır. Bu çalışma COVID-19'lu HD ve BN hastalarında prognostik laboratuvar sonuçlarını değerlendirmiştir.
Yöntemler: Bu retrospektif, vaka kontrol çalışması, PCR (+) COVID-19 HD ve BN hastaları ve kontrol grubu ile gerçekleştirildi. Tüm hastalar hastalık şiddetine göre iki alt gruba ayrıldı. Hastaların demografik kayıtları ve laboratuvar sonuçları takip dosyalarından elde edildi.
Bulgular: Çalışmaya toplam 30 HD, 20 BN hastası ve 40 kontrol grubu dahil edildi. Cinsiyet ve hastanede yatış süresi gruplar arasında farklılık göstermedi. BN grubunda %10, HD grubunda %27 ölüm oranı vardı. Bilgisayarlı Tomografide (BT) akciğer tutulumu HD hastalarında (%47) BN'ye (%25) göre daha yüksekti. Alt grup değerlendirmelerinde hastalık şiddetinin belirlenmesinde HD hastalarında fibrinojen, BN hastalarında ise LDH ve Ferritin öne çıkan laboratuvar değerleriydi.
Sonuç: BT ve laboratuvar sonuçları COVID-19 pandemisinde bu tarz hasta gruplarında prediktif olmadığı için erken yatış ve tedavi uygulamaları HD ve BN hastalarında iyi bir prognoz ile ilişkili olacaktır.

Anahtar Kelimeler: Böbrek nakli, COVID-19, Hastalık şiddeti, Hemodiyaliz

Introduction

Coronaviruses are influential pathogens in human life. A new type of coronavirus, 2019 coronavirus disease (COVID-19), persists in spreading via the variants in the 3rd year of its pandemic (1). According to the WHO data, the disease has already affected more than 480 million people, with around 6 million deaths worldwide (2). Estimated mortality rates among the hospitalized patients with COVID-19 differ concerning advanced age and comorbidities (3). The spectrum of the clinics is expanding along with the new variants, which may begin with flu-like symptoms, ranging from mild to severe, and may end by death (4). Although severe lung injuries have been reported at all ages, in older patients with multiple comorbidities, the virus mainly causes severe interstitial pneumonia, acute respiratory distress syndrome (ARDS), macrophage activating syndrome, and multiorgan failure (4).

The progression of COVID-19 in particular patient groups, such as organ transplant patients and end-stage renal disease, may be more destructive (5). Studies have revealed that chronic renal disease (CKD) is around 2-8% of the comorbidities accompanying COVID-19 (6, 7). Since kidney transplant patients are both on continuous immunosuppressive therapy and organ recipients, there is a higher risk of morbidity than the average population (8, 9). The number and functionality of polymorphonuclear leukocytes (PMNL), T lymphocytes, B lymphocytes, and other immune system cell subsets decrease in hemodialysis patients; consequently, the immune response becomes defective (10).

COVID-19 infects the respiratory system, but it also affects the gastrointestinal tract, causing nausea, vomiting, and gastroenteritis, affecting the body fluid, electrolyte balance, and, therefore, the kidneys (11, 12). Medications and complications during treatment indirectly affect the kidneys as well (13-14). Therefore, evaluating morbidity and mortality in renal transplant

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Complaints: geneltip@selcuk.edu.tr

and hemodialysis patient groups will raise awareness. This study, thus, compared COVID-19 patients who were kidney transplanted and on a dialysis treatment with controls without comorbidities other than COVID positivity in terms of demographic data, laboratory parameters, radiological involvements, comorbidities, and mortality. Furthermore, we shared our clinical experiences in this regard.

Materials ve Methods

Study design and patient selection

This article was a retrospective study conducted with patients diagnosed with COVID-19 between 2020 and 2022. An ethics committee approval was obtained from the Pharmaceuticals and Non-Medical Device Research Ethics Committee of Necmetti Erbakan University Faculty of Medicine under grant number 2020/2893 prior to the study. The protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration.

The study was conducted with the patient group who had kidney transplants or still receiving dialysis treatment and a control group with no comorbidity other than COVID-19 positivity. Patients over 18 years of age and those with RT-PCR confirmed COVID-19 were included in the study. All patient groups were then evaluated into three categories: kidney transplant recipients, those on dialysis, and the control group without comorbidities other than COVID-19 positivity. Furthermore, the categorized groups were separated into two subgroups according to disease severity. Accordingly, patients who were asymptomatic or had no findings on imaging methods were defined as non-severe, whereas patients with imaging positivity supporting the symptomatic clinic were defined as severe (15). The groups were compared regarding hospitalization time, need for intensive care or intubation, death or discharge rates, laboratory parameters, and the prevalence of lung involvement on computed tomography (CT).

Data obtaining

All patients and controls data, demographic characteristics, and laboratory test results were noted during hospitalization. Accordingly, hospital digital patient files were retrospectively analyzed. Patients' demographic characteristics, vital signs, laboratory parameters, radiological findings, treatment regimens, length of hospitalization, and mortality data were recorded. Daily vital examinations such as finger oxygen saturation, fever monitoring records, heart rate, laboratory results, and CT involvements that have prognostic significance for COVID-19 were evaluated (16, 17). Notable supplemental laboratory test results were also noted. Cases with an absolute lymphocyte count of < 1000 x106/L were considered lymphopenia (18).

Statistical analysis

Statistical Package for the Social Sciences (SPSS) IBM version 22.0 software was used for statistical analysis. The distribution analysis of continuous numerical data was performed using the Kolmogorov-Smirnov Test. In comparing three or more groups, the Kruskal-Wallis test

Table 1: Demographic, survival, and vital features of the subgroups per disease severity.

	Hemodialysis group		P^1	Kidney Tx group		P^2	Controls	P^3
	Non-Severe	*Severe*		*Non-Severe*	*Severe*		*Non-Severe*	
	(n = 13)	(n = 17)		(n = 6)	(n = 14)		(n = 40)	
Age, (year)	64.7 ± 14.73	65.0 ± 9.46	0.711	53.33 ± 18.77	48.66 ± 8.47	0.999	49.5 ± 11.59	0.001
Gender, F/M (%)	5 (38) / 8 (62)	10 (41) / 7 (59)	0.148	2 (33) / 4 (67)	4 (29) / 10 (71)	0.770	13 (25) / 27 (75)	0.153
Hospitalization (day)	12.5 (9.5-16.2)	13 (9-24)	0.749	5 (5-15)	12 (6.5-21.25)	0.136	9 (7-12.75)	0.087
MV, n (%)	3 (23)	4 (23.5)	0.831	0 (0)	3 (21)	0.448	0 (0)	0.034
Stay in ICU, (day)	1 (0-5.25)	1 (0-5.5)	0.863	0 (0)	1 (0-8.25)	0.536	0 (0)	0.083
Recovery, n (%)	11 (85)	11 (65)	0.401	6 (100)	12 (86)	0.448	40 (100)	0.007
Exitus, n (%)	2 (15)	6 (35)	0.401	0 (0)	2 (14)	0.448	0 (0)	0.007
Fever, n (%)	4 (31)	7 (41)	0.708	2 (33)	3 (21)	0.612	29 (72)	0.001
Tachycardia, n (%)	1 (7.7)	4 (23)	0.355	0 (0)	4 (28)	0.267	2 (5)	0.220
Hypotension, n (%)	1 (7.7)	5 (29)	0.196	0 (0)	3 (21)	0.521	0 (0)	0.015
SPO_2 level, (%)	93.2 ± 1.26	89.23 ± 1.76	0.001	93.71 ± 1.36	91.72 ± 1.84	0.001	94.14 ± 1.25	0.001
CT involvement, n (%)	5 (38)	11 (65)	0.001	3 (50)	12 (85)	0.001	39 (97)	0.002

p^1, and p^2 values are the comparison of non-severe to severe subgroup in the hemodialysis and kidney transplant groups, respectively (Mann-Whitney U test, Chi-Squared test). P^3 values are the intergroup evaluations (Kruskal Wallis-H Test, Chi-Squared test); Data are the median (INQ), *n* (%), or *n/N* (%); **Tx**, Transplant; **F**, Female; **M**, Male; **MV**, Mechanical Ventilation; **ICU**, Intensive care unit; **SPO_2**, Blood oxygen saturation; **CT**, Computed tomography.

Table 2: Laboratory results of the subgroups based on disease severity.

	Hemodialysis group		P^1	Kidney Tx group		P^2	Controls	P^3
	Non-Severe (n = 13)	*Severe* (n = 17)		*Non-Severe* (n = 6)	*Severe* (n = 14)		*Non-Severe* (n = 40)	*All*
WBC, x10³/µL	5.04 ± 1.85	6.71 ± 2.21	0.604	5.81 ± 2.20	5.11 ± 1.45	0.840	5.83 ± 2.57	0.857
ALC, x10³/µL	1.22 ± 0.59	0.92 ± 0.44	0.127	0.79 ± 0.30	0.86 ± 0.37	0.840	1.10 ± 0.45	0.231
ANC, x10³/µL	3.32 ± 1.35	5.29 ± 1.04	0.155	4.48 ± 2.74	3.79 ± 1.36	0.840	4.33 ± 2.42	0.937
Hemoglobin, g/dL	10.97 ± 2.05	10.73 ± 1.97	0.639	12.93 ± 1.05	12.62 ± 2.28	0.945	14.16 ± 1.25	0.001
Hematocrit, (%)	33.72 ± 5.95	36.12 ± 13.70	0.711	40.40 ± 2.32	38.35 ± 6.59	0.734	42.01 ± 3.33	0.001
MCV, fL	93.37 ± 6.46	91.81 ± 4.68	0.359	84.60 ± 3.10	83.80 ± 6.57	0.840	87.76 ± 4.35	0.001
NLR	2.9 (1.7-4.4)	5.7 (2.9-7.6)	0.093	6.2 (2.8-4.2)	3.8 (3-6.1)	0.633	3.3 (2.5-5.5)	0.547
PLR	81.7(63.2-177)	231(150-317)	0.011	245(218-262)	202(153-239)	0.180	179 (130-223)	0.213
PLT, x10³/µL	130.9 ± 49.6	194.3 ± 91.4	0.027	207.6 ± 41.5	181.9 ± 58.1	0.448	186 ± 62.8	0.189
RDW, fL	29.12 ± 2.59	15.03 ± 1.17	0.786	15.10 ± 3.73	14.57 ± 1.24	0.633	13.32 ± 0.71	0.001
Ig G, mg/dL	10.2 ± 6.7	10.9 ± 3.1	0.661	12.4 ± 3.1	10.01 ± 4.9	0.600	11.62 ± 2.05	0.360
Ig A, mg/dL	2.45 ± 1.23	2.17 ± 0.47	0.783	1.77 ± 0.66	1.79 ± 0.78	0.909	2.28 ± 0.77	0.236
ALT, U/L	14.7 (9-28.5)	13.8 (8.2-27.7)	0.980	8.6 (7.5-8.6)	17 (11-19.4)	0.448	25.7 (18.4-40.7)	0.020
AST, U/L	20.6 (14-25.6)	24 (17.4-36.1)	0.414	13.4 (10-13)	18.7 (16-31)	0.180	27.8 (21.8-44.8)	0.025
CPK, U/L	45 (37-153)	75 (49-223)	0.187	54 (19-54)	61 (45-233)	0.448	124 (71-380)	0.027
Urea, mg/dL	92 (71-141)	96 (72-146)	0.980	37 (29-43)	50 (25-79)	0.448	25 (21-31)	0.001
Creatinine, mg/dL	6.96 (4.72-8.5)	6.21 (4.53-8.5)	0.639	1.31 (1-1.31)	1.63(1.1-2.27)	0.295	1.03 (0.90-1.14)	0.001
CRP, mg/L	37 (12-65)	87 (33-153)	0.083	14 (4-15)	58 (22-91)	0.365	41 (20-73)	0.465
Troponin, ng/mL	0.11 (0.01-0.19)	0.01 (0.01-0.11)	0.204	0.01 (0.01-0.10)	0.01 (0.01-0.02)	0.536	0.01 (0.01-0.02)	0.457
D-dimer, ng/mL	813(376-1779)	459(321-570)	0.170	302(155-330)	350 (159-940)	0.734	138 (94-198)	0.001
Ferritin, µg/L	813(393-2010)	1664(734-2786)	0.187	79 (72-83)	549(187-2270)	0.004	404 (184-834)	0.001
Fibrinogen, mg/dL	304 (260-397)	445 (375-562)	0.009	223 (52-298)	502 (375-614)	0.295	449 (363-530)	0.370
Glucose, mg/dL	111.69 ± 35.33	171.96 ± 102.1	0.363	96.06 ± 18.42	141.54 ± 89.7	0.365	118.12 ± 38.7	0.590
LDH, U/L	363 (242-446)	269 (214-154)	0.204	363(242-446)	269 (214-366)	0.009	307 (227-366)	0.947
PCT, µg/L	0.37 (0.26-3.7)	0.8 (0.37-1.21)	0.286	0.15(0.08-0.21)	0.08 (0.03-0.2)	0.295	0.09 (0.06-0.19)	0.001
ESR, mm/h	60 (25-90)	82 (57-94)	0.334	15 (5-18)	32 (17-50)	0.233	47 (24-53)	0.001

p¹, and p² values are the comparison of non-severe to severe subgroup in the hemodialysis and kidney transplant groups, respectively (Mann-Whitney U test). P³ values are the intergroup evaluations (Kruskal Wallis-H Test); Data are the median (INQ), *n* (%), or *n/N* (%); **WBC**, White blood cell; **ALC**, Absolute lymphocyte count; **ANC**, Absolute neutrophil count; **MCV**, Mean corpuscular volüme; **NLR**, Neutrophil to lymphocyte ratio; **PLR**, Platelet to lymphocyte ratio; **PLT**, Platelet; **RDW**, Red cell distribution width; **ALT**, Alanine transaminase; **AST**, Aspartate aminotransferase; **CPK**, Creatine phosphokinase; **CRP**, C-Reactive protein; **LDH**, Lactate dehydrogenase; **PCT**, Procalcitonin; **ESR**, Erythrocyte sedimentation rate.

was used for dispersed continuous variables or n<30. In case of significance, paired groups were compared using the Mann-Whitney-U test and interpreted by Bonferroni correction. Categorical variables were expressed as percentages (%) and compared using the Chi-square test. P values below 0.05 were considered statistically significant.

Results

A total of 90 patients with positive PCR test results from three distinct groups, including 20 patients with a kidney transplantation history, 30 patients receiving hemodialysis, and 40 patients without other chronic diseases, were included in the study. The renal transplantation period or renal replacement therapy initiation had already been completed before COVID-19, and their medical status was stable for at least one year. All groups received similar treatments for COVID-19.

Overall, the control group had only a subgroup rated as non-severe. The mean age of the patients was 55.4 ± 1.3, and 46 of them (65.7%) were male. Gender did not differ a statistical significance in all evaluated parameters. The median hospitalization day of all groups was twelve days. There was no difference in hospitalization days between the study groups; however, the mean hospital stay in the control group was three days less. In addition, a Mann-Whitney U test has failed to reject the null hypothesis of no significant difference in the length of hospitalization between the compared patient groups (p = 0.445). The overall length of stay in the intensive care unit was ten days for all patients. Eighty of the patients (88.9%) were discharged with complete recovery. All patients in the control group were discharged with full recovery; conversely, the number of deaths in the transplant patients group was two (10 %) and eight (27 %) in the hemodialysis patients group (Figure 1).

In comparing the vital signs of all patients, fever, hypotension, or hypoxemia were statistically different between the groups; however, tachycardia was not. A similar evaluation was also valid for the laboratory results; accordingly, there was statistical significance in prognostic factors such as D-Dimer, ferritin, erythrocyte sedimentation rate, and creatinin (p < 0.05) (Figure 2). However, no significance was found in the Mann-Whitney U test evaluations (Figure 2). Lymphopenia was quite common in all patients (54%). The frequency of lymphopenia kept increasing in the KTx (67%) and HD group (56%), whereas it decreased in the control group (46%). Among all patients, those with lymphopenia had statistically significantly lower IgA levels (p = 0.011, η2 = 0.094), while hospitalization durations were longer (p = 0.001, η2 = 0.128). In addition, fibrinogen levels decreased in KTx patients with lymphopenia (p = 0.013, η2 = 0.408).

When the kidney transplant group was compared with the hemodialysis group, a statistically significant increase was noticed in the laboratory values of age (p = 0.001, η2 = 0.321), ESR (p = 0.001, η2 = 0.262), PRC (p = 0.001, η2 = 0.396), ferritin (p = 0.019, η2 = 0.134),

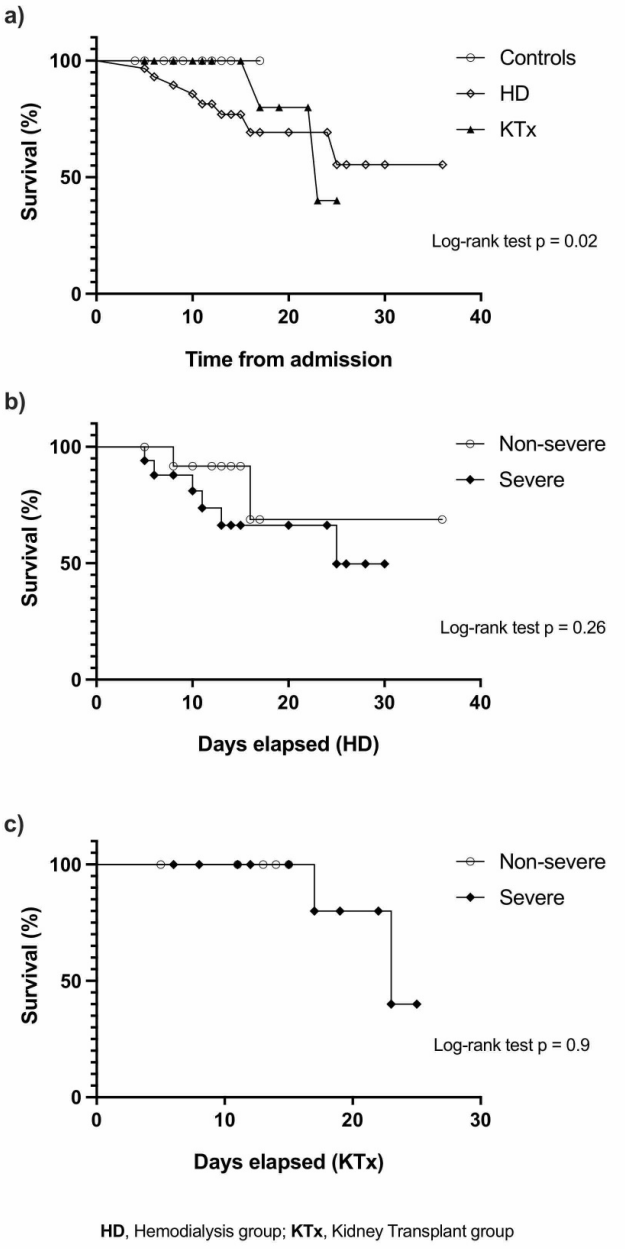

Figure 1: Kaplan Meier curves of demonstrating COVID-19 on patient survival, **a)** Overall evaluation, **b)** Survival duration according to disease severity in hemodialysis patients, and **c)** In kidney transplant patients.

and troponin levels (p = 0.026, η2 = 0.120), which are also prognostic, in the hemodialysis group. Although there was a proportional difference in the comparison between transplant and dialysis patient groups regarding death, no statistically significant difference was found (p = 0.286).

Intriguingly, an extensive involvement was observed in CT in control patients (n = 39, 97%). On the contrary, no CT finding was reported in 5 (25%) kidney transplant patients and 14 (47%) dialysis patients. However, diffuse involvement was proportionally higher in the transplanted patients (n = 15, 75%) than dialysis patients (n = 16, 53%). Other notable features and laboratory

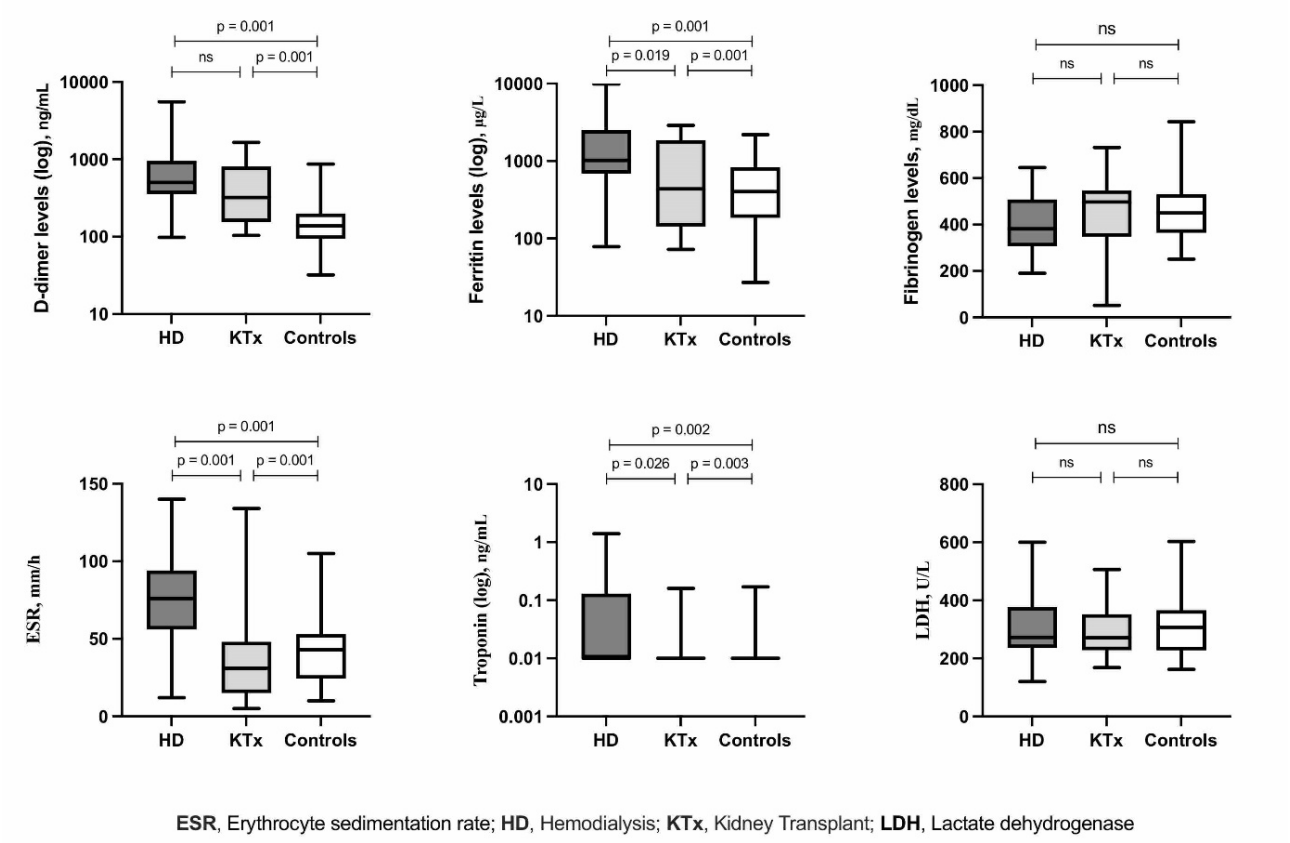

Figure 2: Comparisons of prognostic laboratory values in COVID-19 infection amid all groups.

results of the groups were summarized in Table 1 and 2.

Comparisons of the subgroups revealed that fibrinogen levels differed between non-severe and severe subgroups in the hemodialysis patients, whereas ferritin and LDH levels made the same difference in the kidney transplant group. Among the many correlations identified, the reasonable ones are: a weak correlation was found between the neutrophil to lymphocyte ratio (NLR) and the length of hospitalization ($r = 0.26$, $p = 0.025$), and a moderate positive correlation was found between NLR and length of hospitalization in dialysis patients ($r = 0.41$, $p = 0.034$).

Discussion

This study evaluated the COVID-19 processes of patients with a kidney transplant or receiving hemodialysis. As a result of many categories studied during their hospitalization, we noticed that morbidity and mortality were higher in hemodialysis patients than in those with kidney transplants. Interestingly, there was no death or need for intensive care in the control group, although their lung involvements were more common.

The cost of kidney transplantation and the economics of maintaining well-being are additional, prominent issues (19). However, patients receiving hemodialysis (HD) may be considered more precarious concerning morbidity and mortality related to COVID-19 since their immunity is suppressed compared to regular individuals (20). The meta-analysis of Marian Goicoechea et al. revealed that the clinical symptoms at admission in HD patients were milder than in the general population, but they worsened over time (21). This progression has been associated with a lack in the immune system of HD patients (22). In our study, the evaluation between the dialysis patients and the control group determined that diffuse pulmonary involvement on CT was higher in those without the additional disease. However, contributing to the current meta-analysis determinations about the immune system, this increase might be linked to the early hospitalization of patients with kidney transplants or receiving HD. Even though renal transplant and dialysis patients were compared, without statistical significance, we found that the prevalence of diffuse involvement was proportionally higher in transplant patients. The hospitalization periods stated that the healing process in hemodialysis patients elongated more than those with kidney transplants or in the control group.

Many publications highlighted the significance of ferritin, d-dimer, and troponin elevations during the pandemic in COVID-19 prognosis (23, 24). In our study, the control group had the lowest D-dimer levels linked to their milder course of COVID-19. On the contrary, the HD group produced more D-dimer results than the other groups. The D-dimer elevation is already a common laboratory finding in CKD patients (24, 25). However, due to its correlation with disease severity, elevated D-dimer levels should be considered even in HD patients during COVID-19. A similar determination may also be valid for troponin results. The median troponin levels were 0.01 ng/mL in all groups. The statistical significance favoring HD patients should suggest the decreased renal clearance of troponin in this group (26,27). Fibrinogen level differences might

help determine disease severity in the HD group. Ferritin levels were insufficient to determine disease severity in HD patients; however, the difference in ferritin elevation in the kidney transplant subgroups was statistically significant, like in the control group. Lactate dehydrogenase (LDH) levels differed between the Tx subgroups as well. These findings support the efficacy of ferritin, D-dimer, and LDH in the management of Tx patients during COVID.

As an inferior determination, the lymphopenic stage is directly related to COVID-19 mortality via lymphocyte apoptosis (28-31). However, although patients with a history of kidney disease tended to be immunocompromised and the prevalence of lymphopenia in those was high, our study revealed that only IgA deficiencies were noticeable in all group evaluations. Another anecdote was the finding that fibrinogen decreased more in lymphopenic KTx patients. The absence of differences in laboratory tests performed in subgroups per disease severity may only indicate that cellular immunity may be more prominent than humoral type in this group of patients with lymphopenia.

Considering the mortality rates, the overall mortality rate in hospitalized COVID-19 patients was 28% in a cohort conducted in China and 21% in New York (32, 33). Akalın et al. reported that 10 (28%) of 36 kidney transplant recipients died (34). In studies conducted with hemodialysis patients, Goicoechea et al. reported a 30.5% mortality rate in Spain (21). Scarpioni et al. and Alberici et al. reported mortality rates of HD patients in Italy as 41% and 25%, respectively (35, 36). We found that the mortality rate was 27% in HD patients and 10% in the Kidney Transplant group. Mortality rates in HD patients were consistent with the literature reports whereas our mortality rates in renal transplant patients were low. We noticed that intensive care need was also higher in HD patients than those with kidney transplants. Another point was that the mortality rate of the patients transferred to the ICU was higher in hemodialysis patients than those with renal transplant. Therefore, these negative results reminded us that the COVID-19 mortality is higher in HD patients, and attentive management should be made in the early period of the disease to reduce intensive care in this group.

Our study's small population makes these findings less generalizable to the daily practices. Another issue was limited to the involvement intensities in CT; it was not feasible to classify the CT reports according to the study groups. When detailed staging is performed according to the severity of involvement on CT, it can be said that we generally consider pulmonary involvement as present or absent since the number of patients at each stage will decrease. This will be challenging to evaluate the disease as a whole. Furthermore, to consider the influence of COVID-19 more objectively, all patients included in the study should be stable regarding their primary disease. Another limitation arose from the retrospective nature of the investigation, which presented difficulties in accessing supplementary information. Specifically, since the majority of patients were assessed during the initial stages of the pandemic, crucial data such as vaccination status and the efficacy of the vaccine could not be obtained.

In conclusion, pulmonary involvement on admission CT is milder in hemodialysis and renal transplant patients than in patients without comorbidities; however, the involvement can progress swiftly. In particular, HD patients tended to be affected more. Laboratory assessments did not support the clinic earlier other than fibrinogen in HD patients; therefore, dynamic effective treatment plans for HD patients with COVID-19 can be preventive in disease progression. KTx patients seem to be more fortunate in laboratory tests and lung involvement.

Author Contributions

Conception: M.H.G., Design: M.H.G., H.A.C., A.C., Supervision: M.H.G., A.C., Resource: M.H.G, H.A.C., A.K.T., Materials: M.H.G, H.A.C., A.K.T., Data Collection and/or Processing: M.H.G, H.A.C., A.K.T., Analysis and/or Interpretation: A.C.,Literature Review: M.H.G., H.A.C., A.C., Writer: A.C., M.H.G., Critical Review: A.C.

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