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The Effects of COVID-19 in Chronic Kidney Disease: Progression and Increased Severity of Chronic Inflammatory

COVID-19 Enfeksiyonunun Kronik Böbrek Hastalığında Progresyon ve Kronik İnflamasyon Şiddetine Etkileri

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ÖZ

Amaç: SARS-COV-2 (Şiddetli akut Solunum Sendromu Virüsü), geniş bir organotropizme sahiptir. Baskın olarak pulmoner sistemi tutsa da, böbreklerde yaygın olarak tutulmaktadır. Kronik böbrek hastalarında (KBH), akut böbrek hasarını ve mortaliteyi artırdığı çalışmalarla gösterilmiştir. Ancak hayatta kalan ve diyalizsiz takipte olan hastalarda progresyon ve kronik inflamasyon şiddetine etkileri henüz bilinmemektedir. Çalışmadaki amacımız post-COVID KBH'da böbrek fonksiyonlarını ve kronik inflamasyon şiddetini araştırmaktır.
Araçlar ve Yöntem: Çalışma retrospektif olarak gerçekleştirildi. COVID-KBH(n=54) ve NON-COVID KBH (kontrol grubu) (n=60) olmak üzere, iki grup oluşturuldu. Grupların bazal Kan Üre Azotu (BUN), Üre, Kreatin (Cre), Glomerüler filtrasyon hızı (GFR), Beyaz kan hücresi (WBC), Nötrofil (Neu), Lenfosit (Ly), Trombosit (Plt), Trombosit/Lenfosit Oranı (PLR) ve Nötrofil/Lenfosit Oranı (NLR) seviyeleri incelendi ve karşılaştırıldı. Akut enfeksiyondan 6 ay sonra olmak üzere, gruplarda aynı parametrelerin değişimleri incelendi.
Bulgular: COVID-KBH grubunda akut enfeksiyondan 6 ay sonra Cre (p=0.002) ve PLR'de artış(p=0.02), Ly(p=0.037) ve GFR'de (p=0.001) azalma görüldü. NON-COVID grubunda herhangi bir değişiklik tespit edilmedi. COVID grubunda PLR ve NLR ile BUN, Üre ve Cre arasında pozitif korelasyon, GFR ile negatif korelasyon izlendi. NON-COVID grubunda ise NLR ile sadece BUN arasında pozitif korelasyon izlendi.
Sonuç: SARS-COV-2 ile enfekte olup hayatta kalan ve diyalizsiz takipte olan kronik böbrek hastalarında, progresyon ve kronik inflamasyon şiddeti artmıştır.

Anahtar Kelimeler: kronik böbrek hastalığı; kronik inflamasyon şiddeti; progresyon; SARS-COV-2

ABSTRACT

Purpose: SARS-COV-2 (Severe acute Respiratory Syndrome Virus) has a wide organotropism. Although it predominantly affects the pulmonary system, it is commonly involved in the kidneys. Studies have shown that it increases acute kidney injury and mortality in patients with chronic kidney disease (CKD). However, its effects on the progression and severity of chronic inflammation in patients who survived and were followed up without dialysis are not yet known. Our aim in the study is to investigate kidney functions and the severity of chronic inflammation in post-COVID CKD.
Materials and Methods: The study was carried out retrospectively. Two groups were created as COVID-CKD(n=54) and NON-COVID CKD (control group)(n=60). Basal Blood Urea Nitrogen (BUN), Urea, Creatinine (Cre), Glomerular Filtration Rate (GFR), White Blood Cell (WBC), Neutrophil (Neu), Lymphocyte (Ly), Platelet (Plt), Plt/Ly ratio (PLR), and Neu/Ly Ratio (NLR) levels were analyzed and compared. Changes in the same parameters were analyzed in the groups, 6 months after the acute infection.
Results: An increase in Cre (p=0.002) and PLR (p=0.02) and a decrease in Ly (p=0.037) and GFR (p=0.001) were observed 6 months after acute infection in the COVID-CKD group. No changes were detected in the NON-COVID group. A positive correlation was found between PLR-NLR and BUN, Cre, and Urea, whilst a negative correlation was detected between PLR-NLR and GFR.
Conclusions: Progression and severity of chronic inflammation increased in SARS-COV-2 infected-survivor, non-dialysis followed-up CKD patients.

Keywords: chronic inflammation severity; chronic kidney disease; progression; SARS-COV-2

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INTRODUCTION

CKD is defined as the observed abnormalities in kidney structure or kidney functions that last longer than 3 months. The most common criteria for the diagnosis are Glomerular Filtration Rate (GFR) <60 Ml/DK/1.73 m² or Albumin/Creatinin Ratio (ACR) ≥30 mg/g.[1] Recently, CKD has increasingly prevailed and become a widespread public health problem. It results in a decline in quality of life, cardiovascular disease (CVD) at young age, malnutrition, psychological disorders, morbidity, and mortality with high hospitalization rates. Treatment costs have become expensive and abrasive.[2] CKD is a chronic inflammatory condition, and it occurs when the suppression of the inflammatory response is not realized or delayed. Tissue damage occurs as a result of an accumulation of pro-inflammatory mediators.[3,4] Increased inflammation is associated with the progression of atherosclerosis, cardiovascular disease, cachexia, anemia, and end-stage renal disease.[5,6] There are some biomarkers that are not expensive and easily measurable in the routine examination for the evaluation of chronic inflammation. Some of them could be listed as complete blood count(CBC) sub-biomarkers such as WBC, Neu, Ly, Plt, NLR, and PLR.[7,8] A recent study has shown that NLR and PLR ratios are significantly higher in non-dialysis followed-up patients with end-stage renal disease (ESRD), and pointed out that chronic inflammation leads to activation and up-regulation of those cells.[9] Furthermore, NLR was shown to be in negative and positive correlation with GFR and CKD stage, respectively.[10] Unfortunately, Coronavirus disease 2019 (COVID-19), which develops due to SARS-COV-2, causing significant morbidity and mortality in the world, has been shown to affect more than one organ, although it predominantly affects the pulmonary system.[11,12] Kidneys are among the most commonly involved organs. It has been determined that acute renal failure (ARF) develops at a rate of 30% in hospitalized patients due to SARS-COV-2, and it also causes an increased level of acute kidney injury in patients with CKD. Hematuria, proteinuria, increase in urea and creatinine levels, renal parenchymal inflammation, and edema findings were detected in computerized tomography (CT). Acute deterioration in renal function increased in-hospital mortality 5.3 times.[13,14] Studies have depicted that COVID-19 infection increases acute kidney injury and mortality in CKD disease. However, its effects on the progression and severity of chronic inflammation in surviving patients are not yet known. Our aim in the study is to investigate kidney functions and the severity of chronic inflammation in post-COVID CKD patients who are in follow-up without dialysis.

MATERIALS and METHODS

Our study was carried out retrospectively. Two groups were created as COVID-CKD and NON-COVID CKD. Patients' records between March 2020 to April 2021 were included in the study. The data set was obtained from the database of Kirsehir Ahi Evran University Training and Research Hospital. CKD diagnosis was determined via the N18.9 ICD (International Statistical Classification of Diseases and Related Health Problems) code. GFR levels were calculated with Chronic Kidney Disease Epidemiology Cooperation (CKD-EPI) formula:

Estimated GFR = 175 × standardized S_{cr} $^{-1.154}$ × age$^{-0.203}$ × 1.212 [if black] × 0.742 [if female], where GFR is expressed as mL/min/1.73 m2 of body surface area[41] and S_{cr} is expressed in mg/dl.[15]

A total of 54 and 60 patients were included in the COVID-CKD and NON-COVID CKD groups, respectively. Patients' age, gender, chronic diseases, and CKD durations (year) were recorded. The COVID–CKD group consisted of patients infected with SARS-COV-2 who survived and were followed up in the outpatient clinic. The values of the last 3 months of basal kidney function tests (BUN, Urea, Creatinine, GFR) and some complete blood count submarkers (WBC, Neu, Ly, Plt, PLR, and NLR), which show the severity of chronic inflammation, were recorded for both of the groups. Changes in basal kidney functions and chronic inflammation markers were analyzed in the COVID-CKD group 6 months after the acute infection. The 6-month changes were also investigated in the NON-COVID group, and comparisons were made across the groups. Complete blood count analysis was performed with the electrical impedance method on the Mindray BC-6800 system in the medical biochemistry laboratory of the Ministry of Health Kirsehir Ahi Evran University Training and Research Hospital of the Republic of Turkey, and the basal kidney tests were analyzed with the electrochemical

luminescence method on the Cobas 702 Auto Analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The NON-COVID CKD group was defined as the control group in this present study, to investigate the progression and chronic inflammation.

Inclusion Criteria

- ≥ 18 years

- GFR levels of 10-60 ml/dk/1.73 m2

- Polymerase Chain Reaction (PCR)-positive, clinical, and radiological final diagnosis in the COVID group

- Being not infected with any microorganism, including COVID infection for the control group

- Being in non-dialysis followed-up with the CKD process

Exclusion Criteria

- < 18 years

- GFR levels were >60 ml/dk/1.73 m^2

- GFR levels <10 ml/dk/1.73 m^2 and patients taking dialysis replacement therapy

- Patients with Acute COVID-19 infection

- Patients who are previously diagnosed with PCR-negative or suspected COVID

- Patients diagnosed with infectious, hypertensive crisis, hyperglycemia, myocardial infarctus /acute coronary syndrome (MI), cerebrovascular disease (CVA), metastatic malignancy, major surgical intervention, progressive liver cirrhosis, all of which are causing abrupt changes in kidney functions and CBC parameters in the last 3-months.

This study was approved by the Kırşehir Ahi Evran University Non-Interventional Clinical Research Ethics Committee with the Approval Date of 22-06-2021 and Approval Number: 2021-11/125.

Statistical Analysis

Mean ± standard deviation (SD) and median, minimum, and maximum values were given for quantitative variables, while frequencies (n) and percentages (%) were reported for categorical variables. Kolmogorov-Smirnov test was used for normality assumption, and Levene Test was applied for testing variance homogeneity assumption. Paired *t*-test or Wilcoxon test was applied for dependent measures. A Chi-Square Test was utilized for determining the association between COVID, NON-COVID groups and chronic diseases. Independent Samples *t*-test or Mann-Whitney U-test was performed for a comparison of values across COVID and NON-COVID groups. Mann-Whitney U-Test was also used for comparing the change between the measurements of before-COVID and 6 months after COVID. The change was defined as measurement at the 6^{th} month after COVID – Laboratory measurement before COVID. Spearman correlation coefficients were calculated to analyze the relationship between the parameters in both COVID and NON-COVID CKD groups. IBM SPSS Statistics version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used for all analysis. The significance level was taken as 0.05.

RESULTS

Mean age was 73.18 ± 8.6 years in total, 71.54 ± 11.1 years in the COVID-CKD group; while 74.65 ± 5.4 years in the NON-COVID-CKD group (p=0.066). No significance was found between the groups in terms of gender, duration of CRF, chronic diseases, baseline renal function tests, and baseline WBC, Neu, Ly, Plt, NLR, and PLR levels (p>0.05, for all) (Table 1).

Statistically significant differences were found between baseline values and Cre(p=0.002), GFR(p=0.001), Ly(p=0.037) and PLR (p=0.02) measurements taken at 6 months post-infection in the COVID-19 group, while GFR and Ly values showed a significant decrease in the 6 months after COVID. Cre and PLR values were observed to increase significantly (Table 2). In the NON-COVID group, however, no significant change was observed in any of the parameters at the 6^{th} month (p>0.05, for all) (Table 3). Results of the analysis of investigating the changes in pre-COVID and post-COVID values across the groups revealed that PLR values in the COVID-19 group were

found to be significantly higher than the PLR values in the NON-COVID group (p=0.023). Similarly, the 6th month Cre values in the COVID group were significantly higher than the 6 months post creatinine values of the NON-COVID group (p=0.013), while GFR levels were found to be significantly lower (p=0.007) (Table 4).

Table 1. Demographic, comorbidity characteristics and laboratory parameters of the groups

Variable	COVID-CKD (n=54)		NON-COVID CKD (n=60)		p-value
Age (Year)	74.59 ± 5.835		71.54 ± 11.113		0.066
Gender (M/F)(%)	(43/37)		(25/30)		0.711
CKD Duration (year)	3.65 ± 1.43		4.067 ± 1.625		0.137
HT	51 (0.46)		60 (0.54)		0.064
DM	27 (0.46)		32 (0.54)		0.722
CAD	23 (0.43)		31 (0.57)		0.333
COPD	4 (0.29)		10 (0.71)		0.133
Laboratory parameters	**Mean ± SD**	**Median [Min- Max]**	**Mean ± SD**	**Median [Min-Max]**	**p-value**
BUN	29.019 ± 10.865	28 [10-75]	32.209 ± 14.241	27 [14 - 78]	0.629*
UREA	62.759 ± 23.375	60 [23- 161]	69.35 ± 30.260	58.5 [30 - 166]	0.668*
CRE	1.513 ± 0.522	1.345 [0.96- 3.47]	1.472 ± 0.428	1.41 [0.96 - 3.42]	0.980*
GFR	43.889 ± 10.897	47 [18- 59]	43.35 ± 9.995	46 [17 - 61]	0.501*
WBC	8.371 ± 2.679	7.955 [2.08 - 14.98]	8.367 ± 2.183	8.12 [3.9 - 14.12]	0.993**
Neu	5.375 ± 2.263	4.87 [0.69 - 13.09]	5.240 ± 1.831	5.025 [1.96 - 10.49]	0.849*
Ly	2.084 ± 1.012	1.91 [0.43 - 5.71]	2.213 ± 0.805	1.97 [1.08 - 4.15]	0.452**
Plt	252.17 ± 72.201	262.5 [121 - 464]	246.933 ± 65.193	233.5 [140 - 433]	0.685**
NLR	3.236 ± 2.266	2.55 [0.68 - 11.33]	2.575 ± 1.154	2.19 [0.95 - 5.79]	0.213*
PLR	151.336 ± 107.467	122.265 [21.1 - 753.4]	123.9 ± 51.247	110.26 [52.04 - 326.05]	0.189*

COVID: Corona Virus Disease; HT: Hypertension; DM: Diabetes Mellitus; CAD: Coronary Artery Disease; COPD: Chronic Obstructive Pulmonary Disease; BUN: Blood Urea Nitrogen; Cre: Creatinin; GFR: Glomerular Filtration Rate;WBC:White Blood Cell; Neu: Neutrophil; Ly: Lymphocyte; Plt:Platelet; NLR: Neutrop-hil/Lymphocyte Ratio; PLR: Platelet/Lymphocyte Ratio

*: Independent samples t –test

**: Mann-Whitney U Test

Table 2. Changes between basal and 6-month after COVID of laboratory parameters in COVID CKD group

	COVID-CKD (n=54)				
Laboratory	**Basal values before**		**At 6th month after**		
Parameters	**Mean ± SD**	**Median [Min-Max]**	**Mean ± SD**	**Median [Min- Max]**	**p-value**
BUN	29.019 ± 10.86	28 [10- 75]	33.074 ± 18.889	25 [12. 95]	0.212**
UREA	62.759 ± 23.375	60 [23-161]	71.37 ± 40.645	54 [20. 205]	0.228**
CRE	1.513 ± 0.522	1.345 [0.96 - 3.47]	1.68 ± 0.713	1.46 [1 . 4.22]	0.002**
GFR	43.889 ± 10.897	47 [18-59]	40.537 ± 13.255	43.5 [11. 72]	0.001**
WBC	8.371 ± 2.679	7.955 [2.08 - 14.98]	8.324 ± 3.126	8.165 [2.69 - 20.23]	0.53*
Neu	5.375 ± 2.263	4.87 [0.69 - 13.09]	5.577 ± 2.708	5.18 [1.45 - 15.37]	0.935*
Ly	2.084 ± 1.012	1.91 [0.43 - 5.71]	1.889 ± 0.850	1.76 [0.34 - 4.49]	0.037*
Plt	252.17 ± 72.201	262.5 [121 - 464]	269.19 ± 95.835	256.5 [95 - 484]	0.102*
NLR	3.236 ± 2.266	2.55 [0.68 - 11.33]	3.893 ± 4.960	2.7 [0.94 - 36.7]	0.221*
PLR	151.336 ± 107.467	122.265 [21.1 - 753.4]	183.82 ± 192.948	144.44 [25 - 1438]	0.02*

BUN:Blood Urea Nitrogen;Cre:Creatinin;GFR:Glomerular Filtration Rate;WBC:White Blood Cell;Neu:Neutrophil;Ly:Lymphocyte;Plt:Platelet;NLR:Neutro-phil/Lymphocyte Ra-tio;PLR:Platelet/Lymphocyte Ratio

*: Wilcoxon Test

**: Paired- t Test

Table 3. Changes between basal and 6-month after COVID of laboratory parameters in NON-COVID CKD group

	NON-COVID-CKD (n=60)				
Laboratory	**Basal values before**		**At 6th month after**		
Parameters	**Mean ± SD**	**Median [Min - Max]**	**Mean ± SD**	**Median [Min - Max]**	**p-value**
BUN	32.209 ± 14.240	27 [14 - 78]	30.691 ± 12.582	26 [15 - 68]	0.147*
UREA	69.35 ± 30.259	58.5 [30 - 166]	65.417 ± 27.066	55 [32 - 146]	0.085*
CRE	1.472 ± 0.438	1.41 [0.96 - 3.42]	1.485 ± 0.559	1.375 [0.98 - 4.24]	0.871*
GFR	43.35 ± 9.995	46 [17 - 61]	43.841 ± 10.979	44.315 [13 - 69]	0.586**
WBC	8.367 ± 2.183	8.12 [3.9 - 14.12]	8.507 ± 2.580	7.98 [4.08 - 16.07]	0.517**
Neu	5.240 ± 1.831	5.025 [1.96 - 10.49]	5.304 ± 1.909	5.2 [1.9 - 11.03]	0.392*
Ly	2.213 ± 0.805	1.97 [1.08 - 4.15]	2.273 ± 0.911	1.965 [0.95 - 4.18]	0.651*
Plt	246.933 ± 65.193	233.5 [140 - 433]	248.1 ± 61.225	234.5 [135 - 435]	0.255*
NLR	2.575 ± 1.154	2.19 [0.95 - 5.79]	2.593 ± 1.103	2.21 [0.45 - 5.03]	0.334*
PLR	123.900 ± 51.247	110.26 [52.04 - 326.05]	122.026 ± 47.316	115.415 [56.2 - 338.94]	0.842*

BUN:Blood Urea Nitrogen;Cre:Creatinin;GFR:Glomerular Filtration Rate;WBC:White Blood Cell;Neu:Neutrophil;Ly:Lymphocyte;Plt:Platelet;NLR:Neutro-phil/Lymphocyte Ra-tio;PLR:Platelet/Lymphocyte Ratio

*: Wilcoxon Test

**: Paired- t Test

Table 4. Change analysis results across COVID and NON-COVID CKD groups (Change = Laboratory values at 6th month after COVID – Values before COVID)

Difference	NON-COVID		COVID		
Laboratory Parameters	**Mean ± SD**	**Median [Min / Max]**	**Mean ± SD**	**Median [Min / Max]**	**p-value**
WBC	0.14 ± 1.664	-0.075 [-3.13 / 7.19]	-0.047 ± 3.047	-0.07 [-6.38 / 9.94]	0.403*
NEU	0.065 ± 1.687	0.145 [-4.7/ 6.36]	0.201 ± 3.000	0 [-6.36 /10.5]	0.746*
LY	0.06 ± 0.594	0.025 [-1.08 / 2.14]	-0.195 ± 0.758	-0.175 [-1.94 / 2.19]	0.052*
PLT	1.167 ± 38.651	2 [-119 / 84]	17.019 ± 73.642	12 [-144 / 261]	0.254*
NLR	0.028 ± 0.936	0.05 [-4.33 /1.8]	0.657 ± 5.290	0.145 [-8.42 / 33.84]	0.376*
PLR	-1.874 ± 35.388	2.32 [-135.02/ 64.17]	32.482 ± 188.869	12.815 [-265.25 / 1275.15]	0.023*
BUN	-1.642 ± 10.150	-1 [-31 / 25]	4.056 ± 13.730	0 [-20 / 49]	0.118*
URE	-3.933 ± 21.410	-3 [-67 / 52]	8.611 ± 29.416	-0.5 [-43 / 106]	0.077*
CRE	0.013 ± 0.249	0.025 [-0.44 / 0.96]	0.167 ± 0.388	0.07 [-0.64 / 1.95]	0.013*
GFR	0.491 ± 6.941	-0.5 [-12 / 18]	-3.352 ± 7.479	-4 [-22 / 15]	0.007*

BUN: Blood Urea Nitrogen;Cre:Creatinin;GFR:Glomerular Filtration Rate;WBC:White Blood Cell;Neu:Neutrophil;Ly:Lymphocyte;Plt:Platelet;NLR:Neutrophil/Lymphocyte Ra-tio;PLR:Platelet/Lymphocyte
Ratio
*: Mann-Whitney U Test

In terms of the results of the correlation analysis of the 6th-month values of the groups, a positive correlation was found between NLR and BUN values in the NON-COVID group. As NLR values increase, BUN values also increase (p=0.049). Furthermore, a negative correlation was observed between Ly and BUN (p=0.001) and UREA (p=0.004) and a positive correlation with GFR (p=0.027) in the COVID group. As the lymphocyte levels of the patients increased, urea and urea values decreased and GFR values increased. There was a positive correlation between NLR and BUN (p=0.003), UREA (p=0.003), and Cre (p=0.01) values in the mentioned group, and a negative correlation was found with GFR (p=0.014) values. As NLR values increased, BUN, UREA, and Cre values increased and GFR values decreased. Similarly, positive correlations between PLR and BUN (p=0.002), UREA (p=0.002) and Cre (p=0.046), and a negative correlation with GFR (p=0.024) values were found. As the PLR values of the individuals increased, BUN, UREA, and Cre values increased and GFR values decreased (Table 5).

Table 5. Correlation analysis results of the 6th month values of the groups

GROUPS	VARIABLE	BUN	UREA	CRE	GFR
NON-COVID GROUP	**WBC**	0.061 (0.642)	0.056 (0.671)	0.063 (0.63)	-0.049 (0.708)
	NEU	0.141 (0.283)	0.135 (0.305)	0.117 (0.372)	-0.112 (0.396)
	LY	-0.09 (0.494)	-0.091 (0.49)	-0.054 (0.683)	0.036 (0.788)
	PLT	-0.095 (0.468)	-0.113 (0.389)	-0.161 (0.218)	0.032 (0.808)
	NLR	0.258 (0.049)	0.254 (0.052)	0.187 (0.156)	-0.195 (0.138)
	PLR	0.103 (0.434)	0.093 (0.48)	0.033 (0.8)	-0.099 (0.451)
COVID GROUP	**WBC**	0.019 (0.894)	0.015 (0.915)	0.071 (0.611)	-0.077 (0.579)
	NEU	0.166 (0.23)	0.165 (0.232)	0.181 (0.192)	-0.187 (0.175)
	LY	-0.428 (0.001)	-0.438 (0.001)	-0.304 (0.025)	0.300 (0.027)
	PLT	0.056 (0.688)	0.053 (0.706)	-0.08 (0.568)	0.059 (0.671)
	NLR	0.393 (0.003)	0.392 (0.003)	0.347 (0.01)	-0.334 (0.014)
	PLR	0.414 (0.002)	0.413 (0.002)	0.272(0.046)	-0.307 (0.024)

BUN: Blood Urea Nitrogen; Cre:Creatinin; GFR:Glomerular Filtration Rate; WBC:White Blood Cell; Neu:Neutrophil; Ly:Lymphocyte; Plt:Platelet; NLR:Neutrophil/Lymphocyte Ratio; PLR:Platelet/Lymphocyte
Ratio

DISCUSSION

Our study is the first to investigate the progression and severity of chronic inflammation in SARS-COV-2 infected-survivors, non-dialysis followed-up CKD patients. Chronic inflammation has an important role in the initiation and progression of various diseases such as diabetes mellitus (DM), cardiovascular disease, and chronic kidney disease (CKD). As the severity of chronic inflammation increases in CKD patients, progression accelerates.[16] The primary endpoint of our study is the progression in COVID patients. The most important findings are the increase in Creatinin (p=0.002) and the decrease in GFR (p=0.001)

(Table 2). The secondary endpoint was the increased severity of chronic inflammation. PLR indicates systemic and chronic inflammation. It is an important participant in thrombosis. It is a biomarker that can be detected very easily in practice.[17] Studies have reported that platelet distribution, number, volume, and PLR are associated with poor prognosis in systemic inflammatory diseases.[18,19] In a retrospective study conducted by Rong et al., it was shown that as the difference in PLR ratios during diagnosis and follow-up of 30 patients infected with SARS-COV-2 increased, the length of stay was prolonged, and the clinical severity increased, and the prognosis was adversely affected.[20] The increase in PLR is associated with increased aggregation. Studies have shown that SARS-COV-2 increases coagulation and aggregation.[21] Ahbap et al., on the other hand, found a correlation between chronic inflammation and PLR and NLR in patients with end-stage renal disease who were non-dialysis followed-ups. As the ratios of PLR and NLR increased, the severity of chronic inflammation increased.[22] Sarkar et al. pointed out in their meta-analysis study that PLR is an important prognostic indicator in COVID-19, and mortality increases as PLR increases during the first admission with acute infection.[23] In our study, PLR was found to be significantly higher in the follow-up (6th month) in patients infected with SARS-COV-2 (Table 2). However, as PLR increased, BUN, UREA, and Cre increased, while GFR decreased (Table 5). No change was detected in the NON-COVID group (Table 3). This indicates the increased severity and progression of chronic inflammation due to SARS-COV-2. Lymphopenia is a very common finding in COVID-19. It shows an inadequate immune response against the viral pathogen.[24] As the severity of the disease and the mortality rate increased, a lower number of lymphopenia was observed. From the onset of symptoms, less than 20% lymphocyte ratio was detected on days 10-12th and less than 5% on days 17-19th, demonstrating that it has a poor prognosis by Tan et al.[25,26] However, low lymphocyte counts in patients with chronic kidney disease have been found to reflect a deterioration in nutritional status, and malnutrition was observed to cause negative kidney outcomes.[27,28] Patients infected with SARS-COV-2 are at risk of malnutrition due to decreased food intake, increased catabolism due to increased inflammation, decreased mobility, advanced age, and comorbidities.[29] In the cohort study of 450 COVID-19 cases conducted by Qin et al., it was found that as the severity of the disease increased, there was an increase in NLR and a decrease in the number of lymphocytes.[25] NLR is an independent risk factor for disease severity in COVID-19.[30] Although it was not statistically significant, NLR increased at the 6th month in SARS-COV-2 infected group (p=0.221) (Table 2). While a positive correlation was found between NLR and BUN in NON-COVID only, a positive correlation was found with BUN, UREA, and Cre, and a negative correlation with GFR in the COVID group (Table 5). Yoshitomi et al. suggested in their prospective study that GFR was negatively correlated with NLR, and it was an important marker in predicting the progression of the disease by increasing the severity of chronic inflammation.[31] Patients in the NON-COVID group also had chronic inflammation. However, no significant change measured after 6 months may indicate that the inflammation is more controlled, or longer follow-up may be required. At this point, the role of SARS-COV-2 is important. In its pathogenesis, incomplete healing, the inability of anti-inflammatory systems to control pro-inflammation, and consequently increased chronic interstitial inflammation may have caused glomerulotubular damage due to chronic micro thrombotic angiopathies. Patients with chronic kidney disease are fragile. Patients infected with SARS-COV-2 are at increased risk of chronic inflammation severity and progression. We recommend careful evaluation by clinicians of CKD patients recovering from COVID-19 with the help of the findings of this current study. Understanding the natural history of the disease is essential for improving outcomes in this patient population. In this study, we propose close follow-up and the development of new treatment strategies. Moreover, better conservative care, being more careful against infections, good regulation of chronic diseases, and adequate and balanced nutrition are recommended. However, in the study, we only searched and focused on some leukocyte sub-markers as a marker of increased chronic inflammation. We recommend testing for sedimentation, C-reactive protein (CRP), MPV (mean platelet volume), MPV/Plt, and IL-6 levels. We also recommend investigating a complete urinalysis, hematuria, and proteinuria levels, which show the progression from another perspective.

Limitations

Unfortunately, due to the ongoing pandemic, the routine treatment of surviving patients' admissions to outpatient follow-ups has also decreased. Therefore, the small sample size and the single-center nature of the study appear to be important limitations. We recommend conducting multi-center studies with at least 1-year follow-up and a larger sample size.

To conclude up, SARS-COV-2 causes an increase in PLR and a decrease in Ly levels in CKD patients who are under dialysis follow-up, increasing the severity of chronic inflammation and thus accelerating its progression.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Ethics Committee Permission

This study was approved by the Kırşehir Ahi Evran University Non-Interventional Clinical Research Ethics Committee with the Approval Date of 22-06-2021 and Approval Number: 2021-11/125.

Authors' Contributions

Concept/Design: HEY. Data Collection and/or Processing: HEY. Data analysis and interpretation: NMK. Literature Search: HEY. Drafting manuscript: HEY, NMK. Critical revision of manuscript: HEY, NMK.

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