Original Article

DOI: 10.4274/haseki.galenos.2022.8694
Med Bull Haseki 2022;60:345-350

Can We Use Inflammation Biomarkers Based on Complete Blood Cell Count in the Follow-up of COVID-19 in Hemodialysis Patients?

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Abstract

Aim: Coronavirus disease-2019 (COVID-19) is more severe in hemodialysis patients than in the average population and causes much higher mortality. This study investigated the effect of inflammation parameters obtained from complete blood count on the prognosis of COVID-19 in hemodialysis patients with COVID-19.

Methods: Hemodialysis patients admitted to our hospital between 11.03.2020 and 01.12.2020 with the diagnosis of COVID-19 were included in this study. The relationship between the oxygen requirement, intensive care requirements, and mortality development of the patients and the parameters obtained from the complete blood count, C-reactive protein (CRP), secondary infection, and demographic characteristics of the patients were investigated.

Results: A total of 94 hemodialysis patients were included in the study. There was a correlation between secondary infections and the need for oxygen and intensive care (p=0.001 and p<0.001, respectively). CRP levels were associated with mortality, need for intensive care and oxygen demand (p=0.031, p=0.019 and p=0.014, respectively). Systemic inflammation index, derived neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio were associated with oxygen demand (p=0.002, p=0.009 and p=0.044, respectively). The systemic inflammation index, platelet-lymphocyte ratio, and derived neutrophil-lymphocyte ratio exhibited the highest specificity (19.4% vs 26.9% vs 16.4%) and sensitivity (96.7% vs 92.6% vs 96.7%) and the largest areas under the curve of 0.672 vs 0.652 vs 0.666, respectively.

Conclusion: Systemic inflammation index, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio obtained from complete blood count parameters in hemodialysis patients are functional parameters that can be used to predict the course of COVID-19.

Keywords: COVID-19, hemodialysis, systemic inflammation index, complete blood cell count

Introduction

Coronavirus disease-2019 (COVID-19) is important because of its rapid spread, incurability, and fatal course. It can cause various signs of infection, from asymptomatic to severe pneumonia. Although studies show that the disease is milder in severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) variants that emerged in the last months of 2021, the disease is especially severe in the elderly and patients with comorbidities. The most common symptoms of COVID-19 are cough, fever, shortness of breath, and fatigue. There is data that COVID-19 is severe in patients undergoing hemodialysis (HD) treatment (1-3). Chronic uremia may cause inflammation at the molecular level in patients with HD, suppressing immunity and altering the immune response to viral diseases (4). Acute respiratory distress associated with the rapid onset of the systemic proinflammatory process is the leading cause of death in COVID-19 patients. According to clinical symptoms and laboratory test results, patients are classified as mild, moderate, severe, and critical (5). Patients with severe symptoms may develop severe pneumonia, acute respiratory distress syndrome (ARDS), or death (6).

In revealing the severity of COVID-19, it is essential to determine the biomarkers with fast results that are easily accessible. These tests can help provide early and aggressive treatment, reduce mortality, and reduce hospital stays and costs. In the early diagnosis of most diseases, routine

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Received: 06.08.2022 **Accepted:** 17.09.2022

blood tests used to evaluate inflammatory processes are often helpful and necessary (7). Complete blood count (CBC), an easy, accessible, and inexpensive test, is frequently used to evaluate inflammatory processes. CBC provides information about the number and morphological appearance of various cell types [white blood count (WBC), neutrophils, lymphocyte monocytes, mean platelet volume (MPV)], platelet, etc (8,9).

Recent studies show that the following factors help predict the severity of COVID-19: platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), derived NLR (dNLR), MPV-platelet ratio (MPR), monocyte-lymphocyte ratio (MLR), neutrophil ratio, lymphocyte x platelet ratio (NLPR), systemic inflammation response index (SIRI), and systemic inflammation index (SII) (7-11).

In this study, we aimed to investigate whether readily available and low-cost CBC parameters-WBC, lymphocyte, platelet, MPV, MPR, NLR, dNRL, PLR, SII, and NLPR-help predict disease severity.

Materials and Methods

Compliance with Ethical Standards

The research protocol was approved by the Kartal Dr. Lutfi Kirdar City Hospital Clinical Research Ethics Committee (approval number: 2020/514/187/13). Our study was retrospective and was waived under the patient consent form.

Study Design

Hemodialysis patients admitted to our hospital between 11.03.2020 and 01.12.2020 with the diagnosis of COVID-19 were included in this study. A real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) test was performed for SARS-CoV-2 with nasopharyngeal and oropharyngeal samples in all patients who applied to our hospital, with findings suggestive of COVID-19. Additionally, chest-computed tomography was performed on all of these patients. The presence of crazy-paving patterns, ground-glass opacities, and consolidation in chest tomography was defined as tomography findings compatible with COVID-19. Patients with HD who had a positive rRT-PCR test for SARS-CoV-2 and/or had typical findings for COVID-19 on lung tomography were included in the study. CBC and CRP tests were performed at the time of admission to the hospital.

The relationship between the oxygen requirement, intensive care requirements, and mortality development of the patients included in the study and the parameters obtained from the CBC, CRP, secondary infection, and demographic characteristics of the patients were investigated.

Clinical Data Collection

The demographic characteristics of all patients (age, gender), chronic diseases [hypertension (HT), diabetes mellitus, congestive heart failure (CHF), asthma, chronic obstructive pulmonary disease], coronary artery diseases (angina pectoris, myocardial infarction, documented coronary heart disease) were recorded. Admission symptoms (fever, cough, shortness of breath, nausea, vomiting, diarrhea, abdominal pain, myalgia, conjunctivitis, loss of smell or taste) were questioned. The need for oxygen support was determined as <93% oxygen saturation in room air, and the patients in need of oxygen were recorded. The diagnosis of secondary infection was made by infectious disease specialists (findings of the presence of additional infection focus; pyuria, abscess, catheter infection, etc. and culture growths were evaluated), and the patients with secondary infection were recorded. The patients needing intensive care were recorded as per the COVID-19 Guidelines of the Ministry of Health (12). Additionally, laboratory values [WBC, neutrophils, platelets, lymphocytes, C-reactive protein (CRP)], and clinical results (cure, in-hospital follow-up, death, and treatments) were evaluated. Leukocytosis, lymphopenia, neutrophilia, and increased CRP were defined as follows, according to the hospital laboratory's given normal ranges: WBC: >10800 u/L leukocytosis, lymphocyte count: ≤1300 u/L lymphopenia, neutrophil count: >7700 u/L neutrophilia, platelet count: <130000 u/L thrombocytopenia and CRP: >3 mg/L CRP increase. MPV value normal range: 9.2-11.2 μm^3.

Complete blood count indices predicting systemic inflammation were calculated using the following formulas: PLR; platelet/lymphocyte, NLR; neutrophil/lymphocyte, dNLR; neutrophils/(WBC-neutrophils), MPR; MPV/platelet, NLPR; neutrophil/(lymphocyte X platelet), SII (neutrophil X platelet/lymphocyte].

Statistical Analysis

Statistical analysis was performed with the software SPSS Statistics for Windows, version 21 (IBM Corporation, Armonk, NY, USA). The statistical significance limit of the p-value was accepted as 0.05. Numerical variables were given as mean + standard deviation if normally distributed and mean + standard deviation (median) if skewed continuous were distributed. Categorical variables are shown as frequencies. Chi-square. A test was used to evaluate the categorical data. In the analysis of continuous variables, the independent samples t-test and Mann-Whitney U were used under the data distribution. Receiver operating characteristic (ROC) analysis was performed with calculations of area under the curve, sensitivity, and specificity to evaluate the predictive value of parameters with significant p-values.

Results

Our study was completed with 94 patients diagnosed with HD and COVID-19. The most common symptom in the patients was dyspnea, and the most common accompanying disease was HT.

At follow-up, oxygen support was required in 72% of the patients (68 patients). Secondary infection was detected in 35% of these 68 patients (24 patients). Secondary infection was observed in 4% (1 patient) of 26 patients who did not need oxygen support (p=0.001). Secondary infection was detected in 53% (16/30 patients) of those who needed intensive care. Secondary infection was observed in 14% (9/64 patients) patients not requiring intensive care (p<0.001).

The mean CRP value of the patients who needed oxygen was 110.2 mg/L, and the mean CRP value of the patients who did not need oxygen was 70.3 mg/L (p=0.014). The mean CRP value of patients requiring intensive care was 128 mg/L, and the mean CRP value of patients not requiring intensive care was 85.5 mg/L (p=0.019). The mean CRP value of seventy-one surviving patients was 88.7 mg/L, while the mean CRP value of the deceased patients was 131.6 mg/L (p=0.031).

The mean PLR value of the patients who needed oxygen was 307.9, the mean dNLR value was 5.41, and the mean SII value was 2025. The mean PLR value of the patients who did not need oxygen was 202, the mean dNLR value was 3.42, and the mean SII value was 1061 (p=0.009, p=0.044, p=0.002, respectively).

These parameters' ROC curves were found to correlate significantly with the oxygen demand (Figure 1) (13,14). SII exhibited the most significant specificity (19.4%) and sensitivity (96.7%) and the largest area under the curve at 0.672. PLR exhibited the highest specificity (26.9%) and sensitivity (92.6%) and the largest area under the curve at 0.652. dNLR exhibited the most significant specificity (16.4%) and sensitivity (96.7%), with the largest area under the curve at 0.666. The optimal threshold values for SII, PLR, and d-NLR were 3184.4, 408.5, and 10.9, respectively.

No significant correlation was found between age, gender, WBC, neutrophil, lymphocyte, platelet, NLR, dNLR, PLR, MPR, NLPR, and SII values of 30 (32%) patients who needed intensive care and 23 (24%) patients who died. There was no significant relationship between oxygen demand and age, gender, WBC, neutrophil, lymphocyte, platelet, CRP, NLR, MPR, or NLPR values. The oxygen demand characteristics of the study population are detailed in Table 1. ROC analysis results for dNLR, SII, and PLR values in the estimation of oxygen demand are detailed in Table 2.

Discussion

COVID-19 is a fatal disease that affects the entire world. It forces the health system to handle a high number

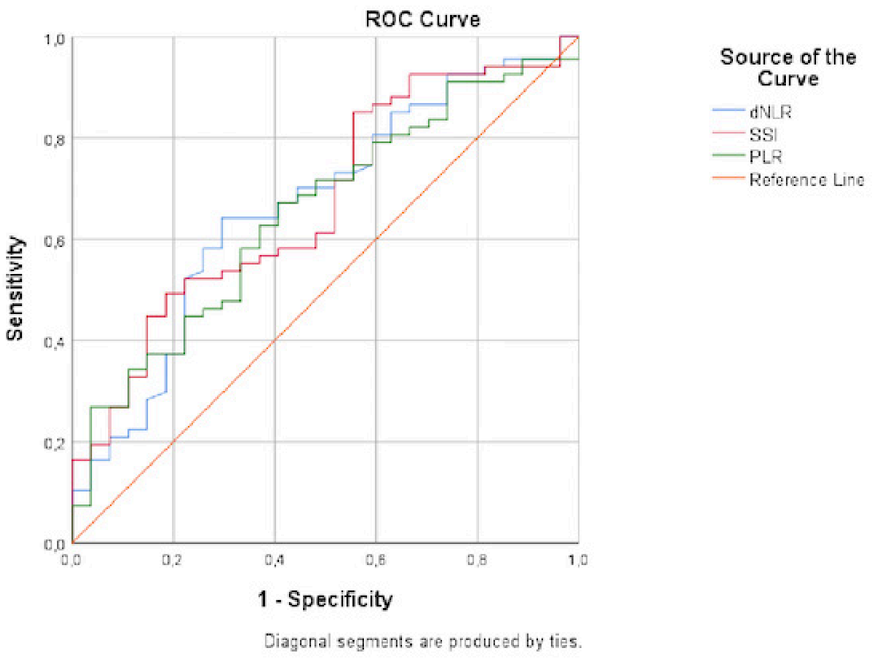

Figure 1. SII, PLR, and dNLR ROC curves in COVID-19 patients developing oxygen demand
ROC: Receiver operating characteristic, SII: Systemic inflammation index, PLR: Platelet-lymphocyte ratio, dNLR: Derived neutrophil-lymphocyte ratio

Table 1. The features of the patients stratified by oxgen support need in the follow-up				
Parameters	**Oxgen support (-)**	**Oxgen support (+)**	**Total**	**p-value**
Demographic features				
Age	60.3±12.6 (67)	63.2±15.8 (66.5)	62.5±15 (65)	0.287
Sex				1
Female, n	11 (42%)	38 (56%)	49 (52%)	
Male, n	15 (58%)	30 (44%)	54 (48%)	
Hypertension, n	16 (57%)	55 (81%)	71 (76%)	0.063
Diabetes mellitus, n	9 (32%)	41 (60%)	50 (54%)	0.417
CHF, n	4 (15%)	11 (16%)	15 (16%)	1
CVD, n	7 (27%)	20 (29%)	27 (29%)	1
COLD, n	3 (12%)	3 (4%)	6 (6%)	0.208
Dispne, n	9 (35%)	39 (57%)	48 (51%)	0.065
Fever, n	8 (31%)	21 (31%)	29 (31%)	1
Cough, n	12 (46%)	21 (31%)	43 (46%)	0.126
Secondary infection, n	1 (4%)	24 (35%)	25 (27%)	0.001
Mortality, n	0 (0%)	23 (34%)	23 (24%)	0.000
Laboratory findings				
WBC, u/L	7192±4483	8217±4483	7821±4438	0.312
Neutrophils, u/L	5388±4074	6522±4252	6208±4213	0.245
Lymphocytes, u/L	1176±557	1004±701	1052±666	0.264
Platelets, u/L	198730±79830 (197000)	213397±97531 (205555)	209340±92788 (204000)	0.704
CRP, mg/dL	70.3±59	110±88.9	99±83.4	0.577
Data calculated from CBC parameters				
NLR,	5.85±3.8	9.8±10.2	8.7±9.3	0.064
dNLR,	3.4±2.9	5.4±4.8	4.9±4.4	0.044
PLR,	202±126	308±251	278±228	0.009
MPR,	0.055±0.039	0.051±0.027	0.052±0.038	0.623
NLPR,	0.046±0.096	0.058±0.086	0.055±0.089	0.559
SII,	1.06±0.91	2.02±1.9	1.75±1.80	0.002

CHF: Congestive heart failure, CVD: Coronary vascular diseases, COLD: Chronic obstructive lung disease, WBC: White blood cell, CRP: C- reactive protein, CBC: Complete blood count, NLR: Neutrophil-to-lymphocyte ratio, dNLR: Derived NLR, PLR: Platelet-lymphocyte ratio, MPR: Mean platelet volume to platelet ratio, NLPR: Neutrophil to lymphocyte x platelet ratio, SII: Systemic inflammation index
Data are given as (mean ± standard deviation) (median)

Table 2. ROC analysis results for dNLR, SII, PLR values in estimating the oxygen demand requirement					
Parameters	**AUC**	**Optimal cut-off**	**p-value**	**Specificity, %**	**Sensitivity, %**
dNLR	0.666	10.9	0.012	16.4	96.7
SII	0.672	3184.4	0.009	19.4	96.7
PLR	0.652	408.5	0.021	26.9	92.6

AUC: Area under the curve, dNLR: Derived neutrophil-lymphocyte ratio, SII: Systemic inflammation index, PLR: Platelet-lymphocyte ratio, ROC:

of patients and increases costs. For this reason, there is a need for fast, easy-to-access and low-cost monitoring parameters.

WBC, lymphocyte, platelet, MPV, MPR, NLR, NLPR, dNRL, PLR, SII, MLR, and SIRI parameters were examined in the general patient population with COVID-19 (7). A limited number of studies show the effect of parameters obtained from CBC count on prognosis in patients with HD. These studies investigated the relationships of WBC, lymphocytes, platelets, NLR, and PLR with disease severity (15,16).

We revealed the relationship between the clinical course of inflammation parameters arising from the whole blood cell count of 94 patients with HD infected with COVID-19 during the 10 months of the pandemic.

The mean age of the patients included in the study was 62.4±15 (median: 65). Similar to other studies (between 57-66) in patients with HD infected with COVID-19, it showed that the patients in our study were generally older (1-3). Most of our patients (72%) were women. The distribution of gender varies according to research (1,17,18).

Cough and shortness of breath were the most common symptoms in our study, similar to the patient groups diagnosed with COVID-19 who received HD treatment and those who did not receive HD treatment (1,3,19,20). Similarly, the most common comorbid disease was HT (21,22).

We examined inflammatory tests related to ICU requirement, oxygen requirement, mortality, and CBC count. The most common abnormal laboratory parameters were lymphopenia and increased CRP.

The severity of COVID-19, mortality rates, need for intensive care, leukocytosis, lymphopenia, high neutrophils, thrombocytopenia, NLR, dNLR, PLR, SII, and high CRP were associated in general population studies (10,17,20,23).

In COVID-19 studies specific to patients with HD, severe COVID-19 was associated with mortality and the need for intensive care, leukocytosis, lymphopenia, neutrophil elevation, thrombocytopenia, NLR, PLR, and CRP (15,16,21). Consistent with the literature data, our study found a statistically significant relationship between the need for intensive care, mortality, and CRP. Additionally, significant relationships were found between oxygen demand and CRP, systemic inflammation index, PLR, and dNLR. In several studies in patients with HD and some normal population studies, SII, PLR, and dNLR parameters have been associated with severe COVID-19 infection (10,24-26). The lack of statistical significance with other parameters may have resulted from the small number of patients limiting the statistical analysis results.

When the data was examined, it was discovered that there was a significant relationship between secondary infection and oxygen demand, as well as between secondary infection and intensive care, which was consistent with the literature (1,17,23). The mortality rate in our patient group was 24% and was similar to other studies in patients with HD (1,3).

Study Limitations

Our study's small number of patients should be noted as a limitation. However, patients with HD are a small group when considering all COVID-19 patients. Additionally, examinations to exclude different atypical pneumonia pathogens may not be performed due to the high patient load, particularly in the first period of the pandemic. Another limitation is the absence of positive rRT-PCR testing for SARS-CoV-2 in all of our study patients. Due to insufficient laboratories in the first period of the pandemic, PCR tests gave results in 48-72 hours. All patients underwent lung CT scans for a rapid diagnosis of COVID-19. In our study, all patients with negative rRT-PCR tests had typical CT lesions suggestive of COVID-19. In some studies, it was observed that the PCR tests of patients with tomography findings were positive in repeated PCR tests but negative in the first PCR test (19,27). Despite these limitations of our study, it was one of the first studies to investigate the subject of the HD patient group, and it was one of the first to deal with dialysis patients.

Conclusions

It has been revealed that secondary infections adversely affect the prognosis of patients with HD with COVID-19. Furthermore, dNLR, PLR, and SII parameters from CBC count were determined as low specificity but high sensitivity parameters for disease severity and hospital stay in patients with HD with COVID-19. Studies with more patients are needed to reveal the place of dNLR, PLR, and SII parameters in the follow-up of COVID-19 in patients with HD with the available data.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Kartal Dr. Lutfi Kirdar City Hospital (decision number: 2020/54/187/13).

Informed Consent: Informed consent was waived.

Peer-reviewed: Internally peer-reviewed.

Authorship Contributions

Concept: K.A.B., Design: K.A.B., T.T., Data Collection and/or Processing: K.A.B., T.T., Analysis and/or Interpretation: K.A.B., Literature Research: K.A.B., T.T., Writing: K.A.B., T.T.

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

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

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