AUCTORES
Globalize your Research

Journal of Clinical and Laboratory Research
Ümmügülsüm Gaygisiz *

Open Access

Research Article

The Prognostic Value of Extended Inflammation Parameters and Soluble Fibrin Monomer Complex in Covid-19 Patients in The Intensive Care Unit

Ümmügülsüm Gaygisiz [1]*, Zühre Kaya [2], Serap Kirkiz [3], Hasan Selçuk Özger [4], Müge Aydoğdu [5], Özlem Güzel Tunçcan[6], Esin Şenol[7]

[1] Department of Anesthesiology and Intensive Care, Faculty of Medicine, Gazi University, Ankara, Turkey.

[2] Department of Pediatric Hematology and Director of Hemostasis and Hematology, Faculty of Medicine, Gazi University, Ankara, Turkey.

[3] Department of Pediatric Hematology, Faculty of Medicine, Gazi University, Ankara, Turkey

[4] Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Gazi University, Ankara, Turkey.

[5] Department of Pulmonary Critical Care Medicine, Faculty of Medicine, Gazi University, Ankara, Turkey.

***Corresponding Author:** Ümmügülsüm Gaygisiz, Department of Anesthesiology and Intensive Care, Faculty of Medicine, Gazi University, Ankara, Turkey.

Received Date: January 09, 2024 | **Accepted Date:** January 24, 2024 | **Published Date:** January 29, 2024

Citation: Ümmügülsüm Gaygisiz, Zühre Kaya, Serap Kirkiz, Hasan Selçuk Özger, Müge Aydoğdu, et al, (2024), The Prognostic Value of Extended Inflammation Parameters and Soluble Fibrin Monomer Complex in Covid-19 Patients in The Intensive Care Unit, *Journal of Clinical and Laboratory Research*, 7(3); **DOI:**10.31579/2768-0487/124

Abstract

Objective: This study aimed to investigate how extended inflammation markers (EIM) and soluble fibrin monomer complex (SFMC) affected the prognosis of COVID-19-infected patients in the intensive care unit (ICU).

Methods: In this study, 73 adults with COVID-19 were included. Patients were divided into two groups: those who died (Group 1; n = 45) and those who survived (Group 2; n = 28). SFMC and EIM [neutrophil reactivity index (NEUT-RI) and neutrophil granularity index (NEUT-GI), reactive lymphocyte (RE-LYMPH), antibodies synthesizing lymphocyte (AS-LYMP), neutrophil/lymphocyte ratio (NLR) and immature granulocyte/lymphocyte ratio (IGLR)], were analyzed in the first 28 days of these patients' follow-up.

Results: The median NLR during the first four weeks, IGLR in the first two weeks, RE-LYMPH in the first three weeks, NEUT-RI and NEUT-GI values in the second week, and AS-LYMP in the third week of follow-up were significantly higher in Group 1 than in Group 2 ($p<0.05$). The median D-Dimer level during the first three weeks and SFMC value in the first week of follow-up were significantly higher in Group 1 than in Group 2 ($p<0.05$). In patients with COVID-19, older age (≥65 years), nosocomial infection, blood product use, longer ICU stay (>7 days), high DIC (>5), and comorbidities (>3) scores were all risk factors for mortality. In ROC analysis, the cut-off values for NLR and SFMC to predict mortality were 6 and 6.5, respectively.

Conclusion: Our data show that elevated NLR and SFMC values in the first week should alert physicians to the risk of life-threatening COVID-19 complications.

Key words: covid-19; extended inflammatory parameters; fibrin monomer; intensive care; mortality

Introduction

Coronavirus disease 2019 (COVID-19) may cause a wide range of clinical symptoms, from asymptomatic infections to fatal disorders.1 In this SARS-CoV-2 viral infection, a mechanism known as immunothrombosis develops, in which the immune and coagulation systems collaborate to stop infections and limit their spread.1,2 Clinicians required quick, low-cost, and routine measures to predict the severity of the disease and demonstrate the dysregulated immune response during the pandemic period. C-reactive protein, ferritin, D-dimer, and lactate dehydrogenase are all easily measured parameters that are routinely used to predict severe disease and mortality.3-5 In recent years, extended inflammation markers (EIM) that can reveal the activation and functional status of the leukocyte series with the onset of an

inflammatory stimulus (neutrophil reactivity and granularity index showing neutrophil activation, immature granulocytes (IG) indicating neutrophil precursors and antibody synthesizing lymphocytes) have been performed in parallel with technological developments.6 This information can be utilized to influence the severity of the immune response and the course of the disease in the early stages of infection.7,8 In addition to D-dimer, soluble fibrin monomer complex (SFMC) can be assessed in a coagulation device, which is considered an early indicator of thrombosis.9 SFMC is significantly elevated at the onset of thrombotic diseases such as myocardial infarction (MI) or deep vein thrombosis (DVT) and is a better indicator than fibrin degradation products (e.g., D-dimer) in revealing disseminated intravascular coagulation (DIC).10,11 Although there is no study in the literature that evaluated the EIM and SFMC together in determining the prognosis of COVID-19 patients, there are a few studies that evaluated the EIM and SFMC separately in terms of the effects on disease prognosis.12-17 We investigated how changes in EIM and SFMC levels predicted mortality in COVID-19 patients who needed intensive care unit (ICU) in our research.

Materials and methods

The cross-sectional study examined COVID-19 patients at the ICU of Gazi University Faculty of Medicine Hospital between April 2020 and December 2021. The ethics committee of the Gazi Clinical Research Ethics Committee approved the study.

Study Population

Adult patients (>18 years old) with ICD U07.3 who were hospitalized in the ICU and tested positive for SARS-CoV-2 PCR in nasopharyngeal, oropharyngeal, or lower respiratory tract samples were included in the study. Patients infected with other viruses have been excluded.

Study Design

Patients were categorized into two groups based on their survival status: those who did not survive (Group 1; n = 45) and those who did survive (Group 2; n = 28). The hospital's record system was used to access detailed file information for each patient. Comorbidities (chronic heart failure, chronic lung disease, chronic renal disease, cancer, diabetes mellitus, etc.) were recorded for each patient, and the Charlson Comorbidity Index18 was calculated. During ICU monitoring, thromboembolic events (pulmonary thromboembolism, DVT, MI, acute stroke), clinically apparent DIC (bleeding or thrombosis), and nosocomial infections were documented. COVID-19 pneumonia severity and the need for ICU were recorded throughout the study, and treatments were planned following the Turkish Ministry of Health's COVID-19 Diagnosis and Treatment Guidelines.19 Blood products, Convalescent plasma, steroids, and tocilizumab were used.

Laboratory Parameters

Blood samples for complete blood count (CBC) parameters containing extended inflammation parameters, as well as coagulation tests including SFMC, were collected from these patients at the following time intervals: during the first week (0-7 days), second week (8-14 days), third week (15-21 days), and fourth week (22-28 days) following the initial diagnosis. The automated blood cell analyzer Sysmex XN® 1000 (Sysmex Corporation, Kobe, Japan) was used to assess routine CBC samples as well as the extended inflammatory parameters. Among these variables, neutrophil reactivity index (NEUT-RI), neutrophil granularity index (NEUT-GI), reactive lymphocytes (RE-LYMPH), and antibody-synthesizing lymphocytes (AS-LYMPH) were studied as research parameters beyond routine assessments. In addition, neutrophil-to-lymphocyte ratios (NLR) and immature granulocyte-to-lymphocyte ratios (IGLR) were calculated.

A coagulation device (Diagnostics Stago®, Asnières sur Seine, France) was used to perform tests on soluble fibrin monomer complex and D-dimer. All hemostatic parameters were used to calculate DIC scores based on ISTH.20,21 All recorded laboratory parameters are presented in Table 1.

Statistical Analysis

The SPSS 22.0 statistical program (SPSS, Inc., Chicago, IL, USA) was used to analyze all data. Continuous variables with a normal distribution were given as mean and standard deviation (SD), while non-normal variables were reported as median and interquartile ranges (IQR). The categorical variables of the patients were recorded as counts and percentages, and they were compared using the chi-square test and the resulting Odds ratio (OR) and 95% confidence intervals (95% CI). Non-parametric data were evaluated using the Mann-Whitney U test, and parametric data were evaluated using the student t-test. To assess the predictive usefulness of EIM and SFMC in predicting mortality among COVID-19 patients, ROC curves were generated and the area under the curve (AUC) was calculated. A p-value of less than 0.05 was considered statistically significant.

Results

During the follow-up period, 45 patients in Group 1 died (62%) while 28 patients in Group 2 survived (38%). Gender distribution did not differ statistically between the two groups (Table 1).

	Nonsurvivor *n*=45	**Survivor *n*=28**	***p* value**	**OR(95%CI)[3]**
Gender, *n* (%)				
Male	27(60%)	19(68%)	0.33	
Female	18(40%)	9(32%)		
Age, *n* (%)				
< 65 year	9(20%)	21(75%)	0.0001	4.3(2.0-8.8)
≥ 65 year	36(80%)	7(25%)		
Charlson comorbidity index, *n* (%)				
≤3	16(36%)	22(78%)	0.001	3.3(1.5-7.3)
>3	29(64%)	6(22%)		
Treatment types, *n* (%)				
Convalescent plasma	16(36%)	6(22%)	0.15	
Blood product	17(38%)	3(10%)	0.01	3.1(1.0-9.2)
Steroids	28(64%)	16(58%)	0.42	
Tocilizumab	20(44%)	16(42%)	0.54	
Nosocomial infection, *n* (%)	33(74%)	2(7%)	0.0001	11.9(3.0-46.8)
DIC[1] score, *n* (%)				
>5	15(34%)	2(7%)	0.008	3.9(1.0-14.9)
≤5	30(66%)	26(93%)		

Thromboembolic events, *n* (%)	6(14%)	0(0%)	0.07	
Length of stay in ICU[2] (days), *n* (%)				
>7	40(91%)	12(%41)	0.0001	3.5(2.0-6.1)
≤7	4(9%)	17(%59)		

Table 1. Demographic data and risk factors for mortality in COVID-19 patients 1Disseminated intravascular coagulation (DIC), 2 Intensive care unit (ICU), 3Odds Ratio (OR), Confidence interval (CI).

Changes in Extended Inflammatory and Coagulation Parameters During 28 days

The median NLR level was significantly higher in nonsurvivors than in survivors during the first four weeks of follow-up ($p<0.05$). The median IGLR level was significantly higher in nonsurvivors than in survivors during the first two weeks of follow-up ($p<0.05$). During the first three weeks of follow-up, the median RE-LYMPH count and percentage were significantly higher in nonsurvivors than in survivors ($p <0.05$). In the second week of follow-up, nonsurvivors had significantly higher median NEUT-RI and NEUT-GI levels than survivors ($p<0.05$). In the third week of follow-up, the median AS-LYMP count and percent were significantly greater in nonsurvivors than in survivors ($p<0.05$). The median D-Dimer level was significantly higher in nonsurvivors than in survivors during the first three weeks of follow-up ($p<0.05$). The median SFMC value in the first week of follow-up was significantly higher in nonsurvivors than in survivors ($p<0.05$). Other parameters showed no significant differences between groups ($p>0.05$) (Table 2).

Median (IQR)	0-7 day			8-14 day			15-21 day			22-28 day		
	Non-survivor n-45	Survivor n-28	*p* value	Non-survivor n-40	Survivor n-25	*p* value	Non-survivor n-30	Survivor n-20	*p* value	Non-survivor n-10	Survivor n-9	*p* value
NLR[1]	10.1 (5.4-16.7)	4.1 (3.0-8.5)	0.001	18.7 (11.6-28.0)	7.4 (4.1-10.5)	0.0001	21.6 (15.1-29.2)	4.2 (2.3-5.9)	0.0001	14.6 (8.8-32.7)	2.6 (1.7-12.6)	0.01
IGLR[2]	9.9 (5.9-27.4)	3.5 (2.2-12.4)	0.01	37.5 (17.4-104.7)	13.8 (7.0-38.2)	0.003	25.0 (13.6-63.4)	17.2 (4.1-32.8)	0.08	16.9 (5.2-46.7)	5.3 (1.2-23.6)	0.21
NEUT-RI[3]	49.5 (44.7-60.1)	49.3 (39.3-61.9)	0.76	50.1 (40.9-63.7)	48.5 (40.3-54.7)	0.04	51.4 (44.7-76.3)	49.9 (44.7-68.8)	0.09	52.0 (44.1-71.4)	51.9 (47.1-69.6)	0.83
NEUT-GI[4]	153.8 (144.8-160.8)	152.5 (146.6-162.7)	0.41	154.1 (146.6-164.3)	150.8 (140.4-156.6)	0.02	154.9 (147.6-164.6)	155.6 (150.5-162.8)	0.83	157.9 (146.6-164.3)	158.4 (155.7-164.2)	0.46
AS-LYMPH[5]	0 (0-20)	0 (0-25)	0.80	20 (0-50)	30 (0-80)	0.40	100 (1-40)	0 (0-22)	0.06	0 (0-20)	0 (0-5)	0.28
AS-LYMPH% [6]	0 (0-20)	0 (0-35)	0.94	4.8 (1.0-10.9)	3.6 (0-8.3)	0.49	3.5 (0-7.1)	0 (0-2.8)	0.009	0 (0-3.6)	0 (0-0.5)	0.19
RE-LYMPH[7]	60 (40-80)	80 (60-90)	0.04	105 (50-180)	130 (80-180)	0.21	600 (300-875)	130 (80-180)	0.01	400 (300-900)	115 (80-150)	0.06
RE-LYMPH% [8]	8.5 (5.4-9.8)	5.5 (4.4-7.4)	0.06	14.6 (9.3-19.3)	10.6 (5.7-14.5)	0.02	13.4 (7.4-16.7)	7.6 (5.0-8.4)	0.0001	10.7 (6.4-12.9)	5.8 (5.2-10.2)	0.08
D-dimer	0.9 (0.6-1.7)	0.5 (0.4-0.9)	0.006	2.2 (1.0-3.8)	0.9 (0.5-2.7)	0.03	1.8 (1.3-5.5)	0.5 (0.3-3.2)	0.006	2.4 (1.3-4.9)	1.5 (0.6-3.2)	0.07
SFMC[9]	8.5 (6.5-16.7)	4.5 (3.4-6.7)	0.0001	9.2 (4.2-80.0)	5.9 (4.3-15.1)	0.65	5.9 (3.6-45.9)	7.7 (5.8-15.2)	0.47	6.0 (3.2-20.9)	3.5 (1.4-5.7)	0.33

Table 2: Changes in extended inflammatory parameters and soluble fibrin monomer complexes during the first 28 days of intensive care monitoring.

[1] Neutrophil-to-lymphocyte ratio, [2] Immature granulocyte-to-lymphocyte ratio, [3] Neutrophil reactivity index [FI], [4] Neutrophil granularity index [GI]
[5] Antibody synthesizing lymphocytes count, [6] Antibody synthesizing lymphocytes as % of lymphocytes
[7] Reactive lymphocytes count, [8]Reactive lymphocytes as % of lymphocytes [9]Soluble fibrin monomer complex.

Risk Factors

The proportion of older patients (age ≥65 years) among non-survivors (80%) was significantly higher than in survivors (25%), with a 4.3-fold increased risk (OR 4.3; 95%CI 2.0-8.8). Patients with Charlson morbidity score >3 had a 3.3-fold (OR 3.3; 95%CI 1.5-7.3) higher probability of death (64%) than survivors (22%). Patients who received blood products had a 3.1-fold (OR 3.1; 95%CI 1.0-9.2) increased risk of death (38%) than those who survived (10%). Patients with nosocomial infection had an 11.9-fold (OR 11.9; 95%CI 3.0-46.8) increased risk of death (74%) than those who survived (7%). Patients who had a DIC score >5 had a 3.9-fold (OR 3.9; 95%CI 1.0-14.9) increased risk of death (34%) compared to those who survived (7%). Patients who had a longer ICU stay >7 days had a 3.5-fold increased risk (OR 3.5; 95%CI 2.0-6.1) of death (91%) compared to those who survived (41%) (Table 2).

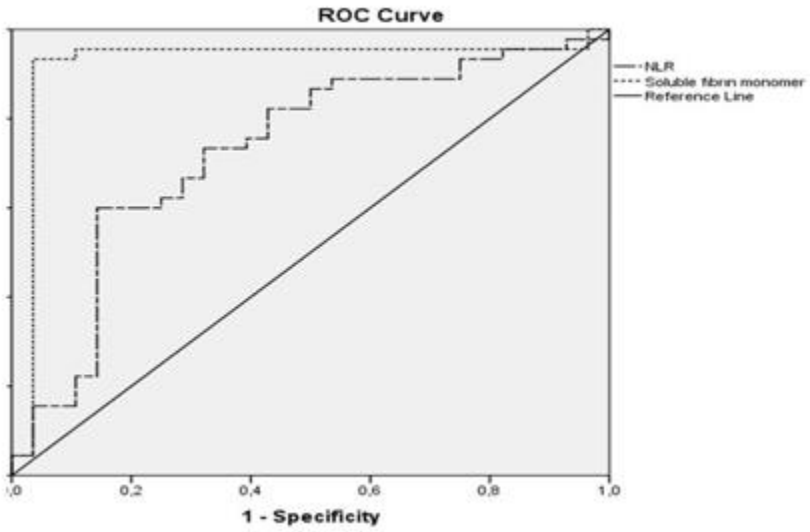
ROC Analysis and Calculation of Threshold Values

In ROC analysis, NLR (AUC: 0.73) and SFMC (AUC: 0.92) had significantly higher AUC values than other parameters. For predicting mortality, NLR had a sensitivity of 79.2% and a specificity of 65.2% with a threshold value of 6, whereas SFMC had a sensitivity of 94.2% and a specificity of 71.2% with a threshold value of 6.5 (Table 3) (Figure 1).

	NLR[1]	SFMC[2]
AUC[3]	0.73	0.92
95%CI[4]	0.61-0.85	0.84-1.00
P value	0.001	0.0001
Cut-off value	6	6.5
Sensitivity (%)	79.2	94.2
95%CI	64.5-89.3	80.8-99.3
Specificity (%)	65.2	71.2
95%CI	42.8-78.4	54.1-84.5
Diagnostic value (%)	72.2	82.2
95%CI	60.8-81.3	71.4-90.1

Table 3: ROC analysis for prognostic evaluation in COVID-19 patients to predict mortality.

[1] Neutrophil-to-lymphocyte ratio (NLR), 2Soluble fibrin monomer complex (SFMC), 3Area under the curve (AUC), [4]Confidence interval (CI).



Discussion

The SARS-CoV-2 virus enters the body via endothelial ACE-2 receptors, causing endothelial damage, and microvascular inflammation. This endothelial disruption activates both the immune and coagulation systems simultaneously, contributing to severe clinical consequences such as severe acute respiratory distress syndrome and multi-organ dysfunction.22,23 Thus, we used research parameters capable of revealing early changes in the leukocyte series and SFMC measurements with the potential to provide early-stage information about coagulation activation. In this cross-sectional study, we examined the risk factors for COVID-19 infection, as well as the role of new extended inflammatory measures and SFMC in ICU patients. Our primary findings are as follows: i- In COVID-19 patients, risk factors for mortality include older age, comorbidities, blood product use, nosocomial infection, a high DIC score, and a longer ICU stay. ii- Elevated NLR, IGLR, NEUT-RI, NEUT-GI, D-dimer, and SFMC in the first two weeks of COVID-19 infection, followed by increasing NLR, D-dimer, RE-LYPMH, and AS-LYMPH in the next two weeks, may play an important role in thromboinflammation during COVID-19 infection. iii- The optimal cut-off values for NLR and SFMC in predicting mortality were 6 and 6.5, respectively. All of these findings suggest that the new extended inflammatory and coagulation parameters, including NLR and SFMC, could be useful for predicting COVID-19-related mortality.

Few studies focusing on the prognostic effect of extended inflammatory parameters in COVID-19 infection have been reported.15-17,24 Linssen and colleagues showed that they developed a prognostic score based on leukocyte data collected from noncritical (NC) and critical-fatal (CF) patient groups throughout a 14-day monitoring period.15 In that study, analysis of the leukocyte series revealed that the CF group had prolonged lymphopenia and high neutrophil counts, as well as elevations in NEUT-RI, IG, and IGLR levels throughout the course of COVID-19 infection. Similarly, we found a significant increase in IGLR and NLR ratios in the non-survivor patient group during the first two weeks of follow-up. This elevation was followed by increases in NEUT-RI and NEUT-GI levels in the second week. Our findings about the elevation in neutrophil precursors during the early stages of infection caused by the SARS-CoV-2 virus are consistent with Linssen and colleagues' 14-day follow-up study, and our data are also supported by previous sepsis studies that have shown increases in neutrophil precursors before the rise in neutrophil counts.7,15,25 Furthermore, we found that, while the increase in NLR continued during the third and fourth weeks of testing, the elevations in IG, NEUT-RI, and NEUT-GI did not. At this point, the AS-LYMPH count and percentage were significantly higher in our patients' survivors during the third week, whereas Linssen and colleagues found that the rate of AS-LYMPH was significantly higher in both (CF and NC) groups compared to baseline values during the second week of hospitalization.15 Similarly, Yip and colleagues found that, despite a gradual decrease in lymphocyte count, AS-LYMPH and RE-LYMH counts increased slowly in the critically ill group, with the most apparent change occurring on the 15th and 16th days.16 Another study by Martens and colleagues found that, while total lymphocyte count decreased in the group developing cytokine storms compared to the non-developing group, lymphocyte subgroups increased (AS-LYMPH, high fluorescence lymphocyte count, RE-LYMPH).24 The increase in AS-LYMP levels as a lymphocyte subgroup was associated with the seroconversion observed in the second week of the disease in those studies.15,16,24 As reported in another study, once antibody production begins, immunopathological events

increase, and disease severity worsens.26 In our study, we examined weekly new extended CBC measures rather than daily ones and found a higher AS-LYMPH level at the beginning of the third week, which might indicate an emphasis on findings related to seroconversion. All of these findings may be linked to the adaptive immune system's increased disease severity.

Few studies revealed that mature and immature neutrophil counts increased at the start of the COVID-19 infection, and that increased AS-LYMPH and RE-LYMPH indicated an adaptive immune response that exacerbated disease severity in the second or third week of COVID-19 infection.15-17,24 On the other hand, NLR has been one of the most researched COVID-19 biomarkers.17,27,28 Kilercik and colleagues examined CBC values in non-critical and critical patients according to survival status.17 They found a decrease in monocyte and lymphocyte percentages, as well as the monocyte-to-neutrophil ratio (MNR), and an increase in neutrophil percentage and NLR as disease severity increased. They also demonstrated that MNR and NLR were the most reliable time-related parameters for predicting outcomes during 30 days.17 Similarly, in our investigation, NLR was the only parameter that remained significantly elevated over the 4-week follow-up period. Furthermore, two extensive meta-analyses of NLR in COVID-19 revealed its potential to predict disease severity and mortality.27,28 However, the predictive NLR threshold value is still debatable. Li and colleagues found an NLR cut-off value of 6.5 with an AUC of 0.92 (95% CI 0.89-0.94) in one of these meta-analyses.27 Another investigation on ICU patients, conducted by Regolo et al., identified an NLR cut-off value of>11.38 (AUC: 0.771, sensitivity 77.5%, specificity 65.9%).29 Using ROC analysis, we identified an NLR> 6 cut-off value with an AUC of 0.73, sensitivity of 79.2%, and specificity of 65.2%. We believe that the prolonged increase in NLR values over the 4-week follow-up period could be attributed to COVID-19-induced inflammation and secondary risk factors such as older age, comorbidities, and nosocomial infections, particularly as the prolonged length of ICU stay may have exacerbated the clinical progression of COVID-19 infection.

Unlike in previous research, SFMC was included in the analysis as a predictive marker in our investigation, along with extended inflammatory parameters. Hypercoagulability is the most common coagulation state in COVID-19 disease, which is caused by excessive inflammation and poor fibrinolysis, and patients are at risk of thromboembolic events.30 It is associated with a poor prognosis.30,31 D-dimer levels were the most often used coagulation parameter during the pandemic period.12 Many studies focused on COVID-19-associated coagulopathy in terms of mortality and critical illness prediction associated with D-dimer levels.32,33 Reduced fibrinolytic capability (fibrinolysis shutdown) was found in one of them, where COVID-associated coagulopathy was studied using thromboelastometry, and paradoxically, elevated D-dimer levels were observed.32 Another study suggested that high D-dimer levels could be caused by intra-alveolar fibrin deposits in the lungs.33 D-dimer levels were observed to be increased in the non-survivor patient group in our study and remained elevated during the 3-week follow-up period. Furthermore, because of difficulties in determining the D-dimer cut-off value and issues with inter-laboratory variability in D-dimer measurements, the development of alternative methods, such as fibrin monomer (FM), appears necessary for describing COVID-19-related coagulation disorders and outcomes.12,13 Severe coagulopathy and cases of DIC have been observed to be more common in severe disease and non-survivor patient groups during the course of COVID-19.34 Consistent with this, a DIC score greater than 5 was revealed as a major risk factor related to higher mortality in our study. The increase in D-dimer, a fibrin degradation product, shows the formation of stable clots by Factor XIII and the onset of fibrinolysis.35 Cross-linked fibrin protofibrils form before Factor XIII stabilization.36 Thrombin cleaves fibrinopeptides A and B from fibrinogen molecules, exposing active binding sites. Fibrin monomer is a modified version of fibrinogen. These monomers bind to other FMs or fibrinogen and circulate in a soluble form. These are known as soluble fibrin monomer complexes.36 Elevated SFMC levels indicate that the coagulation pathway has been activated and the clotting process has begun. This early information on the coagulation process presented by SFMCs is thought to guide optimal treatment.37 High D-dimer levels in COVID-19 have been linked to the extent of lung damage outside of the coagulation system, and this has been explained by the breakdown of extravascular fibrin deposits.38 Fibrin monomers, on the other hand, are restricted to the intravascular area. A few studies have been carried out to examine the prognostic value of FM in COVID-19.12,39,40 The majority of them demonstrated that SFMC levels were not superior to D-dimer levels in predicting multiple thrombotic events on admission. The largest study in this field, however, was conducted by Smadja et al., who analyzed FM levels in 246 patients who were observed in the ICU and general hospital for 9 days.14 They showed that SFMC levels in patients admitted promptly to the ICU began to rise dramatically on day 3 and remained elevated for at least 9 days. They established the FM detection limit at 7 g/mL. These findings are consistent with our findings, which indicated a similar cut-off value of 6.5 g/mL for FM with a sensitivity of 94.2% (95% CI 80.8-99.3) and specificity of 71.2% (95% CI 51.1-84.5) in predicting mortality. Finally, similar to our study, SFMC levels were significantly higher in non-survivor patients compared to survivors in the first week of ICU follow-up. All of these findings suggested that monitoring FM levels during the follow-up period, rather than just at the time of admission, could be valuable for predicting death.

Our study's main limitations are the small number of patients and the lack of a healthy control group. One of our study's advantages is its potential to guide future research on COVID-19-like viruses that influence the hemostatic system. Future research will require a large patient group as well as a healthy control group.

Finally, increasing NEUT-RI, NEUT-GI, NLR, and IGLR during the first two weeks of COVID-19 infection may support acute inflammation, whereas increasing RE-LYPMH and AS-LYMPH during the next two weeks may indicate COVID-19 seroconversion. Elevated D-dimer and SFMC levels in the first week of COVID-19 infection could support the prethrombotic process, and significantly higher D-dimer levels in the next three weeks may assist the thrombotic process. Our findings suggest that elevated NLR and SFMC cut-off values in the first week should alert clinicians to the possibility of life-threatening COVID-19 complications and highlight the importance of prophylactic treatments such as broad-spectrum antibiotics or anticoagulant therapy.

References

1. de Andrade SA, de Souza DA, Torres AL, de Lima CFG, Ebram MC, et al. (2022). Pathophysiology of COVID-19: Critical Role of Hemostasis. *Front Cell Infect Microbiol*; 12:896-972.
2. Engelmann B, Massberg S. (2013). Thrombosis as an intravascular effector of innate immunity. *Nat Rev Immunol*; 13(1):34-45.
3. Henry BM, De Oliveira MHS, Benoit S, Plebani M, Lippi G. et al. (2020). Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clinical Chemistry and Laboratory Medicine (CCLM)*; 58(7):1021-1028.
4. Zhou F, Yu T, Du R, Fan G, Liu Y, et al. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The lancet*; 395(10229):1054-1062.
5. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. (2020). Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. Journal of clinical virology; 127:104-370.
6. Sysmex E. (2017). Novel Haematological Parameters for Rapidly Monitoring the Immune System Response. *Sysmex White Paper Infection/Inflammation*:1-5.

7. Ayres LS, Sgnaolin V, Munhoz TP. Immature granulocytes index as early marker of sepsis. Int J Lab Hematol. 2019;41(3):392-396.
8. Linssen J, Jennissen V, Hildmann J, Reisinger E, Schindler J, et al. (2007). Identification and quantification of high fluorescence-stained lymphocytes as antibody synthesizing/secreting cells using the automated routine hematology analyzer XE-2100. Cytometry Part B: Clinical Cytometry: *The Journal of the International Society for Analytical Cytology*; 72(3):157-166.
9. Hou H, Ge Z, Ying P, Dai J, Shi D, et al. (2012). Biomarkers of deep venous thrombosis. *Journal of thrombosis and thrombolysis*; 34:335-346.
10. Singh N, Pati HP, Tyagi S, Upadhyay AD, Saxena R. et al. (2017). Evaluation of the diagnostic performance of fibrin monomer in comparison to d-dimer in patients with overt and nonovert disseminated intravascular coagulation. *Clinical and Applied Thrombosis/Hemostasis*; 23(5): 460-465.
11. Dopsaj V, Bogavac-Stanojevic N, Vasic D, Vukosavljevic D, Martinovic J, et al. (2009). Excluding deep venous thrombosis in symptomatic outpatients: *is fibrin monomer aid to D-dimer analysis? Blood coagulation & fibrinolysis*; 20(7):546-551.
12. Godon A, Durand Z, Agier L, Lecompte T, Mullier F, et al. (2021). Comparison of Fibrin Monomers and D-dimers to predict thrombotic events in critically ill patients with COVID-19 pneumonia: A retrospective study. *Thrombosis research*; 205:8-10.
13. Sridharan M, D Navitskas S, M Kock E, E Houghton D, M Heikal N, et al. (2022). Evaluation of soluble fibrin monomer complex in patients in SARS-CoV-2 COVID-19 infection-associated coagulopathy. *European Journal of Haematology*; 108(4):319-326.
14. Smadja DM, Gendron N, Philippe A, Diehl JL, Ochat N, et al. (2023). Fibrin monomers evaluation during hospitalization for COVID-19 is a predictive marker of in-hospital mortality. *Front Cardiovasc Med*; 10:1001530.
15. Linssen J, Ermens A, Berrevoets M, Seghezzi M, Previtali G, et al. (2020). A novel haemocytometric COVID-19 prognostic score developed and validated in an observational multicentre *European hospital-based study. Elife*; 9: e63195.
16. Yip CY, Yap ES, De Mel S, Teo WZ, Lee CT, et al. (2020). Temporal changes in immune blood cell parameters in COVID-19 infection and recovery from severe infection. *British Journal of Haematology*; 190(1):33.
17. Kilercik M, Demirelce Ö, Serdar MA, Mikailova P, Serteser M. (2021). A new haematocytometric index: Predicting severity and mortality risk value in COVID-19 patients. *PLoS One*.;16(8): e0254073.
18. Charlson ME, Carrozzino D, Guidi J, Patierno C. (2022). Charlson Comorbidity Index: A Critical Review of Clinimetric Properties. *Psychother Psychosom*.;91(1):8-35.
19. T.C. Eriskin hasta yönetimi ve tedavi rehberi. https://covid19.saglik.gov.tr/Eklenti/43095/0/covid-19 rehberi eriskin hasta yonetimi ve tedavi 12042022pdf.pdf: T.C Sağlık Bakanlığı;
20. Taylor Jr FB, Toh C-H, Hoots KW, Wada H, Levi M. et al. (2001). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thrombosis and haemostasis*.;86(11):1327-1330.
21. Dempfle CE, Wurst M, Smolinski M, Lorenz S, Osika A, et al. (2004). Use of soluble fibrin antigen instead of D-dimer as a fibrin-related marker may enhance the prognostic power of the ISTH overt DIC score. *Thromb Haemost*; 91(4):812-818.
22. Teuwen L-A, Geldhof V, Pasut A, Carmeliet P. (2020). COVID-19: the vasculature unleashed. *Nature Reviews Immunology*; 20(7):389-391.
23. Libby P, Lüscher T. (2020). COVID-19 is, in the end, an endothelial disease. *European Heart Journal*.;41(32):3038-3044.
24. Martens RJ, Van Adrichem AJ, Mattheij NJ, Brouwer CG, Van Twist DJ, et al. (2021). Hemocytometric characteristics of COVID-19 patients with and without cytokine storm syndrome on the Sysmex XN-10 hematology analyzer. *Clinical Chemistry and Laboratory Medicine (CCLM)*; 59(4):783-793.
25. Park SH, Park CJ, Lee BR, Nam KS, Kim MJ, et al. (2015). Sepsis affects most routine and cell population data (CPD) obtained using the Sysmex XN-2000 blood cell analyzer: neutrophil-related CPD NE-SFL and NE-WY provide useful information for detecting sepsis. *Int J Lab Hematol*; 37(2):190-198.
26. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. et al. (2020). The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol*; 20(6):363-374.
27. Li X, Liu C, Mao Z, Xiao M, Wang L, et al. (2020). Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: a systematic review and meta-analysis. *Crit Care*; 24(1):647.
28. Simadibrata DM, Calvin J, Wijaya AD, Ibrahim NAA. (2021). Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 patients: A meta-analysis. *The American journal of emergency medicine*; 42:60-69.
29. Regolo M, Vaccaro M, Sorce A, Stancanelli B, Colaci M, et al. (2022). Neutrophil-to-Lymphocyte Ratio (NLR) Is a Promising Predictor of Mortality and Admission to Intensive Care Unit of COVID-19 Patients. *J Clin Med*; 11(8).
30. Gorog DA, Storey RF, Gurbel PA, Tantry US, Berger JS, et al. (2022). Current and novel biomarkers of thrombotic risk in COVID-19: a Consensus Statement from the International COVID-19 Thrombosis Biomarkers Colloquium. *Nature Reviews Cardiology*;19(7):475-495.
31. Arachchillage DR, Laffan M. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of thrombosis and haemostasis*; 18(5):1233-1237.
32. Wright FL, Vogler TO, Moore EE, Moore HB, Wohlauer MV, et al. (2020). Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. *Journal of the American College of Surgeons*; 231(2):193-203. e1.
33. Thachil J, Longstaff C, Favaloro EJ, Lippi G, Urano T, et al. (2020). The need for accurate D-dimer reporting in COVID-19: communication from the ISTH SSC on fibrinolysis. *Journal of Thrombosis and Haemostasis*;18(9):2408-2411.
34. Tang N, Li D, Wang X, Sun Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of thrombosis and haemostasis*;18(4):844-847.
35. Adam SS, Key NS, Greenberg CS. (2009). D-dimer antigen: current concepts and future prospects. Blood, *The Journal of the American Society of Hematology*;113(13):2878-2887.
36. Vilar R, Fish RJ, Casini A, Neerman-Arbez M. (2020). Fibrin (ogen) in human disease: both friend and foe. *Haematologica*;105(2):284-247.
37. Bull BS, Hay KL, Herrmann PC. (2022). Fibrin Strands Will Grow from Soluble Fibrin and Hang Up in an In Vitro Microcirculatory Viscoelastic Model: Is This a Major Cause of COVID-19 Associated Coagulopathy? *Journal of Clinical Medicine*.;11(8):2084.
38. Trimaille A, Thachil J, Marchandot B, Curtiaud A, Leonard-Lorant I, et al. (2020). D-dimers level as a possible marker of extravascular fibrinolysis in COVID-19 patients. *Journal of Clinical Medicine*;10(1):39.

39. Sridharan M, S DN, E MK, D EH, N MH, et al. (2022). Evaluation of soluble fibrin monomer complex complex in patients in SARS-CoV-2 COVID-19 infection-associated coagulopathy. *Eur J Haematol*.;108(4):319-326.

40. Hardy M, Michaux I, Dive A, Lecompte T, Mullier F. (2021). Could daily monitoring of fibrin-related markers help suspect a thrombotic event in COVID-19 patients? A prospective pilot study. *TH Open*; 5(02): e152-e154.

DOI:10.31579/2768-0487/124