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Persistence of Abnormal Inflammatory and Coagulation Laboratory Tests in Critically-ill COVID-19 Survivors: Case Series

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ABSTRACT

Aim: In this study, the aim was to evaluate the persistence of abnormalities in laboratory variables regarding inflammation and coagulation during the recovery process of the critically-ill COVID-19 patients.

Materials and methods: Medical records of patients who were treated for COVID-19 in our intensive care unit (ICU) were examined retrospectively. Baseline characteristics and latest abnormal test result dates for lymphocyte counts, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, fibrinogen and D-dimer levels from the first day of ICU admission were noted.

Results: In total, 15 patients were enrolled in the final analysis. Overall median value (Interquartile range) for the latest abnormal test result dates from the first day of ICU admission and the ratio of patients with abnormal test results after hospital discharge were 11 (7.5-17) days and 7.7% for lymphocyte count, 15 (8-20) days and 20% for LDH, 15 (10.5-40) days and 30% for CRP, 15.5 (10.3-30.3) days and 25% for ferritin, 17 (12-95.5) days and 50% for fibrinogen, and 28 (18-68.5) days and 71.4% for D-dimer.

Conclusion: In critically-ill COVID-19 survivors, abnormality of laboratory tests regarding inflammation and coagulopathy persists after hospital discharge and even after 90 days after ICU admission which suggests the probability of sustained risk for multi-organ damage and thromboembolic events.

Keywords: critical care; fibrin-fibrinogen degradation products; follow-up studies; lymphocyte count; SARS-CoV-2

Introduction

A novel Coronavirus was recognized in Wuhan, China, in December 2019. It is known as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), and the disease is known as coronavirus disease-2019 (COVID-19). On March 11th, 2020, The World Health Organization (WHO) declared COVID-19 outbreak as a pandemic (1).

In general, the clinical features of COVID-19 vary from asymptomatic carriage to acute respiratory distress syndrome (ARDS) and even multi-system involvement (2). Rate of intensive care unit (ICU) admission was reported as 5 to 32%, whereas severe pneumonia and ARDS were reported in 60 to 70% and sepsis and septic shock were reported in 30% of the patients with SARS-CoV-2 infection. In addition, ICU mortality ranges from 16 to 78% (3).

Regarding laboratory tests; lymphopenia, leukocytosis, neutrophilia, thrombocytopenia, abnormal renal and liver function tests and coagulopathy are frequently encountered (4). Laboratory tests are non-specific, but usually associated with disease severity and prognosis (2, 4). Leukocytosis is encountered in a relatively small percentage of patients (4.8% and 11.4% in mild-to-moderate and severe disease, respectively) (5). Lymphopenia suggests abnormal immunological response to the virus, and is encountered in especially severe COVID-19 cases (5, 6). Increased C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels are indicative for disease severity (4, 7). Ferritin suggests infection or inflammation and is higher in severe COVID-19 cases (8). Also, when compared to healthy individuals, COVID-19 infected patients have higher levels of fibrinogen and D-dimer, and elevations in D-dimer levels are also associated with severe disease (9–11).

Although laboratory tests for inflammation and coagulation have been widely used to evaluate disease severity and prognosis, their course during follow-up have not been extensively evaluated. Therefore, the aim of this case series is to evaluate persistence of abnormal inflammatory and coagulation laboratory tests on a time-scale in critically-ill COVID-19 survivors.

Materials and Methods

This study was carried out retrospectively and was approved by both the University Ethics Committee in June 23rd, 2020 (file number GO 20/627) and Turkish Ministry of Health. Medical records of COVID-19 patients with respiratory failure, who met the 'Critical COVID-19' definition due to WHO severity definitions of COVID-19 (12) and who were admitted to our ICU between March 29th and June 1st, 2020, and discharged until July 18th 2020 were examined. Because this is a retrospective study, patient consent was waived.

Variables recorded for each case were age, sex, comorbidities, smoking history, Eastern Cooperative Oncology Group (ECOG) Performance Status, Clinical Frailty Scale® (CFS®) (appropriate permission was obtained), APACHE (Acute Physiology And Chronic Health Evaluation) II score, Sequential Organ Failure Assessment (SOFA) score, Partial arterial pressure of oxygen/Fraction of inspired oxygen (PaO_2/FiO_2) on admission, invasive mechanical ventilation (IMV) requirement and duration, symptom onset to hospital and ICU admission, hospital and ICU length of stay (LOS), type and duration of medication and duration of follow-up. Laboratory tests of inflammation and coagulation (lymphocyte count, CRP, LDH, ferritin, fibrinogen and D-dimer) were recorded for each patient until December 15th 2020. Last date for abnormal results from ICU admission and number of tests performed during the entire follow-up period were recorded, as well. For each parameter, the date of last abnormal test result before normal results was accepted as last abnormal test date. Infections determined within and after first 72 hours of ICU admission were accepted as co-infections and secondary infections, respectively. Normal range of levels for each evaluated parameter in our institution were 1200 to 3600/mm^3 for lymphocyte count, 0 to 248 U/L for LDH, 0 to 0.8 mg/dL for CRP, 20 to 336 mcg/L for ferritin, 180 to 350 mg/dL for fibrinogen and 0 to 0.55 mg/L for D-dimer.

The obtained variables were evaluated with descriptive statistics. Categorical and continuous variables were expressed as 'number of patients (%)', and 'median (interquartile range (IQR)', respectively. R Statistical Software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis and generation of graphics.

Results

In total, 30 patients with positive reverse-transcriptase polymerase chain reaction (RT-PCR) or antibody tests for COVID-19 were admitted to our ICU during the study period. Fifteen patients were excluded; 9 due to ICU mortality, 2 due to transfer to nursing home, 2 due to the presence of concurrent tuberculosis and 2 due to not having follow-up results for variables. Fifteen patients were included for the final analysis. Patient characteristics and data regarding medications are summarised on Table 1. Overall, 6 (40%) patients received immunomodulatory treatment including steroids. One (6.7%) patient had a co-infection and three (20%) patients had secondary infections, respectively. The patients were followed-up for a median of 89 days, overall.

Table 1. Patient characteristics

	n=15
Age, years	55 (49-74)
Male sex*	10 (66.7)
Co-morbidities	
Hypertension*	7 (46.7)
Diabetes mellitus*	4 (26.7)
Chronic cardiac disease*	2 (13.3)
Pregnancy*	2 (13.3)
Chronic pulmonary disease*	1 (6.7)
Malignancy*	1 (6.7)
None	6 (40.0)
Smoking status	
Non-smoker*	10 (66.7)
Smoker*	3 (20.0)
Ex-smoker*	2 (13.3)
ECOG Performance Status	0 (0-1)
CFS®	1 (1-2)
APACHE II score	15 (12-18.5)
SOFA on ICU admission	4 (2-6.5)
PaO_2/FiO_2 on ICU admission	156.5 (143.5-193.8)
Invasive mechanical ventilation requirement*	5 (33.3)
Invasive mechanical ventilation, days	7 (4-14)
Co-infection on ICU admission*	1 (6.7)
Secondary infection during ICU admission*	3 (20)
Symptom to hospital admission, days	6 (4.5-7)
Symptom to ICU admission, days	8 (5.5-10)
ICU length of stay, days	12 (7-18)
Hospital length of stay, days	19 (15-26.5)
Overall follow-up, days	89 (41-146)
Follow-up after hospital discharge, days	57 (21.5-84.1)
Medications	
Hydroxychloroquine*	13 (86.7)
Azithromycin*	12 (80)
Favipiravir*	12 (80)
Steroid*	4 (26.7)
Lopinavir/Ritonavir*	4 (26.7)
Intravenous immunoglobulin*	2 (13.3)
Convalescent plasma*	1 (6.7)
Tocilizumab*	1 (6.7)
Treatment days	
Hydroxychloroquine	7 (6-10)
Azithromycin	6 (4.8-6)
Favipiravir	7 (6-9)
Steroid	4.5 (4-5.3)
Lopinavir/Ritonavir	9 (7.8-11)
Intravenous immunoglobulin	2 (2-2)
Convalescent plasma	3 (3-3)
Tocilizumab	1 (1-1)

*: Number of patients (%), others median (IQR).
ECOG: Eastern Cooperative Oncology Group, **CFS®:** Clinical Frailty Scale®, **APACHE:** Acute Physiology and Chronic Health Evaluation, **SOFA:** Sequential Organ Failure Assessment, **ICU:** intensive care unit, **PaO_2/FiO_2:** Partial pressure of oxygen/Fraction of inspired oxygen

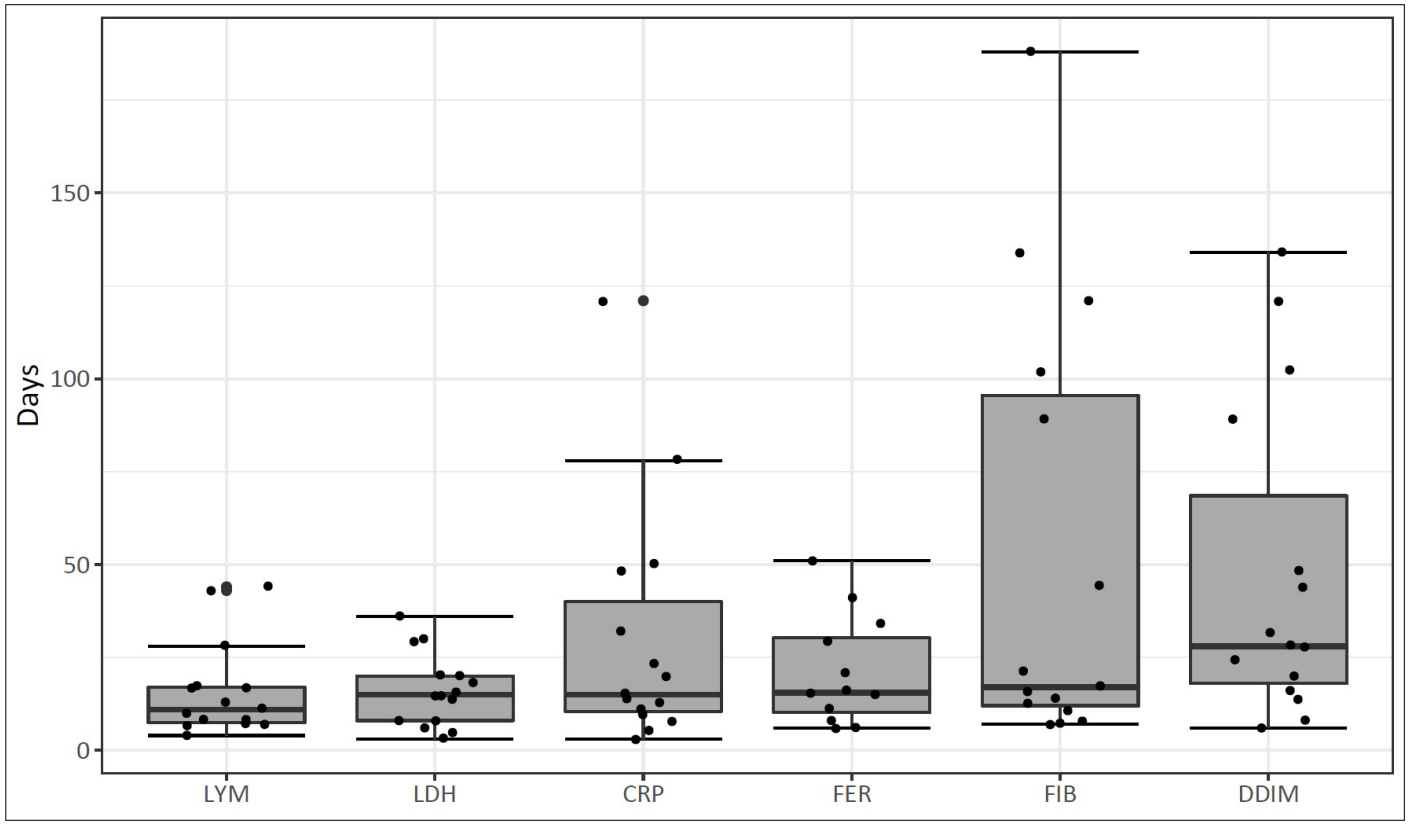

Figure 1. The last abnormal value of the evaluated laboratory tests from ICU admission, days. The box plots represent the medians (middle line) and first and third quartiles (boxes), the whiskers represent 1.5x the IQR above and below the box, and y-axes represent days. Jittered points represent individual cases. **LYM:** lymphocyte count, **LDH:** lactate dehydrogenase, **CRP:** C-reactive protein, **FER:** ferritin, **FIB:** fibrinogen, **DDIM:** D-dimer

Table 2. Follow-up duration, test counts and last abnormal dates of each laboratory test for each patient from the first day of ICU admission

Patient no	Follow up duration, days	Test count		Last abnormal date of each laboratory test for each patient from the first day of ICU admission					
		Total	After hospital discharge	LYM	LDH	CRP	FER	FIB	DDIM
1	89	114	10	11	30	32	51	89	89
2	48	88	23	13	20	48	34	11	48
3	53	57	6	7	6	11	6	14	14
4	134	44	6	4	5	5	NA	8	8
5	28	93	10	17	15	14	11	21	28
6	225	63	22	8	8	78	NA	102	102
7	44	101	3	44	16	23	21	44	44
8	105	72	5	8	15	10	16	16	16
9	233	110	38	17	20	20	41	188	20
10	220	81	30	17	8	15	NA	17	32
11	28	60	4	10	14	13	15	13	28
12	134	226	12	43	29	50	29	134	134
13	29	28	4	7	3	3	6	7	6
14	158	159	22	28	36	121	15	121	121
15	38	107	4	7	18	8	8	7	24

LYM: lymphocyte count, **LDH:** lactate dehydrogenase, **CRP:** C-reactive protein, **FER:** ferritin, **FIB:** fibrinogen, **DDIM:** D-dimer,
NA: Not applicable, as 3 patients did not have any abnormal ferritin levels during the study period.

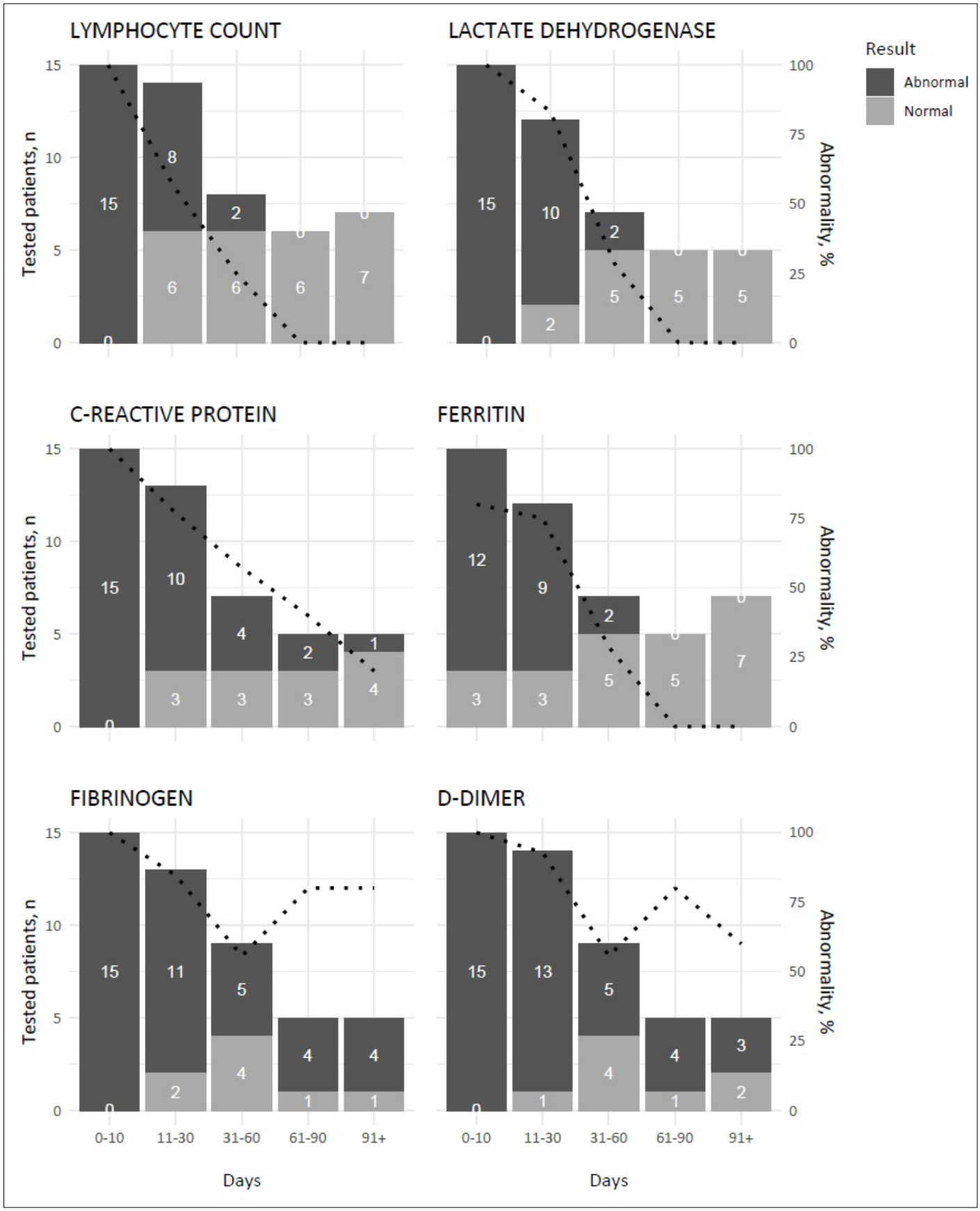

Figure 2. Frequency of abnormal laboratory tests in defined time periods from ICU admission. The numbers on the bar charts represent patients with abnormal (in dark grey) and normal (in light grey) laboratory tests. Dashed lines represent abnormality percentage of individual test

The last median abnormal days for the laboratory variables are demonstrated on Figure 1. Three patients never had abnormal ferritin levels. Lymphocyte count was the variable with the shortest persistence of abnormality, followed by LDH, CRP, ferritin and fibrinogen. D-dimer was the variable with the longest persistence of abnormality. The latest abnormal test result dates, from the first day of ICU admission were 11 (7.5-17) days for lymphocyte count, 15 (8-20) days for LDH, 15 (10.5-40) days for CRP, 15.5 (10.3-30.3) days for ferritin, 17 (12-95.5) days for fibrinogen and 28 (18-68.5) days for D-dimer. For each patient, total follow-up days, total and after hospital discharge counts and last abnormal date of each laboratory test are listed on Table 2.

After hospital discharge, the abnormal test results were noted in 1 out of 13 tested patients for lymphocyte count, as well as 2 out of 10 patients tested for LDH, 3 out of 10 patients for CRP, 3 out of 12 patients for ferritin, 6 out of 12 patients for fibrinogen and 10 out of 14 patients for D-dimer.

We also categorised the overall results into periods of first 10 days, 11 to 30 days, 31 to 60 days, 61 to 90 days and 91 days to the end of follow-up, according to ICU admission dates. The number of tested patients decreased with each period. After 90 days, no patients had abnormal lymphocyte counts, LDH or ferritin levels, whereas 20% of the patients had abnormal CRP, 80% had abnormal fibrinogen and 60% had abnormal D-dimer levels. The chronological results are demonstrated on Figure 2.

Discussion

Our study demonstrated the persistence of abnormality of inflammatory and coagulation tests for more than 90 days in our case series of critically-ill COVID-19 survivors. In COVID-19 patients, haematological and immunological markers have been evaluated for diagnostic and prognostic value and deemed useful for predicting severe disease and mortality, such as elevated levels of Interleukin-6 (IL-6), CRP, D-dimer, neutrophil count, neutrophil/lymphocyte ratio (NLR) and low levels of lymphocyte count (13, 14). In the current study, our main purpose was to reveal the abnormal sequence of these variables during the disease and the following course. In terms of inflammation, we evaluated lymphocyte count, CRP, LDH and ferritin and for coagulation, we evaluated fibrinogen and D-dimer levels. We have not investigated neutrophil count or related variables, such as NLR, since they might be affected by various factors such as steroid treatment and bacterial infections. In addition, IL-6 was not evaluated, since it is not feasible to do so, routinely.

Several follow-up studies about COVID-19 have been conducted with various time-scales ranging from 14 to 60 days, in which dynamic changes of inflammatory and coagulation variables were analysed, and risk factors for organ dysfunction, severity and mortality were evaluated (15–22). Mandal et al. (19) analysed long term consequences of COVID-19 in aspect of physical and psychological symptom burden, recovery of blood biomarkers and imaging in 384 patients for a median follow-up of 54 days after discharge. On a single post-discharge follow-up date, 7.3% of 247 patients had persisting lymphopenia, 9.5% of 190 patients had elevated CRP and 30.1% of 229 patients had elevated D-dimer levels. Median follow-up date and proportion of patients with lymphopenia in our study are similar. However, CRP and D-dimer abnormalities were more commonly observed in our study. This might be due to the fact that our patients were critically-ill patients solely, whereas in the referenced study only 14.5% of the patients required ICU treatment. In addition, the referenced study was multi-centre cross-sectional, although our study was designed as single-centre follow-up.

Lymphopenia, which was caused by direct impact of SARS-CoV-2 infection to CD4+ T and CD8+ T cells, has been considered to mark defective host response and encountered in 35 to 75% of COVID-19 patients (23). Lui et al. (17) showed that the decline of T cells was seen in the first week of severe COVID-19 infection. During second week of disease process, lymphocyte levels begin to rise and the third week seems to be the recovery period for mild cases. Persistence of low lymphocyte counts was also associated with mortality in hospitalized COVID-19 patients (24). During our study period, the median value of the last abnormal test results of lymphocyte counts were 11 days, and 7.7% of the patients had abnormal lymphocyte counts after hospital discharge. CRP is an acute phase reactant (APR) and generally suggests infection or inflammation. It is elevated in 75 to 93% of patients infected with COVID-19 (23). Ferritin is also an APR and suggestive of infection or inflammation like CRP. As Henry et al. (8) reported in their recent meta-analysis, ferritin was significantly higher in severe cases of COVID-19, when compared to non-severe cases (p=0.01). In a follow-up study, Manson et al. (20) reported association of high or rising CRP levels with hyperinflammatory state. In the same study, when evaluated on a time-scale, respiratory support and death were commonly confronted with persistence of high ferritin levels. In our study, the median last abnormal date of CRP and ferritin were 15 and 15.5 days, and patients with abnormal CRP and ferritin levels after discharge were 30% and 25%, respectively. These findings may suggest a prolonged and persistent inflammation, even after patients recover from critical COVID-19.

Fibrinogen is another positive APR (25). It promotes endothelial repair and has a complement function. Fibrinogen levels were reported to be higher in COVID-19 infected patients, when compared to healthy individuals (5.02±1.53 and 2.90±0.53 g/L, p=<0.001, respectively) (9). In addition, Pawlowski et al. (21) appraised COVID-19 associated coagulopathy with follow-up laboratory tests, and despite higher fibrinogen levels in COVID-19 patients when compared to healthy individuals. They reported a decline in fibrinogen levels, as the infection evolves. This may contradict to our findings for some degree. However, the population in the mentioned study was not specifically composed of critically-ill patients. D-dimers are fibrin fragments present in the circulation, and elevated levels are found in conditions associated with thrombosis (26). COVID-19 is associated with thrombosis which was demonstrated both clinically and in post-mortem studies (27). In COVID-19 patients, high D-dimer levels are frequently seen, and D-dimer levels of >0.5 mg/L are encountered in 60% of severe COVID-19 cases (28). Regarding the pathophysiology of coagulopathy, especially sustained complement pathway activation and microvascular injury were emphasised (29). Hardy et al. (16) reported that D-dimer levels tended to increase and then decrease

over time. However, to what extent D-dimer levels normalise was not clear in that study. The latest median abnormal test result dates of fibrinogen and D-dimer were 17 and 28 days, respectively in the current study. In addition, 50 and 71.4% of the patients had abnormal fibrinogen and D-dimer levels after hospital discharge, respectively. These findings may suggest sustained coagulopathy.

There is lack of consensus for anticoagulation in the COVID-19 infected patients for both aspects of venous thromboembolism (VTE) prophylaxis and therapy (30). Our anticoagulation protocol was low-molecular-weight heparin (LMWH) 1 mg/kg bid or unfractionated heparin (UFH) or 5000 IU b.i.d. or t.i.d. according to renal functions. We also added acetyl salicylic acid to our treatment protocol, afterwards. After hospital discharge, all patients received LMWH prophylaxis for at least one month. No clinical thromboembolic complications were encountered during follow-up period. Increasing number of studies have been providing evaluation for more aspects of COVID-19, and thus we now have a better comprehension of the long-term clinical consequences. However, the full scopes of sustained inflammation and coagulopathy and whether the patients will benefit from long-term immunomodulatory or anticoagulant treatments remain yet to be elucidated. In our study, the evaluated biomarkers, produced as a result of the COVID-19 process were evaluated over time. Therefore, their biological half-lives deserve attention. The biological half-lives are 19 hours for CRP, 7 to 48 hours for LDH isoenzymes, 30 hours for ferritin, 4.14 days for fibrinogen and 8 hours for D-dimer (31–35). With these findings, persistent abnormal values in these tests cannot be explained solely by 'the biological half-life' concept.

There are some limitations in this study. The study was designed as a retrospective single-centre cohort with limited number of patients. Due to small sample size, we could not make group comparisons, regarding disease severity or immunomodulatory treatment. In addition, the number of tested patients decreased with time. Also, timing of the follow-up tests was at discretion of the attending physician. Moreover, it is difficult to demonstrate the clinical relevance of the abnormal laboratory results with this study. A prospectively designed study that will provide higher proportion of patients tested within all-time blocks will yield more precise insight to the nature of prolonged inflammation and coagulopathy. Approximately two-thirds of the ICU survivors and 10% of COVID-19 survivors are confronted with post-intensive care syndrome and long-COVID, respectively (36). These conditions constitute serious health burden and necessitate long-term follow-up and treatment in post-intensive care outpatient clinics. The contribution of the long-term follow-up of the examined parameters for follow-up and treatment processes of this group of patients should be evaluated with further studies. Finally, prolonged abnormality of these parameters can be evaluated in between COVID-19 patients and other critically-ill patients with other pathologies, such as ARDS, sepsis, shock, etc.

Conclusions

In critically-ill COVID-19 survivors, both inflammation and coagulopathy in terms of laboratory variables persist even after hospital discharge. Especially the abnormal CRP, fibrinogen and D-dimer levels persist even after 90 days after ICU admission. Sustained inflammation may contribute to multi-organ damage and prolonged coagulopathy carries risk of thromboembolic events. A large sample sized study with precise follow-up test dates is vital to investigate all possible aspects of inflammation and coagulopathy, and will possibly provide better insight on treatment options.

AUTHOR CONTRIBUTIONS:

Concept: BH; **Design:** BH; **Supervision:** EOE, SO, AT; **Data Collection and/or Processing:** ITG, BE, MY, GT; **Analysis and/or Interpretation**: ITG, BH; **Literature Search:** ITG, BH, AT; **Writing Manuscript**: ITG, BH; **Critical Review:** AT.

Ethics Committee Approval: This study was approved by both the Hacettepe University Ethics Committee in June 23rd, 2020 (file number GO 20/627) and Turkish Ministry of Health.

Informed Consent: This is a retrospective study

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors have no conflicts of interest to declare.

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