European Review for Medical and Pharmacological Sciences 2022; 26: 7290-7296

The effect of lymphocyte blood levels on mortality of COVID-19 patients under intensive care unit follow-up

E. DIZEN KAZAN[1], S. ORHAN[2], D. KORKMAZ[3], A. SARI[1], S. KAZAN[4]

[1]Internal Medicine, [2]Intensive Care Unit, [3]Infectious Disease, [4]Nephrology Department, Faculty of Medicine, Afyonkarahisar Health Science University, Afyonkarahisar, Turkey

Abstract. – OBJECTIVE: Lymphocytes are the most important cells in defending the human body against viral pathogens. In this study, we aimed at investigating the relationship between lymphocyte blood levels and patient survival in COVID-19 patients hospitalized in the intensive care unit.

PATIENTS AND METHODS: We retrospectively evaluated patients hospitalized with COVID-19 pneumonia in the intensive care unit. Patients were divided into two groups in terms of blood lymphocyte levels; increased lymphocyte and decreased lymphocyte groups on the 5th day of hospitalization. Mortality rates were compared between groups.

RESULTS: Two groups were similar in terms of laboratory tests and comorbidities. Overall survival was 63.8% (n=102) in patients with increased lymphocytes and 33.2% (n=68) in patients with decreased lymphocytes. Mortality rates were significantly higher in decreased lymphocyte group than in increased lymphocyte group (p=0.003).

CONCLUSIONS: Our study reveals that mortality is higher in patients with a lower lymphocyte count on the 5th day compared to the day of hospitalization.

Key Words:
COVID-19, Lymphocyte, Mortality.

Introduction

In December 2019, an outbreak of pneumonia of unknown etiology was reported in Wuhan, China[1]. After a short while, the cause of this outbreak was identified as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which was defined as a new type of coronavirus, and the emerging disease was named coronavirus-related disease-19 (COVID-19). Since that day, the virus has spread all over the world and still shows its impact. Although it is still not clear how and where the first patient was infected by the disease, transmission from one person to another has caused the disease to spread rapidly[2]. While complaints including dry cough, fever, and shortness of breath are observed in the majority of patients, symptoms such as sore throat, headache, myalgia, and diarrhea have also been reported[3]. However, cases of a bilateral patchy lung infiltrate, leucopenia and lymphopenia, acute respiratory distress syndrome, and resulting refractory hypoxemia have been reported in more severe patients[4-7].

Particularly during the first few months of the disease, there has been confusion regarding most of the theoretical information on the prognostic markers, primarily smoking and antihypertensive drugs[8-11]. It has even been asserted that the nicotine in cigarettes may reduce the risk of cytokine storms in COVID-19 patients[9]. However, recent meta-analyses have more clearly revealed the prognostic markers for COVID-19[12-15]. Even so, further publications are required to investigate the severity and mortality markers in COVID-19 patients.

Lymphocytes are a component of the cellular immune system. They are composed of T lymphocytes, B lymphocytes, and natural killer (NK) cells. T lymphocytes and NK cells play an important role in the control of viral infections[16,17]. Lymphopenia has been used as a diagnostic and prognostic marker since the first days of COVID-19[18-20]. Although peripheral lymphocyte count cannot be used to show lymphocyte subtypes, there have been studies[21,22] demonstrating that it may be an indicator of severe COVID-19.

In this study, we aimed at investigating the relationship between lymphocyte blood levels and patient survival in COVID-19 patients hospitalized in the intensive care units.

Corresponding Author: Dizen Kazan Elif, MD; e-mail: elifdizen@hotmail.com

Patients and Methods

Patients Selection

The files of all patients hospitalized in our hospital's COVID-19 intensive care unit between March 2020 and December 2020 were examined retrospectively. Exclusion criteria included < 18 years of age, pregnancy, a history of the hematologic or oncologic disease, organ transplant, rheumatic disease, use of immunosuppressive drugs for any reason, lacking sufficient file data, and having no change in their absolute lymphocyte values at Day 5 and at admission for hospitalization (Figure 1). Patients' demographics, comorbidities, Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA) scores, first application, Day 5 laboratory results, and final statuses were recorded.

Lymphocytes and Patient Groups

Patients were divided into two groups, in terms of lymphocyte blood levels. Increased lymphocyte group was composed by patients who showed a higher lymphocyte count on the 5th day of hospitalization compared to the first day. Decreased lymphocyte group was composed by patients having a lower lymphocyte count on the 5th day of hospitalization compared to the first day.

Laboratory Measurements

All complete blood counts of patients were analyzed with an automatic analyzer (Cobas 6000, Roche, Switzerland). A complete blood count was performed for all COVID-19 patients at the central laboratory using the same device.

Statistical Analysis

Categorical variables were presented as percentage and frequency. The Chi-square test was used to compare the categorical variables between the groups. The Shapiro-Wilk test was used to examine if the continuous variables are normally distributed. Continuous variables with normal distribution were presented as mean and standard deviation, while continuous variables with non-normal distribution were presented as median and interquartile range. Independent samples *t*-test was used to perform between-group comparisons for continuous variables with normal distribution, while the Mann-Whitney U test was used for comparisons of continuous variables with non-normal distribution. Overall survival analysis was done with Kaplan-Meier curves and a log-rank test was used to compare lymphocyte group survival rates. Univariate and multivariate cox regression analyses were done to the determination of risk factors for mortality. All *p*-values presented were two-sided and values $p<0.05$ were considered statistically significant. The data were analyzed using the SPSS 26.0 program (IBM Corp., Armonk, NY, USA).

Results

The study included a total of 365 patients. The median age of the study group was 68 years (interquartile range 25-75 = 62-76 years). Of the patients, 68.2% were male (n=249). According to the distribution of patients by the lymphocyte groups, 56.2% (n=205) was in the

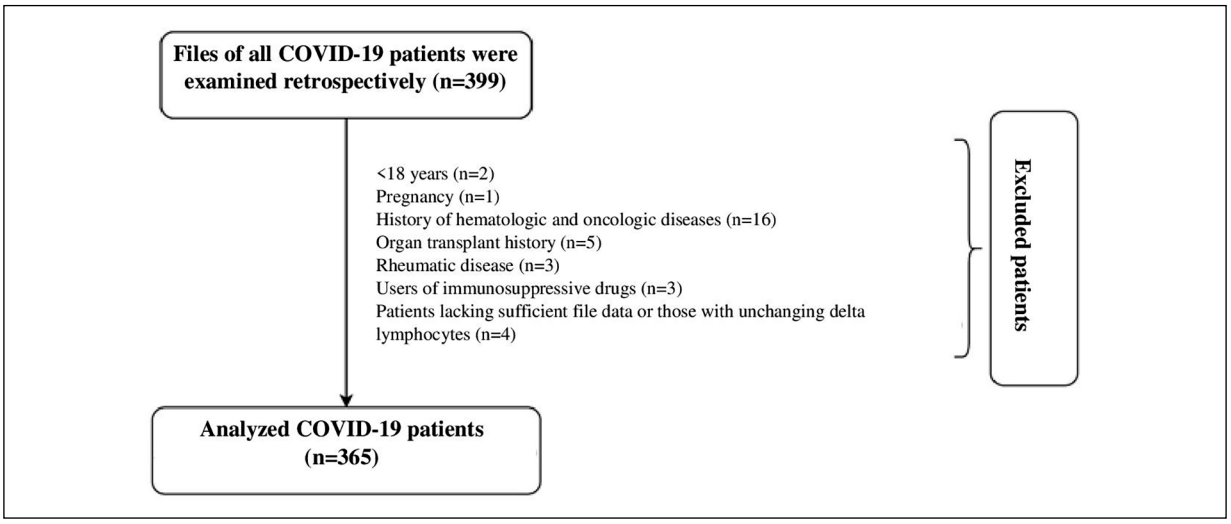

Figure 1. Study design – Patients included in the study and exclusion criteria.

Table I. Comparison of patient demographics by patient groups.

Characteristic	Increased Δlymphocytes	Reduced Δlymphocytes	Total	*p*-value
Median age (IQR)	67.5	69	68	0.160*
Male gender (%-n)	64.4-103	71.2-146	68.2-249	0.175**
Hypertension (%-n)	41.9-67	51.2-105	47.1-172	0.091**
GCS (IQR)	14 (4.75)	12 (5)	12 (5)	0.194*
SOFA score (IQR)	4 (2)	4 (3)	4 (3)	0.668*
DM (%-n)	30-48	39-80	35.1-128	0.078**
CAD (%-n)	21.9-35	26.8-55	24.7-90	0.328**
COPD (%-n)	21.3-34	21-43	21.1-77	1**
CKD (%-n)	5.6-9	11.2-23	8.8-32	0.065**
Fever (%-n)	8.1-13	11.2-23	9.9-36	0.379
Shortness of breath (%-n)	100-160	99.5-204	99.7-364	1**
Cough (%-n)	62.5-100	58-119	60-219	0.451**
Malaise (%-n)	21.9-35	22.9-47	22.5-82	0.900**
Muscle-joint pain (%-n)	9.4-15	4.9-10	6.8-25	0.099**
Headache (%-n)	3.8-6	5.9-12	4.9-18	0.467**

*Mann-Whitney U test, **Fisher's exact test, GCS = Glasgow Coma Scale, SOFA = Sequential Organ Failure Assessment, DM = Diabetes Mellitus, CAD = Coronary Artery Disease, COPD = Chronic Obstructive Pulmonary Disease, CKD = Chronic Kidney Disease.

group of decreased lymphocytes, while 43.8% (n=160) was in the group of increased lymphocytes. A comparison of the patients by the lymphocyte groups showed similar results in terms of age, gender, comorbidities, and complaints at admission ($p > 0.05$). Table I shows the comparison of patient demographics and complaints at admission.

A comparison of the groups in terms of laboratory parameters showed similar results for leukocytes, hemoglobin, thrombocytes, C-reactive protein, ferritin, alanine aminotransferase, creatinine, albumin, and erythrocyte sedimentation rate between groups of increased and decreased lymphocytes ($p > 0.05$). Day 0 and Day 5 lymphocyte values of the groups were statistically significantly different ($p < 0.05$). Table II shows the comparison of laboratory parameters by lymphocyte groups.

Overall survival was 63.8% (n = 102) in patients with increased lymphocyte and 33.2% (n= 68) in patients with decreased lymphocyte. The survival difference between these two groups was statistically significant when compared using the log-rank test (p= 0.003). Figure 2 shows the survival function of the patients in terms of lymphocyte groups. Univariate Cox regression analysis showed that hypertension (HR = 1.338, 95% CI = 1.005-1.782 and p = 0.046), diabetes mellitus (HR = 1.336, 95% CI = 1.006-1.779, p = 0.046), chronic kidney disease (HR = 1.605, 95% CI = 1.027-2.506, p = 0.039), decreased lymphocyte

Table II. Comparison of laboratory parameters by patient groups.

Parameter	Increased Δlymphocytes	Reduced Δlymphocytes	*p*-value
Leukocytes ($\times 10^9/mm^3$)	9638 ± 7050	9767 ± 4595	0.265*
Hb (g/dL)	12.58 ± 2.61	12.8 ± 2.45	0.353*
Thrombocytes ($\times 10^9/mm^3$)	217.5 ± 100.5	223.7 ± 95.7	0.172*
Lymphocytes-0 ($\times 10^9/mm^3$)	637.24 ± 375.1	908.11 ± 484.8	< 0.001*
Lymphocytes-5 ($\times 10^9/mm^3$)	1059.17 ± 689.9	556.47 ± 335.4	< 0.001*
CRP (mg/dL)	35.53 ± 8.3	32.17 ± 8.8	0.628*
Ferritin (ng/mL)	998.82 ± 960.9	833.44 ± 624.4	0.156*
ALT (IU/L)	45.21 ± 55.3	35.1 ± 32.5	0.138*
Creatinine (mg/dL)	1.38 ± 2	1.49 ± 1.5	0.412*
Albumin (g/dL)	3.08 ± 0.4	3.18 ± 0.4	0.953*
Sedimentation (mm/h)	62.36 ± 27.3	61.56 ± 25.1	0.767*

*Independent samples *t*-test, Hb = hemoglobin, CRP = C-reactive protein, ALT = alanine aminotransferase.

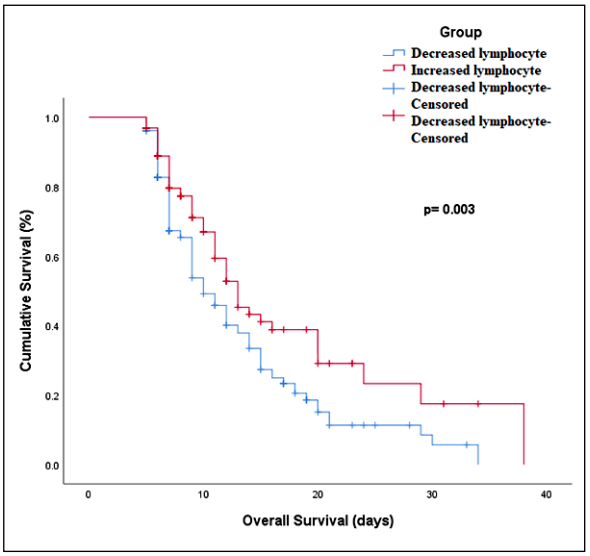

Figure 2. Overall survival functions of patients in terms of lymphocyte groups.

(HR = 1.550, 95% CI = 1.137-2.114, p = 0.006), lower GCS (HR = 1.094, 95% CI = 1.049-1.141, p < 0.001) and higher SOFA (HR = 1.182, 95% CI = 1.093-1.278, p < 0.001) were found to be significant parameters for mortality.

Multivariate Cox regression analysis showed that decreased lymphocyte (HR = 1.461, 95% CI = 1.067-2.004, p = 0.018) and higher SOFA (HR = 1.101, 95% CI = 1.000-1.212, p = 0.049) were independent risk factors for mortality (Table III).

Discussion

Lymphopenia has been used as a diagnostic and prognostic marker since the first days of COVID-19. Although studies[23] have report varying rates of lymphopenia in patients, a meta-analysis has indicated that 70% of intensive care patients had lymphopenia. Cytotoxic lymphocytes, such as T and NK cells, play a critical role in keeping the viral infection under control[24]. A study by Zheng et al[25] has demonstrated considerably reduced cytotoxic T lymphocytes and NK cells in severe COVID-19 patients compared to mild COVID-19 patients. The same study has emphasized that T lymphocyte and NK cell counts may be increased by efficient treatment.

Table III. Prognostic factors for mortality by multivariate Cox regression analysis.

Risk factor	HR (95% CI)	*p*-value
Hypertension	1.167 (0.867-1.572)	0.309
Diabetes mellitus	1.113 (0.827-1.499)	0.481
Chronic kidney disease	1.322 (0.837-2.089)	0.231
Reduced Δlymphocyte	1.461 (1.067-2.004)	0.018
Lower GCS	1.051 (0.997-1.109)	0.065
Higher SOFA	1.101 (1.000-1.212)	0.049

HR = Hazard Ratio, CI = Confidence Interval, GCS = Glasgow Coma Scale, SOFA = Sequential Organ Failure Assessment.

A great number of studies[26-30] have been conducted to predict the prognosis and mortality of COVID-19. Despite the challenges in reaching a shared decision due to the design differences between the studies, a systematic review[26] evaluating 207 studies has reported that a total of 49 parameters including demographics such as age and gender, laboratory parameters such as ferritin and interleukin-6, comorbidities such as hypertension and diabetes, and clinical findings such as hypoxia and hypotension may be used to predict severity and mortality in COVID-19. An association was established between the disease and hypercoagulopathy, while increased angiopoietin-2, Von Willebrand factor, and soluble thrombomodulin levels were also associated with poor prognosis[27-30]. However, the majority of the markers studied to predict prognosis are not widely used. Easily accessed prognostic markers that do not cause additional costs in healthcare expenses are required particularly in developing countries like our country. The current study showed an increased mortality risk in patients whose lymphocyte levels continued to decline on day 5 of hospitalization.

Although peripheral lymphocyte count is not sensitive to adequately reflect the lymphocyte subgroups, it has also been shown to be a predictor of severe COVID-19[22,31-33]. Hence, we had planned our study to compare the mortality between patients with decreased and increased lymphocyte count. Our study has demonstrated that the decreased lymphocyte is an independent risk factor for mortality. While the patients' groups with increased or decreased lymphocyte values were found to be similar in terms of demographics and laboratory parameters, the detection of higher mortality in the decreased lymphocyte group is a striking finding. Also, absolute lymphocyte count is a laboratory parameter that is easily accessible from complete blood count results. Our literature search did not reveal any study investigating the blood lymphocyte count changes, which can be calculated using the com-

plete blood count parameters that are regularly monitored in COVID-19 patients hospitalized in the intensive care unit, and COVID-19 severity and mortality. Hence, our study is the first in this area. Patients whose day 5-lymphocyte values tended to decrease compared to those at hospitalization should be monitored more closely and steps toward an aggressive treatment should be taken earlier for these patients.

Limitations

The major limitations of our study are its retrospective design and lack of lymphocyte subgroup investigation. Another limitation of our study may be the lack of assessments of the treatments received by the patients and concomitant secondary bacterial infections. Prospective studies examining the prognosis of patients with lymphocyte count tending to decrease may provide more reliable information regarding survival in these patients.

Conclusions

Our study has demonstrated that the mortality risk in patients with decreased lymphocytes is higher than in patients with increased lymphocytes. These patients should be followed more closely and treated more aggressively for COVID-19 infection.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The study was approved by the Ethics Committee of Afyonkarahisar Health Sciences University (date: 05.02.2021, meeting no: 2021/2, approval number: 126).

Funding

There is no funding for the study.

Authors' Contribution

All authors contributed to the design, implementation of the research, and to the writing of the manuscript. Statistical analyses were done by Kazan S.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

ORCID ID

Dizen Kazan E: 0000-0003-3550-0964; Orhan S: 0000-0003-2617-6197; Korkmaz D: 0000-0001-7236-2161; Sari A: 0000-0002-4327-8032; Kazan S: 0000-0001-7290-4680.

References

1) Lu H, Stratton CW, Tang YW. The outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol 2020; 92: 401-402.
2) Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020; 395: 514-523.
3) Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, Ippolito G, Mchugh TD, Memish ZA, Drosten C, Zumla A, Petersen E. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020; 91: 264-266.
4) Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270-273.
5) Tavakolpour S, Rakhshandehroo T, Wei EX, Rashidian M. Lymphopenia during the COVID-19 infection: What it shows and what can be learned. Immunol Lett 2020; 225: 31-32.
6) Fathi N, Rezaei N. Lymphopenia in COVID-19: Therapeutic opportunities. Cell Biol Int 2020; 44: 1792-1797.
7) Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Deng Y, Weng Z, Yang L. Lymphopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A systemic review and meta-analysis. Int J Infect Dis 2020; 96: 131-135.
8) Rossato M, Russo L, Mazzocut S, Di Vincenzo A, Fioretto P, Vettor R. Current smoking is not associated with COVID-19. Eur Respir J 2020; 55: 2001290.
9) Farsalinos K, Barbouni A, Niaura R. Systematic review of the prevalence of current smoking among hospitalized COVID-19 patients in China: could nicotine be a therapeutic option? Intern Emerg Med 2020; 15: 845-852.
10) Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D,

Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM. A crucial role of angiotensin-converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005; 11: 875-879.

11) Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui CC, Hein L, Uhlig S, Slutsky AS, Jiang C, Penninger JM. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005; 436: 112-116.

12) Tleyjeh IM, Bin Abdulhak AA, Tlayjeh H, Al-Mallah MH, Sohail MR, Hassett LC, Siller-Matula JM, Kashour T. Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers and the Risk of SARS-CoV-2 Infection or Hospitalization With COVID-19 Disease: A Systematic Review and Meta-Analysis. Am J Ther 2020; 29: e74-e84.

13) Xie J, Wang Q, Xu Y, Zhang T, Chen L, Zuo X, Liu J, Huang L, Zhan P, Lv T, Song Y. Clinical characteristics, laboratory abnormalities and CT findings of COVID-19 patients and risk factors of severe disease: a systematic review and meta-analysis. Ann Palliat Med 2021; 10: 1928-1949.

14) Gülsen A, Yigitbas BA, Uslu B, Drömann D, Kilinc O. The Effect of Smoking on COVID-19 Symptom Severity: Systematic Review and Meta-Analysis. Pulm Med 2020; 2020: 7590207.

15) Koshy AN, Murphy AC, Farouque O, Ramchand J, Burrell LM, Yudi MB. Renin-angiotensin system inhibition and risk of infection and mortality in COVID-19: a systematic review and meta-analysis. Intern Med J 2020; 50: 1468-1474.

16) Gerdemann U, Keirnan JM, Katari UL, Yanagisawa R, Christin AS, Huye LE, Perna SK, Ennamuri S, Gottschalk S, Brenner MK, Heslop HE, Rooney CM, Leen AM. Rapidly generated multivirus-specific cytotoxic T lymphocytes for the prophylaxis and treatment of viral infections. Mol Ther 2012; 20: 1622-1632.

17) Biron CA. Activation and function of natural killer cell responses during viral infections. Curr Opin Immunol 1997; 9: 24-34.

18) Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, Wang Q, Miao H. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther 2020; 5: 33.

19) Liu J, Li H, Luo M, Liu J, Wu L, Lin X, Li R, Wang Z, Zhong H, Zheng W, Zhou Y, Jiang D, Tan X, Zhou Z, Peng H, Zhang G. Lymphopenia predicted illness severity and recovery in patients with COVID-19: A single-center, retrospective study. PLoS One 2020; 15: e0241659.

20) Jafarzadeh A, Jafarzadeh S, Nozari P, Mokhtari P, Nemati M. Lymphopenia an important immunological abnormality in patients with COVID-19: Possible mechanisms. Scand J Immunol 2021; 93: e12967.

21) Wang S, Sheng Y, Tu J, Zhang L. Association between peripheral lymphocyte count and the mortality risk of COVID-19 inpatients. BMC Pulm Med 2021; 21: 55.

22) Yamasaki Y, Ooka S, Tsuchida T, Nakamura Y, Hagiwara Y, Naitou Y, Ishibashi Y, Ikeda H, Sakurada T, Handa H, Nishine H, Takita M, Morikawa D, Yoshida H, Fujii S, Morisawa K, Takemura H, Fujitani S, Kunishima H. The peripheral lymphocyte count is a predictor of severe COVID-19 and the effect of treatment with ciclesonide. Virus Res 2020; 290: 198089.

23) Zhong Z, Li H, Zhu J, Ji P, Li B, Pang J, Zhang J, Liang X. Clinical characteristics of 2,459 severe or critically ill COVID-19 patients: A meta-analysis. Medicine (Baltimore) 2021; 100: e23781.

24) Zhang C, Wang X, Li S, Twelkmeyer T, Wang W, Zhang S, Wang S, Jin X, Wu Y, Chen X, Wang S, Niu J, Chen H, Tang H. NKG2A is a NK cell exhaustion checkpoint for HCV persistence. Nat Commun 2019; 10: 1507.

25) Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, Xu Y, Tian Z. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol 2020; 17: 533-535.

26) Izcovich A, Ragusa MA, Tortosa F, Lavena Marzio MA, Agnoletti C, Bengolea A, Ceirano A, Espinosa F, Saavedra E, Sanguine V, Tassara A, Cid C, Catalano HN, Agarwal A, Foroutan F, Rada G. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLoS One 2020; 15: e0241955.

27) Dudley AC. Introduction to special issue: vascular co-option in cancer. Angiogenesis 2020; 23: 1-2.

28) Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Fagot Gandet F, Fafi-Kremer S, Castelain V, Schneider F, Grunebaum L, Anglés-Cano E, Sattler L, Mertes PM, Meziani F; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020; 46: 1089-1098.

29) Goshua G, Pine AB, Meizlish ML, Chang CH, Zhang H, Bahel P, Baluha A, Bar N, Bona RD, Burns AJ, Dela Cruz CS, Dumont A, Halene S, Hwa J, Koff J, Menninger H, Neparidze N, Price C, Siner JM, Tormey C, Rinder HM, Chun HJ, Lee AI. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol 2020; 7: e575-e582.

30) Hendrickson CM, Matthay MA. Endothelial biomarkers in human sepsis: pathogenesis and prognosis for ARDS. Pulm Circ 2018; 8: 2045894018769876.

31) Deng Z, Zhang M, Zhu T, Zhili N, Liu Z, Xiang R, Zhang W, Xu Y. Dynamic changes in peripheral blood lymphocyte subsets in adult patients with COVID-19. Int J Infect Dis 2020; 98: 353-358.

32) Qian F, Gao G, Song Y, Xu Y, Wang A, Wang S, Hao Y, Chen M, Ma X, Zhao T, Guo X, Chen Z, Zhang F. Specific dynamic variations in the peripheral blood lymphocyte subsets in COVID-19 and severe influenza A patients: a retrospective observational study. BMC Infect Dis 2020; 20: 910.

33) Khalid AMAM, Suliman AM, Abdallah EI, Abakar MAA, Elbasheir MM, Muddathir AM, Aldakheel FM, Bin Shaya AS, Alfahed A, Alharthi NS, Aloraini GS, Alenazi MM, Waggiallah HA. Influence of COVID-19 on lymphocyte and platelet parameters among patients admitted to intensive care unit and emergency. Eur Rev Med Pharmacol Sci 2022; 26: 2579-2585.