HEALTH SCIENCES QUARTERLY

Volume: 3
Issue: 1
2023

E-ISSN: 2791-6022
https://journals.gen.tr/jsp

Received: 2022-04-21
Accepted: 2022-09-21

ORIGINAL ARTICLE

Significance of laboratory biomarkers in monitoring patients with COVID-19 pneumonia

Hasan Ölmez[1] **Mustafa Tosun**[1]

[1] Department of Chest Diseases, Faculty of Medicine, Erzincan Binali Yildirim University. Erzincan / Türkiye

Abstract

Clinical and laboratory parameters are useful tools to improve success rates in the management of COVID-19 patients. Indices such as NLR, PLR, MHR, SII, AIP and CAR may indicate poor prognosis in predicting poor prognosis in COVID-19. It was aimed to identify such parameters of disease progression in COVID-19 patients by examining demographic data, comorbid conditions, some biochemical and hematological parameters. A retrospective analysis was performed for patients admitted to intensive care unit or pulmonary diseases department or treated on an outpatient basis due to a diagnosis of COVID-19. Patients with positive PCR test and thoracic CT compatible with COVID-19 pneumonia were included in the study. A control group was formed from volunteers of similar age and gender. The study population was divided into four groups as follows: patients admitted to intensive care unit (ICU group); patients admitted to chest diseases department (Inpatient Group); patients treated on an outpatient basis (Outpatient Group); and controls (Control Group). There were 61, 201, and 30 patients in the ICU, inpatient, and outpatient groups, respectively. A total of 96 subjects served as controls. Study groups were comparable with respect to gender distribution. ICU patients had higher NLR, PLR, AIP, SII, and CAR, and lower LMR as compared to other groups. NLR, SII, AIP, and CAR emerged as predictors of ICU admission, while MHR was predictive of inpatient treatment. Certain clinical and laboratory parameters may be useful tools for improving the success of COVID-19 management. High NLR, SII, AIP, CAR, and MHR values may indicate low prognosis in COVID-19 patients.

Keywords: Biochemical indexes, COVID-19, laboratory parameter, intensive care unit

Abbreviations: NLR, Neutrophil to lymphocyte ratio; LMR, Lymphocyte to monocyte ratio; PLR, Platelet to lymphocyte ratio. MHR, monocyte to HDL-C ratio; SII, Systemic immun inflammatory index; AIP Atherogenic index of plasma; CAR, C-reactive protein to albumin ratio; PCR, Polymerase Chain Reaction; ICU, intensive care unit.

Citation: Ölmez et al. / Significance of laboratory biomarkers in monitoring patients with COVID-19 pneumonia. Health Sci Q. 2023;3(1):13-25. https://doi.org/10.26900/hsq.1771

Corresponding Author:
Hasan Ölmez
Email: drhasan2024@gmail.com

Introduction

In December 2019, a cluster of pneumonia cases with unknown etiology has been observed in Wuhan city of China. Subsequently, the causative agent was found to be a novel type of enveloped RNA beta-coronavirus, later termed as the *severe acute respiratory syndrome coronavirus-2* (SARS-CoV-2) [1]. Lungs are the most important site of involvement for coronavirus disease 2019 (COVID-19) [2]. Therefore, it is very important to show radiologically pulmonary involvement. The low specificity could be associated with other etiological factors that can cause similar thorax computer tomography (CT) findings [3]. Although certain thorax CT signs are characteristic of COVID-19, no specific sign is able to completely rule out a diagnosis of COVID-19 [4]. Inconsistency between radiological and clinical findings may also present certain diagnostic challenges. Therefore, laboratory parameters represent a very important tool for predicting the course and progression of COVID-19. Patients with COVID-19 may experience severe pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ failure leading to hospitalization or death [5]. Laboratory parameters or biochemical indexes that can reflect the COVID-19 severity may allow administration of earlier aggressive treatments and reduce mortality. Lymphocyte count, platelet count, albumin, C-reactive protein to albumin (CAR) fibrinogen, procalcitonin, D-dimer, and interleukin-6 (IL-6) have been shown to predict the disease severity in COVID-19 patients [6-10]. Recently, similar benefits for diagnosing and assessing the severity of COVID-19 have been reported for several indexes such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), and systemic immune inflammation index (SII) [11-13]. Despite these reports, no single reliable diagnostic and/or prognostic marker is available that can guide clinicians in the management of COVID-19. Thus, widely available, inexpensive, and rapidly measurable biomarkers are warranted for timely clinical decisions. In this study, we aimed to find demographic data, biochemical and haematological parameters of comorbid diseases that may show COVID-19 progression.

Materials and Methods

A total of 403 patients diagnosed with COVID-19 and admitted to intensive care unit (ICU) or chest diseases ward, or treated on an outpatient basis between 1 January 2021 and 31 June 2021 at the Medical Faculty Hospital, Erzincan Binali Yildirim University (EBYU), were retrospectively screened. 109 were excluded due to missing data. 3 patients were excluded due to current treatment with statins and/or fenofibrate. The study was approved by the EBYU Ethics Committee for Clinical Research (2021:10/20). Patients with positive PCR (Polymerase Chain Reaction) test and thoracic CT compatible with COVID-19 pneumonia were included in the study. A control group was formed from volunteers of similar age and gender. Also, a group of subjects with no COVID-19 infection served as controls. Thus, a total of 292 patients and 96 control group participated the study. Data on demographics, comorbid conditions, and laboratory results were retrieved from the hospital's electronic database. Study subjects were divided into four groups as follows: patients admitted to intensive care unit (ICU Group, n=61); patients admitted to chest diseases ward (Inpatient Group, n=201); patients treated on an outpatient basis (Outpatient Group, n=30); and the control group (Control Group, n=96). ICU group consisted of patients with the following characteristics: respiratory rate > 30/min, presence of severe respiratory symptoms, oxygen saturation (SpO2) < 90% at ambient air, PaO2/FiO2 < 200, in addition to requirement for high flow oxygen therapy (HFOT), non-invasive mechanical ventilation (NIMV), or invasive mechanical ventilation (IMV). Subjects in the Inpatient Group had symptoms such as productive cough and myalgia with positive PCR test result, in addition to the presence of radiological signs of COVID-19 pneumonia. Outpatients consisted of those with cough, sputum, myalgia, positive PCR test, with no radiological signs of COVID-19 pneumonia. Age and gender matched subjects who applied to the hospital for other reasons and did not have COVID-19 or comorbidities constituted the control group.

The test results obtained from the first measurements of the patients recorded in the system were evaluated in this study. Venous blood samples were collected after 12 hours of fasting. Fasting total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides, albumin, creatine kinase (CK), lactate dehydrogenase (LDH), ferritin, C-reactive protein (CRP), D-dimer, Hematocrit (Htc), neutrophil count, lymphocyte count, monocyte count, and mean red cell distribution width (RDW) at presentation were recorded. The complete blood counts were performed using a Sysmex XN-1000 autoanalyzer (Sysmex Corporation, Kobe, Japan), and biochemical assays were carried out with spectrophotometric methods using an Olympus AU2700 Plus Chemistry Analyzer (Beckman Coulter, Tokyo, Japan). Serum ferritin was determined by chemiluminescence using a Centaur XP device (Siemens Healthcare, Germany). C-reactive protein (CRP) was measured in serum by nephelometric methods using a BN™ II device (Siemens, Munich, Germany). D-dimer were measured from the whole blood with AQT90 flex Radiometer® (Bronshoj, Denmark). Also calculated for each patient were the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), systemic immune inflammation index (SII: neutrophils × platelets/lymphocytes), monocyte to HDL-C ratio (MHR), C-reactive protein to albumin ratio (CAR: CRP/albumin × 100), and AIP (as the base 10 logarithm of triglyceride to HDL-C ratio).

Exclusion criteria included the presence of connective tissue disorders, hematological disorders, renal or hepatic dysfunction, thyroid disorders, cancer, age < 18 years, pregnancy, albumin transfusion prior to treatment, and use of antifibrotic treatments.

IBM SPSS 22 (Armonk, NY: IBM Corp.) package program was used in statistical analysis of the data. Descriptive statistics for variables were presented as numbers and percentages for categorical variables and average ± standart deviation (FA) for continuous variables. Chi-square test was used in the analysis of categorical data. The suitability of continuous variables to normal distribution was tested by the *Kolmogorov-Smirnov* normality test. One-way ANOVA performed in group comparison. After ANOVA pairwise comparisons were done by using *Bonferroni* post-hoc test. The ROC curve was used to test whether the variables had diagnostic value. Area under roc curve (AUC), *Youden* index, optimum cut-off, sensitivity and speciality values of the optimum cutting point were presented. In all statistical tests, situations with $p < 0.05$ were considered significant.

Results

There were 61, 201, and 30 patients in the ICU, inpatient, and outpatient groups, respectively a total of 96 subjects served as controls. Female and male patients comprised 41% and 59%, 39.8% and 60.2%, and 46.7% and 53.3% of the patients in the ICU, inpatient, and outpatient groups, respectively. Of the control subjects, 43.8% were female and 56.3% were male. Gender distribution was comparable across the study groups ($p = 0.855$). The mean age in ICU, inpatient, outpatient, and control groups was 67.79 ± 13.624, 53.25 ± 19.292, 44.54 ± 12.128, and 50.15 ± 14.375 years, respectively. ICU patients were significantly older as compared to other groups ($p < 0.001$). In our study, cardiovascular disease (CVD), diabetes mellitus (DM), chronic pulmonary disease (CPD) and charlson comorbidity index (CCI) scores were higher in the ICU group compared to other groups ($p < 0.001$) (Figure 1). Also, mean CK, LDH, ferritin, CRP, D-dimer, triglyceride, neutrophil, and RDW were higher among ICU patients than in other groups ($p < 0.001$) (Figure 2, Table 1). However, ICU patients had lower Htc, lymphocyte count, and albumin vs. other groups ($p < 0.001$) (Table 1).

In our study, it was seen that the total-C value in the ICU group is similar to the inpatient group (p = 0.632), but lower than the values in the Outpatient and Control group (p < 0.001). In our study, HDL-C values were similar to the inpatient group and the ICU group (p=0.14). However, HDL-C values in these two groups were lower than in the outpatient and control groups. In addition, in our study, the values in the LDL-C ICU group were lower than other groups (p < 0.001). The triglyceride values were higher in the ICU group than other groups (p < 0.001). Finally, the AIP values in the ICU group were higher compared to other groups (p < 0.001) (Figure 4). When NLR, LMR, PLR, AIP, SII, CAR, and MHR indexes are calculated, ICU patents were found to have higher NLR, PLR, AIP, SII, and CAR (p < 0.001) and lower LMR (p < 0.001) as compared to

Table 1. Laboratory values used in the follow-up of patients with COVID-19 infection

Laboratory Parameters	**ICU Group (n=61)**	**Inpatient Group (n=201)**	**Outpatient Group (n=30)**	**Control Group (n=96)**	***p***
Albumin (g/L)	30.2 ± 5.7	39.8 ± 4.4*	40.6 ± 3*	41.9 ± 3.3*	< 0.001
TC (mg/dL)	175.9 ± 77.53	174.1 ± 49	199.2 ± 39.6*	198.4 ± 42.2*	< 0.001
Triglyceride (mg/dL)	208 ± 106.5	134.4 ± 77*	199 ± 130.8	143.5 ± 93*	< 0.001
HDL-C (mg/dL)	33.8 ± 10	38.4 ± 11.8	45.1 ± 10.3*	47.6 ± 11.8*	< 0.001
LDL-C (mg/dL)	92.3 ± 35.4	108 ± 41*	114 ± 33.4*	125.1 ± 36*	< 0.001
CK (u/L)	265 ± 293.5	168.6 ± 215.4*	117.4 ± 43.4*	138 ± 165.3*	< 0.001
LDH (u/L)	520.1 ± 419	274.2 ± 103.4*	233.4 ± 90*	256.2±82*	< 0.001
WBC (10^3/ mm^3)	11.5 ± 7.5	8.5 ± 3.9*	7.1 ± 2.2*	7.0 ± 2.0*	< 0.001
Htc (%)	35.6 ± 6.3	41.5 ± 4.5*	42.4 ± 3.8*	43.1 ± 3.9*	< 0.001
RDW %	15.2 ± 2.6	13.5 ± 1.8*	13.4 ± 1.6*	13.1 ± 1.0*	< 0.001
PLT (10^3/ µL)	237 ± 113	240 ± 72*	249 ± 676*	277 ± 78*	< 0.001
Lymphocyte (10^3/ µL)	1.20 ± 0.74	1.86 ± 0.83*	2.11 ± 0.86*	2.19 ± 0.70*	< 0.001
Monocytes (10^3/ µL)	0.93 ± 1.50	0.68 ± 0.31	0.55±0.20	0.52±0.19	< 0.001
Neutrophil (10^3/ µL)	7.82 ± 5.32	4.04 ± 2.01*	4.48 ± 1.69*	4.10 ± 1.59*	< 0.001
Ferritin (ng/mL)	680.8 ± 527.5	231.8 ± 293.8	187.7 ± 308	111 ± 79.8*	< 0.001
Fibrinogen (mg/dL)	313.9±113.9	351.6±81.7*	296±78.6*	263.2±64.8*	< 0.001
CRP (mg/L)	72.7 ± 61.40	35.6 ± 45.1*	6.0 ± 7.5*	3.5 ± 3.1*	< 0.001
D-dimer (µg/L)	3829 ± 6891	1885 ± 6995*	446 ± 291*	359 ± 144*	< 0.001
AIP	6.59 ± 4.0	3.81 ± 2.49*	4.75 ± 3.39*	3.33 ± 2.48*	< 0.001
SII	2281.4 ± 2570.2	664.6 ± 694.8*	584.0 ± 327.7*	557.1 ± 309.3*	< 0.001
CAR	2.684 ± 2.687	0.942 ± 1.276*	0.150 ± 0.194*	0.084 ± 0.076*	< 0.001
MHR	0.032 ± 0.06	0.019 ± 0.011*	0.013 ± 0.006*	0.012 ± 0.005*	< 0.001
NLR	10.17 ± 10.85	2.78 ± 2.73*	2.31 ± 1.08*	2.02 ± 1.04*	< 0.001
LMR	2.68 ± 2.22	3.167 ± 1.70*	3.93 ± 1.09*	4.52 ± 1.46*	< 0.001
PLR	265.5 ± 187.2	158.4 ± 112.6*	134.3 ± 62.7*	135.2 ± 44.3*	< 0.001

*Statistically significant difference was found when compared to intensive care (p<0.05)

Abbreviations: *TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CK, creatinine kinase; LDH, lactate dehydrogenase; WBC, white blood cell; Htc, Hematocrit; RDW, mean red cell distribution width; PLT, Platelets; CRP, C-reactive protein; AIP, Atherogenic index of plasma; SII, Systemic immun inflammatory index; CAR, C-reactive protein to albumin ratio; MHR, monocyte to HDL-C ratio; NLR, Neutrophil to lymphocyte ratio; LMR, Lymphocyte to monocyte ratio; PLR, Platelet to lymphocyte ratio.*

other groups (Figure 4). Also, ICU and inpatient groups had higher MHR than in outpatient and control groups ($p < 0.001$). MHR was found to be a significant predictor of hospitalization. An assessment of the diagnostic accuracy of NLR, LMR, PLR, AIP, SII, and CAR indexes indicated that SII, NLR, AIP, and CAR were significant predictors of ICU admission (Figure 5A), while LMR and PLR were not statistically significant predictors of ICU admission. Table 2 shows the sensitivity and specificity of NLR, AIP, SII, and CAR for predicting ICU admission, and Figure 5A shows the ROC curve analysis. Figure 5B shows an area under the ROC curve analysis of the sensitivity and specificity of MHR for hospitalization.

Discussion

COVID-19 remains a major global cause of morbidity and mortality with high rates of transmission. Increasing clinical evidence also shows that the most common comorbidities associated with poor prognosis and higher mortality rates in COVID-19 patients include systemic hypertension (HT), DM, and obesity. In our study, CVD, DM, CPD diseases and CCI scores were higher in the ICU group compared to other groups. However, patients with additional

Tablo 2. CAR, AIP, SII, and NLR values are observed in patients diagnosed with COVID-19 Pneumonia and treated in an outpatient setting in the intensive care unit, chest diseases department.

Indexes	AUC	95%CI for AUC	*p*-value	Optimum cut-off	Youden Index	Sensitivity (%)	Specificity (%)
SII	0.756	(0.674-0.838)	<0.001	960.6	0.48	62.3	85.7
NLR	0.816	(0.751 -0.882)	<0.001	3.91	0.51	65.6	85.7
AIP	0.740	(0.670-0.810)	<0.001	0.32	0.39	63.9	75.8
CAR	0.762	(0.693-0.832)	<0.001	1.11	0.43	65.6	77.5

Abbreviations: *CAR, C-reactive protein to albumin ratio; AIP, Atherogenic index of plasma; SII ,Systemic immun inflammatory index; NLR, Neutrophil to lymphocyte ratio.*

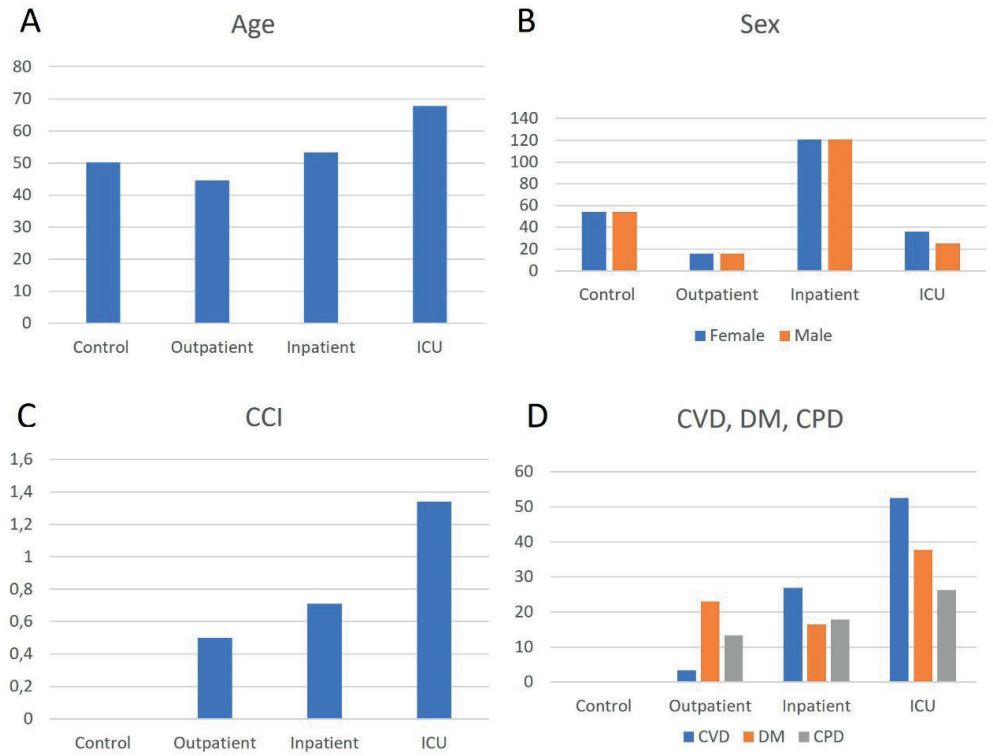

Figure 1. Shows the distribution of A: Age, B: Gender, C: CCI (charlson comorbidity index) and D: CVD, DM, CPD by groups. (CVD, cardiovascular disease; DM, diabetes mellitus; CPD, chronic pulmonary diseases)

infection or pulmonary thrombolysis were not included in the study.

Unfortunately no practical, rapid, and reliable tests are available for the diagnosis of this condition. Thus, more practical and available routine laboratory tests are required both for the diagnosis and prognosis prediction. Our results showed that a significant proportion of our patients experienced alterations in their routine laboratory tests that were more pronounced among patients admitted to an ICU. Fundamental pathophysiological mechanisms of multi-organ damage secondary to COVID-19 infection include direct viral toxicity, endothelial injury, thrombo-inflammation, dysregulation of

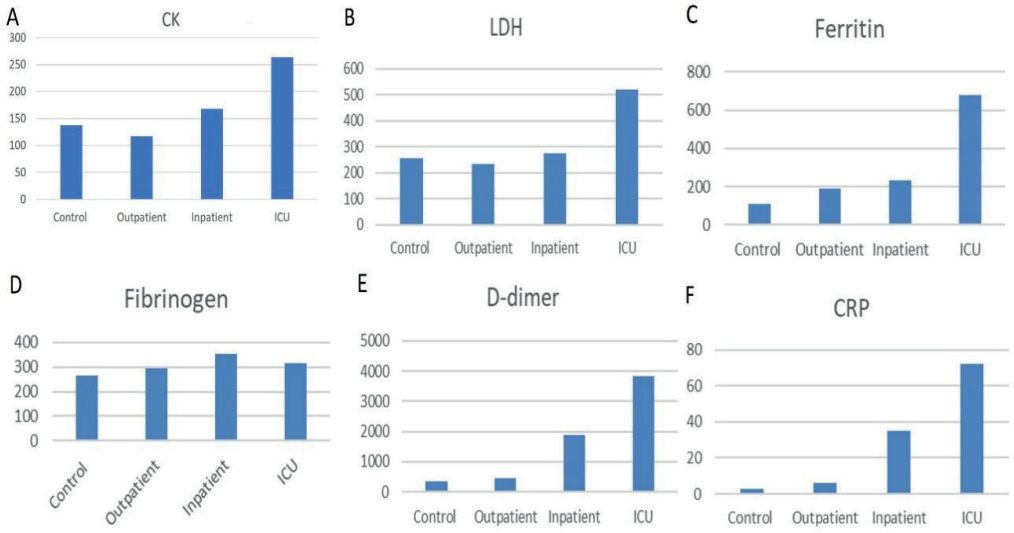

Figure 2. Distribution of A: CK, B: LDH, C: Ferritin, D: Fibrinogen, E: D-dimer, F: CRP according to groups is observed. (CK, creatinine kinase (μ/L); LDH, lactate dehydrogenase (μ/L), Ferritin (ng/ml), Fibrinogen (mg/dl), D-dimer (μg/L) CRP, C-reactive protein (mg/L)).

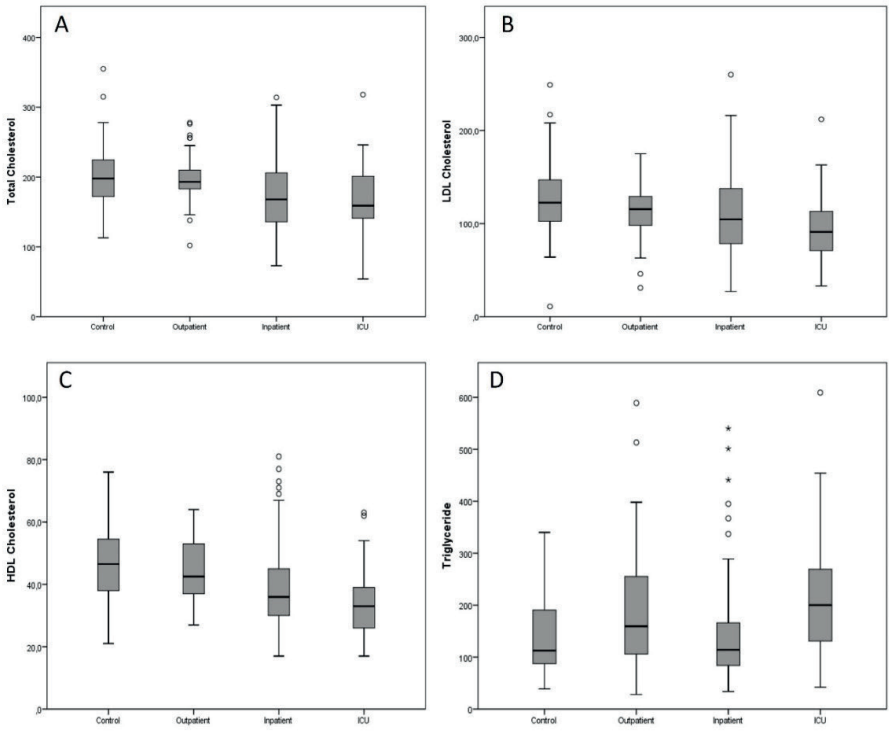

Figure 3. A: Total cholesterol (mg/dL), B: LDL-cholesterol (mg/dL), C: HDL-cholesterol (mg/dL) and D: Triglyceride (mg/dL) groups according to the distribution.

the immune responses, and dysregulation of the renin-angiotensin-aldosterone (RAAS) system [14]. It is highly probable that endothelitis, endothelial injury, endothelial cell dysfunction, and impaired micro-circulation in different vascular beds may contribute significantly to life-threatening complications of COVID-19, such as venous thromboembolic disease [15]. It appears that endothelial dysfunction plays a determinative role in the progression of COVID-19 [16]. Previously, elevated MHR has been shown to be associated with systemic inflammation and endothelial dysfunction, and has been proposed to be a prognostic marker for cardiovascular disorders [17-20]. In our study, ICU and inpatient treatment groups had higher MHR as compared to outpatients and control subjects ($p < 0.001$). Also, MHR emerged as a significant predictor of hospital admission. The height of the MHR index may be due to older,

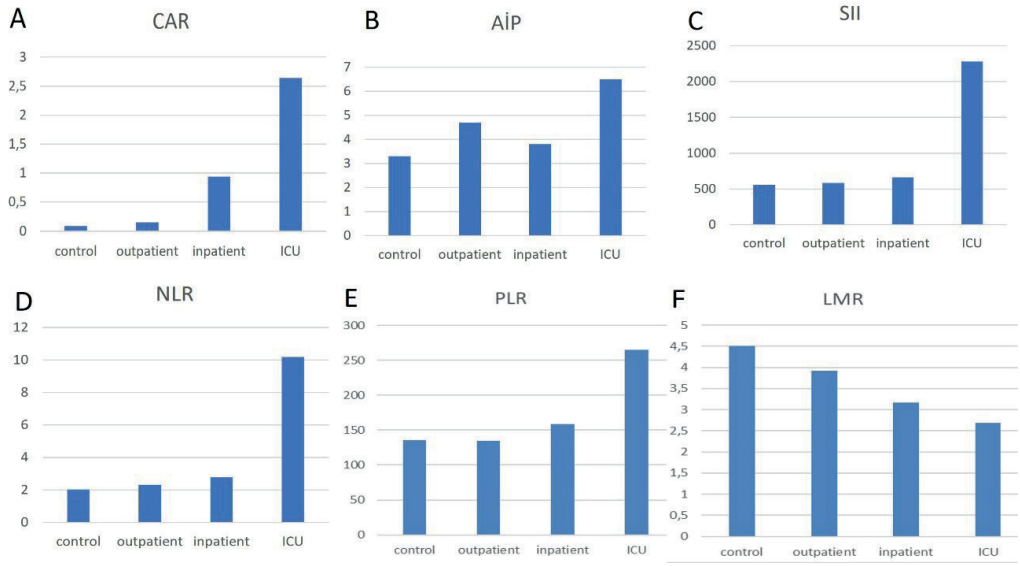

Figure 4. A: CAR, C-reactive protein to albumin ratio, B: AIP, Atherogenic index of plasma, C: SII, Systemic immun inflammatory index; D: NLR, Neutrophil to lymphocyte ratio; E: PLR, platelet to lymphocyte ratio F: LMR, Lymphocyte to monocyte ratio; shows the distribution according to groups.

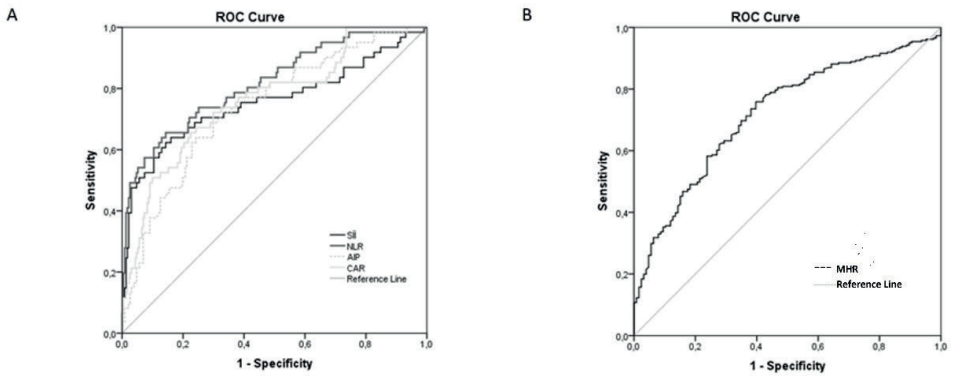

Figure 5. A: When the diagnostic accuracy of indexes were evaluated, AIP SII, CAR and NLR were found significant for determining B: The diagnostic value of the monocyte to HDL-C ratio (MHR) index was tested to determine hospitalization (ICU+Inpatient) and it was found to be significant in determining hospitalization ($p<0.001$). The area under the curve was found to have an AUC of: 0.719 (95%CI: 0.667-0.772). The diagnostic cut-off value for hospitalization was calculated as 11.6 (sens: 75.9%; spec: 60.3%). ICU admission (Table 2 and ROC curve).

Abbreviations: *AIP, Atherogenic index of plasma; SII, Systemic immun inflammatory index; CAR, C-reactive protein to albumin ratio; NLR, Neutrophil to lymphocyte ratio; MHR, monocyte to HDL-C ratio; HDL-C, high density lipoprotein cholesterol.*

DM and CVD patients in the ICU group, and may show poor prognosis. In a similar way in our study, it was seen that the most common comorbidities in patients with COVID-19 were diagnosed in patients with COVID-19 were found to be hypertension and diabetes mellitus diseases [21]. It has been reported that a progressive increase in RDW occurs in correlation with the severity of COVID-19 infection. On the basis of this information, it has been suggested that RDW should be a part of routine laboratory assessments and monitoring of COVID-19 patients [22]. Similar to previous observations, our ICU patients had higher RDW as compared to other groups. Systemic immune inflammation index (SII), estimated using the parameters of neutrophil, platelet, and lymphocyte counts, is a marker for the systemic inflammation, and may be utilized to predict poor prognosis in cardiovascular disorders [23]. Recent observations suggest that COVID-19 patients may have significant elevation of SII as compared to healthy controls, indicating a potential diagnostic role in these patients [11]. It appears that SII may be a particular marker of respiratory injury in COVID-19 patients, rather than a general impairment due to comorbidities [24]. In our study, patients admitted to the ICU also had higher SII than other groups ($p < 0.001$), with an additional role to predict the ICU admission. As stated earlier, these findings suggest that elevated SII in COVID-19 patients may be an indicator of poor prognosis. While neutrophils mediate the innate immune responses mainly involving the production of mediators, lymphocytes mediate the adaptive immune responses via regulation of inflammation [25]. Lymphopenia and neutrophilia are common hematological abnormalities in COVID-19 patients and also have been found to be significant predictors of disease severity and poor prognosis. In a recent study, Nalbant et al. showed that NLR index, which may be readily calculated by dividing neutrophil count to lymphocyte count, is an independent predictor of a diagnosis of COVID-19 infection [26]. Also, other studies suggest that NLR index may be closely associated with the course of COVID-19 infection [27]. In our study, ICU patients had higher NLR as compared to other groups. Also, NLR index was previously reported to be a significant predictor of ICU admission. LMR was proposed as an inflammatory marker with prognostic and predictive values [28, 29]. LMR measurements may have a prognostic value also in COVID-19 patients. Accordingly, our ICU patients had lower LMR values than other groups. Recently, PLR has emerged as an inflammatory marker that could predict the adverse outcomes in patients with CVD [30-32]. Also, Qu R. et al. reported that PLR could be used as a predictor of mortality in COVID-19 patients [33]. In the current study, ICU patients had higher PLR values as compared to other study groups. Hypercoagulation and dissemine intravascular coagulopathy (DIC) can be seen in some viral infections [34]. Grillet et al. detected the presence of acute pulmonary embolism in 23% of the patients with COVID-19 pneumonia [35]. Hypercoagulation may also be associated with hyperinflammatory responses. Also, acute pulmonary edema may occur in critically ill COVID-19 patients who have occlusion of the smaller pulmonary vessels and micro-thrombi [36]. Significantly increased fibrinogen and D-dimer levels may reflect a worse prognosis [37, 38]. In our study, ICU patients had higher D-dimer levels than other groups. CRP is a positive acute phase reactant that increases in infections, inflammation, and in response to tissue injury [39]. It has been reported that CRP may be elevated without any CT findings in some cases of severe COVID-19 infection, hence its proposed role as an early marker of severe disease [40]. It has been reported that there is a positive correlation between CRP levels and the diameter of the lung lesion and that CRP indicates disease severity [41]. In the current study, patients admitted to an ICU had higher CRP levels than in other subjects. Albumin is a negative acute phase reactant that tends to decrease in response to conditions such as inflammation, trauma, surgery, and burns [42]. Inflammation decreases albumin synthesis via IL-6 and TNF-α and increases the catabolism, leading to reduced serum albumin [43,44]. In hospitalized COVID-19 patients, an induced cytokine storm may lead to hypoalbuminemia, with an eventually elevated risk of mortality.

Low albumin levels may predict the course of the disease irrespective of other markers [45,46]. In our study, patients admitted to ICU had lower albumin levels than other groups. CAR can be estimated using only two laboratory parameters that are widely available, and therefore it can be used as a simple, practical, and inexpensive prognostic marker of disease severity in COVID-19. Furthermore, CAR can be used as a marker of pro-inflammation, which is closely linked with pro-thrombotic states. In patients with higher thrombotic burden, elevated CAR levels have been observed. In contrast with assessments performed using albumin and CRP separately, CAR may be a more reliable bio-marker of disease severity and prognosis [47]. In recent years, it has emerged as a useful prognostic factor to predict mortality in patients with sepsis, septic shock, or in critically ill subjects [48-50]. CAR is independent risk factors that can forecast how severe the patients COVID-19 disease will progress [51]. Zeynep et al. looked at LDH/albumin, CRP/albumin, and urea/albumin levels in COVID-19 patients and showed that these 3 indices can predict poor prognosis and may be effective in deciding to transfer these patients to the intensive care unit [52]. In line with these previous publications, our ICU patients had higher CAR index values than other patient groups. Also, CAR emerged as a significant predictor of ICU admission. In patients with COVID-19, myocardial injury, myocarditis, and cardiac failure may occur, and acute myocardial infarction may develop as a result of hypercoagulability [53-55]. High triglyceride and low HDL-C levels are known to be associated with cardiovascular disorders [56]. AIP combines these two risk factors, and has been found to be associated with atherosclerosis, CVD, DM, HT, vascular disorders, and endothelial injury [56-59]. All viruses of the Coronaviridae family require host cells for viral replication, which leads to increased host metabolism in order to combat the virus [54]. Yan et al. showed that viruses can modulate the lipid metabolism of the host to obtain optimal viral replication [60]. Huang et al. showed a higher viral load among patients who died during the COVID-19 pandemic, suggesting that total cholesterol, LDL-C, and HDL-C could be reduced due to this reason [61]. Also, elevated triglycerides were associated with increased mortality. In the current study, total cholesterol levels in ICU patients were comparable to those in the inpatient treatment group, although they were lower as compared to outpatients and control subjects. Similar to total cholesterol, HDL-C was comparable between ICU and inpatient groups, both of whom had lower HDL-C than outpatients and controls. Furthermore, LDL-C among ICU patients was significantly lower than in other patient groups, while triglycerides were higher in the ICU patients as compared to other patient groups. Based on these observations, it may be proposed that elevated AIP may be associated with increasing viral load and poor prognosis in COVID-19 patients.

Our study had some limitations. This was a single-center retrospective study. Also, confounding factors for laboratory results such as cigarette smoking, alcohol use, and body mass index were not taken into consideration. Further multi-center studies with larger patient populations are required to reinforce our observations.

Conclusion

In our study, patients in the ICU group were older and had higher number of comorbid conditions (particularly DM, CVD, and CPD). Obviously, closer monitoring of patients with comorbid conditions would be an appropriate clinical approach, as such conditions may have a negative impact on the prognosis. Clinical and laboratory data bear significant clinical importance, particularly in the management of patients admitted to ICUs. As a result, indexes such as AIP, SII, CAR, NLR, LMR, PLR and MHR calculated in COVID-19 patients can help predict poor prognosis. However, multi-center, randomized, controlled studies with larger sample size are warranted to reach firmer conclusions regarding the utility of these parameters and indexes.

Acknowledgment

We thank Assoc. Prof. Cuma Mertoğlu his support for this article.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare that there are no conflict of interests.

References

1. Lu R, Zhao X, Li J, Niu P, Yang B, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565-74. doi: 10.1016/S0140-6736(20)30251-8.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, et al. A novel coronavirus from patients with pneumonia in China, 2019. New England J Med. 2020;382(8):727-33. doi: 10.1056/NEJMoa2001017.
3. Hassan SA, Sheikh FN, Jamal S, Ezeh JK, Akhtar A. Coronavirus (COVID-19): A Review of clinical features, diagnosis, and treatment. Cureus. 2020;12(3):e7355. doi: 10.7759/cureus.7355.
4. ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection, American College of Radiology. Accessed May 25, 2020. https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID-19-Infection.
5. Sun P, Qie S, Liu Z, Ren J, Li K, et al. Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: a single arm meta-analysis. J Med Virol. 2020;92 6):612-7. doi: 10.1002/jmv.25735.
6. Gao Y, Li T, Han M, Li X, Wu D, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 2020;92(7):791-6. doi: 10.1002/jmv.25770.
7. Fu J, Kong J, Wang W, Wu M, Yao L, et al. The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: A retrospective study in Suzhou China. Thrombosis Res. 2020;192:3-8. doi: 10.1016/j.thromres.2020.05.006.
8. Bi X, Su Z, Yan H, Du J, Wang J et al. Prediction of severe illness due to COVID-19 based on an analysis of initial Fibrinogen to Albumin Ratio and Platelet count. Platelets. 2020;31(5):674-9. doi: 10.1080/09537104.2020.1760230.
9. Liu F, Li L, Xu MD, Wu J, Luo D, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020;127:104370. doi: 10.1016/j.jcv.2020.104370.
10. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. Crit Care. 2020;24(1):255. doi: 10.1186/s13054-020-02995-3.
11. Usul E, San I, Bekgoz B, Sahin A. Role of hematological parameters in COVID-19 patients in the emergency room. Biomark Med. 2020;14(13):1207-15. doi: 10.2217/bmm-2020-0317.
12. Peng J, Qi ǀ Di, Yuan G, Deng X, Mei Y, et al. Diagnostic value of peripheral hematologic markers for coronavirus disease 2019 (COVID-19): A multicenter, cross-sectional study. J Clin Lab Analy. 2020;34(10):e23475. doi: 10.1002/jcla.23475.
13. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504 doi: 10.1016/j.intimp.2020.106504.
14. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26(7):1017-32. doi: 10.1038/s41591-020-0968-3.
15. Huertas A, Montani D, Savale L, Pichon J, Parent F et al. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)? Eur Resp J. 2020;56(1):2001634. doi: 10.1183/13993003.01634-2020.
16. Huertas A, Guignabert C, Barberà JA, Bärtsch P, Bhattacharya S, et al. Pulmonary vascular endothelium: the orchestra conductor in respiratory diseases: Highlights from basic research to therapy. Eur Resp J. 2018;51(4):1700745. doi: 10.1183/13993003.00745-2017.
17. Canpolat U, Aytemir K, Yorgun H, Sahiner L, Kaya EB, et al. The role of preprocedural monocyte-to-high-density lipoprotein ratio in prediction of atrial fibrillation recurrence after cryoballoon-based catheter ablation. Europace. 2015;17(12):1807-15. doi: 10.1093/europace/euu291.
18. Kanbay M, Solak Y, Unal HU, Kurt YG, Gok M, et al. Monocyte count/HDL cholesterol ratio and cardiovascular events in patients with chronic kidney disease. Int Urol Nephrol. 2014;46(8):1619-25. doi: 10.1007/s11255-014-0730-1.
19. Cetin EHO, Cetin MS, Canpolat U, Aydin S, Topaloglu S, et al. Monocyte/HDL-cholesterol ratio predicts the definite stent thrombosis after

primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Biomark Med. 2015;9(10):967-77. doi: 10.2217/bmm.15.74.

20. Karatas MB, Canga Y, Ozcan KS, Ipek G, Gungor B, et al. Monocyte to high-density lipoprotein ratio as a new prognostic marker in patients with STEMI undergoing primary percutaneous coronary intervention. American J Emerg Med. 2016;34(2):240-4. doi: 10.1016/j.ajem.2015.10.049.
21. Dizman GT, Metan G, Ceylan CMA, Altunay H, Uzun M, et al. A COVID-19 First evaluation clinic at a university hospital in Turkey. Turkish J Med Sci. 2022;52:1-10. doi: 10.3906/sag-2104-152.
22. Sorokin AV, Karathanasis SK, Yang ZH, Freeman L, Kotani K, Remaley AT. COVID-19—Associated dyslipidemia: Implications for mechanism of impaired resolution and novel therapeutic approaches. FASEB J. 2020; 34(8):9843-53. doi: 10.1096/fj.202001451.
23. Li B, Li W, Li X, Zhou H. Inflammation: A novel therapeutic target/direction in atherosclerosis. Curr Pharm Design. 2017; 23 (8):1216-27. doi: 10.2174/1381612822666161230142931.
24. Fois AG, Paliogiannis P, Scano V, Cau S, Babudieri S, et al. The systemic inflammation index on admission predicts in-hospital mortality in COVID-19 patients. Molecules. 2020;5(23):5725. doi: 10.3390/molecules25235725.
25. de Jager CP, van Wijk PT, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, Wever PC. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Crit Care 2010;14(5):R192. doi: 10.1186/cc9309.
26. Nalbant A, Kaya T, Varim C, Yaylaci S, Tamer A, et al. Can the neutrophil/lymphocyte ratio (NLR) have a role in the diagnosis of coronavirus 2019 disease (COVID-19)? Revis Assoc Méd Brasileira. 2020;66(6):746-51. doi: 10.1590/1806-9282.66.6.746.
27. Sun S, Cai X, Wang H, He G, Lin Y, et al. Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. Clin Chim Acta. 2020; 507: 174-180. doi: 10.1016/j.cca.2020.04.024.
28. Ertem AG, Yayla C, Acar B, Kirbas O, Unal S, et al. Relation between lymphocyte to monocyte ratio and short-term mortality in patients with acute pulmonary embolism. Clin Resp J. 2018;12(2):580-6. doi: 10.1111/crj.12565.
29. Yayla Ç, Akboğa MK, Yayla KG, Ertem AG, Efe TH, et al. A novel marker of inflammation in patients with slow coronary flow: lymphocyte-to-monocyte ratio. Biomark Med. 2016;10(5):485-93. doi: 10.2217/bmm-2016-0022.
30. Lattanzi S, Cagnetti C, Provinciali L, Silvestrini M. Neutrophil-to-lymphocyte ratio and neurological deterioration following acute cerebral hemorrhage. Oncotarget. 2017;8(34):57489-94. doi: 10.18632/oncotarget.15423.
31. Yu S, Arima H, Bertmar C, Clarke S, Herkes G, Krause M. Neutrophil to lymphocyte ratio and early clinical outcomes in patients with acute ischemic stroke. J Neurol Sci. 2018;387:115-8. doi: 10.1016/j.jns.2018.02.002.
32. Dotsenko O, Chaturvedi N, Thom SAM, Wright AR, Mayet J, et al. Platelet and leukocyte activation, atherosclerosis and inflammation in European and South Asian men. J Throm Haemost. 2007;5(10):2036-42. doi: 10.1111/j.1538-7836.2007.02711.x.
33. Qu R, Ling Y, Zhang YHZ, Wei LY, Chen X, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol. 2020;92(9):1533-41. doi: 10.1002/jmv.25767.
34. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol. 2020;127:104362. doi: 10.1016/j.jcv.2020.104362.
35. Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. Acute pulmonary embolism associated with COVID-19 pneumonia detected with pulmonary CT angiography. Radiology. 2020;296(3):E186-E188. doi: 10.1148/radiol.2020201544.
36. Xu Z, Shi L, Wang Y, Zhang J, Huang L, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Resp Med. 2020;8(4):420-2. doi: 10.1016/S2213-2600(20)30076-X.
37. Wang D, Yin Y, Hu C, Liu X, Zhang X, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Crit Care. 2020; 24 (1): 188. doi: 10.1186/s13054-020-02895-6.
38. Di Micco P, Russo V, Carannante N, Imparato M, Rodolfi S, et al. Clotting factors in COVID-19: Epidemiological association and prognostic values in different clinical presentations in an Italian cohort. J Clin Med. 2020;9(5):1371. doi: 10.3390/jcm9051371.
39. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Inves. 2003;111(12):1805-12.

doi: 10.1172/jci18921.

40. Tan C, Huang Y, Shi F, Tan K, Ma Q, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol. 2020;92(7):856-62. doi: 10.1002/jmv.25871.
41. Wang L. C-reactive protein levels in the early stage of COVID-19. Méd Maladies Inf. 2020;50(4):332-4. doi: 10.1016/j.medmal.2020.03.007.
42. Yap FHY, Joynt GM, Buckley TA, Wong ELY. Association of serum albumin concentration and mortality risk in critically ill patients. Anaesth Intensive Care. 2002;30(2):202-7. doi: 10.1177/0310057X0203000213
43. Alves FC, Sun J, Qureshi AR, Dai L, Snaedal S, et al. The higher mortality associated with low serum albumin is dependent on systemic inflammation in end-stage kidney disease. PLoS One. 2018;13(1):e0190410. doi: 10.1371/journal.pone.0190410.
44. Li Y, Liu FY, Liu ZH, Huang YF, Li LS, et al. Effect of tacrolimus and cyclosporine A on suppression of albumin secretion induced by inflammatory cytokines in cultured human hepatocytes. Inflam Res. 2006;55(5):216-20. doi: 10.1007/S00011-006-0074-0.
45. Huang W, Li C, Wang Z, Wang H, Zhou N, et al. Decreased serum albumin level indicates poor prognosis of COVID-19 patients: Hepatic injury analysis from 2,623 hospitalized cases. China Life Sci. 2020;63(11):1678-87. doi: 10.1007/S11427-020-1733-4.
46. Huang J, Cheng A, Kumar R, Fang Y, Chen G, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol. 2020;92(10):2152-8. doi: 10.1002/jmv.26003.
47. Duman H, Cinier G, Bakirci EM, Duman H, Simsek Z, et al. Relationship between C-reactive protein to albumin ratio and thrombus burden in patients with acute coronary syndrome. Clin App Thrombosis/hemostasis. 2019;25:1076029618824418. doi: 10.1177/1076029618824418.
48. Kaplan M, Duzenli T, Tanoglu A, Guney BC, Tastan YO, et al. Presepsin: albumin ratio and C-reactive protein: albumin ratio as novel sepsis-based prognostic scores: A retrospective study. Wiener Klinische Wochenschrift 2020;132(7-8):182-7. doi: 10.1007/S00508-020-01618-9.
49. Ranzani OT, Zampieri FG, Forte DN, Azevedo LCP, Park M. C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. PLoS One. 2013;8(3):e59321. doi: 10.1371/journal.pone.0059321.
50. Llop-Talaveron J, Badia-Tahull MB, Leiva-Badosa E. An inflammation-based prognostic score, the C-reactive protein/albumin ratio predicts the morbidity and mortality of patients on parenteral nutrition. Clin Nutr. 2018;37(5):1575-83. doi: 10.1016/j.clnu.2017.08.013.
51. Karakoyun I, Colak A, Turken M, Altin Z, Arslan FD, et al. Diagnostic utility of C-reactive protein to albumin ratio as an early warning sign in hospitalized severe COVID-19 patients. Int Immunopharmacol. 2021;91:107285. doi: 10.1016/j.intimp.2020.107285.
52. Ergenç Z, Ergenç H, Araç S, Usanmaz M, Alkılınç E, Kaya G, et al. Novel biochemical prognostic indicators in COVID-19: Can CRP/albumin, urea/albumin, andLDH/albumin ratios be used to predict mortality and length of hospitalization? Med Sci Discover. 2022;9(6):310-8. doi: 10.36472/msd.v9i6.741.
53. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020;395(10223):470-3. doi:10.1016/S0140-6736(20)30185-9.
54. Gualdoni GA, Mayer KA, Kapsch AM, Kreuzberg K, Puck A, et al. Rhinovirus induces an anabolic reprogramming in host cell metabolism essential for viral replication. Proceedings of the National Academy of Sciences of the United States of America 2018;115(30):E7158-E7165. doi: 10.1073/pnas.1800525115.
55. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. J Am Coll Cardiol. 2020;75(18):2352-71. doi: 10.1016/j.jacc.2020.03.031.
56. Turgay Yıldırım Ö, Kaya Ş. The atherogenic index of plasma as a predictor of mortality in patients with COVID-19. Heart Lung. 2021;50(2):329-33. doi: 10.1016/j.hrtlng.2021.01.016.
57. Onat A, Can G, Kaya H, Hergenç G. "Atherogenic index of plasma" (log10 triglyceride/high-density lipoprotein-cholesterol) predicts high blood pressure, diabetes, and vascular events. J Clin Lipidol. 2010;4(2):89-98. doi: 10.1016/j.jacl.2010.02.005.
58. Yildiz G, Duman A, Aydin H, et al. Evaluation of association between atherogenic index of plasma and intima-media thickness of the carotid artery for subclinic atherosclerosis in patients on maintenance hemodialysis. Hemodial Int. 2013;17(3):397-405. doi: 10.1111/hdi.12041.
59. Dobiásová M, Frohlich J, Sedová M, Cheung

MC, Brown BG. Cholesterol esterification and atherogenic index of plasma correlate with lipoprotein size and findings on coronary angiography. J Lipid Res. 2011;52(3):566-71. doi: 10.1194/jlr.P011668.

60. Yan B, Zou Z, Chu H, Chan G, Tsang JOL, et al. Lipidomic profiling reveals significant perturbations of intracellular lipid homeostasis in enterovirus-infected cells. Int J Mol Sci. 2019;20(23):5952. doi: 10.3390/ijms20235952.
61. Huang JT, Ran RX, Lv ZH, Feng LN, Ran CY, et al. Chronological changes of viral shedding in adult ınpatients with COVID-19 in Wuhan, China. Clin Inf Dis. 2020;71(16):2158-66. doi: 10.1093/cid/ciaa631.