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Effectiveness of Laboratory Tests in Tracking Severely COVID-19 Infections

Şiddetli COVID-19 Enfeksiyonlarının İzlenmesinde Laboratuvar Testlerinin Etkinliği

Erdoğan YAYLA[1], Seniz KORKMAZ[2], Samican OZMEN[3]

[1]Medical Microbiology, Karacabey State Hospital, Bursa, Türkiye
[2]Medical Biochemistry, Bursa City Hospital, Bursa, Türkiye
[3]Gynecology and Obstetrics, Torbalı State Hospital, İzmir, Türkiye

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Abstract

Aim: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a virus that causes COVID-19 (Coronavirus Disease 2019), and poses serious difficulties in terms of healthcare systems and global public health. With the large number of publications on COVID-19, clinicians need a synthesis of evidence to provide guidance when dealing with patients with COVID-19. Emerging studies reveal the existence of numerous demographic, clinical, immunological, biochemical and radiographic data that may be useful for clinicians to predict the severity and mortality of COVID-19. The aim of this study; to determine laboratory parameters that can predict the course and severity of COVID-19 disease in patients, independently of the clinic status of selected patients and based on laboratory findings.

Methods: This study is a retrospective cross-sectional study conducted at Karacabey State Hospital between January and April 2022. Among the patients who applied to the COVID-19 outpatient clinic, 469 patients (261 females, 208 males) over the age of 18 and positive for SARS-CoV-2 RT-PCR were included in the study. The patients were divided into groups as outpatients, inpatients and patients in need of intensive care (intensive care unit, ICU). Demographic data (age, gender), COVID-19 RT-PCR results, and simultaneous laboratory parameters of the patients were scanned retrospectively.

Results: When CRP, urea, ferritin, LEU, NEU, MONO, RBC, HGB, HCT, MCV, NLR, PLR, CRP-NR, and SII index values were taken into consideration, a statistically significant difference was found between the groups. Creatinine, ALT, AST, LDH, troponin I, mass CK-MB, D dimer, LYM, EOS, PLT, ELR, and PNR values were not significantly different between the groups.

Conclusion: Advantages of this study; Comparing the changes in the patient's other laboratory findings based on a single positive PCR test result and finding meaningful rates in terms of serious covid risk. The disadvantage of this study is that it is a study independent of the patient's clinic and disease stage. In this study, we found that particularly increased SII was associated with more severe disease progression in patients diagnosed with COVID-19 along with laboratory findings. CRP, urea, ferritin, and indexes such as NLR, PLR, CRP-NR, and SII index values can be used to predict the severity of the disease.

Keywords: SARS-CoV-2, NLR, CRP-NR, SII index

Corresponding Author: Erdağon Yayla,Spec Dr, Medical Microbiology, Karacabey State Hospital, Bursa, Türkiye. E mail: erdoganyayla2005@gmail.com

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Öz

Amaç: Şiddetli akut solunum yolu sendromu koronavirüs-2 (SARS-CoV-2), COVID-19'a (Koronavirüs Hastalığı 2019) neden olan bir virüstür ve sağlık sistemleri ve küresel halk sağlığı açısından ciddi zorluklar oluşturmaktadır. COVID-19 ile ilgili çok sayıda yayın olması nedeniyle, klinisyenlerin COVID-19'lu hastalarla ilgilenirken rehberlik sağlamak için bir kanıt sentezine ihtiyaçları vardır. Ortaya çıkan çalışmalar, klinisyenlerin COVID-19'un şiddetini ve mortalitesini tahmin etmelerinde yararlı olabilecek çok sayıda demografik, klinik, immünolojik, biyokimyasal ve radyografik verinin varlığını ortaya koymaktadır. Bu çalışmanın amacı; yalnızca SARS-CoV 2 PCR test pozitifliği tanısı almış hastalarda ve seçilmiş hastaların klinik durumlarından bağımsız olarak ve laboratuvar bulgularına dayanarak COVID-19 hastalığının seyrini ve şiddetini tahmin edebilen laboratuvar parametrelerini belirlemektir.
Yöntem: Bu çalışma Ocak-Nisan 2022 tarihleri arasında Karacabey Devlet Hastanesi'nde yürütülen retrospektif kesitsel bir çalışmadır. COVID-19 polikliniğine başvuran hastalar arasından 18 yaş üstü, SARS-CoV-2 RT-PCR pozitif 469 hasta (261 kadın, 208 erkek) çalışmaya dahil edildi. Hastalar ayaktan, yatan ve yoğun bakıma (yoğun bakım ünitesi, yoğun bakım) ihtiyaç duyan hastalar olarak gruplara ayrıldı. Hastaların demografik verileri (yaş, cinsiyet), COVID-19 RT-PCR sonuçları ve eş zamanlı laboratuvar parametreleri retrospektif olarak tarandı.
Bulgular: CRP, üre, ferritin, LEU, NEU, MONO, RBC, HGB, HCT, MCV, NLR, PLR, CRP-NR ve SII indeks değerlerine bakıldığında gruplar arasında istatistiksel olarak anlamlı fark bulundu. Kreatinin, ALT, AST, LDH, troponin I, kütle CK-MB, D dimer, LYM, EOS, PLT, ELR ve PNR değerleri gruplar arasında anlamlı farklılık göstermedi.
Sonuç: Bu çalışmanın avantajları; tek bir pozitif PCR test sonucuna göre hastanın diğer laboratuvar bulgularındaki değişimleri karşılaştırmak ve ciddi covid riski açısından anlamlı oranlar bulmaktır. Bu çalışmanın dezavantajı ise hastanın kliniğinden ve hastalık evresinden bağımsız bir çalışma olmasıdır. CRP, üre, ferritin ve NLR, PLR, CRP-NR ve SII indeks değerleri gibi indeksler hastalığın şiddetini tahmin etmede kullanılabilir.
Anahtar Kelimeler: SARS-CoV-2, NLR, CRP-NR, SII index

INTRODUCTION

At the end of 2019, in Wuhan, China, a virus that belongs to the Coronavirus family which causes severe pneumonia attracted attention because of its contagious and pandemic features. This enveloped RNA virus was associated with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The transmission route was found to be the scattering of virus-laden droplets from person to person by coughing-speaking and inanimate surface contact (1). The virus outbreak spread quickly. As of 20 November 2022, over 634 million cases and 6.6 million deaths have been reported from SARS-CoV-2 infection globally (2).

SARS-CoV-2 infection is mostly asymptomatic. The disease can cause insignificant upper respiratory tract infections. However, severe pneumonia, respiratory failure, hyperinflammation, hypercoagulation and death due to multiple organ failure can occur (3,4). Prompt evaluation of clinical and biochemical findings to predict the progression of the disease can lead to the prevention of adverse outcomes (5). Therefore, it is crucial to determine reliable parameters that can predict the severity and mortality of the disease in terms of early intervention and treatment and to deliver health services on a regular and appropriate basis.

According to the recommendations published by the International Federation of Clinical Chemistry (IFCC) COVID-19 Working Group, biochemical and hematological tests in COVID-19 patients may be helpful in the diagnosis of infection-related tissue-organ damage, identifying infected patients at lower risk of severe disease, defining the

patients with a poor prognosis, determining and monitoring the progression of the disease. In this context, the main tests are defined as complete blood count (CBC), D-dimer, PT/APTT, fibrinogen, CRP, ferritin, erythrocyte sedimentation rate (ESR), procalcitonin, troponin, ALT (alanine aminotransferase), albumin, creatinine, urea, LDH (lactate dehydrogenase). These tests have an indicator role in the follow-up of the patients, and also have a prognostic value in terms of the development of the disease and predicting the mortality (6).

The aim of this study is to identify the most relevant biochemical and hematological tests and indices that can help predict poor prognosis and progressive disease of COVID-19.

MATERIALS AND METHODS

This study is a single-centered, retrospective, cross-sectional study conducted at Karacabey State Hospital (Bursa, Türkiye) between January and April 2022. Among the patients who applied to COVID-19 outpatient clinic, 469 patients (261 females, 208 males) over the age of 18 and positive for SARS-CoV-2 real-time reverse transcription polymerase chain reaction assay (RT-PCR) were included in the study. Demographic data (age, gender), COVID-19 RT-PCR results, and simultaneous routine laboratory parameters of the patients were scanned retrospectively from the hospital information management system (HIMS). The patients were divided into groups as outpatients, inpatients, and patients in need of intensive care (intensive care unit, ICU). Following the approval from the T.C. Ministry of Health Scientific Research Platform, permission to conduct this study was obtained from the Bursa City Hospital Clinical Research Ethics Committee (2022-6/3, 20.04.2022).

The detection of SARS-CoV-2 RNA was made in Bursa Public Health Laboratories by the RT-PCR method (outside the institution) (kits used: RTA RT-PCR kit (TÜRKİYE) and diakit (TUSEB-TÜRKİYE), which is the gold standard in the diagnosis of the disease from naso-oropharyngeal swabs. The results obtained from the laboratory information management system (LIMS) system were recorded. CRP, urea, creatinine, ALT (alanine aminotransferase), AST (aspartate aminotransferase), LDH (lactate dehydrogenase), troponin-I, mass creatine kinase-myoglobin binding (CK-MB), ferritin, D-dimer, complete blood count (CBC) parameters (LEU (leukocyte), NEU (neutrophil), LYM (lymphocyte), MONO (monocyte), EOS (eosinophil), RBC (red blood cell), HGB (hemoglobin), HCT (hematocrit), MCV (mean corpuscular volume), PLT (platelet), indices such as NLR (neutrophil-to-lymphocyte ratio), ELR (eosinophil-to-lymphocyte ratio), PNR (platelet-to-neutrophil ratio), PLR (platelet-to-lymphocyte ratio), systemic immune-inflammatory index (SII) and CRP-NR (CRP-to-neutrophil ratio) levels were recorded. The NLR, ELR, PNR, PLR, SII index, and CRP-NR levels were calculated using the relevant data. The SII index was defined as follows: SII: PLTcount×NEU count/LYM count according to the formula described by Bo Hu et al. (7).

CBC was analyzed using Mindray BC-5800 and BC-6000 Hematology analyzer (Mindray Medical International Co. Ltd., Shenzhen, China). The D-dimer was studied in the Diagon with the immunoturbidimetric method (Diagon, Hungary). Ferritin, hs-troponin-I, mass CK-MB measured by chemiluminescence microparticle immunoassay (CMIA) using Abbott Architect I2000SR (Abbott Diagnostics, USA). Urea, creatinine, AST, ALT, LDH (Beckman Coulter, Inc, USA), and CRP (Kinetik Kimya Diagnostics, Turkey) were measured by spectrophotometric assays using Beckman Coulter AU680 analyzer (Beckman Coulter K. K., Tokyo, Japan).

Statistical analysis

The Shapiro-Wilk's test was applied to determine the normality of distribution. The results were presented as median (IQR (interquartile range), minimum-maximum) for continuous variables and numbers and percentages for categorical variables. The One-Way ANOVA test was used to analyze whether the means of group variables differed significantly from dependent variables. Levene's test was used to evaluate the homogeneity of variances between groups. Games-Howell analysis was used to evaluate inhomogeneous variables, and Hochberg's GT2 test was used to evaluate homogeneous variables. $p<0.05$ was used as the significance level. Statistical analyzes were performed in SPSS 24.0 program (IBM SPSS, Chicago, IL, USA).

Results

A total of 469 patients (261 (55,7%) females, 208 (44,3%) males) with positive SARS-CoV-2 RT-PCR results were included in the study. The mean age of all subjects was calculated as 61.37±19.23. (min 18, max 97). In our study, since the measurement of SII index values was retrospectively carried out on patients with RT-PCR positive results, we did not have the opportunity to study the clinical picture and disease severity of the patient. The mean age of male cases with COVID-19 was 63.55±18.83; and 59.64±19.41 years for female cases. Accordingly, the mean age of male and female cases was not significantly different (p>0,5). While the p value was found to be <0.01 for CRP and urea values, the p value was found to be <0.001 for RBC, HGB, HCT and PLR. It was shown that 341 (72.7%) of the patients were followed in the outpatient, 104 (22.2%) in the inpatient, and 24 (5.1%) in the ICU. Gender did not pose a significant risk in terms of hospitalization (p>0,5). The median age of the outpatients was significantly lower than the inpatient and ICU. Patients' age, CRP, urea, creatinine, ALT, AST, LDH, troponin-I, mass CK-MB, ferritin, D-dimer, CBC parameters (LEU, NEU, LYM, MONO, EOS, RBC, HGB, HCT, MCV, PLT), NLR, ELR, PNR, PLR, SII, and CRP-NR data were given in Figure 1 as median, (minimum and maximum), and p values between groups were given in Figure 2.

	Outpatient-Inpatient	Outpatient-ICU	Inpatient-ICU
CRP	**<0,01**	**<0,01**	0,607
Urea	**<0,01**	**<0,01**	**0,04**
Creatinin	0,351	0,585	0,984
ALT	0,834	0,98	0,863
AST	0,535	0,276	0,725
LDH	0,325	0,06	0,181
Troponin I	0,995	1	0,998
CK-MB	0,927	0,82	0,657
Ferritin	**0,036**	**0,038**	0,244
D-Dimer	0,327	0,299	0,391
WBC	**0,031**	0,084	0,74
NEU	**0,001**	**0,006**	0,374
LYM	0,134	0,079	0,624
MONO	0,938	**0,04**	0,097
EOS	0,073	0,106	0,782
RBC	**<0,001**	**0,001**	1
HGB	**<0,001**	**0,047**	0,933
HCT	**<0,001**	**0,037**	1
MCV	**0,003**	0,502	0,956
PLT	0,462	0,426	0,152
NLR	**0,003**	**0,005**	0,076
ELR	0,228	0,408	0,957
PLR	**<0,001**	**<0,001**	0,059
CRP-NR	**0,027**	0,179	0,767
PNR	0,557	0,095	0,585
SII Ind.	**0,002**	**0,047**	0,415

Figure 1: Laboratory findings according to groups, median (minimum-maximum)

(Units are given in parentheses)

	Outpatient	Inpatient	ICU
Age (year)	57(18-97)	75(33-96)	79,5(62-91)
CRP (mg/L)	12,7 (0,8-135,9)	64,1 (2,30-137)	92,6 (5-134,2)
Urea (mg/dL)	26,6 (9,3-390,3)	40,6 (15,1-207,3)	58,4 (35,7-251,5)
Creatinin (mg/dL)	0,84 (0,18-7,94)	0,94 (0,50-5,07)	1,07 (0,21-2,42)
ALT (U/L)	18 (5-286)	18 (6-158)	17 (6-52)
AST (U/L)	22 (10-679)	26 (9-331)	36 (16-161)
LDH (U/L)	213 (113-386)	224 (117-679)	288 (195-896)
Troponin I (ng/L)	4,45 (0,10-17109,10)	16,80 (1,10-3976)	43,05 (3,60-512-40)
CK-MB (µg/L)	1 (0,10-39,70)	1,3 (0,30-14)	2,1 (0,70-12,90)
Ferritin (µg/L)	79,49 (8,71-1111,52)	203,12 (7,25-2000)	522,86 (33,03-2000)
D-Dimer (µg FEU/mL)	500 (220-16600)	804,50 (222-13200)	975 (250-27100)
WBC (10^3/µL)	6,72 (0,85-24,17)	7,24 (0,25-30)	8,66 (1,58-19,23)
NEU (10^3/µL)	4,31 (0,46-16,90)	5,35 (0,01-25,05)	7,02 (0,89-16,83)
LYM (10^3/µL)	1,43 (0,16-18,80)	1,21 (0,23-5,02)	0,89 (0,33-3,80)
MONO (10^3/µL)	0,51 (0,00-1,78)	0,45 (0,01-2,10)	0,37 (0,03-1,41)
EOS (10^3/µL)	0,07 (0,00-4,02)	0,25 (0,00-0,46)	0,00 (0,00-0,14)
RBC (10^6/µL)	4,6 (2,52-7,03)	4,12 (0,44-5,59)	4,2 (2,56-5,20)
HGB (g/dL)	13,3 (6-17,5)	12,1 (6,1-16)	12,5 (7-16,9)
HCT (%)	40,7 (4,09-52,50)	36,85 (5,60-49,30)	38 (21,70-50,90)
MCV (fL)	88,70 (60,30-107,90)	90,20 (71,90-140,50)	91,10 (67,30-103,30)
PLT (10^3/µL)	228 (37-598)	238,50 (49-638)	207 (69-334)
NLR	2,87 (0,26-30,68)	4,42 (0,05-30,10)	6,28 (1,35-28,67)
ELR	0,05 (0,00-3,98)	0,02 (0,00-0,24)	0,00 (0,00-0,23)
PLR	155,79 (9,89-786,96)	170,99 (54,78-1130,43)	229,35 (74,19-1000)
CRP-NR	3,51 (0,20-211,30)	10,07 (0,24-12920)	10,30 (0,73-50,56)
PNR	52,89 (12,13-487,23)	42,81 (10,12-130,2)	35,2 (8,66-130,34)
SII Ind.	685,10 (47,8-7796,9)	924,45 (11,3-8965,6)	1405,7 (145,4-9702,7)

Figure 2: Comparison of laboratory parameters between groups (statistically significant differences (p<0,05) are marked in bold).

There was a significant difference between the three groups in terms of CRP, urea, ferritin, LEU, NEU, MONO, RBC, HGB, HCT, MCV, NLR, PLR, CRP-NR, and SII index values. There was no significant difference between the groups in creatinine, ALT, AST, LDH, troponin I, mass CK-MB, D dimer, LYM, EOS, PLT, ELR, and PNR values.

DISCUSSION

COVID-19 disease is a highly contagious disease with a wide spectrum from subclinical disease to severe pneumonia. Several laboratory tests are used to assess the progression and the prognosis of the disease. Biomarkers related to organ dysfunction, coagulation, inflammation and cytokine storm are changed significantly during the disease (8).

In COVID-19, laboratory tests are used to evaluate the severity of the disease. Significant decreases in LYM and increments in D-dimer and other biochemical and inflammatory markers have been shown in the progression of the disease. Especially the gradual increment in LDH, AST, CK, troponin I and urea are early warning signals for severe disease and poor prognosis (9). The aim of this study was to analyze laboratory data and identify parameters that can predict the severity of COVID-19 disease.

Studies have shown that advanced age is a significant risk factor for hospitalization (10). In our study, similar to the previous studies, advanced age was found to be a significant risk factor for hospitalization. Although literature data shows that the male gender is a risk factor for hospitalization (10), we found no significant difference between male and female patients in terms of hospitalization.

Studies have shown that various biomarkers can be useful in predicting the severity and the course of the disease. Ferrari et al. showed that there is a significant difference in serum LEU, CRP, AST, ALT, and LDH levels between COVID-19 positive and negative patients (11). In their study, Castro-Castro MJ. et al. showed that age, kidney disease, serum creatinine, LDH, CRP, and LYM levels can provide crucial information in terms of the prognosis of COVID-19 disease (12). Aloisio E. et al (13) defined related cut-offs for serum CRP, LDH, D-Dimer, albumin, ferritin, and cardiac Troponin T to aid clinicians in risk stratification and to predict the severity of the disease for hospitalized COVID-19 patients. Singh et al. (14) showed that the decreased levels of serum NEU and LYM levels along with increased CRP and D-dimer levels were associated with disease progression, while moderate changes of these serum biomarkers were seen in patients that had a mild-to-moderate disease. The increment of biochemical markers was related to the severity of the disease. The most significant change was in serum LDH levels; followed by AST, ALT, CK, and creatinine levels, respectively (15). In this study, similar to the previous studies, significant differences were observed in terms of serum CRP, urea, and ferritin values between outpatients and inpatients or ICU. However, we found no difference between the groups in terms of serum creatinine, ALT, AST, LDH, troponin I, and CK-MB levels.

In the studies conducted, the serum LEU and NEU levels were found to be higher in ICU patients compared to non-ICU, while the LYM levels were found to be significantly lower (16-19). Also, the increase in NEU and NLR levels indicates critical illness with a poor prognosis (20). Georgakopoulou et al. (21) reported that lower values of EOS and ELR were associated with worse outcomes and longer duration of hospitalization. The continuous decrease in EOS levels is an indicator of a poor prognosis (22). Similar to these studies, in our study, we found that high levels of serum LEU, NEU, and NLR levels were significantly different between groups. We found no significant difference

in terms of LYM, EOS, and ELR values.

COVID-19 causes hypercoagulation and fibrinolysis abnormalities. Sometimes excessive inflammation causes thrombotic complications such as pulmonary embolism (PE) and disseminated intravascular coagulation (DIC) (15,18,19,23). As a result, abnormal biomarkers of coagulation and fibrinolysis have been linked to poor prognosis in COVID-19 patients. The most typical outcome was an increased concentration of D-dimer. A retrospective study showed a gradual increment in serum D-dimer levels between non-severe, severe, and critical illness (15). In this study, we showed no significant difference between groups.

An innovative marker called SII can predict the prognosis for tumors and other inflammatory diseases of the organism (24). Severe progression can be observed in patients with advanced age and high SII. In these patients, the risk of intubation, mortality, and the need for intensive care is increased (25). In our study, since the measurement of SII index values was based entirely on laboratory studies and was performed by retrospectively screening patients with RT-PCR positive results, we did not have the opportunity to investigate the clinical picture of the patient and the severity of the disease. Similar to previous studies, we found that increased SII was associated with severe disease progression in patients with similar laboratory findings.

Like SII, PLR, a novel indicator of inflammation, reflects the level of systemic inflammation. PLR is found to be associated with malignancies, diabetes, coronary artery disease, and connective tissue diseases (26). In a meta-analysis, it has been shown that the increment in PLR rates is associated with the severe prognosis in COVID-19 patients (27). In this study, our findings were consistent with previous studies in terms of PLR rates.

The limitations of this study are that the study was performed in a single center, the number of patients included in our study was relatively low, the viral load of the patients was unknown and the comorbid diseases of the patients were not taken into account.

CONCLUSION

The advantageous aspects of this study are that proportional data that can determine the course of the disease are obtained by using measurable laboratory result values of patients in laboratory procedures. In this respect, significant results may be guiding in serious viral infections with similar clinical features. The disadvantages of the study are; being a retrospective evaluation, interpretation of test results being based on PCR positive test results; the only standard parameter is the selection of reference intervals. We did not have any data regarding the clinical conditions (comorbidity status) of the patients, the medications used in the patients' information, the treatment protocols applied to the patients, and at what stage of the disease blood samples were taken from the patients. In this study, we found that there was a significant difference between the three groups in CRP, urea, ferritin, LEU, NEU, MONO, RBC, HGB, HCT, MCV, NLR, PLR, CRP-NR and SII index values. There was no significant difference between the groups in creatinine, ALT, AST, LDH, troponin I, mass CK-MB, D dimer, LYM, EOS, PLT, ELR and PNR values. A gradual and significant increase was observed only in urea values in the outpatient, inpatient and intensive care groups. Monitoring markers of severity can help clinicians identify and monitor patients at increased risk of progression to severe COVID-19 infection and similar viral infections. These key biomarkers may help in the early detection of serious diseases. Further research is needed to determine the role of these biomarkers in the clinical progression of COVID-19 patients.

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Ethics Committee Approval: The study was approved by Bursa City Hospital Clinical Research Ethics Committee (2022-6/3, 20.04.2022).

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