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RESEARCH ARTICLE

Is Lymphopenia a sign of mortality in coronavirus disease 2019 patients?

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ABSTRACT

Aim: A novel type of coronavirus was detected after the first case of an atypical pneumonia in Wuhan, China in December 2019; the World Health Organization (WHO) named the virus SARS-CoV-2 in February 2020 and the disease it caused COVID-19. This classification has allowed clinicians to plan its treatment process to progress faster. We aim to compare laboratory parameters in COVID-19.

Material and Methods: The patient population of the study has been formed by retrospectively examining the files of patients who had been admitted with COVID-19 complaints to an emergency department at a faculty of medicine between April 27 and December 18, 2020. Patients were divided into two groups: the surviving group and the mortal group.

Results: In the ROC analysis, we evaluate the effect of lymphocyte on mortality, the cut-off value for lymphocyte was found as 1.3 (sensitivity = 58.14%; specificity = 78.92%). The sensitivity and specificity of this cutoff value are at good levels (AUC = 0.712; $p < 0.05$).

Conclusion: We believe that lymphocyte levels in particular may be used to distinguish severe COVID-19 cases from mild to moderate cases in the days after hospital admissions.

ARTICLE HISTORY

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KEYWORDS

Lymphopenia • mortality • COVID-19

A novel type of coronavirus was detected after the first case of an atypical pneumonia in Wuhan, China in December 2019; the World Health Organization (WHO) named the virus SARS-CoV-2 in February 2020 and the disease it caused COVID-19 (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020; Guan et al., 2020; Zhu et al., 2020).

A COVID-19 infection can manifest with symptoms such as fever, weakness, dry cough, and shortness of breath or result in severe respiratory failure, shock, coagulation dysfunction, and death in advanced stages (Huang et al., 2020). Although COVID-19 primarily involves the lungs (i.e., respiratory system), it may also show multisystemic spread in neurological, cardiovascular, and hematopoietic systems (Mehta et al., 2020). Various studies are found focusing mostly on determining the clinical course of the disease, identifying patients who are in high-risk group in line with all symptoms, how the disease spreads, evaluating the probability of mortality, and what the biochemical parameters are for planning treatment (Huang et al., 2020; Kermali et al., 2020; Wang et al., 2020). Hematological and biochemical biomarkers provide objective values throughout the progression of the disease, helping to classify it as mild, severe, or critical. This classification also allows clinicians to diagnose and plan the treatment process to progress faster.

The presence of advanced age, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and lymphopenia in particular are classified as the high-risk groups in a COVID-19 prognosis (Rothan & Byrareddy, 2020).

The purpose of the present study is to compare laboratory parameters with respect to mortality, survival, hospitalization, recovery, discharge, and/or outpatient-home follow-ups for patients with real-time reverse transcription polymerase chain reaction (RT-PCR), and to evaluate the effectiveness of laboratory parameters and demographic conditions in predicting patients' clinical progression.

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Materials and Methods

The patient population of the study has been formed by retrospectively examining the files of patients admitted with COVID-19 complaints to an emergency department of a faculty of medicine between April 27 and December 18, 2020 after receiving the approval of the ethics committee. The patients included in the study are shown in the flow diagram (see Figure 1).

Figure 2: Flow Diagram of Patient Selection

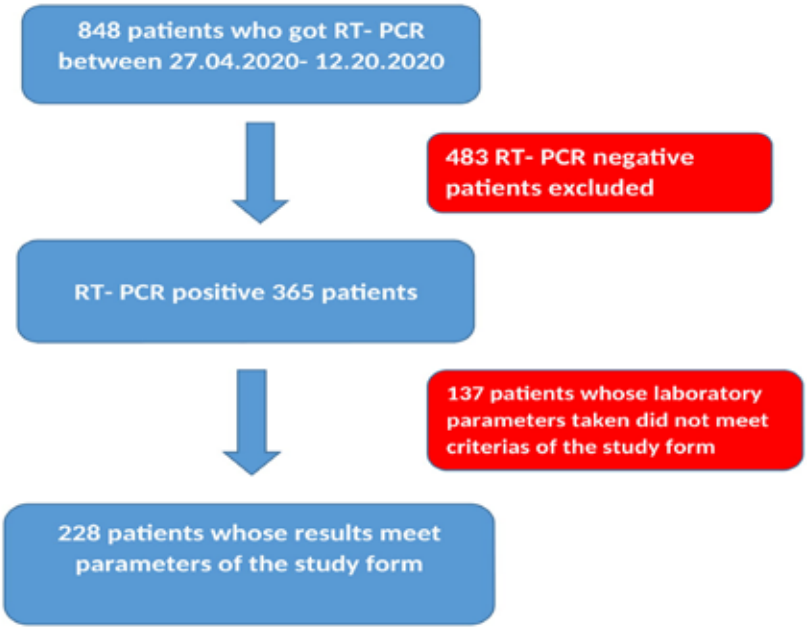

Figure 1. The flow diagram for patient selection.

Patients were divided into two groups. One is the surviving group, consisting of patients who were discharged, received outpatient treatment after hospitalization, and were found to have survived for the 14-day follow-up. The other is the mortality group, consisting of patients who were hospitalized at the time of first admission but died in the hospital treatment process. The patients' demographic data, blood-test results, and comorbidities are examined retrospectively using the RT-PCR that was performed during initial admission.

Exclusion Criteria

Patients, who had infections other than COVID-19, had been diagnosed with malignancies, are under 18, are pregnant, were admitted to the hospital two days or more after the onset of initial complaints, or died in another hospital after first being admitted to our hospital were not included in the study.

Statistical Analysis

The descriptive statistics of the data obtained in the study have been analyzed using mean values for the numerical variables, frequency and percentage analyses for the categorical variables, and standard deviations. The normal distribution of values was examined using the Shapiro-Wilk test; the Mann-Whitney U test was used to compare the variables according to mortality status. Also, whether the study's variables affected mortality was examined using multivariate logistic regression analysis. ROC analysis has been used to determine the cut-off value with respect to mortality status. The analyses were made using the program SPSS 22.0.

The leukocyte (WBC), neutrophil/lymphocyte ratio (NLR), lymphocyte, ferritin, and C-reactive protein (CRP) values have been analyzed using the Shapiro-Wilk test; the values were determined to not show normal distribution ($p < 0.05$). For this reason, the Mann-Whitney U-test has been used to compare these variables with respect to mortality status.

Results

The patients' mean age in our study is 50.48 ± 20.06, with 51.75% (*n* = 118) being female, and 48.25% (*n* = 110) being male. A total of 57.89 % (*n* = 132) of patients did not have comorbidities; the comorbidities detected the most are: hypertension (20.61%; *n* = 47), diabetes mellitus (16.23%; *n* = 37), coronary artery disease (7.46%; *n* = 17), COPD (8.77%; *n* = 20; see Table 1).

Table 1

Comorbidities of COVID-19 Patients

Comorbid Disease Status	**n (%)**
Any comorbidity	96 (42.11%)
Hypertension	47 (20.61%)
Diabetus mellitus	37 (16.23%)
Heart failure	9 (3.95%)
Coronary artery disease	17 (7.46%)
Cerebrovascular event	1 (0.44%)
Chronic kidney disease	3 (1.32%)
Chronic obstructive pulmonary disease	20 (8.77%)

A total of 32.3% patients smoke. The most common complaints respectively are cough, fever, dyspnea, and sore throat (see Table 2). The most prevalent admission complaint among patients has been determined as fever (*n* = 74) in 32.46% of patients. Patients' average body temperature was calculated as 36.4°C on average. The mean values of the patients' clinical and laboratory parameters are given in Table 3.

Table 2

First-Admission Symptoms of COVID-19 Patient to the Emergency Department

Symptoms	n (%)
Fever	74 (32.46%)
Cough	81 (35.53%)
Shortness of breath	47 (20.61%)
Joint pain	16 (7.02%)
Loss of taste	4 (1.75%)
Loss of smell	3 (1.32%)
Chest pain	6 (2.63%)
Sore throat	61(26.75%)

Table 3

Clinical and Laboratory Parameters COVID-19 Patients

Patient values	Mean ± SD	Median (Min-Max)
Clinical Parameters		
Fever (°C)	36.56 ± 0.54	36.4 (35.8-38.5)
SaO_2 (%)	95.33 ± 4.84	97 (64-99)
Laboratory Parameters		
Leukocyte (10^3/Ul)	8.92 ± 4.7	7.9 (1.48-37.86)
Neutrophil (10^3/uL)	6.27 ± 5.54	5.05 (0.7-60)
Lymphocyte (10^3/uL)	1.84 ± 0.78	1.8 (0.2-3.8)
Platelet (10^3/uL)	233.32 ± 76.08	223 (2.32-598)
C-Reactive Protein (mg/L)	41.2 ± 130.58	5.85 (0.01-1747.4)
Ferritin (ug/L)	210.46 ± 341.4	91 (1-2000)

Table 4 shows the following results from assessing the age and laboratory parameters of COVID-19 for the mortality and survival groups.

Age is higher in the mortality group compared to the surviving group at a statistically significant level ($p = 0.001$). The median age is 43 in the survival group and 68 in the mortality group.

Statistically significant differences were detected between the neutrophil count, lymphocyte count, CRP, ferritin, and NLR values between the groups all at $p = 0.001$ (see Table 4).

Table 4

Assessment of Age and Laboratory Parameters of COVID-19 between the Mortality and Survival Groups

Variables	**Survival Group (n = 185) Median (Q1-Q3)**	**Mortality Group (n = 43) Median (Q1-Q3)**	**p**
Age	43 (30-61)	68 (61-79)	0.001
Leukocyte (10^3/Ul)	7.8 (6.11-9.92)	8.72 (5.94 -11.6)	0.115
Neutrophil/ Lymphocyte Ratio	2.4 (1.75-4.17)	5 (2.56-8.67)	0.001
Lymphocyte (10^3/uL)	1.8 (1.4-2.4)	1.3 (0.9-1.8)	0.001
Ferritin (ug/L)	80 (32-175)	220 (65-663)	0.001
C-Reactive Protein (mg/L)	3.2 (0.5-16.8)	56.8 (19.7-115.6)	0.001

A multivariate logistic regression analysis was used to examine whether the demographics and laboratory parameters independently affect mortality; the results are given in Table 5. A positive correlation has been detected between age and mortality, with a one-unit increase in age increasing an outcome of mortality by 1.04 ($p = 0.03$; $OR = 1.04$). When the relation between comorbidities and mortality was examined, the risk of mortality was 6.14 times higher in those with comorbidities ($p = 0.03$; $OR = 6.14$). When examining the relation hemogram parameters have with mortality, only the number of lymphocytes were determined to have independent and statistically significant relations with mortality ($p = 0.031$). An receiver operating characteristic (ROC) analysis was made to evaluate the effect of lymphocyte on mortality, and the cut-off value for lymphocyte was found as 1.3 (sensitivity = 58.14%; specificity = 78.92%). The sensitivity and specificity of this cutoff value is at a good level ($AUC = 0.712$; $p < 0.05$).

Table 5

Multivariate Analyze of Comorbid and Laboratory Parameters for Mortality in COVID-19

Variable	**OR [95% CI]**	**p**
Age	1.04 [1.01-1.08]	0.003
Any comorbidity	6.14 [1.88-19.99]	0.003
Hypertension	0.99 [0.38-2.61]	0.990
Diabetus mellitus	0.74 [0.29-1.9]	0.526
Coronary artery disease	0.64 [0.19-2.18]	0.472
Neutrophil / lymphocyte ratio	0.97 [0.92-1.02]	0.241
Lymphocyte (10^3/uL)	0.48 [0.24-0.93]	0.031
Ferritin (ug/L)	1.000 [0.999-1.001]	0.416

Discussion

Clinical diagnosis and treatment research for COVID-19 needs to be continuously improved and accelerated to control its rapid spread and serious systemic effects (Öztürk Sönmez et al., 2021; Zhao et al., 2020).

Our study has detected statistically significant differences in terms of age for the mortality and survival groups; this may be due to diseases increasing age with age. Gender distributions of patients were found to be similar in various studies in the literature (females 51.75%, males 48.25%, respectively) (Fu et al., 2020; Guan et al., 2020).

Previous studies have reported the presence of comorbidity to deteriorate the prognosis of COVID-19 patients (Liu et al., 2020; Katipoğlu et al., 2020). Our study has found a statistically significant relation to exist between comorbidity status and mortality. Our study has shown those with comorbidities to have a 614% higher risk of mortality than those without comorbidity ($p = 0.03$; OR = 6.14; see Table 5).

A total of 47 (20.61%) patients in our study have hypertension, 9 (3.95%) have chronic heart disease, 17 (7.46%) have coronary artery disease, and 37 (16.23%) have diabetes mellitus (see Table 1). We believe these different rates may be related to the eating habits, geographical areas, and living standards as these rates differ with the results of previous studies in the literature evaluating comorbidities (Zhao et al., 2020; Zhu et al., 2020).

Previous studies have detected the most common complaints in COVID-19 patients to be cough, fever, and sore throat (Fu et al., 2020; Katipoğlu et al., 2020; Mikami et al., 2020). In line with the literature data, the most common admission complaints in our study are cough, fever, and shortness of breath, respectively (see Table 2). When examining the admission complaints, 32.46% ($n = 74$) of the patients admitted to our hospital were found to have fever; 35.53% ($n = 81$) with cough, 20.61% ($n = 47$) with shortness of breath; this resembles the data in the literature (Katipoğlu et al., 2020; Rodriguez-Morales, 2020). Also, 1.75% ($n = 4$) of patients complained of loss of taste, while1.32% ($n = 3$) complained of loss of smell. The fact that this rate is lower than that reported in some studies in the literature might be due to the earliness of the data from the patients recorded in our study (Katipoğlu et al., 2020; Rodriguez-Morales, 2020).

Yang et al.'s (Yang et al., 2020) separated COVID-19 patients into two groups (i.e., severe and non-severe) and found WBC values to be significantly lower in the non-severe group. Terpos et al. (2020) reported the WBC count to be normal in the onset of the disease. Another study investigating the laboratory parameters in COVID-19 diagnosis detected a decrease in WBC in 33.7% of patients (Guan et al., 2020). Our study found patients with COVID-19 to have low WBC counts. This may be associated with the decrease in neutrophil and lymphocyte parameters; however, no associations were detected between WBC and mortality in our study. No statistically significant differences were detected in WBC values between the mortality and survival groups (see Table 4); this may be due to the blood samples being taken in the early stages of the disease, which is in line with Terpos et al.'s (2020) study.

NLR levels have previously been reported to be elevated in COVID-19 groups and this increase to be associated with intra-hospital mortality (Fu et al., 2020; Liu et al., 2020). In our study, the difference in NLR levels is statistically significant in the mortality group compared to the survival group (see Table 4).

Lymphocytes have great importance in the fight against viral infections and for maintaining the immune system (Chan et al., 2004; Dong et al., 2019; Mescher et al., 2006). As a result of continuous exposure to the virus, the lymphocyte count decreases (Ng et al., 2013). Various studies have shown a low lymphocyte count in patients who test positive for COVID-19 and this decrease to have associations with the prognosis (Fu et al., 2020). The reason for this has been determined as the lithic effect of SARS-COV-2 in the cell attaching to the angiotensin-converting enzyme-2 receptors that are expressed on the lymphocyte surface and cytokine activation decreasing lymphocyte turnover with the atrophy effect on the lymphoid organs (Chan et al., 2020; Xu et al., 2020).

Lymphopenia development in severe patients is mostly associated with the reduction of T cells; however, it does not depend on the absolute numbers of B cells or natural killer cells. A meta-analysis study involving 4,655 candidate articles conducted by Yan et al. (2021) showed lymphopenia to play important roles in COVID-19 prognosis. Seyit et al.'s (2020) retrospective study conducted with 233 patients determined the prognosis to deteriorate as the lymphocyte count decreases. Mo et al.'s (2020) study conducted with 208 patients detected an association between lymphopenia and severe disease. Our study has found the number of lymphocytes to be low in the entire patient group and to vary significantly between the mortality and survival groups (median = 1.8 [0.2-3.8], $p = 0.001$, respectively). When evaluating the lymphocyte count as an independent factor for mortality, our study detected a statistically significant association only in the lymphocyte counts from the lab findings ($p = 0.031$; see Table 5). When evaluating the cut-off value with respect to mortality status using the ROC Analysis (specificity = 78.92%; see Figure 2), the cut-off value for lymphocyte is found as 1.3 (sensitivity = 58.14%). The sensitivity and specificity of the cut-off value is statistically important at a good level ($AUC = 0.712$; $p < 0.05$). Lymphopenia has been concluded to be an important laboratory marker in evaluating mortality.

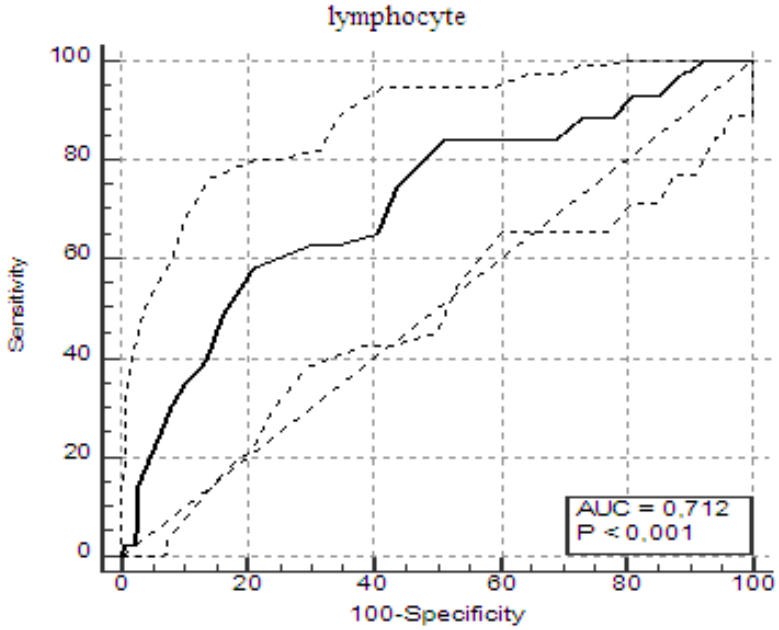

Figure 2. ROC analysis of the independent relationship of lymphocyte with mortality in COVID-19 patients.

CRP is a known parameter indicating inflammation (Sproston & Ashworth, 2018). The elevated level of CRP in our study is an expected result due to COVID-19 inducing inflammation through the endothelial damage caused in the course of the disease (Fu et al., 2020). The CRP values differ between the survival and mortality groups ($p = 0.001$). Liu et al.'s (2020) study reported CRP to be able to be used effectively to evaluate disease severity and to have predicative value in determining COVID-19 outcomes. The results from our study also correspond with these results.

Zhou et al.'s (2020) retrospective cohort study with 191 patients found serum ferritin levels to be significantly higher in COVID-19 patients compared to survivors during the clinical course and increased with the deterioration of the disease. They also reported elevated ferritin levels to be associated with the development of the cytokine storm and argued

the concentration of ferritin in the circulation to possibly be used to predict the progression of COVID-19. Lukasz et al.'s (2020) meta-analysis associated high ferritin values with high mortality in COVID-19 patients. In our study, ferritin values varied significantly between the mortality and survival groups ($p = 0.001$).

Conclusion

In brief, our study has shown the epidemiological and clinical characteristics of COVID-19 cases to resemble those reported in previous studies. Our study has detected statistically significant differences between the survival and mortality groups regarding lymphocyte values, NLR, ferritin, and CRP values. This supports previous studies conducted on this subject in the literature. We believe lymphocyte levels in particular to be able to be used to distinguish severe COVID-19 cases from mild to moderate in the days following hospital admission. Studies are needed in this field that will include more patients.

Limitations

The primary limitation of our study is its design using a single center as well as the low number of patients due to excluding 137 of the 365 PCR-positive patients for not meeting all the parameters in their enrollment documentation. Another limitation was the first admission complaints possibly having been suppressed because of tendencies to use over-the-counter antipyretics and traditional approaches to reduce fever in Turkey as well as different treatment modalities.

Authors' contribution

LÖS, TE, performed the concepts, study design, data collection and analysis and manuscript writing; NA, GE, SG: study design, statistical analysis and manuscript writing; and AMŞ, KO, EK, study design, data collection , manuscript preparation, manuscript editing and manuscript review; ÇY and LÖS, literature search and manuscript writing and; KO and EK manuscript writing, data collection.

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Disclosure statement

The authors report no conflict of interest.

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