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The impact of laboratory features and comorbidities on the prognosis of patients with COVID-19

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ABSTRACT

Objective: Demographic and laboratory values predicting clinical severity in coronavirus disease 2019 (COVID-19) patients have been a matter of curiosity since the beginning of the disease. We aimed to show the relationship between the severity of COVID-19 disease and comorbidities, clinical and laboratory features of the patients.

Material and Method: The data of COVID-19 patients diagnosed with polymerase chain reaction (PCR), were analyzed retrospectively. The patients were divided into 3 groups according to their clinical severity as mild, moderate and severe. Comorbidities and the Charlson comorbidity index (CCI) at the time of diagnosis were calculated for each patient from the patients' records. Demographic data, laboratory values, comorbidity and CCI scores were compared between the patient groups. The effect of CCI on survival and length of hospital stay was examined.

Results: One hundred and four patients were included in the trial. The most common comorbid disease in the patients included in the trial was hypertension. The moderate-severe stage patients were statistically significantly older ($p<0.001$). The CCI was found to be statistically significantly different between mild, moderate and severe groups ($p<0.001$). When CCI increases by one unit, the risk of death increases by 1.193 times ($p=0.017$). The neutrophil-to-lymphocyte ratio (NLR) was statistically significantly different between the mild, moderate and severe patient groups. It was observed that as the severity of the disease increased, the NLR increased. Older age, WBC, neutrophil count, NLR, BUN, creatinine, AST, potassium level, C-reactive protein (CRP), procalcitonin, aPTT, fibrinogen, d-dimer, and ferritin levels were found to be higher in the clinically severe patient group. Lymphocyte and eosinophil counts, total protein, albumin and sodium levels were found to be lower in the clinically severe patient group.

Conclusion: This trial showed that calculating the CCI score in COVID-19 patients can be useful in predicting the severity of the disease. Examination of CCI, age, WBC, neutrophil, lymphocyte, eosinophil counts, BUN, creatinine, AST, total protein, albumin, sodium, potassium level, CRP, procalcitonin, aPTT, fibrinogen, d-dimer and ferritin levels at the time of diagnosis can be suggested.

Keywords: COVID-19, Charlson comorbidity index, mortality, neutrophil-to-lymphocyte ratio, laboratory features

INTRODUCTION

At the end of 2019, a new coronavirus was detected in Wuhan, China. It spread rapidly and caused an epidemic across China, followed by an increasing number of cases followed in other countries around the world, causing the pandemic.

Pneumonia appears to be the most common manifestation of infection, characterized by fever, cough, shortness of breath, and bilateral infiltrates on lung imaging (1). Other features such as upper respiratory symptoms, myalgias, diarrhea, and smell or taste disturbances have also been widely reported (2).

While coronavirus disease 2019 (COVID-19) is mild in some patients, it can be moderate or severe in some patients. It has been reported age, presence of comorbidity, lymphopenia, thrombocytopenia, acute renal failure, increased LDH, elevated transaminases, d-dimer, CRP, ferritin and IL-6 as factors determining the severity of the disease in COVID-19 patients (3).

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The clinical course and hospital stay are directly related to the comorbidities and ages of COVID-19 patients. People with chronic obstructive pulmonary disease (COPD) or any lung disease are candidates for more severe COVID-19 disease (4). It has been reported that patients diagnosed with diabetes mellitus (DM) have higher morbidity and mortality rates and longer hospital stay (5). Cardiovascular diseases and hypertension have also been reported as risk factors for mortality in COVID-19 patients (6,7).

We aimed to investigate the effect of age, laboratory features and comorbidities of patients followed up with a diagnosis of COVID-19 disease on the severity of the disease and survival. Charlson comorbidity index (CCI) was calculated as the comorbidity index and its effect on survival and hospital stay was examined.

MATERIAL AND METHOD

The trial was approved by İnonu University Research Ethics Committee (date/reference number: 10-11-2020/1255). The trial was conducted in accordance with the Helsinki Declaration principles.

Study Design

The data of COVID-19 patients diagnosed with polymerase chain reaction (PCR), between August 01, 2020 and August 30, 2020 were analyzed retrospectively. Laboratory results were analyzed retrospectively from patients' files. Comorbidities and the CCI at the time of diagnosis were calculated for each patient from the patients' records (8).

The patients were divided into 3 groups as mild, moderate and severe. Stage 1 (mild): Patients with mild and nonspecific symptoms and no findings other than lymphopenia and neutrophilia in the complete blood count. Stage 2 (moderate): There is viral involvement and localized inflammation in the lung. Patients have fever, cough, and hypoxia (PaO_2/FiO_2<300 mm Hg). There are bilateral infiltrates or grass opacids on chest radiography or computed tomography. Stage 3 (severe): There is an extrapulmonary systemic hyperinflammation syndrome. Inflammatory markers (IL-2, IL-6, tumor necrosis factor-alpha, CRP, ferritin, and d-dimer) were increased. Shock, respiratory failure and cardiopulmonary collapse may occur. Systemic organ involvement, even myocarditis, can occur at this stage (9).

Real-time reverse transcriptase-PCR tests for SARS-CoV-2 RNA were performed using nasopharyngeal swabs. Total nucleic acid extraction of nasopharyngeal swabs of viral isolates was performed using a biospeedy and coyote extraction system (Bioeksen ltd and Coyote Bioscience ltd). Real-time PCR (RT-PCR) assays for SARS-CoV-2 RNA detection were performed using Biospeedy COVID-19 RT-qPCR Detection Kit (Bioeksen, İstanbul, Turkey). The ARCHITECT ci16200 automatic biochemistry analyzer was used to measure the biochemical parameters and Sysmex Corporation was used to measure the hematologic parameters.

One hundred and four COVID-19 patients were included in this trial. The patients were divided into 3 groups according to their clinical severity as mild, moderate and severe. Among these 3 groups age, gender, leukocytes, neutrophils, lymphocytes, eosinophils, monocytes, hemoglobin, hematocrit, platelets, BUN, creatinine, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), sodium, potassium, CRP, procalcitonin, International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT), fibrinogen, d-dimer, ferritin, hospitalization time, CCI and mortality rates data were compared.

Statistical Analysis

Data analysis was performed using IBM SPSS v22 software. Descriptive statistics were used to summarize data. Variables assessed for normal distribution with the Kolmogorov Smirnov test. Categorical data were presented as number-percentages, and numerical data were presented as median, minimum, and maximum. Differences between categorical variables were analyzed with the Chi-Square test, and numeric variables were compared with the Mann-Whitney U test. Statistical significance level was accepted as $p<0.05$.

RESULTS

A total of 104 patients were included in the trial (66 males, 38 females). The demographic and characteristic characteristics of the patients are summarized in **Table 1**.

Table 1. Patient characteristics

Total patients, n	104
Age, years (median, min.-max.)	58 (12-92)
Gender, n (M/F),	66 (63.5)/38 (36.5)
Stage, n (%)	
Stage I (Mild)	31 (29.8)
Stage II (Moderate)	60 (57.7)
Stage III (Severe)	13 (12.5)
Hospitalization (day)	6 (1-32)
Mortality, n (%)	11 (10.6)

The most common comorbid disease in the patients included in the trial was hypertension, which occurred in 17 patients (13.6%). 64 patients (51.2%) had no comorbid disease. Comorbid diseases seen in patients and their frequency are in **Table 2**.

The clinical and laboratory values of the patients who were divided into 3 groups as mild, moderate and severe patients according to their clinical severity are shown in **Table 3**.

Table 2. Comorbidities

Disease	n (%)
Hypertension (HT)	17 (13.6)
Coronary arter disease	15 (12)
DM	9 (7.2)
Asthma/COPD	9 (7.2)
Chronic renal failure	4 (3.2)
Arrhythmia	2 (1.6)
Cerebrovascular disease (CVD)	2 (1.6)
Benign prostat hyperplasia	1 (0.8)
Hypothroidism	1 (0.8)
Psychiatric disease	1 (0.8)
None	64 (51.2)
Total number of comorbidities	125 (100)

Among the patients whose ages at the time of diagnosis were between mild stage and moderate-sever stages, the moderate-severe stage patients were statistically significantly older ($p<0.001$).

In accordance with the literature, age, WBC, neutrophil count, neutrophil-to-lymphocyte ratio (NLR), BUN, creatinine, AST, potassium level, CRP, procalcitonin, aPTT, fibrinogen, d-dimer, and ferritin levels were found to be higher in the clinically severe patient group. Lymphocyte and eosinophil counts, total protein, albumin and sodium levels were found to be lower in the clinically severe patient group.

The NLR was statistically significantly different between the mild, moderate and severe patient groups. It was observed that as the severity of the disease increased, the NLR increased.

Table 3. Comparison of mild, moderate and severe patients

		Stage 1 (mild) (n=31)	Stage 2[a] (moderate) (n=60)	Stage 3 (severe) (n=13)	p
Age at diagnosis		29 (12-73)[a]	59.5 (30-92)[b]	68 (48-85)[b]	<0.001
Sex n (%)	Female	14 (45.2)	20 (33.3)	4 (30.8)	0.485
	Male	17 (54.8)	40 (66.7)	9 (69.2)	
CCI		0 (0-1)[a]	0 (0-5)[b]	1 (0-2)[c]	<0.001
WBC at diagnosis ($\times10^9$/L)		6.09 (2.93-11.75)[a]	6.31 (2.7-20.57)[a]	13.1 (4.89-23.7)[b]	0.001
Neutrophil (2-6$\times10^3$/μL)		3.63 (1.20-6.84)[a]	4.95 (0.03-18.81)[b]	11.99 (4.51-22.02)[c]	<0.001
Hemoglobin at diagnosis (g/dL)		13.9 (10.5-16.4)	13.45 (8.5-16.5)	13.2 (11.1-15.4)	0.372
Hematocrit (39-50%)		39.7 (34.7-52.2)	40.75 (25.6-49)	40.6 (34.7-48.1)	0.943
Platelet at diagnosis ($\times10^9$/L)		248 (170-389)[a]	209 (100-506)[b]	219 (89-467)[a,b]	0.040
Lymphocyte (1.3-3.5$\times10^3$/μL)		1.28 (0.79-4.56)[a]	1 (0.3-15.3)[b]	0.7 (0.31-3.89)[c]	0.001
Monocyte (0.3-0.9$\times10^3$/μL)		0.49 (0.25-1.14)	0.47 (0.16-10.4)	0.44 (0.07-0.80)	0.207
Eosinophils (0-0.5$\times10^3$/μL)		0.05 (0.00-0.35)[a]	0.01 (0.00-0.15)[b]	0 (0-0.1)[b]	<0.001
BUN (5.1-16.8 mg/dL)		28 (15-47)[a]	36 (19-270)[b]	76 (29-187)[c]	<0.001
Creatinine (0.57-1.25 mg/dL)		0.71 (0.20-1.14)[a]	0.9 (0.4-3.23)[b]	1.69 (0.7-2.87)[c]	<0.001
Neutrophil/Lymphocyte		2.13 (0.75-6.58)[a]	5.01 (0.01-29.74)[b]	15 (3.52-31.46)[c]	<0.001
Total protein (6.4-8.3 g/dL)		7.5 (6.4-8.7)[a]	6.8 (4.6-8.6)[b]	6.5 (5.6-7.6)[c]	<0.001
Albumin (3.5-5 gr/dL)		4.4 (3.9-5.04)[a]	3.4 (1.8-4.6)[b]	2.9 (2.2-3.6)[c]	<0.001
AST (5-34 U/L)		25 (11-73)[a]	35.5 (15-575)[b]	49 (29-1654)[c]	<0.001
ALT (0-55 U/L)		21 (9-86)[a]	29.5 (10-532)[b]	28 (15-882)[a,b]	0.033
ALP (40-150U/L)		80 (11-284)[a,b]	74 (41-584)[b]	97 (53-199)[a]	0.047
GGT (9-64 U/L)		17 (8-189)[a]	32 (10-819)[b]	36 (15-106)[b]	<0.001
Sodium (136-145 mmol/L)		138 (134-144)[a]	136 (127-151)[b]	135 (124-151)[b]	0.013
Potassium (3.5-5.1 mmol/L)		4.08 (3.25-5.08)[a]	4.3 (2.9-8.4)[b]	5 (4.3-6.2)[c]	<0.001
C-reactive protein (0-0.35 mg/dL)		0.26 (0.02-1.98)[a]	5.09 (0.03-35)[b]	18.36 (0.14-35.2)[c]	<0.001
Procalcitonin (0-0.5 ng/mL)		0.04 (0.02-0.27)[a]	0.1 (0.02-10.32)[b]	1.22 (0.06-33.2)[c]	<0.001
INR (0.8-1.2)		1.08 (0.83-1.97)[a]	1.16 (0.92-2.6)[b]	1.2 (1-1.48)[a,b]	0.048
APTT (23-35 sn)		22.2 (17.9-26.5)[a]	24.9 (15-63.3)[b]	25.3 (21.2-30.1)[b]	0.001
Fibrinogen (150-350 mg/dL)		244.5 (177-413)[a]	470 (76.7-1187)[b]	609 (49-1218)[b]	<0.001
d-dimer (0-0.55 mg/L)		0.10 (0.00-1.08)[a]	0.52 (0.01-9.16)[b]	2.4 (0.5-32.5)[c]	<0.001
Ferritin level (22-322 ng/mL)		63 (7.69-268)[a]	354.75 (21-2300)[b]	834 (363-2002)[c]	<0.001
Hospitalization (day)		6 (1-17)[a,b]	7 (1-32)[a]	5 (2-12)[b]	0.047
Mortality, n (%)		0 (0)[a]	4 (6.7)[a]	7 (53.8)[b]	<0.001

Abbreviations: It shows a statistically significant difference among the a, b, c markers.

The CCI was found to be statistically significantly different between mild, moderate and severe groups (p<0.001). Univariate logistic regression analysis was performed to determine the effect of CCI on survival. When CCI increases by one unit, the risk of death increases by 1.193 (95% CI=1.120-3.268) times (p=0.017). However, no relationship was determined between CCI and length of stay.

DISCUSSION

Since the beginning of the pandemic, it has been a matter of wonder in which patients the clinical course of COVID-19 disease will be mild or severe. The presence of comorbidity has been associated with the severity of COVID-19 disease. It has been reported that older age, presence of lymphopenia and/or thrombocytopenia, increased LDH, d-dimer, CRP, fibrinogen, IL-6, transaminases are associated with severe disease (10). In our trial, age, WBC, neutrophil count, NLR, AST, CRP, procalcitonin, fibrinogen, d-dimer, and ferritin levels were found to be higher in the clinically severe patient group.

Christensen et al. (11) investigated the effect on survival by calculating the CCI score in 4480 COVID-19 patients. The median age of the patients included in the study was 55 years. The patients were classified according to the CCI score as 0, 1–2, 3–4, and >4. The likelihood of severe COVID-19 increased significantly in CCI score 1–2 (odds ratio [OR], 1.76), CCI 3-4 (OR, 2.36) and CCI >4 (OR, 2.67) compared to those in CCI 0. Mortality rates for CCI score 1–2 (OR, 2.13), CCI 3–4 (OR, 3.00) and CCI >4 (OR, 3.85) were significantly increased compared to those for CCI 0. In our trial, we also found a statistically significant difference in CCI score between mild, moderate and severe patient groups (p<0.001). When CCI increases by one unit, the risk of death increases by 1.193 (95% CI=1.120-3.268) times (p=0.017).

Sun et al. (12) evaluated 63 COVID-19 patients. The median age of the patients was 47 years. The patients were divided into 4 groups as mild, moderate, severe and critically ill. Nineteen of the patients (30.2%) were in the severe and critically ill group. Patients with comorbidity were in the severe patient group. Twenty nine of 63 patients had 1 or more comorbid diseases. Comorbid diseases are hypertension in 12 patients, DM in 5 patients, thyroid disease in 3 patients, cerebral infarction in 2 patients, cardiac arrhythmia in 2 patients, bronchial asthma in 2 patients, respectively. Leukocyte, neutrophil, lymphocyte, eosinophil counts and hemoglobin levels differed statistically significantly among the four patient groups (p=0.007, p=0.001, p=0.001, p=0.000, p=0.021, respectively). In our trial, the most common comorbid disease in the patients included in the trial was hypertension, which occurred in 17 patients (13.6%).

Garcia et al. (13) included 639 serious COVID-19 patients, with a median age of 63 [53–71] years. In a multivariate Cox proportional hazard regression model, patients' creatinine, d-dimer, lactate, and potassium levels at presentation were independently associated with intensive care unit (ICU) mortality (p<0.01). In our trial, creatinine, potassium level, and d-dimer levels were found to be higher in the clinically severe patient group.

Bastug et al. (14) reported 191 hospitalized COVID-19 patients that patients who needed an intensive care unit were elderly and had more comorbidity. Lower lymphocyte count, hemoglobin, total protein and albumin levels were reported in patients in the ICU compared with non-critical patients. However, higher WBC, neutrophil count, urea, creatinine, AST, LDH, d-dimer levels were reported (p<0.001). Hypertension, DM and cardiovascular diseases were reported to be the most common comorbidities in the patients included in the study (30.9%, 14.1% and 10.5%, respectively. Comorbidity was found more frequently in patients who needed ICU [35 (76.1%) versus 48 (33.1%); p<0.001].

Liu et al. (15) reported that the rate of NLR was an independent measure of mortality in hospitalized patients in a study in which they studied 245 COVID-19 patients. Lagunas-Rangel et al. (16) reported that in a meta-analysis involving 6 severe COVID-19 patients, NLR values increased significantly in COVID-19 patients with severe disease. Liu et al. (17) identified NLR as an independent risk factor for critical disease in their study of 61 patients with COVID-19 infections. In our trial, the NLR was statistically significantly different between the mild, moderate and severe patient groups. It was observed that as the severity of the disease increased, the NLR increased.

In our trial, in accordance with the literature, age, WBC, neutrophil count, BUN, creatinine, AST, potassium level, CRP, procalcitonin, aPTT, fibrinogen, d-dimer, and ferritin levels were found to be higher in the clinically severe patient group. In addition, lymphocyte and eosinophil counts, total protein, albumin and sodium levels were found to be lower in the clinically severe patient group.

This trial showed that calculating the CCI score in COVID-19 patients can be useful in predicting the severity of the disease. Examination of CCI, age, WBC, neutrophil, lymphocyte, NLR, eosinophil counts, BUN, creatinine, AST, total protein, albumin, sodium, potassium level, CRP, procalcitonin, aPTT, fibrinogen, d-dimer and ferritin levels at the time of diagnosis can be suggested.

ETHICAL DECLARATIONS

Ethics Committee Approval: The trial was approved by İnonu University Research Ethics Committee (date/ reference number: 10-11-2020/1255).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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