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ORIGINAL RESEARCH

Evaluation of the Charlson Comorbidity Index and Laboratory Parameters as Independent Early Mortality Predictors in Covid 19 Patients

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Purpose: Various parameters have been proposed to predict the outcome of patients with coronavirus disease. The aim of this study was to evaluate the utility of the age-adjusted CCI score and biochemical parameters for predicting outcomes for COVID-19 patients on admission.

Patients and methods: A total of 511 patients were included in the study. Only swab or serological tests positive patients were included. The clinical characteristics of the patients were compared between survival and non-survival COVID-19 inpatients. Hemoglobin, platelet, sedimentation, creatinine, AST, ALT, LDH, CK, albumin, ferritin, lymphocyte, neutrophil, CRP (1–5;5–10;10–20 × upper limit), procalcitonin (5–10;10–20; > 20 × upper limit), D Dimer (> 2 × upper limit), age, gender, chronic diseases and CCI scores were compared between the two groups.

Results: 68 patients died and 443 patients survived. Mean age was 74.3±7.3 years in survival group and 76.7±8.0 in nonsurvival group. Age, male sex, ischemic heart disease (CHD), chronic kidney disease and active malignancy was statistically higher in non-survivor group. The biochemical parameters was compared in survival and nonsurvival group. CCI score, AST, LDH, CK, Ferritin, CRP are significantly higher and albumin, lymphocyte levels are significantly lower in nonsurvival group. D-dimer and procalcitonin levels are significantly higher in nonsurvival group. CCI score and neutrophil, creatinine, ALT, AST, d-dimer and procalcitonin elevations were correlated. Low albumin and lymphocyte levels were correlated with the CCI score. There was no significant correlation between ferritin, sedimentation, CRP levels and CCI score. A multivariate logistic regression analysis indicated that anaemia, elevated CRP (> 10–20 × upper limit), procalcitonin (> 5–10 × upper limit), ALT, AST levels and higher CCI score were independent risk factors for mortality in COVID-19 patients.

Conclusion: Anaemia, elevated CRP, procalcitonin levels, ALT, AST levels and higher CCI score were found independent risk factors for mortality in COVID-19 patients.

Keywords: CCI score, laboratory parameters, mortality, COVID 19

Introduction

Since 2020 March, which was accepted as a pandemic by the World Health Organization; the coronavirus disease 2019 (COVID-19) pandemic has changed our lifestyle dramatically.[1] In Turkey, the first case of COVID-19 was detected on March 11, 2020. Since then, it has been one of the causes of increased mortality. The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic infection to severe pneumonia requiring admission to the intensive care unit (ICU).[2] Patients with these severe conditions often have comorbid diseases, such as hypertension (HT), diabetes mellitus (DM) and heart diseases.[3] Laboratory parameters are important for both diagnosis and prediction of prognosis in COVID-19 patients.[4] Routine blood tests requested for COVID-19 patients include complete blood count (CBC), coagulation cascade (including PT, aPTT, and D-dimers) parameters and inflammation-related parameters such as CRP, ferritin,

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and procalcitonin.[5] Neutrophilia and lymphopenia are the most common laboratory parameters in these patients.[6] Abnormal liver function test findings have also been reported.[7,8] Developing prognostic parameters to accurately predict the prognosis of COVID-19 is important for clinical management of patients. Various parameters have been proposed to predict the outcome of patients with coronavirus disease-2019 (COVID-19). These include clinical parameters, laboratory parameters and radiological parameters.[9,10] In some systematic review and meta-analysis, comorbid conditions (chronic respiratory disease, cardiovascular disease, hypertension, and diabetes), clinical parameters (dyspnea, fatigue and anorexia) and laboratory parameters (high WBC count, increased neutrophils and lymphopenia) were associated with mortality.[11] Shang et al show that laboratory parameters like lymphocyte percentage, CRP, and D-dimer are risk factors of mortality in Covid 19 Patients.[12]

The Charlson comorbidity index (CCI) score was developed in 1987 and it is an approved, simply applicable method for estimating the risk of death from comorbid diseases.[13] It is widely used as an indicator of prognosis and mortality. Charlson Comorbidity Index (CCI) is the most common and valid method to estimate mortality by classifying comorbidities such as cardiovascular, metabolic, renal, hepatic, pulmonary diseases, and malignancy. The age-adjusted Charlson comorbidity index (CCI) consists of age and 19 medical comorbidities to calculate the total score with a specific score assigned to each comorbid condition.[14] The severity of COVID-19 pneumonia is affected by age and comorbid diseases, so this simple comorbidity index can be used to predict mortality in patients hospitalized with COVID-19. According to such studies; elevated CCI score is associated with poor outcomes and mortality in COVID-19 patients.[15,16]

The aim of this study was to evaluate and predict the prognosis of hospitalized COVID-19 patients by using CCI score and biochemical parameters.

Methods

Data Source

This multicenter retrospective study was made using the data collected from pandemic units of internal medicine clinics of largest five training and research hospitals in Istanbul. Covid-19 patients were hospitalized and followed up in pandemic units these internal medicine clinics. This study was approved by the Health Sciences University Istanbul Haseki Training and Research Hospital Ethics Committee (Reference No: 44–2020), Istanbul, Türkiye and performed in accordance with National Institute of Health guidelines. The study was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki. All data were collected anonymously without including patient-identifying information, and consent to review the patient medical records. Informed consent was waived due to the global urgent data requirement.

Study Population, Data Collection

The data of all consecutive adult patients admitted to the pandemic units of the participating hospitals' internal medicine clinics with the diagnosis of Covid-19 disease were gathered between April 2020 and July 2021. A total of 511 patients were included in the study. Only swab or serological tests positive patients and clinical and/or radiological findings were considered to have Covid-19 disease were included in the study. Patients with having negative swab tests were excluded. We included patients who fully recovered and deceased patients. Patients hospitalized for other reasons were not included. Re-admissions were not included. The patients data were recorded such as demographic information, laboratory analyzes, erythrocyte sedimentation rate (ESR), serum creatinine, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatinine kinase, C-reactive protein (CRP), d-dimer, ferritin, Procalcitonin, hemoglobin, lymphocyte, neutrophil, platelet count. On the first day of hospitalisation and before treatment period blood samples were obtained from all patients. The clinical characteristics of the patients were compared between survival and non-survival COVID-19 inpatients. Patients age, gender, chronic diseases, CCI scores were recorded. Hemoglobin, platelet, sedimentation, creatinine, AST, ALT, LDH, CK, albumin, ferritin, lymphocyte, neutrophil, CRP (1–5;5–10;10–20 × upper limit), procalcitonin (5–10;10–20; > 20 × upper limit), D Dimer (> 2 × upper limit), age, gender, chronic diseases and CCI scores were compared between the two groups.

Statistical Method

IBM SPSS Statistics for Windows (Version 25.0, IBM Corp., Armonk, NY, USA) was used for statistical analysis. Descriptive statistics were given as numbers and percentages for categorical variables, and mean, standard deviation for numerical variables. The ratios in the groups were compared with the Chi-square test. The relationships between numerical variables were analyzed by Spearman Correlation Analysis when the parametric test condition was not met. The recorded parameters were compared between survivors and non-survivors. The Student's *t*-test was used to compare two independent groups in the analyses of normally distributed numerical data. In the case of abnormal distribution of numerical data, the Mann-Whitney-*U* test was used to compare the two groups. Cox regression analysis was used in non-survival analyzes. Parameter found to be different between outcomes (non-survivor) were included in the regression models to find out parameters showing independent relationship with these outcomes. A p-value of less than 0.05 was considered significant.

Results

A total of 511 patients (263 females and 248 males) were included in this study. During their follow-up; 68 patients died and 443 patients survived. Mean age was 74.3±7,3 years in survival group and 76.7±8,0 in nonsurvival group. The most common comorbidity of which were hypertension (64.9%) followed by coronary diabetes (31.2%) and ischemic heart disease (30.6%). Age, male sex, ischemic heart disease (CHD), chronic kidney disease and active malignancy was statistically higher in non-survivor group(Table 1).

The biochemical parameters was compared in survival and nonsurvival group. CCI score, AST, LDH, CK, Ferritin, CRP are significantly higher and albumin, lymphocyte levels are significantly lower in nonsurvival group. D-dimer and procalcitonin levels are significantly higher in nonsurvival group. (Table-2).

CCI score and neutrophil, creatinine, ALT, AST, d-dimer and procalcitonin elevations were correlated. Low albumin and lymphocyte levels were correlated with the CCI score. There was no significant correlation between ferritin, sedimentation, CRP levels and CCI score. (Table-3).

Table 1 Baseline Characteristics of Covid 19 Patients

	Survival	Non-Survival	P
Age	74.3±7.3	76.7±8.0	0.003*
Male	208 (47%)	40 (58.8%)	0.068*
Female	235 (53%)	28 (41.2%)	0.068*
Diabetes Mellitus	138 (31.2%)	26 (38.8%)	0.211
Hypertension	286 (64.9%)	50 (74.6%)	0.115
Ischemic Heart Disease	134 (30.6%)	29 (43.3%)	0.039*
Cerebrovascular/Neurological Disease	47 (10.7%)	12 (17.9%)	0.087
Heart Failure	52 (12%)	14 (20.6%)	0.052
Chronic Kidney Disease	35 (8%)	14 (20.6%)	0.001*
COPD	74 (16.9%)	17 (25%)	0.105
Active malignancy	17 (3.9%)	8 (11.9%)	0.010*
Chronic Liver Disease	3 (0.7%)	2 (2.9%)	0.136
Autoimmune Disease	14 (3.2%)	5 (7.4%)	0.158

Note: *Statistically significant variables (p<0.05).
Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 2 Baseline Laboratory Parameters of Between COVID-19 Patients Survival and Non-Survival Groups

	Survival	Non-Survival	P
CCI score	4.44±1.98	5.99±2.52	0.001*
Hemoglobin (g/dL)	12.4±1.8	11.2±2.4	0.001*
Neutrophil count (/mm^3)	4872.0±2929.8	5457.2±3757.8	0.187
Lymphocyte count (/mm^3)	1365.3±711.7	1087.0±622.0	0.020*
Thrombocyte count (×1000/mm^3)	219.6±83.3	217.4±104.0	0.799
Sedimentation (mm/hour)	45±27.1	55.0±35.4	0.917
Creatinine (mg/dL)	1.2±1.0	1.85±2.01	0.091
Albumin (g/dL)	3.5±0.5	3.2±0.5	0.001*
AST (U/L)	31.4±24.0	62.2±136.8	0.011*
ALT (U/L)	25.7±25.9	38.6±73.0	0.619
LDH (U/L)	353.0±167.9	484.4±556.9	0.012*
CK (U/L)	198.8±538.0	521.2±1950.4	0.003*
Ferritin (ng/mL)	756.3±4499.9	804.3±1472.3	0.019*
CRP, n/N (%) (> 1–5 × upper limit)	124 (28%)	20 (29.4%)	0.001*
CRP, n/N (%) (> 5–10 × upper limit)	93 (21%)	6 (8.8%)	0.001*
CRP, n/N (%) (> 10–20 × upper limit)	89 (21.1%)	16 (23.5%)	0.001*
Procalcitonin, n/N (%) (> 5–10 × upper limit)	4 (1.1%)	7 (11.3%)	0.001*
Procalcitonin, n/N (%) (> 10–20 × upper limit)	5 (1.3%)	2 (3.2%)	0.001*
Procalcitonin, n/N (%) (> 20 × upper limit)	7 (1.9%)	7 (11.3%)	0.001*
D dimer n/N (%) (> 2 × upper limit)	99 (23.6%)	28 (49.1%)	0.001*

Note: *Statistically significant variables ($p< 0.05$).
Abbreviations: CCI, Charlson Comorbidity Index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatinine kinase; CRP, C reactive protein.

Table 3 Correlation Analysis Between CCI Scores and Laboratory Parameters

	r	P
Hemoglobin (g/dL)	−0.402	0.001*
Neutrophil (/mm3)	0.170	0.001*
Lymphocyte (/mm3)	−0.095	0.032*
Thrombocyte (×1000/mm3)	0.028	0.521
Sedimentation (mm/hour)	−0.063	0.291
Creatinine (mg/dL)	0.243	0.001*
Albumin (g/dL)	−0.253	0.001*
AST (U/L)	0.108	0.016*

(*Continued*)

Table 3 (Continued).

	r	P
ALT (U/L)	0.223	0.001*
LDH (U/L)	−0.085	0.065
CK (U/L)	−0.063	0.211
Ferritin (ng/mL)	−0.058	0.227
CRP, n/N (%) (> 1–5 × upper limit)	0.036	0.423
Procalcitonin, n/N (%) (> 5–10 × upper limit)	0.264	0.001*
D dimer n/N (%) (> 2 × upper limit)	0.237	0.001*

Note: *Statistically significant variables (p< 0.05).
Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatinine kinase; CRP, C reactive protein.

Table 4 Logistic Regression Analysis Predicting Mortality on Covid 19 Inpatients

	OR	P
Hemoglobin gdl	0.8	0.040*
AST (UL)	1	0.001*
ALT (UL)	1	0.019*
CRP, n/N (%) (> 10–20 × upper limit)	11.3	0.036*
Procalcitonin, n/N (%) (> 5–10 × upper limit)	49.2	0.001*
CCI score	1.2	0.012*

Note: *Statistically significant variables (p< 0.05).
Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C reactive protein; CCI, Charlson Comorbidity Index.

A multivariate logistic regression analysis indicated that anaemia, elevated CRP (> 10–20 × upper limit), procalcitonin (> 5–10 × upper limit), ALT, AST levels and higher CCI score were independent risk factors for mortality in hospitalized COVID-19 patients (Table 4).

Discussion

COVID-19 is a viral infection that is a serious public health problem and currently causes high death rates. Countries around the world are experiencing serious difficulties in economy and health systems with the pandemic. New findings about the disease are emerging every day, and algorithms for treatment are constantly updated.

In this study, elevated levels of ALT, AST, CRP, Procalcitonin and higher CCI score were shown to be independent predictors for hospitalized COVID-19 patient's mortality.

Our results revealed that anemia is an independent risk factor for severe COVID-19 pneumonia. Anaemia commonly aggravates the severity of respiratory diseases and Doshi et al finded out that respiratory diseases combined with anaemia are associated with poor outcomes and increased mortality.[17] Moreover, Tao et al showed that severe cases of pneumonia seen in COVID-19 patients had severely reduced hemoglobin levels.[18] The low concentration of hemoglobin in the circulation reduces the oxygen transport to the organs. This causes hypoxia and multiple organ dysfunction. This mechanism can explain the high rate of severe COVID-19 cases with anemia.

Liver dysfunction is common in covid 19 patients[19,20] and various underlying mechanisms have been demonstrated. First, SARS-CoV-2 can bind to the up-regulated angiotensin converting enzyme 2 (ACE 2) and can attack liver cells.[21] Second, the cytokine storm results in increased release of inflammatory factors and decreased CD4+ and CD8+ T lymphocyte counts.[22,23] Also, the overactivation of inflammatory response can lead to dysfunction of multiple organs, including the liver. Third, hepatic ischemia and hypoxia due to respiratory failure and circulatory disorder occur.[19] Fourth, drug hepatotoxicity caused by antiviral agents, nonsteroidal anti-inflammatory drugs, glucocorticoids should not be forgotten. Similar to the other studies; in our study, the liver enzymes were significantly elevated in non-survival group.[24,25]

In this study, the high CCI Score an independent risk factor for patient mortality. Chen et al showed that advanced age is an important risk factor for a fatal outcome.[26] In addition to advanced age, co-morbidities, high procalcitonin and aspartate aminotransferase levels were associated with fatal outcomes. Ji et al further evaluated that the presence of comorbidities and advanced age both contribute to the risk of disease progression.[27] In this study, the high CCI Score was also shown as an independent risk factor for mortality.

Shang et al reported that the mean CRP level was statistically higher in severe cases.[12] In a study on biochemical parameters in the early disease period, it was observed that the CRP level was higher in critically ill patients.[8] Moreover, Bilgir et al showed that CRP is significant for mortality and ICU admission in COVID-19 patients.[28] It has been determined that our findings regarding CRP values are compatible with the literature.

Previous studies show that level of procalcitonin does not elevate in patients with viral infections.[29] Bairwa et al determined that the procalcitonin level was significantly higher in the death cohort than that of the survived group as our study in COVID-19 patients. They explain that high procalcitonin level indicates the possibility of multiple infections at a time.[30]

Our study has some limitations. First, our study is a retrospective. Secondly, a limited number of hematological and biochemical markers have been studied, which limits the implications of the findings. These markers and clinical features need further investigation.

Conclusion

In our study, anaemia, elevated CRP, procalcitonin levels, ALT, AST levels and higher CCI score were found independent risk factors for mortality in hospitalized COVID-19 patients. These laboratory parameters, together with the CCI score, may predict mortality in patients with COVID 19.

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Author Contributions

All authors contributed to the data analysis, drafting or revision of the article have accepted the journal to which the article will be submitted, have given final approval of the version to be published and agreed to be responsible for all aspects of the work.

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The authors report no conflicts of interest in this work.

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