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Research

Prognostic Significance of Soluble CD163 in Hospitalized Patients with COVID-19

COVİD-19 ile Yatırılan Hastalarda Soluble CD163'ün Prognostik Önemi

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ABSTRACT

Objective: Soluble CD163 (sCD163) is a biomarker involved in inflammation. There is little data on the prognostic utility of sCD163 in coronavirus disease-2019 (COVID-19). This study investigated the relationship between serum sCD163 and the prognosis of COVID-19.

Methods: A total of 79 hospitalized patients diagnosed with COVID-19 were included in this retrospective study. Patients were divided into two groups as survivors and non-survivors. The clinical characteristics, serum sCD163 level, and other laboratory data of patients were compared between the groups.

Results: Forty-two (53.2%) of the 79 cases were male. The mean age was 70.4±12 years in the non-survivor group and 64.2±14 years in the survivor group (p=0.079). Serum sCD163, prothrombin time, and lactate were significantly higher in non-survivors than in survivors (p=0.023, p=0.015, p=0.018, respectively). The optimum cutoff value of serum sCD163 by receiver operating curve analysis was 2.92 ng/mL, resulting in 74% sensitivity and 52% specificity for predicting mortality (area under the curve: 0.620, 95% confidence interval: 0.481-0.759, p=0.048). Serum sCD163≥2.92 ng/mL was associated with 4.3 times higher mortality risk as assessed by logistic regression analysis (p=0.014).

Conclusion: sCD163 is an independent predictor of mortality in COVID-19 positive patients who have a fatal course of the disease.

Keywords: Soluble CD163, COVID-19, inflammation, mortality

ÖZ

Amaç: Suluble CD163 (sCD163) enflamasyonla ilgili biyobelirteçlerinden biridir. Koronavirüs hastalığı-2019'da (COVİD-19) sCD163'ün prognostik faydası hakkında çok az veri var. Bu çalışma sCD163 seviyeleri ve hastalığın prognozu arasında ilişki olup olmadığının araştırılmasını amaçladı.

Gereç ve Yöntem: Bu retrospektif çalışmaya COVİD-19 tanısı konan toplam 79 hastanede yatan hasta dahil edildi. Hastalar sağ kalanlar ve sağ kalmayanlar olarak iki gruba ayrıldı. Hastaların klinik özellikleri, serum sCD163 düzeyi ve diğer laboratuvar verileri gruplar arasında karşılaştırıldı.

Bulgular: Yetmiş dokuz olgunun 42'si (%53,2) erkek idi. Hayatta olmayan grupta yaş ortalaması 70,4±12 yıl ve hayatta olan grupta 64,2±14 yıl saptandı (p=0,079). Hayatta olmayanlarda sCD163, protrombin zamanı ve laktat düzeyleri hayatta olanlara göre istatistiksel olarak anlamlı yüksek bulundu sırasıyla (p=0,023, p=0,015, p=0,018). Hayatta olmayan grupta alıcı çalışma karakteristik analizi yapıldığında sCD163≥2,92 olduğunda eğrinin altındaki alan (AUC) değeri (AUC: 0,620, %95 güven aralığı: 0,481-0,759, p=0,048), sensitivitesi %74, spesifitesi %52 bulundu. Lojistik regresyon analizinde sCD163≥2,92 olduğunda mortalite riski 4,3 kat daha fazla olarak saptandı (p=0,014).

Sonuç: sCD163 ölümcül seyri olan COVİD-19 pozitif hastalarda mortalitenin bağımsız bir öngördürücüsüdür.

Anahtar Kelimeler: Soluble CD163, COVİD-19, enflamasyon, mortalite

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INTRODUCTION

Coronavirus disease-2019 (COVID-19) worldwide is an infection caused by the respiratory syndrome coronavirus-2 (1). The effects of COVID-19 may be different clinical pictures, from an asymptomatic carrier ship to respiratory system findings such as fever, sore throat, shortness of breath, cough and bilateral pneumonic infiltration, and acute respiratory distress syndrome. Cases presenting findings such as abdominal pain, headache, diarrhea, smell and taste disorders, and skin lesions have also been reported (2). Death generally occurs in older people or individuals with accompanying systemic diseases (hypertension, diabetes mellitus, chronic lung diseases, cardiovascular disease, and cancer) (3). Soluble CD163 (sCD163) has been described as a cell surface molecule, which is a member of the scavenger receptor cysteine-rich superfamily, that is present in particular on the surface of monocytes and macrophages as a haptoglobin-hemoglobin receptor (4). A soluble form of CD163 ectodomain is present in normal plasma comprising at least 94% of all CD163 and binds haptoglobin-hemoglobin complexes (5). The known most potent known stimulators of sCD163 expression are glucocorticoids, interleukin (IL)-6, IL-10, and heme/hemoglobin (6). sCD163 has a weak apoptosis inducer similar to tumor necrosis factor-α (7), and viruses (8). sCD163 may play an essential role in resolving inflammation (9). sCD163 is an indicator for the activation of macrophages and is increased in macrophage activation syndrome (10). Macrophages expressing CD163 have been detected in the vicinity of chronically inflamed joints (11), and tumor cells (tumor-associated macrophages) (12). sCD163 has been associated with disease progression in viral hepatitis B and C (13), increased mortality after sepsis (14), and stenosis and coronary lesions in human immunodeficiency virus (HIV)-infected individuals (15). COVID-19 is a novel disease, and it has been found in the literature that many pro-inflammatory cytokines and other acute-phase reactants correlate with a poor prognosis of the disease (16). However, there are no specific biomarkers for the prognosis and survival of COVID-19. There are limited data on the prognostic utility of sCD163 in COVID-19. This study investigated the relationship between serum sCD163 and the prognosis of COVID-19.

METHODS

A total of 79 patients who had were hospitalized [in intensive care unit (ICU) and in non-ICU)] between 01.09.2020 and 31.10.2020. Patients over the age of 18 who were positive for COVID-19 were included in the study. All data of the patients were obtained retrospectively. Patients were divided into two groups as survivors and non-survivors. The clinical characteristics and other laboratory data of the patients were compared.

Within the scope of the study, serum albumin, glucose, lactate dehydrogenase (LDH), urea, and creatinine were measured using the spectrophotometric method, and C-reactive protein (CRP) was measured using the immunoturbidimetric method in an auto analyzer. Complete blood count parameters were measured with the light emitting diode flow cell method. Prothrombin time (PT) was measured using the optical method, D-dimer by the latex agglutination test. For sCD163, the sera were stored at -80 °C until the working day. The serum sCD163 level was measured using the sandwich ELISA method (Elabsience, Bioassay Technology Laboratory, Shangai, China). In the precision study conducted by the manufacturer, the CV% of the kits within and between studies was given as <10%. Our study was approved by Sakarya University Non-Interventional Clinical Research Ethics Committee on 04/09/2020 with the decision number 71522473/050.01.04/462.

Statistical Analysis

Data analyses were performed using SPSS version 20 for Windows software (SPSS Inc. Chicago, IL, USA). The suitability of the variables to normal distribution was examined using Kolmogorov-Smirnov. Normally distributed data were compared with one away. Abnormally distributed data were evaluated with the Mann-Whitney U test. Categorical associations were assessed using the χ^2 test. Receiver operating curve (ROC) analysis was used to calculate for sCD163 the required cut-off values to distinguish survivor and non-survivor patients by calculating the area under the curve (AUC) of the ROC curves. The predictive value of the CD163 was determined by logistic regression analysis. Statistical significance was defined as $p \leq 0.05$.

RESULTS

Of the 79 cases included in the study, 37 (46.8%) were female. There was no significant difference in gender between the groups (p=0.407). The total number of survivors was 54 (68.4%), and the total number of non-survivors was 25 (31.6%). The mean age was 70.4±12 years in the non-survivors and 64.2±14 years in the survivors (p=0.079). Looking at the symptoms at the time of admission to the hospital, while 26 (48%) of the patients who survived had fever, only 6 (25%) of the patients with non-survivors had fever exceeding 38 °C (p=0.017). Twenty (37%) survivors and 18 (72%) of non-survivors had shortness of breath (p=0.004). Thirty (55%) of survivors and 10 (40%) of non-survivors had coughs (p=0.198). Twenty-two (22%) survivors and 5 (20%) of

non-survivors had fatigue (p=0.823). Eleven (20%) survivors and 2 (0.07%) of non-survivors had myalgia-arthralgia (p=0.310). Two (3.7%) survivors and 3 (12%) of non-survivors had throat ache (p=0.159).

Comorbidities such as hypertension and cerebrovascular disease were compared in terms of mortality and were found statistically significant (p=0.020, p=0.005, respectively) (Table 1).

sCD163, PT, and lactate was higher in the non-survivors than in the survivors (p=0.023, p=0.015, p=0.018, respectively). Compared to survivors d-dimer (p=0.029), ferritin (p=0.002), LDH (p<0.001), erythrocyte sedimentation rate (p=0.003), CRP (p=0.001), neutrophil count (p=0.001) and neutrophil to lymphocyte ratio (p=0.001) were found to be significantly higher in the non-survivors and the lymphocyte count was found to be significantly lower (p=0.001). The sCD163 levels were significantly higher in the non-survivors than

Table 1. Clinical, demographic and laboratory characteristics of patients with COVID-19

Characteristics	Survivor (n=54)	Non-survivor (n=25)	p-value
Age, years	64.2±14	70.4±12	0.079
Men	27 (50%)	15 (60%)	0.407
Women	27 (50%)	10 (40)	0.407
Hypertension	15 (28%)	11 (46%)	0.020
Diabetes mellitus	24 (48%)	13 (52%)	0.531
COLD	2 (3.7%)	0 (0%)	0.330
Asthma	3 (5.5%)	3 (12%)	0.315
CAD	7 (12.9%)	4 (16%)	0.717
Malignity	1 (1.85%)	3 (12.5%)	0.056
CVD	3 (5.5%)	7 (29%)	0.005
CRP (mg/L)	39 (13-109)	122 (55-168)	0.001
Sedimentation (mm/h)	41±20	59±19	0.003
Procalcitonin (ng/mL)	2.3±1.4	4.7±2	0.548
WBC (K/uL)	6355 (4915-8160)	9630 (6190-12000)	0.747
Neutrophil K/uL	4887±2400	7300±3312	0.001
Lymphocyte K/uL	1150 (857-1407)	639 (501-1018)	0.001
NLR	6.6±3.1	10.9±5.2	0.001
Hemoglobin (g/dL)	12.0±1.5	12.2±1.9	0.747
D-dimer (Ug/FEu)	564 (260-1310)	1210 (792-2120)	0.029
Ferritin (ug/L)	138 (67-387)	731 (296-1900)	0.002
Glucose (mg/dL)	139±66	157±57	0.056
Urea (mg/dL)	45 (29-56)	69 (38-85)	0.026
Creatinine (mg/dL)	1.0 (0.6-0.9)	1.3 (0.7-1.0)	0.500
Prothrombin time (sn)	12.7±2.8	14±1.9	0.015
INR	1.1±0.2	1.2±0.1	0.038
LDH (U/L)	345±150	495±173	0.001
Lactate (mmol/L)	1.65±0.5	2.02±0.7	0.018
CD163 (ng/mL)	2.81±0.8	3.47±1.7	0.023

Data are presented as mean (SD), for continuous variables with normal.

Distribution, median and 25th and 75th percentiles (P25-P75) for variables with non-normal distribution.

COLD: Chronic obstructive lung disease, CAD: Coronary artery disease, CVD: Cerebrovascular disease, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio; INR: International normalized ratio, WBC: White blood cells, LDH: Lactate dehydrogenase, COVID-19: Coronavirus disease-2019, SD: Standard deviation

in the survivors (3.47±1.7 vs. 2.81±0.8, p=0.023) (Table 1). Serum sCD163 levels of survivor and non-survivor COVID-19 patients are shown in Figure 1. The ROC curve analyzed the effect of sCD163 on mortality in hospitalized COVID-19 patients. The optimum cutoff value of serum sCD163 by ROC analysis was 2.92 ng/mL, resulting in 74% sensitivity and 52% specificity for predicting mortality (AUC: 0.620, p=0.048) (Figure 2). We built a logistic regression model for survival as a dependent variable, and CD163≥2.92, PT, and lactate as independent predictors. In the logistic regression, the mortality risk was found to be 4.3 times higher in CD163≥2.92 (p=0.014). The results of the logistic regression analysis are summarized in Table 2.

DISCUSSION

This study showed that the sCD163, PT, and lactate levels were significantly higher in non-survivors than in survivors. In previous studies, non-survivor patients with HIV (17), hepatitis B virus (18), and sepsis (19) had higher sCD163 levels, compared to survivors. Elevated plasma sCD163 levels are an independent predictor of death in HIV-positive adults (20) and hepatitis B infection (18). An increased sCD163 plasma concentration has been observed in diseases related to macrophage activity, including acute and chronic inflammations (9). CD163 staining in infiltrating macrophages was more evident in COVID-19 patients (21). Since sCD163 concentrations in viral infections are associated with mortality, it was thought that it may also be associated with COVID-19, which is a novel viral infection. Gómez-Rial et al. (21) found no difference between sCD163 levels in ICU and non-ICU patients, but showed that it was significantly higher in COVID-19 patients than in the healthy control group. Bowman et al. (22) found no difference in sCD163 levels when COVID-19 patients were categorized as mild, moderate, and critical, but a significant increase in sCD163 was shown in those who died. Our study showed that sCD163 levels were significantly higher in patients who died of COVID-19 than in survivors. There was a significant relationship between the admission sCD163 level and mortality. Our findings suggest that the sCD163 level, combined with patient features, can be used to identify individuals with poor prognoses and death.

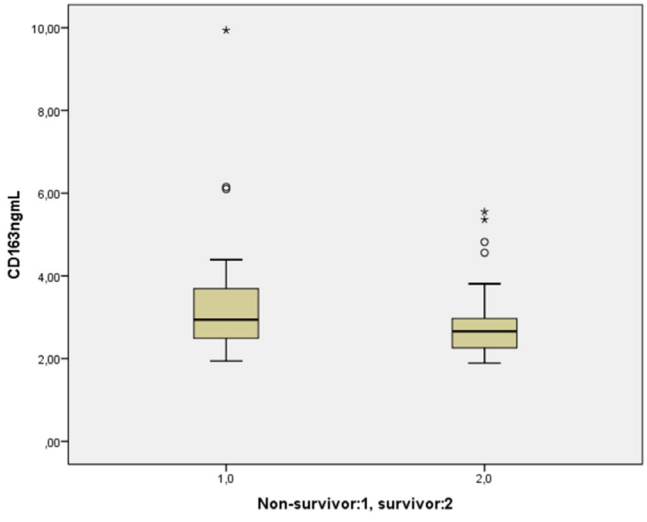

Figure 1. Serum sCD163 levels of survivor and non-survivor (p=0.023)
sCD163: Soluble CD163

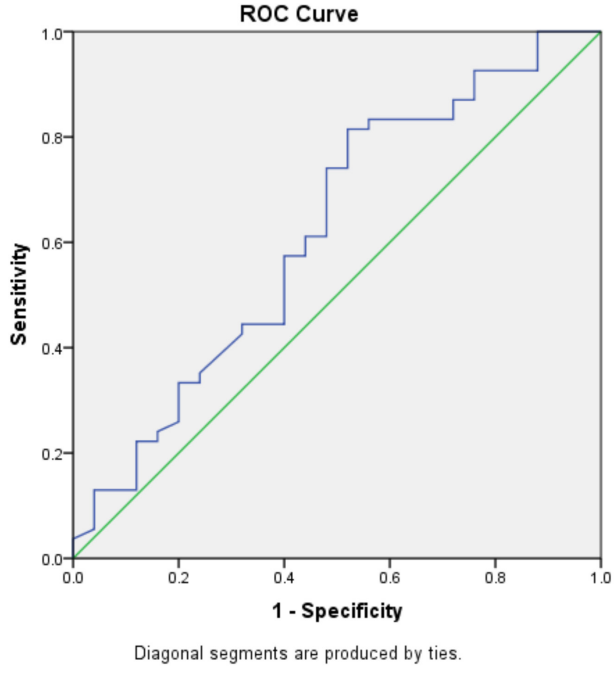

Figure 2. Receiver operating characteristic curve for CD163 ratio in patients with survivor or non-survivor COVID-19
ROC: Receiver operating characteristic, COVID-19: Coronavirus disease-2019

Table 2. Binary logistic regression analysis results of the parameters for survival

Parameters	B	SE	Wald	Odds ratio	p-value
CD163≥2.92	1.455	0.592	6.032	4.3	0.014
Prothrombin time	-0.664	-0.305	5.313	0.737	0.021
Lactate	-1.101	0.469	5.502	0.333	0.019

B: Standardized regression coefficients, SE: Standard error

Previous reports have shown that COVID-19 cases could be severe and fatal in individuals with comorbidities (3). In a multi-center cohort study conducted in China, diabetes mellitus and coronary artery disease were shown as the most common causes of comorbidity, respectively, after hypertension (23). In our study, diabetes mellitus, hypertension, cerebrovascular disease, and coronary artery disease was common in patients hospitalized for COVID-19 with a mortal course. Statistical significance with mortality was with hypertension and cerebrovascular disease. It was reported that elevated d-dimer levels, LDH, PT, and lymphopenia were commonly seen in severe COVID-19 (23). Our study showed that d-dimer, PT, LDH, and CRP were significantly higher in non-survivors than in survivors. The results were similar to those of the previous studies.

In one study, the mortality rate in hospitalized COVID-19 patients was 23.8% (24). According to the results of our research, the case fatality rate was 32%. 68% of the patients who died were older than 65 years. Although many factors affecting mortality have been elucidated, many unknowns are related to this disease.

COVID-19 is a novel disease, and it has been found in the literature that many pro-inflammatory cytokines and other acute phase reactant levels correlate with a poor prognosis (16). However, there are no specific biomarkers showing the prognosis of COVID-19 and their relationship with mortality. CD163 is a biomarker of inflammatory diseases. In this research, sCD163, PT, and lactate were associated with mortality in COVID-19 patients. In the logistic regression, when sCD163 was ≥2.92, the mortality risk was 4.3 times higher.

Our study has some limitations, including a single-center cohort study, the small sample size, a retrospective design, and the lack of anthropometric data due to the urgency of epidemics.

CONCLUSION

Serum sCD163 is a valuable biomarker indicating the prognosis of COVID-19 and is an independent predictor of mortality. Further studies may be useful in clarifying the role of serum sCD163 in COVID-19 severity.

ETHICS

Ethics Committee Approval: Our study was approved by Sakarya University Non-Interventional Clinical Research Ethics Committee on 04/09/2020 with the decision number 71522473/050.01.04/462.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.N., T.K., S.Y., D.Ç., K.S., C.K., E.Ç., C.B., Concept: S.Y., Design: S.Y., C.K., Data Collection or Processing: D.Ç., K.S., C.K., E.Ç., Analysis or Interpretation: A.N., T.K., E.Ç., C.B., Literature Search: A.N., S.Y., C.B., Writing: A.N., T.K.

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