Dicle Tıp Dergisi / Dicle Med J (2022) 49 (4) : 612-618

www.diclemedj.org

Original Article / Özgün Araştırma

Relationship Between Systemic Immune Inflammation Index and Prognosis in Patients with COVID-19

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Received: 17.05.2022; Revised: 07.09.2022; Accepted: 08.09.2022

Abstract

Objectives: Inflammation and coagulation perform a substantial act in the pathophysiology of COVID-19 cases. The systemic immune-inflammation index (SII) is a novel prognosis and inflamation index. In this study, we aimed to research the relation between SII and prognosis in COVID-19 patients.

Methods: 315 cases (males, 136 ; females, 179 ; 63.2 ± 11.4 years) with positive PCR and lung tomography evidences compatible with COVID-19 pneumonia were recorded in the research. Patients were separated into 2 groups according to the mortality (Group 1; Surviving patients, Group 2; Ex patients). Clinical, demographic, and laboratory datas for whole patients were registered Laboratory datas were measured from blood parameters taken during hospitalization. The SII was calculated as " SII = neutrophil count × platelet count / lymphocyte count ".

Results: The mean hospital stay of the patients is 12 (5-26) days. When the patients were assessment of according to clinical features, an important distinction was found between the two groups according to age, gender, cardiovascular disease, chronic renal failure, neurolvascular disease, and diabetes mellitus. When the patients were evaluated according to laboratory parameters, white blood cells, neutrophils, creatinine, D-Dimer, ferritin, CRP values were observed to be significantly higher in Group 2 patients than Group-1 patients. However, lymphocyte count, serum potassium level, albumin and calcium levels were observed to be significantly lower in Group-2 patients than in Group-1 patients. SII level was significantly higher in Group 2 patients than Group-1 patients (1813.4 ±118.7 vs 978.2 ± 93.1, p<0.001).

Conclusions: Our results suggested that a relation between a higher SII value and a death in COVID-19 patients. As a simple parameter, SII is a significantly estimating of death in COVID-19 patients.

Key words: COVID-19, inflammation index, prognosis

DOI: 10.5798/dicletip.

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COVID-19 Hastalarında Sistemik İmmün İnflamasyon İndeksi ile Prognoz Arasındaki İlişki

Öz

Amaç: İnflamasyon ve pıhtılaşma, COVID-19 hastalarının patofizyolojisinde önemli bir rol oynamaktadır. Sistemik immün inflamasyon indeksi (SII) yeni bir prognostik ve inflamasyon indeksidir. Araştırmamızda COVID-19 hastalarında SII ile prognoz arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Araştırmaya PCR pozitif ve akciğer tomografisi bulguları COVID-19 pnömonisi ile uyumlu 315 hasta (erkek, 136 ; kadın, 179 ; 63.2 ± 11. yıl) kaydedildi. Hastalar surveye göre 2 gruba ayrıldı (Grup 1; Sağ kalan hastalar, Grup 2; Ex olan hastalar). Tüm hastaların klinik, demografik ve laboratuvar parametreleri kaydedildi. Laboratuvar parametreleri hastanede yatış sırasında alınan kan parametrelerinden ölçüldü. SII, " SII = trombosit sayısı × nötrofil sayısı / lenfosit sayısı olarak hesaplandı.

Bulgular: Hastaların ortalama hastanede kalış süresi 12 (5-26) gündür. Hastalar klinik özelliklerine göre değerlendirildiğinde, yaş, cinsiyet, kardiyovasküler hastalık, kronik böbrek yetmezliği, nörovasküler hastalık ve diabetes mellitus açısından iki grup arasında önemli bir fark bulundu. Hastalar laboratuvar parametrelerine göre değerlendirildiğinde Grup 2 hastalarında, Grup 1hastalarına göre beyaz küre, nötrofil, kreatinin, D-Dimer, ferritin, CRP düzeyleri anlamlı olarak yüksek bulundu. Ancak lenfosit sayısı, serum potasyum düzeyi, albümin ve kalsiyum değerleri Grup-2 hastalarında Grup-1 hastalarına göre anlamlıi düzeyde düşük bulundu. Grup 2 hastalarında SII düzeyi Grup-1 hastalarına göre önemli derecede yüksekti (1813,4 ±118,7 vs 978,2 ± 93,1).

Sonuçlar: Sonuçlarımız, COVID-19 hastalarında daha yüksek bir SII seviyesi ile mortalite arasında bir ilişki olduğunu göstermiştir. Basit bir biyobelirteç olarak SII, COVID-19 hastalarında mortalitenin bağımsız bir öngörücüsüdür.

Anahtar kelimeler: COVID-19, inflamasyon indeksi, prognoz.

INTRODUCTION

The Coronavirus disease-2019 (COVID-19) disease is a signficant causes of pandemia[1]. A significant portion of COVID-19 patients have non-serious disease. However, about 15-20% of cases have a serious illness, so hospitalization is required[2]. In recent years, it has been investigated that the inflammatory reaction has a significant role in viral infections. Inflammatory response is responsible for serious complications in patients with COVID-19. (pulmonary complications, ARDS, septic shock, multiorgan failure)[3]. Routine blood tests that evaluate the inflammatory state are beneficial in the early determination of some illness. Especially, whole blood count is a parameter that can be easily performed in every center, is inexpensive, and provides important information.

Peripheral white blood cell (WBC) subgroups are useful in predicting the systemic inflammatory response and prognosis[4].

Neutrophils are a significant parameter of the inflammatory reaction. Neutrophil count is regulated by epithelial cells, mast cells, and macrophages. Lymphocytes have a significant effect in both infection and inflammation. Thrombocytes are involved in coagulation, hemostasis, angiogenesis, and inflammatory reaction. SII is an index dependent on neutrophil, platelet and lymphocyte counts. SII is computed from the formula "platelet x neutrophil / lymphocyte". SII is an index that reflects both inflammatory and immune status[5]. In some studies, SII has been shown to be involved with outcome in cancers and inflammatory diseases[6].

However, clinical studies researched the association among SII and the prognosis of COVID-19 cases are limited. The objectives of this research is to detect the relationship between SII and in-hospital death in cases with the identification of COVID-19.

METHODS

Study participants and design

Patient selection

315 patients with PCR positive and chest tomography results appropriate for hospitalized with the identification of COVID-19 pneumonia were retrospectively registered in this study between 1 April 2021 and 30 June 2021. Cases were separated into 2 groups with respect to the mortality (Group 1: Surviving patients, Group 2: Ex patients). Clinical, demographic, and laboratory parameters for all patients were registered. Complete blood count parameters were studied using Mindray BC 6800 device (Mindray Building, High-Tech Industrial Park, China). The biochemical parameters and CRP were studied using ARCHITECT c16000 (Abbott Laboratories, USA) device. Among the biochemical parameters, ferritin was studied using PCT Cobas e601 (Roche diagnostics, Germany), D-Dimer was studied using IL ACL TOP 500 (Instrumentation Laboratory, Werfen Company, Spain) devices. Laboratory parameters were measured from blood parameters taken during 24 hours of hospitalization. The SII was described as“ SII = platelet count × neutrophil count / lymphocyte count ”. The study was approved by the ethics committee of Health Sciences University, Gazi Yaşargil Education and Research Hospital (817-2021).

PCR Analyses for COVID-19

Nasopharyngeal swab technique (nose or throat) for specimen collecting for COVID-19 based upon the disease control recommendations for COVID-19[7]. Nasopharyngeal and oropharyngeal specimens were gathered from the cases by swabs (Citotest Scientific Co, Haimen City, PR China). The swab materials were put into 3 ml aseptic viral carrying material (Citotest Scientific Co) in the course of the gathering and carried with biohazardous sample pouch. Thereafter the specimen were received, they were carried to the PCR analyses laboratory and tested about a few hours. Specimens were swirled previous to analysis and a adjusted pipette was utilized to carry the specimen volume defined in producer’s directives for utilization. The molecular identification methods include the analysis of nucleic acids present in the sample to detection the virus. The identification of COVID-19 was done by reverse transcription-polymerase chain reaction (RT-PCR) testing utilizing the CFX96 Real-Time System (Bio-Rad, USA)[8]. Identification was made with the RT-PCR kits, the Bio-Speddy (Bioeksen R&D Technologies Inc. COVID-19 RT-qPCR Detection Kit v2.0, Istanbul, Turkey). Viral RNA subtraction from specimen were carried to with respect to the producer’s directives. In order to automated viral nucleic acid subtraction process CFX96 Real-Time System (Bio-Rad, USA) was utilized. A negative (human specimen control) was contained in each RNA subtraction process, and a non formwork (water) control was contained in each RT-PCR actuate. An interior control magnification was carried out to observe RNA subtraction and RT-PCR quality.

Statistical Analysis

Statistical analysis was carried out utilizing the SPSS for Windows (Version 16.0; SPSS Inc., Chicago, IL, USA). All clinical variables were calculated. The continuous variables were showed as mean ± SD. The Kolmogorov–Smirnov test was utilized to define the normal dispersion of the variable. The Mann-Whitney U test was used. The categorical variables were demonstrated as frequencies and percentages. Chi-square test was utilized to crosscheck this type of parameters. The receiver operating characteristic (ROC) calculation was carried out to assessment the capability of SII in estimating clinical prognosis. Spearman Rank correlation analysis was performed. Multivariate logistic regression analysis was implemented to analyze the relation between SII and clinical findings. A p value of < 0.05 was contemplated statistically important.

RESULTS

Patient characteristics

Baseline clinical parameters of the 315 research cases are listed in Table I. Mean patient age was 63.2 ± 11 years, and 179 of the patients (56%) were female. Cardiovascular comorbidities contained arterial hypertension (n = 51), systolic heart failure (n = 7), coronary artery disease (n = 19), diabetes mellitus (n = 52), renal failure (n=10), and cerebrovascular disease (n=4), (Table I).

Table I: Demographic and clinical features of COVID-19 patients

	Surviving patients (n=295)	Ex patients (n=20)	p value
Age (years)	57.2 ± 17.7	74.5 ± 19.8	0.013
Gender (F/M)	171 / 124	8 / 12	0.046
Smoking, n	94	7	0.723
Heart failure, n	6	1	0.592
Hypertension, n	47	4	0.061
Coronary artery disease, n	17	2	0.039
Cerebrovascular disease, n	3	1	0.045
Diabetes mellitus, n	47	5	0.036
Chronic kidney disease, n	9	1	0.028

The average hospital stay of the patients is 12 (5-26) days. Based on assessment of patients clinical features, an important distinction was found between the two groups with respect to age, gender, ischemic heart disease, chronic kidney disease, neurologic disease and diabetes mellitus. When the patients were evaluated according to laboratory parameters, white blood cells, neutrophils, creatinine, ferritin, D-Dimer, CRP, SII variables were observed to be significantly higher in ex patients group than surviving patients group. Lymphocyte count, serum potassium level, albumin and calcium levels were observed to be significantly lower in ex patients group than in surviving patients group.

The laboratory parameters of the cases at the admission to hospitalization presentation are demonstrated in Table II. SII was significantly higher in ex patients group than surviving patients group. Analyses of the ROC curve of SII and mortality results shown in Figure 1, when 1152 was set as the cut-off point, SII showed the best predictive value with the receiver operating characteristic analysis (sensitivity: 69% and specificity: 70 %). Area under the curve (AUC) of SII value 0.75 (p=0.006).

Table II: Laboratory features of COVID-19 patients.

Parameters	Surviving patients (n=295)	Ex patients (n=20)	P value
Hemoglobin, g/dL	12.8 ± 1.9	11.9 ± 2.3	0.875
Platelet count, (×10^3/μL)	289 ± 147	197 ± 123	0.619
White blood cell count, (× 10^3/μL)	9.2 ±3.2	11.2 ±4.3	0.037
Neutrophil cell count, (×10^3/μL)	5.4 ± 2.3	8.1 ± 3.2	0.029
Lymphocyte cell count, (×10^3/μL)	1.5 ± 0.9	0.8 ± 0.5	<0.001
Serum creatinine, mg/dL	1.07 ± 0.85	1.34 ± 0.78	0.019
Serum potassium, mEq/L	4.3 ± 0.6	3.3 ± 0.5	0.024
Serum sodium, mEq/L	138.1 ± 3.6	136.4 ± 2.7	0.741
Albumin , g/L	42 ± 8	37 ± 6	<0.001
Calcium , mg/dL	8.97 ± 0.8	8.23 ± 0.7	0.019
C-reactive protein, mg/dL	35.2 ± 26.4	87.1 ± 39.2	<0.001
Ferritin, ng/mL	118 ± 26	352 ± 79	0.014
D-dimer, ng / mL	213 ± 57	495 ± 103	<0.001
SII	978.2 ± 93.1	1813.4 ±118.7	<0.001

SII: SII: Systemic immune inflammation index.

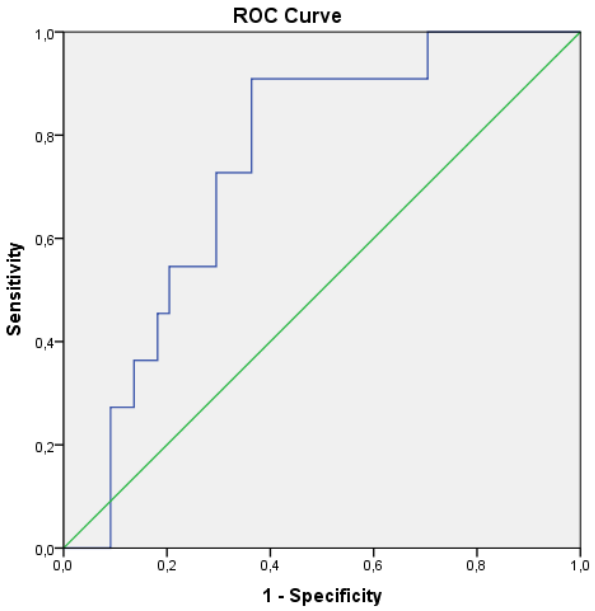

Figure 1: ROC curve analyses of SII and mortality.

SII positively correlated with WBC, D-Dimer, ferritin, CRP and mortality. However, SII negatively correlated with albumin (Table III). Multivariate logistic regression analysis show that, there are a significant relation among SII and WBC, CRP, D-Dimer, albumin, and mortality (Table IV).

Table III: Correlation analysis between SII and clinical parameters in COVID-19 patiens.

Parameters	Sperman's correlation coefficient (*r*)	p Value
WBC	0.562	0.019
CRP	0.497	0.035
Ferritin	0.316	0.042
D-Dimer	0.405	0.032
Albumin	-0.269	0.042
Mortality	0.427	0.024

WBC, white blood cell; CRP, C-reactive protein, SII: Systemic immune inflammation index.

Table IV: Multivariate logistic regression analysis between SII and clinical parameters in patients with COVID-19 infections

Parameters	B	p Value
WBC	0.645	0.037
CRP	0.391	0.029
D-Dimer	0.255	0.045
Albumin	0.279	0.025
Mortality	0.560	0.019

WBC, white blood cell; CRP, C-reactive protein, SII: Systemic inflammation index.

DISCUSSION

COVID-19 is a serious disease. This disease has got a high morbidity and mortality. The clinical manifestations of the disease can vary from mild symptoms to serious symptoms. Herewith, early, easy, fast and reliable tests that support the clinical diagnosis of COVID-19 infection are very important. Early diagnosis ensures early treatment. Until a definitive diagnosis is made with other available methods, treatment is started in the early period. Early treatment also reduces mortality and morbidity.

Zhou F et al. found that increasing death in COVID-19 patients who have atherosclerotic cardiac disease[9]. In our research, coronary artery disease was observed to be significantly high in ex COVID-19 patients. In the research of Yang J et al., they demonstrated that diabetic COVID-19 patients have high mortality[10]. In our study, diabetes mellitus was observed to be significantly high in ex-COVID-19 patients.

Chen YT et al. demonstrated that increasing death in COVID-19 cases with kidney disease[11]. Similarly, in our clinical study, chronic renal failure was associated with high death in COVID-19 patients. Lazcano U et al. found

increasing death in COVID-19 cases with previous cerebrovascular disease[12].

WBC is frequently used as a test in the diagnosis of many diseases and inflammatory processes[13]. Neutrophils are the first defense of innate immunity. Neutrophils have a significant roles in protection against bacterial and fungal infections. The role of neutrophils in viral infections is unknown. However, autopsies of patients with COVID-19 showed that significant neutrophil accumulation in the lung capillaries[14]. Lympopenia has been defined in COVID-19 patients. The cause of lymphopenia depends on the virus binding and infecting T cells with ACE-2 receptors and CD147 spike protein[15]. Neutrophil and lymphocyte parameters are recommended for the diagnosis, advancement and risk calculation of inflammation[16].

Ullah W et al they found that higher values of CRP values at presentation are related with higher in-hospital death in COVID-19 patients[17]. In our study, we found that serum CRP levels were importantly higher ex COVID-19 patients. In a previous research, higher values of serum ferritin were related with hospital death in COVID-19 patients[18]. In our investigation, we found that serum ferritin values were significantly higher ex COVID-19 cases. Danwang C et al found that higher D-dimer concentrations in COVID-19 cases were related with severity and death in these patients[19]. In our research, we found that serum D-dimer levels were significantly higher ex COVID-19 patients. Zerbato V et al suggested that low serum albumin on admission to hospital may determine cases with COVID-19 pneumonia at higher risk of serious respiratory failure and mortality[20]. In our study, we found that serum albumin values were significantly lower in ex COVID-19 cases.

SII is an index developed based on platelets, lymphocytes and neutrophils. SII is a prognostic marker used to evaluate the inflammatory response in patients with sepsis[21]. However, SII can effectively estimate the prognosis in patients with lung and hepatocellular cancer[22].

In a study, it was shown that SII has a diagnostic role in COVID-19 patients. Nalbant A et al they suggested that, SII was significantly higher in intensive care unit patients compared with clinic patients[23]. Our study, we found that relation between a higher SII level and a mortality in COVID-19 cases. ROC analysis was calculated to find the optimum cut-off value of SII. The optimum cut-off value for SII was found to be 1152. In our study, high SII was found to be related with increased mortality. In the study of Fois AG et al., inflammation parameters were found to be associated with survey[24]. As a result of our study, high SII is a significantly estimate of death in COVID-19 cases. Closer monitoring of these cases may reduce mortality.

CONCLUSION

In our retrospective research of COVID-19 patients, it can be concluded that SII may be an important predictor of mortality. Large multicentre and prospective researchs are essential to approve the prognostic power of SII in COVID-19 cases. As a result of these researchs, patients with high-risk COVID-19 can be diagnosed early and appropriate treatment can be started in the early period.

Ethics Committee Approval: The study was approved by the ethics committee of Health Sciences University, Gazi Yasargil Education and Research Hospital (817-2021).

Conflict of Interest: The authors declared no conflicts of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

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