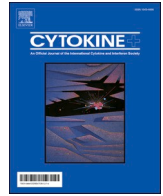




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Prognostic significance of serum galectin-3 in hospitalized patients with COVID-19

Sevgi Özcan^a, Esra Dönmez^{a,*}, Sevil Tuğrul Yavuz^b, Murat Ziyrek^a, Orhan İnce^a, H. Suat Küçük^c, Zeynep Atam Taşdemir^d, İshak Yılmaz^a, Sinan Varol^a, İrfan Şahin^a, Ertuğrul Okuyan^a

^a Bağcılar Training and Research Hospital, Dept of Cardiology, Bağcılar, İstanbul, Turkey

^b Başakşehir Çam ve Sakura City Hospital, Dept of Cardiology, Başakşehir, İstanbul, Turkey

^c Bağcılar Training and Research Hospital, Dept of Biochemistry, Bağcılar, İstanbul, Turkey

^d Bağcılar Training and Research Hospital, Dept of Pulmonology, Bağcılar, İstanbul, Turkey

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ABSTRACT

Background: There are no major tools that could predict disease severity in COVID-19. The aim of this study is to evaluate if serum galectin-3 levels can identify disease progression in COVID-19.

Methods: Patients that were hospitalized due to COVID-19 between March and June 2020 were included in this cross-sectional prospective study. Baseline demographic and clinical data in addition to levels of serum parameters including galectin-3 were measured at the time of hospital admission. Patients with COVID-19 were categorized into two groups (non-severe and severe illness). The need for ICU during hospital stay, duration from hospital admission to the transfer to the ICU, and the total length of hospital stay were recorded.

Results: A total of 175 patients were included in the study and among these, 64 patients formed the severe illness group whereas 111 comprised the non-severe illness group. There was statistically significant difference in terms of galectin-3 levels between groups (1.07 ± 0.75 vs 0.484 ± 0.317 , $p < 0.0001$, respectively). Our results showed that galectin-3, IL-6 and CRP levels at admission were independent risk factors associated with transfer to the ICU whereas only galectin-3 was an independent factor for the need for advanced ventilatory support. Also, galectin-3 and IL-6 were independent risk factors related to in-hospital mortality.

Conclusion: In conclusion, our results indicated that galectin-3 had moderate power in outlining disease severity and the need for ICU transfer throughout the clinical course in COVID-19.

1. Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic still threatens human health around the world. Although most of the patients have a milder clinical course, some face with more severe disease that necessitates intensive care unit (ICU) admission. It might be crucial to indicate these high-risk patients upon hospitalization in order to maximize the efficiency of in-hospital management. Therefore, determining predictive indicators for severe infection has utmost importance [1]. On this regard, biomarkers play important role in predicting the severity and prognosis of COVID-19 [2,3]. The essential biomarkers used to define severe to critical COVID-19 patients were evaluated in a recent meta-analysis, however, no consensus has been achieved [4]. Compared to patients with mild disease, patients with severe disease have

significantly higher levels of inflammatory response reflected by parameters such as lymphocyte count, IL-6, TNF- α , C-reactive protein (CRP) and D-dimer [5,6].

Galectins belong to the family of β -galactocyt-binding lectins that are widely expressed in modulating “cell-to-cell” and “cell-to-matrix” interactions in all organisms and play a central role in inflammation and fibrosis [7]. The biological functions of galectins include development, regulation of immune cell activities, tissue regeneration, and other important cellular functions [7,8]. Increased galectin-3 levels in patients with cardiac fibrosis were found to be associated with longer hospital stay and death [9–12]. Moreover, elevated galectin-3 level was associated with interstitial lung abnormalities and was shown to have a potential role in the early stages of pulmonary fibrosis [13]. Single cell analysis also showed significantly higher galectin-3 levels in

* Corresponding author.

E-mail address: dresradonmez@yahoo.com (E. Dönmez).

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macrophages, monocytes and dendritic cells in patients with severe COVID-19 compared to those who have mild disease [14].

The major cause of fatality in COVID-19 patients, referred as the “Cytokine Storm Syndrome” (CSS), is a direct result of aberrant immune activation following SARS-CoV2 infection and results in excessive release of inflammatory cytokines, such as interleukin (IL)-1, tumor necrosis factor α (TNF- α), and IL-6, by macrophages, monocytes, as well as dendritic cells. Inhibition of galectin-3 reduced the release of IL-1, IL-6, and TNF- α from macrophages in vitro, and as such, may be promising in reducing the incidence of CSS. In addition, galectin-3 inhibition showed promising results in reducing transforming growth factor β (TGF- β) mediated pulmonary fibrosis, likely to be a major consequence in survivors of severe COVID-19 infection [15].

However, little is known about the role of galectin-3 in COVID-19 in the clinical context. In this study, we explored the utility of galectin-3 as a biomarker in COVID-19. We also examined potential correlations between plasma galectin-3 levels and disease severity and patient outcomes as well as the need for the transfer to the ICU.

2. Methods

2.1. Study design and participants

All consecutive patients hospitalized at Bağcılar Training and Research Hospital with a diagnosis of COVID-19 (confirmed by detecting SARS-CoV-2 RNA in oro-nasopharyngeal swab sample) between March and June 2020 were included in this cross-sectional prospective study. Patients were treated according to the Ministry of Health COVID-19 guidelines [16]. Patients under 18 years of age and those with a prior diagnosis of chronic liver disease, idiopathic pulmonary fibrosis and a history of organ transplantation were excluded.

The study was approved by the Institutional Research Ethics Committee. Written informed consent was obtained from all study participants. The STROBE check list for case control studies is used in the study [17].

2.2. Data collection

Clinical data were collected including demographic characteristics (age, gender, education level, occupation and smoking habit); clinical characteristics (self-reported comorbidities, time of symptom onset). Laboratory test results and radiologic findings at the time of admission were noted. Treatments (such as; corticosteroids, intravenous immunoglobulin, antibiotics, antivirals, vitamin C, enoxaparin, N-acetylcysteine (NAC), and hydroxychloroquine), the need for transfer to the intensive care unit (ICU) during the hospital stay, the duration from hospital admission to the transfer to the ICU, and the total length of hospital stay were also recorded.

On admission, patients with COVID-19 were categorized into two groups (non-severe and severe illness) according to the National Institutes of Health (NIH) classification based on disease severity [18]. Severe infection was identified by the presence of any of the following: respiratory rate ≥ 30 breaths/minute; blood oxygen saturation $\leq 94\%$ on room air at sea level; a ratio of the arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) < 300 ; $>50\%$ radiologic progress in 24 to 48 h; respiratory failure necessitating mechanical ventilation, and direct admission to the intensive care unit.

2.3. Definitions

Acute kidney injury (AKI) [19], deep venous thrombosis (DVT) [20], pulmonary embolism (PE) [21], chronic obstructive pulmonary disease (COPD) [22], cerebrovascular accident (CVA) [23], myocardial infarction (MI) [24], hypertension (HT) [25], and diabetes mellitus (DM) [26] were identified according to the accepted definitions. A diagnosis of coronary artery disease (CAD), percutaneous coronary intervention or peripheral

artery disease (PAD) or previous MI or bypass surgery were taken as surrogates of vascular disease.

The primary outcome of our study was to evaluate the relation between galectin-3 levels and in-hospital mortality, need for advanced ventilator support (high-flow oxygen and/or invasive mechanical ventilation therapy), need for transfer to the intensive care unit (ICU) and total length of the hospital stay whereas secondary end points were major cardiovascular ischemic events.

2.4. Blood collection and quantification

Blood samples were collected into yellow top blood tubes without anticoagulant (BD Vacutainer®, Becton, Dickinson and Company, NJ) within 24 h of admission. All serum samples were centrifuged at 1500 rpm for 10 min, the supernatant was taken into Eppendorf tubes and kept frozen at $-80\text{ }^{\circ}\text{C}$. On the day of analysis, the serum samples were thawed by letting them stand at room temperature for at least 1 h. After inverting samples 10 times, analyses were performed within 4 h from the start of thawing. The Galectin 3 level measurements were performed using the ELISA Kit of the Ela Science Diagnostic Company (14780 Memorial Drive, Suite 216, Houston, Texas, USA).

2.5. Statistical analysis

All statistical tests were conducted using the statistical Package for the Social Sciences 19.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyze normality of the data. Continuous data are expressed as mean \pm SD, and categorical data are expressed as percentages. Chi-square test was used to assess differences in categorical variables between groups. Student's *t*-test or Mann Whitney *U* test was used to compare unpaired samples as needed. Variables having linear correlation were evaluated by using Pearson's correlation test and nonlinear variables were evaluated by using Spearman's correlation test. Binary logistic regression analysis was used to identify independent variables of advanced ventilator support, transfer to the intensive care unit, major vascular ischemic events and in-hospital death. Receiver operating characteristic (ROC) curves analysis were used to determine the diagnostic accuracy of IL-6, galectin-3, proBNP and CRP levels for prediction of advanced ventilator support need, transfer to the intensive care unit, major cardiovascular ischemic events, in-hospital mortality. Significance was assumed at a 2-sided $p < 0.05$. Bonferroni adjusted p value of < 0.0056 was considered as statistically significant for multiple comparisons of the given biomarkers.

3. Results

A total of 175 patients were enrolled. Overall, 64 patients (36 male, 28 female) formed the severe illness group and 111 patients (60 male, 51 female) comprised the non-severe illness group. Both groups were similar in terms of age, gender, smoking, rates of COPD, asthma, and CAD. However, number of DM and HT patients were significantly higher in severe illness group (40.60% vs 15.3%, $p < 0.0001$; 35.93% vs 21.62%, $p = 0.031$ respectively). In-hospital mortality was 20% (35 patients). Thirty patients had major vascular ischemic events (19 patients had MI, 5 patients had DVT, and 6 patients had CVA). There was statistically significant difference in terms of galectin-3 levels between severe and non-severe groups (1.07 ± 0.75 vs 0.484 ± 0.317 , $p < 0.0001$, respectively). Additionally, galectin-3 level was significantly higher in diabetics than non-diabetics (1.77 ± 1.17 vs 0.67 ± 0.54 , $p < 0.001$). Concerning biochemical parameters at admission; CRP [34.03 mg/L (0.94–279) vs 18.50 mg/L (0.60–193.5), $p = 0.005$], Pro-BNP (4142.33 ± 834.48 ng/mL vs 816.43 ± 185.12 ng/mL, $p < 0.0001$), IL-6 (1621.64 ± 616.59 pg/mL vs 127.67 ± 68.40 pg/mL, $p < 0.0001$), procalcitonin [0.64 ng/mL (0.01–100) vs 0.05 ng/mL (0.01–98.32), $p < 0.0001$], ferritin [498.50 ng/mL (9.6–15000) vs 222.30 ng/mL (7.0–10286), $p < 0.0001$] and troponin-I [8.65 pg/mL (1.1–4350) vs

3.60 pg/mL (0.90–70.7), $p < 0.0001$] were significantly higher in severe illness group. All demographical, clinical, and biochemical characteristics of the two groups are presented in detail in [Table 1](#).

Correlation analysis was performed to evaluate the associations between length of hospital stay and various parameters. Statistically significant correlation observed only between length of hospital stay and IL-6 levels ($r = 0.294$; $p < 0.0001$ and galectin-3 ($r = 0.213$, $p = 0.005$). Furthermore, correlation analysis between IL and 6, galectin-3 and other biomarkers were performed. Subsequently, moderate positive correlation between IL and 6 and proBNP ($r = 0.601$; $p < 0.0001$), ferritin ($r = 0.515$; $p < 0.0001$), procalcitonin ($r = 0.699$; $p < 0.0001$), troponin-I ($r = 0.517$; $p < 0.0001$) and fibrinogen ($r = 0.413$; $p < 0.0001$) were observed. Likewise, there were moderate positive correlations between galectin-3 and; procalcitonin ($r = 0.428$; $p < 0.0001$), troponin-I ($r = 0.450$; $p < 0.0001$), CRP ($r = 0.419$; $p < 0.0001$). There were weak positive correlations between galectin-3 and proBNP ($r = 0.337$; $p < 0.0001$), ferritin ($r = 0.369$; $p < 0.0001$) and fibrinogen ($r = 0.312$; $p < 0.0001$). Moreover, there was a moderate positive correlation between IL and 6 and galectin-3 levels ($r = 0.438$; $p < 0.0001$).

We also analyzed the correlation between IL and 6, galectin-3 and blood count parameters at admission. Moderate negative correlation between IL and 6 and; lymphocyte count ($r = -0.537$; $p < 0.0001$), RBC

($r = -0.401$; $p < 0.0001$), hemoglobin ($r = -0.451$; $p < 0.0001$) were found. Similarly, moderate positive correlation between IL and 6 and RDW ($r = 0.467$; $p < 0.0001$), Neutrophil/lymphocyte count ratio ($r = 0.408$; $p < 0.0001$), and weak positive correlation between IL and 6 and neutrophil count ($r = 0.258$; $p < 0.0001$) were noted. Moreover, there were weak negative correlations between galectin-3 and lymphocyte count ($r = -0.370$; $p < 0.0001$), RBC ($r = -0.362$; $p < 0.0001$), and hemoglobin ($r = -0.327$; $p < 0.0001$). Furthermore, weak positive correlation between galectin-3 and RDW ($r = 0.369$; $p < 0.0001$), Neutrophil/lymphocyte count ratio ($r = 0.299$; $p < 0.0001$) were observed.

Regression analysis to determine independent risk factors such as advanced ventilator support, transfer to the intensive care unit, major cardiovascular ischemic events (MI, DVT, CVA) and in-hospital mortality was performed according to the adjusted Bonferroni p value. Our results showed that galectin-3 [$p = 0.002$, β : 1.326 OR (95% CI):1.294–1.372], IL-6 [$p = 0.001$, β : 1.126 OR (95% CI):1.100–1.132] and CRP [$p = 0.003$, β : 0.962 OR (95% CI):0.935–0.987] levels at admission to the hospital were independent risk factors linked with transfer to the intensive care unit however, only galectin-3 [$p = 0.004$, β : 1.436 OR (95% CI):1.212–1.624] was found as an independent risk factor for the need for advanced ventilatory support. Furthermore, galectin-3 [$p = 0.001$, β : 1.710 OR (95% CI):1.640–1.750] and IL-6 [$p < 0.0001$, β : 1.001, OR (95% CI): 1.000–1.001] were independent risk factors related to in-hospital mortality. However, none of the variables revealed as independent risk factor associated with occurrence of major ischemic events. Regression analysis data are presented in [Table 2](#).

ROC analysis was performed to evaluate diagnostic accuracy of various parameters for mentioned conditions. A cut-off value of 0.455 for galectin-3 was associated with 71.4% sensitivity and 71.2% specificity (AUC: 0.805; %95 CI: 0.878–0.984) in prediction of the need for advanced ventilator support ([Fig. 1a](#)).

A cut-off value of 0.460 for galectin-3 was associated with 71.4% sensitivity and 72.2% specificity (AUC: 0.802; %95 CI: 0.730–0.879), a cut-off value of 15 for IL-6 was associated with 89.8% sensitivity and 91.2% specificity (AUC: 0.901; %95 CI: 0.826–0.961), and a cut-off value of 30.31 for CRP was associated with 61.2% sensitivity and

Table 1
Clinical and demographic data of two groups.

Variables	Severe group (n = 64)	Non severe group (n = 111)	p
Age (years)	56.90 ± 15.41	54.66 ± 15.34	0.171
Male, n (%)	38 (59.37)	60 (54.05)	0.779
Smoking, n (%)	3 (4.68)	8 (7.20)	0.578
COPD, n (%)	2 (3.12)	4 (3.60)	0.866
Asthma, n (%)	2 (3.12)	6 (5.40)	0.158
CAD, n (%)	5 (7.81)	6 (5.40)	0.534
Hypertension, n (%)	23 (35.93)	24 (21.62)	0.031
Diabetes mellitus, n (%)	26 (40.62)	17 (15.31)	<0.0001
Laboratory findings			
Haemoglobin(g/dL)	10.64 ± 2.16	12.25 ± 1.79	<0.0001
Platelet (10^3 / μ l)	219 (159–511)	212 (157–494)	0.249
WBC (10^3 / μ l)	9.68 ± 6.75	6.86 ± 3.28	0.017
Neutrophil (10^3 / μ l)	7.92 ± 5.07	4.94 ± 2.86	<0.0001
Lymphocyte (10^3 / μ l)	0.68 ± 0.35	1.30 ± 0.75	<0.0001
Neut/Lymp. ratio	7.91 ± 3.11	3.72 ± 2.67	<0.0001
BUN (mg/dL)	31.55 (12.50–132.20)	28.50 (9.10–123.40)	0.796
Creatinine (mg/dL)	1.41 ± 0.89	1.37 ± 0.41	0.204
GFR (mL/dk/1.73 m ²)	72.31 ± 21.43	75.21 ± 16.19	0.318
Sodium (mmol/L)	135.7 ± 3.3	134.3 ± 4.3	0.591
Potassium (mmol/L)	4.2 ± 0.3	4.4 ± 0.2	0.801
Glucose (mg/dL)	140.90 ± 62.30	122.24 ± 55.47	0.006
AST (u/L)	35.12 ± 22.60	31.22 ± 15.80	0.310
ALT (u/L)	25.27 ± 14.80	22.352 ± 15.30	0.360
LDH (u/L)	376.90 ± 34.81	245.71 ± 27.90	<0.0001
Galectin-3 (ng/mL)	1.07 ± 0.75	0.484 ± 0.317	<0.0001
CRP (mg/L)	34.03 (0.94–279)	18.50 (0.60–193.5)	0.005
Pro-BNP (ng/mL)	4142.33 ± 834.48	816.43 ± 185.12	<0.0001
IL-6 (pg/mL)	1621.64 ± 616.59	127.67 ± 68.40	<0.0001
Procalcitonin (ng/mL)	0.64 (0.01–100)	0.05 (0.01–98.32)	<0.0001
Ferritin (ng/mL)	498.50 (9.6–15000)	222.30 (7.0–10286)	<0.0001
Fibrinogen (mg/L)	571.28 ± 135.65	473.03 ± 126.90	<0.0001
D-dimer (ng/mL)	1.14 ± 0.93	0.64 ± 0.47	<0.0001
Troponin-I (pg/mL)	8.65 (1.1–4350)	3.60 (0.90–70.7)	<0.0001

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; GFR: Glomerular filtration rate; IL-6: Interleukin 6; LDH: Lactate dehydrogenase; BNP: Brain natriuretic peptide;

Table 2
Binary logistic regression analysis results of the study population.

Advanced ventilator support	β	p
Galectin-3	1.436	0.004
Pro-BNP	0.215	0.107
IL-6	1.126	0.01
CRP	0.981	0.021
Procalcitonin	0.025	0.241
Troponin-T	0.013	0.139
Transfer to the intensive care unit		
Galectin-3	1.326	0.002
Pro-BNP	0.245	0.128
IL-6	1.126	0.001
CRP	0.962	0.003
Procalcitonin	0.076	0.711
Troponin-T	0.113	0.393
Major cardiovascular ischemic events		
Galectin-3	1.377	0.246
Pro-BNP	1.00	0.006
IL-6	1.00	0.063
CRP	1.001	0.899
Procalcitonin	0.057	0.947
Troponin-T	1.00	0.992
In-hospital mortality		
Galectin-3	1.710	0.001
Pro-BNP	1.000	0.732
IL-6	1.001	<0.0001
CRP	0.980	0.009
Procalcitonin	1.026	0.241
Troponin-T	1.000	0.742

BNP: Brain natriuretic peptide; CRP: C-reactive protein; IL-6: Interleukin 6.

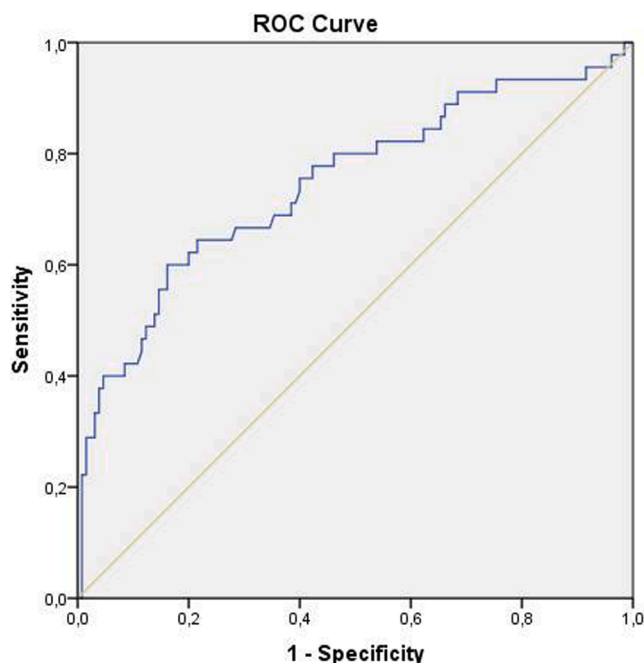


Fig. 1a. ROC curves showing the diagnostic accuracy of galectin-3 need for advanced mechanical ventilation.

61.6% specificity (AUC: 0.649; %95 CI: 0.551–0.762) in prediction of the transfer to the intensive care unit (Fig. 1b).

A cut-off value of 0.552 for galectin-3 was associated with 75.0% sensitivity and 76.8% specificity (AUC: 0.843; %95 CI: 0.771–0.915), a cut-off value of 51.5 for IL-6 was associated with 88.9% sensitivity and 88.4% specificity (AUC: 0.931; %95 CI: 0.878–0.984) in prediction of the in-hospital mortality (Fig. 1c).

4. Discussion

In this prospective study, we demonstrated that; CRP, IL-6, proBNP and galectin-3 levels were significantly higher in severe illness group. There was a positive correlation between galectin-3 and IL-6, procalcitonin, troponin-I, CRP. Our data showed that galectin-3, IL-6 and CRP levels at admission to the hospital were independent risk factors

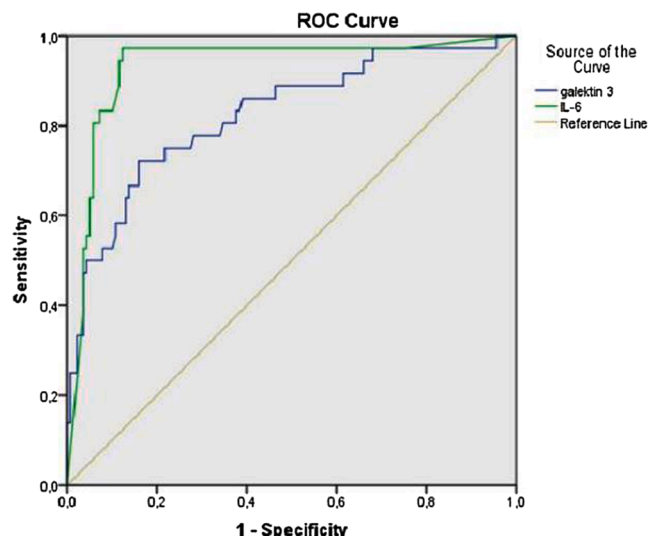


Fig. 1c. ROC curves showing the diagnostic accuracy of galectin-3, IL-6 for in-hospital mortality.

associated with transfer to the intensive care unit, on the other hand, only galectin-3 was found as an independent risk factor for need of advanced ventilatory support. Furthermore, galectin-3 and IL-6 were detected as independent risk factors related to in-hospital mortality. Hence galectin-3 has moderate power in determining outcomes, it may provide additional information for disease severity.

The structural similarity between the N-terminal domain of spike proteins of β -coronaviruses and human galectins-3 may end up with binding the galectin inhibitors to the S1-N-terminal domain of β -coronaviridae, and exhibit a dual benefit in both inhibiting viral attachment and reducing the host inflammatory response [15,27]. There are a few studies showing the association between serum galectin-3 levels and COVID-19 courses. This study is designed to assess this relationship more comprehensively. We found galectin-3 levels were higher in patients with severe COVID-19 disease compared to those with non-severe disease. However, serum galectin-3 levels were moderately positive correlated with IL-6, procalcitonin, troponin-I, CRP; whereas weakly positive correlated with proBNP, ferritin, and fibrinogen. We evaluated the diagnostic accuracy of serum galectin-3 for severe COVID-19 outcomes (in-hospital mortality, major cardiovascular ischemic events, need for advanced ventilator support, intensive care unit transfer). According to our results, galectin-3 has moderate power to predict outcomes; lower than IL-6 and pro-BNP, however, better than CRP.

Pathogenesis and severity of COVID-19 still remain unclear while many different methods such as laboratory parameters, biomarkers, genetic analyzes have been investigated to evaluate its course. Compared with non-severe patients, severe COVID-19 patients had significantly elevated inflammatory biomarkers such as D-dimer, neutrophil/lymphocyte ratio (NLR), CRP and cytokines [6,28,29]. In our study, galectin-3, pro-BNP, procalcitonin, CRP, D-dimer, ferritin, IL-6, troponin-I, LDH, and fibrinogen were observed higher in the severe COVID-19 group compared to the non-severe counterparts, which was consistent with the literature [30].

In previous studies, lymphopenia was associated with the development of acute respiratory distress syndrome (ARDS), while peripheral blood neutrophilia was shown to be an independent predictor of mortality in COVID-19 patients [31,32]. In our study, WBC, neutrophil counts and neutrophil/lymphocyte ratio were significantly higher and lymphocyte counts, hemoglobin levels were significantly lower in the severe illness group than those in the non-severe group. On the other hand, correlation analyses demonstrated that there is weak negative correlation between galectin-3 and lymphocyte count, RBC, hemoglobin levels and weak positive correlation between galectin-3 and RDW,

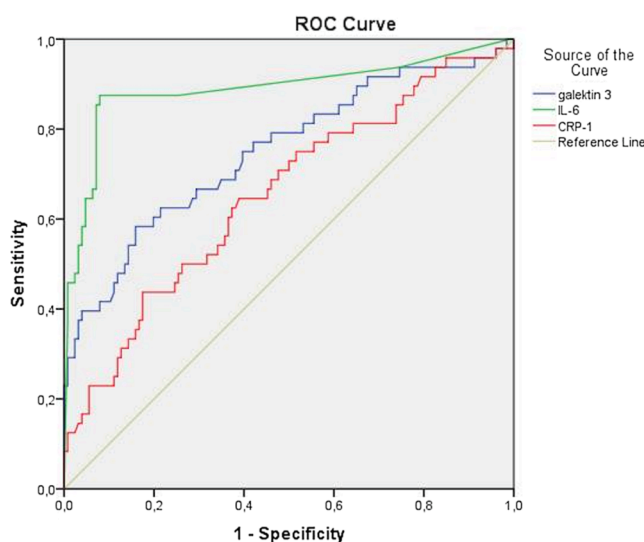


Fig. 1b. ROC curves showing the diagnostic accuracy of galectin-3, IL-6, CRP for transfer to the intensive care unit.

neutrophil/lymphocyte ratio.

Previously, Galectin-3 levels were evaluated in studies with low patient numbers. De Biasi et al. reported a detailed analysis of immune changes in lymphopenic patients with COVID-19 pneumonia and observed elevated galectin-3 levels in patients with COVID-19 pneumonia compared to healthy controls [33]. Kazancioglu et al. evaluated COVID-19 patients with healthy controls where they did a subgroup analysis for severe and non-severe patients. They reported an increase in galectin-1, galectin-3, and prostaglandin E2 levels in patients with COVID-19 than healthy controls [2]. They found no significant association between serum galectin-3 and inflammatory markers such as CRP, IL-6, ferritin, procalcitonin while reporting significant differences between severe and non-severe patients [2]. In another report including serum sFlt-1, PTX-3, and galectin-3 in samples of 70 patients diagnosed with COVID-19 and 31 healthy volunteers, the authors observed galectin-3 had moderate diagnostic accuracy for COVID-19 pneumonia and high diagnostic accuracy for the need for ICU transfer in hospitalized COVID-19 patients [8]. They observed galectin-3 was positively correlated with the most commonly studied inflammatory markers (CRP, IL-6, PTX3, WBC, ferritin), and negatively correlated with serum albumin. It did not correlate with neutrophil, lymphocyte, monocyte count, or neutrophil/lymphocyte ratio (NLR). Although, our results revealed that galectin-3, IL-6 and CRP levels at admission to the hospital were independent risk factors associated with transfer to the intensive care unit, galectin-3 was found to be the only predictor for advanced ventilatory support. Both galectin-3 and IL-6 were observed as independent risk factors for in-hospital mortality. Additionally, we detected weak correlation between galectin-3 and blood count parameters. This may relate to different time periods of blood collection or different patient characteristics with a small sample size.

As it takes a long-time frame to perform studies on large numbers of different populations, bringing out a useful biomarker to use in clinical practice is demanding. So far, no clear prognostic biomarker has been identified for COVID-19, however age and comorbidities are unique parameters in the prognosis of the disease. Considering this, the hyperinflammatory phase is the main feature of severe COVID-19 disease. We suggest that galectin-3 may be used as a biomarker of the inflammatory state in COVID-19 patients given that immune cells can secrete it during the inflammatory process [34,35]. In fact, serum galectin-3 is elevated under the conditions of robust inflammatory states [36]. Furthermore, cardiovascular diseases, pneumonia and diabetes are major risk factors for severe COVID-19 patients, all of which have been shown to increase galectin-3 levels [37,38]. Notably, several previous studies have shown elevated plasma galectin-3 levels in COVID-19 patients which in turn may support galectin-3 to be used as a prognostic marker for severe COVID-19 and high plasma levels of galectin-3 itself may be involved in triggering the cytokine storm observed in severe COVID-19 patients [2,8,36]. Our results indicated plasma galectin-3 levels were significantly associated with in-hospital mortality, need for advanced ventilatory support, transfer to the intensive care unit, length of total hospital stay, which also supports its use as a marker for inflammatory prognosis in COVID-19.

4.1. Limitations

Even though we designed a prospective single-center study with a larger patient population than previously published studies, multicenter studies with an even higher patient number would be optimal to validate the role of galectins in COVID-19 severity prediction as our results may not be generalizable to all patient groups. Although we evaluated predictors of severity for COVID-19, cardiovascular ischemic events were not addressed. Finally, the parameters were achieved only at the time of admission. Our study population consisted of patients in the relatively earlier periods of the pandemic; thus, new variants may alter the prognosis due to changes in inflammation and thrombogenicity. An upcoming study with several galectin-3 level measurements throughout

hospitalization might help clinicians to better estimate which patients might have a worse course.

5. Conclusion

The role of galectins in COVID-19 severity prediction is an important research topic. Our results indicated that galectin-3 had moderate power in outlining disease severity especially the need for transfer to ICU. Hence galectin-3 has moderate power in determining outcomes, it could provide additional information for disease course. Galectin-3 may not only act as an important mediator for disease progression but also may be a potential drug target in COVID-19.

6. Ethical Standard

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Formal consents were obtained from parents.

CRedit authorship contribution statement

Sevgi Özcan: Conceptualization, Investigation, Data curation, Writing – original draft, Formal analysis, Methodology, Project administration, Software, Visualization, Writing – review & editing. **Esra Dönmez:** Conceptualization, Investigation, Data curation, Writing – original draft, Formal analysis, Methodology, Project administration, Software, Visualization, Writing – review & editing. **Sevil Tuğrul Yavuz:** Conceptualization, Investigation, Visualization. **Murat Ziyrek:** Software, Supervision. **Orhan İnce:** Conceptualization, Investigation, Software. **H.Suat Küçük:** Data curation, Writing – original draft, Formal analysis, Validation. **Zeynep Atam Taşdemir:** Methodology, Project administration, Validation. **İshak Yılmaz:** Methodology, Project administration, Software. **Sinan Varol:** Conceptualization, Investigation, Data curation, Writing – original draft, Formal analysis. **İrfan Şahin:** Supervision, Validation, Visualization, Writing – review & editing. **Ertuğrul Okuyan:** Supervision, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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