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# Galectin-3: can it be a diagnostic tool for pneumonia in covid-19 patients?

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**Background/aim:** Biochemical markers are needed to show lung involvement in COVID-19 disease. Galectin-3 is known to play a key role in the inflammation and fibrosis process. We aimed to evaluate the predictive role of galectin-3 levels for pneumonia in patients with COVID-19.

**Materials and methods:** Total of 176 patients with COVID-19, confirmed with reverse transcriptase polymerase chain reaction, admitted to the Erzurum Regional Training and Research Hospital was analyzed. The study was designed as a cross sectional. The baseline data of laboratory examinations, including galectin-3 were collected at the time of diagnosis. CT images evaluated by a single radiologist according to the recommendation of the Radiological Society of North America Expert Consensus Document for pulmonary involvement. The severity of COVID-19 pneumonia was assessed using the total severity score.

**Results:** The mean galectin-3 level in patients with typical pneumonia was found to be significantly higher than those patients with atypical ($p < 0.01$) and indeterminate appearance ($p < 0.01$) and patients without pneumonia ($p < 0.01$). The severity of lung involvement was significantly associated with Galectin-3 levels ($p < 0.01$ r: 0.76). Stepwise logistic regression model showed that the levels of ferritin (odds ratio [OR] = 0.05, p: 0.08) and galectin-3 (OR = 0.1, $p < 0.01$) were significantly and independently associated with typical pneumoniain COVID-19 patients. When COVID-19 patients were evaluated in terms of typical pneumonia, we determined a cut-off value of 18.9 ng/mL for galectin-3 via ROC analysis (87% sensitivity; 73% specificity; area under curve (AUC): 0.89; $p < 0.001$).

**Conclusion:** Galectin-3 was found as a diagnostic tool for COVID-19 associated typical pneumonia and as an indicator of both pneumonia and its severity.

**Key words:** Galectin-3, covid-19, pneumonia

## 1. Introduction

At the end of 2019, a novel coronavirus was identified as the cause of a series of pneumonia cases in Wuhan, a city in Hubei Province of China. The World Health Organization (WHO) named this disease as Coronavirus-2019 (COVID-19) [1]. COVID-19 is typically characterized by fever, dry cough, malaise and it often manifests with pulmonary involvement. The most common finding on computed tomography (CT) imaging, which is the most effective method for detecting lung abnormalities, is bilateral sub-pleural ground glass appearance [2]. Pneumonia is observed with a frequency of 50%–75% during the disease [3]. Acute respiratory distress syndrome (ARDS) with severe respiratory failure is seen in 17%–29% of the patients [4].

The major cause of death in COVID-19 is the aberrant activation of the immune system called the "cytokine storm syndrome" (CSS), which causes severe respiratory failure. Consequently, it results in an overexpression of the inflammatory cytokines, such as interleukin (IL)-1, tumor necrosis factor α (TNF-α), and IL-6 from the macrophages, monocytes, and dendritic cells [5]. Studies have shown thata significant amount of galectin-3 is released from the inflammatory cells in severe COVID-19 patients [6].

Galectin-3 is a carbohydrate-binding protein and it is most highly expressed in tissue resident macrophages. It affects several macrophage functions including efferocytosis of apoptotic neutrophils, phagocytosis and contributes to a pro-fibrotic macrophage phenotype by binding to the trans membrane receptor CD98 and engaging integrins to signal via PI3-K [7].

There is a plethora of evidence emphasizing importance of galectin-3 in prognosis of COVID-19 disease. CSS complicated by the development of ARDS is the major cause of fatality in COVID-19 patients. Elevated serum levels of galectin-3 are significantly associated with worse outcomes and lower survival in patients suffering from ARDS[8]. Additionally, serum galectin-3 levels of patients suffering from severe COVID-19 is significantly elevated than those

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with mild disease [9]. On a cellular level, galectin-3 was shown to be most elevated in immune cells, responsible for initiating CSS, during severe COVID-19 [10,11]. In addition to its effect on inflammation, galectin-3 also plays a key role in the development of fibrosis. In multiple models of organ fibrosis, it has been demonstrated that galectin-3 is potently pro-fibrotic and modulates the activity of fibroblasts and macrophages in inflamed organs [12,13].The role of galectin-3 as a mediator of lung fibrosis has long been studied since the discovery that its levels are elevated in alveolar macrophages following lung injury. Higher levels of galectin-3 have now been extensively associated with the development of restrictive lung diseases [14,15]

CT is often useful in demonstrating lung involvement in COVID-19. Due to the dynamic nature of the disease, exposure to radiation as a result of repeated CT scan and CT findings that are not always associated with symptomatic disease, there is a need for practical bedside testing to assess disease progression. USG is used as a choice to show lung involvement. However, its low sensitivity and specificity is an important limitation for use. In our study, we aimed to investigate the predictive role of galectin-3, which plays a key role in inflammation and fibrotic processes, in pulmonary involvement.

## 2. Materials and methods

### 2.1. Study groups

Patients older than 18 years of age tested for COVID-19 by reverse transcriptase polymerase chain reaction (RT-PCR) and had thorax CT after being admitted to our clinic were considered eligible for inclusion in the study. Patients with negative RT-PCR test results, patients without thorax CT, and thosewho wereusingthe medication forCOVID-19 treatment at the time of application were excluded from the study. The control group consisted of patients with chronic diseases but without COVID-19 clinical findings and negative RT-PCR test andthorax CT scan results for COVID-19. Patients with a positive RT-PCR test result for COVID-19 were evaluated for the presence of pneumonia on a CT scan.

When COVID-19 pneumonia was detected, scoring was performed to assess its severity. Blood samples of all study participants were obtained on admission for the laboratory investigations (hemogram, routine biochemistry, and level of galectin-3). CT scan was performed within the first 24 h after diagnosis. After the results of laboratory and imaging studies were obtained, the relationships between the parameters of infection, blood galectin-3 levels, and CT scan imaging of lung involvement and severity were evaluated.

The ethics committee for clinical researches of Erzurum Regional Training and Research Hospital approved the study protocol (2020/21-206), and signed informed consents were obtained from participants of the study.

### 2.2. Study protocol

Noncontrast thorax CT scan for all participants was performed using a TOSHIBA AQUILLION 64 and was evaluated by a single radiologist according to the recommendation of the Radiological Society of North America Expert Consensus Document for pulmonary involvement [16]. Common imaging features of greater specificity for COVID-19 pneumonia as typical appearance, nonspecific imaging features of COVID-19 as indeterminate appearance, uncommonly or not reported features of COVID-19 as atypical, and the absence of findings suggestive of pneumonia were reported as negative for pneumonia. The severity of COVID-19 pneumonia was assessed using the total severity score [17]. Each lobe in the lungs were evaluated for the severity of the involvement and scored accordingly, ranging between 0 and 4 points. In the scoring system, 0 points were given to the lack of involvement, while 1, 2, 3, and 4 points were given to the degrees of 1%–25%, 26%–50%, 51%–75%, and 76%–100%, respectively. The sum of the scores from 5 lobes was considered as the total severity score.

Blood samples were collected after eight hours of fasting. Automated biochemical and hemogram tests were performed using the ATELLICA (Siemens) and SYSMEX XN – 1000 systems, respectively. RT-PCR testing of nasopharyngeal or oropharyngeal swabs was performed using the Qiagen rotor-gene Q system in the Department of Microbiology, Erzurum Training and Research Hospital.

The ELISA method using the human galectin-3 PLATINUM kit (Ebioscience, Austria) was performed for measuring the levels of galectin-3. All blood samples collected in sodium citrate tubes were centrifuged at 1,000 g for 10 min and stored at –80 ℃ until samples from all participants were obtained for measuring all at once. Other laboratory parameters were studied separately.

### 2.3. Statistical analysis

SPSS v: 17.0 was used for statistical analyses. Numerical variables with normal distribution were shown as mean ± SD. Categorical variables were presented as numbers and percentages. Categorical variables were compared with $\chi 2$ and Fisher's exact $\chi 2$ tests. The difference between the laboratory results of the group with pneumonia and the control group was evaluated by student t test. The differences between the CT findings recommended by the Radiological Society of North America Expert Consensus Document classification and the galectin-3 level were evaluated by ANOVA. post-hoc analysis was used for the differences of subgroups with each other. Pearson's correlation analysis was used to determine the direction and strength of the relationship between the severity of pneumonia, galectin-3 and other inflammation markers. Various markers that could potentially affect patients with typical pneumonia were evaluated by creating a single block with binary logistic analysis. The effect size of the model was evaluated by Nagelkerke R-square. The odds ratio was calculated for markers with potentially significant effects on the development of pneumonia. Possible diagnostic tests for development of typical pneumonia were evaluated with the ROC curve. Area under curve values were calculated, in order to determine which of the diagnostic tests are more valuable. Sensitivity and specificity ratios for galectin-3 were calculated.

## 3. Results

The study was conducted with a total of 176 patients of which, 83 (47.2%) were male and 93 (52.8%) were female. Glucose, creatinine, AST, ALT, D-dimer, fibrinogen, ferritin, CRP, and galectin-3 levels were found to be higher in the patient group. Platelet and lymphocyte counts were lower in the patient group than that of the control group (Table 1).

When the patients are evaluated in terms of lung involvement, no signs of pneumonia were observed in 36 (26.5%) patients. The typical findings for COVID-19 pneumonia were present in 64 (47.1%), atypical findings in 22 (16.2%), and indeterminate appearance in 14 (10.3%) patients.

Among the comorbid diseases, 78 (44.3%) patients had diabetes mellitus, coronary artery disease, hypertension, asthma, and chronic obstructive pulmonary disease. Twenty-two (12.5%) patients had at least two of those diseases. The remaining 10 (5.7%) patients had epilepsy, cerebrovascular disease, prostate Ca, and Hashimoto thyroiditis.

Mean galectin-3 levels were found to be 44.7 ± 23.6 ng/mL in patients with typical COVID-19 pneumonia in Thorax CT; 16.5 ± 9.5 ng/mL in those with atypical findings;15.5 ± 6.7 ng/mL in those with indeterminate appearance while in those with no signs of pneumonia, it was found to be 15.1 ± 8.2 ng/mL (Figure 1). In the post-hoc analysis, the mean Galectin-3 level in patients with typical pneumonia was found to be significantly higher than those patients with atypical ($p < 0.01$) and indeterminate appearance ($p < 0.01$) and patients without pneumonia ($p < 0.01$) (Figure 2).

The severity of lung involvement was significantly associated with Galectin-3 levels ($p < 0.01$, r: 0.76), d-dimer ($p < 0.01$ r: 0.44), fibrinogen ($p < 0.01$, r: 0.58), ferritin ($p < 0.01$, r: 0.51), CRP ($p < 0.01$, r: 0.69), neutrophil/lymphocyte ratio ($p < 0.01$, r: 0.35), lymphocyte/CRP ratio ($p < 0.01$ r: –0.28). When galectin-3 level is evaluated by Radiological Society of North America Expert Consensus Document classification, association was also significant in patients with typical findings (r: 0.62 $p < 0.01$) and with indeterminate appearance ($p < 0.01$, r: 0.88). No significant relationship was found for patients with atypical findings (p: 0.52) (Figure 3).

Stepwise logistic regression model showed that the levels of ferritin (odds ratio [OR] = 0.005, p: 0.08) and galectin-3 (OR = 0.1, $p < 0.01$) were significantly and independently associated with lung involment in COVID-19 patients (Table 2).

**Table 1.** *Demographic and laboratory results of patients.*

| | Patient group N:136 | Control group N:40 | P value |
|---|---|---|---|
| Sex (female) | 69 (50.7%) | 24 (60%) | 0.3 |
| Age | 62.2 ± 14.7 | 58.2 ± 9.3 | 0.1 |
| Glucose (mg/dL) | 118.8 ± 55.9 | 96.1 ± 15.7 | 0.01* |
| Creatinine (mg/dL) | 1 ± 0.48 | 0.7 ± 0.2 | 0.07* |
| AST (IU/L) | 41 ± 25 | 19.7 ± 8.8 | <0.01* |
| ALT (IU/L) | 36 ± 20 | 25.3 ± 13.4 | 0.02* |
| Hemoglobin (g/dL) | 14.4 ± 1.8 | 14.8 ± 2.6 | 0.32 |
| Platelet (K/mm$^3$) | 213.2 ± 61.3 | 276.2 ± 52.1 | <0.01* |
| Wbc (10$^9$/L) | 6.2 ± 2.7 | 8.6 ± 2.6 | <0.01* |
| Lymphocyte (mcL) | 1.5 ± 0.8 | 2.2 ± 0.8 | <0.01* |
| Neutrophil (mcL) | 4.9 ± 6.6 | 5.4 ± 2.6 | 0.43 |
| D-dimer (ng/mL) | 861.9 ± 105.7 | 343.9 ± 174.8 | <0.01* |
| Fibrinogen (mg/dL) | 444.3 ± 136.1 | 335.2 ± 59.7 | <0.01* |
| Ferritin (ng/mL) | 321 ± 127.6 | 67.6 ± 56.6 | <0.01* |
| CRP (mg/L) | 30.9 ± 42.9 | 1.9 ± 2 | <0.01* |
| Galectin-3 (ng/mL) | 29.1 ± 21.4 | 15.5 ± 6.8 | <0.01* |

Abbreviation: AST, aspartate transaminase; ALT, alanine transaminase; Wbc, white blood cell; CRP, C-reactive protein.

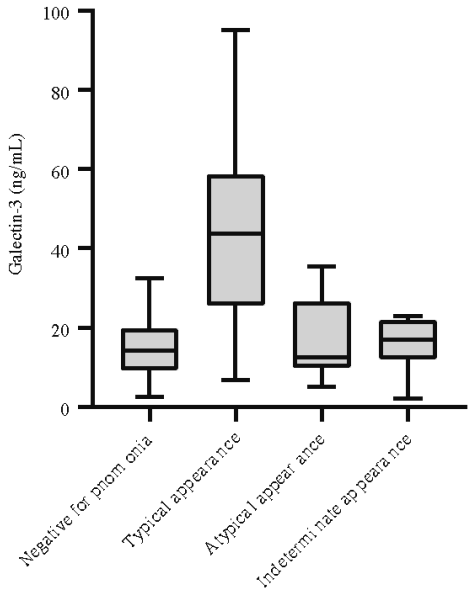


**Figure 1.** CT results with galectin-3 levels (*thorax CT results were evaluated by the recommendation of the Radiological Society of North America Expert Consensus Document).

Mean ratios of neutrophil/lymphocyte (NLR) (4.41 ± 5.03; 2.49 ± 2.12 p: 0.008) and lymphocyte/CRP (LCR) (1.25 ± 4.41; 3.4 ± 4.65 p: 0.03) were significantly different when compared topatients with typical pneumonic infiltration and without pneumonia. There were significant correlations between the severity of pneumonia and NLR (r: 0.35 p < 0.01) and LCR (r: –0.28, p < 0.01)

ROC analysis was performed to evaluate galectin-3, CRP, and ferritin for prediction of typical pneumonia in COVID-19 disease which demonstrated that area under the curve (AUC) of galectin-3, CRP, and ferritin for predicting typical pneumonia were 0.89 (95% Cl 0.83-94 p < 0.01); 0.85 (95% Cl 0.78–0.92 p < 0.01) and 0.79 (95% Cl 0.72–0.86 p < 0.01) respectively. ROC analysis also demonstrated at a cut-off value of 18.9 ng/ml for galectin-3 sensitivity and spesificity were 87% and 73% respectively (Figure 4).

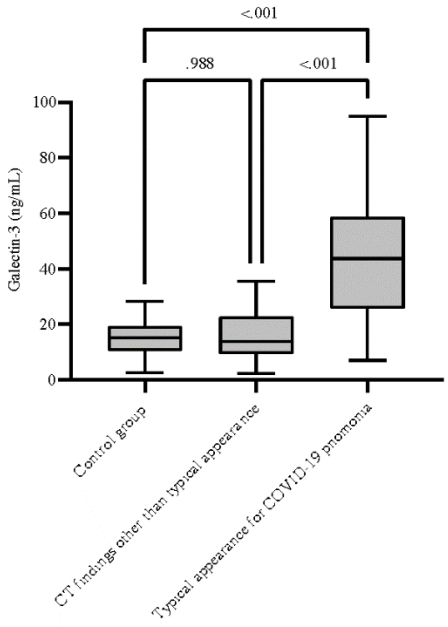


**Figure 2.** Galectin-3 levels and comparison of groups according to CT results.

## 4. Discussion

Pulmonary inflammation in COVID-19 patients significantly affects the prognosis [18]. In our study, we investigated the relationship between lung infection and galectin-3, which has a critical role in inflammation and fibrotic remodeling. We found that the galectin-3 level was a good indicator of lung infection and the severity of involvement in COVID-19 patients.

SARS-CoV-2 primarily causes acute infection in the lungs. Subsequently, the severity of the disease is associated with accompanying hyperinflammation, the release of pro-inflammatory cytokines (cytokine storm), and fibrosis. ARDS develops in 40% of COVID-19 patients, in 20% of which is severe [15]. Galectin 3 is thought to exacerbate inflammation by accumulating macrophages in the lungs, thus, playing a key role in the development of cytokine storm [18]. Zhiheng et al.

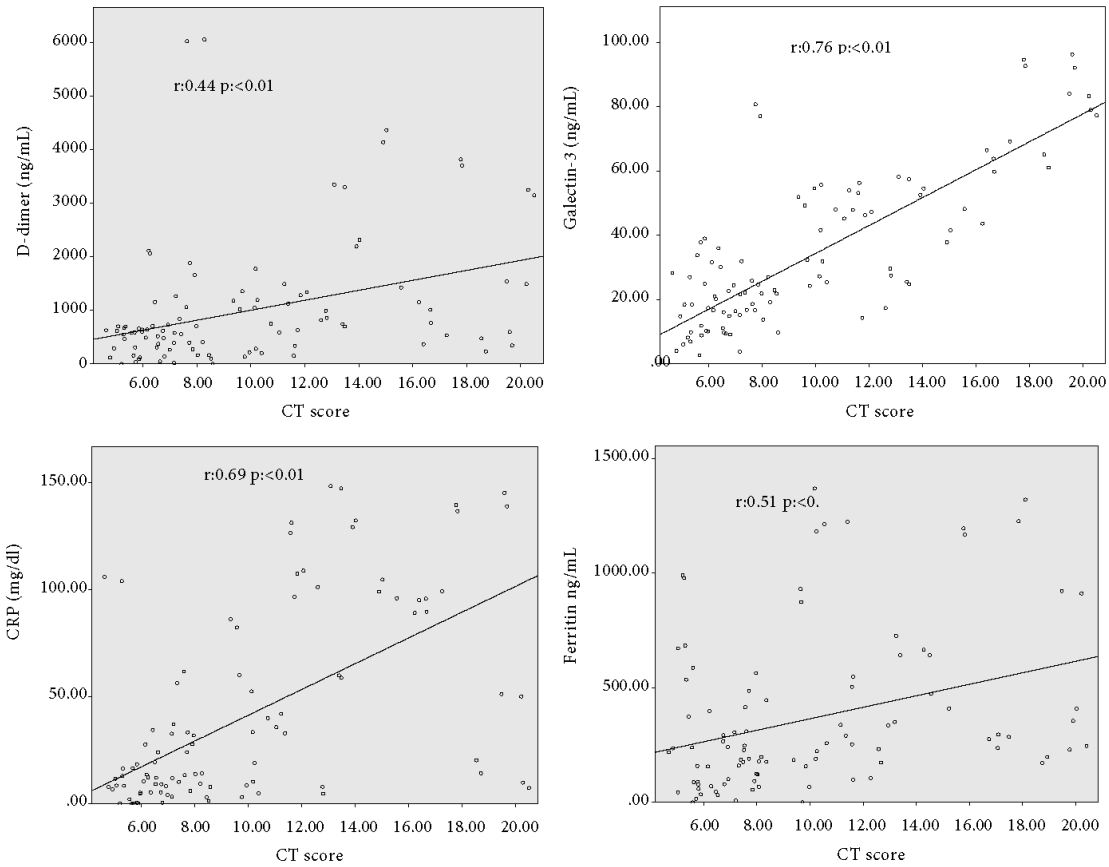


**Figure 3.** Correlation analysis between CT score galectin-3, CRP, D- dimer, and ferritin.

[8] found that the levels of galectin-3 in ARDS patients were high and closely related to the severity of the disease. ARDS is a process that intertwines with fibrosis. High galectin-3 levels have been shown to impair gas exchange and remain high even in the early stages of fibrosis [19]. In other studies, galectin-3 levels were found to be associated with the development of cardiac and renal fibrosis, long hospitalization periods, and mortality [12,13]. In idiopathic pulmonary fibrosis, galectin-3 level was found to be higher in bronchial secretions (BALF) obtained from those patients with the active disease than those with the stable disease. High levels of galectin-3 had been observed to regress after steroid therapy [14].

The diagnosis and the follow-up of lung infection are important in patients with COVID-19. The sensitivity of CT imaging in the diagnosis of COVID-19 disease ranges from 60% to 98% while the specificity ranges between 25% and 53%. In addition to the higher sensitivity compared to the sensitivity of RT-PCR in COVID-19 diagnosis, CT provides information about the progression of the disease [20,21]. Lung infection observed in CT imaging studies does not always relate to the symptomatic disease. Supporting these findings, Hu et al. [22] reported that 70.8% of RT-PCR positive asymptomatic patients had abnormalities in CT scan. Inui et al. [23] observed 44/82 (54%) CT scan abnormalities in 112 asymptomatic and RT-PCR positive patients in the "Diamond Princess" cruise ship. Although typical CT image related to COVID-19is often the bilateral peripheral "ground-glass" opacity, atypical presentations such as hilar consolidation or pleural thickening are also encountered. In order to standardize the findings, various consensus reports have been prepared regarding the CT findings frequently observed during the course of COVID-19 [16,24]. Fang et al. [25] reported the typical and atypical CT features in 78% and 28% of the patients, respectively. Tao et al. [21] observed typical COVID-19 pulmonary features in 60% of the patients. In our study, we detected the typical, indeterminate, and atypical CT findings in 64%, 14%, and 22% of the patients diagnosed by RT-PCR.

**Table 2**. Significant predictors of pneumonia in COVID-19 disease in multivariable logistic regression analysis.

| | OR | 95%Cl lower-upper | P value |
|---|---|---|---|
| Galectin-3 | 0.1 | 1.04–1.17 | 0.01 |
| Ferritin | 0.05 | 1.00–1.01 | 0.08 |
| Nagelkerke $R^2$: 0.51 p < 0.01. | | | |

Abbreviation: Cl, confidence interval, d-dimer, CRP, WBC, galectin-3, ferritin, age, and sex were included in stepwise regression analysis as probable predictors.

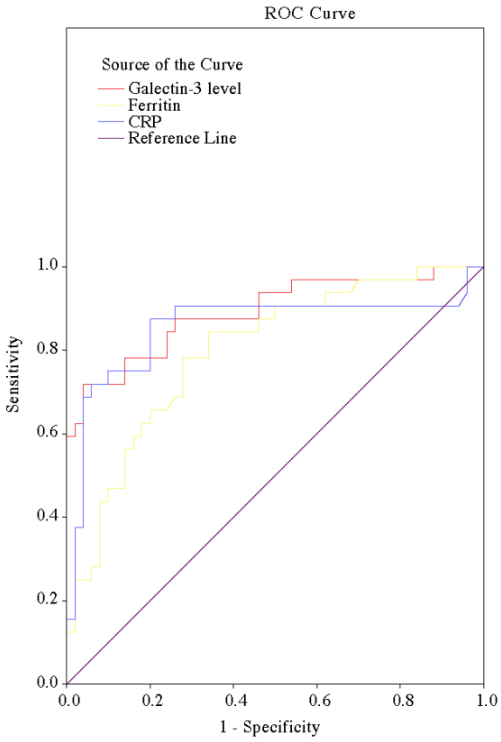


**Figure 4.** ROC curve for galectin-3, CRP, and ferritin in the diagnosis of typical pneumonia.

Although CT imaging is a highly sensitive method, its specificity is low; for instance,similar findings forpneumonia caused by influenza, cytomegalovirus, and miscellaneous agents of atypical pneumonia result in diagnostic difficulties [26]. Another disadvantage of CT imaging for the patient is the exposure to radiation. In particular, more than a single CT scan sessionis required in case of ambivalent results as well as evaluating the prognosis. Although thorax USG can easily be performed at the bedside of the patient and repeated when necessary, the low sensitivity and specificity limit its use in diagnosis and follow-up [20,24]. It is obvious that a rapid and practical procedure is needed to demonstrate the lung infection in COVID-19 patients. As a result of our study, we suspect that galectin-3 levels could be used asan indicator of lung infection (cut-off value: 18.9 ng/mL [0.83–0.94]; sensitivity: 87%; specificity 73%; AUC: 0.89; p < 0.001)

Various studies that have suggested the severity of the COVID-19 varied with gender revealed that male patients had been affected more severely [27,28]. In our study, we did not observe a gender difference in neither the CT score nor the Galectin-3 levels.

High levels of IL-6, CRP, LDH, AST, WBC and notrophil count are associated with respiratory failure in COVID-19 disease [29,30]. Among these markers, harold et al. [29] emphasized that high IL-6 and crp values were an important indicator to show the need for a mechanical ventilator.Although we did not evaluate respiratory failure with blood gas analysis in our study, it was observed that d-dimer, fibrinogen, lymphocytes, ferritin, CRP, NLR, LCR, galectin-3 and AST values were correlated with CT score. Similarly to our results tan et al. [31] reported that CRP ($r = 0.62$, $p <$ 0.01), granulocyte/lymphocyte ratio ($r = 0.49$, $p < 0.01$) and the number of lymphocytes (r = –0.37; p < 0.01) were associated with CT severity score and they observed CRP was found to be significantly increased in the initial phases of the infection for severe COVID-19 patients. We observed the strongest association with CT severity score was high levels of galectin-3 (r: 0.76 p < 0.01) followed by CRP

(r: 0.69 p < 0.01), and ferritin (r: 0.51 p < 0.01).When patients with typical appearance in ct scan were evaluated, this association was also significant for galectin (r: 0.74 p < 0.01), CRP (r: 0.50 p < 0.01) and ferritin (r: 0.27 p: 0.02).

Today, the severity of COVID-19 is best evaluated with CT.It is important to predict the severity of the disease in order to reduce mortality with an effective treatment.Many biomarkers have been studied for this purpose. Among these, CRP, erythrocyte sedimentation rate, IL-6, ferritin, procalcitonin and d-dimer are the most frequently studied [32,33]. Presence of pneumonia provides important information about the prognosis of the disease. In our study, when ROC analysis was performed to predict typical pneumonia for galectin-3, CRP and ferritin, AUC values were 0.89 (95% Cl 0.83–94); 0.85 (95% Cl 0.78–0.92), and 0.79 (95% Cl 0.72–0.86), respectively.

Our study had several limitations. The most important of these is the lack of follow-up for CT scan images in the patients. CT scans in the early period in COVID-19 may not show abnormalities. High galectin-3 levels were detected in patients in whom no signs of pneumonia were detected, possibly due to the early stage of the disease. We consider that the sensitivity of Galectin-3 levels for indicating lung involvement in the disease would increase when the patients who developed pneumonia after follow-up CT scans were included. Other limitations of our study were the small size of the study group and the lack of blood gas results of the patients.

## 5. Conclusion

Pneumonia is an important factor determining mortality in COVID-19 patients. Galectin-3 plays a key role in the inflammation and fibrosis process. Galectin-3 was found as a diagnostic tool for COVID-19 associated typical pneumonia and as an indicator of both pneumonia and its severity.

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## Conflict of interest

The authors do not report any conflict of interest.

## Informed consent

Ethics committee approval was received for this study from the Ethics Committee (2020/21-206). Written informed consent was obtained from the patients who participated in this study.

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