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Effect of galectin-3, IL-1, IL-6 and TNF-alpha on disease prognosis and mortality in COVID-19 patients

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Abstract

Introduction: COVID-19 is a significant cause of morbidity and mortality. It is crucial to identify biomarkers that can aid in predicting patients' prognosis and mortality. This study evaluated the relationship between galectin-3 (Gal-3), interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) levels and the prognosis and mortality of COVID-19 patients.

Methodology: The study included 69 COVID-19 patients (32 outpatients, 37 inpatients) and 19 healthy controls. Gal-3, IL-1, IL-6, and TNF-α levels in serum samples were measured using an ELISA test.

Results: In a comparison between the patient and healthy control groups, it was observed that the patient group had significantly higher levels of Gal-3, IL-6, and TNF-α. Comparison between the outpatient and inpatient groups revealed that the hospitalized patient group had significantly higher levels of IL-6 and TNF-α, while the Gal-3 levels were lower in this group. In the analysis of subgroups to assess disease severity, critical COVID-19 patients exhibited elevated levels of Gal-3 and IL-6 compared to those with severe COVID-19. Moreover, Gal-3 and IL-6 were identified as having predictive value for mortality in hospitalized patients, while both IL-6 and TNF-α demonstrated diagnostic accuracy across all patient groups.

Conclusions: The study results indicate that the levels of IL-6 TNF-α play a crucial role in determining the hospitalization and mortality of COVID-19 patients. Additionally, it was observed that Gal-3 and IL-6 levels can be utilized to assess the severity of the disease and predict mortality in patients who require hospitalization.

Key words: COVID-19; biomarker; galectin-3; IL-6; TNF-alpha.

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Introduction

Coronavirus disease 2019 (COVID-19) has gained importance rapidly due to its ability to induce pneumonia, progress to acute respiratory distress syndrome (ARDS), and lead to death due to multiple organ failure [1]. Considering the course of the disease, it is imperative to search for potential prognostic markers for COVID-19 to delay or stop its progression. The available research suggests that cytokine storms are the primary factor contributing to an unfavorable prognosis and increased mortality rates [2]. The cytokine storm is primarily caused by the release of cytokines, including IL-1, IL-6, and TNF-α [2], as well as proteins, such as Gal-3 [3], produced by monocytes, macrophages, and dendritic cells. Given the correlation between hyperinflammation and COVID-19, there is potential for identifying novel therapeutic targets, particularly in severe cases [2,3].

Gal-3 is mainly expressed in the cell cytoplasm. It is a carbohydrate-binding protein that plays a role in many tasks, such as cell growth, differentiation, angiogenesis, inflammation, and fibrosis [4]. Gal-3 has been identified as having potential roles in severe COVID-19 due to its similarity to the N-terminal domain of the virus's S1 protein. This can lead to hyperinflammation associated with monocytes/macrophages and contribute to the development of fibrous scars by stimulating TGF-β receptors on fibroblasts and myofibroblasts [3,5,6]. IL-1, IL-6, and TNF-α are proinflammatory cytokines essential to immune defense [7-9].

This study aimed to investigate the effectiveness of Gal-3, IL-1, IL-6, and TNF-α in predicting disease prognosis and mortality in COVID-19 patients.

Methodology

Patients

The study was conducted by Çukurova University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, between March 2021 and

May 2021. Sixty-nine COVID-19 patients over 18 years of age who were diagnosed with a reverse transcriptase polymerase chain reaction (RT-PCR) test on nasopharyngeal swab samples, and 19 healthy controls were included. Written informed consent was obtained from all participants who agreed to participate in the study. Patients were evaluated based on the clinical classification in the COVID-19 Guidelines of the Ministry of Health and then divided into two groups. The clinical classification outlined in the Ministry of Health COVID-19 Guidelines [10]:

1. Uncomplicated patient
   a. Symptoms include fever, muscle/joint pains, cough, sore throat, and no respiratory distress (respiratory rate < 24/minute, SpO_2 level > 93% in room air).
   b. And patients with normal chest X-rays and/or lung tomography.
2. Mild to moderate pneumonia
   a. Symptoms include fever, muscle/joint pain, cough, and sore throat; a respiratory rate < 30/min; and a SpO_2 level > 90% in room air.
   b. And patients with mild to moderate pneumonia on a chest X-ray or CT scan.
3. Severe pneumonia
   a. Symptoms include fever, muscle/joint pain, cough, sore throat, tachypnoea (≥ 30/minute), and SpO_2 level ≤ 90% in room air.
   b. And patients with bilateral diffuse pneumonia on a chest X-ray or CT scan.

The initial group was identified as uncomplicated outpatients, while the second group consisted of inpatients with pneumonia who were treated in hospitals. Subsequently, the hospitalized patient group was divided into two subgroups: critical and severe. According to the World Health Organization, COVID-19 classification [11].

This study was approved by Çukurova University Faculty of Medicine Ethics Committee (decision no. 46 dated January 22, 2021) and supported by Çukurova University Research Projects as project number TTU-2021-13577.

Cytokine assay

Gal-3, IL-1, IL-6, and TNF-α values were analyzed with Gal-3 Human Enzyme-Linked ImmunoSorbent Assay (ELISA) Kit (96 Tests) (Cloud-Clone, USA), IL-1 Human ELISA Kit (96 Tests) (DIAsource, Belgium), IL-6 Human ELISA Kit (96 Tests) (DIAsource), TNF-α Human ELISA Kit (96 Tests) (DIAsource). Biomarkers were analyzed using a BiotekELX800 ELISA device following the instructions provided in the ELISA kit manual. Cytokine analyses were conducted on samples obtained from patients within the first seven days of symptom onset.

Statistics

Categorical variables were summarized as frequencies and percentages, while continuous variables were reported as mean and standard deviation, or as median and range (minimum-maximum) or

Table 1. Comparison of variables in patient and control groups.

Variables	Control (n = 19) n (%)	Patient (n = 69) n (%)	*p*
Demographic data			
Age (years, mean ± SD)	48.2 ± 5.5	53.1 ± 18.4	0.263
Male gender	9 (47.4)	38 (55.1)	0.551
Comorbidity			
Chemotherapy history	0 (0)	4 (5.8)	0.283
Diabetes mellitus	4 (21.1)	17 (24.6)	0.745
Hypertension	4 (21.1)	27 (39.1)	0.144
Chronic kidney disease	0 (0)	4 (5.8)	0.283
Heart failure	0 (0)	4 (5.8)	0.283
Coronary artery disease	1 (5.3)	11 (15.9)	0.230
Chronic obstructive pulmonary disease	1 (5.3)	1 (1.4)	0.323
Asthma	1 (5.3)	4 (5.8)	0.929
Neurological system disease	0 (0)	3 (4.3)	0.355
Rheumatological disease	1 (5.3)	1 (1.4)	0.323
Biomarker			
Gal-3 [median (Q1–Q3)], ng/mL	0.0375 (0.025–0.049)	0.248 (0.145–0.351)	< 0.001
IL-1 [median (Q1–Q3)], pg/mL	1.101 (0.737–2.193)	1.465 (0.372–4.379)	0.539
IL-6 [median (Q1–Q3)], pg/mL	13.881 (12.432–31.959)	44.211 (21.844–102.155)	< 0.001
TNF-α [median (Q1–Q3)], pg/mL	13.847 (13.305–14.781)	16.282 (14.379–20.124)	< 0.001

In summarizing categorical data, n (%) were presented as descriptive statistics, while summarizing continuous data, mean ± standard deviation or median (Q1, first quartile to Q3, third quartile) according to distribution type. When comparing the age of the groups, the t-test was used in the independent groups, and the Mann–Whitney U test was used for Gal-3, IL-1, IL-6 and TNF-α. Chi-square test was used in the analysis of categorical data.

interquartile range (Q1-Q3), where appropriate. The chi-square test statistic was used to compare categorical variables between groups. The Kolmogorov-Smirnov test was used to assess whether the numerical variables met the assumption of normal distribution. Independent samples *t*-test was used to compare numerical variables between groups. ROC analysis was performed to test the diagnostic accuracy of Gal-3, IL-1, IL-6, and TNF-α variables, and the area under the curve (AUC) reported along with confidence intervals. The Youden index was calculated to determine the optimum cut-off points. Sensitivity and specificity were presented as measures of diagnostic accuracy. IBM SPSS Statistics Version 20.0 package program was used for the statistical analysis of the data. The statistical significance level was taken as 0.05 in all tests.

Results

Of the patients who participated in the study, 47 (53.4%) were male, 41 (46.6%) were female, and the mean age was 52.0 ± 16.6 years (19-92). Forty-seven (53.4%) of the patients were unvaccinated for SARS-CoV-2, 4 (4.5%) were vaccinated with a single dose, 37 (42%) were vaccinated with two doses, and all vaccinated patients were immunized with the Sinovac inactivated vaccine.

Of the total study population, 36.4% (n = 32) were classified as outpatients, while 42.0% (n = 37) were categorized as inpatients. Among the inpatients, 27 cases were classified as severe, and 10 were classified as critical. The remaining 21.5% (19) of patients were referred to as controls. The mean hospitalization duration of inpatients (n = 37) was 12.6 ± 7.9 (3-45) days. Fourteen patients (37.8%) were hospitalized in the intensive care unit. The mean intensive care unit stay duration was 10.7 ± 6.6 (3-24) days. The characteristics of the patient and control groups are presented in Table 1. Biomarkers Gal-3, IL-6, and TNF-α were significantly higher in the patient group than in healthy controls (Table 1).

Table 2 compares laboratory parameters between outpatients and inpatients who have contracted COVID-19. When comparing the laboratory parameters of outpatients and inpatients, it was observed that inpatients had reduced levels of platelet, lymphocyte, and hemoglobin. The biomarkers revealed that inpatients exhibited elevated levels of IL-6 and TNF-α in comparison to outpatients. Inpatients, on the other hand, exhibited decreases in Gal-3 levels. The values of IL-1 were comparable in both groups, as detailed in Table 2.

When comparing laboratory parameters based on disease severity, critically ill patients had lower platelet, lymphocyte, and hemoglobin levels, while BUN levels were higher. Table 2 shows that critically ill patients had higher levels of Gal-3 and IL-6 biomarkers than other

Table 2. Laboratory characteristics of COVID-19 patients.

Lab. parameter	All patients			Inpatients		
	Outpatient (n = 32)	Inpatient (n = 37)	*p*	Severe (n = 27)	Critical (n = 10)	*p*
CRP, mg/L	7 (1.09–43.8)	61.9 (3.4–264.0)	< 0.001	32.4 (3.4–264)	95.8 (21–145)	0.146
D-dimer, mg/L	0.37 (0.19–1.26)	0.68 (0.19–13.6)	< 0.001	0.6 (0.19–8.68)	1.8 (0.24–13.6)	0.180
Ferritin, ng/mL	52.5 (4.0–372.0)	215.6 (0–9434)	0.001	208.8 (4–1192)	284 (0–9434)	0.448
Leukocyte, 10^3/μL	6,387.5 ± 1,768.3	5,905.6 ± 3258	0.445	5,100 (500–14,400)	5,300 (200–12,300)	0.517
Lymphocyte, 10^3/μL	1,550 (700–3,800)	750 (100–1,800)	< 0.001	900 (200–1,800)	400 (100–1,200)	0.024
Hemoglobin, g/dL	13.9 ± 1.6	12.2 ± 2.2	0.001	12.5 (7.2–16.1)	10.6 (8.4–13.1)	0.008
Thrombocyte, 10^3/μL	22,7843.8 ± 55,760.5	17,3941.7 ± 9,7471.6	0.006	187,000 (14,000–446,000)	127,000 (15,000–210,000)	0.017
LDH, U/L	175 (123–585)	286 (100–654)	< 0.001	215 (100–654)	315 (210–498)	0.128
BUN, mg/dl	13.1 ± 14.6	24.4 ± 23.3	0.019	15.7 (6.6–84.3)	20.3 (13–127)	0.036
Creatinine, mg/dL	0.74 (0.56–7.27)	0.96 (0.50–5.10)	0.017	0.95 (0.5–4.3)	1.04 (0.63–5.1)	0.387
AST, U/L	20 (11–61)	36 (16–116)	< 0.001	33 (16–116)	39 (17–71)	0.590
ALT, U/L	19 (7–66)	23 (6–144)	0.201	25 (11–144)	19 (6–49)	0.146
Biomarker						
Gal-3 [median (Q1–Q3)], ng/mL	0.293 (0.239–0.376)	0.180 (0.064–0.308)	0.007	0.136 (0.023–0.431)	0.2615 (0.136–1.67)	0.007
IL-1 [median (Q1–Q3)], pg/mL	1.465 (0.372–3.104)	2.193 (0.372–4.744)	0.691	2.193 (0.001–16.422)	2.011 (0.009–8.025)	0.724
IL-6 [median (Q1–Q3)], pg/ml	21.844 (17.140–42.770)	75.775 (43.491–192.299)	< 0.001	55.714 (13.157–378.3)	249.838 (43.491–743.936)	0.006
TNF-α [median (Q1–Q3)], pg/mL	14.624 (14.101–18.487)	17.247 (15.564–21.280)	0.001	17.197 (13.424–32.652)	19.199 (12.712–40.491)	0.242

While summarizing continuous data, mean ± standard deviation or median (Q1, first quartile to Q3, third quartile) according to distribution type are presented as descriptive statistics. Mann–Whitney U test was used when comparing groups. CRP: C-reactive protein; LDH: lactate dehydrogenesis; BUN: Blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

groups. However, IL-1 and TNF-α values were similar across all groups.

ROC analysis was used to determine the diagnostic significance of biomarkers that exhibited significant differences between the groups. Those with diagnostic accuracy and their optimum cut-off points are presented in Table 3. Based on the ROC analysis of Gal-3, IL-6, and TNF-α, all three biomarkers showed high diagnostic accuracy, with Gal-3 displaying the best diagnostic discrimination for detecting sick individuals at a level of ≥ 0.094 ng/mL, with a sensitivity of 82.4% and a specificity of 94.4%. These biomarkers significantly differed in the patient and control groups, demonstrating their potential as effective diagnostic tools (Table 3).

The ROC analysis of Gal-3, IL-6, and TNF-α revealed significant differences in their levels between the outpatient and inpatient groups. This indicates that all three biomarkers can be used to determine the need for hospitalization accurately. The diagnostic discrimination of IL-6 is the best at a level of ≥ 39.89 pg/mL with 75% sensitivity and 81.1% specificity. TNF-α has a sensitivity of 68.8% and a specificity of 81.1% at ≥ 15.386 pg/mL. Gal-3 has a sensitivity of 87.5% and specificity of 56.8% at ≤ 0.198 ng/mL (Table 3).

A ROC analysis was performed to assess the diagnostic value of Gal-3 and IL-6 in detecting disease severity in severe and critical COVID-19 patients. The results revealed that Gal-3 with a cut-off value of ≥ 0.175 ng/mL had a sensitivity of 90% and a specificity of 59.3%, while IL-6 at a level of ≥ 219.4 pg/mL had a sensitivity of 60% and a specificity of 96.3%. Both markers were found to have diagnostic accuracy, as shown in Table 3, and were significantly different between the two patient groups.

ROC analysis was also employed to predict mortality and establish biomarkers' diagnostic efficacy in inpatient and outpatient COVID-19 patients. Gal-3 levels at ≥ 0.175 ng/mL demonstrated a sensitivity of 90% and specificity of 59.3% in hospitalized patients. Meanwhile, IL-6 levels at ≥ 219.4 pg/mL showed 70% sensitivity and 100% specificity, indicating that these biomarkers were diagnostically accurate in predicting mortality. Furthermore, the analysis of both inpatients and outpatients determined that a level of IL-6 at ≥ 158.7 pg/mL had 80% sensitivity and 93.2% specificity. In comparison, TNF-α at a level of ≥ 18.14 pg/mL had 70% sensitivity and 71.2% specificity, predicting mortality, as shown in Table 3.

An analysis of patient outcomes revealed that 10 out of 37 patients (27.0%) had died, while 27 (73.0%) were discharged. Among the deceased, two deaths were attributed to cardiac arrest, one to multiple organ failure, and seven to multiple organ failure with concurrent sepsis.

Discussion

This study shows that IL-6 and TNF-α levels are valuable for predicting hospitalization and mortality in all COVID-19 patients, while Gal-3 and IL-6 levels are effective indicators of disease severity and mortality in hospitalized patients.

Gal-3 was reported to be associated with COVID-19 disease severity [12-14] and pneumonia severity [15] in the literature. Moreover, it was disclosed that augmented levels of Gal-3 in patients with acute respiratory distress syndrome (ARDS) are linked with the severity of ARDS and unfavorable prognoses

Table 3. Diagnostic accuracy measures and optimum cut-off points of biomarkers in different patient groups.

Biomarkers	AUC	95% CI for AUC		*p*	Opt. cut-off point	Sensitivity	Specificity
		Lower	Upper				
Gal-3, ng/mL							
Patient vs control	0.929	0.877	0.982	< 0.001	0.094	82.4%	94.4%
Outpatient vs inpatient	0.690	0.561	0.820	0.007	0.198	87.5%	56.8%
Severe vs critical COVID-19	0.787	0.663	0.941	0.008	0.175	90.0%	59.3%
Hospitalized patients	0.813	0.669	0.957	0.004	0.175	90.0%	59.3%
IL-6, pg/mL							
Patient vs control	0.792	0.664	0.920	< 0.001	17.864	85.5%	66.7%
Outpatient vs inpatient	0.835	0.740	0.930	< 0.001	39.890	75.0%	81.1%
Severe vs critical COVID-19	0.793	0.614	0.971	0.007	219.4	60.0%	96.3%
Hospitalized patients	0.883	0.747	1.000	< 0.001	219.4	70.0%	100.0%
Outpatients and inpatients	0.926	0.837	1.0	< 0.001	158.7	80.0%	93.2%
TNF-α, pg/mL							
Patient vs control	0.799	0.705	0.892	< 0.001	14.812	68.1%	88.9%
Outpatient vs inpatient	0.723	0.597	0.849	< 0.001	15.386	68.8%	81.1%
All patients	0.737	0.550	0.925	0.017	18.14	70.0%	71.2%

AUC: Area under curve; CI: confidence interval.

[16,17]. Gaughan *et al*. reported that inhaled Gal-3 inhibitors can reach high serum concentrations in patients with COVID-19 pneumonia, reducing inflammation with a significant decrease in Gal-3 levels [18]. Likewise, the current research revealed that COVID-19 patients exhibit substantially elevated levels of Gal-3 compared to healthy individuals. Moreover, it was established that Gal-3 could be a reliable diagnostic tool for gauging disease severity and mortality rates among hospitalized patients. Nonetheless, including outpatients and inpatients resulted in an ineffective mortality prediction model. This may be due to one potential limitation of the study: the measurement of the plasma Gal-3 levels once without any follow-up measurements. The possible consequences of these factors should be considered regarding the validity and reliability of the results. Hospitalized patients with Gal-3 levels above 0.175 ng/mL were found to have a 90.0% sensitivity and 59.3% specificity for critical illness and mortality. The study revealed that hospitalization rates were notably lower in the inpatient group than in the outpatient group. However, the diagnostic accuracy of determining hospitalization was inconclusive. Therefore, more studies are suggested since Gal-3 is a new molecule, and the previous studies represent small patient groups. In addition, the demonstration of the role of Gal-3 in other viral infections supports its active role in the immunopathogenesis of COVID-19 [19].

IL-1β is an essential element of the innate immune system [20,21]. With increased IL-1β production in COVID-19, IL-6 production is triggered, more innate immune cells are stimulated, and an autoinflammatory cycle is triggered. Research has demonstrated that a significant factor contributing to the destruction of epithelial tissue is the production of IL-1β from monocytes/macrophages. [20,22]. Anakinra treatment, which inhibits the IL-1β receptor, may contribute to treating COVID-19 infection by interrupting the autoinflammatory cycle. Meta-analyses have shown that anakinra treatment administered to COVID-19 patients reduces the mortality rate and the need for invasive mechanical ventilation [23-25]. In the meta-analysis conducted by Qin *et al*., elevated serum IL-1β levels were associated with disease severity and mortality [26]. In another meta-analysis conducted by Zawawi *et al*., the IL-1 level was studied in only four studies, and the IL-1β level was found to be associated with disease severity in only 1 study [27]. No significant result was found regarding the IL-1β level in the current study. However, there is no uncertainty that IL-1β plays a crucial role in the pathological process of COVID-19. The reason why IL-1B was not found to be associated with COVID-19 disease severity and mortality maybe the accumulation of the inactive precursor form of IL-1β in the cytosol until it's activated by auxin-rich repeat pyrene-containing protein-3 (NLRP3) and is, therefore, difficult to be isolated from peripheral blood [21]. The study's limitations section noted that the absence of serial measurements could have been a contributing factor.

Several meta-analyses reported the impact of IL-6 levels on COVID-19 severity and mortality [27-29]. For instance, in the study of Zawawi *et al*., which included 18 studies investigating circulating cytokine levels in patients with COVID-19, MERS and SARS, a significant increase in IL-6 levels was found in patients with severe disease compared to those with non-severe disease [27]. In the meta-analysis of 16 studies, including 8,752 patients, by Zhang *et al*., high IL-6 levels were an independent risk factor associated with adverse outcomes in COVID-19 patients, namely severe illness, admission to the intensive care unit, and mortality [28]. This study, it was significantly higher in the patient group than in the healthy controls, and it had higher diagnostic accuracy in determining hospitalization, disease severity, and predicting mortality in the evaluations that included inpatients and others. It was shown that IL-6 is the biomarker with the highest diagnostic accuracy for determining the need for hospitalization. In addition, IL-6 levels predicted various outcomes with high accuracy. Hospitalization was predicted with 75% sensitivity and 81.1% specificity at levels ≥ 39.89 pg/mL. For critically ill patients, IL-6 predicted severity with 60% sensitivity and 96.3% specificity. In hospitalized patients, a level of IL-6 ≥ 219.4 pg/mL predicted mortality with 70% sensitivity and 100% specificity. Additionally, IL-6 levels ≥ 158.7 pg/mL predicted mortality in all patients with 80% sensitivity and 93.2% specificity.

Recent studies in the field have demonstrated a correlation between COVID-19 severity and mortality and the level of TNF-α, which contradicts previous literature findings [27,29-32]. In the study of Jia *et al*., in which 149 patients were included, TNF-α was detected at higher levels in patients who died and was determined to be an independent risk factor for mortality [31]. In Udomsinprasert *et al*., although the relationship between systemic TNF-α level and disease severity could not be demonstrated, TNF-α level was higher in deceased patients than survivors [29]. Observations align with the findings of Abers *et al*., who also observed a higher TNF-α level in the COVID-19 patient group of 175 patients, compared to the control group. Nevertheless, they observed no

statistically significant differences among severity groups [32]. This study revealed that TNF-α level was significantly higher in patients than healthy controls. Furthermore, it was found diagnostically accurate in predicting the need for hospitalization. However, the diagnostic accuracy of this method in assessing disease severity and mortality among hospitalized patients remained undetermined. In the analysis, including all patients, above 18.14 pg/mL, it predicted mortality, with 70% sensitivity and 71.2% specificity. Therefore, more studies are needed to elucidate TNF-α's role in COVID-19 severity and mortality.

The current data suggests that early hospitalization and timely initiation of treatment protocols lead to better outcomes and lower mortality rates. Expanding the analysis of biomarkers to larger patient cohorts, including those with other viral infections, could provide valuable insights for their evaluation.

Limitations

This study is subject to several limitations. Firstly, the sample size was relatively small, which may limit the generalizability of the findings. Secondly, the analysis was confined to evaluating serum levels of Gal-3, IL-1, IL-6, and TNF-α at the time of admission, without subsequent monitoring of patients' plasma concentrations over time.

Conclusions

Timely medical intervention is essential for COVID-19 patients, as delays in treatment have been associated with increased mortality rates. The findings of this study show that elevated IL-6 and TNF-α levels are indicative of hospitalization and mortality risk in all COVID-19 patients. Furthermore, the research found that Gal-3 and IL-6 levels are useful in assessing disease severity and predicting mortality in hospitalized patients.

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