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Ahmet Yatır **Murat Yücel** **Hatice Turan** **Behçet Varışlı**

Sorumlu Yazar
(Corresponding Author)

Beni Tara!

THE ROLE OF CLAUDİN-5 İN COVID-19 DİSEASE AS A SEVERE ACUTE RESPİRATORY ILLNESS

Abstract: COVID-19 disease typically begins with symptoms of an upper respiratory tract infection and may progress to pulmonary involvement and severe respiratory failure in some patients. The human body possesses several structures that protect against external harmful agents and infections, one of which is claudins. Claudin-5 is predominantly expressed in endothelial structures and is widely distributed in the lungs. This study investigated the relationship between serum Claudin-5 levels and diagnosis and prognosis in patients with COVID-19. Between March and April 2021, a total of 60 patients aged ≥18 years who presented to the emergency department, had a positive real-time polymerase chain reaction (RT-PCR) test, and demonstrated pulmonary parenchymal involvement on chest computed tomography, along with 20 healthy volunteers as a control group, were included in the study. Claudin-5 levels were found to be independently predictive of severe pulmonary involvement (p = 0.018). Following oxygen saturation and respiratory rate, the strongest predictors were C-reactive protein (CRP), creatinine, and urea levels, respectively. Serum Claudin-5 levels are elevated in patients with COVID-19 and may serve as a useful biomarker in diagnosis.

Keywords: COVID-19, Claudin-5, barrier-strengthening proteins, pulmonary involvement, severe respiratory failure

Şiddetli Akut Solunum Yolu Hastalığı Olarak COVID-19 Hastalığında Claudin-5'in Rolü

Özet: COVID-19 hastalığı genellikle üst solunum yolu enfeksiyonu bulgularıyla başlayıp bazı hastalarda akciğer tutulumu ve ciddi solunum yetmezliğine neden olmaktadır. İnsan vücudunda kişiyi dışarıdan gelecek zararlı etkenlere ve enfeksiyonlara karşı koruyan bazı yapılar vardır. Bu yapılarından biri de claudinlerdir. Claudin-5 özellikle endotel yapısında ve akciğerlerde yaygın olarak yer almaktadır. Bu çalışmada COVID-19 hastalarında serum Claudin-5 düzeylerinin tanı ve prognozla olan ilişkisi araştırıldı. Çalışmaya Mart 2021 ile Nisan 2021 tarihleri arasında acil servise başvuran ve yatış planlanan 18 yaş üstü gerçek zamanlı polimeraz zincir reaksiyonu (RT-PCR) testi pozitif, akciğer tomografisinde parankim tutulumu olan 60 COVID-19 hastası ve 20 sağlıklı gönüllüden oluşan kontrol grubu dahil edildi. Claudin-5 seviyelerinin ağır şiddette akciğer tutulumda tek başına belirleyici olduğu görüldü (p=0,018), oksijen saturasyonu ve solunum sayısından sonra en iyi belirleyiciler sırasıyla CRP, kreatinin ve üre değerleri idi. COVID-19 hastalarında serum Claudin-5 düzeyleri yükselmektedir ve tanıda yol gösterici olabilir. COVID-19, Claudin-5, akciğer tutulumu.

Anahtar Kelimeler: COVID-19, Claudin-5, bariyer güçlendirici proteinler, akciğer tutulumu, ciddi solunum yetmezliği,

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INTRODUCTION

On December 31, 2019, 27 pneumonia cases of unknown cause were reported in Wuhan, China. Lung imaging revealed bilateral infiltrates with peripheral predominance, suggesting a viral respiratory infection (Zhu et al., 2020). Subsequently, the causative agent was identified as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and the disease was named Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO). (Dünya Sağlık Örgütü [DSÖ], 2020) On January 30, 2020, WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern, and on March 11, 2020, it was recognized as a pandemic (Sohrabi vd., 2020). Clinically, COVID-19 presents with symptoms such as fever, cough, shortness of breath, muscle pain, headache, sore throat, runny nose, chest pain, diarrhea, and nausea (Chen vd., 2020). Severe disease typically develops with dyspnea and hypoxemia approximately one week after symptom onset, and in advanced stages, it can lead to respiratory failure, multi-organ failure, and death (Berlin, Gulick ve Martinez, 2020). The most widely used and reliable diagnostic test is the real-time polymerase chain reaction (RT-PCR), performed using nasopharyngeal swabs or other respiratory tract samples (Erensoy, 2020). In patients with negative RT-PCR results but clinical symptoms consistent with COVID-19, lung computed tomography (CT) imaging is also helpful for diagnosis (Lieveld vd., 2021).

SARS-CoV-2 is an enveloped, single-stranded RNA virus belonging to the coronavirus family. It enters host cells by binding with high affinity to the angiotensin-converting enzyme 2 (ACE-2) receptor via its spike protein (Asselah, Durantel, Pasmant, Lau ve Schinazi, 2021). After infection, viral replication occurs, inducing acute respiratory distress syndrome (ARDS), triggering an excessive immune response known as a cytokine storm, and causing vascular injury (Amraei ve Rahimi, 2020). Cell polarity and paracellular permeability in endothelial and epithelial cells are regulated by important cellular structures known as tight junctions (TJs) (Zeissig vd., 2007). These junctions function as a barrier by controlling substance passage between epithelial cells. The TJ structure consists of occludins, adhesion molecules, and claudin proteins (Kojima vd., 2013). Claudins are proteins primarily responsible for intercellular permeability. The claudin family constitutes the most abundant transmembrane (TM) proteins in TJs. They were first isolated as junctional proteins from chicken liver in 1998 by Furuse in Shoichiro Tsukita's laboratory (Furuse, Fujita, Hiiragi, Fujimoto ve Tsukita, 1998). Claudins consist of approximately 207 to 305 amino acids and have a calculated molecular weight of 21–34 kDa. (Furuse, Fujita, Hiiragi, Fujimoto ve Tsukita, 1998). They are found in the gastrointestinal system, male reproductive system, and ovaries in females (Fujita vd., 2006). Claudins are essential proteins in the respiratory epithelium and vascular endothelial cells (Kaarteenaho-Wiik ve Soini, 2009). In lung epithelial cells, they are classified as either barrier-strengthening proteins that prevent leakage (e.g., Claudin-1, 3, 4, 5, 7, and 18) or pore-forming proteins that facilitate substance passage (e.g., Claudin-2, 10, and 15) (Krause vd., 2008; Günzel ve Yu, 2013). There are a limited number of studies in the literature related to Claudin-5 (Jang vd., 2011; Soini, 2011). It has been reported that Claudin-5 may serve as a protective factor in preventing endothelial damage in chemically induced tissue-level injuries on the pulmonary endothelium (Soini, 2011). Animal studies investigating the role of Claudin-5 in acute lung injury have shown that it prevents the leakage of inflammatory cells from the endothelium into the alveoli (Jang vd., 2011).

This study aims to evaluate to determine serum Claudin-5 levels in COVID-19 patients according to disease severity and to examine the relationship between diagnosis and prognosis. By

elucidating the role of Claudin-5 in COVID-19, we aim to determine whether it could serve as a potential biomarker or therapeutic target in the future.

Materials and methods

Ethical Approval

This study was conducted with approval from the Scientific Research Platform of the Turkish Ministry of Health following an application submitted on 16.06.2020 (application number: 2020-06-16T10_41_03). Additionally, the study was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University Faculty of Medicine on 25.02.2021 (approval number: OMU KAEK 2021/007).

Study Design and Patient Selection

This study was designed as a prospective, descriptive, and analytical study. It included individuals over the age of 18 who presented to the Emergency Department of Samsun Training and Research Hospital due to COVID-19 between 01.03.2021 and 30.04.2021 and who were subsequently admitted to hospital wards or intensive care units dedicated to COVID-19.

A power analysis based on Claudin-5 levels indicated that, for a 95% confidence interval (1-alpha), 95% test power (1-beta), and an effect size of d = 1.767, a minimum of 10 participants per group (20 in total) would be required using a two-tailed independent samples t-test. During the study period, a total of 150 patients presented to the emergency department. Based on the exclusion criteria, 60 patients and 20 individuals in the control group were included in the study. The patient selection flowchart is shown in Figure 1.

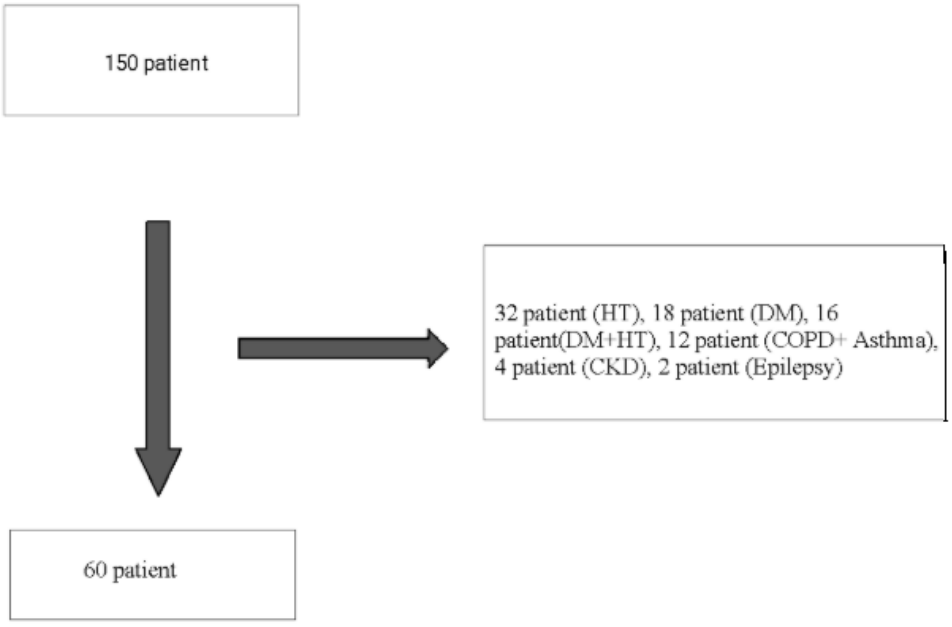

Figure 1: The patient selection flowchart.

Inclusion Criteria

- Age ≥ 18 years
- Positive RT-PCR test for SARS-CoV-2
- Evidence of viral pneumonia on thoracic CT scan

Exclusion Criteria

- Age < 18 years
- History of hypertension or cardiovascular disease
- Diagnosis of diabetes mellitus
- Presence of chronic respiratory disease (e.g., COPD, asthma)
- Diagnosis of cerebrovascular disease or epilepsy
- Presence of chronic kidney disease
- Diagnosis of any malignancy

Study Procedure

Age and gender information for both the patient and control groups were recorded. Patients who presented to the emergency department with positive RT-PCR results and CT findings consistent with viral pneumonia were enrolled. Comorbidities and chronic medication use were documented.

Patients were categorized into three groups based on CO-RADS classification and CT severity scoring:

- Mild viral pneumonia involvement
- Moderate viral pneumonia involvement
- Severe viral pneumonia involvement

The following data were recorded: respiratory rate, oxygen saturation, vital signs, CRP, D-dimer, biochemical parameters (AST, ALT, urea, creatinine, glucose), leukocyte, lymphocyte, and neutrophil counts. The type of hospital admission (COVID-19 ward vs. intensive care unit) and patient outcomes (mortality or discharge) were also noted.

Patients were informed about the study upon admission, and written consent was obtained. Blood samples were collected to measure Claudin-5 levels.

Analysis of Serum Claudin-5 Levels

Venous blood samples obtained from all participants were centrifuged and stored at -80°C until analysis. Serum Claudin-5 levels were measured using a commercially available ELISA kit. The analyses were performed with the Claudin-5 Human ELISA Kit/96 (Bioassay Technology Laboratory®, Shanghai, China) following the manufacturer's instructions. The results were read at a wavelength of 450 nm using an ELISA reader (Tecan® Infinite M200 pro, Austria).

Statistical Analysis

All statistical analyses were conducted using SPSS version 15.0 (Chicago, USA). The normality of the distribution of variables was assessed visually (histograms and probability plots) and analytically (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive statistics were expressed as mean ± standard deviation for normally distributed data, median (minimum–maximum) for non-normally distributed data, and number and percentage for categorical variables.

Independent samples t-test was used for normally distributed variables between two groups. The Mann–Whitney U test was used for non-normally distributed variables. The Kruskal–Wallis test was applied for comparisons among three groups of non-normally distributed variables. Chi-square analysis was used for categorical variables.

Sensitivity and specificity analyses were performed using 2×2 contingency tables in the MedCalc software (MedCalc Software Ltd, Ostend, Belgium). Diagnostic performance metrics such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated. A p-value of <0.05 was considered statistically significant in all analyses.

FINDINGS

A total of 60 COVID-19 patients without comorbidities and 20 healthy individuals were included in the control group. The mean age of the patients was 47.8 ± 14.2 years, while that of the control group was 44.0 ± 8.5 years (p = 0.152). Among the patients, 65% were female and 35% were male; in the control group, the gender distribution was equal (50% female, 50% male) (p = 0.233). (Table 1)

Table 1: Demographic characteristics of the patient and control groups

	Patient (n=60)	Control (n=20)	p value
Age (Mean ± SD)	47,8 ± 14,2	44,0 ± 8,5	0,152†
Gender (N[%])			
Female	39 (65,0)	10 (50,0)	0,233††
Male	21 (35,0)	10 (50,0)	

Lung involvement was classified as mild in 38.3% of the patients, moderate in 35.0%, and severe in 26.7%. Of all patients, 15% were admitted to the intensive care unit (ICU), and 6.7% died due to COVID-19. (Table 2)

Table 2: Clinical Characteristics of the Patients

Characteristic		Value
Prognosis	*N (%)*	
	Deceased	4 (6,7)
	Survived	56 (93,3)
ICU Admission	*N (%)*	
	Yes	9 (15,0)
	No	51 (85,0)
Length of Hospital Stay (days)	*Med (min-max)*	5 (3-26)
Systolic Blood Pressure (mmHg)	*Mean ± SD*	111 ± 14
Diastolic Blood Pressure (mmHg)	*Mean ± SD*	67 ± 10
Lung Involvement	*N (%)*	
	Mild	23 (38,3)
	Moderate	21 (35,0)
	Severe	16 (26,7)
O_2 Saturation (%)	*Mean ± SD (range)*	88,6 ± 6,5 (68-95)
Respiratory Rate (breaths/min)	*Mean ± SD (range)*	17,5 ± 5,2 (12-32)

The laboratory results of the patients are shown in Table 3.

Table 3: Laboratory Results of the Patients

Parameter	Median (min–max)
C-reactive Protein (CRP) (mg/L)	6,5 (1-339)
White Blood Cell Count (WBC) (×10^3/µL)	6,9 (2,6-20,0)
D-Dimer (mg/L)	0,86 (0,21-17,40)
Glucose (mg/dL)	108 ± 24
Urea (mg/dL)	29 (12-104)
Creatinine (mg/dL)	0,6 (0,3-1,7)
Aspartate Aminotransferase (AST) (U/L)	27 (16-104)
Alanine Aminotransferase (ALT) (U/L)	31 (9-124)
Neutrophil Count (×10^3/µL)	4,9 (1,4-16,4)
Lymphocyte Count (×10^3/µL)	1,1 (0,2-3,6)
Neutrophil-to-Lymphocyte Ratio (NLR)	4,0 (0,9-50,0)

Claudin-5 Levels and Related Factors

The median serum Claudin-5 concentration was 6.598 ng/mL in COVID-19 patients and 5.108 ng/mL in the control group. Claudin-5 levels were significantly higher in patients than in the control group (p = 0.005) (Table 4).

Table 4: Claudin-5 Levels in the Patient and Control Groups

Parameter	**Patient Group (n=60**	**Control Group (n=20)**	**p-value**
Claudin-5 (ng/ml)	6,598 (4,069-8,540)	5,108 (2,522-7,812)	*0,005†*

*Data are presented as median (min–max). †Mann-Whitney U test.

ROC analysis revealed that serum Claudin-5 levels alone had a diagnostic value for COVID-19 (AUC = 0.712, 95% CI: 0.600–0.808, p = 0.004) (Figure 2).

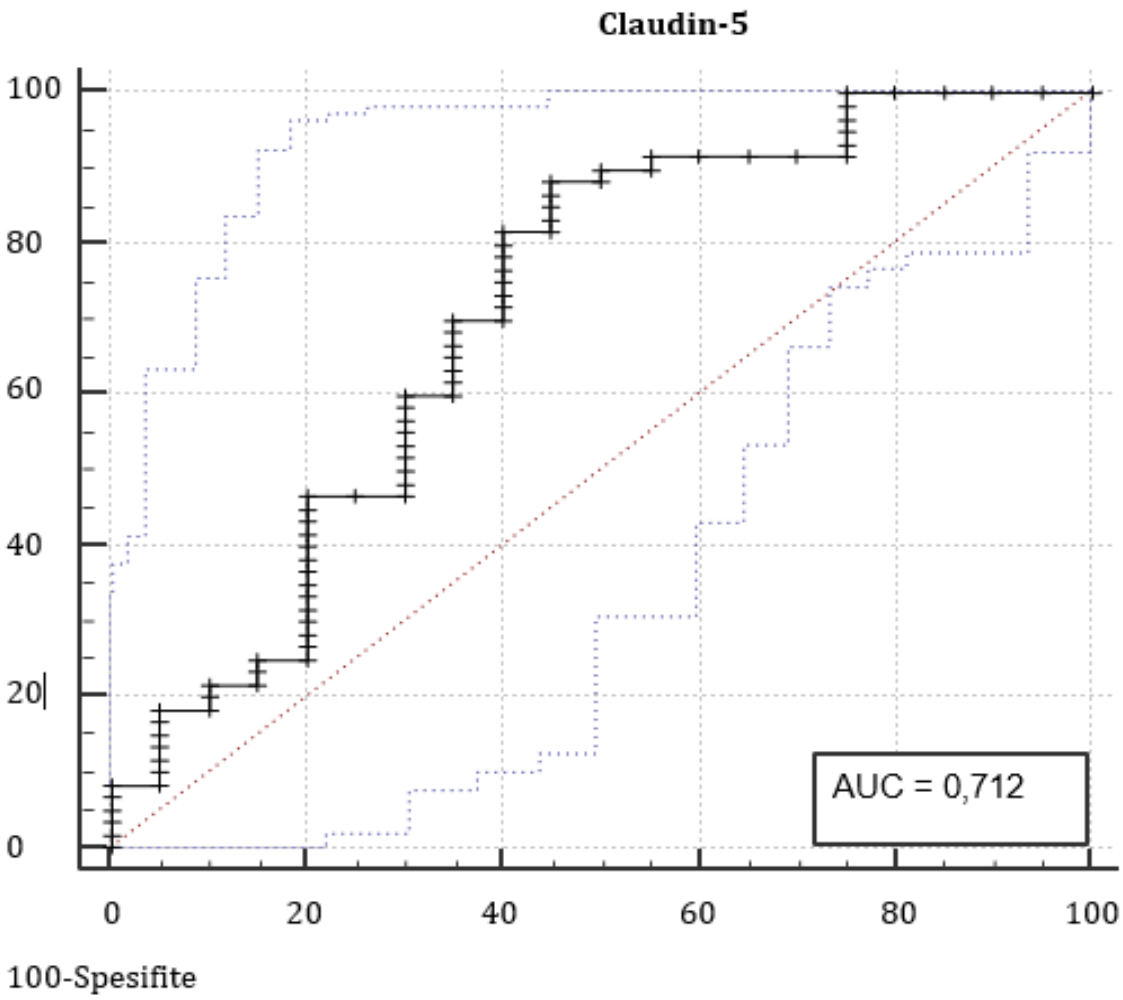

Figure 2: ROC Curve Analysis of Claudin-5 Levels in the Diagnosis of COVID-19

The best diagnostic performance was observed at a Claudin-5 cut-off level of >5.128 ng/mL. A Claudin-5 level above 5.128 ng/mL distinguished COVID-19 patients from the control group with 88.3% sensitivity and 55.0% specificity (Table 5).

Table 5:Diagnostic Performance of Claudin-5 Concentration in the Diagnosis of COVID-19

	Cut-off Value (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cluadin-5 (ng/ml)	>5,128	88,3	55,0	85,5	61,1

**PPV: Positive Predictive Value; NPV: Negative Predictive Value.*

There was no statistically significant difference in Claudin-5 levels by gender in either group (p = 0.310 and p = 0.705, respectively).(Table 6)

Table 6: Distribution of Claudin-5 Levels by Gender in Patient and Control Groups

Gender	Patient (n=60)	Control (n=20)
Female	6,574 (4,069-8,076)	5,108 (2,522-7,086)
Male	6,647 (4,362-8,540)	5,437 (3,767-7,812)
p value	0,310†	0,705†

†Mann-Whitney U test

*Values are expressed as median (min–max).

Additionally, Claudin-5 levels did not correlate with age in either group (p = 0.705 and p = 0.557, respectively). The correlation between age and Claudin-5 levels is shown in Table 7.

Table 7: Correlation Between Age and Claudin-5 Levels in Patient and Control Groups

Age	Patient (n=60)	Control (n=20)
Correlation coefficient	0,050	0,140
p value	0,705†	0,557†

†Spearman correlation test

Claudin-5 concentrations were also analyzed according to patients' clinical characteristics. The median Claudin-5 level was 6.222 ng/mL in deceased patients and 6.607 ng/mL in survivors. However, due to the small number of deaths (n = 4), mortality was not included in the Claudin-5 statistical analysis.

Patients admitted to the ICU had a median Claudin-5 level of 6.827 ng/mL, while those admitted to inpatient wards had a level of 6.554 ng/mL. There was no significant difference in Claudin-5 levels between ICU and ward-admitted patients (p = 0.203).

Due to the clinical relevance of severe lung involvement, patients were categorized into two groups: mild-moderate and severe involvement. The Claudin-5 levels were 6.512 ng/mL in the mild-moderate group and 6.898 ng/mL in the severe group. Claudin-5 levels were significantly higher in patients with severe lung involvement compared to those with mild to moderate involvement (p = 0.030). The relationship between clinical characteristics and Claudin-5 levels is summarized in Table 8.

Table 8: Distribution of Claudin-5 Levels According to Clinical Characteristics of Patients

Characteristic		Value Median (min–max)
Prognosis		
	Deceased	6,222 (4,456-6,827)
	Survived	6,607 (4,069-8,540)
p value		-
ICU		
	Yes	6,827 (4,456-7,966)
	No	6,554 (4,069-8,540)
p value		0,203
Lung involvement	Mild to moderate	6,512 (4,069-8,540)
	Severe	6,898 (4,456-7,966)
p value		***0,030†***

†Mann–WhitneyUtest
††Kruskal–Wallis test

In the ROC analysis, the predictive power of Claudin-5 and other clinical/laboratory parameters for severe lung involvement was evaluated. As expected, the most predictive factors were oxygen saturation (AUC = 0.966) and respiratory rate (AUC = 0.969). However, Claudin-5 levels also independently predicted severe lung involvement (AUC = 0.685, 95% CI: 0.552–0.799, p = 0.018). Following oxygen saturation and respiratory rate, the best predictors were CRP (AUC = 0.878), creatinine (AUC = 0.858), and urea (AUC = 0.844) (Table 9).

Table 9: Diagnostic Performance of Claudin-5, O_2 Saturation, Respiratory Rate, and CRP Levels in Severe Lung Involvement

	AUC	%95 CI	p value
Claudin-5	0,685	0,552-0,799	***0,018***
O_2 Saturation (%)	0,966	0,884-0,996	***<0,001***
Respiratory Rate	0,969	0,888-0,997	***<0,001***
Body Temperature (°C)	0,506	0,373-0,637	0,944
Systolic BP (mmHg)	0,563	0,429-0,691	0,517
Diastolic BP (mmHg)	0,544	0,410-0,673	0,650
CRP (mg/dL)	0,878	0,768-0,948	***<0,001***
WBC (10^3/µL)	0,519	0,386-0,650	0,825
D-Dimer (ng/mL)	0,790	0,666-0,885	***<0,001***
Glucose (mg/dL)	0,714	0,582-0,823	***0,006***
Urea (mg/dL)	0,844	0,727-0,925	***<0,001***
Creatinine (mg/dL)	0,858	0,744-0,935	***<0,001***
AST (U/L)	0,681	0,548-0,796	***0,025***
ALT(U/L)	0,771	0,645-0,870	***<0,001***
Neutrophils (10^3/µL)	0,539	0,404-0,669	0,656
Lymphocytes (10^3/µL)	0,549	0,414-0,679	0,597
NLR	0,540	0,405-0,671	0,639

AUC: area under the curve, CI: confidence interval

The best diagnostic performance of Claudin-5 for severe lung involvement was observed at a cut-off level>6.647 ng/mL, with 75% sensitivity and 65.9% specificity. The diagnostic performance of Claudin-5 and other laboratory parameters is presented in Table 10.

Table 10: Diagnostic Performance of Claudin-5, O_2 Saturation, Respiratory Rate, and CRP Levels in Severe Lung Involvement

	Cut-off Value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Claudin-5	>6,647	75,0	65,9	44,4	87,8
O_2 Saturation (%)	≤86	100	93,2	84,2	100
Respiratory Rate	>18	100	93,2	84,2	100
Body Temperature (°C)	>37,1	93,7	22,7	30,6	90,9
Systolic BP (mmHg)	≤100	43,7	75,0	38,9	78,6
Diastolic BP (mmHg)	≤80	81,3	0	22,8	0
CRP (mg/dl)	>120	75,0	88,6	70,6	90,7
WBC (10^3/µL)	>5,8	75,0	38,6	30,8	81,0
D-Dimer (ng/mL)	>2,16	56,3	90,9	69,2	85,1
Glucose (mg/dL)	>125	50,0	90,9	66,7	83,3
Urea (mg/dL)	>32	87,5	77,3	58,3	94,4
Creatinine (mg/dL)	>0,7	75,0	81,8	60,0	90,0
AST (U/L)	>41	50,0	84,1	53,3	82,2
ALT(U/L)	>33	75,0	81,8	60,0	90,0
Neutrophils (10^3/µL)	>4	80,0	43,2	32,4	86,4
Lymphocytes (10^3/µL)	≤0,8	53,3	65,9	34,8	80,6
NLR	>6,75	46,7	70,5	35,0	79,5

PPV: positive predictive value, NPV: negative predictive value

The ROC curves of Claudin-5, oxygen saturation, respiratory rate, and CRP in severe lung involvement are shown in Figure 3.

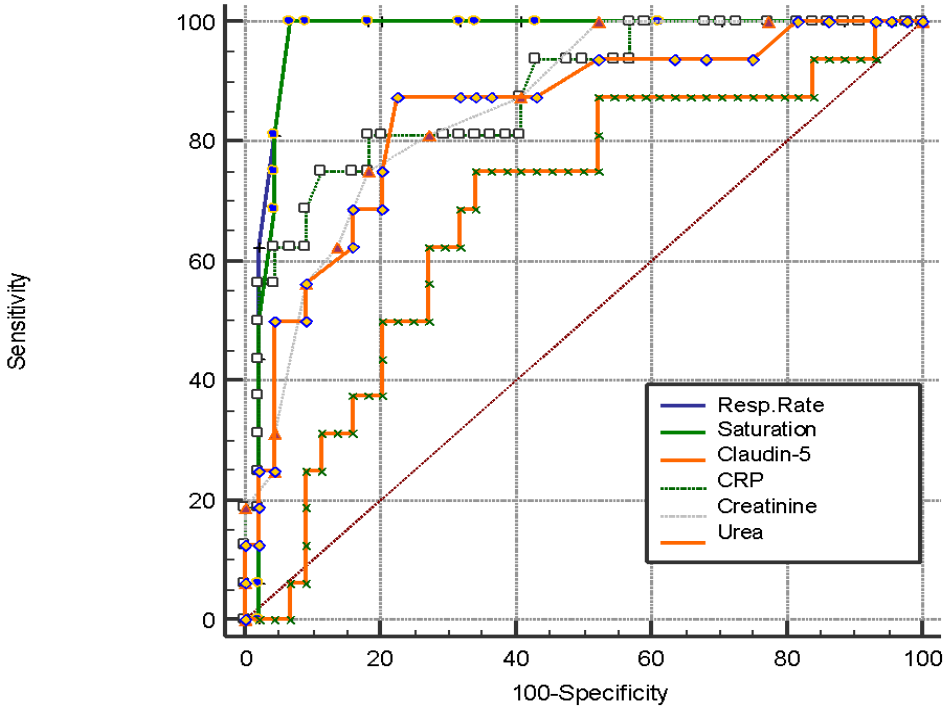

Figure 3: Diagnostic Performance of Claudin-5, O_2 Saturation, Respiratory Rate, CRP, Creatinine, and Urea Levels in Severe Lung Involvement

Among COVID-19 patients, Claudin-5 levels showed a statistically significant positive correlation with respiratory rate (p = 0.031) and systolic blood pressure (p = 0.039). However, no significant correlation was found between Claudin-5 and other clinical or laboratory parameters (Table 11).

Table 11: Correlation of O_2 Saturation, Respiratory Rate, and CRP Levels with Claudin-5 Levels in Patients

	Claudin-5 Correlation Coefficient (r)	p-value
O_2 Saturation	-0,232	0,075
Respiratory Rate	0,279	***0,031***
Body Temperature	-0,016	0,906
Systolic Blood Pressure	0,268	***0,039***
Diastolic Blood Pressure	0,104	0,430
Hospitalization Duration	0,153	0,244
CRP	0,194	0,138
WBC	0,080	0,544
D-Dimer	0,153	0,242
Glucose	-0,089	0,499
Urea	0,088	0,503
Creatinine	0,107	0,417
AST	-0,178	0,173
ALT	-0,039	0,767
Neutrophil	0,040	0,761
Lymphocyte	0,030	0,822
NLR	0,016	0,907

**Spearman correlation test was used for all analyses.*

CONCLUSION

Claudin-5 is expressed in endothelial cells of various organs, including the brain, lungs, liver, kidneys, and skin. However, its expression is reported to be particularly higher in the brain and lung tissues (Daneman vd., 2010; Greene, Hanley ve Campbell, 2019). It is well established that vascular endothelial injury plays a central role in the severe course of COVID-19 infection (Yamaoka-Tojo, 2020). Indeed, autopsy findings of patients who died from COVID-19 have revealed significant endothelial damage (Ackermann vd., 2020). Given that Claudin-5 is primarily expressed by endothelial cells and that alterations in its expression are associated with endothelial dysfunction (Escudero-Esparza, Jiang ve Martin, 2012), this molecule may represent a potential marker for vascular damage related to COVID-19.

In our study, serum Claudin-5 levels were found to be significantly higher in COVID-19 patients compared to age- and sex-matched healthy controls. According to the ROC analysis, Claudin-5 (>5.128 ng/ml) was able to differentiate COVID-19 patients from healthy controls with 88.3% sensitivity and 55.0% specificity. This suggests that Claudin-5 may have diagnostic value as a biomarker. In patients with severe pulmonary involvement, Claudin-5 levels were also significantly elevated and were able to distinguish this group from others with 75% sensitivity and 65.9% specificity. These findings indicate that Claudin-5 may be valuable not only for diagnosis but also for prognosis.

There are a limited number of studies evaluating Claudin-5 levels in COVID-19. Most of these studies are experimental in nature (Yamaoka-Tojo, 2020); Reynolds ve Mahajan, 2021), focusing

on transcriptional changes and lacking clinical comparisons. In this context, our study contributes to the literature by providing clinical data based on serum Claudin-5 measurements.

Claudin-5 levels have also been evaluated in other viral infections. For example, in Dengue fever, a viral infection characterized by plasma leakage, Claudin-5 has been shown to be associated with changes in vascular permeability (Srikiatkhachorn, 2009; Rajapakse, Rodrigo, Maduranga ve Rajapakse, 2014; de Azeredo, Monteiro ve de-Oliveira Pinto, 2015; Suwarto, Sasmono, Sinto, Ibrahim ve Suryamin, 2017). In such infections, Claudin-5 levels have been correlated with disease severity. Furthermore, various other viruses (such as RSV, rhinovirus, coxsackievirus, enterovirus, influenza A/H1N1, HIV, parainfluenza virus, and bocavirus) are known to disrupt tight junction proteins, including claudins (Linfield, Raduka, Aghapour ve Rezaee, 2021). Therefore, it should be considered that the increase in Claudin-5 levels observed in our study may not be specific to COVID-19, but rather may reflect a broader viral endothelial response.

The underlying mechanisms of increased Claudin-5 levels remain unclear. However, studies in acute lung injury models have reported increased Claudin-5 expression. Jang et al. (Jang vd., 2011) demonstrated that Claudin-5 transcription increased following pulmonary edema induced by acrolein in an experimental model. This finding suggests a pathophysiological process similar to that observed in COVID-19, where pulmonary edema is also common (Zwaveling, Gerth van Wijk ve Karim, 2020).

Endothelial cells line the inner surface of blood vessels and are supported by pericytes (Sturtzel, 2017). Pulmonary endothelial cells, in particular, play a critical barrier role between the bloodstream and the interstitial tissue (Zeng vd., 2012 ; 32 Aird, 2007). Dysfunction of these cells is a key feature of ARDS (Matthay, McAuley ve Ware, 2017). Increasing evidence suggests that COVID-19 affects both vascular and pulmonary endothelial cells (Bermejo-Martin, Almansa, Torres, Gonzalez-Rivera ve Kelvin, 2020; Teuwen, Geldhof, Pasut ve Carmeliet, 2020). Comorbidities such as advanced age, diabetes, hypertension, and cardiovascular diseases worsen the prognosis of COVID-19 and are thought to contribute to chronic endothelial dysfunction (Jin vd., 2020).

In our study, Claudin-5 had lower predictive value for severe pulmonary involvement compared to oxygen saturation, respiratory rate, and CRP levels. Therefore, the use of Claudin-5 as a standalone biomarker in clinical practice may be limited. Nevertheless, its involvement in pathogenesis suggests it could be considered a therapeutic target in future studies.

Of the 60 patients with COVID-19 included in our study, four died. Due to the limited number of deaths, Claudin-5 levels in these patients could not be analyzed. However, the positive correlation between severe pulmonary involvement and Claudin-5 levels suggests that this molecule may have prognostic value.

This study has some limitations. The sample size was relatively small, and only patients with pulmonary involvement were included. Additionally, Claudin-5 levels were measured only once, limiting our ability to evaluate temporal changes. Serum levels were measured using the ELISA method, and direct comparisons with tissue-based assessments such as PCR or immunohistochemistry are not feasible. Methodological differences across studies require careful interpretation of findings. Prospective studies with repeated, time-dependent measurements could provide more comprehensive insights into the role of Claudin-5 in disease progression and its therapeutic potential.

In conclusion, Claudin-5 levels are higher in patients with COVID-19 compared to healthy individuals. Patients with severe pulmonary involvement exhibit significantly higher Claudin-5 levels. Clinically, decreased oxygen saturation and increased respiratory rate are important indicators for identifying severe pulmonary involvement. Elevated serum CRP, urea, and creatinine levels were also found to be significant predictors. Serum Claudin-5 levels were diagnostically significant in COVID-19. A positive correlation was observed between Claudin-5 levels and respiratory rate as well as systolic blood pressure in patients with COVID-19. However, it could not be determined whether there was a significant difference in Claudin-5 levels with respect to mortality outcomes. Further studies with larger patient populations are required to evaluate the predictive value of Claudin-5 levels for mortality.

GENİŞLETİLMİŞ ÖZET

Şiddetli Akut Solunum Yolu Hastalığı Olarak COVID-19 Hastalığında Claudin-5'in Rolü

COVID-19 hastalığı tüm dünyada birçok ölüme neden olmuş, insan yaşamını ciddi düzeyde etkilemiş bir halk sağlığı problemidir. COVID-19 hastalığı genellikle üst solunum yolu enfeksiyonu bulgularıyla başlayıp bazı hastalarda akciğer tutulumu ve ciddi solunum yetmezliğine neden olmaktadır. Farklı doku ve organ tutulumlarına neden olarak da hastalarda mortalite ve morbidite artışına sebebiyet vermektedir. İnsan vücudunda kişiyi dışarıdan gelecek zararlı etkenlere ve enfeksiyonlara karşı koruyan bazı yapılar vardır. Bu yapılar arasında sıkı bağlantılar (SB), hücreler arası madde geçişini sağlayan, hücreler arası sinyal iletimine katkı veren ve enfeksiyonlara karşı koruyucu bariyer oluşturan yapılardır. Bu bağlantıların ana yapılarından biri de claudinlerdir. Günümüzde insan vücudunda farklı organ ve yapılarda tespit edilen 27 çeşit claudin bulunmaktadır ve Claudin-5 özellikle endotel yapısında ve akciğerlerde yaygın olarak yer almaktadır. Bu çalışmada COVID-19 hastalarında serum Claudin-5 düzeylerinin tanı ve prognozla olan ilişkisi araştırıldı. Çalışmaya Mart 2021 ile Nisan 2021 tarihleri arasında acil servise başvuran ve yatış planlanan 18 yaş üstü gerçek zamanlı polimeraz zincir reaksiyonu (RT-PCR) testi pozitif, akciğer tomografisinde parankim tutulumu olan 60 COVID-19 hastası ve 20 sağlıklı gönüllüden oluşan kontrol grubu dahil edildi. Serum Claudin-5 düzeyini etkilemesi beklenen ve kronik hastalığı olan kişiler (diyabetes mellitus, hipertansiyon, koroner arter hastalığı, kronik obstruktif akciğer hastalığı, astım, serebrovasküler hastalık, epilepsi, kronik böbrek yetmezliği) çalışmaya dahil edilmedi. Hastaların yaşı, cinsiyeti, solunum sayısı, oksijen saturasyonu, serum C- reaktif protein (CRP) düzeyleri, glukoz, aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), üre, kreatin, D-dimer, nötrofil, lenfosit değerleri, hastanede kalış süreleri ve tomografi bulguları radyolojik olarak COVID-19 veri raporlama sistemi (CO-RADS) şiddet derecesine göre sınıflandırılarak kayıt altına alındı. Hem hastalarda hem de kontrol grubunda serum Claudin-5 düzeyleri Enzyme-Linked Immunosorbent Assay (ELISA) yöntemiyle çalışılarak değerlendirildi. Çalışmaya dahil edilen hastaların yaş ortalaması 47,8 ± 14,2 yıl, kontrol grubunun ise 44,0 ± 8,5 idi (p=0,152). Hastaların %65'i kadın, %35'i erkek, kontrol grubunun ise %50'si kadın, %50'si erkekti (p=0,253). Hastaların %6,7'si COVID-19 nedeniyle kaybedilmişti. Hastaların %15'i YBÜ' ne kabul edilmişti. Akciğer tutulumu hastaların %38,3'ünde hafif şiddetli, %35'inde orta şiddetli, %26,7'sinde ağır şiddetliydi. COVID-19 hastalarının Claudin-5 düzeyi median 6,598 ng/ml, kontrol grubunda ise median 5,108 ng/ml idi ve hastaların Claudin-5 seviyesi kontrol grubundan anlamlı derecede daha yüksekti (p=0,005). Ağır şiddette akciğer tutulumu olanların Claudin-5 düzeyleri hafif-orta şiddette akciğer tutulumu olanlardan anlamlı derecede daha yüksekti (p=0,030). Ağır akciğer tutulumunda en belirleyici faktörlerin

oksijen saturasyonu (p<0,001) ve solunum sayısı (p<0,001) olduğu izlendi. Claudin-5 seviyelerinin ağır şiddette akciğer tutulumda tek başına belirleyici olduğu görüldü (p=0,018), oksijen saturasyonu ve solunum sayısından sonra en iyi belirleyiciler sırasıyla CRP, kreatinin ve üre değerleri idi. COVID-19 hastalarında solunum sayısı (p=0,031) ve sistolik kan basıncı (p=0,039) ile Claudin-5 seviyeleri arasında pozitif yönde anlamlı bir korelasyon izlendi. COVID-19 hastalarında serum Claudin-5 düzeyleri yükselmektedir ve tanıda yol gösterici olabilir. Radyolojik sınıflandırmaya göre ağır şiddette akciğer tutulumu olan hastalarda tanısal ve prognostik değeri olduğu sonucuna varılmıştır.

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MAKALE BİLGİLERİ

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Etik Kurulumuza sunmuş olduğunuz Covid19 Hastalarında Claudin5 Düzeylerinin Tanı ve Prognozdaki Yeri başlıklı OMÜ KAEK 2021/**007** Karar nolu Mikrobiyoloji çalışması nitelikli araştırma projeniz amaç, gerekçe, yaklaşım ve yöntemle ilgili açıklamaları açısından Klinik Araştırmalar Etik Kurulu yönergesine göre incelenmiş ve etik açıdan bir sakınca olmadığına, çalışmanın süresi 6 ayı geçerse 6 aylık bildirimlerinin yapılmasına, çalışma tamamlandıktan sonra sonucunun tarafımıza en geç üç(3) ay içerisinde bildirilmesine 25.02.2021 tarihli Etik kurulumuzda oy birliği ile karar verilmiştir.

Bilgilerinize arz/rica ederim.

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