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Prognostic significance of the chemerin level in coronavirus disease 2019 patients

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Abstract

Increased serum chemerin levels have been reported in several inflammatory diseases. Few studies have investigated the relationship between chemerin and clinical features of COVID-19. Thus, chemerin may modulate the development and progression of COVID-19. We compared the serum chemerin concentration between patients with and without SARS-CoV-2 infection and its association with the severity and prognosis of COVID-19 pneumonia. This is a prospective, single-center, cross-sectional study. We enrolled COVID-19 patients who presented to our tertiary hospital and healthy controls. The COVID-19 patients were conducted and the dates of symptom onset were recorded. After admission to the hospital and stabilization, blood samples were obtained for routine hemogram, biochemistry, and chemerin. The chemerin level was 37.93 ± 17.3 ng/mL in patients followed in the ICU, 29.41 ± 12.79 ng/mL in inpatients, 30.48 ± 10.86 ng/mL in outpatients, and 25.12 ± 9.82 ng/mL in healthy controls. The difference between patients treated in the ICU and healthy controls was significant ($P < .001$). The high-sensitivity C-reactive protein (hs-CRP), ferritin, procalcitonin (PCT), and D-dimer levels were significantly higher in the intensive care unit (ICU) group ($P < .001$). Moreover, the chemerin level of patients who died was significantly higher than that of those who survived ($P < .001$). The chemerin level was increased in COVID-19 patients and also increased with increasing disease severity. The chemerin level was higher in the COVID-19 patients than healthy controls and was significantly higher in patients who died compared to those who did not.

Abbreviations: AS = atherosclerosis, BMI = body mass index, COVID-19 = coronavirus disease 2019, CT = computed tomography, hs-CRP = high-sensitivity C-reactive protein, ICU = intensive care unit, NSE = neuron-specific enolase, PCT = procalcitonin, ROC = receiver operating characteristic, RT-PCR = reverse transcription polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2, TREM = triggering receptor expressed on myeloid.

Keywords: Chemerin, coronavirus disease 2019, intensive care unit, outpatient

1. Introduction

Cases of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), which became a pandemic, were first noticed in Wuhan City of Hubei Province, China in December 2019. The World Health Organization named this viral pneumonia coronavirus disease 2019 (COVID-19). Laboratory conditions and individual circumstances may delay the diagnosis.[1] Symptoms of pneumonia caused by the virus, which spreads rapidly through respiratory droplets and direct contact, include fever, cough, headache, widespread muscle pain, and decreased appetite and sense of smell. Although COVID-19 pneumonia is typically mild, it is fatal in patients with comorbidities such as diabetes, obesity, cancer, and chronic lung and cardiovascular diseases.[1,2] In addition to reverse transcription polymerase chain reaction (RT-PCR), diagnostic imaging such as plain radiography and computed tomography (CT) are important for diagnosing and treating COVID-19.[3,4]

Chemerin is an adipocytokine with pleiotropic effects in humans. In addition to its function as a chemotactic factor in the early phase of the inflammatory response, chemerin exerts an anti-inflammatory effect by suppressing macrophage activation. Chemerin also suppresses acute inflammation at an early stage.[5] An increased serum chemerin level has been reported in various inflammatory diseases.[5–8] Few studies have investigated the relationship of chemerin with the clinical features of COVID-19.[9,10]

Chemerin may modulate the development and progression of COVID-19. We compared the serum chemerin concentration between patients with and without SARS-CoV-2 infection and its association with the severity and prognosis of COVID-19 pneumonia.

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The datasets generated during and/or analyzed during the current study are publicly available.

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2. Materials and methods

2.1. Study design and ethics

This is a prospective, single-center, cross-sectional study. The study protocol was approved by the local scientific ethics committee of Gazi Yasargil Training and Research Hospital (Clinical Research Ethics Committee, Decision No. 786, June 11, 2021). Demographic details, disease severity, and disease symptoms were obtained during one-on-one interviews with the participants and a specialist physician using a preprepared information form.

2.2. Study population

From September 2021 to February 2022, we enrolled COVID-19 patients who presented to our tertiary hospital (affiliated with the University of Health Science, Gazi Yasargil Training and Research Hospital) and healthy controls. The study groups were as follows: Group 1, patients diagnosed with COVID-19 in the outpatient clinic and followed up in the service ($n = 50$); Group 2, patients who were hospitalized and treated in the ICU ($n = 50$); Group 3, outpatients diagnosed with COVID-19 with a good general condition and vital signs, and no lung lesions ($n = 52$); and Group 4, healthy controls with similar demographic characteristics to the patients ($n = 35$).

The patients had complaints such as fever, shortness of breath, nausea, vomiting, weakness, fatigue, loss of appetite, and decreased sense of smell and taste. COVID-19 was diagnosed based on patient history and the results of physical examinations, PCR tests, and radiological and laboratory results. The exclusion criteria were pregnant and breastfeeding women, use of immunosuppressive drugs in the last 6 months, undergoing dialysis for severe liver or kidney dysfunction, immune system disease, organ transplant, cancer, and drug or alcohol addiction.

Individual interviews with the COVID-19 patients were conducted and the dates of symptom onset were recorded. After admission to the hospital and stabilization, 3 blood samples were obtained for routine hemogram, biochemistry, and chemerin. The other 2 samples were centrifuged at $1500 \times g$ for 10 minutes. Blood levels of ferritin, coagulation factors, hemogram, and hs-CRP were analyzed within 1 to 2 hours. The serum was separated from the blood and stored at −80 °C for measurement of the serum chemerin level.

2.3. Reverse transcription polymerase chain reaction

Nasopharyngeal swabs were collected using standard procedures and analyzed using the Bio-speedy SARS-COV-2 (2019-nCoV) RT-qPCR Detection Kit (Bioeksen, Istanbul, Turkey).

2.4. Analysis of the serum chemerin level

Samples were placed in prenumbered Eppendorf tubes and stored at −80°C. Serum chemerin levels were measured using the Human Chemerin ELISA Kit (Sun Red; 201 12-1436) in accordance with the manufacturer's instructions. Absorbance at 450 nm was determined spectrophotometrically using the Anthos Zenyth (Biochrom, Cambridge, UK) microplate reader.

2.5. Statistical analysis

The data were analyzed using SPSS software (ver. 20.0; SPSS Inc., Chicago, Illinois). A power analysis was conducted to determine the total number of cases required for the study. With an $\alpha = 0.05$ of Chemerin's standard deviation and 80% power, the number of subjects needed per group was calculated as 35. The normality of the data distribution was determined by the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation and categorical variables as frequencies and percentages. Continuous variables were calculated using ANOVA and Student *t* test. Categorical variables were analyzed by the chi-squared test. Receiver operating characteristic (ROC) curve analyses were conducted and areas under the ROC curves were estimated to assess the diagnostic accuracy of chemerin. Specificity, sensitivity, and cutoff values were determined. A *P* value < .05 was taken to indicate statistical significance.

3. Results

Demographic and physiological data of patients and healthy controls are seen in Table 1. The mean age of the patients was 57.74 ± 16.72 years in Group 1, 57.02 ± 17.82 years in Group 2, 55.92 ± 17.89 years in Group 3, and 56.34 ± 18.38 years in Group 4. Neither age ($P = .265$) nor gender ($P = .960$) differed significantly among the groups. The chemerin level was 37.93 ± 17.3 ng/mL in patients followed in the ICU, 29.41 ± 12.79 ng/mL in inpatients, 30.48 ± 10.86 ng/mL in outpatients, and 25.12 ± 9.82 ng/mL in healthy controls (Table 2). The difference between patients treated in the ICU and healthy controls was significant ($P < .001$) (Fig. 1). The hs-CRP, ferritin, procalcitonin (PCT), and D-dimer levels were significantly higher in the ICU group ($P < .001$).

A comparison of the levels of chemerin and other inflammation parameters in dead and surviving patients is shown in Table 3. The chemerin level of patients who died was significantly higher than that of those who survived (62.05 ± 15.41 vs 28.68 ± 10.27 ng/mL; $P < .001$, Fig. 2). The hs-CRP level (307.87 ± 149.23 mg/L and 61.99 ± 47.13 mg/L), white blood cell count (16.11 ± 6.93 and 12.03 ± 8.11), ferritin level

Table 1

Mean age and gender distribution of patients according to groups.

Groups (*N*, %)					
Variables	**Group 1 50 (26.7%)**	**Group 2 50 (26.7%)**	**Group 3 52 (27.8%)**	**Group 4 35 (18.8%)**	***P***
Male (*N*, %)	23 (46%)	30 (60%)	27 (51.9%)	23 (65.7%)	.265*
Female (*N*, %)	27 (54%)	20 (40%)	25 (48.1%)	23 (65.7%)	
Age (Mean ± SD)	57.74 ± 16.72	57.02 ± 17.82	55.92 ± 17.89	56.34 ± 18.38	.960[β]
Pulse (beats/min)	78.08 ± 7.83	100.14 ± 13.08[a]	77.90 ± 9.95	75.09 ± 8.52	<.001[β]
SBP (mm Hg)	128.58 ± 10.12	138.26 ± 12.53[a]	127.50 ± 9.79	126.40 ± 9.91	<.001[β]
DBP (mm Hg)	81.74 ± 9.63	85.16 ± 10.60[a]	78.50 ± 10.32	76.20 ± 8.82	<.001[β]
BMI (kg/m²)	29.27 ± 2.54	32.67 ± 6.51[a]	29.07 ± 2.83	27.78 ± 1.87	<.001[β]

BMI: body mass index, DBP: diastolic blood pressure, SBP: systolic blood pressure.

*Chi-square test.

[β]Analysis of variance (ANOVA).

[a]$P < .05$ values are significant for Tukey test used in group comparisons (2 & 1, 2 & 3, and 2 & 4).

Table 2

Distributions of chemerin, hs-CRP, ferritin, PCT, and D-dimer levels in patient groups and control participants.

Groups (*N*, %)					
Parameters	**Group 1 50 (26.7%)**	**Group 2 50 (26.7%)**	**Group 3 52 (27.8%)**	**Group 4 35 (18.8%)**	**ANOVA *P***
Chemerin (ng/mL)	29.41 ± 12.79	37.93 ± 17.38[a]	30.48 ± 10.86	25.12 ± 9.82	<.001
hs-CRP (mg/L)	27.80 ± 21.20	182.24 ± 164.71[a]	36.46 ± 34.26	1.89 ± 1.10	<.001
Ferritin (µg/L)	528.88 ± 503.48	603.32 ± 345.06[a]	142.71 ± 123.59	45.20 ± 24.31	<.001
PCT (ng/mL)	0.97 ± 0.82	4.93 ± 3.82[a]	0.85 ± 0.48	0.04 ± 0.02	<.001
D-dimer (Ug/mL)	211.34 ± 163.82	432.86 ± 283.34[a]	116.64 ± 97.19	56.68 ± 37.66	<.001

hs-CRP = high-sensitivity C-reactive protein, PCT = procalcitonin. All data are presented as mean ± SD of patients and healthy control participants. $P < .05$ values indicate the level of significance for the ANOVA test.

[a]$P < .05$ values are significant for Tukey test used in group comparisons (2&1, 2&3, and 2&4).

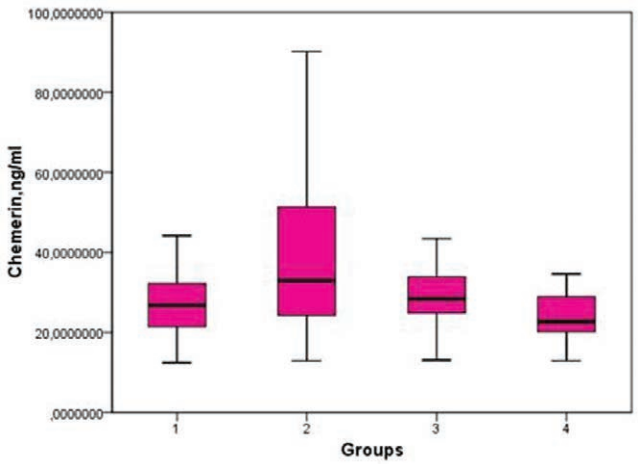

Figure 1. The chemerin levels of the patients followed in the ICU, in inpatients, in outpatients, and in healthy controls.

(813.36 ± 309.59 µg/L and 313.45 ± 180.22 µg/L), D-dimer level (760.92 ± 182.00 Ug/mL and 171.13 ± 63.48 Ug/mL), and PCT level (7.01 ± 4.96 ng/mL and 1.40 ± 0.23 ng/mL) were significantly higher in patients who died ($P < .001$). BMI was non-significantly higher in patients who died ($P = .187$). The distributions of other laboratory parameters are shown in Table 4.

There was a significant positive correlation between the chemerin level and those of hs-CRP ($R = 0.541$, $P < .00$), ferritin ($R = 0.269$, $P \leq .001$), and PCT ($R = 0.350$, $P \leq .001$) in COVID-19 patients (Table 5). In a binary logistic regression analysis, the odds ratio (OR) for chemerin was significantly higher for COVID-19 patients hospitalized in the ICU (95% confidence interval [CI] 0.572–0.767, $P < .001$). In COVID-19 patients in the ICU, the area under ROC curve was 0.669 (sensitivity = 0.600, specificity = 0.723) and the cutoff value was 30.74. The sensitivities, specificities, and cutoff values were lower in the other groups (Table 6 and Fig. 3).

4. Discussion

An elevated chemerin level was predictive of mortality and morbidity in COVID-19 patients. The chemerin level was higher in COVID-19 patients than healthy controls, and in patients in the ICU compared to those not in the ICU. Moreover, the chemerin level was significantly higher in patients who died.

Adipokines, which are implicated in the pathogenesis of metabolic disorders, are biologically active molecules with pro- and anti-inflammatory activities. Chemerin is an adipokine secreted by white adipose tissue involved in the metabolic and inflammatory processes of many tissues, including in the lung.[11]

Table 3

Distribution of chemerin, hs-CRP, ferritin, D-dimer, PCT, and BMI levels in died and surviving patients.

Variables	Survivor (*N* = 173) Mean ± SD	Died (*N* = 14) Mean ± SD	*P*
Chemerin (ng/mL)	28.68 ± 10.27	62.05 ± 15.41	<.001
hs-CRP (mg/L)	61.99 ± 47.13	307.87 ± 149.23	<.001
WBC (10^3/µL)	12.03 ± 8.11	16.11 ± 6.93	.069
Ferritin (µg/L)	313.45 ± 180.22	813.36 ± 309.59	<.001
D-dimer (Ug/mL)	171.13 ± 63.48	760.92 ± 182.00	<.001
PCT (ng/mL)	1.40 ± 0.23	7.01 ± 4.96	<.001
BMI (kg/m²)	29.73 ± 3.64	31.28 ± 9.34	.223

BMI = body mass index, hs-CRP = high-sensitivity C-reactive protein, PCT = procalcitonin, WBC = white blood cells. All data are presented as mean ± SD of the survivor and died patients, $P < .05$ values indicate the level of significance for the Student *t* test.

Maintaining the chemerin concentration is important for the functioning of organ systems. Elevated serum chemerin levels trigger lipid metabolism and carbohydrate catabolism disorders. Chemerin levels are often elevated in chronic inflammatory diseases. Chemerin regulates the adhesion between inflammatory and endothelial cells and the production of inflammatory factors that contribute to the inflammatory response associated with atherosclerosis (AS). In addition, chemerin has regulatory roles in insulin resistance, glucose metabolism, and hepatic gluconeogenesis, and is thus implicated in AS-related metabolic disorders.[12] The role of chemerin in cancer is controversial; it can prevent or facilitate carcinogenesis via its effects on innate immunity and angiogenesis.[13] Zhou et al reported that the serum chemerin level is a prognostic indicator of chronic heart failure.[14] Although chemerin promotes the inflammatory response, it also impairs glucose and lipid metabolism.[15]

Lung injury can be triggered by SARS-CoV-2 infection, which also causes damage to other organs.[16] There is no parameter predictive of the prognosis of COVID-19. However, the degree of lung tissue involvement, immunodeficiency, comorbidities, and failure to vaccinate are known risk factors. Cytokines have been used as biomarkers of COVID-19 morbidity and mortality,[17] among other markers.[17,18] Cione et al showed that neuron-specific enolase (NSE) can be used to differentiate patients who will develop dyspnea in the early course of COVID-19, and the serum NSE level in COVID-19 is associated with the severity of lung injury.[18] Alay et al reported that surfactant protein D and angiopoietin-2 are markers of the severity of lung lesions in COVID-19,[19] while Kerget et al reported that levels of triggering receptor expressed on myeloid (TREM)-cells 1 and TREM-2 in myeloid cells determine the clinical severity of COVID-19 pneumonia.[20] Lavis et al showed that the blood chemerin concentration is

Table 4

Distribution of vital signs and routine laboratory data in patient groups and healthy control participants.

Groups (*M*)					
Parameters	**Group 1(50) Mean ± SD**	**Group 2(50) Mean ± SD**	**Group 3(52) Mean ± SD**	**Group 4(35) Mean ± SD**	***P***
WBC (10^3/μL)	15.60 ± 11.89	15.60 ± 6.69[a]	7.97 ± 3.10	9.47 ± 2.34	<.001
Neu (10^3/μL)	6.66 ± 4.23	10.62 ± 6.60[a]	5.19 ± 3.03	5.93 ± 2.44	<.001
LYM (10^3/μL)	1.48 ± 1.33	1.78 ± 1.47[a]	1.71 ± 1.00	2.51 ± 0.92	.002
MCV (fL)	87.73 ± 6.71	91.31 ± 7.47[a]	86.98 ± 5.51	86.87 ± 6.69	.003
HCT (g/dL)	40.73 ± 7.64	37.61 ± 6.18[a]	42.85 ± 4.48	44.94 ± 5.28	<.001
Glucose (mg/dL)	165.98 ± 106.85	173.86 ± 88.42[a]	128.57 ± 53.24	105.88 ± 19.37	<.001
Urea (mg/dL)	38.18 ± 20.99	61.76 ± 40.47[a]	53.84 ± 36.52	38.20 ± 21.96	<.001
Cre (mg/dL)	1.02 ± 0.53	2.05 ± 1.65[a]	1.00 ± 0.70	0.75 ± 0.19	<.001
K (mmol/L)	4.08 ± 0.37	4.35 ± 0.63[a]	4.23 ± 0.35	4.19 ± 0.41	.041
CL (mmol/L)	101.58 ± 5.34	101.14 ± 14.38	103.76 ± 4.16	104.62 ± 3.80	.158
Na (mmol/L)	136.18 ± 4.94	133.71 ± 19.42	137.73 ± 3.70	138.80 ± 2.85	.126
AST (U/L)	38.50 ± 42.98	64.29 ± 83.60[a]	28.65 ± 19.71	21.62 ± 18.12	<.001
ALT (U/L)	30.34 ± 14.57	64.61 ± 39.88[a]	29.21 ± 18.49	23.68 ± 13.76	<.001
Alb (g/L)	32.73 ± 7.16	29.24 ± 4.73[a]	37.58 ± 6.01	44.43 ± 1.91	<.001
Ca (mg/dL)	8.51 ± 0.67	9.21 ± 1.32[a]	8.65 ± 0.70	9.63 ± 0.79	<.001
LDH (U/L)	353.56 ± 184.97	505.50 ± 335.09[a]	249.42 ± 122.30	189.06 ± 38.25	<.001

ALB = albumin, ALT = alanine aminotransferase, Ca = calcium, CL = chlorine, CRE = creatinine, HCT = hematocrit, K = potassium, LDH = lactate dehydrogenase. $P < .05$ values indicate the level of significance for the ANOVA test.

[a]$P < .05$ values are significant for Tukey test used in group comparisons (2&1, 2&3, and 2&4). LYM = lymphocyte, MCV = mean corpuscular volume, Na = Sodium (natrium) AST = aspartate aminotransferase, NEU = neutrophil, WBC = white blood cells.

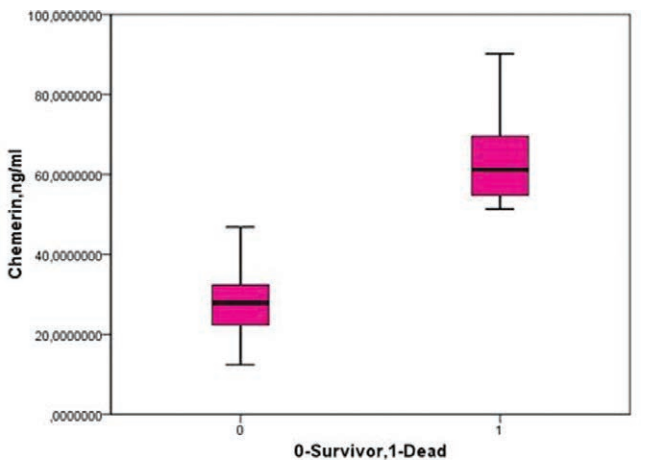

Figure 2. The comparison of the chemerin levels of the dead and survivor patients.

Table 5

Correlation relationship of chemerin with BMI, hs-CRP, ferritin, D-dimer, and PCT.

	BMI	**hs-CRP**	**Ferritin**	**D-Dimer**	**PCT**
Chemerin					
R	0.099	0.541	0.269	0.559	0.350
*P**	.178	<.001	<.001	<.001	<.001

*Correlation is significant at the 0.01 level (2-tailed). BMI = body mass index, hs-CRP = high-sensitivity C-reactive protein, PCT = procalcitonin.

Table 6

ROC curve parameters of chemerin in Groups 1, 2, 3, and 4.

	Group 1	**Group 2**	**Group 3**	**Group 4**
AUC	0.445	0.669	0.528	0.315
95%CI	0.354–0.537	0.572–0.767	0.443–0.613	0.222–0.408
P	.254	<.001	.550	.001
Cutoff	29.16	30.74	28.51	26.88
Sensitivity	0.400	0.600	0.500	0.400
Specificity	0.555	0.723	0.511	0.388

AUC = area under curve, $P < .05$ values are significant.

elevated in COVID-19 patients and is associated with disease severity, inflammation, and mortality.[9] Kukla et al reported that the chemerin level was significantly higher in COVID-19 patients than in healthy controls. Moreover, the chemerin level increased in direct proportion to body weight and was lower in patients with lung pneumonic infiltration.[8] In this study, body mass index (BMI) was similar between patients and healthy controls and was not correlated with the chemerin level.

In this study, the chemerin level was highest in patients treated in the ICU and lowest in healthy controls, in agreement with the findings of Levis et al. Moreover, the serum chemerin level was significantly higher in patients who died than in those who did not. The sensitivity, specificity, and cutoff values for chemerin were significantly higher in patients in the ICU. A chemerin cut-off value of 30.74 ng/mL in patients in the ICU had high sensitivity and specificity. The hs-CRP, ferritin, PCT, and D-dimer levels were significantly higher in patients in the ICU. Moreover, the chemerin level was significantly positively correlated with those of hs-CRP, ferritin, and PCT in COVID-19 patients.

While there is a sufficient amount of literature on inflammation parameters in COVID-19 disease, there are a limited number of studies examining chemerinin in COVID-19 patients.[21,22] Yue ve meslektaşları, terapötik ajanların kardiyovasküler hastalığın tedavisine yönelik açık perspektifleri hedeflediğini belirtti.[21] A recent study suggested that increased plasma chemerin levels are an indicator of disease severity and may predict death in COVID-19 patients.[22] On the other hand, another recent study suggested that chemerinin did not provide any benefit in the diagnosis of COVID-19, despite its limitations. Therefore, the serum chemerin level may be predictive of the prognosis of COVID-19 patients; further studies are needed to confirm this.

Our findings suggest that chemerin has utility for the emergency and intensive care management of COVID-19 patients.

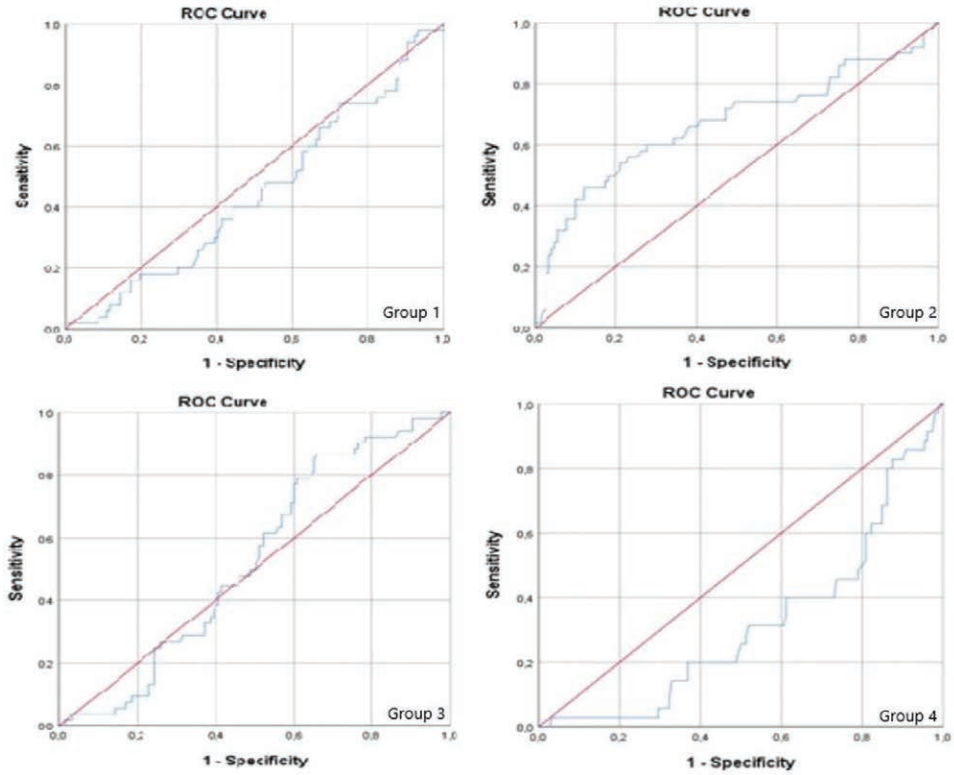

Figure 3. ROC curve of chemerin in groups 1, 2, 3, and 4.

The limitations of this study included its single-center design, small number of healthy controls, and use of a single blood sample obtained within 1 hour of hospital admission.

5. Conclusion

The chemerin level was increased in COVID-19 patients and also increased with increasing disease severity. The chemerin level was higher in the COVID-19 patients than healthy controls and was significantly higher in patients who died compared to those who did not. Therefore, COVID-19 patients with high chemerin levels at hospital admission require critical care.

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