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# The Role of MR-proADM in Determining COVID-19 Pneumonia and Clinical Severity

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## ABSTRACT

**Introduction:** This study aimed to compare the success of mid-regional pro adrenomedullin (Mr-proADM) levels, in determining disease severity in coronavirus disease-2019 (COVID-19) patients with other inflammatory biomarkers and Pneumonia Severity Index (PSI) scores.

**Methods:** This prospective, observational, analytical, cross-sectional study was conducted at Sakarya Training and Research Hospital, Department of Emergency Medicine. The 88 patients who presented with suspected COVID-19 and were diagnosed accordingly were included in the examination. The patients were organized into four groups based on reverse transcription polymerase chain reaction and chest computed tomography outcomes. Demographic data, presenting complaints, comorbidities, laboratory values, imaging modalities, PSI score, and pneumonia diagnosis data were documented for each patient. All data were examined with SPSS software, and a $p<0.05$ was considered statistically significant.

**Results:** The patients' mean age was 53 and 60% were female. Fatigue (58%) was the most typical complaint, and hypertension (39%) was the most prevalent comorbidity. When comparing the groups, it was observed that patients in group 4 exhibited a decrease in white blood cell counts and increased levels of C-reactive protein (CRP), ferritin, and D-dimer, which was statistically significant. Nevertheless, no significant distinction was seen in Mr-proADM levels among the groups. The comparison based on the PSI score determined that Mr-proADM levels were significantly raised in the high-risk group.

**Conclusion:** Mr-proADM levels correlated with CRP, ferritin, and procalcitonin levels in predicting patients in the high-risk group based on the PSI score. Based on these determinations, Mr-proADM levels may also help predict clinical severity in the emergency department. Nevertheless, further studies incorporating larger datasets are needed to support these data.

**Keywords:** Emergency department, COVID-19, Mr-proADM, PSI

## Introduction

Coronavirus disease-2019 (COVID-19), which emerged in China in late 2019 and affected the entire world, has caused significant challenges in clinical management. In diagnostic approaches, detecting severe acute respiratory syndrome coronavirus-2 in respiratory specimens and characteristic lung infiltrations on chest computed tomography (CT) scans has been used for definitive diagnosis (1). Although not specific, certain laboratory parameters (such as leukocyte, lymphocyte, and platelet counts), biochemical analyses (such as ferritin levels, troponins, and renal function tests), serological tests [such as D-dimer, C-reactive protein (CRP), and procalcitonin], and arterial blood gas analysis (such as lactate) have been recommended to support the diagnosis in suspected cases (2).

Additionally, the need to assess pneumonia, which is frequently observed in COVID-19 patients, has emerged. In this context, the Pneumonia Severity Index (PSI) scoring system has gained prominence (1,3). According to the PSI scoring system, grades 1-3 indicate mild disease, whereas grades 4-5 classify cases as severe, implying a higher risk of mortality and an increased need for hospitalization (4).

The PSI score considers various parameters associated with an elevated risk of mortality in COVID-19 patients, such as age, comorbidities, and hypoxemia (1,3). However, despite these approaches, there remains a demand for novel diagnostic mechanisms because of limitations in certain patients and the persistently high mortality rate. One emerging biomarker in this context is mid-regional pro adrenomedullin (MR-proADM) (5).

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MR-proADM is a polypeptide with multiple physiological effects, including vasodilation, natriuresis, diuresis, antioxidation, antimicrobial activity, anti-inflammatory properties, and metabolic regulation. It is produced by endothelial cells in cardiovascular, pulmonary, cerebrovascular, renal, and endocrine tissues (5). Given these characteristics, studies have suggested that MR-proADM can be used for diagnosis, monitoring, and prognosis in bacterial infections such as pneumonia and sepsis. However, there is currently insufficient evidence regarding its effectiveness in viral infections (6). The literature provides limited information on the relationship between MR-proADM and COVID-19 (7).

This study aims to investigate the contribution of MR-proADM to the diagnostic process and its effectiveness in assessing disease severity in patients presenting with COVID-19 symptoms in the emergency department (ED) by comparing MR-proADM with other inflammatory biomarkers and the PSI score.

## Methods

### Study Type

This prospective, observational, analytical, cross-sectional study included patients who presented with COVID-19 symptoms at Sakarya Training and Research Hospital (SEAH) ED and underwent MR-proADM testing.

### Study Design

The study was conducted between May 4 and November 4, 2020, with 88 patients presenting COVID-19 symptoms at SEAH ED. Patients were classified into four subgroups based on reverse transcription polymerase chain reaction (RT-PCR) and thoracic CT findings:

**Group 1**: RT-PCR negative, CT pneumonia negative

**Group 2**: RT-PCR positive, CT pneumonia negative

**Group 3**: RT-PCR negative, CT pneumonia positive

**Group 4**: RT-PCR positive, CT pneumonia positive

MR-proADM testing was performed alongside routine laboratory tests. Patients were assigned to groups based on the researchers' shifts in the ED, and recruitment ceased once each group reached the specified sample size.

The study was approved by the Non-Interventional Clinical Research Ethics Committee of Sakarya University (approval number: 212, date: 20.04.2020). Written informed consent was obtained from all participants. The study adhered to the 2004 World Medical Association Declaration of Helsinki.

### Diagnosis

RT-PCR testing was conducted on both nasopharyngeal and oral swab samples. Thoracic CT images were classified as CT pneumonia positive if CO-RADS scores were 4 or 5 (8).

### Data Collection

Patient data were obtained from the hospital automation system and recorded on a structured study form. The collected data included:

- Demographics (age, gender)
- Presenting complaints and comorbidities
- Vital parameters (blood pressure, pulse rate, temperature, respiratory rate, peripheral oxygen saturation)
- Laboratory results [RT-PCR, white blood cell (WBC), CRP, procalcitonin, troponin, ferritin, D-Dimer, Lactate, MR-proADM]
- Thoracic CT results and PSI scores

**Inclusion criteria:** Patients 18 and older with COVID-19 symptoms undergoing MR-proADM testing.

**Exclusion criteria:** Pregnant patients and those with missing study-relevant data.

### Statistical Analysis

Normal distribution was assessed using Skewness-Kurtosis values (-2 to +2 range) and the Kolmogorov-Smirnov test (9). Non-normally distributed continuous variables were reported as median interquartile range values. Statistical tests included:

- **Mann-Whitney U test**: Comparison between two groups
- **Kruskal-Wallis test**: Comparison among four groups, with posthoc pairwise comparisons using the Mann-Whitney U test
- **Chi-square test**: Analysis of categorical variables among groups

A $p<0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics 21.

## Results

Of the patients participating in the study, 60% were female, with a mean age of 53.3 years (range: 18-90). Fatigue (58%) and fever (55.7%) were the most common presenting complaints. A statistically significant difference was observed between the groups in terms of age. In subgroup analyses, statistically significant differences were found between Group 2 and Group 3, as well as between Group 2 and Group 4 ($p=0.035$ and $p=0.009$, respectively).

Regarding symptoms, statistically significant differences were observed among the groups for fever, shortness of breath, and fatigue ($p=0.036$, $p=0.004$, $p=0.003$, respectively). Subgroup analyses revealed a statistically significant difference in fever between Group 2 and Group 3 ($p=0.004$). Regarding shortness of breath, a statistically significant difference was found between Group 1 and Group 2 ($p=0.004$). Additionally, subgroup analyses showed significant differences in malaise between Group 1 and Group 2, as well as between Group 2 and Group 3 ($p=0.003$, $p=0.001$, respectively). While the most common symptoms in Group 4 were fever and fatigue, shortness of breath was predominant in Group 1. Hypertension was the most frequently observed comorbidity (Table 1).

Among the study participants, 43.2% were discharged from the ED, 48.8% were admitted to a standard hospital room, and 8% required admission to the intensive care unit (ICU). Statistically significant differences were observed between the groups regarding discharge rates and standard

**Table 1. Demographic datas, admission complaints and comorbidity**

| | | Total n=88 | Group 1 n=20 | Group 2 n=20 | Group 3 n=20 | Group 4 n=28 | p |
|---|---|---|---|---|---|---|---|
| **Age, years (min.-max.)** | | 53.30 (18-90) | 48.10 (20-80) | 44.15 (18-88)[a,b] | 59.35 (21-90)[a] | 59.21 (40-88)[b] | **0.032*** |
| **Gender, female (%)** | | 53 (60,2) | 13 (65) | 14 (70) | 8 (40) | 18 (64.3) | 0.608** |
| **Admission complaint n (%)** | Fever | **49 (55.7)** | 10 (50) | 16 (80)[a] | 7 (35)[a] | **16 (57.1)** | **0.036**** |
| | Cough | 42 (47.7) | 13 (65) | 9 (45) | 9 (45) | 11 (39.3) | 0.346** |
| | Sore throat | 25 (28.4) | 9 (45) | 5 (25) | 5 (25) | 6 (21.4) | 0.307** |
| | Shortness of breath | 30 (34.1) | **12 (60)[a]** | 2 (10)[a] | 9 (45) | 7 (25) | **0.004**** |
| | Muscle/joint pain | 29 (33.0) | 7 (35) | 9 (45) | 5 (25) | 8 (28.6) | 0.538** |
| | Resentment | **51 (58.0)** | 8 (40)[a] | 17 (85)[a,b] | 7 (35)[b] | **19 (67.9)** | **0.003**** |
| | Abdominal pain/diarrhea | 10 (11.4) | 1 (5) | 3 (15) | 4 (20) | 2 (7.1) | 0.385** |
| **Comorbidity n (%)** | Diabetes mellitus | 23 (26.1) | 3 (15) | 6 (30) | 5 (25) | 9 (32.1) | 0.261** |
| | Hypertension | **34 (38.6)** | 8 (40) | 5 (25) | 8 (40) | **13 (46.4)** | 0.409** |
| | Cardiovascular disease | 16 (18.2) | 3 (15) | 2 (10) | 5 (25) | 6 (21.4) | 0.362** |
| | Chronic lung disease | 7 (8.0) | 1 (5) | 1 (5) | 2 (10) | 3 (10.7) | 0.386** |
| **Outcome n (%)** | Discharge | 38 (43.2) | **19 (95)[a,b]** | 15 (75)[c,d] | 3 (15)[a,c] | 1 (3.6)[b,d] | **0.000**** |
| | Standart room | 43 (48.8) | 1 (5)[a,b] | 5 (25)[c] | 13 (65)[a] | **24 (85.7)[b,c]** | **0.000**** |
| | Intensive care unit | 7 (8) | 0 (0) | 0 (0) | 4 (20) | 3 (10.7) | 0.054** |

*The Kruskal Wallis test is used for 4 group analyses. **Chi-square test is used for analysis. [a,b,c,d] There is no significant difference between the groups indicated with the same letter in the same row. Min.: Minimum, Max.: Maximum

room admissions (p=0.000, p=0.000, respectively). Subgroup analyses, showed statistically significant differences in discharge rates between Group 1 and Group 3, Group 1 and Group 4, Group 2 and Group 3, and Group 2 and Group 4 (p=0.000 for all comparisons). Similarly, subgroup analyses of standard room admissions revealed significant differences between Group 1 and Group 3, Group 1 and Group 4, and Group 2 and Group 4 (p=0.000 for all comparisons) (Table 1).

Laboratory data are presented in Table 2. No significant differences were found in procalcitonin, lactate, or Mr-proADM levels (p=0.061, p=0.601, p=0.151, respectively). However, significant differences were observed among the groups for WBC, CRP, ferritin, troponin, and D-dimer levels: p=0.001; p=0.002; p=0.000; p=0.025; p=0.029, respectively. In subgroup analyses of WBC levels, statistically significant differences were noted between Group 1 and Group 2, as well as between Group 1 and Group 4 (p=0.014, p=0.000, respectively). For CRP values, a significant difference was found between Group 2 and Group 3 (p=0.029). Regarding ferritin levels, subgroup analyses revealed significant differences between Group 1 and Group 3 (p=0.028), Group 1 and Group 4 (p=0.010), and between Group 2 and Group 3 (p=0.019), Group 2 and Group 4 (p=0.007). In subgroup analyses of troponin levels, significant differences were found between Group 2 and Group 3, as well as between Group 2 and Group 4 (p=0.005, p=0.026, respectively). Subgroup analyses of D-Dimer levels showed significant differences between Group 2 and Group 3, as well as between Group 3 and Group 4 (p=0.003, p=0.036, respectively).

Based on the PSI score, Mr-proADM levels were significantly higher in the high-risk group compared to the low-risk group (p=0.008). Additionally, in the high-risk group, Mr-proADM levels was correlated with increased levels of CRP, ferritin, and procalcitonin (p=0.003, p=0.000, p=0.001, respectively) (Table 3).

**Table 2. Laboratory values of the groups**

| | Reference value | Total n=88 | Group 1 n=20 | Group 2 n=20 | Group 3 n=20 | Group 4 n=28 | p |
|---|---|---|---|---|---|---|---|
| **WBC** | 4.60-10.20 K/uL (IQR) | 6.96 (5.22-9.52) | 10.12 (7.69-12.12)[a,b] | 6.24 (5.35-8.52)[a] | 6.84 (4.86-10.61) | **5.72 (5.06-7.52)[b]** | **0.001*** |
| **CRP** | 0-5 mg/L (IQR) | 11.15 (4.22-32.55) | 8.09 (0.85-24.08) | 5.98 (1.87-10.58)[a] | 15.15 (6.40-78.05)[a] | **18.33 (7.72-59.97)** | **0.002*** |
| **Prokalsitonin** | <0.5 ng/mL (IQR) | 0.04 (0.02-0.07) | 0.04 (0.02-0.06) | 0.03 (0.02-0.06) | 0.05 (0.04-0.83) | 0.04 (0.02-0.08) | 0.063* |
| **Ferritin** | 21.8-274.6 µg/L (IQR) | 90.92 (30.31-203.41) | 55.39 (14.67-97.39)[a,b] | 30.31 (20.20-70.20)[c,d] | 135.05 (85.22-250.67)[a,c] | **202.55 (82.52-339.26)[b,d]** | **0.000*** |
| **Troponin** | 0-34.2 ng/L (IQR) | 2.40 (0.65-6.10) | 1.30 (0.52-5.37) | 0.85 (0.25-3.47)[a,b] | **4.70 (1.32-4.70)[a]** | 3.20 (1.27-6.60)[b] | **0.025*** |
| **D-Dimer** | 0-500 ugFEU/L (IQR) | 400.0 (208.0-814.0) | 311.0 (189.0-1003.25) | 314.0 (176.25-488.00)[a] | **736.0 (350.0-2615.0)[a,b]** | 379.50 (197.25-693.25)[b] | **0.029*** |
| **Laktat** | 0.5-1.6 mmol/L (IQR) | 1.50 (1.20-1.90) | 1.40 (1.12-1.87) | 1.40 (1.12-1.87) | 1.65 (1.32-1.90) | 1.55 (1.22-1.87) | 0.601* |
| **Mr-proADM** | pmol/mL (IQR) | 0.54 (0.39-1.26) | 0.88 (0.43-3.25) | 0.45 (0.37-1.68) | 0.68 (0.36-1.32) | 0.53 (0.37-0.94) | 0.151* |

*Kruskal Wallis test is used for 4 group analyse. The Mann-Whitney U test is used for subgroup analysis. [a,b,c,d] There is a significant difference between the groups indicated with the same letter in the same row. WBC: White blood cell, CRP: C-reactive protein, IQR: Interquartile range, Mr-proADM: Mid-regional pro adrenomedullin

**Table 3. Laboratory values according to the PSI results**

| | PSI (1-3) low-risk n=73 | PSI (4-5) high-risk n=15 | p-value |
|---|---|---|---|
| **WBC** 4.60-10.20 K/uL (min.-max.) | 7.65 (2.56-14.99) | 7.70 (3.32-17.70) | 0.829* |
| **CRP** 0-5 mg/L (min.-max.) | 27.01 (0.21-333.80) | **44.46 (9.40-136.00)** | **0.003*** |
| **Prokalsitonin** <0.5 ng/mL (min.-max.) | 0.15 (0.01-3.50) | **1.16 (0.02-15.10)** | **0.000*** |
| **Ferritin** 21.8-274.6 µg/L (min.-max.) | 116.52 (1.80-697.00) | **351.44 (16.88-1248.40)** | **0.001*** |
| **Laktat** 0.5-1.6 mmol/L (min.-max.) | 1.59 (0.70-4.10) | 1.69 (0.80-4.20) | 0.807* |
| **Mr-proADM** (pmol/mL) (min.-max.) | 1.31 (0.34-13.97) | **2.54 (0.34-25.37)** | **0.008*** |

*Mann Whitbey U test is usedfor analyse.WBC: White blood cell, CRP: C-reactive protein, PSI: Pneumonia severity index, Mr-proADM: Mid-regional pro adrenomedullin, Min.: Minimum, Max.: Maximum

## Discussion

According to this study, patients who presented to the ED due to COVID-19 exhibited symptoms such as fever, shortness of breath, and fatigue. In the group analysis of laboratory data, significant differences were observed in WBC, CRP, ferritin, troponin, and D-dimer levels. At the same time, no distinctions were observed in procalcitonin, lactate, and Mr-proADM levels. The levels of Mr-proADM do not provide an additional contribution to the diagnostic process. However, the levels of Mr-proADM, CRP, ferritin, and procalcitonin, which are correlated with Mr-proADM levels, can predict the high-risk group according to the PSI scoring system.

A review of the literature indicates that numerous symptoms have been identified as reasons for hospitalization in COVID-19 patients. However, the most commonly reported symptoms include fever, cough, and fatigue (10-12). Given that COVID-19 is a viral infection, the prominence of fever and fatigue is expected. In our study, the highest incidence of fever and fatigue was observed in RT-PCR and CT pneumonia-positive patients (Group 4), which aligns with the literature. However, it is noteworthy that shortness of breath was more prominent in RT-PCR and CT pneumonia-negative patients (Group 1), which contrasts with previous findings.

Extensive studies on laboratory parameters in COVID-19 patients have highlighted WBC, CRP, ferritin, troponin, D-dimer, and procalcitonin as key indicators. Generally, a normal WBC count is expected, whereas elevated CRP and Ferritin levels are associated with disease severity and poor prognosis. Studies have reported increased CRP levels in 55-85% of patients and elevated ferritin levels in 90.7% of cases (12-18). In our study, although significant differences were observed among groups in WBC counts and ferritin levels, the values remained within the reference range, aligning with existing literature. Similarly, the elevated CRP levels observed in our study are consistent with previous findings.

Several publications suggest a positive correlation between COVID-19 severity and cardiac involvement; this leads to increased troponin levels, a classic marker of myocardial injury. However, studies indicate that elevated Troponin levels are more closely associated with inflammatory markers such as CRP and Ferritin, suggesting that the increase is due to inflammatory damage rather than primary myocardial injury (19-22). Additionally, research has shown that elevated D-dimer levels in COVID-19 patients result from disease-related coagulopathy, with high serum levels indicating thromboembolic risk. Elevated D-dimer levels are more frequently observed in severe COVID-19 cases, and an increase beyond 1 mcg/mL has been associated with poor prognosis (23,24). Procalcitonin levels, on the other hand, generally remain within normal limits in COVID-19 patients, with elevated levels potentially indicating bacterial superinfection (25,26). In our study, we found that D-dimer levels exceeded the reference range, only in RT-PCR-negative and CT pneumonia-positive patients (Group 3), while no significant subgroup differences were observed in troponin levels. This result may be attributed to differences in the patient population. Additionally, our Procalcitonin findings remained within normal limits supporting the existing literature.

Many studies have attempted to develop predictive models for assessing COVID-19 severity. Previous research has identified PCT, CRP, ferritin, and lymphocyte count as biomarkers associated with severe disease. However, the comparative discriminatory ability of these biomarkers has not been extensively studied. The widely used PSI score has demonstrated strong performance in comparison with these biomarkers (27,28). One commonly used inflammatory marker in ED patients with suspected infection is MR-proADM. A study on this topic suggested that MR-proADM levels below 0.9 nmol/L may indicate a lower likelihood of hospitalization and re-presentation, whereas levels above 1.5 nmol/L may suggest severe and progressive disease, emphasizing the importance of early antibiotic treatment (29). Another study on COVID-19 reported that high MR-proADM levels were associated with ICU admission and mortality (7). In our study, the mean MR-proADM levels were found to be approximately 0.54 nmol/L, which is below the <0.9 nmol/L threshold reported in the literature. This finding suggests that the patients included in our study had milder cases of COVID-19, which explains why only 8% required ICU admission. Furthermore, the lack of significant differences among patient groups suggests that MR-proADM levels do not provide additional diagnostic value. However, another study on pneumonia-one of the most common clinical presentations of COVID-19-reported a positive correlation between MR-proADM levels and severity assessed by the PSI score. Our study also identified a positive correlation with the PSI severity score, suggesting that MR-proADM levels could serve as an indicator of clinical severity and hospitalization requirements in COVID-19 patients with pneumonia.

### Study Limitations

The primary limitations of this study include its single-center design and limited sample size. Additionally, as a cross-sectional study, it did not comprehensively assess patient prognosis. Another limitation is the lack of randomization, as data collection was restricted to the authors' ED shifts.

## Conclusion

MR-proADM levels do not provide additional diagnostic value in predicting RT-PCR or CT scan results in COVID-19 patients. However, the PSI score demonstrates a correlation of CRP, Ferritin, and Procalcitonin levels with identifying high-risk patients. Based on these findings, MR-proADM levels may serve as an indicator of clinical severity in the ED. Nonetheless, further studies with larger datasets are necessary to validate these findings.

### Ethics

**Ethics Committee Approval:** The study was approved by the Non-Interventional Clinical Research Ethics Committee of Sakarya University (approval number: 212, date: 20.04.2020).

**Informed Consent:** Written informed consent was obtained from all participants.

### Footnotes

**Authorship Contributions:** Concept - S.A., Y.Y., N.G.G., N.A., F.G.; Design - S.A., Y.Y., H.Y., N.G.G., N.A., F.G.; Data Collection or Processing - S.A., N.G.G., N.A., E.D.; Analysis or Interpretation - S.A., H.Y., N.G.G., E.D., F.G.; Literature Search - S.A., Y.Y., H.Y., N.A.; Writing - S.A., Y.Y., E.D., F.G.

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