Clinical Utility of Midregional Proadrenomedullin in Patients with COVID-19

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ABSTRACT

Objective: The aim of the study was to assess the role of midregional proadrenomedullin (MR-proADM) in patients with COVID-19.

Methods: We included 110 patients hospitalized for COVID-19. Biochemical biomarkers, including MR-proADM, were measured at admission. The association of plasma MR-proADM levels with COVID-19 severity, defined as a requirement for mechanical ventilation or in-hospital mortality, was evaluated.

Results: Patients showed increased levels of MR-proADM. In addition, MR-proADM was higher in patients who died during hospitalization than in patients who survived (median, 2.59 nmol/L; interquartile range, 2.3–2.95 vs median, 0.82 nmol/L; interquartile range, 0.57–1.03; $P < .0001$). Receiver operating characteristic curve analysis showed good accuracy of MR-proADM for predicting mortality. A MR-proADM value of 1.73 nmol/L was established as the best cutoff value, with 90% sensitivity and 95% specificity ($P < .0001$).

Conclusion: We found that MR-proADM could represent a prognostic biomarker of COVID-19.

Keywords: biomarker, COVID-19, inflammation, MR-proADM, respiratory disease

COVID-19 is caused by SARS-CoV-2, which primarily infects the respiratory system in humans. It is characterized by a broad spectrum of clinical manifestations with varying degrees of severity, from asymptomatic form to pneumonia, which can evolve into acute respiratory distress syndrome and multiorgan failure syndrome, until death.[1-4]

SARS-CoV-2 internalization occurs by the viral spike glycoprotein that binds to angiotensin-converting enzyme 2 (ACE2), which is mainly expressed on type II alveolar epithelial cells, myocardial cells, proximal tubule cells of the kidney, bladder urothelial cells, and enterocytes.[5,6] This interaction results in the downregulation of ACE2 expression and excessive angiotensin production, enhancing an inflammatory response that contributes to acute organ injury.[7]

The clinical course of the disease is unpredictable, and there is an urgent need for biomarkers that could reliably stratify patients into different classes of risk. Early identification of hospitalized patients who are more vulnerable to clinical deterioration could guide clinicians for risk stratification and monitoring.

The hallmark of SARS-CoV-2 infection is the activation of the immune system, which can lead to an uncontrolled and

Abbreviations:

MR-proADM, midregional proadrenomedullin; ACE2, angiotensin-converting enzyme 2; IL, interleukin; CRP, C-reactive protein; PCT, procalcitonin; ADM, adrenomedullin; ICU, intensive care unit; LOS, length of stay; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; sCR, serum creatinine; hs-TnT, high-sensitivity troponin T; eGFR, estimated glomerular filtration rate; IQR, interquartile range; ROC, receiver operating characteristic; CI, confidence interval; AUC, area under the curve.

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generalized inflammatory response and to the so-called cytokine storm.[8] Indeed, patients with COVID-19 have significantly increased circulating levels of inflammatory biomarkers, such as interleukin (IL)-6, C-reactive protein (CRP), and procalcitonin (PCT). Moreover, several biochemical parameters, such as D-dimer, cardiac troponin, and homocysteine, are altered.[9-13] These biomarkers have been associated with disease severity and mortality.[2,14,15] However, there is ongoing research for biomarkers to better define the biochemical phenotype of COVID-19 patients to improve their management.

Midregional proadrenomedullin (MR-proADM) is a surrogate biomarker of adrenomedullin (ADM), a 52–amino acid peptide belonging to the Calc gene family. Under physiological conditions, ADM levels are very low. Several factors, including catecholamines, hypoxia, oxidative stress, inflammatory mediators, and cytokines, induce their increase.[16] Thus, it has been evaluated in several inflammatory conditions.[17,18] However, the measurement of ADM has several technical issues, such as a short half-life and rapid degradation by proteases. The more stable MR-proADM provides a solution to these problems. The latter is secreted in equimolar amounts with ADM and is more stable in vitro. Moreover, it can be easily measured on a fully automated platform.

Research has recently proposed MR-proADM as a biomarker of organ failure.[19-22] Specifically, increased MR-proADM levels have been associated with short- and long-term mortality in patients with community-acquired pneumonia and sepsis.[23-26] In addition, MR-proADM has emerged as a prognostic biomarker in critically ill patients admitted to the intensive care unit (ICU) independently by their underlying clinical conditions.[23,24] Considering that patients with COVID-19 are at high risk of developing organ failure, MR-proADM could represent a useful prognostic biomarker.

The aim of the present study was to evaluate the potential prognostic value of MR-proADM to predict in-hospital mortality in patients with COVID-19.

Methods

Study Population

In this retrospective observational study, we enrolled all consecutive adult patients admitted to the COVID-19 units at the University Hospital P. Giaccone in Palermo, Italy, from September to October 2020. A SARS-CoV-2 infection was confirmed by a positive real-time reverse-transcription polymerase chain reaction mainly using naso-oropharyngeal swabs, in accordance with guidelines.[27]

Demographical and clinical information, including the length of stay (LOS), in-hospital mortality, and admission to ICU, was recorded for each patient. The primary endpoints for assessing COVID-19 severity were the requirement for mechanical ventilation and in-hospital mortality.

The local ethics committee approved the study, and all the clinical and biological assessments were carried out in accordance with the Declaration of Helsinki. For privacy respect, each patient was identified with an alphanumeric code. Informed consent was not required because the blood specimen used for study procedures was residual material that would have otherwise been discarded.

Hematological and Biochemical Analysis

All laboratory analyses were performed at the Laboratory Medicine Unit of the University Hospital P. Giaccone in Palermo. Routine hematological and biochemical parameters were measured upon admission. Specifically, hematological tests, including red and white blood cells, platelets, neutrophils, lymphocytes, and monocytes, were performed using the UniCel DxH 900 hematology analyzer (Beckman Coulter's Inc., Brea, CA).

Serum biochemical parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatine kinase (CK), lactate dehydrogenase (LDH), serum creatinine (sCR), high-sensitivity troponin T (hs-TnT), vitamin D, high-sensitivity CRP, IL-6, and PCT were measured on the Cobas 8000 (Roche, Basel, Switzerland), according to the manufacturer's procedures. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease EPIdemiology collaboration equation expressed for specified race, sex, and sCR in mg/dL.[28]

After the routine analyses were performed, an aliquot of plasma was collected within 3 hours of blood collection and stored at –80°C. The MR-proADM was measured by the time-resolved amplified cryptate emission technology (TRACE-Kryptor MR-proADM; BRAHMS AG, Henningsdorf, Germany), as previously described.[19,24] The MR-proADM

assay has a limit of detection of 0.05 nmol/L and a limit of quantification of 0.23 nmol/L, as declared by the manufacturer.

Statistical Analysis

Statistical analysis was performed using MedCalc v12.1.4.0 statistical software (MedCalc Software, Mariakerke, Belgium). Demographic and clinical characteristics were expressed as frequencies (percentage) for categorical data and median with interquartile ranges (IQR) for continuous data.

A Spearman correlation coefficient was used to assess the relationships between plasma MR-proADM levels and several clinical and laboratory parameters. Finally, receiver operating characteristic (ROC) curves with 95% confidence intervals (CI) were calculated to assess the prognostic ability of MR-proADM. A *P* value <.05 was considered statistically significant in all the calculations.

Results

Demographic and Clinical Features

One hundred ten patients admitted to converted COVID-19 units for SARS-CoV-2 infection were included in the study. Demographic and baseline clinical characteristics of patients are shown in **Table 1**.

Overall, 92 (84%) patients had pneumonia, and none of the patients at admission required intubation; 60 (55%) had more severe infections and needed noninvasive ventilation with positive airway pressure, and 50 (45%) had moderate respiratory symptoms. The median LOS was 13 days (IQR, 8–19). According to the clinical course of the disease, 2 (2%) patients were transferred to the ICU, and 14 patients (13%) died during hospitalization. The median (IQR) time to death was 9 (8–10) days.

Laboratory Findings

Table 2 shows the laboratory test findings. In the overall study population, we observed lymphocytopenia (lymphocytes <1.50 × $10^3/\mu L$). On admission, most patients showed normal levels of AST, ALT, total bilirubin, sCR, LDH, and CK. A weak increase in serum D-dimer and hs-TnT concentrations were observed in 37% and 51% of patients, with a median level of 850 ng/mL (IQR, 477–1420) and 19 pg/mL (IQR, 16–35), respectively. In addition, a moderate decrease in vitamin D levels in most patients (76%) was found, with a median level of 23 ng/mL (IQR,15.5–30). Similarly, eGFR values were reduced in only 24% of patients.

Table 1. General Characteristics, Comorbidities and Clinical Outcomes in the Study Population (n = 110)

Demographic Characteristics	
Median age, (IQR), y	62 (52–76)
Male sex, n (%)	61 (55)
Comorbidities	
Chronic respiratory disease, n (%)	93 (84)
Chronic kidney disease, n (%)	6 (5)
Diabetes, n (%)	8 (7)
Hypertension, n (%)	19 (17)
Severe cardiovascular disease, n (%)	2 (2)
Clinical outcomes	
Hospital stay, median (IQR), d	13 (8–19)
Hospital discharge, n (%)	29 (26)
ICU transfer, n (%)	2 (2)
Death, n (%)	14 (13)

ICU, intensive care unit; IQR, interquartile range.

As reported in **Table 2**, inflammation was the prominent feature of our studied population, with significantly higher CRP and IL-6 levels. In particular, CRP was >40 mg/L in nearly half of patients (47%), and IL-6 was elevated in 81 (74%) patients with a median level of 19 pg/mL (IQR, 7–38). The PCT was increased in 17 (15%) patients (median levels 0.103 ng/mL; IQR, 0.05–0.17).

In addition to classical inflammatory biomarkers, MR-proADM plasma levels were also significantly increased in 79 (72%) patients, with a median level of 0.93 nmol/L (IQR, 0.58–1.09).

We found that MR-proADM levels were correlated with biochemical parameters reflecting inflammation. In particular, we observed a statistically significant correlation between MR-proADM and CRP (r = .49; 95% CI, 0.30–0.64; P <.0001), LDH (r = .56; 95% CI, 0.39–0.69; P <.0001), IL-6 (r = .50; 95% CI, 0.29–0.66; P <.0001), PCT (r = .58; 95% CI, 0.39–0.73; P <.0001), and hs-TnT (r = .80; 95% CI, 0.68–0.88; P <.0001) values. Moreover, MR-proADM had a weakly positive correlation with total bilirubin (r = .28; 95% CI, 0.01–0.48; P = .01)

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Table 2. Laboratory Findings of Study Population (n = 110)

	Median (IQR)	Reference Interval	
Hematological parameters		**M**	**F**
White blood cell count, $10^3/\mu L$	8.0 (5.96–10.8)	3.6–10.2	3.8–11.8
Neutrophils, $10^3/\mu L$	6.2 (3.90–8.90)	1.7–8.2	
Lymphocytes, $10^3/\mu L$	0.90 (0.68–1.30)	1.0–3.2	
Monocytes, $10^3/\mu L$	0.55 (0.20–0.70)	0.2–1.1	
Eosinophils, $10^3/\mu L$	0 (0–0.02)	0–0.5	
Basophils, $10^3/\mu L$	0.01 (0–0.02)	0–0.1	
Red cells, $10^6/\mu L$	4.5 (4.1–4.8)	4.0–5.6	3.6–4.9
Hemoglobin, g/dL	13.4 (12–14)	12.5–16.0	11.0–14.0
MCV, fL	85 (82–90)	75–95	
MCH, pg	29 (28–31)	30–36	
RDW, fL	42 (39–44)	36.5–50.3	
Platelets, $10^3/\mu L$	222 (155–307)	150–400	
Biochemical parameters			
ALT, U/L	34 (21–51)	0–41	
AST, U/L	27 (20–40)	0–37	
Bilirubin, mg/dL	0.6 (0.4–0.8)	<1.20	
CK, U/L	70 (41–181)	26–192	
sCR, mg/dL	0.7 (0.55–0.8)	0.50–1.20	
D-dimer, ng/mL	850 (477–1420)	0–800	
eGFR, mL/min	82.5 (67–92.3)	>90	
LDH, U/L	228 (181–325)	50–250	
hs-TnT, pg/mL	19 (16–35)	<14	
Vitamin D, ng/mL	23.0 (15.5–30)	≥30	
Inflammatory parameters			
CRP, mg/dL	33 (18–79)	<5	
IL-6, pg/mL	19 (7–38)	<7	
PCT, ng/mL	0.103 (0.05–0.17)	<0.05	
MR-proADM, nmol/L	0.93 (0.58– 1.09)	<0.55	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; CK, creatine kinase; eGFR, estimated glomerular filtration rate; hs-TnT, high-sensitivity troponin T; IL-6, interleukin-6; IQR, interquartile range; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; MR-proADM, midregional proadrenomedullin; PCT, procalcitonin; RDW, red cell distribution width; sCR, serum creatinine.

and sCR (r = .25; 95% CI, 0.04–0.45; P = .02) and a negative correlation with vitamin D (r = –.37; 95% CI, –0.61 to –0.07; P = .01) and lymphocytes % (r = –.46; 95% CI, –0.66 to –0.20; P = .0009). No significant correlation was found between MR-proADM and ALT (r = .007; 95% CI, –0.21 to 0.23; P = .95), AST (r = .18; 95% CI, –0.04 to 0.38; P = .10), and CK (r = –.01; 95% CI, –0.23 to 0.20; P = .91).

MR-proADM in Risk Stratification of Patients with SARS-CoV-2

We found that MR-proADM was significantly associated with in-hospital mortality but not with LOS (r = .19; 95% CI, –0.13 to 0.48; P = .23). Indeed, patients who died (n = 14) during hospitalization had higher MR-proADM levels than patients who survived (n = 96; median, 2.59; IQR, 2.3–2.95 nmol/L; range, 1.89–10.58 nmol/L vs median, 0.82; IQR, 0.57–1.03 nmol/L; range, 0.44–2.63 nmol/L; P <.0001). According to the ROC curve analysis, the area under the curve (AUC) of MR-proADM for predicting mortality was 0.95 (95% CI, 0.86–0.99; Figure 1). An MR-proADM value of 1.73 nmol/L was identified as the optimal cutoff value for mortality prediction, with 90% sensitivity and 95% specificity (P <.0001).

Discussion

In this study, we sought to evaluate the prognostic value of MR-proADM in patients with COVID-19. Only a few studies have evaluated the role of such a biomarker in patients with SARS-CoV-2 infection.[29,30]

In our study, most patients showed altered levels of inflammatory biomarkers, such as lymphocytopenia, reduced vitamin D levels, and eGFR, along with increased D-dimer, hs-TnT, IL-6, CRP, and PCT levels, in accordance with the literature.[10,31] Notably, MR-proADM was significantly increased in 72% of patients. In addition, nonsurvivors

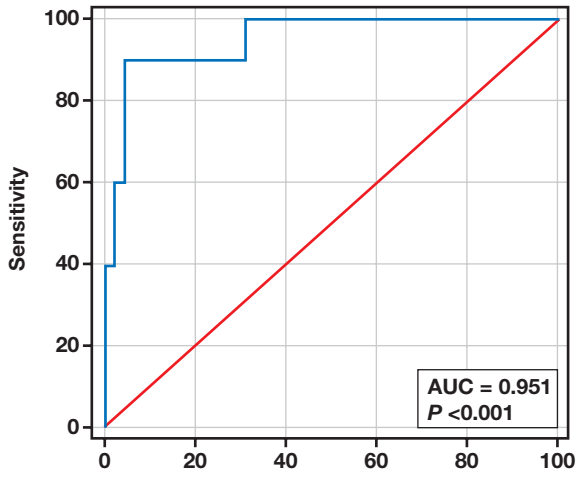

Figure 1

ROC curve analysis of MR-proADM for predicting in-hospital mortality. MR-proADM showed sensitivity of 90% and specificity of 95%; the cutoff value was 1.73 nmol/L. MR-proADM, midregional proadrenomedullin; ROC, receiver operating characteristic.

showed higher MR-proADM levels than survivors. The ROC analysis revealed a good accuracy of MR-proADM for predicting mortality with an AUC of 0.95 at a cutoff value of 1.73 nmol/L.

Finally, we found a significant correlation between MR-proADM and inflammatory biomarkers, as previously shown by studies performed in patients with other clinical conditions, such as pneumonia.[32-36] Overall, our findings suggest that the measurement of MR-proADM upon hospital admission could provide important prognostic information in patients with COVID-19.

To date, the role of different biomarkers in COVID-19 management, from diagnosis to treatment monitoring, has been assessed.[37] However, contrasting results have been achieved.[38-40] Indeed, COVID-19 is a disease about which much is still unknown, and there is active research to understand its pathogenesis and consequently to identify useful biomarkers. Among all the biomarkers currently studied, a role for hypovitaminosis D has been reported. Recently, Hernández et al[41] showed that more than 80% of patients hospitalized with COVID-19 had vitamin D deficiency, which was associated with inflammatory biomarkers. In accordance with such evidence, we found an association between reduced vitamin D levels and higher levels of MR-proADM. In addition, a recent review highlighted that approximately one-third of patients with COVID-19 showed neurological manifestations, particularly seizures and status epilepticus.[42-45]

In this study, we found an optimal MR-proADM cutoff value of 1.73 nmol/L, which is slightly lower than that established by Spoto et al[29] (2 nmol/L) but higher than that reported by Gregoriano et al[30] (0.93 nmol/L). Larger studies are required before introducing such a biomarker into clinical practice to confirm these preliminary findings and establish a unique cutoff value. Moreover, the mechanism underlying the increase of MR-proADM in patients with COVID-19 should be elucidated.

Our study presents some limitations. First, it is a single, monocenter, and retrospective study. Thus, it provides a snapshot of the biomarker within patients with COVID-19, allowing us to draw some conclusions mainly about the distribution of MR-proADM in our study population. In addition, the low rate of mortality could affect the robustness of the ROC curve analysis findings. Our strength is that we first evaluated the role of MR-proADM in a large population of patients with COVID-19.

Conclusion

The identification of biomarkers to define patients who are likely to deteriorate during their hospitalization could help clinicians to improve their clinical management. In this study, at hospital admission, patients with more severe COVID-19 showed higher levels of MR-proADM, together with other inflammatory biomarkers. Noteworthy, a variability in MR-proADM levels in COVID-19 patients exists. Our results agree with those of Spoto et al[29] but are different from those of Gregoriano et al,[30] who reported lower MR-proADM concentrations. Thus, further studies to determine a cutoff value are imperative.

Our findings encourage further investigation to confirm the usefulness of MR-proADM as a prognostic biomarker in patients with COVID-19. Such a biomarker can be easily and rapidly measured on a fully automated platform. Thus, MR-proADM could be part of a panel of biomarkers to evaluate the prognosis and assess the risk of developing complications.[46-50] **LM**

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