Mid-regional Proadrenomedullin Biomarker Predicts Coronavirus Disease 2019 Clinical Outcomes: A US-Based Cohort Study

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Background. Mid-regional proadrenomedullin (MR-proADM) is a biomarker released following endothelial damage. Studies have shown a correlation in predicting coronavirus disease 2019 (COVID-19) outcomes with MR-proADM levels. Our study aimed to investigate baseline MR-proADM as a predictor of a wider range of clinical outcomes of varying severity in patients admitted with COVID-19, and to compare to other biomarkers.

Methods. Data from the Boston Area COVID-19 Consortium (BACC) Bay Tocilizumab Trial was used in this study. Patients with biomarker determinations, and not admitted to the intensive care unit (ICU) on admission, were included. MR-proADM cutoff of 0.87 nmol/L was assessed in predicting clinical outcomes.

Results. Of 182 patients, 11.0% were mechanically ventilated or dead within 28 days. Of patients with MR-proADM >0.87 nmol/L, 21.1% were mechanically ventilated or dead within 28 days, compared with 4.5% of those with MR-proADM ≤0.87 nmol/L (P < .001). The sensitivity, specificity, negative predictive value, and positive predictive value of MR-proADM cutoff of 0.87 nmol/L in predicting mechanical ventilation or death were 75%, 65%, 95%, and 21%, respectively, with an area under the receiver operating characteristic curve of 0.76. On multivariable logistic regression analysis, MR-proADM >0.87 nmol/L was independently associated with mechanical ventilation or death, ICU admission, prolonged hospitalization beyond day 4, and day 4 COVID-19 ordinal scale equal to or worse than day 1.

Conclusions. MR-proADM functions as a valuable biomarker for the early risk stratification and detection of severe disease progression of patients with COVID-19. In the prediction of death, MR-proADM performed better compared to many other commonly used biomarkers.

Keywords. biomarkers; COVID-19; ICU; MR-proADM; viral pneumonia.

Infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), manifest in a range of symptoms, ranging from mild flu-like symptoms to severe pneumonia, leading to acute respiratory distress syndrome (ARDS) and resulting in significantly high rates of mortality and complications [1, 2].

A central component of the SARS-CoV-2 infection and disease pathogenesis is vascular endothelial damage and dysfunction [3–5]. SARS-CoV-2 enters host cells using angiotensin-converting enzyme 2 receptors, which are mainly found on alveolar epithelial type 2 cells, and on vascular endothelial cells, enterocytes, pancreas, heart, and tubular epithelium of the kidney [6–10]. SARS-CoV-2 proliferation in endothelial cells has been hypothesized to cause dysfunction and apoptosis, in addition to systemic effects mediated by an extensive release of cytokines and adhesion molecules. These events lead to an induction of a procoagulative state, endothelial inflammation, and vascular leakage [3, 11, 12].

Adrenomedullin (ADM) is mainly produced in vascular endothelial cells [13], and its main role is vasodilation [14], especially in coronary and pulmonary arteries [15, 16]. ADM has additional physiologic roles including inhibition of neovascularization [14] and maintenance of vascular integrity [17].

Thus, the endothelial damage caused by SARS-CoV-2 and the resulting increased vascular permeability interferes with the ADM system and leads to increased production of ADM, which...
plays a protective role on vascular integrity [18–20]. Mid-regional proadrenomedullin (MR-proADM) is a byproduct released during the cleavage and maturation process of adrenomedullin precursor proteins [21]. In a recent randomized controlled trial (RCT), MR-proADM was shown to be significantly elevated in sepsis, serving as a reliable biomarker in identifying disease severity and response to treatment [22]. MR-proADM has also been shown to be a prognostic tool in patients with lower respiratory tract infections [23, 24]. A limited number of small sample–sized studies suggested a possible role of MR-proADM in predicting clinical outcomes, mainly mortality, in patients with COVID-19 [25–33].

The MR-proADM cutoff of 0.87 nmol/L was previously derived for early identification of disease progression and guiding hospital admission of patients presenting to the emergency department with suspected infection [34, 35]. In this study, we sought to investigate the prognostic performance of MR-proADM in patients with COVID-19 in predicting a wide variety of clinical outcomes, by performing an exploratory analysis using data for MR-proADM results from a recently completed multicenter, randomized, double-blinded, placebo-controlled trial investigating tocilizumab for COVID-19 (the Boston Area COVID-19 Consortium [BACC] Bay Tocilizumab Trial) [36]. The trial found tocilizumab, a monoclonal antibody that blocks the interleukin 6 (IL-6) receptor, not to be effective in treating patients with COVID-19 early in their infection course [36].

We hypothesized that the MR-proADM cutoff of 0.87 nmol/L could have clinically relevant prognostic performance for the risk stratification of patients with COVID-19.

METHODS

Patients

Data from the BACC Bay Tocilizumab Trial, which was collected from 7 hospitals in Boston, were used in this study [36].

Patient Consent Statement

Informed consent was obtained on all subjects enrolled in the study. All procedures and design of work were approved and conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975. This work was approved by the Mass General Brigham Institutional Review Board on 15 April 2020 as protocol 2020P001159 and registered on ClinicalTrials.gov (NCT04356937).

In brief, the inclusion criteria for the BACC Bay Tocilizumab Trial were patients aged 19–85 years, with a positive SARS-CoV-2 infection by nasopharyngeal swab polymerase chain reaction or serum immunoglobulin M antibody assay. Additionally, the patients had to be symptomatic with at least 2 of the following: fever >38°C, lung infiltrates, or needing supplemental oxygen. The detailed inclusion and exclusion criteria are found in the methods and protocol of the BACC Bay Tocilizumab Trial [36]. Patients underwent randomization on the day of admission in a 2:1 ratio to receive tocilizumab (8 mg/kg with an upper limit of 800 mg) or placebo. Patients with complete data on all studied biomarkers, who underwent randomization, and were not already admitted to the intensive care unit (ICU) at enrollment were included in this study. Both study arms were pooled due to comparable efficacy and adverse events.

The main outcome, also primary endpoint of the BACC Bay Tocilizumab Trial, was the composite endpoint mechanical ventilation or death within 28 days of randomization, since some patients had died without being mechanically ventilated. Secondary outcomes studied that occurred within the 28 days were death, ICU admission, clinical worsening on the COVID-19 ordinal scale, composite severity endpoint (at least 1 of the following: death, ICU admission, mechanical ventilation), day 4 COVID-19 ordinal scale ≥4, prolonged hospitalization beyond day 4, day 4 COVID-19 ordinal scale equal to or worse than day 1, mechanical ventilation, deep vein thrombosis (DVT), pulmonary embolism (PE), and stroke. The composite endpoint “any thrombotic event” was defined as patients with any of the following outcomes: DVT, PE, or stroke. The COVID-19 ordinal scale is a graded clinical scale representing disease severity. It is based on ICU admission, oxygen supplementation, mechanical ventilation, death, or if the patient is ready to be discharged to home. Worsening on the COVID-19 ordinal scale is defined as an increase of 2 points or more in patients not receiving supplemental oxygen, or an increase of 1 point or more in patients on supplemental oxygen [36].

Plasma Samples

Ethylenediaminetetraacetic acid plasma samples were collected, isolated, and aliquoted into cryovials within 2–12 hours of venipuncture. Cryovials were stored at −80°C until they were thawed to be assayed on a Brahms MR-proADM KRYPTOR for MR-proADM concentration determination [37]. Storage durations from collection to MR-proADM concentration determination were between 2.5 and 8 months. Other biomarkers were assayed through standard methods in the clinical core laboratory during the period of the trial.

The main biomarker analyzed in this study was day 1 MR-proADM, measured on the day of admission and randomization, and was compared to other biomarkers measured on day 1, including C-reactive protein (CRP), D-dimer, ferritin, IL-6, lactate dehydrogenase, lymphocytes, and procalcitonin (PCT). All other biomarkers were determined through standard assays available through the clinical core laboratory.

The following standard cutoffs from the literature were used to binarize biomarker results: 0.87 nmol/L for MR-proADM [34, 35] and 35 pg/mL for IL-6 [38, 39]. The MR-proADM cutoff of 0.87 nmol/L was derived as an optimal cutoff value using Youden criterion in a multicenter derivation and validation.
study, aiming to identify disease progression early on in patients with suspected infection in the emergency department [34]. The cutoff was later found to be effective in reducing hospitalization in a low-severity cohort of patients with infections [35].

Statistical Analysis
Standard descriptive statistics methods were used to summarize patient characteristics. Differences between patient groups were analyzed by statistical hypothesis testing, applying the χ² test or Fisher’s exact test when applicable for categorical factors, and the Mann-Whitney U test for numeric factors.

Biomarker results were visualized by boxplots stratified by patient risk factors and outcome level (event vs no event). Measures of prognostic performance were sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) for binary biomarkers, and area under the receiver operating characteristic (ROC) curve (AUC) for numeric biomarkers. Estimates and 95% confidence intervals (CIs) were reported. CIs of sensitivity, specificity, PPV, and NPV were computed according to Clopper and Pearson.

Kaplan-Meier curves were plotted and the log-rank test was performed, stratified by binary MR-proADM (levels ≤0.87 nmol/L vs >0.87 nmol/L).

Multiple multivariable logistic regression analyses with different variables being controlled for were conducted to evaluate if MR-proADM was an independent predictor of clinical outcomes. Variables adjusted for included age (numeric), sex (levels: female, male), body mass index (BMI) (>30 kg/m², ≤30 kg/m²), diabetes (yes, no), hypertension (yes, no), heart failure (yes, no), history of myocardial infarction (MI) (yes, no), chronic obstructive pulmonary disease (COPD) (yes, no), chronic kidney disease (CKD) (yes, no), and days from symptom onset to randomization and MR-proADM measurement (days). Odds ratios (ORs) were reported for binary MR-proADM (levels ≤0.87 nmol/L vs >0.87 nmol/L) with estimate, 95% CIs, and P values.

All statistical testing was 2-sided and P values <.05 were considered statistically significant. P values were not adjusted for multiple testing. Software R version 3.5.1 and the R package pROC version 1.15.3 were used for statistical analyses [40, 41], with R package ggplot2 version 3.2.1 to generate boxplots [42]. Stata version 14.1 was used to generate Kaplan-Meier figures, log-rank tests, and multivariable logistic regression analyses [43].

RESULTS
Overall Cohort Characteristics
Of the 243 patients who underwent randomization in the trial, 191 patients had data on all biomarkers. Additionally, 9 patients who were already admitted to the ICU at enrollment were not included in this study. In the included study sample, 68.1% were in the tocilizumab arm and 31.9% were in the placebo arm (Supplementary Figure 1).

Of the remaining 182 patients, 11.0% were mechanically ventilated or dead within 28 days. Of patients with day 1 MR-proADM >0.87 nmol/L, 21.1% were mechanically ventilated or dead within 28 days, compared with 4.5% of those with MR-proADM ≤0.87 nmol/L (P <.001). Demographics of the study population are summarized in Table 1. The median age was 56.5 years, 41.2% were female, and 51.7% had a BMI ≥30 kg/m². The rates of diabetes, hypertension, heart failure, history of MI, and COPD were 28.2%, 45.1%, 8.8%, 9.4%, and 7.2%, respectively. Median time from symptom onset to MR-proADM measurement was 9 days (interquartile range [IQR], 6–13). Median (IQR) day 1 biomarker levels were as follows: MR-proADM, 0.76 nmol/L (0.59–1.17); IL-6, 22.08 pg/mL (13.53–40.25); lymphocytes, 1.04 K/µL (0.73–1.36); LDH, 325.00 U/L (286.50–397.75); CRP, 99.55 mg/L (64.08–147.70); D-dimer, 794.00 ng/mL (507.25–1526.50); PCT, 0.15 ng/mL (0.09–0.30); and ferritin, 668.00 ng/mL (376.50–1011.50). When stratified by risk factors, the median level of MR-proADM was significantly higher in patients who had hypertension, heart failure, history of MI, COPD, or CKD (Supplementary Figure 2).

Elevated MR-proADM Correlates With Worse Clinical Outcomes in SARS-CoV-2 Infection
Patients with MR-proADM >0.87 nmol/L had significantly higher rates of ICU admission, compared to those with levels ≤0.87 nmol/L (18.3% vs 8.1%, P = .039), and prolonged hospitalization beyond day 4 (91.6% vs 55.9%, P <.001). Additionally, patients with MR-proADM >0.87 nmol/L had significantly higher rates of clinical worsening on the COVID-19 ordinal scale compared to those with ≤0.87 nmol/L (26.8% vs 11.7%, P = .009), with 83.1% of those with MR-proADM >0.87 nmol/L having day 4 COVID-19 ordinal scale equal to or worse than day 1 compared to 46.9% for ≤0.87 nmol/L (P <.001). No significant difference was observed in DVT, PE, stroke, or any thrombotic event between patients with MR-proADM >0.87 nmol/L compared to those with MR-proADM ≤0.87 nmol/L (Table 2).

Kaplan-Meier curves for mechanical ventilation or death, ICU admission, and clinical worsening on the COVID-19 ordinal scale are shown in Figure 1. The respective log-rank test P values comparing MR-proADM ≤0.87 nmol/L to >0.87 nmol/L were P <.001, P = .038, and P = .010.

MR-proADM Is Equivalent to IL-6 for Prognostication of ICU-Level Needs
The median level of day 1 MR-proADM in the study population was 0.76 nmol/L, and the median level of day 1 IL-6 was 22.08 pg/mL. Median levels of MR-proADM were significantly higher in patients who were mechanically ventilated or dead within 28 days compared to those who were not (1.42 nmol/L [IQR, 0.88–1.98] vs 0.73 nmol/L [IQR, 0.58–1.04], event vs no event), had a prolonged hospitalization beyond day 4 (0.89 nmol/L [IQR,
Median levels of IL-6 followed a similar trend as MR-proADM, between MR-proADM strata was determined by the 𝜒² test or the Fisher’s exact test when applicable for categorial factors, and the Mann-Whitney U test for numeric factors. P-values were not corrected for multiple testing.

Unless otherwise noted, data are presented as No. (%); percentages indicate either the proportion of the total population or the respective MR-proADM stratum. Statistical significance between MR-proADM strata was determined by the 𝜒² test or the Fisher’s exact test when applicable for categorial factors, and the Mann-Whitney U test for numeric factors. P-values were not corrected for multiple testing.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; MR-proADM, mid-regional proadrenomedullin.

aOne patient with MR-proADM ≥0.87 nmol/L was excluded from statistical testing due to missing data on diabetes, heart failure, history of myocardial infarction, chronic obstructive pulmonary disorder, asthma, chronic kidney disease, and history of cancer.

bTwo patients with MR-proADM ≥0.87 nmol/L were excluded from statistical testing due to missing data on smoking status.

0.65–1.30] vs 0.68 nmol/L [IQR, 0.55–0.77], event vs no event), were admitted to the ICU (0.93 nmol/L [IQR, 0.74–1.83] vs 0.74 nmol/L [IQR, 0.58–1.07], event vs no event), and had a day 4 COVID-19 ordinal scale equal to or worse than day 1 (0.90 nmol/L [IQR, 0.65–1.26] vs 0.69 nmol/L [IQR, 0.56–0.81], event vs no event) (Table 3 and Supplementary Figure 3). Median levels of IL-6 followed a similar trend as MR-proADM, being significantly higher in patients with the aforementioned clinical outcomes (Table 3 and Supplementary Figure 4).

MR-proADM and IL-6 were compared for prognostic performance (Supplementary Table 1). The sensitivity, specificity, NPV, and PPV of MR-proADM at the cutoff of 0.87 nmol/L in predicting mechanical ventilation or death were 75% (95% CI, 51%–91%), 65% (95% CI, 58%–73%), 95% (95% CI, 90%–99%), and 21% (95% CI, 12%–32%), respectively. Compared to MR-proADM, plasma IL-6 had a lower sensitivity of 65% (95% CI, 41%–85%), a higher specificity of 72% (95% CI, 65%–79%), and similar NPV and PPV of 94% (95% CI, 89%–98%) and 22% (95% CI, 13%–35%), respectively. MR-proADM also had a high NPV of 92% (95% CI, 85%–96%) in predicting ICU admission, similar to the 95% NPV of IL-6 (95% CI, 90%–98%). In predicting prolonged
hospitlization beyond day 4, and a worsening day 4 COVID-19 ordinal scale compared to day 1, MR-proADM had high specificity and PPV (89% [95% CI, 78%–96%] and 92% [95% CI, 83%–97%] for prolonged hospitalization beyond day 4; 83% [95% CI, 72%–91%] and 83% [95% CI, 72%–91%] for worsening day 4 COVID-19 ordinal scale compared to day 1), but low sensitivity and NPV (51% [95% CI, 42%–60%] and 44% [95% CI, 35%–54%] for prolonged hospitalization beyond day 4; 53% [95% CI, 43%–63%] and 53% [95% CI, 43%–63%] for worsening day 4 COVID-19 ordinal scale compared to day 1), slightly outperforming plasma IL-6.

MR-proADM Has High Prognostic Performance Compared to Other Inflammatory Biomarkers

Given the general utilization of other inflammatory biomarkers in the management of patients with COVID-19, we next sought to perform a comparison to other conventional inflammatory biomarkers. We compared MR-proADM to IL-6, CRP, D-dimer, ferritin, LDH, lymphocyte cell counts, and PCT. MR-proADM had a high AUC for the ROC curve of 0.76 (95% CI, 0.66–0.86) in predicting mechanical ventilation or death (Figure 2). For prolonged hospitalization beyond day 4 and worsening day 4 COVID-19 ordinal scale compared to day 1, MR-proADM and IL-6 had similar AUCs for the ROC curve: 0.71 (95% CI, 0.63–0.78) vs 0.70 (95% CI, 0.62–0.77), and 0.67 (95% CI, 0.59–0.75) vs 0.68 (95% CI, 0.61–0.76), respectively. For ICU admission, IL-6 had a higher AUC for the ROC curve of 0.78 (95% CI, 0.68–0.88) compared to MR-proADM (0.69 [95% CI, 0.59–0.80]) (Table 4).

On multivariable logistic regression analysis, when controlling for age, sex, BMI, and diabetes, binary MR-proADM with cutoff 0.87 nmol/L was found to be independently associated with mechanical ventilation or death, ICU admission, prolonged hospitalization beyond day 4, and day 4 COVID-19 ordinal scale equal to or worse than day 1, with odds ratios of 5.25 (95% CI, 1.47–18.71), 2.97 (95% CI, 1.03–8.55), 7.72 (95% CI, 2.9–20.56), and 4.58 (95% CI, 2.1–9.98), respectively (Supplementary Table 2).

When additional regression models were made to control for hypertension, heart failure, history of MI, COPD, and CKD, MR-proADM with cutoff 0.87 nmol/L remained significantly associated with the outcomes mechanical ventilation or death, prolonged hospitalization beyond day 4, and day 4 COVID-19 ordinal scale equal to or worse than day 1. However, when different regression models were performed controlling for hypertension, heart failure, history of MI, COPD, and CKD, MR-proADM with cutoff 0.87 nmol/L was not significantly associated with ICU admission. Additionally, when controlled for duration of symptoms, MR-proADM >0.87 nmol/L remained independently associated with the outcomes prolonged hospitalization beyond day 4 and day 4 COVID-19 ordinal scale equal to or worse than day 1, but not with mechanical ventilation or death and ICU admission (Supplementary Table 2).

We also performed further analyses of the 2 arms of the BACC Bay Tocilizumab Trial using MR-proADM levels, looking at the performance of tocilizumab in patients with COVID-19 with MR-proADM >0.87 nmol/L compared to those with ≤0.87 nmol/L. The tocilizumab arm did not have any significant difference in mortality or mechanical ventilation compared to the control arm for both groups: patients with MR-proADM >0.87 nmol/L (17.7% vs 30.0%, P = .333) and ≤0.87 nmol/L (5.5% vs 2.6%, P = .659), when using the Fisher’s exact test.

DISCUSSION

In this study, we demonstrate that elevated MR-proADM levels on admission correlate with adverse clinical outcomes in patients with COVID-19.

Studies from several centers in Europe have reported MR-proADM as a predictor of mortality with cutoffs ranging
Figure 1. Kaplan-Meier curves for mid-regional proadrenomedullin cutoff 0.87 nmol/L. A, Mechanical ventilation or death. B, Intensive care unit admission. C, Clinical worsening on the coronavirus disease 2019 ordinal scale.
We showed that an MR-proADM cutoff of 0.87 nmol/L predicts not only the composite outcome of mechanical ventilation or death within 28 days, but also ICU admission, prolonged hospitalization beyond day 4, day 4 COVID-19 ordinal scale equal to or worse than day 1, and clinical worsening on the COVID-19 ordinal scale. When controlled for age, sex, BMI, and diabetes, binary MR-proADM (cutoff 0.87 nmol/L) remained an independent predictor of clinical outcomes.

We attribute the absence of a significant difference in the outcomes of DVT, PE, and stroke between patients with high and low MR-proADM levels, potentially due to the low number of patients with these outcomes in our study sample. IL-6 has been reported as a useful tool for the prediction of disease severity and clinical outcomes in patients with COVID-19 [38, 44], with a focus mainly on mortality [38, 45] and mechanical ventilation [39]. In our study, we show that an MR-proADM cutoff of 0.87 nmol/L has a higher sensitivity than an IL-6 cutoff of 35 pg/mL in predicting mechanical ventilation or death. We also demonstrate that MR-proADM is equivalent to IL-6 for prognostication of ICU-level needs with a high NPV, and for predicting prolonged hospitalization beyond day 4. Additionally, when comparing to other biomarkers such as CRP, D-dimer, ferritin, LDH, lymphocytes, and PCT, MR-proADM has a superior AUC for the ROC curve of 0.76 in predicting mechanical ventilation or death.

Our study has several limitations. This study is based on an RCT of patients with COVID-19, and the role of MR-proADM in other types of infections (other viruses, bacteria, or fungi) or clinical settings such as vascular diseases needs to be determined. Interestingly, MR-proADM has been shown to be
Table 4. Area Under the Receiver Operating Characteristic Curves With 95% Confidence Intervals of Biomarkers in Predicting Clinical Outcomes

| Biomarker | Mechanical Ventilation or Death | ICU Admission | Prolonged Hospitalization Beyond Day 4 | Day 4 COVID-19 Ordinal Scale Equal to or Worse Than 1 | Death Within 28 Days | Death or ICU Admission or Mechanical Ventilation | Mechanical Ventilation Within 28 Days | Day 4 COVID-19 Ordinal Scale 2-4 | Clinical Worsening on the COVID-19 Ordinal Scale |
|-----------|---------------------------------|--------------|--------------------------------------|---------------------------------|---------------------|---------------------------------------|-----------------------------------|-----------------|----------------------------------|
| MR-proADM | 0.76 (0.66–0.86)                | 0.69 (0.59–0.80) | 0.71 (0.63–0.78)                      | 0.67 (0.59–0.75)               | 0.86 (0.78–0.94)   | 0.73 (0.64–0.83)                      | 0.69 (0.57–0.82)       | 0.69 (0.58–0.79)       | 0.70 (0.60–0.80)       |
| IL-6      | 0.73 (0.63–0.83)                | 0.78 (0.68–0.88) | 0.70 (0.62–0.77)                      | 0.68 (0.61–0.76)               | 0.67 (0.52–0.83)   | 0.75 (0.65–0.84)                      | 0.76 (0.66–0.87)       | 0.73 (0.61–0.85)       | 0.73 (0.63–0.83)       |
| Lymphocytes* | 0.65 (0.50–0.80)              | 0.64 (0.50–0.78) | 0.66 (0.58–0.75)                      | 0.65 (0.57–0.73)               | 0.68 (0.40–0.91)   | 0.66 (0.53–0.79)                      | 0.67 (0.51–0.83)       | 0.66 (0.51–0.80)       | 0.69 (0.58–0.80)       |
| LDH       | 0.63 (0.48–0.78)                | 0.68 (0.54–0.82) | 0.58 (0.50–0.67)                      | 0.61 (0.52–0.69)               | 0.56 (0.33–0.78)   | 0.68 (0.54–0.81)                      | 0.65 (0.48–0.82)       | 0.68 (0.53–0.82)       | 0.60 (0.50–0.71)       |
| CRP       | 0.62 (0.50–0.75)                | 0.61 (0.48–0.74) | 0.51 (0.42–0.59)                      | 0.51 (0.43–0.60)               | 0.69 (0.56–0.81)   | 0.62 (0.51–0.74)                      | 0.59 (0.44–0.74)       | 0.67 (0.54–0.79)       | 0.48 (0.37–0.59)       |
| D-dimer   | 0.56 (0.42–0.70)                | 0.49 (0.37–0.61) | 0.56 (0.47–0.64)                      | 0.57 (0.48–0.65)               | 0.60 (0.36–0.83)   | 0.53 (0.41–0.66)                      | 0.49 (0.36–0.63)       | 0.51 (0.38–0.64)       | 0.47 (0.37–0.58)       |
| PCT       | 0.54 (0.40–0.67)                | 0.57 (0.45–0.69) | 0.60 (0.50–0.69)                      | 0.54 (0.45–0.62)               | 0.60 (0.36–0.83)   | 0.55 (0.44–0.67)                      | 0.52 (0.38–0.66)       | 0.55 (0.42–0.67)       | 0.48 (0.36–0.59)       |
| Ferritin  | 0.49 (0.34–0.63)                | 0.45 (0.31–0.59) | 0.58 (0.49–0.67)                      | 0.56 (0.48–0.64)               | 0.47 (0.36–0.68)   | 0.48 (0.36–0.61)                      | 0.47 (0.29–0.64)       | 0.42 (0.29–0.55)       | 0.70 (0.60–0.80)       |

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ICU, intensive care unit; IL-6, interleukin 6; LDH, lactate dehydrogenase; MR-proADM, mid-regional proadrenomedullin; PCT, procalcitonin.

*For lymphocytes, we assumed that risk increased with decreasing lymphocyte levels.
COVID-19, to better define the applicability and utility of this novel biomarker in the management, prognosis, and monitoring of the clinical response of patients with SARS-CoV-2 and other respiratory infections. Further studies are also warranted to better understand the correlation of MR-proADM with symptom onset in COVID-19, in addition to the validation of MR-proADM in breakthrough infections of SARS-CoV-2 among vaccinated patients against COVID-19. Additional studies are also required to define the role of MR-proADM in patients with COVID-19 with thrombosis and proven vascular diseases, such as PE, DVT, microvascular diseases including ARDS, rheumatologic vasculitides, and systemic infectious diseases, in addition to non–COVID-19–related pathologies.

CONCLUSIONS

MR-proADM functions as a valuable prognostic biomarker in predicting clinical outcomes, specifically death at 28 days, by performing better than other biomarkers commonly used in the management of COVID-19. MR-proADM with cutoff 0.87 nmol/L is independently associated with mechanical ventilation or death, ICU admission, prolonged hospitalization beyond day 4, and a worsening day 4 COVID-19 ordinal scale compared to day 1. Additional studies including serial measurements are required to better define utilization of MR-proADM in management and prognosis of patients with SARS-CoV-2.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. N. J. A., V. S. P., C. J. A., and M. K. M. designed the study. N. J. A. and M. K. M. acquired the data. V. S. P., A. S., S. J., and J. W. analyzed the data. N. J. A., V. S. P., C. J. A., and M. K. M. interpreted the results and wrote the manuscript. All authors revised and approved the final manuscript and agree to be accountable for all aspects of the work.

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