Open Forum Infectious Diseases

MAJOR ARTICLE

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

Natalie J. Atallah,[1,2,3,a] Vahe S. Panossian,[4,a] Christine J. Atallah,[5] Andrej Schwabe,[6] Sascha Johannes,[6] Jan Wiemer,[6] and Michael K. Mansour[1,2,3]

[1]Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts, USA, [2]Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA, [3]Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA, [4]Faculty of Medicine, American University of Beirut Medical Center, Beirut, Lebanon, [5]Faculty of Medicine, University of Balamand, Beirut, Lebanon, and [6]B·R·A·H·M·S GmbH, part of Thermo Fisher Scientific, Hennigsdorf, Germany

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

Received 29 June 2022; editorial decision 11 August 2022; published online 24 August 2022
[a]N. J. A. and V. S. P. contributed equally to this work.

Correspondence: Michael K. Mansour, MD, PhD, Massachusetts General Hospital, Division of Infectious Diseases, Gray-Jackson Bldg, Room 1328A, 55 Fruit St, Boston, MA 02114 (mkmansour@mgh.harvard.edu).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofac423

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 $\geq$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 χ^2 test or Fisher's exact test when applicable for categorial 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/m^2, ≤30 kg/m^2), 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/m^2. 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,

Table 1. Demographics and Baseline Characteristics of the Study Population: Total and Stratified by Binary Mid-regional Proadrenomedullin (Cutoff 0.87 nmol/L)

Characteristic	Total (n = 182)	MR-proADM ≤0.87 nmol/L (n = 111)	MR-proADM >0.87 nmol/L (n = 71)	*P* Value
Age, y, median (IQR)	56.5 (44.0–67.0)	48.0 (42.0–60.0)	65.0 (57.0–75.0)	<.001
Female sex	75 (41.2)	42 (37.8)	33 (46.5)	.248
Race				<.001
American Indian/Alaska Native	1 (0.6)	1 (0.9)	0 (0.0)	
Asian	6 (3.3)	2 (1.8)	4 (5.6)	
Black	27 (14.8)	18 (16.2)	9 (12.7)	
Native Hawaiian/Pacific Islander	1 (0.6)	1 (0.9)	0 (0.0)	
White	82 (45.1)	37 (33.3)	45 (63.4)	
Other	38 (20.9)	31 (27.9)	7 (9.9)	
Unknown	27 (14.8)	21 (18.9)	6 (8.5)	
Ethnicity				<.001
Hispanic or Latino	89 (48.9)	73 (65.8)	16 (22.5)	
Not Hispanic or Latino	86 (47.3)	34 (30.6)	52 (73.2)	
Unknown	7 (3.9)	4 (3.6)	3 (4.2)	
BMI, kg/m^2, median (IQR)	30.2 (26.6–34.2)	30.7 (27.4–34.4)	29.5 (24.2–34.0)	.063
BMI ≥30 kg/m^2	94 (51.7)	61 (55.0)	33 (46.5)	.264
Days from symptom onset to MR-proADM measurement, median (IQR)	9.0 (6.0–13.0)	10.0 (8.0–13.0)	8.0 (4.0–12.0)	.005
Diabetes[a]	51 (28.2)	29 (26.4)	22 (31.0)	.500
Hypertension	82 (45.1)	37 (33.3)	45 (63.4)	<.001
Heart failure[a]	16 (8.8)	3 (2.7)	13 (18.3)	<.001
History of myocardial infarction[a]	17 (9.4)	4 (3.6)	13 (18.3)	.001
COPD[a]	13 (7.2)	5 (4.6)	8 (11.3)	.087
Asthma[a]	16 (8.8)	12 (10.9)	4 (5.6)	.222
Smoking status[b]				.001
Current	4 (2.2)	3 (2.8)	1 (1.4)	
Former	49 (27.2)	18 (16.5)	31 (43.7)	
Never	115 (63.9)	78 (71.6)	37 (52.1)	
Unknown	12 (6.7)	10 (9.2)	2 (2.8)	
Chronic kidney disease[a]	25 (13.8)	2 (1.8)	23 (32.4)	<.001
History of cancer[a]	22 (12.2)	11 (10.0)	11 (15.5)	.269
Baseline COVID-19 ordinal scale				.665
2	28 (15.4)	18 (16.2)	10 (14.1)	
3	153 (84.1)	92 (82.9)	61 (85.9)	
4	1 (0.6)	1 (0.9)	0 (0.0)	

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 χ^2 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.

[a]One 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.

[b]Two 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

Table 2. Outcomes Within 28 Days: Total and Stratified by Binary Mid-regional Proadrenomedullin (Cutoff 0.87 nmol/L)

Outcome	Total (n = 182)	MR-proADM ≤0.87 nmol/L (n = 111)	MR-proADM >0.87 nmol/L (n = 71)	*P* Value
Mechanical ventilation or death within 28 d	20 (11.0)	5 (4.5)	15 (21.1)	<.001
ICU admission	22 (12.1)	9 (8.1)	13 (18.3)	.039
Day 4 COVID-19 ordinal scale ≥4	20 (11.0)	9 (8.1)	11 (15.5)	.120
Clinical worsening on the COVID-19 ordinal scale	32 (17.6)	13 (11.7)	19 (26.8)	.009
Prolonged hospitalization beyond day 4	127 (69.8)	62 (55.9)	65 (91.6)	<.001
Death or ICU admission or mechanical ventilation	26 (14.3)	9 (8.1)	17 (23.9)	.003
Death within 28 d	9 (5.0)	1 (0.9)	8 (11.3)	.003
Day 4 COVID-19 ordinal scale equal to or worse than day 1	111 (61.0)	52 (46.9)	59 (83.1)	<.001
Mechanical ventilation within 28 d	15 (8.2)	5 (4.5)	10 (14.1)	.022
Deep vein thrombosis	3 (1.7)	2 (1.8)	1 (1.4)	.999
Pulmonary embolism	3 (1.7)	2 (1.8)	1 (1.4)	.999
Stroke	1 (0.6)	0 (0.0)	1 (1.4)	.390
Any thrombotic event[a]	7 (3.9)	4 (3.6)	3 (4.2)	.999

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 χ^2 test or the Fisher's exact test when applicable. *P* values were not corrected for multiple testing.

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; MR-proADM, mid-regional proadrenomedullin.

[a]Any thrombotic event was defined as patients with any of the following outcomes: deep vein thrombosis, pulmonary embolism, or stroke.

hospitalization 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, .66–.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, .63–.78) vs 0.70 (95% CI, .62–.77), and 0.67 (95% CI, .59–.75) vs 0.68 (95% CI, .61–.76), respectively. For ICU admission, IL-6 had a higher AUC for the ROC curve of 0.78 (95% CI, .68–.88) compared to MR-proADM (0.69 [95% CI, .59–.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

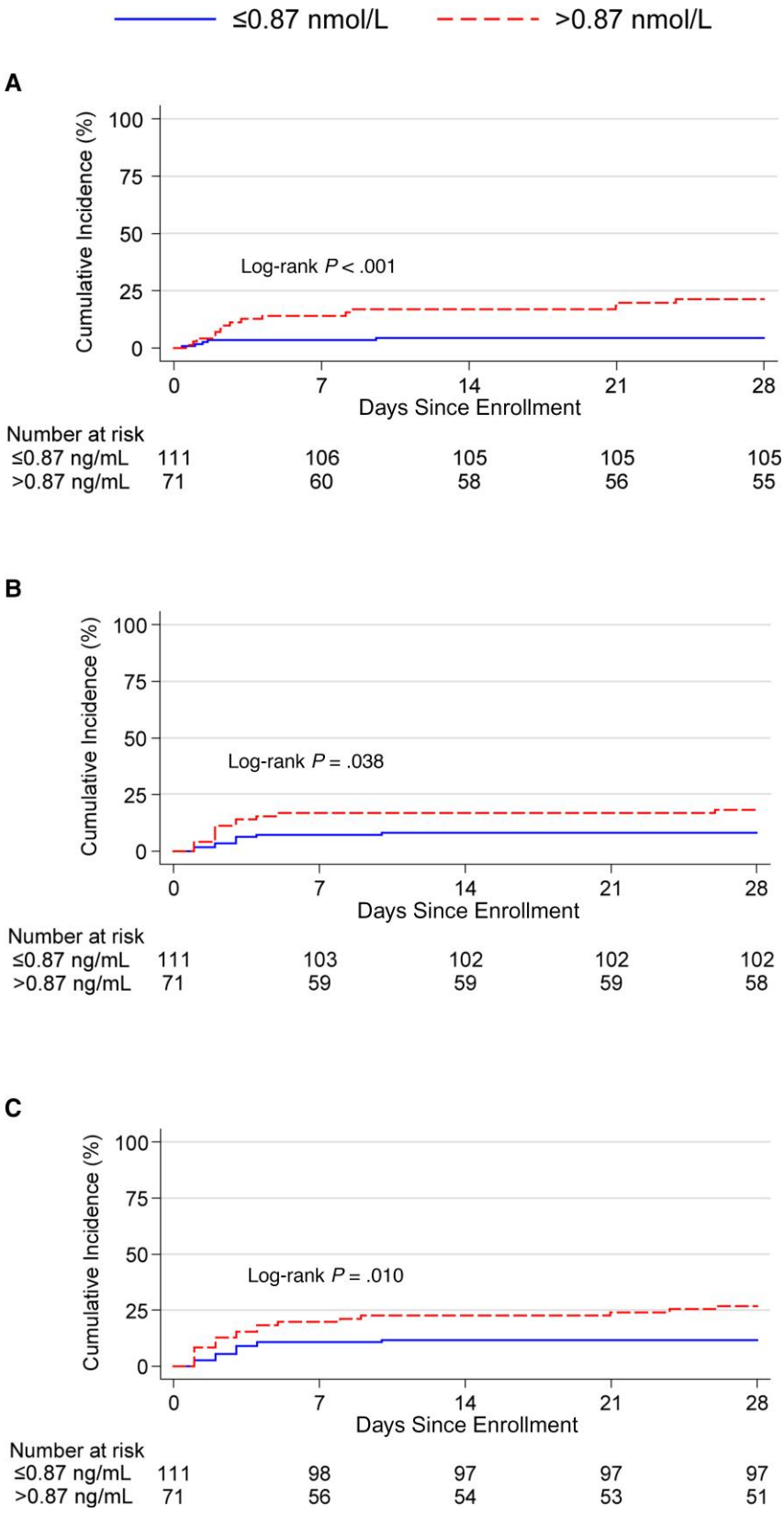

Figure 1. Kaplan-Meier curves for mid-regional proadrenomedullin cutoff 0.87 nmol/L. *A*, Mechanical ventilation or death. *B*, Intensive care unit admission. *C*, Clinical worsening on the coronavirus disease 2019 ordinal scale.

Table 3. Distribution of Mid-regional Proadrenomedullin Levels and Interleukin 6, Stratified by Studied Clinical Outcomes

Biomarker	Outcome	Median (IQR)			*P* Value
		All Patients	Patients With Event	Patients Without Event	
MR-proADM, nmol/L	Mechanical ventilation or death	0.76 (0.59–1.17)	1.42 (0.88–1.98)	0.73 (0.58–1.04)	<.001
	Prolonged hospitalization beyond day 4		0.89 (0.65–1.30)	0.68 (0.55–0.77)	<.001
	ICU admission		0.93 (0.74–1.83)	0.74 (0.58–1.07)	.004
	Day 4 COVID-19 ordinal scale equal to or worse than day 1		0.90 (0.65–1.26)	0.69 (0.56–0.81)	<.001
	Death within 28 d		1.84 (1.58–2.21)	0.74 (0.59–1.06)	<.001
	Death or ICU admission or mechanical ventilation		1.22 (0.78–1.89)	0.73 (0.57–1.04)	<.001
	Mechanical ventilation within 28 d		0.95 (0.85–1.71)	0.74 (0.59–1.1)	.013
	Day 4 COVID-19 ordinal scale ≥4		0.91 (0.75–1.86)	0.74 (0.58–1.08)	.006
	Clinical worsening on the COVID-19 ordinal scale		1.03 (0.74–1.87)	0.73 (0.57–1.04)	<.001
IL-6, pg/mL	Mechanical ventilation or death	22.08 (13.53–40.25)	41.06 (25.49–60.31)	21.08 (11.38–36.78)	.001
	Prolonged hospitalization beyond day 4		25.48 (16.96–48.88)	15.10 (8.5–26.72)	<.001
	ICU admission		47.00 (35.38–71.61)	20.83 (11.32–35.53)	<.001
	Day 4 COVID-19 ordinal scale equal to or worse than day 1		26.87 (17.64–51.37)	17.83 (8.92–27.91)	<.001
	Death within 28 d		35.00 (20.43–61)	22.02 (12.33–39)	.079
	Death or ICU admission or mechanical ventilation		42.30 (25.48–67.84)	20.96 (11.2–35.53)	<.001
	Mechanical ventilation within 28 d		43.20 (35.76–60.54)	20.97 (11.92–36.97)	.001
	Day 4 COVID-19 ordinal scale ≥4		46.90 (25.49–67.24)	21.08 (11.71–36.78)	.001
	Clinical worsening on the COVID-19 ordinal scale		42.30 (22.96–68.57)	20.83 (11.25–35.08)	<.001

Statistical significance between outcome strata was determined by the Mann-Whitney *U* test. *P* values were not corrected for multiple testing.

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; MR-proADM, mid-regional proadrenomedullin.

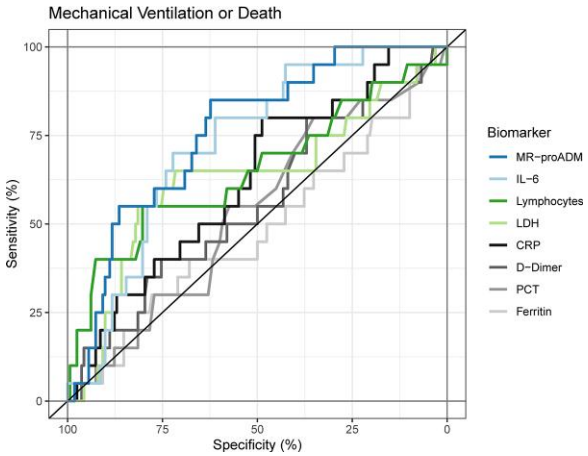

Figure 2. Receiver operating characteristic curves of biomarkers for predicting mechanical ventilation or death. Abbreviations: CRP, C-reactive protein; IL-6, interleukin 6; LDH, lactate dehydrogenase; MR-proADM, mid-regional proadrenomedullin; PCT, procalcitonin.

between 0.80 and 2.00 nmol/L [25–33]. To our knowledge, our study is the first to show the prognostic performance of MR-proADM in a patient cohort from the United States. In addition, our data defined a broader role of MR-proADM in predicting a wider range of COVID-19 clinical outcomes of varying severity, using high-quality data from a multicenter, randomized, double-blinded, placebo-controlled clinical trial. 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 Day 1	Death Within 28 Days	Death or ICU Admission or Mechanical Ventilation	Mechanical Ventilation Within 28 Days	Day 4 COVID-19 Ordinal Scale ≥4	Clinical Worsening on the COVID-19 Ordinal Scale
MR-proADM	0.76 (.66–.86)	0.69 (.59–.80)	0.71 (.63–.78)	0.67 (.59–.75)	0.86 (.78–.94)	0.73 (.64–.83)	0.69 (.57–.82)	0.69 (.58–.79)	0.70 (.60–.80)
IL-6	0.73 (.63–.83)	0.78 (.68–.88)	0.70 (.62–.77)	0.68 (.61–.76)	0.67 (.52–.83)	0.75 (.65–.84)	0.76 (.66–.87)	0.73 (.61–.85)	0.73 (.63–.83)
Lymphocytes[a]	0.65 (.50–.80)	0.64 (.50–.78)	0.66 (.58–.75)	0.65 (.57–.73)	0.66 (.40–.91)	0.66 (.53–.79)	0.67 (.51–.83)	0.66 (.51–.80)	0.69 (.58–.80)
LDH	0.63 (.48–.78)	0.68 (.54–.82)	0.58 (.50–.67)	0.61 (.52–.69)	0.56 (.33–.78)	0.68 (.54–.81)	0.65 (.48–.82)	0.68 (.53–.82)	0.60 (.50–.71)
CRP	0.62 (.50–.75)	0.61 (.48–.74)	0.51 (.42–.59)	0.51 (.43–.60)	0.69 (.56–.81)	0.62 (.51–.74)	0.59 (.44–.74)	0.67 (.54–.79)	0.48 (.37–.59)
D-dimer	0.56 (.42–.70)	0.49 (.37–.61)	0.56 (.47–.64)	0.57 (.48–.65)	0.60 (.36–.83)	0.53 (.41–.66)	0.49 (.36–.63)	0.51 (.38–.64)	0.47 (.37–.58)
PCT	0.54 (.40–.67)	0.57 (.45–.69)	0.60 (.50–.69)	0.54 (.45–.62)	0.60 (.36–.83)	0.55 (.44–.67)	0.52 (.38–.66)	0.55 (.42–.67)	0.48 (.36–.59)
Ferritin	0.49 (.34–.63)	0.45 (.31–.59)	0.58 (.49–.67)	0.56 (.48–.64)	0.47 (.26–.68)	0.48 (.36–.61)	0.47 (.29–.64)	0.42 (.29–.55)	0.70 (.60–.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.

[a]For lymphocytes, we assumed that risk increased with decreasing lymphocyte levels.

useful in predicting disease severity and outcomes in additional lower respiratory tract infections [23, 24], sepsis and septic shock [22, 46], and early detection of sepsis in burn patients [47]. Additionally, the patients included in this study were enrolled between the months of April and June 2020, and since then several variants of SARS-CoV-2 have surfaced. Thus, additional work is needed to assess the role of MR-proADM in the new SARS-CoV-2 variants. Further limitations include confounding variables not controlled for in the multivariable logistic regression analyses.

MR-proADM levels have also been shown to increase in patients with chronic renal failure who are on or off dialysis [48–50]. This suggests that MR-proADM, similar to other biomarkers, does not function well in chronic renal failure, and populations with renal dysfunction may require a unique cutoff of MR-proADM specific to their comorbid state. We performed additional multivariable logistic regression analyses to control for chronic kidney disease, and MR-proADM >0.87 nmol/L remained significantly associated with mechanical ventilation or death, prolonged hospitalization beyond day 4, and a day 4 COVID-19 ordinal scale equal to or worse than day 1. Although the cutoff performed poorly for the outcome ICU admission when controlled for additional variables including CKD, the sample size and the number of outcome events were small and would require additional investigation in future larger studies with an ICU cohort.

We also attempted to include binary MR-proADM with a higher cutoff (2.25 nmol/L) in our analyses (Supplementary Figure 2), which has been studied in sepsis [22]. However, the limited number of patients with MR-proADM >2.25 nmol/L hindered any applicable analyses, and only prolonged hospital discharge beyond day 4 was found to be a significantly different outcome between patients with >2.25 nmol/L compared to those ≤2.25 nmol/L (100% vs 67.1%, $P = .006$).

Furthermore, the absence of a significant difference in mortality or mechanical ventilation compared to the control arm for both groups: patients with MR-proADM >0.87 nmol/L, and ≤0.87 nmol/L, suggests that MR-proADM, as was concluded for other inflammatory biomarkers, is not helpful in determining response to IL-6 blockade in patients with early SARS-CoV-2. IL-6 blockade has demonstrated efficiency in late COVID-19 [51], and whether there is utility in MR-proADM stratifying responders in this late cohort has to be determined.

Based on our study, baseline MR-proADM is a useful biomarker in predicting clinical outcomes of patients with COVID-19. It can be used, in addition to other biomarkers and clinical assessment, for augmenting patient care, risk stratification, early assessment for the need for ICU admission, and better hospital resource utilization. Further studies including those with larger sample sizes should be performed including serial MR-proADM measurements of patients with

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.

Financial support. This work was supported, in part, by the National Institutes of Health (grant number AI132638 to M. K. M.). M. K. M. is the recipient of an unrestricted research fund from Thermo Fisher Scientific for the clinical trial ProSAVE (NCT04158804).

Potential conflicts of interest. M. K. M. reports consultation fees from Safi Biosolutions, Clear Creek Bio, Vericel, NED Biosystems, and Day Zero Diagnostics; grant support from Thermo Fisher Scientific and Genentech; and medical editing/writing fees from UpToDate, outside the submitted work. M. K. M. also reports patents 14/110 443 and 15/999 463 pending. A. S., S. J., and J. W. are employees of Thermo Fisher Scientific and Brahms GmbH. Thermo Fisher had no role in the formation, design, or execution of the study. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Potere N, Valeriani E, Candeloro M, et al. Acute complications and mortality in hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. Crit Care **2020**; 24:389.
2. Lin L, Liu Y, Tang X, He D. The disease severity and clinical outcomes of the SARS-CoV-2 variants of concern. Front Public Health **2021**; 9:775224.
3. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet **2020**; 395:1417–8.
4. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med **2020**; 383:120–8.
5. Jin Y, Ji W, Yang H, Chen S, Zhang W, Duan G. Endothelial activation and dysfunction in COVID-19: from basic mechanisms to potential therapeutic approaches. Signal Transduct Targeted Ther **2020**; 5:293.
6. Wang Q, Zhang Y, Wu L, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell **2020**; 181:894–904.e9.
7. Li Z, Tomlinson AC, Wong AH, et al. The human coronavirus HCoV-229E S-protein structure and receptor binding. Elife **2019**; 8:e51230.
8. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol **2020**; 17:259–60.
9. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. Clin Gastroenterol Hepatol **2020**; 18:2128–30.e2.
10. Diao B, Wang C, Wang R, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 infection. Nat Commun **2021**; 12:2506.
11. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. Nat Rev Immunol **2020**; 20:389–91.
12. Bermejo-Martin JF, Almansa R, Torres A, González-Rivera M, Kelvin DJ. COVID-19 as a cardiovascular disease: the potential role of chronic endothelial dysfunction. Cardiovasc Res **2020**; 116:e132–3.
13. Sugo S, Minamino N, Kangawa K, et al. Endothelial cells actively synthesize and secrete adrenomedullin. Biochem Biophys Res Commun **1994**; 201:1160–6.
14. Cheung BM, Li CY, Wong LY. Adrenomedullin: its role in the cardiovascular system. Semin Vasc Med **2004**; 4:129–34.
15. Terata K, Miura H, Liu Y, Loberiza F, Gutterman DD. Human coronary arteriolar dilation to adrenomedullin: role of nitric oxide and K(+) channels. Am J Physiol Heart Circ Physiol **2000**; 279:H2620–6.
16. Feng CJ, Kang B, Kaye AD, Kadowitz PJ, Nossaman BD. L-NAME modulates responses to adrenomedullin in the hindquarters vascular bed of the rat. Life Sci **1994**; 55:PL433–8.
17. Voors AA, Kremer D, Geven C, et al. Adrenomedullin in heart failure: pathophysiology and therapeutic application. Eur J Heart Fail **2019**; 21:163–71.
18. Xie Z, Chen WS, Yin Y, et al. Adrenomedullin surges are linked to acute episodes of the systemic capillary leak syndrome (Clarkson disease). J Leukoc Biol **2018**; 103:749–59.
19. Wilson DC, Schefold JC, Baldirà J, Spinetti T, Saeed K, Elke G. Adrenomedullin in COVID-19 induced endotheliitis. Crit Care **2020**; 24:411.
20. Temmesfeld-Wollbrück B, Brell B, Dávid I, et al. Adrenomedullin reduces vascular hyperpermeability and improves survival in rat septic shock. Intensive Care Med **2007**; 33:703–10.
21. Struck J, Tao C, Morgenthaler NG, Bergmann A. Identification of an adrenomedullin precursor fragment in plasma of sepsis patients. Peptides **2004**; 25:1369–72.
22. Elke G, Bloos F, Wilson DC, et al. The use of mid-regional proadrenomedullin to identify disease severity and treatment response to sepsis—a secondary analysis of a large randomised controlled trial. Crit Care **2018**; 22:79.
23. Albrich WC, Dusemund F, Rüegger K, et al. Enhancement of CURB65 score with proadrenomedullin (CURB65-A) for outcome prediction in lower respiratory tract infections: derivation of a clinical algorithm. BMC Infect Dis **2011**; 11:112.
24. Spoto S, Legramante JM, Minieri M, et al. How biomarkers can improve pneumonia diagnosis and prognosis: procalcitonin and mid-regional-pro-adrenomedullin. Biomark Med **2020**; 14:549–62.
25. García de Guadiana-Romualdo G, Calvo Nieves MD, Rodríguez Mulero MD, et al. MR-proADM as marker of endotheliitis predicts COVID-19 severity. Eur J Clin Invest **2021**; 51:e13511.
26. García de Guadiana-Romualdo L, Martínez Martínez M, Rodríguez Mulero MD, et al. Circulating MR-proADM levels, as an indicator of endothelial dysfunction, for early risk stratification of mid-term mortality in COVID-19 patients. Int J Infect Dis **2021**; 111:211–8.
27. Gregoriano C, Koch D, Kutz A, et al. The vasoactive peptide MR-pro-adrenomedullin in COVID-19 patients: an observational study. Clin Chem Lab Med **2021**; 59:995–1004.
28. Minieri M, Di Lecce VN, Lia MS, Maurici M, Bernardini S, Legramante JM. Role of MR-proADM in the risk stratification of COVID-19 patients assessed at the triage of the emergency department. Crit Care **2021**; 25:407.

29. Montrucchio G, Sales G, Rumbolo F, et al. Effectiveness of mid-regional pro-adrenomedullin (MR-proADM) as prognostic marker in COVID-19 critically ill patients: an observational prospective study. PLoS One **2021**; 16:e0246771.
30. Sozio E, Tascini C, Fabris M, et al. MR-proADM as prognostic factor of outcome in COVID-19 patients. Sci Rep **2021**; 11:5121.
31. Spoto S, Agrò FE, Sambuco F, et al. High value of mid-regional proadrenomedullin in COVID-19: a marker of widespread endothelial damage, disease severity, and mortality. J Med Virol **2021**; 93:2820–7.
32. van Oers JAH, Kluiters Y, Bons JAP, et al. Endothelium-associated biomarkers mid-regional proadrenomedullin and C-terminal proendothelin-1 have good ability to predict 28-day mortality in critically ill patients with SARS-CoV-2 pneumonia: a prospective cohort study. J Crit Care **2021**; 66:173–80.
33. Zaninotto M, Mion MM, Marchioro L, Padoan A, Plebani M. Endothelial dysfunction and mid-regional proadrenomedullin: what role in SARS-CoV-2 infected patients? Clin Chim Acta **2021**; 523:185–90.
34. Saeed K, Wilson DC, Bloos F, et al. The early identification of disease progression in patients with suspected infection presenting to the emergency department: a multi-centre derivation and validation study. Crit Care **2019**; 23:40.
35. Gonzalez Del Castillo J, Clemente-Callejo C, Llopis F, et al. Midregional proadrenomedullin safely reduces hospitalization in a low severity cohort with infections in the ED: a randomized controlled multi-centre interventional pilot study. Eur J Intern Med **2021**; 88:104–13.
36. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med **2020**; 383:2333–44.
37. Thermo Fisher Scientific. B·R·A·H·M·S MR-proADM. **2022**. https://www.brahms.de/en-gb/products/mr-proadm/brahms-mr-proadm.html. Accessed 4 April 2022.
38. Guirao JJ, Cabrera CM, Jiménez N, Rincón L, Urra JM. High serum IL-6 values increase the risk of mortality and the severity of pneumonia in patients diagnosed with COVID-19. Mol Immunol **2020**; 128:64–8.
39. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol **2020**; 146:128–36.e4.
40. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinf **2011**; 12:77.
41. R Core Team. R: a language and environment for statistical computing. Austria, Vienna: R Foundation for Statistical Computing. https://www.R-project.org/. Accessed 4 April 2022.
42. Wickham H. Ggplot2: elegant graphics for data analysis. New York: Springer-Verlag; **2016**.
43. StataCorp LLC. Stata Statistical Software: release 14. College Station, TX: StataCorp; **2015**.
44. Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: a systematic review and meta-analysis. Rev Med Virol **2020**; 30:1–9.
45. Zhang J, Hao Y, Ou W, et al. Serum interleukin-6 is an indicator for severity in 901 patients with SARS-CoV-2 infection: a cohort study. J Transl Med **2020**; 18:406.
46. Önal U, Valenzuela-Sánchez F, Vandana KE, Rello J. Mid-regional pro-adrenomedullin (MR-proADM) as a biomarker for sepsis and septic shock: narrative review. Healthcare (Basel) **2018**; 6:110.
47. Gille J, Ostermann H, Dragu A, Sablotzki A. MR-proADM: a new biomarker for early diagnosis of sepsis in burned patients. J Burn Care Res **2017**; 38:290–8.
48. Dieplinger B, Mueller T, Kollerits B, et al. Pro-A-type natriuretic peptide and pro-adrenomedullin predict progression of chronic kidney disease: the MMKD Study. Kidney Int **2009**; 75:408–14.
49. Gouya G, Sturm G, Lamina C, et al. The association of mid-regional pro-adrenomedullin and mid-regional pro-atrial natriuretic peptide with mortality in an incident dialysis cohort. PLoS One **2011**; 6:e17803.
50. Yoshihara F, Ernst A, Morgenthaler NG, et al. Midregional proadrenomedullin reflects cardiac dysfunction in haemodialysis patients with cardiovascular disease. Nephrol Dial Transplant **2007**; 22:2263–8.
51. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med **2021**; 384:1491–502.