Received: 17 January 2021 | Accepted: 8 February 2021

DOI: 10.1111/eci.13511

ORIGINAL ARTICLE

WILEY

MR-proADM as marker of endotheliitis predicts COVID-19 severity

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Funding information
Universidad Católica San Antonio de Murcia (UCAM), Grant/Award Number: PMAFI-COVID19/04; Gerencia Regional de Salud de Castilla y León, Grant/Award Number: GRS COVID 108/A/20

Abstract

Background: Early identification of patients at high risk of progression to severe COVID-19 constituted an unsolved challenge. Although growing evidence demonstrates a direct association between endotheliitis and severe COVID-19, the role of endothelial damage biomarkers has been scarcely studied. We investigated the relationship between circulating mid-regional proadrenomedullin (MR-proADM) levels, a biomarker of endothelial dysfunction, and prognosis of SARS-CoV-2-infected patients.

Methods: Prospective observational study enrolling adult patients with confirmed COVID-19. On admission to emergency department, a blood sample was drawn for laboratory test analysis. Primary and secondary endpoints were 28-day all-cause mortality and severe COVID-19 progression. Area under the curve (AUC) and multivariate regression analysis were employed to assess the association of the biomarker with the established endpoints.

Results: A total of 99 patients were enrolled. During hospitalization, 25 (25.3%) cases progressed to severe disease and the 28-day mortality rate was of 14.1%.

MR-proADM showed the highest AUC to predict 28-day mortality (0.905; [CI] 95%: 0.829-0.955; $P < .001$) and progression to severe disease (0.829; [CI] 95%: 0.740-0.897; $P < .001$), respectively. MR-proADM plasma levels above optimal cut-off (1.01 nmol/L) showed the strongest independent association with 28-day mortality risk (hazard ratio [HR]: 10.470, 95% CI: 2.066-53.049; $P < .005$) and with progression to severe disease (HR: 6.803, 95% CI: 1.458-31.750; $P = .015$).

Conclusion: Mid-regional proadrenomedullin was the biomarker with highest performance for prognosis of death and progression to severe disease in COVID-19 patients and represents a promising predictor for both outcomes, which might constitute a potential tool in the assessment of prognosis in early stages of this disease.

KEYWORDS

COVID-19, endotheliitis, mid-regional proadrenomedullin, prognosis, SARS-CoV-2, severity

1 | INTRODUCTION

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the etiological agent for the pneumonia cases of unknown origin in Wuhan (Hubei Province, China), a disease termed as coronavirus disease-2019 (COVID-19).[1] On March 11, COVID-19 was declared as a pandemic. According to the World Health Organization, nearly 2 million patients are currently dead after more than 82 million confirmed cases worldwide.[2]

Despite the exponential growth in research related to COVID-19 pandemic, the underlying pathophysiological mechanisms of this disease remain unclear. The incidence of complications associated to different organs and tissues and sepsis-like multiple organ dysfunction suggests the involvement of multiple pathways. Accordingly, recent studies have proposed that virus-induced endothelial dysfunction, resulting in impaired vascular blood flow, coagulation and leakage, may partially explain the development of organ dysfunction.[3-5] Hence, the development of endotheliitis may be a prominent feature of COVID-19-induced severe illness.[6]

The role of clinical laboratories in this viral outbreak includes staging, prognostication and therapeutic monitoring.[7] Different biomarkers have been identified as predictors of severe forms of COVID-19.[8] Most of them are related to inflammation or the dysregulated immune response that characterizes this disease. Although endothelial damage has been shown to be a decisive pathophysiological factor, there are scarce studies that evaluate biomarkers of endothelial damage in severe forms of COVID-19. Here, mid-regional proadrenomedullin (MR-proADM), measured as a surrogate of adrenomedulin secretion,[9] may be of interest within COVID-19-induced endotheliitis.[10] This hormone is produced by endothelial and vascular smooth muscle cells throughout the vascular tree to maintain endothelial barrier function. It freely diffuses through the blood and interstitium and binds to specific widespread receptors and has been showed to play a key role in reducing vascular permeability, promoting endothelial stability and integrity following severe infection.[11,12] The extensive endothelial and pulmonary damage related to SARS-CoV-2 infection may cause a relevant disruption of the ADM system, mainly in severe cases and therefore an elevation of plasma levels of MR-proADM. This disruption of the adrenomedullin system results in vascular leakage that represents the first step of inflammation and coagulation cascade activation.[6]

Mid-regional proadrenomedullin has been widely reported as a prognostic marker in infectious and non-infectious diseases.[13] In sepsis and community acquired pneumonia, this biomarker predicts organ damage, poor progression and mortality[14-16] and this predictive ability is independent of the aetiology of pneumonia.[17] MR-proADM has also been showed as a prognostic marker in viral infections[18,19] and its measurement has been recently postulated in a consensus document as a potential tool in the future for prognosis of COVID-19 patients.[20]

However, the role of MR-proADM in COVID-19 patients has been scarcely studied. Herein, the aim of this prospective study was to evaluate the relationship between MR-proADM levels and prognosis of hospitalized SARS-CoV-2-infected patients as well as its potential role as a marker of SARS-CoV-2-related widespread endothelial damage.

2 | MATERIAL AND METHODS

2.1 | Study design and population

This was a prospective observational study including consecutive adult patients admitted to Santa Lucía

University Hospital and Clínico Universitario Hospital, by confirmed SARS-CoV-2 infection between March and April 2020. COVID-19 was diagnosed by a positive result of real-time reverse transcriptase-polymerase chain reaction testing of a nasopharyngeal specimen. Exclusion criteria were as follows: (a) patients <18 years; (b) pregnant women; (c) patients transferred from or to other hospital and (d) lack of samples for the biomarkers measurement.

This study was approved by the Ethics Committee of both hospitals and performed under a waiver of informed consent. The work was carried out by following the guidelines of the Declaration of Helsinki of the World Medical Association.

2.2 | Data collection

Data collection was performed from electronic medical records and laboratory information systems. For eligible patients, we extracted the demographic information, comorbidities, laboratory test results and variables required for the previously defined endpoints.

2.3 | Blood sampling and laboratory analysis

In all patients, venous blood samples for biochemical analysis, including glucose, creatinine, sodium, potassium, albumin, bilirubin, alanine aminotransferase (ALT), ferritin, C-reactive protein (CRP), lactate dehydrogenase (LDH) and procalcitonin (PCT), haematological analysis, including haemoglobin, cell blood and platelet counts and coagulation markers, including D-dimer, were collected on admission to the Emergency Department and analysed in the laboratory within 1 hour, by using the habitual methods currently used in the participating laboratories. For measurement of MR-proADM and interleukin 6 (IL-6), blood samples collected in tubes containing EDTA K3 as anticoagulant were centrifuged at 2000 *g* for 10 min and plasma was subsequently frozen and stored to −80°C until testing, according to stability results previously reported.[9]

Mid-regional proadrenomedullin was measured by a homogeneous sandwich immunoassay with fluorescent detection using a time-resolved amplified cryptate emission (TRACE) technology assay (KRYPTOR®, Brahms Thermo Fisher Scientific Inc). According to manufacturer´s data, the detection limit, functional sensitivity and quantification limit were 0.05 nmol/L, 0.23 nmol/L and 0.25 nmol/L; intra-assay coefficient of variation (CV) and inter-assay CV were ≤10% and ≤20%, for a level ranging from 0.2 to 0.5 nmol/L, respectively.

2.4 | Study endpoints

The primary endpoint was all-cause mortality at 28-days. Secondary endpoint was severe COVID-19 progression, defined as a composite of admission to Intensive Care Unit during the index hospital stay and/or need for mechanical ventilation and/or 28-day mortality, both verified by chart review.

2.5 | Statistical analysis

The normality of continuous variables was tested by Kolmogorov-Smirnov or Shapiro-Wilk test, and they are presented as median (interquartile range [IQR]) or mean (standard deviation [SD]), as appropriate. Comparisons for continuous variables were performed by Student's *t* test, for the normally distributed data; for skewed distribution, Mann-Whitney *U* non parametric tests were used for comparisons. Categorical variables are presented as frequency and percentage in each category. The significance of differences in percentages was tested by the chi-squared test. Discriminatory ability for both outcomes was evaluated by calculating the area under the receiver operating characteristic curve (ROC AUC). We additionally calculated the optimal ROC-derived cut-offs (Youden Index, corresponding to the maximum of the sum 'sensibility + specificity') and sensitivity, specificity, likelihood ratios and predictive values. The association between the biomarkers and the risk for both outcomes was assessed by Cox regression analysis, adjusted by confounding variables. Variables yielding a $P < .10$ in the univariate regression analysis were further included in the multivariate using the backward stepwise selection method. In a further step, the impact of the biomarkers on outcomes along time was assessed by using Kaplan-Meier curves and the Mantel-Haenszel log-rank test. Time was censored at 28 days following admission to the Emergency Department. Software packages SPSS *vs*. 22 (SPSS Inc), and MedCalc 15.0 (MedCalc Software) were used for statistical analysis, with a $P < .05$ considered statistically significant.

Reporting of the study conforms to CONSORT-revised and the broader EQUATOR guidelines.[21]

3 | RESULTS

3.1 | Patient characteristics

Main baseline and clinical characteristics on admission according to the endpoints previously defined are listed in Table 1. A total of 99 patients, 60 from Santa Lucía University Hospital (Cartagena, Spain) and 39 from Clínico University Hospital

TABLE 1 Demographics, comorbidities and laboratory findings on admission, grouped according to survival status at 28 d and progression to severe disease

	All patients	Survivors	Non-survivors	*P*-value	Non-severe	Severe	*P*-value
n (%)	99	85 (13.3)	14 (14.1)		74 (75.7)	25 (25.3)	
Demographics							
Age (y), mean (SD)	66 (15)	64 (15)	76 (8)	.005	65 (16)	70 (12)	.054
Gender, male (n [%])	61 (61.6)	51 (60)	10 (71.4)	.415	45 (60.8)	16 (64.0)	.777
Medical history (n [%])							
Hypertension	54 (54.5)	41 (48.2)	13 (92.9)	.002	36 (48.6)	18 (72.0)	.043
Diabetes mellitus	28 (28.3)	21 (24.7)	7 (50.0)	.052	19 (25.7)	9 (36.0)	.322
COPD	6 (6.1)	5 (5.9)	1 (7.1)	.855	5 (6.8)	1 (4.0)	.617
Cardiovascular disease	18 (18.2)	12 (14.1)	6 (42.9)	.010	8 (10.8)	10 (40.0)	.001
Chronic kidney disease	9 (9.1)	3 (3.5)	6 (42.9)	<.001	2 (2.7)	7 (28.0)	<.001
Cancer	3 (3.0)	2 (2.4)	1 (7.1)	.333	5 (6.8)	1 (4.0)	.617
Cerebrovascular disease	7 (7.1)	6 (7.1)	1 (7.1)	.991	5 (6.8)	2 (8.0)	.834
Laboratory findings							
Glucose (mg/dL)	129 (110-154)	123 (108-146)	157 (114-270)	.007	126 (108-150)	138 (111-175)	.146
Sodium (mmol/L)	137 (134-139)	137 (134-139)	137 (129-143)	.805	136 (134-139)	137 (132-140)	.747
Potassium (mmol/L)	4.3 (0.6)	4.2 (0.6)	4.4 (0.7)	.243	4.2 (0.6)	4.4 (0.7)	.197
Creatinine (mg/dL)	0.93 (0.76-1.14)	0.91 (0.75-1.03)	1.49 (1.02-2.04)	.002	0.91 (0.75-1.00)	1.13 (0.80-1.73)	.015
Bilirubin (mg/dL)	0.41 (0.30-0.61)	0.40 (0.30-0.60)	0.55 (0.38-0.70)	.184	0.41 (0.30-0.60)	0,48 (0.37-0.65)	.241
Albumin (g/dL)	4.0 (3.6-4.2)	4.0 (3.7-4.2)	3.5 (3.2-4.0)	.016	4.0 (3.7-4.2)	3.7 (3.3-4.2)	.024
ALT (U/L)	26 (18-43)	26 (17-41)	22 (20-52)	.614	26 (17-41)	26 (21-50)	.342
LDH (U/L)	281 (220-374)	269 (213-360)	368 (288-511)	.005	260 (210-318)	376 (303-499)	<.001
Ferritin (μg/L)	432 (270-1250)	412 (244-1244)	845 (429-1401)	.043	360 (223-1109)	944 (468-1526)	.001
CRP (mg/L)	71 (27-128)	60 (23-118)	130 (95-276)	.001	57 (20-108)	109 (92-214)	<.001
PCT (μg/L)	0.09 (0.06-0.20)	0.08 (0.05-0.18)	0.19 (0.11-1.15)	.003	0.08 (0.05-0.16)	0.16 (0.11-0.61)	<.001
IL-6 (pg/mL)	34.8 (18.4-87.9)	30.5 (17.1-72.0)	126.9 (27.5-157.2)	.008	29.7 (16.0-60.4)	79.8 (29.9-135.7)	.003
Haemoglobin (g/dL)	13.7 (1.8)	13.8 (1.6)	13.3 (2.7)	.338	13.7 (1.7)	13.5 (2.1)	.548
WBC (*10^9/L)	7.03 (5.35-8.71)	7.03 (5.38-8.65)	6.78 (5.27-9.46)	.952	6.97 (5.38-8.76)	7.11 (5.33-8.65)	.994
Neutrophil count (*10^9/L)	4.92 (3.77-7.01)	4.92 (3.76-6.91)	5.39 (4.19-8.21)	.366	4.85 (3.76-6.89)	5.88 (4.19-7.58)	.280
Lymphocyte count (*10^9/L)	1.21 (0.81-1.48)	1.24 (0.88-1.63)	0.77 (0.45-1.23)	.015	1.27 (0.88-1.64)	1.01 (0.64-1.21)	.005
NLR	5.06 (2.87-7.48)	4.51 (2.73-6.98)	8.20 (4.17-10.98)	.025	4.32 (2.33-6.90)	6.55 (4.17-9.98)	.013

(Continues)

TABLE 1 (Continued)

	All patients	Survivors	Non-survivors	*P*-value	Non-severe	Severe	*P*-value
Platelet count (*10^9/L)	188 (165-243)	194 (167-251)	174 (126-209)	.037	193 (167-267)	181 (151-212)	.095
D-dimer (ng/mL FEU)	678 (470-1224)	624 (427-935)	1742 (946-4532)	.001	612 (447-935)	1044 (520-2679)	.007
MR-proADM (mmol/L)	0.74 (0.60-1.02)	0.68 (0.57-0.94)	1.54 (1.05-2.12)	<.001	0.68 (0.54-0.91)	1.36 (0.93-1.78)	<.001

Note: Laboratory tests levels are expressed as median (IQR) or mean (SD), as appropriate.

Abbreviations: ALT, Alanine aminotransferase; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; IL-6, Interleukin-6; LDH, Lactate dehydrogenase; MR-proADM, Mid-regional proadrenomedullin; NLR, Neutrophil-to-lymphocyte ratio; PCT, Procalcitonin; WBC, White blood cell.

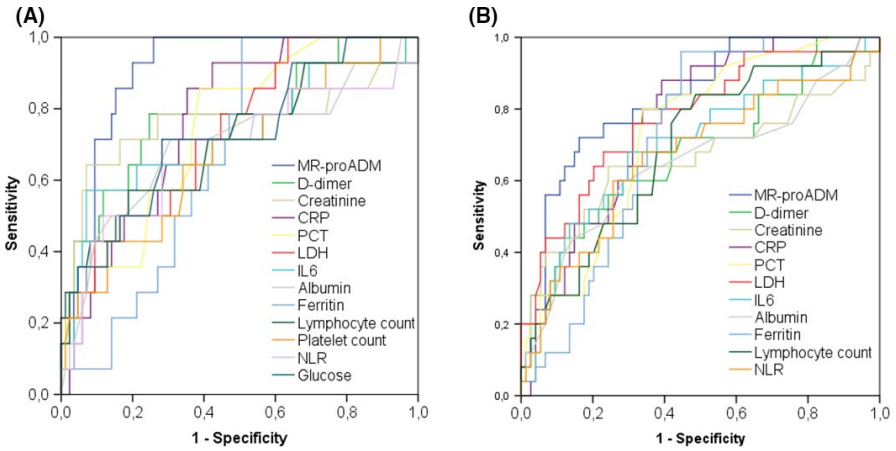

FIGURE 1 Receiver operating characteristic curves of biomarker levels on admission to predict 28-d mortality (A) and progression to severe disease (B)

TABLE 2 Receiver operating characteristic (ROC) curves for prediction of primary and secondary endpoints

	Prediction of 28-d mortality		Prediction of progression to severe disease	
Biomarker	**AUC**	**95% CI%; *P***	**AUC**	**95% CI; *P***
MR-proADM	0.905	0.829-0.955; <.001	0.829	0.740-0.897; <.001
Glucose	0.727	0.628-0.812; .004	–	–
Creatinine	0.764	0.668-0.843; .005	0.663	0.561-0.755; .031
Albumin	0.701	0.601-0.789; .024	0.651	0.548-0.744; .034
LDH	0.737	0.639-0.820; <.001	0.776	0.681-0.853; <.001
D-dimer	0.781	0.686-0.858; <.001	0.682	0.581-0.772; .006
CRP	0.769	0.673-0.848; <.001	0.766	0.670-0.845; <.001
Ferritin	0.670	0.568-0.761; .004	0.719	0.620-0.805; <.001
PCT	0.747	0.650-0.829; <.001	0.735	0.637-0.819; <.001
IL-6	0.724	0.625-0.809; .011	0.698	0.598-0.787; .002
NLR	0.687	0.586-0.777; .044	0.668	0.566-0.759; .014
Lymphocyte count	0.703	0.603-0.791; .020	0.688	0.587-0.777; .002
Platelet count	0.675	0.573-0.766; .035	–	–

Note: Only biomarkers with significant differences in comparisons among groups according to the outcome were included in the table.

Abbreviations: AUC, Area under the curve; CI, Confidence interval; CRP, C-reactive protein; IL-6, Interleukin-6; LDH, Lactate dehydrogenase; MR-proADM, Mid-regional proadrenomedullin; NLR, neutrophil-to-lymphocyte ratio; PCT, Procalcitonin.

(Valladolid, Spain), were admitted due to COVID-19, with a mean age of 66 years (61.6% were male). Hypertension was the most common comorbidity, with a greater prevalence among non-survivors (48.2% *vs*. 92.9%, $P = .002$), followed by diabetes mellitus (28.3%) and cardiovascular disease (18.2%). During hospitalization, 25 (25.3%) cases progressed to severe disease, of whom 16 (16.2%) required intensive care, 12 (12.1%) underwent mechanical ventilation and 14 (14.1%) died of any cause within the first 28 days of hospital stay. There were not significant differences between the two participating centres regarding to the rates of 28-day mortality (11.7% *vs*. 17.9%; $P = .381$) and progression to severe disease (23.3% *vs*. 28.2%; $P = .582$). In overall population, median hospital stay was 17 (IQR: 8-16) days and 12 (IQR: 7-19) days in patients requiring Intensive Care Unit care.

3.2 | Laboratory tests for prediction of 28-day mortality

According to survival status, the biomarker levels are summarized in Table 1. Glucose, creatinine, albumin, LDH, ferritin, CRP, IL-6, PCT, D-dimer and MR-proADM levels and neutrophil-to-lymphocyte ratio (NLR) were significantly higher in patients who died, while platelet and lymphocyte counts were significantly lower.

The accuracy of biomarkers for predicting 28-days mortality, evaluated by ROC curve analysis, is showed in Figure 1.A and Table 2. MR-proADM was the biomarker with the highest AUC (0.905, 95% confidence interval [CI]: 0.829-0.955; $P < .001$).

According to the Youden index, we calculated the optimal cut-offs for differentiating between survivors and non-survivors (Table 3). Notably, Kaplan-Meier analysis showed that no patient with a MR-proADM value ≤0.88 nmol/L, recommended as cut-off by the manufacturer, died in the first 28 days following Emergency Department admission (Figure 2A). Survival analysis for the cut-off from Youden index is showed in Figure 2B.

In the multivariate Cox regression analysis (Table 4), after adjusting for confounders, MR-proADM >1.01 nmol/L showed the strongest independent association with 28-day mortality risk (hazard ratio [HR]: 10.470, 95% CI: 2.066-53.049; $P = .005$). D-dimer >935 ng/mL FEU (HR: 4.521, 95% CI: 1.185-17.238; $P = .027$) and IL-6 >117.8 pg/mL (HR: 3.739, 95% CI: 1.207-11.585; $P = .022$) were also independent predictors associated with 28-day mortality.

TABLE 3 Accuracy of biomarkers for 28-d mortality

Biomarker	Cut-off	Sensitivity [95% CI] (%)	Specificity [95% CI] (%)	LR+ [95% CI]	LR− [95% CI]	PPV [95% CI] (%)	NPV [95% CI] (%)
MR-proADM (nmol/L)	≤0.88[a]	100 (76.8-100)	68.2 (57.2-77.9)	3.2 (2.7-3.6)	0	34.1 (19.9-50.8)	100 (93.8-100)
	>1.01	85.7 (57.2-98.2)	84.7 (75.3-91.6)	5.6 (4.4-7.1)	0.17 (0.04-0.7)	48.0 (27.8-68.7)	97.3 (90.6-99.7)
D-dimer (ng/mL FEU)	>935	78.6 (49.2-95,3)	75.3 (64.7-84.0)	3.2 (2.4-4.3)	0.4 (0.1-0.8)	34.4 (18.6-53.2)	95.5 (87.4-99.1)
CRP (mg/L)	>71	92.9 (66.1-99.8)	57.7 (46.4-68.3)	2.2 (1.7-2.8)	0.12 (0.02-0.8)	26.5 (14.9-41.1)	98.0 (89.2-100.0)
Creatinine (mg/dL)	>1.37	64.3 (35.1-87.2)	92.9 (85.3-97.4)	9.1 (6.1-13.5)	0.38 (0.1-1.1)	60.0 (31.3-84.4)	94.0 (86.6-98.1)
PCT (μg/L)	>0.10	85.7 (57.2-98.2)	61.2 (50.0-71.6)	2.2 (1.7-2.9)	0.23 (0.06-0.9)	26.7 (14.5-42.1)	96.3 (87.3-99.5)
LDH (U/L)	>331	57.1 (28.9-82.3)	69.4 (58.5-79.0)	1.9 (1.2-3.0)	0.62 (0.3-1.2)	23.5 (10.7-41.2)	90.8 (80.9-96.6)
Glucose (mg/dL)	>139	71.4 (41.9-91.6)	71.8 (61.0-81.0)	2.5 (1.8-3.6)	0.4 (0.2-1.0)	29.4 (15.1-47.5)	93.8 (84.9-98.3)
IL-6 (pg/mL)	>117.8	57.1 (28.9-82.3)	92.9 (85.3-97.4)	8.1 (5.1-12.8)	0.46 (0.2-1.2)	57.1 (27.8-83.1)	92.9 (85.3-97.4)
Lymphocyte count ($*10^9$/L)	≤0.79	57.1 (28.9-82.3)	81.2 (71.2-88.8)	3.0 (1.9-4.8)	0.53 (0.2-1.1)	33.3 (15.3-55.8)	92.0 (83.4-97.0)
Albumin (g/dL)	≤3.7	71.4 (41.9-91.6)	69.4 (58.5-79.0)	2.3 (1.6-3.3)	0.41 (0.2-1.0)	27.8 (14.2-45.2)	93.7 (84.4-98.3)
NLR	>6.11	71.4 (41.9-91.6)	71.8 (61.0-81.0)	2.5 (1.8-3.6)	0.4 (0.2-1.0)	29.4 (15.1-47.5)	93.8 (84.9-98.3)
Platelet count ($*10^9$/L)	≤178	64.3 (35.1-87.2)	65.9 (54.8-75.8)	1.9 (1.2-2.9)	0,54 (0.3-1.2)	23.7 (11.4-40.2)	91.8 (81.8-97.3)
Ferritin (μg/L)	>381	92.9 (66.1-99.8)	49.4 (38.4-60.5)	1.8 (1.4-2.4)	0.14 (0.02-1.0)	23.2 (13.0-36.4)	97.7 (87.5-99.9)

Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; LDH, Lactate dehydrogenase; LR, Likely hood ratio; MR-proADM, Mid-regional proadrenomedullin; NLR, neutrophil-to-lymphocyte ratio; NPV, Negative predictive value; PCT, Procalcitonin; PPV, Positive predictive value.

[a]Cutoff recommended by manufacturer to assess early the risk for progression to a more severe disease condition.

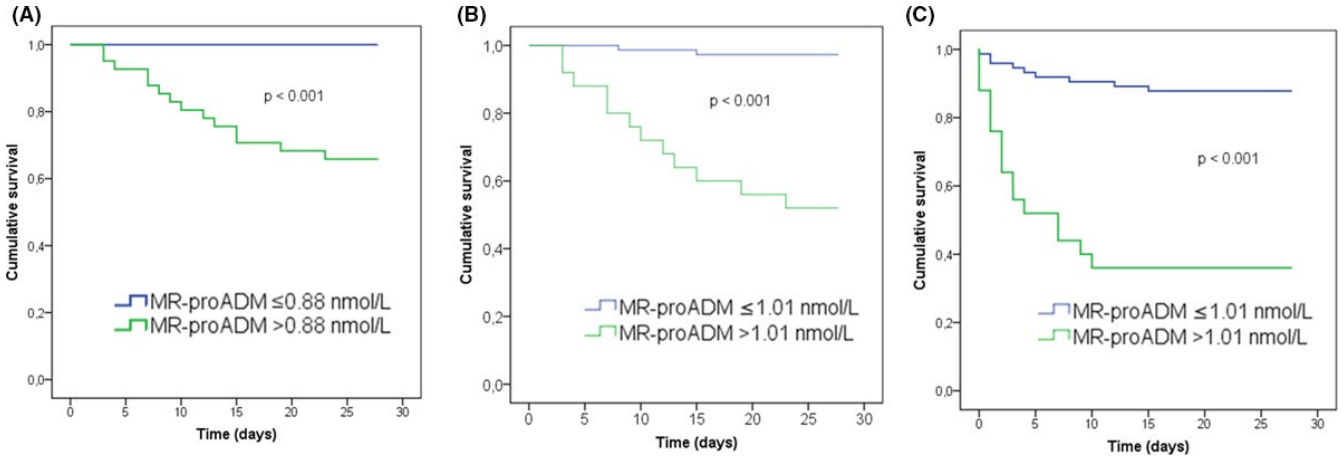

FIGURE 2 Cumulative incidence of (A) 28-d mortality during hospitalization stratified by MR-proADM on admission ≤0.88 nmol/L, (B) 28-d mortality during hospitalization stratified by MR-proADM on admission >1.01 nmol/L, and (C) progression to severe disease stratified by MR-proADM on admission >1.01 nmol/L

TABLE 4 Uni- and multivariate Cox regression analysis for 28-d mortality

	Univariate analysis		Multivariate analysis	
Variable	**HR (CI 95%)**	***P*-value**	**HR (CI 95%)**	***P*-value**
Age	1.061 (1.017-1.107)	.007	n.s	
Hypertension	12.346 (1.614-94.423)	.015	n.s	
Cardiovascular disease	4.053 (1.404-11.700)	.010	n.s	
Chronic kidney disease	10.208 (3.506-29.723)	<.001	n.s	
Diabetes melitus	2.739 (0.960-7.814)	.06	n.s	
Glucose	1.007 (1.003-1.011)	<.001	n.s	
Creatinine	2.433 (1.633-3.625)	<.001	n.s	
Albumin	0.235 (0.077-0.714)	.011	n.s	
NLR	1.122 (1.029-1.224)	.009	n.s	
Platelet count	0.989 (0.980-0.999)	.024	n.s	
Ferritin >381 µg/L	11.051 (1.445-84.503)	.021	n.s	
CRP >71 mg/L	15.079 (1.972-115.31)	.009	n.s	
PCT >0.10 µg/L	8.386 (1.875-37.500)	.005	n.s	
IL-6 >117.8 pg/mL	8.741 (3.051-25.042)	<.001	3.739 (1.207-11.585)	.022
MR-ProADM >1.01 nmol/L	23.247 (5.189-104.152)	<.001	10.470 (2.066-53.049)	.005
D-Dimer >935 ng/mL FEU	9.468 (2.637-33.995)	.001	4.521 (1.185-17.238)	.027
LDH >331 U/L	2.816 (0.977-8.120)	.055	n.s	

Note: Only variables with a $P < .10$ for HR in univariate analysis were included in the table.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IL-6, interleukin-6; LDH, lactate dehydrogenase; MR-proADM, Mid-regional proadrenomedullin; n.s, non significant; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin.

3.3 | Laboratory tests for prediction of progression to severe disease

Creatinine, albumin, LDH, ferritin, CRP, PCT, IL-6 and MR-proADM levels and NLR were significant higher in patients who progressed to severe disease, while lymphocyte count was significant lower (Table 1).

Again, MR-proADM was the biomarker with the highest ROC AUC (0.829, 95% CI: 0.740-0.897; $P < .001$) (Figure 1B and Table 2). Optimal cut-offs for the biomarkers are showed in Table 5. Kaplan-Meier analysis showed a higher likelihood of progression to severe disease in patients with a MR-proADM level >1.01 nmol/L (Figure 2C).

Multivariate adjusted Cox regression model showed that MR-proADM >1.01 nmol/L [HR: 6.803, 95% CI: 1.458-31.750; $P = .015$) and ferritin >376 ng/ml (HR: 5.525, 95% CI; 1.042-29.308; $P = .045$) at admission were the only independent variables associated with progression to severe disease (Table 6).

4 | DISCUSSION

Our study suggests that MR-proADM may be used as an accurate marker of fatal outcome and progression to severe disease in COVID-19. Its accuracy was significantly better than that showed by other previously investigated biomarkers. Patients who presented MR-proADM levels above 1.01 nmol/L showed an association with 28-day mortality and progression to severe disease independent of other factors.

Endothelial dysfunction is known to be involved in organ dysfunction during bacterial sepsis[22,23] and viral infections,[24] as it induces a pro-coagulant state, microvascular leak and organ failure.

Unlike other types of serious infections of different aetiology, epidemiological studies show that COVID-19 patients requiring hospital admission present frequently with accompanying conditions such as hypertension, diabetes, chronic renal failure and cardiovascular diseases.[25,26] These comorbidities are associated with chronic endothelial dysfunction and could predispose these patients to a worse outcome.[27] The endothelium plays major roles in the response to infection: endothelial cells release chemokines, to guide leucocytes to the infected tissue, and cytokines that activate inflammatory responses. Patients with endothelial dysfunction present major alterations at the glycocalyx, intercellular junctions and endothelial cells, resulting in enhanced leucocyte adhesion and extravasation, and also in the induction of a procoagulant and antifibrinolytic state. Prior endothelial dysfunction could thus predispose to the development of severe forms of COVID-19.[28]

In fact, emerging data suggest a crucial role of endothelial dysfunction during SARS-CoV-2 infection.[29] In this regard, recent histopathological studies have evidenced the presence of virus within endothelial cells of different organs beyond the lungs, suggesting a direct viral effect, as well as the accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death, thus contributing directly to severity. Shortly, SARS-CoV-2 infection would facilitate the induction of endotheliitis in different organs as a direct consequence of

TABLE 5 Accuracy of biomarkers for progression to severe disease

Biomarker	Cut-off	Sensitivity (%)	Specificity (%)	LR+	LR−	PPV (%)	NPV (%)
MR-proADM (nmol/L)	≤0.88[a]	76.0 (54.9-90.6)	70.3 (58.5-80.3)	2.6 (2.0-3.3)	0.34 (0.2-0.7)	46.3 (30.5-62.8)	89.7 (78.8-96.1)
	>1.01	64.0 (42.5-82.0)	87.8 (78.2-94.3)	5.3 (3.9-7.1)	0.41 (0.2-0.9)	64.0 (42.0-82.4)	87.8 (78.2-94.3)
LDH (U/L)	>331	68.0 (46.5-85.1)	77.0 (65.8-86.0)	3.0 (2.2-4.0)	0.42 (0.2-0.8)	50.0 (32.4-67.6)	87.7 (77.2-94.5)
CRP (mg/L)	>67	88.0 (68.8-97.5)	60.8 (48.8-72.0)	2.3 (1.8-2.8)	0.20 (0.07-0.6)	43.1 (29.3-57.8)	93.7 (82.8-98.7)
PCT (μg/L)	>0.10	80.0 (59.3-93.2)	66.2 (54.3-76.8)	2.4 (1.8-3.1)	0.30 (0.1-0.7)	44.4 (29.6-60.0)	90.7 (79.6-97.0)
Ferritin (μg/L)	>376	96.0 (79.6-99.9)	55.4 (43.4-67.0)	2.2 (1.7-2.7)	0.07 (0.01-0.5)	42.1 (29.1-55.9)	97.6 (87.4-99.9)
IL-6 (pg/mL)	>50.6	58 (46.5-85.1)	70.3 (58.5-80.3)	2.3 (1.7-3.1)	0.46 (0.2-0.49)	43.6 (27.8-60.4)	86.7 (75.4-94.1)
Lymphocyte count (*10^9/L)	≤1.23	80.0 (59.3-93.2)	55.4 (43.4-67.0)	1.8 (1.4-2.4)	0.36 (0.2-0.8)	37.7 (24.8-52.1)	89.1 (76.2-96.4)
D-dimer (ng/mL FEU)	>935	56.0 (34.9-75,6)	75.7 (64.3-84.9)	2.3 (1.6-3.3)	0.58 (0.3-1.1)	43.8 (26.1-62.6)	83.6 (72.5-91.5)
NLR	>6.11	60.0 (38.7-78.9)	74.3 (62.8-83.8)	2.3 (1.7-3.3)	0.54 (0.3-1.0)	44.1 (27.2-62.1)	84.6 (73.4-92.4)
Creatinine (mg/dL)	>1.00	64.0 (42.5-82.0)	75.7 (64.3-84.9)	2.6 (1.9-3.6)	0.48 (0.2-0.9)	47.1 (29.5-65.1)	86.2 (75.3-93.5)
Albumin (g/dL)	≤3.7	60.0 (38.7-78.9)	71.6 (59.9-81.5)	2.1 (1.5-3.0)	0.56 (0.3-1.0)	41.7 (25.3-59.5)	84.1 (72.7-92.1)

Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase; LR, likely hood ratio; MR-proADM, Mid-regional proadrenomedullin; NLR, neutrophil-to-lymphocyte ratio; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value.

[a]Cut-off recommended by manufacturer to assess early the risk for progression to a more severe disease condition.

TABLE 6 Uni- and multivariate Cox regression analysis for progression to severe disease

	Univariate analysis		Multivariate analysis	
Variable	**HR (CI 95%)**	***P*-value**	**HR (CI 95%)**	***P*-value**
Hypertension	2.320 (0.969-5.558)	.059	n.s	
Cardiovascular disease	3.646 (1.632-8.149)	.002	n.s	
Chronic kidney disease	6.145 (2.537-14.880)	<.001	n.s	
Glucose	1.006 (1.002-1.011)	.006	n.s	
Creatinine	3.062 (1.875-5.000)	<.001	n.s	
Albumin	0.334 (0.144-0.771)	.010	n.s	
Ferritin >376 ng/mL	10.861 (2.558-46.120)	.001	5.525 (1.042-29.308)	.045
CRP >67 mg/L	8.130 (2.429-27.205)	<.001	n.s	
PCT >0.10 μg/L	6.083 (2.278-16.243)	.002	n.s	
IL-6 >50.6 pg/mL	3.985 (1.717-9.247)	.001	n.s	
NLR	1.113 (1.033-1.199)	.005	n.s	
Platelet count	0.994 (0.988-1.000)	.059	n.s	
MR-ProADM >1.014 nmol/L	7.740 (3.392-17.661)	<.001	6.803 (1.458-31.750)	.015
D-Dimer >935 ng/mL FEU	3.129 (1.419-6.903)	.005	n.s	
LDH >331 U/L	5.330 (2.293-12.394)	<.001	n.s	

Note: Only variables with a $P < .10$ for HR in univariate analysis were included in the table

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IL-6, interleukin-6; LDH, lactate dehydrogenase; MR-proADM, Mid-regional proadrenomedullin; n.s, non-significant; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin.

virus involvement and of the host inflammatory response.[3,4] While endotheliopathy is thought to be a key factor of severe COVID-19 pathogenesis, markers indicative of this process have not been well-established. Only isolated little studies analyse the role of endothelium-related molecules such as thrombomodulin,[5] angiopoietin 2,[30,31] VCAM or ICAM[32] in COVID-19.

Among the endothelial dysfunction markers associated with sepsis, MR-proADM appears to be the most promising, as reported by Martin-Fernandez et al. in a recent study.[22] This biomarker can be automated with an adequate turn-around-time for its implementation as a stat laboratory test for clinical practice.[9]

In our study, MR-proADM was the biomarker with the highest accuracy for 28-day mortality, with a ROC AUC of 0.905. Furthermore, after adjusting for confounding variables, multivariate analysis showed the highest HR (10.47) when plasma MR-proADM levels on admission were above 1.01 mmol/L for the primary outcome, together with levels of D-dimer >935 ng/mL FEU and IL-6 > 117.8 pg/mL (HR: 4.521 and 3.739, respectively). These findings support the association of the triad composed of endothelial damage, inflammation and coagulopathy with COVID-19 severity.[33] In this line, there are numerous studies that describe the association between elevated plasma levels of D-dimer or IL-6 and poor prognosis.[34,35]

Again, and similar to results for 28-day mortality, ROC AUC analysis evidenced that accuracy of MR-proADM was the highest to detect progression to severe disease (with AUC above 0.80), better than other inflammation markers, such as CRP, ferritin, LDH and PCT, all of them recommended for monitoring COVID-19 patients.[8] In addition, MR-proADM, together with ferritin, was the only biomarkers independently associated with progression to severe disease in the multivariate analysis. The same cut-off (>1.01 nmol/L) for MR-proADM on admission showed the highest HR (6.803), while ferritin >376 ng/mL achieved a HR of 5.525. Serum ferritin, a feature of haemophagocytic lymphohistiocytosis, which is a known complication of viral infection, is closely related to poor recovery of COVID-19 patients, and those with impaired lung lesion are more likely to have increased ferritin levels.[36] Again, the binomial composed by an inflammatory marker, in this case ferritin, together with an endothelial damage marker, such as MR-proADM, seems crucial in the development of complications and fatal evolution in COVID-19.

In the setting of infectious disease, MR-proADM has been reported as a useful marker for differentiating between infection and sepsis[22,37] and for an early stratification of severity in patients with sepsis.[15,38,39] Few studies have evaluated the potential role of MR-ProADM in viral infections and most of them have been limited to

influenza virus. Thus, Valero-Cifuentes et al.[19] reported a moderate ROC AUC (0.68) to predict a poor outcome in a cohort of patients admitted to hospital with influenza syndrome. On the contrary, Valenzuela et al.,[18] in a small cohort of patients with influenza A virus pneumonia, obtained a ROC AUC of 0.871 to predict mortality, with an optimal cut-off of 1.12 nmol/L. In turn, Bello et al.,[17] reported a ROC AUC of 0.859 and an optimal cut-off point of 1.09 nmol/L in patients with community-acquired pneumonia of different aetiology, including virus.[16] These data are consistent with those obtained in our study.

To our knowledge, only a previous study has analysed the prognostic value of MR-proADM in COVID-19. Spoto et al.[40] have recently reported a ROC AUC for 28-day mortality of 0.89 in 69 patients, similar to that reported in our study (0.905) in a larger sample. Further, there were substantial differences regarding baseline characteristics between the populations of both studies. These disparities may partially explain the different optimal cut-offs (1.01 nmol/L *vs*. 2.0 nmol/L). This disagreement is likely due to differences in both study population characteristics. Hence, Spoto et al. cohort[40] included older patients than those in our study (79 years *vs*. 66 years), with a higher incidence of comorbidities such as cardiovascular disease (68.1% *vs*. 18.2%) and a greater severity, with a higher rate of death (23.2% *vs*. 14.1%) and of patients requiring admission to ICU (43.5% *vs*. 16.2%).

In addition, it is noteworthy that we observed that a MR-proADM level ≤0.88 nmol/L allows to rule out mortality in the 28 days following admission to hospital, as previously reported by Andaluz-Ojeda et al.[15,41] in critically ill patients with sepsis diagnosis.

This study presents some limitations, namely the small sample size. Besides, the measurement of other blood biomarkers previously reported as predictors for a poor outcome, such as troponin,[42] was not available in all the patients and it was not included in the study. Finally, we did not measure serial biomarkers and their values may therefore change during the patient's course, thereby making it possible to better identify deterioration or improvement.

In conclusion, the present study reports that plasma MR-proADM levels, measured on admission to Emergency Department, were increased in COVID-19 patients who died or progressed to severe disease. Besides, it was the biomarker with highest performance, expressed as ROC AUC, being MR-proADM value levels above 1.01 nmol/L the only independent factor predictor for both outcomes. Our results suggest that MR-proADM levels have a potential role in the assessment of prognosis in early stages of COVID-19 and might be a candidate to be incorporated in an early management protocol. Further studies, with a larger sample size, are required to confirm these findings.

ACKNOWLEDGEMENTS

This research has been partially funded by Universidad Católica San Antonio de Murcia (UCAM) (reference: PMAFI-COVID19/04) and Gerencia Regional de Salud de Castilla y León under grant number GRS COVID 108/A/20.

CONFLICT OF INTEREST

Authors state no conflict of interest.

AUTHOR CONTRIBUTIONS

LGGR and DAO designed this study, analysed the data and wrote the manuscript. All authors contributed to the enrollment of patients, data collection, sample collection and biomarkers measurement. LCS provided statistical advice. All authors reviewed and approved the final manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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How to cite this article: García de Guadiana-Romualdo L, 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. https://doi.org/10.1111/eci.13511