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RESEARCH ARTICLE

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Prognostic value of copeptin and mid-regional proadrenomedullin in COVID-19-hospitalized patients

Rita Indirli[1,2] | Alessandra Bandera[3] | Luca Valenti[4] | Ferruccio Ceriotti[5] | Adriana Di Modugno[5] | Mauro Tettamanti[6] | Roberta Gualtierotti[7] | Flora Peyvandi[7] | Nicola Montano[8] | Francesco Blasi[9,10] | Giorgio Costantino[11] | Veronica Resi[1] | Emanuela Orsi[1] | Maura Arosio[1,2] | Giovanna Mantovani[1,2] | Emanuele Ferrante[1] | the COVID-19 Network Working Group

[1]Endocrinology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[2]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

[3]Infectious Diseases Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[4]Transfusion Medicine (Biobank), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[5]Clinical Laboratory, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[6]Department of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

[7]Internal Medicine and Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[8]Internal Medicine, Immunology and Allergology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[9]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

[10]Respiratory Unit and Adult Cystic Fibrosis Center, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy

[11]Emergency Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Correspondence
Giovanna Mantovani, Department of Clinical Sciences and Community Health, University of Milan, Endocrinology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via F. Sforza, 35, Milan 20122 Italy.
Email: giovanna.mantovani@unimi.it

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Abstract

Background: Biomarkers are used for diagnosis, risk stratification and medical decisions. Copeptin and mid-regional proadrenomedullin (MR-proADM) are markers of stress and endothelial function, respectively, which have been studied in pneumonia, sepsis and septic shock. This study aimed to assess whether copeptin and MR-proADM could predict coronavirus disease 2019 (COVID-19) in-hospital outcomes, that is multi-system complications, length of stay and mortality.

Methods: Copeptin and MR-proADM were assessed at admission in 116 patients hospitalized with COVID-19. Data were retrospectively extracted from an online database. The primary endpoint was in-hospital mortality. The secondary endpoints were in-hospital complications, the composite outcome 'death, or admission to intensive care unit, or in-hospital complications', and length of stay. The

On behalf COVID-19 Network Working Group members are listed in Acknowledgements section.

predictive power was expressed as area under the receiver operator characteristic curve (AUROC).

Results: Copeptin was increased in non-survivors (median 29.7 [interquartile range 13.0–106.2] pmol/L) compared to survivors (10.9 [5.9–25.3] pmol/L, $p < 0.01$). The AUROC for mortality was 0.71, with a hazard ratio of 3.67 ($p < 0.01$) for copeptin values > 25.3 pmol/L. MR-proADM differentiated survivors (0.8 [0.6–1.1] nmol/L) from non-survivors (1.5 [1.1–2.8] nmol/L, $p < 0.001$) and yielded a AUROC of 0.79 and a hazard ratio of 7.02 ($p < 0.001$) for MR-proADM values > 1.0 nmol/L. Copeptin and MR-proADM predicted sepsis (AUROC 0.95 and 0.96 respectively), acute kidney injury (0.87 and 0.90), the composite outcome (0.69 and 0.75) and length of stay ($r = 0.42$, $p < 0.001$, and $r = 0.46$, $p < 0.001$).

Conclusions: Admission MR-proADM and copeptin may be implemented for early risk stratification in COVID-19-hospitalized patients to help identify those eligible for closer monitoring and care intensification.

KEYWORDS

biomarkers, copeptin, COVID-19, mid-regional proadrenomedullin, mortality, prognosis

1 | INTRODUCTION

Since December 2019, when the coronavirus disease 2019 (COVID-19) first emerged in Wuhan, China, a total of 250 million cases have been reported globally, including 5 million deaths as of 9 November 2021 (https://covid19.who.int/). Italy has been the first European country to be severely affected, and Lombardy, in Northern Italy, was the epicentre of the first Italian outbreak. Between March and June 2020, among 240,455 people diagnosed with COVID-19 throughout Italy, 93,839 were detected in Lombardy, and, in the same time period, lethality was estimated to be about 17% in this region.[1] Many factors were likely to contribute to the high fatality rate, including delay in diagnosis and hospitalization, hesitations in implementing local lock-downs, and flaws in the contact tracing systems.[2]

Besides the socio-demographic and infrastructural factors, many studies have tried to define the clinical and biochemical features associated with COVID-19 complications and death. Male sex, older age, current smoking status and some chronic medical conditions have been related with poor prognosis.[3-6]

Biomarkers are widely used to help diagnosis, risk stratification and medical decisions. In COVID-19-hospitalized patients, an association has been observed between markers of inflammation, coagulation and organ dysfunction, and mortality.[3,5,6] Nevertheless, results of observational studies and metaanalyses have been sometimes controversial, and robust biomarkers for the early risk stratification and clinical management of COVID-19 patients have not yet been defined. Identifying patients at risk of fatal outcome may enhance closer monitoring and early treatment intensification. Furthermore, investigation of novel biomarkers may shed new light on the pathophysiology behind COVID-19 and its complications.

Copeptin is the C-terminal peptide resulting from the cleavage of pre-pro-arginine vasopressin.[7] It is released from the posterior pituitary into the systemic circulation in response to a variety of stimuli, including stress.[7] The prognostic and, in some cases, diagnostic value of copeptin has been documented in clinical conditions like sepsis and septic shock,[8] community-acquired and ventilator-associated pneumonia[9,10] and other critical illnesses.[11] Only one study has investigated the prognostic role of copeptin in COVID-19, showing a significant association with all-cause 30-day mortality.[12]

Mid-regional proadrenomedullin (MR-proADM) is one of the peptides released from pre-proadrenomedullin and commonly assessed as a surrogate marker of adrenomedullin.[13] Adrenomedullin and MR-proADM are synthetized by a variety of cell types, mainly vascular endothelial cells within several organ systems and are considered a marker of endothelial function.[14] MR-proADM has been studied for the prediction of short-term mortality in community-acquired pneumonia,[15] sepsis[16] and COVID-19 as well. In COVID-19-hospitalized patients, MR-proADM has been documented to accurately predict mortality,[17,18] development of acute respiratory distress syndrome (ARDS),[19] need for renal replacement therapy[20]

and progression to severe disease[21,22] in medium and high intensity-of-care departments.

Overall, evidence on the prognostic role of copeptin in COVID-19 is promising but still poor, while data on MR-proADM appear fragmentary and incomplete, since most studies focused on mortality and few respiratory outcomes, but not on the possible multi-system complications of the disease. The aim of this study was to investigate whether copeptin and MR-proADM concentrations assessed at hospital admission, could help predict the subsequent clinical course, in particular development of different multi-system complications, transfer to intensive care unit (ICU), length of stay and mortality, in a single-centre cohort of COVID-19 patients hospitalized during the first outbreak in Lombardy.

2 | MATERIALS AND METHODS

2.1 | Study design, setting and participants

This was a single-centre, observational, retrospective, case–control study, including adult patients admitted to medium intensity-of-care COVID-19 departments of the tertiary university hospital 'Ospedale Maggiore Policlinico' in Milan, Lombardy, between March and June 2020. Reporting of the study conforms to broad EQUATOR guidelines.[23]

COVID-19 was diagnosed by a positive result of real-time reverse transcriptase-polymerase chain reaction testing of a nasopharyngeal swab specimen.

Availability of a plasma sample of 200 μl or more taken at hospital admission and stored in the institutional biobank was required for study inclusion. Patients younger than 18 years and pregnant women were excluded.

2.2 | Data collection and variables

Data were retrospectively extracted from the COVID-19 Network registry. Since March 2020 indeed, a registry known as the COVID-19 Network was established at our institution, and a biobank of biological samples was set up as described elsewhere.[24] Briefly, the registry included all consecutive adults with confirmed COVID-19 admitted to our hospital. All the patients' data assessed as part of the clinical routine and including demographics, medical history, laboratory and radiological results, as well as the clinical course, were recorded prospectively into an online database (REDCap). All patients were asked to sign a written informed consent prior to registry inclusion.

For the present study, the following data were retrieved from the online database: age, sex, pre-existing comorbidities, smoking status; vital signs, need for oxygen support and laboratory assessments at hospital admission; length of hospital stay; outcome (dead/alive); admission to ICU; in-hospital complications.

As for pre-existing comorbidities, conditions recognized to be relevant to COVID-19 prognosis have been considered,[3-6] that is obesity, diabetes mellitus, chronic kidney disease, chronic congestive heart failure, coronary artery disease, arterial hypertension, cerebrovascular disease, chronic obstructive pulmonary disease and active malignancy (solid or haematologic).

As for in-hospital complications, the following were considered[3,6]: ARDS,[25] COVID-19-related viral sepsis,[26] acute kidney injury,[27] venous thromboembolism,[28] ischaemic stroke[29] and cardiac complications. Venous thromboembolism included deep vein thrombosis and pulmonary embolism. Cardiac complications included the following: new-onset or worsening heart failure,[30] myocardial infarction[31] and new-onset arrhythmia.

Criteria for admission to ICU were as follows: need for mechanical ventilation for longer than 24 hours; PaO2/FIO2 ratio <150; respiratory rate >30 breaths per minute and respiratory distress; hypercapnia and/or pH < 7.3; haemodynamic instability (mean arterial pressure <65 mm Hg, diuresis < 0.5 ml/Kg/h, no response to fluid challenge, need for amine infusion).

Criteria for hospital discharge were as follows: apyrexia for 72 h or more, and respiratory rate <22 breaths per minute, and oxygen support withdrawal since 24 h or longer.

2.3 | Laboratory assays

For copeptin and MR-proADM assessment, blood samples were collected at hospital admission in tubes containing EDTA K3 as anticoagulant, centrifuged at 3000 *g* for 10 min, and plasma was subsequently frozen and stored to −80°C in the institutional biobank until testing.

Copeptin was assessed using a commercially available automated sandwich immunoassay (B.R.A.H.M.S. Copeptin proAVP KRYPTOR, ThermoFisher Scientific). The immunoassay has a limit of detection of 0.69 pmol/L, a functional sensitivity of 1.08 pmol/L and an interassay coefficient of variation <18%.

MR-proADM was assessed using a commercially available automated sandwich immunoassay (B.R.A.H.M.S. MR-proADM KRYPTOR, ThermoFisher Scientific). The assay has a limit of detection of 0.05 nmol/L, a functional sensitivity of 0.25 nmol/L and an interassay coefficient of variation <17.5%.

2.4 | Study endpoints

The primary endpoint was the accuracy of admission copeptin and MR-proADM in predicting in-hospital mortality.

The secondary endpoint was the association and predictive power for the following outcomes: length of hospital stay; in-hospital complications; admission to ICU; the composite outcome 'death or admission to ICU or in-hospital complications'.

For the composite outcome, patients who developed one or more of the following outcomes were included as 'cases': death, transfer to ICU, ARDS, sepsis, acute kidney injury, venous thromboembolism, ischaemic stroke and cardiac complications; patients who did not experience either of the listed outcomes were considered as 'controls'.

2.5 | Combined scores

To test the performance of combining MR-proAMD and copeptin into a single scoring system, patients were assigned a score of 0, 1 or 2 according to the number of markers increased above the respective cut-offs (none, one only, or both copeptin and MR-proADM). To this purpose, outcome-specific cut-offs were calculated in the present cohort. The predictive power of the combined score was tested for the primary endpoint in-hospital mortality and for the secondary composite outcome.

Moreover, we tested two established clinical scoring systems for prediction of in-hospital mortality and of the composite outcome in our cohort: the CURB-65[32] and the Sequential Organ Failure Assessment (SOFA) score.[33] These scoring systems were then further combined with copeptin and MR-proADM by adding 0, 1 or 2 points according to the number of biomarkers increased above the respective thresholds.

2.6 | Statistics

Qualitative variables were reported as absolute and relative (per cent) frequencies. Ordinal variables were compared by chi-square test for trend. The distribution of continuous quantitative variables was analysed by D'Agostino–Pearson test. Normally distributed variables were expressed as mean and standard deviation (SD) and compared with unpaired Student's t-test. Non-normally distributed variables were presented as median and interquartile range (IQR) and compared with Mann–Whitney or Kruskal–Wallis tests. Correlation was assessed with Pearson's or Sperman's tests as appropriate in case of a continuous dependent variable; univariate or multivariable logistic regression was used for categorical dependent variables.

The predictive accuracy of the test variables 'copeptin' and 'MR-proADM', relative to the study endpoints, was assessed with the receiver operator characteristic (ROC) curve and reported as the area under the ROC curve (AUROC). The optimal ROC-derived cut-offs were identified using the Youden Index, and sensitivity, specificity, positive and negative likelihood ratios were calculated. Kaplan–Meier curves and log-rank test were employed for survival analysis.

A two-sided *p*-value was considered statistically significant when less than 0.05.

Statistical analysis was performed with GraphPad Prism (version 9.1.2).

2.7 | Ethics

The study was conducted in accordance with the World Medical Association's Declaration of Helsinki and approved by Milan Area 2 ethics committee (reference number 673_2020bis).

3 | RESULTS

3.1 | Baseline characteristics

The study population consisted of 116 patients. Demographics, pre-existing comorbidities, vital signs and laboratory results at hospital admission are reported in Table 1.

Copeptin at admission was significantly higher in patients with pre-existing chronic congestive heart failure, obesity, coronary artery disease, cerebrovascular disease, chronic kidney disease and malignancy, compared to unaffected patients (Table 2).

MR-proADM at admission was significantly higher in patients with diabetes mellitus, obesity, chronic obstructive pulmonary disease, chronic congestive heart failure, arterial hypertension, chronic kidney disease and malignancy (Table 2).

Both biomarkers were positively associated with age (copeptin r = 0.48 [$p < 0.001$]; MR-proADM r = 0.63 [$p < 0.001$]), but not with sex, need for supplemental oxygen or ventilation, arterial oxygen saturation, or radiological findings on chest imaging studies.

Copeptin was non-significantly lower in patients with hyponatremia at admission compared with

TABLE 1 Baseline characteristics of the study population

Total, *n*	116
Males, *n*	65 (56%)
Age, years [mean (SD)]	66 (15)
Chronic obstructive pulmonary disease, *n*	10 (9%)
Chronic congestive heart failure, *n*	8 (7%)
Coronary artery disease, *n*	15 (13%)
Arterial hypertension, *n*	56 (48%)
Diabetes, *n*	23 (20%)
Obesity, *n*	16 (14%)
Current smoker[a], *n*	2 (2%)
Cerebrovascular disease, *n*	13 (11%)
Chronic kidney disease, *n*	13 (11%)
Malignancy[b], *n*	9 (8%)
At hospital admission	
Heart rate, beats per minute	82 (75–93)
Respiratory rate, breaths per minute	20 (18–24)
Systolic blood pressure, mm Hg	130 (120–145)
Diastolic blood pressure, mm Hg	75 (70–85)
Fever, *n*	88 (76%)
Oxygen supply by nasal cannula, *n*	34 (29%)
Oxygen supply by Venturi mask, *n*	24 (21%)
Oxygen supply by reservoir mask, *n*	6 (5%)
Continuous positive airway pressure, *n*	20 (17%)
Haemoglobin, g/dl [mean (SD)]	12.5 (2.0)
Haematocrit, % [mean (SD)]	36.4 (5.4)
Neutrophils, $\times 10^9$/L	4.820 (3.305–7.890)
Lymphocytes, $\times 10^9$/L	1.030 (0.675–1.460)
Platelets, $\times 10^9$/L	243 (165–309)
C reactive protein, mg/dl	7.2 (3.0–12.5)
Procalcitonin, ng/ml	0.20 (0.10–0.35)
Interleukin−6, pg/ml[c]	51 (23–65)
D-Dimer, mg/L	894 (549–1782)
Fibrinogen, mg/dl[d]	512 (435–654)
Creatinine, mg/dl	0.9 (0.7–1.1)
Urea, mg/dl	32 (27–43)
Sodium, mEq/L	140 (136–142)
Hyponatremia, *n*	15 (13%)
Copeptin, pmol/L	13.2 (6.3–30.8)
MR-proADM, nmol/L	0.9 (0.6–1.3)

Note: Unless otherwise indicated, quantitative variables are presented as median and interquartile range. For categorical variables, absolute and percentage frequencies are reported. MR-proADM, mid-regional proadrenomedullin.

[a]Information on smoking status was missing in 31 subjects.

[b]Active solid tumour in 8 subjects, hematologic malignancy in 1. One patient was receiving chemotherapy, 1 radiotherapy and 1 biological therapy at hospital admission, while 6 were not receiving any cancer-directed treatment.

[c]Available in 31 subjects.

[d]Available in 59 subjects.

normonatremic subjects ($p = 0.07$, Table 2) and lacked association with plasma sodium concentrations (r = 0.15, $p = 0.16$).

3.2 | In-hospital outcomes

The median length of stay was 14 days (IQR 8–22). Twenty-one patients (18%) died during hospitalization, and 8 were transferred to ICU.

ARDS occurred in 13 patients (11%), sepsis in 4 (3%) and venous thromboembolism in 7 (6%). Eighteen (16%) patients experienced cardiac complications, 4 (3%) developed acute kidney injury, and ischaemic stroke occurred in 10 (9%) subjects.

3.3 | Primary endpoint

Median copeptin at admission was significantly higher in non-survivors (29.7 [IQR 13.0–106.2] pmol/L) compared to survivors (10.9 [5.9–25.3] pmol/L, $p < 0.01$; unadjusted odds ratio, OR, 1.019, 95% confidence interval, CI, 1.008–1.033, $p < 0.001$; Table 3). In the multivariable analysis including age, sex and comorbidities (diabetes, obesity, chronic congestive heart failure, cerebrovascular disease, coronary artery disease, chronic kidney disease, arterial hypertension, chronic obstructive pulmonary disease and malignancy), copeptin was significantly associated with in-hospital mortality (adjusted OR 1.016, 95% CI 1.003–1.035, $p = 0.04$). According to ROC curve analysis, copeptin showed moderate accuracy in predicting in-hospital mortality (AUROC 0.71, $p < 0.01$, Figure 1). A cut-off of 25.3 pmol/L displayed a sensitivity of 75.5% and a specificity of 70.0% (Table 4), and the risk of death resulted 3.67 times higher ($p < 0.01$) in patients with copeptin concentrations above this cut-off level in survival analysis (Figure 2).

MR-proADM was significantly associated with mortality (median 1.5 [IQR 1.1–2.8] nmol/L in non-survivors *vs.* 0.8 [0.6–1.1] nmol/L in survivors, $p < 0.001$, unadjusted OR 2.265, 95% CI 1.453–4.103, $p < 0.001$; Table 3). In multivariable analysis including age, sex and comorbidities listed above, mortality resulted significantly associated with MR-proADM (adjusted OR 2.844, 95% CI 1.421–7.671, $p = 0.01$) and malignancy (adjusted OR 6.739, 95% CI 1.135–44.680, $p = 0.04$).

The AUROC for MR-proADM was 0.79 ($p < 0.001$, Figure 1). A cut-off of 1.0 nmol/L identified patients at risk of dying with 71.3% sensitivity, 85.7% specificity, 5.0 positive likelihood ratio and 0.33 negative likelihood ratio (Table 4). The hazard ratio resulted 7.02 ($p < 0.001$) in survival analysis (Figure 2).

TABLE 2 Median (with interquartile range, IQR) admission copeptin and mid-regional proadrenomedullin (MR-proADM) concentrations according to baseline characteristics and pre-existing comorbidities

	Copeptin		MR-proADM	
	Median (IQR) pmol/L	***p*-value**	**Median (IQR) nmol/L**	***p*-value**
Baseline characteristics and pre-existing comorbidities				
Males	12.5 (6.5–27.8)	0.42	0.8 (0.6–1.1)	0.08
Females	15.8 (6.0–43.0)		1.0 (0.7–1.5)	
Diabetic patients	21.3 (9.5–33.9)	0.13	1.1 (0.8–1.5)	0.03
Non-diabetic patients	11.1 (5.9–27.4)		0.9 (0.6–1.2)	
Obese patients	25.5 (15.7–35.3)	0.02	1.1 (0.9–1.6)	0.01
Non-obese patients	11.1 (5.8–28.4)		0.9 (0.6–1.2)	
Chronic obstructive pulmonary disease	14.2 (7.1–73.4)	0.41	1.3 (1.0–1.8)	<0.01
No chronic obstructive pulmonary disease	12.6 (6.1–28.5)		0.9 (0.6–1.2)	
Chronic congestive heart failure	60.5 (20.2–112.4)	<0.01	2.0 (1.2–3.7)	<0.001
No chronic congestive heart failure	12.0 (5.6–27.6)		0.9 (0.6–1.2)	
Coronary artery disease	28.6 (13.4–80.6)	0.04	1.1 (0.8–2.2)	0.054
No coronary artery disease	11.5 (6.1–27.6)		0.9 (0.6–1.2)	
Arterial hypertension	16.3 (6.7–47.0)	0.11	1.0 (0.9–1.6)	<0.001
No arterial hypertension	10.9 (5.7–25.6)		0.7 (0.5–1.1)	
Cerebrovascular disease	45.1 (18.7–70.3)	<0.01	1.1 (0.8–1.8)	0.12
No cerebrovascular disease	11.4 (5.9–27.6)		0.9 (0.6–1.2)	
Chronic kidney disease	52.8 (26.1–115.2)	<0.001	2.3 (1.3–3.6)	<0.001
No chronic kidney disease	10.9 (5.8–26.6)		0.9 (0.6–1.1)	
Malignancy	34.2 (17.8–58.0)	0.03	1.2 (1.1–1.5)	0.02
No malignancy	12.0 (5.9–27.6)		0.9 (0.6–1.3)	
Hyponatremia at presentation	8.2 (5.3–21.3)	0.07	1.0 (0.6–1.2)	0.94
Normonatremia at presentation	16.1 (6.6–30.9)		0.9 (0.7–1.3)	
Infiltrates on chest imaging studies	14.2 (5.9–27.6)	0.89	0.9 (0.7–1.3)	0.82
No infiltrates on chest imaging studies	12.4 (6.4–35.3)		0.9 (0.6–1.3)	
Supplemental oxygen/ventilation				
None	11.5 (5.5–30.9)	0.77	0.9 (0.6–1.3)	0.68
Nasal cannula or Venturi mask or Reservoir mask	13.2 (6.3–42.3)		0.9 (0.6–1.4)	
Continuous positive airway pressure	18.3 (8.7–27.6)		0.9 (0.8–1.1)	

3.4 | Secondary endpoints

Both copeptin and MR-proADM were positively associated with length of hospital stay (r = 0.42 [$p < 0.001$], and r = 0.46 [$p < 0.001$] respectively).

Copeptin and MR-proADM at presentation were significantly associated with the occurrence of sepsis and of acute kidney injury during hospital stay (Table 3), and this was confirmed after adjusting for age and sex (copeptin—sepsis adjusted OR 1.019, 95% CI 1.004–1.041, $p = 0.03$; copeptin—acute kidney injury adjusted OR 1.012, 95% CI 1.001–1.026, $p = 0.04$; MR-proADM—sepsis adjusted OR 2.845, 95% CI 1.461–9.895, $p = 0.02$; MR-proADM—acute kidney injury adjusted OR 1.838, 95% CI 1.136–3.078, $p < 0.01$). The two biomarkers accurately predicted the two complications, as shown by ROC curve analysis (Figure 1).

A significant association was found for the composite outcome 'death or admission to ICU or in-hospital complications' with both copeptin (Table 3; age and

TABLE 3 Median (with interquartile range, IQR) admission copeptin and mid-regional proadrenomedullin (MR-proADM) concentrations according to outcomes and in-hospital complications

	Copeptin		MR-proADM	
	Median (IQR) pmol/L	*p*-value	Median (IQR) nmol/L	*p*-value
Outcomes and in-hospital complications				
Non-survivors	29.7 (13.0–106.2)	<0.01[a]	1.5 (1.1–2.8)	<0.001[a]
Survivors	10.9 (5.9–25.3)		0.8 (0.6–1.1)	
Admission to ICU				
Yes	15.8 (2.5–24.0)	0.32	0.9 (0.6–1.5)	0.90
No	13.1 (6.5–33.6)		0.9 (0.7–1.2)	
ARDS				
Yes	16.1 (3.2–18.3)	0.17	0.8 (0.6–1.2)	0.61
No	12.6 (6.4–34.7)		0.9 (0.6–1.3)	
Sepsis				
Yes	159.5 (47.0–222.2)	<0.01[b]	5.9 (1.7–7.0)	0.001[b]
No	12.6 (6.5–27.8)		0.9 (0.6–1.2)	
Venous thromboembolism				
Yes	8.2 (4.1–38.3)	0.46	1.0 (0.7–1.3)	0.67
No	14.2 (6.6–30.8)		0.9 (0.6–1.2)	
Acute kidney injury				
Yes	110.2 (29.2–208.6)	<0.01[c]	3.0 (1.6–6.1)	<0.01[c]
No	12.6 (6.4–27.9)		0.9 (0.6–1.2)	
Cardiological complications				
Yes	22.4 (10.0–45.6)	0.07	1.0 (0.8–1.3)	0.22
No	11.4 (5.9–27.4)		0.9 (0.6–1.3)	
Neurological complications				
Yes	37.3 (7.2–80.9)	0.15	1.2 (1.0–2.5)	0.04
No	12.6 (6.1–27.9)		0.9 (0.6–1.2)	
Composite: death or admission to ICU or any complication				
Yes	25.3 (8.6–52.2)	<0.001[d]	1.1 (0.8–1.8)	<0.001[d]
No	8.7 (5.8–18.7)		0.7 (0.5–0.9)	

Abbreviations: ICU, intensive care unit. ARDS, acute respiratory distress syndrome.

[a]Copeptin unadjusted odds ratio, OR, 1.019, 95% confidence interval, CI, 1.008–1.033, $p < 0.001$. MR-proADM unadjusted OR 2.265, 95% CI 1.453–4.103, $p < 0.001$.

[b]Copeptin unadjusted OR 1.016, 95% CI 1.004–1.032, $p = 0.01$. MR-proADM unadjusted OR 2.030, 95% CI 1.302–3.605, $p < 0.01$.

[c]Copeptin unadjusted OR 1.015, 95% CI 1.003–1.028, $p = 0.02$. MR-proADM unadjusted OR 1.720, 95% CI 1.133–2.696, $p = 0.01$.

[d]Copeptin unadjusted OR 1.032, 95% CI 1.014–1.056, $p < 0.001$. MR-proADM unadjusted OR 5.084, 95% CI 2.215–14.400, $p < 0.001$.

sex-adjusted OR 1.029, 95% CI 1.009–1.055, $p = 0.01$) and MR-proADM (Table 3; age and sex adjuster OR 4.837, 95% CI 1.814–16.900, $p < 0.01$). The two biomarkers had moderate accuracy in predicting the composite outcome (Figure 1).

Table 4 summarizes the sensitivity, specificity, positive and negative likelihood ratios of the cut-offs identified by Youden's index for each outcome.

Copeptin and MR-proADM lacked association with ARDS, venous thromboembolism, cardiological or neurological complications and admission to ICU.

3.5 | Combination of biomarkers and clinical risk scores

Copeptin and MR-proADM were then combined into a single scoring system for mortality prediction, employing the outcome-specific cut-offs (25.3 pmol/L for copeptin and 1.0 nmol/L for MR-proADM). The mortality rate was 5% in patients scoring 0 ($N = 64$), 18% in patients scoring 1 ($N = 22$) and 47% in patients scoring 2 ($N = 30$, p for trend <0.0001) (Appendix S1). The three scoring groups also showed significantly different survival curves (p for

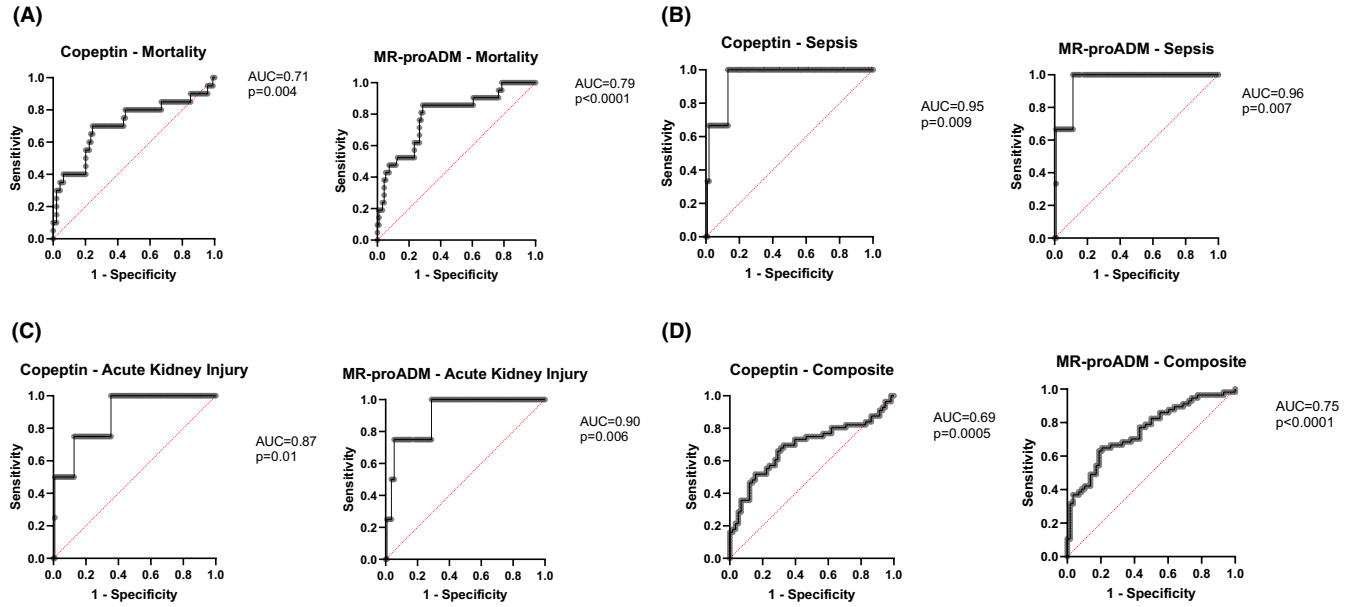

FIGURE 1 Receiver operator characteristic (ROC) curves of copeptin and mid-regional proadrenomedullin (MR-proADM) for prediction of in-hospital mortality (A), sepsis (B), acute kidney injury (C) and the composite outcome 'death or admission to intensive care unit or complications' (D). AUC, area under the curve

TABLE 4 Optimal cut-offs calculated by Youden's index for copeptin and mid-regional-proadrenomedullin (MR-proADM) relative to the different clinical outcomes

	Cut-off	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
Copeptin					
Mortality	25.3 pmol/L	75%	70%	2.5	0.4
Sepsis	45.8 pmol/L	87%	100%	–	0.1
AKI	21.3 pmol/L	65%	100%	–	0.3
Composite	12.6 pmol/L	67%	70%	2.2	0.5
MR-proADM					
Mortality	1.0 nmol/L	71%	86%	5.0	0.3
Sepsis	1.7 nmol/L	89%	100%	–	0.1
AKI	1.2 nmol/L	72%	100%	–	0.3
Composite	0.9 nmol/L	79%	65%	2.3	0.3

Note: Composite, composite outcome 'death or admission to intensive care unit or any in-hospital complication'.

Abbreviation: AKI, acute kidney injury.

trend =0.002) (Appendix S1), and AUROC resulted 0.80 (Appendix S2).

Consistent results were observed for the composite outcome by employing specific cut-offs (copeptin>12.6 pmol/L, MR-proADM>0.9 nmol/L). The prevalence of the composite outcome increased along with the score obtained (12 out of 41 patients scoring 0; 13/31 patients scoring 1; 30/44 patients scoring 2; *p* for trend <0.0001) and AUROC resulted 0.69 (Appendix S2).

Finally, we tested two clinical scoring systems for prediction of in-hospital mortality and of the composite outcome in our cohort: CURB-65 (available in 72 patients), which yielded an AUROC of 0.75 and 0.73 for the two endpoints, respectively, and the SOFA score (available in 71 patients), with AUROC of 0.83 and 0.80 for the two outcomes respectively. When these scoring systems were combined with copeptin and MR-proADM, the prognostic sensitivity improved as shown in Appendix S2.

4 | DISCUSSION

According to the World Health Organization's recent estimates, COVID-19 has been responsible for at least

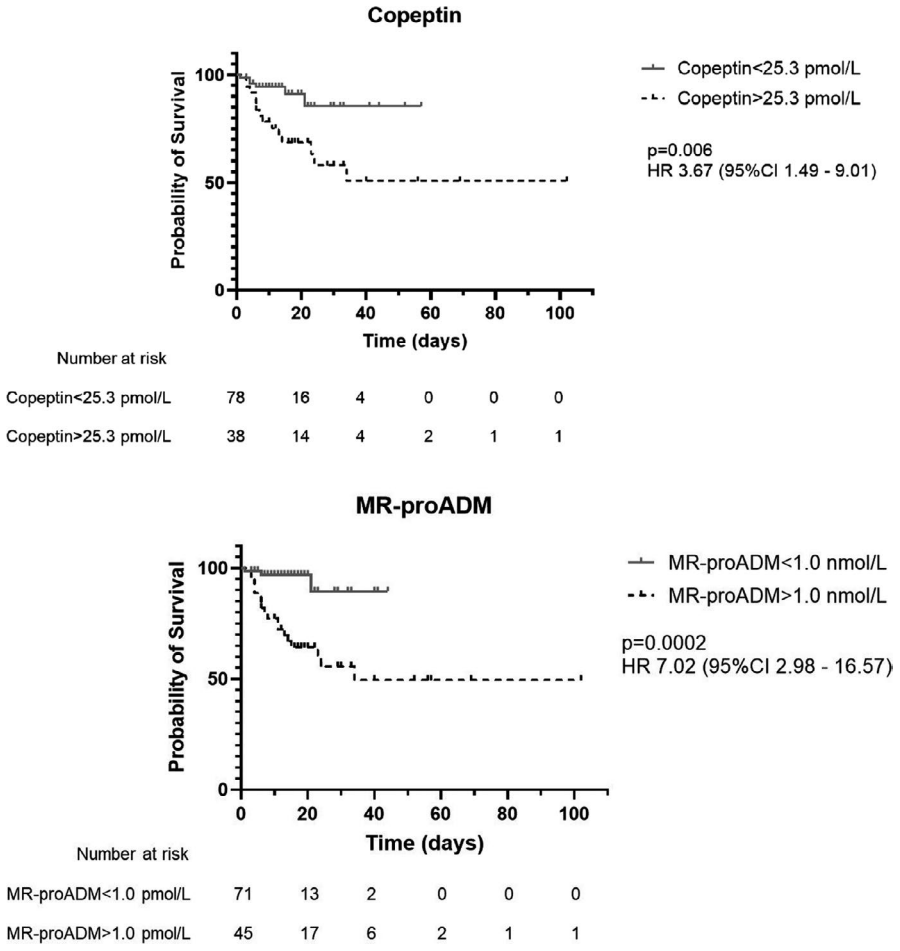

FIGURE 2 Survival analysis according to copeptin and mid-regional proadrenomedullin (MR-proADM) concentrations at hospital admission. HR, hazard ratio. CI, confidence interval

3 million excess deaths in 2020 worldwide (https://www.who.int/news-room/spotlight/the-impact-of-covid-19-on-global-health-goals). Efforts are being made to develop targeted treatments and improve clinical management. To this purpose, the identification of early robust biomarkers to define a patient's individual risk may help guide clinical decisions.

In the present study, we reported that two biomarkers from distinct biological pathways, that is the stress marker copeptin and the marker of endothelial function MR-proADM, assessed at hospital admission, accurately predicted in-hospital mortality, occurrence of sepsis or acute kidney injury, and the composite outcome 'death or admission to ICU or in-hospital complications' in COVID-19-hospitalized patients.

Copeptin and MR-proADM are surrogate markers for other biologically active molecules. Copeptin is the C-terminal segment of the arginine vasopressin precursor peptide and is easily measured in place of vasopressin, since the two molecules are co-released in equimolar quantities from the posterior pituitary in response to a variety of stimuli, including systemic inflammation and stress response.[7] Likewise, MR-proADM is assessed as a surrogate marker of adrenomedullin.[13] They are co-released from many different cell types, mainly vascular endothelial cells,[14] in response to different stimuli, including hypoxia, inflammatory cytokines and endothelial injury.[13,14] Both biomarkers have been extensively studied as predictors of morbidity[8] and short- and long-term mortality in community-acquired pneumonia,[15] sepsis[11,16] and other critical illnesses.[7]

To date, only one other study has investigated copeptin levels in COVID-19.[12] Gregoriano C. et al. showed that copeptin at admission accurately predicted all-cause 30-day mortality in a cohort of 74 COVID-19-hospitalized patients, with AUROC of 0.81 and an optimal cut-off of 20.0 pmol/L. In our study, we confirmed these results in a larger cohort and identified a similar cut-off level of 25.3 pmol/L despite a slightly lower AUROC. In addition, we showed that copeptin was associated with length of hospital stay and, consistently, with a more complicated clinical course, as it predicted the composite outcome, acute kidney injury and sepsis.

In COVID-19, whole-blood adrenomedullin RNA expression is higher than in other respiratory infections, and it is increased in severe disease compared to moderate disease.[34] In the present study, we showed that MR-proADM predicts in-hospital mortality with AUROC of

0.79, and proposed a cut-off of 1.0 nmol/L to identify high-risk patients. Consistently, smaller studies conducted in similar settings—COVID-19 patients admitted to medicine departments during the first outbreak[18,21]—reported mortality rates and median MR-proADM levels close to those observed in our series, and identified optimal MR-proADM cut-offs of 0.93–1.01 nmol/L for short-term mortality prediction.[18,21] Interestingly, in a larger Spanish cohort including COVID-19 patients hospitalized during the second wave,[35] MR-proADM was the biomarker with the highest discriminating power for longer-term (i.e. 90-day) mortality with a negative predictive value of 99.5%. For this reason, authors suggested implementation of MR-proADM to identify low-risk patient candidate to outpatient management. Finally, it should be noted that higher MR-proADM thresholds—between 1.07 and 2.0 nmol/L—have been reported for mortality prediction in critical patients in intensive care settings.[17,19]

Previous studies have shown that MR-proADM concentrations above 0.895–1.01 nmol/L correlate also with a higher risk of progression to severe disease, variably defined as a combination of admission to ICU, ventilation and death.[21,22] In our series as well, MR-proADM showed a moderate predictive power for the composite outcome 'death or admission to ICU or in-hospital complications', and an optimal cut-off of 0.9 nmol/L was identified.

Overall, it could be concluded that admission MR-proADM concentrations above 0.9–1.0 nmol/L appear to be associated with a more complicated clinical course and in-hospital mortality. Interestingly, our results also suggest that copeptin and MR-proADM may not only be employed as stand-alone parameters, but could also be combined together or even with other clinical risk scores, like the SOFA score, to improve the prognostic sensitivity.

As for copeptin, association of admission MR-proADM with some specific in-hospital complications, that is sepsis and acute kidney injury, was observed in our series, and outcome-specific cut-offs were proposed. Only one other study tested MR-proADM as an independent predictor for renal replacement therapy, albeit in a higher intensity-of-care setting.[20]

Of note, both copeptin and MR-proADM at admission were more elevated in patients with some comorbidities known to negatively impact on COVID-19 prognosis. However, the association of the two biomarkers with in-hospital mortality remained significant after adjusting for all the comorbidities considered. We could speculate that patients with some pre-existing clinical conditions may have chronically increased baseline levels of such biomarkers, as reported previously,[7,14] or, alternatively, may have a predisposition to develop an early exaggerated systemic response.

COVID-19 multi-system complications, particularly viral sepsis and renal injury, involve pathogenetic mechanisms like hyperinflammation, haemodynamic instability, hypoxia, insult to the vascular endothelium and stress response.[36,37] All these triggers can stimulate the secretion of copeptin[38] and MR-proADM.[13,14] Hence, the elevation of these molecules may serve as an early, highly sensitive marker which anticipates the presentation of clinically evident complications. Moreover, it remains to be clarified if the enhanced secretion of copeptin and MR-proADM directly contributes to poor clinical outcomes, based on the multi-system actions of their biologically active counterpart arginine vasopressin and adrenomedullin. Indeed, vasopressin induces vasoconstriction, stimulates the release of von Willebrand Factor and platelets aggregation, and modulates the stress response of the hypothalamus–pituitary–adrenal axis.[38] Adrenomedullin promotes the endothelial barrier function but, at the same time, causes vasodilatation,[14] which can be detrimental in critical patients. The potential pathogenetic role of these molecules may deserve consideration for the development of new therapeutic strategies, indeed. Preliminary promising results were obtained in COVID-19 critical patients receiving Adrecizumab, a humanized monoclonal antibody targeting the N-terminus of adrenomedullin.[39]

The ability to predict not only in-hospital mortality, but also some specific complications, is a novel finding for both MR-proADM and, most of all, copeptin. This aspect and the reporting of one of the largest cohorts on this specific topic are the strengths of this study. However, populations with a higher incidence of sepsis and renal events are needed to confirm the predictive power of the two biomarkers.

This study has some limitations. First, the observational design, along with the lack of clear-cut indications for the management of COVID-19 patients at the time of the study, limited procedure standardization. Second, the cut-offs obtained for copeptin and MR-proADM are from a population of medium intensity of care only, and our study lacked a validation cohort. Third, medications currently recommended for COVID-19-hospitalized patients, like corticosteroids, were not employed at the time of the study. Some of these medications impact on COVID-19 prognosis and may modify circulating biomarkers' concentrations.[14] For these reasons, the same biomarkers should be re-evaluated in the light of approved treatments. Conversely, the first COVID-19 outbreak may represent a unique setting to study the potential role of biomarkers in COVID-19 natural history without interfering drugs. Moreover, different biomarkers' levels may be observed in subsequent COVID-19 waves, due to a lower disease severity of patients admitted to hospitals, for instance.[40] However, the predictive power of MR-proADM

has been confirmed in studies carried out during the second COVID-19 outbreak,[35] but data on copeptin are not available yet.

In conclusion, our study documented that MR-proADM and copeptin concentrations, assessed upon hospital admission, may be employed as early markers to identify patients at increased risk for in-hospital complications—in particular acute kidney injury and sepsis—and death, who may be eligible for closer monitoring or early intensification of care. Larger prospective studies are warranted to clarify whether and in which way copeptin and MR-proADM could be implemented in the management of COVID-19-hospitalized patients.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

E. Ferrante, G. Mantovani and M. Arosio designed the study. L. Valenti selected patients. F. Ceriotti and A. Di Modugno performed laboratory analyses. M. Tettamanti retrieved the clinical data from the online database. R. Indirli and E. Ferrante analysed data and wrote the manuscript. A. Bandera, L. Valenti, F. Ceriotti, R. Gualtierotti, F. Peyvandi, N. Montano, F. Blasi, G. Costantino, V. Resi, E. Orsi, M. Arosio and G. Mantovani critically revised the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Rita Indirli https://orcid.org/0000-0001-5642-0563
Luca Valenti https://orcid.org/0000-0001-8909-0345
Maura Arosio https://orcid.org/0000-0003-3988-3616
Giovanna Mantovani https://orcid.org/0000-0002-9065-3886
Emanuele Ferrante https://orcid.org/0000-0002-0556-7650

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SUPPORTING INFORMATION

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