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Mid-regional pro-atrial natriuretic peptide independently predicts short-term mortality in COVID-19

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Abstract

Background: Mid-regional pro-atrial natriuretic peptide (MR-proANP) is a strong prognostic marker in several inflammatory, respiratory and cardiovascular conditions, but has not been studied in COVID-19 yet.

Methods: This prospective, observational study of patients with COVID-19 infection was conducted from 6 June to 26 November 2020 in different wards of a tertiary hospital. MR-proANP, N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitive cardiac troponin I levels on admission were collected and tested for their association with disease severity and 28-day mortality.

Results: A total of 213 eligible patients with COVID-19 were included in the final analyses of whom 13.2% (n = 28) died within 28 days. Median levels of MR-proANP at admission were significantly higher in nonsurvivors (307 pmol/L IQR, [161 - 532] vs 75 pmol/L [IQR, 43 - 153], $P < .001$) compared to survivors and increased with disease severity and level of hypoxaemia. The area under the ROC curve for MR-proANP predicting 28-day mortality was 0.832 (95% CI 0.753 - 0.912, $P < .001$). An optimal cut-off point of 160 pmol/L yielded a sensitivity of 82.1% and a specificity of 76.2%. MR-proANP was a significant predictor of 28-day mortality independent of clinical confounders, comorbidities and established prognostic markers

of COVID-19 (HR 2.77, 95% CI 1.21 - 6.37; $P = .016$), while NT-proBNP failed to independently predict 28-day mortality and had a numerically lower AUC compared to MR-proANP.

Conclusion: Higher levels of MR-proANP at admission are associated with disease severity of COVID-19 and act as a powerful and independent prognostic marker of 28-day mortality.

KEYWORDS

COVID-19, disease severity, high-sensitive cardiac troponin I, Mid-regional pro-atrial natriuretic peptide, Mortality, N-terminal pro-brain natriuretic peptide

1 | INTRODUCTION

Coronavirus disease-19 (COVID-19) originated late December 2019 in Wuhan, China, and has since spread across the globe causing an international pandemic. The single-stranded enveloped RNA virus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—has been identified as the causative agent for infection.[1] While most patients experienced mild illness without significant respiratory involvement, up to 19% of patients had a more severe course of disease with reported case fatality rates of up to 49% among critically ill patients.[2] Cardiovascular morbidity and mortality is high in patients with COVID-19, and those with pre-existing cardiovascular disease are at considerably higher risk of worse outcome.[3,4] Several cardiovascular biomarkers—including cardiac troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP)—have been identified as prognostic markers in COVID-19.[5-7]

Atrial natriuretic peptide (ANP) is primarily expressed in the right atrium following atrial distension and exerts several physiological effects, including natriuresis, diuresis and vasodilation.[8] Hypoxaemia has also been suggested as a trigger of ANP release, which makes it an interesting target in both respiratory and cardiovascular disease.[9] Mid-regional pro-atrial natriuretic peptide (MR-proANP), the mid-regional fragment of the precursor hormone of ANP, is characterized by excellent ex vivo stability making it the preferred biomarker in clinical practice.[10] Several studies have reported on the prognostic value of MR-proANP in a variety of clinical conditions, including sepsis, inflammation and cardiovascular disease, respectively.[11-13] Higher levels of MR-proANP were significantly and independently associated with short-term and long-term mortality of patients with community-acquired and ventilator-associated pneumonia.[14-17] However, there are currently no research data available on MR-proANP in COVID-19.

In the present study, we aimed to evaluate the association of MR-proANP with disease severity of COVID-19 and its prognostic impact for prediction of short-term mortality in a well-defined cohort of hospitalized patients with COVID-19, while adjusting for established biomarkers of risk in COVID-19, including NT-proBNP and high-sensitive cardiac troponin I (hs-cTnI).

2 | MATERIALS AND METHODS

2.1 | Study design and patient population

A total of 213 hospitalized patients with laboratory-confirmed SARS-CoV-2 infection were included in this prospective, observational, single-centre study in different wards of the Wilhelminenhospital in Vienna, Austria. (Suppl. Figure 1) All patients presented to the emergency department between 6 June and 26 November 2020 at our institution and were admitted for in-hospital care. The diagnosis of COVID-19 was made according to the WHO interim guidance and a polymerase chain reaction proven ribonucleic acid detection of SARS-CoV-2 on nasal and/or pharyngeal swabs was required. The study was approved by the local ethics committee of the city of Vienna (EK 20-100-VK) and complies with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

Demographic data, clinical features, laboratory results and medical history were obtained from patient records on admission. Pre-existing cardiovascular disease was defined by a history of coronary artery disease or heart failure. Chronic pulmonary disease was defined by a history of chronic obstructive pulmonary disease, asthma bronchiale or obstructive sleep apnoea. Comorbidities were defined at the discretion of the treating physician. Follow-up data were collected through the electronic patient record system of our institution until 19 December 2020.

The primary endpoint of our study was 28-day all-cause mortality. We also assessed the association of MR-proANP with levels of hypoxaemia, using oxygen saturation levels and Horowitz index (pO2/FiO2 < 200 mmHg) at admission, and the association with disease severity, using the pneumonia

severity index (PSI) at admission, which is an established risk stratification tool for patients with community-acquired pneumonia and has also been studied in COVID-19.[18] The PSI was calculated according to the recommendations of the publishers.

2.2 | Biomarker analysis

Blood samples were collected by trained nurses or doctors upon presentation of the patient to the emergency department. After centrifugation, blood samples for biomarker analysis were divided into 0.5 ml aliquots and stored at −80°C until measurement. MR-proANP was evaluated by TRACE (Time Resolved Amplified Cryptate Emission) on the KRYPTOR compact PLUS (BRAHMS GmbH, Thermo Scientific, Hennigsdorf, Germany). Commercially available kits (BRAHMS GmbH, Thermo Scientific, Hennigsdorf, Germany) were used for measurement of MR-proANP, which was performed in line with the manufacture's guidelines. According to the manufacture's specification, the detection limit of MR-proANP and the 97.5% percentile of the reference range are 2.1 pmol/L and 85.2 pmol/L, respectively.

Routine assessment of biomarkers of inflammation, cardiovascular disease and organ dysfunction were performed at the certified central laboratory of the Wilhelminenhospital and included: white blood cells, neutrophil granulocytes, lymphocytes, C-reactive protein (CRP), platelets, haemoglobin, creatinine, BUN, sodium, potassium, hs-cTnI, NT-proBNP and lactate dehydrogenase (LDH). Neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

2.3 | Statistical analysis

Continuous data are reported as median and interquartile range (IQR), and categorical data are expressed as frequency and percentage. Normality was checked by the Shapiro-Wilk normality test. Mann-Whitney U test and Pearson's chi-squared test were used to compare continuous and categorical data between survivors and nonsurvivors and Kruskal-Wallis test and Pearson's chi-squared test across quartiles of MR-proANP and pneumonia severity index. Correlation between MR-proANP and biomarkers was assessed by Spearman's correlation.

Univariable and multivariable Cox regression analyses were performed to determine the prognostic impact of MR-proANP on 28-day mortality. Since all investigated biomarkers had a non-normal distribution, we performed log-transformation and standardization (subtracting the mean and dividing by the standard deviation) prior to regression analyses. Variables found to be significant ($P < .05$ for baseline characteristics and < 0.01 for laboratory markers) upon univariable Cox regression were included in subsequent multivariable models. We also performed univariable Cox regression in selected subgroups to test for consistency of the prognostic impact of MR-proANP and displayed the results with forest plots.

We used ROC analysis to determine the performance of each biomarker for predicting survival or death at 28 days. The statistically optimal cut-off of MR-proANP yielding the highest sensitivity and specificity for discrimination of the primary endpoint was determined by the Youden index. Kaplan-Meier curves and log-rank tests were used to compare survival time stratified by quartiles for MR-proANP, NT-proBNP and hs-cTnI.

All statistical analyses were performed using SPSS 26.0 (SPSS Inc, Chicago, IL, USA), and a two-sided p-value < 0.05 was required for statistical significance. Graphics were generated using GraphPad Prism 9.0 (GraphPad Software, Inc, San Diego, CA).

3 | RESULTS

3.1 | Baseline characteristics

A total of 213 patients with COVID-19 were included in the study, and 13.2% (n = 28) reached the primary endpoint of 28-day mortality. Mean age was 65.6 years (SD ± 16.8), and 55.9% (n = 119) were male. Comorbidity burden was high among hospitalized patients with COVID-19 as 57.3% of patients had a history of arterial hypertension (n = 122), 31.5% (n = 67) diabetes mellitus, 20.7% (n = 44) cardiovascular disease, 13.1% (n = 28) chronic pulmonary disease and 16.9% chronic kidney disease (n = 36). Fever was the most common presenting symptom found in 77.5% (n = 165) of patients followed by dyspnoea (60.6%, n = 129) and coughing (53.5%, n = 114). Upon admission, median blood pressure values were 137 mmHg (IQR, 120 - 150 mmHg) systolic and 80 mmHg (IQR, 70 - 90) diastolic and median heart rate was 95 beats/min (IQR, 82 - 105 beats/min) on average. Radiographic signs of infiltrates were recorded in 75.1% (n = 160) of cases on chest X-ray at admission.

3.2 | Clinical characteristics and biomarkers stratified by primary endpoint

Patients who died within 28 days of admission were significantly older and had more frequently a history of arterial hypertension, as well as pre-existing cardiovascular disease and/or renal disease. Dyspnoea, desaturation of oxygen and increased respiratory rate were more common in nonsurvivors. There was no difference in sex, diabetes mellitus,

chronic pulmonary disease, body temperature or presence of infiltrates on chest X-ray. Median levels of MR-proANP at admission were significantly higher in nonsurvivors (307 pmol/L IQR, [161 - 532] vs 75 pmol/L [IQR, 43 - 153), P <.001) compared to survivors. White blood cells, neutrophil granulocytes, C-reactive protein and creatinine were significantly higher in nonsurvivors, while lymphocytes and haemoglobin were lower. (Table 1).

3.3 | Clinical characteristics stratified by MR-proANP and correlation with other biomarkers

The median level of MR-proANP in our study population was 93.2 pmol/L (IQR, 46.9 to 186.8 pmol/L), and patients were stratified according to MR-proANP quartiles. Patients with higher concentrations of MR-proANP upon admission were older and had a higher rate of arterial hypertension (Q1, n = 11 vs Q4, n = 44), cardiovascular disease (Q1, n = 0 in vs Q4, n = 25) and chronic kidney disease (Q1, n = 0 vs Q4, n = 24). Upon chest X-ray, cardiomegaly, as a sign of chronic cardiovascular disease, and pleural effusion, as a sign of hypervolaemia, were more prevalent in higher quartiles of MR-proANP. Patients with higher baseline MR-proANP concentrations also had higher levels of neutrophil granulocytes, CRP and creatinine and had lower levels of lymphocytes and haemoglobin. (Suppl. Table 1).

MR-proANP correlated with markers of inflammation (leucocytes, NLR and CRP), myocardial injury (determined by hs-cTnI), myocardial ventricular stretch (determined by NT-proBNP) and renal function (determined by creatinine and BUN). However, no correlation was observed with lactate dehydrogenase (LDH). (Table 2).

3.4 | Association of MR-proANP with hypoxaemia and disease severity

MR-proANP levels were significantly higher in patients with a Horowitz index (PaO2/FiO2) of < 200 mmHg compared to those with ≥ 200 mmHg (151.5 pmol/L [IQR, 66.4 - 382.8] vs 91.7 pmol/L [IQR 46.7 - 181.8]; P =.047), and we also observed a significant, weak inverse relationship between MR-proANP and oxygen saturation upon admission (ρ −0.177, P =.010). (Table 2).

Pneumonia severity index, as a marker of disease severity, was calculated in 179 patients and was significantly associated with higher concentrations of MR-proANP with levels ranging from 53.3 pmol/L (IQR, 33.1 – 75.8) in PSI class I/II to 336.9 pmol/L (IQR, 183.6 – 562.3) in PSI class V. (Figure 1).

TABLE 1 Baseline characteristics of the study population stratified by survival status

Characteristics	Survivors (n = 185)	Nonsurvivors (n = 28)	P-value
Baseline characteristics			
Age, years	63 ± 16.1	82 ± 11.4	**<0.001**
Male sex	103 (55.7%)	16 (57.1%)	0.884
Arterial hypertension	100 (54.1%)	22 (78.6%)	**0.015**
Diabetes mellitus	58 (31.4%)	9 (32.1%)	0.933
Cardiovascular disease	30 (16.2%)	14 (50.0%)	**<0.001**
Chronic pulmonary disease	22 (11.9%)	6 (21.4%)	0.164
Chronic kidney disease	25 (13.5%)	11 (39.3%)	**0.001**
Signs and symptoms			
Fever	148 (80.0%)	17 (60.7%)	**0.023**
Coughing	102 (55.1%)	12 (42.9%)	0.226
Dyspnoea	107 (57.8%)	22 (78.6%)	**0.037**
Physical examination			
Temperature, °C	38.1 (37.4 - 38.9)	38.2 (37.5 - 38.7)	0.938
Systolic blood pressure, mmHg	138 (120 - 150)	136 (118 - 148)	0.695
Diastolic blood pressure, mmHg	80 (73 - 90)	73 (67 - 85)	**0.005**
Heart rate, beats / min	93 (81 - 105)	99 (90 - 115)	0.137
Oxygen saturation, %	93 (90 - 96)	91 (82 - 93)	**0.001**
Chest radiography			
Infiltrate	139 (76.0%)	21 (75.0%)	0.912
Cardiomegaly	96 (52.5%)	17 (60.7%)	0.415
Interstitial oedema	30 (16.4%)	7 (25.0%)	0.265
Pleural effusion	24 (13.1%)	8 (28.6%)	**0.034**
Routine blood samples at admission			
White blood cells, G/L	6.5 (5.1 - 8.7)	8.2 (6.1 - 10.6)	**0.008**
Neutrophil granulocytes, G/L	4.9 (3.6 - 6.7)	7.0 (4.6 - 9.5)	**0.002**
Lymphocytes, G/L	1.02 (0.74 - 1.55)	0.63 (0.55 - 1.07)	**0.003**
C-reactive protein, mg/L	64 (27 - 113)	88 (51 - 160)	**0.030**
Haemoglobin, g/dL	13.6 (12.3 - 14.7)	12.9 (11.7 - 14.0)	0.051

(Continues)

TABLE 1 (Continued)

Characteristics	Survivors (n = 185)	Nonsurvivors (n = 28)	P-value
Platelets, G/L	201 (160 - 240)	203 (173 - 267)	0.367
Creatinine, mg/dL	1.0 (0.8 - 1.2)	1.4 (1.0 - 1.8)	**<0.001**
Sodium, mmol/L	137 (135 - 139)	137 (134 - 139)	0.845
Potassium, mmol/L	4.0 (3.7 - 4.2)	4.0 (3.8 - 4.4)	0.179

3.5 | Association of MR-proANP and other biomarkers with 28-day mortality

Univariable Cox regression analysis demonstrated that higher levels of MR-proANP, NT-proBNP, hs-cTnI, NLR, creatinine, BUN and LDH were associated with the primary endpoint. After adjustment for age and comorbidity burden (model 1), all biomarkers remained significantly associated with 28-day mortality except for NT-proBNP. Final inclusion of baseline characteristics and biomarkers (model 1 + all biomarkers) in a multivariable Cox regression model identified MR-proANP (P =.016), hs-cTnI (P <.001), age (P =.001) and history of arterial hypertension (P =.037) as independently associated with the primary endpoint. NT-proBNP lost significance after adjustment for clinical confounders (P =.050) and biomarkers (P =.057). (Table 3 and Suppl. Table 2).

Upon subgroup analysis, MR-proANP remained a significant predictor of short-term mortality across all groups, which included age, gender, history of arterial hypertension, diabetes mellitus and cardiovascular disease as well as myocardial injury, decline of renal function and hypoxaemia upon admission. (Figure 2).

3.6 | Receiver operating curves for prediction of 28-day mortality by cardiovascular biomarkers and Kaplan-Meier analysis

Receiver operating characteristic curve analyses were performed to determine the area under the curves (AUC) for prediction of 28-day mortality. MR-proANP achieved AUC statistics of 0.832 (95% CI 0.753 - 0.912, P <.001). The optimal cut-off level of MR-proANP to discriminate for the primary endpoint was 160.0 pmol/L according to Youden's index, which yielded a sensitivity of 82.1% and a specificity of 76.2%. Only hs-cTnI had a slightly higher AUC for the prediction of the primary endpoint (AUC 0.847, 95% CI 0.778 - 0.917), and NT-proBNP reached a numerically lower AUC compared to MR-proANP (AUC 0.811, 95% CI 0.728 - 0.985). (Table 3).

Kaplan-Meier estimates showed increasing risk of 28-day mortality with higher quartiles of MR-proANP with log-rank test indicating statistically significant differences between the survival curves (P <.001). (Figure 3) Similar results were observed for hs-cTnI and NT-proBNP with both parameters exhibiting significant differences between the short-term survival curves upon comparison of quartiles (hs-cTnI: P <.001; NT-proBNP: P <.001). (Suppl. Figure 2).

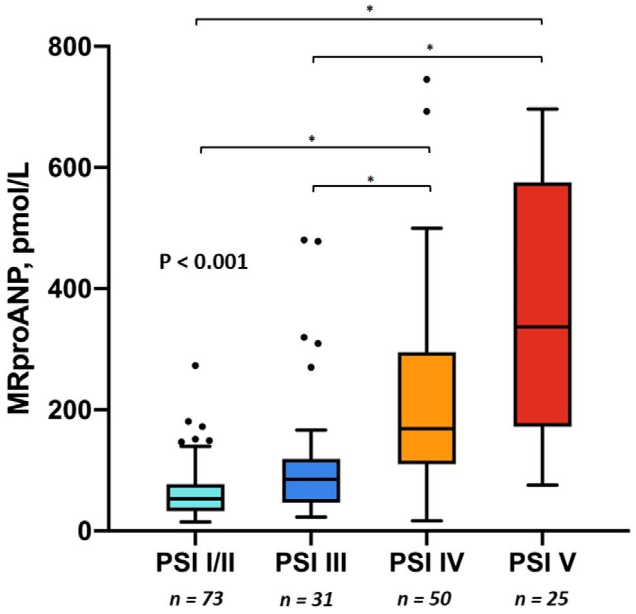

FIGURE 1 MR-proANP levels stratified by disease severity (pneumonia severity index). Abbreviations: PSI = pneumonia severity index. * P-value < 0.01. The box represents the 25th and 75th percentiles, and the whiskers are the upper and lower adjacent values; one outlier of 1211 pmol/L in the PSI V group was removed for visual presentation; n = 179

TABLE 2 Correlation of MR-proANP with hypoxaemia and markers of inflammation, cardiovascular disease and organ dysfunction with 28-day mortality

		SpO2	WBC	CRP	NLR	Creatinine	BUN	Hs-cTnI	NT-proBNP	LDH
MR-proANP	P	-0.177	0.170	0.179	0.388	0.416	0.623	0.646	0.895	0.086
	P-value	**0.010**	**0.013**	**0.009**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.210

Abbreviations: ρ = Spearman's correlation coefficient, SpO2 = peripheral oxygen saturation, WBC = white blood cell count, CRP = C-reactive protein, NLR = neutrophil-to-lymphocyte ratio, hs-cTnI = high-sensitive troponin I and LDH = lactate dehydrogenase.

TABLE 3 Association of biomarkers of inflammation, cardiovascular disease and organ dysfunction with 28-day mortality

Biomarkers	Survivors n = 185	Nonsurvivors n = 28	Unadjusted P-value	Area under the receiver operating curve (95% CI)	Adjusted P-value	
					Model 1	Model 2
Neutrophil-to-lymphocyte Ratio	4.4 (2.8 - 8.0)	10.0 (7.1 - 13.1)	**<0.001**	0.754 (0.655 - 0.852)	**0.011**	0.151
Creatinine, mg/dL	1.0 (0.8 - 1.2)	1.4 (1.0 - 1.8)	**<0.001**	0.731 (0.615 - 0.847)	**0.017**	0.216
Blood urea nitrogen, mg/dL	15 (12 - 21)	31 (20 - 45)	**<0.001**	0.779 (0.686 - 0.873)	**0.018**	0.860
Lactate dehydrogenase, U/L	279 (225 - 370)	322 (230 - 516)	**0.004**	0.601 (0.468 - 0.734)	**0.001**	0.060
High-sensitive troponin I, ng/L	11 (6 - 23)	62 (23 - 217)	**<0.001**	0.847 (0.778 - 0.917)	**<0.001**	**<0.001**
N-terminal pro-B-type natriuretic peptide, ng/L	177 (58 - 736)	1706 (600 - 7136)	**<0.001**	0.811 (0.728 - 0.895)	0.050	0.057
Mid-regional pro-atrial natriuretic peptide, pmol/L	75 (43 - 153)	307 (161 - 532)	**<0.001**	0.832 (0.753 –0.912)	**0.005**	**0.016**

Note: Model 1 was adjusted for age, arterial hypertension, history of cardiovascular disease and chronic kidney disease; Model 2 was adjusted for Model 1 and all other biomarkers (NLR, creatinine, BUN, LDH, hs-cTnI, NT-proBNP and MR-proANP). Concentrations of biomarkers among survivors and nonsurvivors are reported as median with IQR. Prior to Cox regression analysis, all biomarkers (except for NLR) were log-transformed.

4 | DISCUSSION

This prospective, observational single-centre study shows for the first time the prognostic impact of MR-proANP in a well-characterized cohort of hospitalized patients with COVID-19. The main findings are (i) the independent prognostic value of MR-proANP for predicting the primary endpoint of 28-day mortality even after adjustment for several established biomarkers and clinical risk factors, (ii) an increase of MR-proANP levels with disease severity, as assessed by the pneumonia severity index, and (iii) a numerically superior prediction of the primary endpoint by MR-proANP compared to NT-proBNP.

4.1 | Clinical evidence

Similar to NT-proBNP and hs-cTnI, MR-proANP has emerged as a powerful predictor of worse outcome in a plethora of clinical conditions, including inflammation, sepsis and cardiovascular disease.[11-17] The excellent ex vivo stability of MR-proANP makes it an interesting target in routine, clinical practice. The impact of MR-proANP in COVID-19-infected patients on short-term mortality was our main goal of investigation.

Krüger et al identified MR-proANP as a valuable, independent predictor of short- and long-term mortality in a large cohort of patients with community-acquired pneumonia (CAP). 28-day mortality was low compared to our results with a mortality rate of 4.5%, which may be partially explained by inclusion of both ambulatory and in-patient cases and increased risk of mortality in COVID-19.[15] Similarly, Prat et al found significantly higher concentrations of MR-proANP in severe cases of CAP and in those with complications or fatal outcome.[17] Our data are consistent with these findings as MR-proANP was significantly associated with disease severity and short-term mortality in our study population of patients with COVID-19.

Our data also strongly underline the prognostic value of hs-cTnI for prediction of short-term mortality in COVID-19, which is in line with previous research data, that have identified myocardial injury as powerful prognostic marker in COVID-19.[5] With respect to the role of natriuretic peptides in COVID-19 infection, an association of both BNP and NT-proBNP with unfavourable outcome has been reported in COVID-19, while the relevance of MR-proANP has not yet been investigated.[6,7]

Interestingly, our study results rather support the use of MR-proANP as an independent predictor of worse outcome than NT-proBNP which failed to yield statistical significance in the multivariable Cox regression model. This premise is further supported by the fact that the area under the curve of MR-proANP was numerically larger compared to NT-proBNP. The value of MR-proANP for prediction

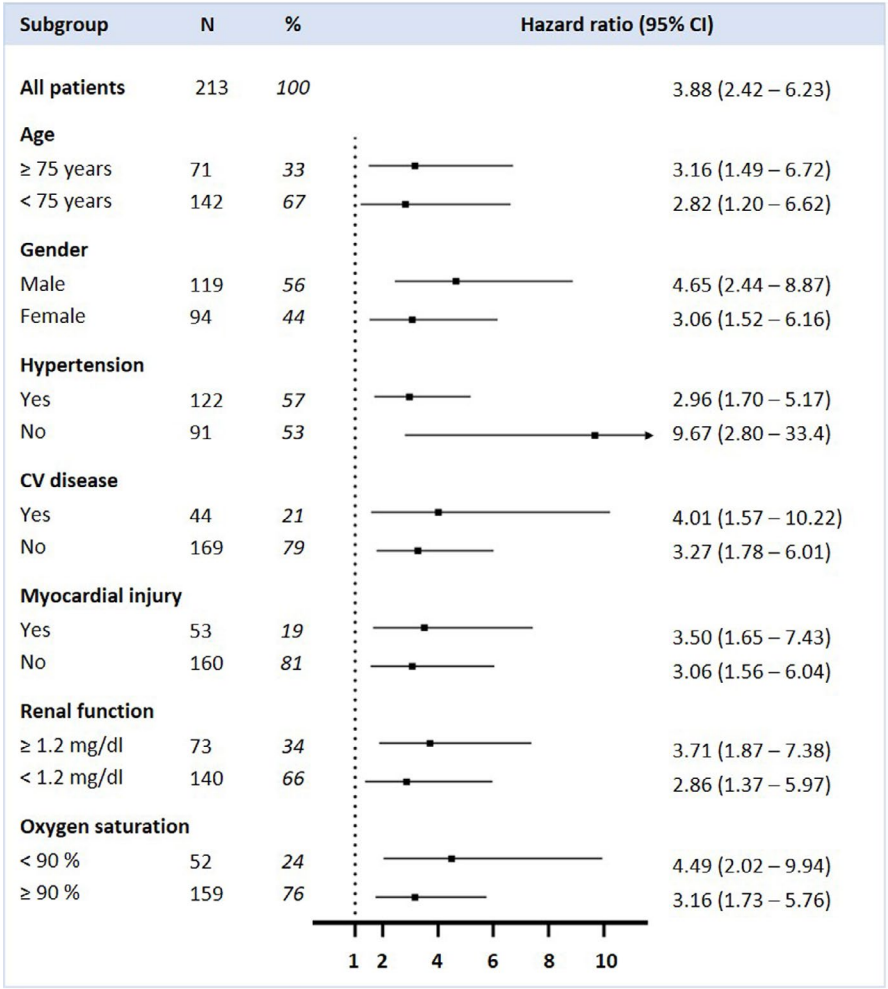

FIGURE 2 Association of MR-proANP with 28-day mortality in specified subgroups. Myocardial injury was defined as an increase of high-sensitive troponin I above 31.5 ng/l, which represents the fourth quartile of hs-cTnI in our study population. Renal function is measured by levels of creatinine. Prior to Cox regression analysis, MR-proANP was log-transformed and standardized by subtracting the mean and dividing by the standard deviation

of the primary endpoint was consistent across multiple subgroups.

4.2 | Pathophysiological mechanisms

While the underlying pathophysiological mechanisms of MR-proANP in COVID-19 infections have not been fully elucidated yet, possible explanations for our findings include that ANP is an important endocrine hormone with several biological effects and is characterized by a wide distribution across the cardiovascular system. It is primarily synthesized in the right atrium and secreted by atrial myocytes secondary to myocardial atrial stretch, which indicates volume overload through atrial wall distension.[19] Regulation of body fluid homeostasis and arterial blood pressure are essential physiological effects of ANP. Accordingly, higher levels of ANP have been recorded in patients with arterial hypertension and heart failure, and ANP also acted as a predictor of worse outcome in this setting.[20] This is in line with the findings of our study, which showed an increasing prevalence of arterial hypertension and cardiovascular disease in higher MR-proANP quartiles.

A second explanation may be direct cardiovascular effects of SARS-CoV-2 on ANP, particularly since the angiotensin-converting enzyme (ACE2) has an important role in virus transmission and has been linked repeatedly to atrial natriuretic peptides in previous studies.[21,22]

Moreover, appropriate management of fluid status is a fundamental concern in the treatment of patients with infectious disease, especially those at risk of developing sepsis. Vascular leakage, secondary to capillary hyperpermeability caused by viral alteration of vessel barrier integrity, with consequent pulmonary oedema has been observed in severe cases of COVID-19.[23] Several international expert panels advise a conservative fluid strategy over a liberal one since worse outcomes have been observed with liberal fluid management in acute respiratory distress syndrome (ARDS).[24,25] Given the pathophysiological properties of MR-proANP, an increase of this biomarker may mirror a hypervolaemic state that is associated with worse outcome in COVID-19, as observed in our study population. Significantly increased levels of natriuretic peptides upon admission should prompt increased vigilance of the treating physician to thoroughly assess fluid status and test for the need of diuresis, while also considering undiagnosed heart failure.

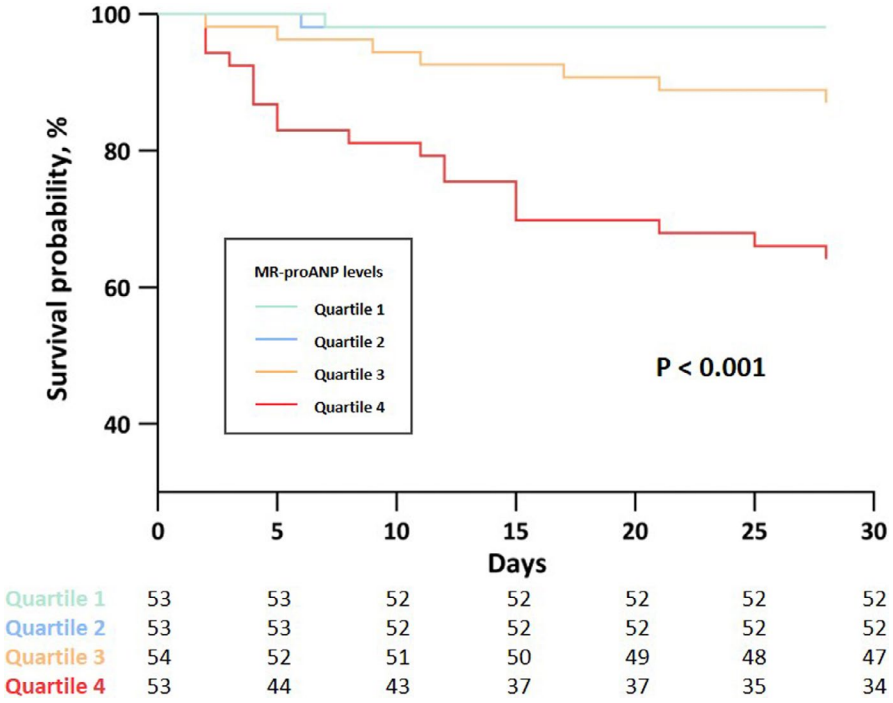

FIGURE 3 Kaplan-Meier survival analysis stratified by MR-proANP quartiles

Basic research and clinical research have linked MR-proANP to hypoxic situations, which may add to the rationale of prognostication in COVID-19.[26] Hypoxaemia has been demonstrated to activate ANP gene promoter activity through induction of hypoxia-inducible factor-1 in ventricular myoblast cells of rats.[27] Another potential mechanism involves anaerobic metabolism in hypoxaemia exposed cardiac myocytes with subsequent secretion of ANP through hyperosmolarity.[9] Hospitalized COVID-19 patients are highly susceptible to hypoxaemia, and an alarming number of cases with silent hypoxaemia have been reported.[28] Our study findings provide evidence that MR-proANP is associated with hypoxaemia in patients with COVID-19. Since hypoxaemia is a valuable predictor of outcome in inflammatory conditions, its association with MR-proANP may also partially explain the prognostic properties of MR-proANP in COVID-19. Finally, another potential pathophysiological link may lie in the association of MR-proANP with inflammation. A highly significant correlation was observed between interleukin-6 and ANP in patients with septic shock, and ANP has been linked to endothelial barrier dysfunction and subsequent inflammation after acute myocardial infarction.[29,30] In our study, a significant correlation of various magnitude of MR-proANP with surrogate markers of inflammation was observed.

4.3 | Limitations

Inherent to the design of our study, only patients admitted for in-hospital treatment were included for further analysis. Therefore, no extrapolation can be made to patients discharged from the emergency department for ambulatory management. Since no gold standard for admission is currently available for patients with COVID-19, generalizability of results may be limited according to local admission standards. Second, before recommending increased MR-proANP as a robust predictor of worse outcome in COVID-19, it should be validated in an independent population. Third, we used baseline levels of MR-proANP and hence cannot draw conclusions as to how temporal changes of MR-proANP may affect the outcome. Finally, we only report short-term mortality rates in our population and therefore cannot assess the impact of MR-proANP on long-term mortality.

5 | CONCLUSIONS

In hospitalized patients with COVID-19, we observed that higher admission levels of MR-proANP levels were significantly and independently associated with 28-day mortality and disease severity. Increased levels of MR-proANP should prompt further work-up, including a thorough assessment of fluid status, to gain an early guess of an unfavourable course of disease and enable early countermeasures.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the design of the study, the interpretation of the data and to drafting, revision and approval of the manuscript. Statistical analysis was performed by CCK and AA. CCK and KH take responsibility for the accuracy and integrity of the data.

ETHICAL APPROVAL

Research involving human subjects complied with all relevant national regulations and institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013) and has been approved by the local ethics committee of the city of Vienna (EK 20-100-VK).

DATA AVAILABILITY STATEMENT

Data available on request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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