DOI: https://doi.org/10.5114/ait.2022.115367

Mid-regional pro-adrenomedullin as a predictor of in-hospital mortality in adult patients with COVID-19: a single-centre prospective study

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Abstract

Backgound: To determine the predictive value of mid-regional pro-adrenomedullin (MR-proADM) compared to routine clinical and laboratory parameters in patients with COVID-19.

Methods: A total of 135 adult patients hospitalized with COVID-19 were included in a prospective single-centre study. In addition to routine parameters, the levels of MR-proADM in blood plasma were measured on the day of hospitalization. The patients were divided into 2 groups: those who survived and were discharged (n = 115, 85%) and those who did not survive (n = 20, 15%). Data are presented as median and interquartile range.

Results: The non-survivors had a statistically significantly greater age (73.4 [63.5–84.8] vs. 62.2 [50.3–71.4] years, P = 0.001), a lower level of haemoglobin oxygen saturation (91 [87–92] vs. 92 [92–93]%, P < 0.001), lower lymphocyte level (13 [7–30] vs. 21 [15–27]%, P = 0.03), higher lactate dehydrogenase (338 [273–480] vs. 280 [233–383] EU L^{-1}, P = 0.04) and aspartate aminotransferase levels (49 [28–72] vs. 33 [23–47] EU L^{-1}, P = 0.03), a higher National Early Warning (NEWS) score (7 [7– 8] vs. 6 [5–7] points, P < 0.001), and higher procalcitonin (0.16 [0.11–0.32] vs. 0.1 [0.07–0.18] ng mL^{-1}, P = 0.006) and MR-proADM levels (1.288 [0.886–1.847] vs. 0.769 [0.6–0.955] nmol L^{-1}, P < 0.001). MR-proADM had the highest predictive value for death during hospital stay (cut-off: 0.895 nmol L^{-1}, AUC ROC 0.78 [95% CI: 0.66–0.90], sensitivity 75%, specificity 69%, OR 6.58 [95% CI: 2.22–19.51]).

Conclusions: Compared with other indicators, MR-proADM has the highest predictive value for in-hospital mortality in patients with COVID-19.

Key words: biomarkers, predictors, COVID-19, mortality, pro-adrenomedullin.

Anaesthesiol Intensive Ther 2022; 54, 3: 242–246

Received: 30.08.2021, **accepted:** 27.11.2021

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The infection caused by the new coronavirus SARS-CoV-2 (COVID-19) was first mentioned and registered in the Chinese province of Wuhan in December 2019 [1], and by August of 2022 the pandemic had affected about 600 million people worldwide. This has been an unprecedented challenge for the modern health care system [2].

COVID-19 is a systemic disease in which the lungs are the main target organ. The progression of COVID-19 is accompanied by the development of respiratory failure of varying severity, from subclinical forms to severe cases requiring respiratory support, up to the use of extracorporeal membrane oxygenation. High contagiousness, a relatively long incubation period, and a significant number of asymptomatic infections have contributed to its widespread incidence. The most severe course of the disease is usually observed in high-risk groups, including elderly and senile people with multiple concomitant pathologies, especially those with diseases of the respiratory and cardiovascular systems, and those with immunodeficiency of various aetiologies. Even with pronounced laboratory and instrumental signs of respiratory failure, a period of clinical well-being can persist for a relatively long time when the experiences and complaints of patients do not correspond to the severity of progressive pathophysiological disorders.

The exponential increase in the number of patients with severe COVID-19, including those with co-morbidities, has caused a significant burden on the healthcare system, with an acute shortage of beds, ventilators, and other intensive care equipment, and a shortage of medical personnel. A consequence of this critical humanitarian situation has been significant changes to patient management.

This includes repurposing specialized medical institutions to provide care to patients with COVID-19, which impacts their primary activities, and opening inpatient beds within exhibition centres, stadiums, and other institutions.

Given the increasing patient numbers and limited medical resources, clinicians need methods that allow quick and objective stratification of patients by the condition severity, prognostic risk, and the level of medical care needed. The severity of patients with pneumonia is assessed using various biomarkers and measures, which makes it possible, with a certain degree of probability, to assess the prognosis and choose the necessary level of medical care to ensure a favourable outcome [3]. These biomarkers include C-reactive protein, procalcitonin, presepsin, soluble trigger receptor expressed on myeloid cells-1 (sTREM-1), membrane protein CD-64, and several others [3]. Integral scores for assessing patient prognosis (for example, the Pneumonia Severity Index [PSI], more compact and simpler than using CURB-65 and CRB-65 etc.), also have a high prognostic value [4]. These assessments can balance the needs of patients and health care system resources, reducing unnecessary costs (for example, hospitalization of patients with a mild course of the disease and an unconditionally favourable prognosis) and ensuring timely and comprehensive treatment of patients at risk.

Recently, new biomarkers have come into use that have a high predictive value for various pathological conditions, including respiratory tract infections. One of these is adrenomedullin, which is of significant interest. Adrenomedullin, first discovered in the adrenal medulla in pheochromocytoma, is synthesized in response to molecular patterns associated with tissue damage or microbial aggression in many tissues and organs [5]. This "hormokine" (a cytokine with hormonal activity), with autocrine and paracrine action, causes a vasodilating and hypotensive effect associated with an increase in the level of cyclic adenosine monophosphate (cAMP) and the formation of nitric oxide (NO). It regulates microcirculation, reduces vascular permeability, reduces the synthesis of pro-inflammatory cytokines, and increases the synthesis of anti-inflammatory cytokines. Under its influence, diuresis and natriuresis are stimulated and adrenomedullin has a direct bactericidal effect. Thus, in cases of microcirculation damage of various aetiologies, adrenomedullin has a protective effect, preventing the development of tissue hypoxia [6]. Also, an increase in its level in the blood indicates these disorders, and this measure can be used as an early marker of organ failure for diagnostic and prognostic purposes in various diseases (cardiac, kidney, urinary tract, and lower respiratory tract diseases, and sepsis), as well as for differential diagnosis of nonspecific complaints (for example, in the elderly) [7]. Interestingly, the use of a genetically engineered biological preparation of humanized monoclonal antibodies to adrenomedullin, which slightly inhibits its activity and significantly reduces its plasma clearance, can lead to an improvement in the treatment results in critically ill COVID-19 patients, which confirms the protective function of adrenomedullin [8].

Determination of the level of adrenomedullin in the blood is difficult because of its rapid clearance (about 22 minutes) due to its rapid degradation by proteases and binding to complement factors. To solve this problem, measuring the level of mid-regional pro-adrenomedullin (MR-proADM) was proposed. This is a fragment of the proADM molecule, consisting of 48 amino acids. MR-proADM is split off from proADM in a 1 : 1 ratio with ADM and, therefore, proportionally reflects the level of the latter [9]. The median normal value of MR-proADM in the blood plasma of healthy adults is 0.38 nmol L^{-1}. Several studies have shown that MR-proADM has a higher predictive value compared to other biomarkers (such as procalcitonin and soluble trigger receptor expressed on myeloid cells-1) in sepsis [10], as well as in community-acquired pneumonia [11]. The study aims to determine the predictive value of MR-proADM in comparison with routine clinical and laboratory parameters in patients with COVID-19.

METHODS

This study was approved by the review board of the A.N. Bakulev National Medical Research Centre of Cardiovascular Surgery (approval number 0016-21), and the requirement for written informed consent was waived by the Ethics Committee. A total of 135 adult patients (age 63.3 [51.7–73.8] years; range 26.2–93.9 years), hospitalized in the Intensive Care Unit with a diagnosis of community-acquired pneumonia, were sequentially included in the prospective single-centre study. The diagnosis of COVID-19 was confirmed by clinical and laboratory data, including a positive result of respiratory smears for SARS-CoV-2 RNA by PCR. Upon admission to the hospital, in addition to routine clinical and laboratory parameters (if applicable, the worst data on the first day of hospitalization were recorded), the levels of procalcitonin (PCT) and MR-proADM in blood plasma were determined in all patients using a KRYPTOR compact PLUS analyser (BRAHMS GmbH, Hennigsdorf, Germany) and appropriate test reagent kits (BRAHMS GmbH, Hennigsdorf, Germany). For the initial assessment of the severity of the patient's condition, the NEWS (National Early Warning Score) scale was used. This scale includes a score for respiratory function (respiratory

TABLE 1. Clinical and laboratory data of the studied patients registered on the day of hospitalization. Data presented as median (IQR) or *n* (%)

Value	Survivors	Non-survivors	*P*-value
Number of patients, *n* (%)	115 (85.2)	20 (14.8)	–
Age, years	62.2 (50.3–71.4)	73.4 (63.5–84.8)	0.001
BMI, kg m^{-2}	28.7 (25.8–32.3)	27.6 (23.5–31.6)	0.29
Charlson Comorbidity Index	3 (2–4)	3 (2–4)	0.23
SpO_2, %	92 (92–93)	91 (87–92)	< 0.001
Initial stage of lung damage on chest CT scan	2 (2–3)	3 (2–3)	0.31
LOS in hospital, days	12 (11–15)	11 (7–17)	0.15
Body temperature, °C	38.1 (37.9–38.5)	38 (37.2–38.5)	0.27
WBC, 10^9 L^{-1}	7.1 (5.0–8.8)	5.5 (4.0–9.6)	0.37
Lymphocytes, %	21 (15–27)	13 (7–30)	0.03
CRP, mg L^{-1}	54.3 (20.6–96.6)	68.1 (44.6–134.0)	0.3
LDH, EU L^{-1}	280 (233–383)	338 (273–480)	0.04
ALT, EU L^{-1}	29 (19–45)	32 (19–58)	0.69
AST, EU L^{-1}	33 (23–47)	49 (28–72)	0.03
Fibrinogen, g L^{-1}	4.1 (3.4–5.0)	3.6 (3.1–5.3)	0.25
D-dimers, ng mL^{-1}	558 (331–870)	695 (398–1892)	0.08
NEWS score, points	6 (5–7)	7 (7–8)	< 0.001
PCT, ng mL^{-1}	0.1 (0.07–0.18)	0.16 (0.11–0.32)	0.006
MR-proADM, nmol/ L^{-1}	0.769 (0.600–0.955)	1.288 (0.886–1.847)	< 0.001

ALT – alanine aminotransferase, AST – aspartate aminotransferase, BMI – body mass index, CRP – C–reactive protein, IQR – interquartile range, LDH – lactate dehydrogenase, LOS – length of stay, MR-proADM – mid-regional pro-adrenomedullin, NEWS – National Early Warning Score, PCT – procalcitonin, SpO_2 – blood oxygen saturation, WBC – white blood cells

rate, haemoglobin oxygen saturation [SpO_2] and the need for its insufflation), body temperature, systolic blood pressure and heart rate, and the presence of impaired consciousness [12].

The severity of lung damage was assessed in accordance with the national recommendations of the Ministry of Health of the Russian Federation: Stage 1 – the total volume of the lung tissue lesion does not exceed 25%; Stage 2 and 3 – the volume of the affected tissue is 25-50% and 50-75%, respectively; Stage 4 – the volume of the lesion exceeds 75%.

Based on their disease outcome, patients included in the study were divided into 2 groups: those who survived and were discharged ($n = 115$), and those who did not survive during their hospital stay ($n = 20$). Statistical processing of the results was carried out using Microsoft Excel 2016 (Microsoft Inc., Redmond, WA, USA) and IBM SPSS Statistics 22 (IBM Software, Chicago, Ill, USA). Data are presented as absolute values, fractions, median, and interquartile range (25^{th}-75^{th} percentile). To compare the data the Mann-Whitney *U*-test was used. *P*-values < 0.05 were taken as statistically significant. To identify the predictive value of the studied predictors, ROC analysis was used.

RESULTS

Clinical and laboratory data of the studied groups registered on the day of hospitalization are presented in Table 1. There was no statistically significant difference in the groups in terms of body mass index, comorbidity index, degree of initial severity of lung lesions based on computed tomography results, body temperature, leukocyte count, or their levels of C-reactive protein, ALT, fibrinogen, and D-dimers. At the time of inclusion in the study the non-survivors had statistically significant older age, a lower level of haemoglobin oxygen saturation according to pulse oximetry data, a lower level of lymphocytes, higher levels of LDH and AST, a higher score on the NEWS scale, and higher levels of the biomarkers PCT and MR-proADM. Table 2 shows statistically significant predictors of hospital mortality in patients with COVID-19. From the data, MR-proADM, compared to the NEWS scale, SpO_2, age, PCT, and lymphocyte levels, had the highest predictive value, confirmed by having the largest area under the ROC curve for this biomarker.

DISCUSSION

Respiratory system infections are among the most common causes of morbidity worldwide. Community-acquired pneumonia is a disease with a wide range of possible outcomes, and a significant proportion of patients can be treated at home and on an outpatient basis. At the same time, pneumonia can be the cause of the development of sepsis,

TABLE 2. Results of ROC analysis of predictors of in-hospital mortality

Value	Cut-off	AUC ROC (95% CI)	Sensitivity, %	Specificity, %	OR (95% CI)
MR-proADM, nmol L^{-1}	> 0.895	0.78 (0.66–0.90)	75	69	6.58 (2.22–19.51)
NEWS score, points	> 7	0.74 (0.62–0.86)	75	63	5.14 (1.74–15.16)
SpO_2, %	< 92	0.74 (0.61–0.87)	80	60	3.59 (1.13–11.43)
Age, years	> 65	0.72 (0.60–0.84)	65	62	3.36 (1.30–10.14)
PCT, ng mL^{-1}	> 0.125	0.69 (0.58–0.80)	65	60	2.79 (1.03–7.51)
Lymphocytes, %	< 18	0.65 (0.48–0.82)	64	70	3.48 (1.29–9.43)

MR-proADM – mid-regional pro-adrenomedullin, NEWS – National Early Warning Score, PCT – procalcitonin, SpO_2 – blood oxygen saturation

which is most likely to lead to death, especially in patients with comorbidities [13]. The limited resources of hospitals dictate the need for a differential approach to the hospitalization of patients, to preserve the possibility of providing medical care to the most difficult groups of patients. In this regard, risk stratification is critical, allowing the choice of the most appropriate level of care, from outpatient treatment to hospitalization in a therapeutic ward or an intensive care unit. Consequently, some studies are focused on finding the most reliable predictive tools for determining the risk in various pathological conditions. To assess the severity of community-acquired pneumonia and predict mortality, several appropriate scales have been developed, in particular PSI and CURB-65 [14, 15]. However, none of them have become an ideal tool due to the relative complexity of their use in everyday practice, and the lack of predictive value in some categories of patients (in particular, the possible underestimation of the severity of the condition of young patients). In addition to specialized pulmonary scales, there are relatively simple universal instruments that allow assessment of outcome in various acute pathologies of an infectious and non-infectious nature. One example is the NEWS (National Early Warning Score) scale, which was developed in 2012 in the United Kingdom [16]. Our data indicate a good predictive value of this scale for COVID-19 in-hospital mortality (cut-off 7 points, AUC ROC 0.74 [0.62–0.86], sensitivity 75%, specificity 63%, OR 5.14 [1.74–15.16]). The use of biomarkers such as C-reactive protein, PCT, sTREM-1, interleukins, etc. can improve the diagnostic accuracy of the scales and provide additional information regarding the prognosis in patients with community-acquired pneumonia [17–20].

MR-proADM is a promising biomarker for determining severity and predicting outcomes in community-acquired pneumonia. It was shown that patients with a more severe course of community-acquired pneumonia and an unfavourable outcome had a statistically significantly higher initial level of MR-proADM, which was not observed for C-reactive protein and the number of leukocytes according to CBC data [21]. In the present study, we have identified similar patterns (Table 1).

The combined use of MR-proADM with an assessment of the severity of community-acquired pneumonia according to the CURB-65 scale, which is used to determine the optimal level of medical care (outpatient treatment, hospitalization in a therapeutic department, treatment in an intensive care unit), can significantly increase the prognostic value of the latter. In a multicentre study, it was found that patients with lower respiratory tract infection who have a CURB-65 score of 0–1 points and an MR-proADM level of 0.75 nmol L^{-1} or less are characterized by a low risk of complications (3.9%) and unfavourable outcome (0.65%), so they can be treated on an outpatient basis. A score of 2 points according to CURB-65 in combination with an MR-proADM level of 0.75–1.5 nmol L^{-1} corresponds to an average risk (the probability of a complicated course is 8.6% and the mortality is 2.6%) and can be considered as a basis for hospitalization in an inpatient department. High-risk patients (CURB-65 – 3–5 points, MR-proADM level more than 1.5 nmol L^{-1}; risk of complications and death – 8.6% and 2.6%, respectively) should be hospitalized for intensive care [22]. Comparison of the predictive value of unfavourable outcome in patients with pneumonia caused by COVID-19 showed that among the indicators studied, the area under the ROC curve was the largest for MR-proADM.

CONCLUSIONS

Stratification of patients with COVID-19 by severity and expected outcome using biomarkers and appropriate scales can promote optimal use of health system resources without compromising the quality of care. Clinical validation of this approach requires appropriate research. Compared with the NEWS scale, SpO_2, age, PCT, and lymphocyte levels, MR-proADM had the highest predictive value of in-hospital death in pneumonia associated with COVID-19.

ACKNOWLEDGEMENTS

1. Financial support and sponsorship: none.
2. Conflicts of interests: none.

3. Presentation: Preliminary data for this study were presented as oral presentations at the Annual Conference of A.N. Bakulev National Medical Research Center of Cardiovascular Surgery (for medical students, trainees, and doctors) in Moscow, Russia, on 16 May 2021.

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