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PROADRENOMEDULLIN AS A BIOMARKER OF COVID -19 POOR OUTCOME: META-ANALYSIS AND SYSTEMIC REVIEW

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The aim of this study was to analyse and summarise all researches about proadrenomedullin (pro-ADM) prognostic value as covid-19 severity and mortality early predictor. After a literature search and selection, we found 19 articles eligible to inclusion in a meta-analysis. We found pro-ADM had significantly high values in patients both admitted to the general department and ICU-patients with unfavourable outcomes. The Pro-ADM measurement in the admission or early stages of the hospitalisation can be used for the patient's risk stratification, to making a decision and a differential treatment approach.

Keywords: coronavirus disease COVID-19, biomarker, proadrenomedullin, severity score, mortality prognosis.

Introduction. The objective assessment of the disease severity and outcome prediction are essential components to make a decision in the patient's management and appropriate treatment definition. Stratification problems and patient's transferring based on the disease severity and the risk of unfavourable outcomes acquired crucial and priority when there are large number of cases and inevitable excessive burden on healthcare systems. These requirements are particularly relevant in diseases with a wide variability of clinical course and rapidly developing severe complications, an example of which was the new coronavirus infection COVID-19.

Currently, different prognostic scales (APACHE II, SOFA, SAPS II, CURB-65, NEWS) and laboratory biomarkers (leukocytes and platelets level, D-Dimer, C-reactive protein (CRP), Interleukin-6, Interleukin-10, Tumor Necrosis Factor-α, procalcitonin and etc.) are used in the Covid-19 severity assessment [8]. However, none of these scale and laboratory tests has any benefits in Covid-19 prognostic effectiveness with low sensitivity and specificity, it requires further searches of reliable predictive biomarkers of disease's severity.

Covid-19 pathways investigation found the key role of endothelial damage which correlate with infection's severity [16]. Therefore, findings of early indicator with high predictive value considering covid-19-associated endothelitis are reasonable. One of the newest biomarker is adrenomedullin (ADM) – hormone with cytokine-like effects, it consist of 52 amino acid peptide and released by endothelial and vascular smooth muscle cells and widely distribute in tissue and this production increased during infections [1]. ADM has vasodilative immunomodulate and anti-inflammatory effects, it's used as early marker in lower respiratory tract infections, community-acquired pneumonia and sepsis [2]. ADM has low metabolic stability and brief half-life, its splits in 1:1 ratio with precursor called mid-regional proadrenomedullin (pro-ADM) and it can proportionally represent the ADM level and it is used in tests. The biomarker showed direct correlation with increased procalcitonin level and prognostic scales (APACHE II, SOFA, SAPS II, CURB-65, NEWS). The Pro-ADM level in sepsis and septic shock were 1,8 (0,4-5,8) nmol/L and 4,5 (0,9-21,0) nmol/L respectively [2,4]. In several single studies pro-ADM level interpretation and combination with other biomarkers and scales demonstrated efficiency in making a decision about admission in ICU or save transferring out, antibiotics escalation or de-escalation and poor prognosis prediction [1].

In view of the above, our research summarised current studies to evaluate proADM as an early biomarker of severity and mortality predictions.

Purpose of the study was combined and analyse articles to assess pro-ADM prognostic ability as an early marker of severity and mortality in Covid-19 patients.

Materials and Methods. In PubMed, EMBASE (Experta Medica), Cochrane Central Register of Controlled Trials, Scholar Google and e-library we selected article were had been published in English and Russian till 25.11.2022 with pro-ADM levels, severity and outcomes information. The search strategy was used with key words and combinations: «new coronavirus infection», «COVID-19», «predict», «midregional

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proadrenomedullin», «proadrenomedullin» and Russian translations.

Eligibility criteria were clinical trials with covid-19 confirmed diagnosis, adults only (18 years old and more).

Exclusion criteria were case studies, clinical trials with less than 5 patients, preclinical studies, opinion articles, thesis, studies with pregnant or patients with decompensation chronic diseases.

For quality assurance the manual article selecting was used following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, www.prisma-statement.org). All included studies had patients' characteristics, laboratory data, course of disease and outcomes. For all patients the measurement of pro-ADM was performed in the plasma by TRACE technique (Time-Resolved Amplified Cryptate Emission, KRYPTOR «BRAHMS»).

All article were divided on two main groups: 1 group include patients admitted to hospital in the general (or infectious diseases) department and 2 group with severe or critically ill patients admitted to the ICU. In each group the proADM level in the survivors and the deceased was compared. In all studies, the main characteristics, laboratory data and assessment by scales (SOFA, NEWS, CURB-65) at admission were collected.

The meta-analysis was conducted according to the Cochrane Collaboration recommendations using the Review Manager (RevMan) program, version 5.4.1 (2020). The meta-analysis included eligibility studies: patients were already separated or they could be grouped into two - survivors and non-survivors; each group had information about total population number, pro-ADM mean level on the 1st day of hospitalization with standard deviations and 95% confidence interval (CI) (or these indicators were converted by us on the website math.hkbu.edu.hk, from available data – sample size, median, maximum, minimum and interquartile interval); statistical significance set up at $p<0.05$. The calculation of the weighted average (arithmetic) is also carried out.

Heterogeneity was evaluated by χ^2 (Chi square) with considered level of p-value 0,10 and I^2 index with values for heterogeneity level indication were 0-40%-low, 30-60% - moderate, 50-90% - significant, 75-100 – high [5]. To assess overall mean difference (MD) fixed effects model was chosen for moderate heterogeneity, and a random effects model was chosen for significant heterogeneity. To assess the publication bias in the meta-analysis with 5 or more studies, a funnel-plot was constructed. The assessment of methodological quality was carried out according to the Russian version of the Newcastle-Ottawa scale for all studies included in the meta-analysis [7].

Result and discussion. After systemic literature search using keywords, 68 publications were selected from a total of 572 references, after initial screening and removing de-duplication publications, 28 articles (5 Russian and 23 foreign studies) were selected. Further selection and check of these articles, 19 articles (3 Russian and 16 foreign studies) were included in the meta-analysis (Fig. 1).

Among selected articles (n=19), 3681 patients were analysed: 3096 patients admitted in the general department and 585 ICU patients.

Meta-analysis of studies with general department patients. 3096 patients admitted in the general department were enrolled, 580 patients deceased (mortality rate was 18,7%). After synthesis the weighted average pro-ADM level in survivors was 0,83 nmol/L, in non-survivors was – 1,57 nmol/L, the mean difference (MD) was statistically significant MD = -0,87 (95% CI: -1,08, -0,67), $p<0,00001$. Heterogeneity was significant ($I^2=86\%$, $\chi^2=76,4$, $p<0,00001$) (Fig. 2,4).

Meta-analysis of studies with ICU patients. Meta-analysis incorporated 585 ICU patients (169 deceased with mortality rate 28,9%). The weighted average pro-ADM level in survivors was 0,90 nmol/L, in non-survivors was – 2,11 nmol/L, the mean difference was statistically significant, MD = - 0,71 (95% CI: -0,80, -0,61), $p<0,0004$. In contrast with results of group with patients hospitalized in the general department, the heterogeneity of the data in ICU patients was moderate ($I^2=44\%$, $\chi^2=10,68$ $p=0,10$) (рис. 3, 4).

Therefore, result of the meta-analysis shows that the level of pro-ADM in non-survivors is significantly higher than survivors in both patients of the general department ($p<0.00001$) and ICU patients ($p<0.0004$). It should be noted that the values of pro-ADM in ICU patients with severe COVID-19 are initially higher even in survivors.

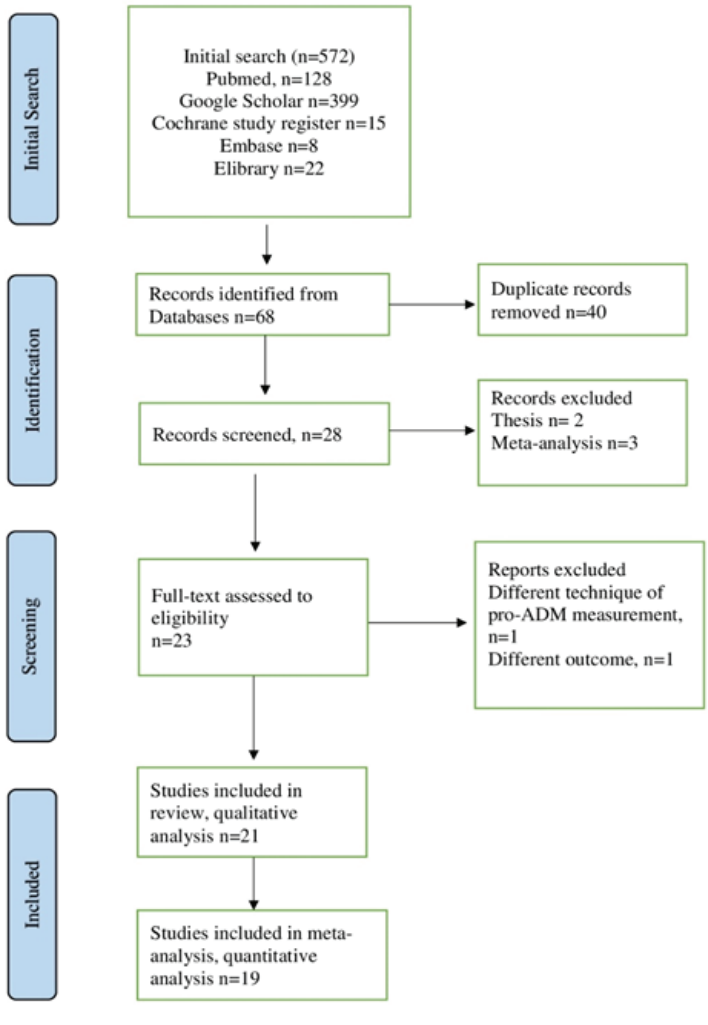

Fig. 1. PRISMA Flow diagram

The main characteristics of articles included in the meta-analysis

Author, Year Country	Type of study	Period	Number of patients survivors/deceased (mortality rate)	Department	AUC (95% ДИ)	Cut Off nmol/L	Findings
Gregoriano C. et al., Italy 2021 [29]	Prospective Observational	February-April 2020	89 72/17 (17.2)	General department	0.78	0.93	Pro-ADM mmeasured daily during hospitalization (till 8 day) Increased in deceased
Mangioni D. et al. Italy, 2022 [26]	Prospective Observational	February-October 2020	100 87/13 (13)	General department	0.87 (0.79–0.94)	1.04	With γ-interferon, it prognostic value was low. Pro-ADM prognostic value increased on day 7
Indirli R. et al., Italy, 2021 [25]	Retrospective Observational	March- June 2020	116 95/21 (18.1)	General department	0.79	1.00	With copeptin, it showed prognostic effectiveness
Méndez R. et al., Spain, 2021 [9]	Prospective	March- June 2020	210 183/27 (12.9)	Emergency department	-	1.16	With proendothelin, it showed correlation with severity and mortality
Lo Sasso B. et al., Italy, 2021 [11]	Retrospective Observational	September- October 2020	110 96/14 (12.7)	General department	0.95 (0.86–0.99)	1.73	The highest pro-ADM level among all studies, wide variability of pro-ADM level
de Guadiana-Romualdo L.G. et al., Spain, 2021 [10]	Prospective	August-October 2020	359 327/32 (8.9)	General department	0.832 (0.77-0.894)	0.8	Pro-ADM level had correlation with SOFA score
Minieri M.,et al., Italy, 2022 [28]	Retrospective Observational	April-December 2020	321 224/97 (30.2)	Emergency department	0.85	1.105	NIMV/IMV need assessed
Попов Д.А. и др., Россия, 2020 [6]	Prospective Observational	May-June 2020	97 83/14 (14.4)	General department	0.75 (0.59—0.91)	0.895	The highest prognostic significance among all indicators
de Guadiana-Romualdo L.G. et al., Spain, 2021 [24]	Prospective Observational	March - April 2020	99[17] 85/14 (14.1)	General department	0.905 (0.829-0.955)	1.01	Separation between severe and non-severe Predicting the progression of the disease
Moore N. et al., UK, 2022 [23]	Prospective Observational	April-June 2020	135 105/30 (22.2)	General department	0.844 (0.776- 0.912)	1.54	Only CRP and Pro-ADM had prognostic value among all indicators. ICU admission and IMV need assessed
Sozio E. et al., International 2022 [17]	Retrospective	March-April 2020	1278 986/292 (22.8)	Emergency department	0.786	0.911	Pro-ADM, CRP and LDH assessed for stratification into group - hospitalization need or not and poor outcome prediction

End of the table

Atallah N. J. et al., USA, 2022 [21]	Retrospective Observational	April-June 2020	182 173/9 (4.9)	General department	0.76 (0.59–1.17)	0.87	IMV need, ICU admission, disease progression and poor outcome assessed
Montrucchio G. et al., Italy, 2021[12]	Retrospective Observational	March-June 2020	57 26/31 (54.4)	Intensive care unit	0.95 (0.86–0.99)	1.8	Comparison with CRP, PCT, LDH Measurement on first 48 hour, 3, 7 and 14 days were done
Попов Д.А. и др., Россия, 2022 [19]	Prospective Observational	No information	135 115/20 (14.8)	Intensive care unit	0.78 (0.66–0.90)	0.895	The highest prognostic significance among all indicators
Малинина Д.А. и др., Россия, 2020 [3]	Retrospective Observational	May-August 2020	37 18/19 (51.3)	Intensive care unit	-	-	The highest prognostic significance among all indicators
Benedetti I. et al. et al., Italy, 2021 [15]	Observational	March-April 2020	21 10/11 (52.4)	Intensive care unit	0.91	1.07	Measurement on 1, 3, 5days were done. The highest prognostic significance among all indicators
Van Oers J.A.H. et al., Netherlands, 2021 [13]	Prospective Observational	March-May 2020	105 75/30 (28.6)	Intensive care unit	0.84 (0.76-0.92)	1.57	With C-terminal proendothelin-1
Oblitas C.M. et al., Spain, 2021 [22]	Prospective Observational	August-November 2020	95 83/12 (12.6)	Intensive care unit	0.73 (0.63–0.81)	1.0	1,0 With methemoglobin and carboxyhemoglobin it prognostic values were low
Montmollin E.et al., France, 2022 [20]	Prospective	April 2020-May 2021	135 89/46 (34.1)	Intensive care unit	0.744	1.0	Measurement on 1, 3, 7 days were done

It's essential to note significant heterogeneity in patients of the infectious department (I^2=86%) is due to the results presented by B. L. Sasso [11], in which the average values of pro-ADM in patients with an unfavorable outcome were noticeably higher and amounted 2.62 nmol/L. In reviewed studies mortality rate in the ICU was high, in three studies it exceeded 50% [3, 12, 15]. The age median among patients of the general department varied 53,3 to 67 years, and among ICU patients - 63,3 to 70,9 years, and male prevailed (in the general department were 51,9-65,2%, in the ICU were 67,4-87,7%).

The results of our systematic review and meta-analysis confirm the conclusions of other researches, which present a significant difference in the values of pro-ADM in surviving and deceased patients. Thus, in the meta-analysis of G. Montruccio et al., the mean difference of pro-ADM among survivors versus non-survivors ICU patients was - 0.96 nmol/L (95% CI:-1.26,-0.65, heterogeneity I^2=0% p<0.00001) [25]. Lippi et al. conducted the meta-analysis with mixed-unfavorable outcomes (ICU-admission, renal replacement therapy, invasive mechanical ventilation, acute respiratory distress syndrome, death) and the same result was obtained – the mean difference between unfavorable/favorable outcomes was 0.67 nmol/l (95% CI: 0.42-0.93, heterogeneity I^2=81% p<0.001) [18]. The meta-analysis by Lampsas et al. included studies about endothelial dysfunction biomarkers among ICU patients, also showed the efficiency of the pro-ADM (the mean difference between the deceased/survivors was 0.71 nmol/L, 95% CI: 0.22, 1.20 nmol/L, p=0.02) [29].

In addition, pro-ADM were measured several times and its increase was noted with the progression of the disease in some studies [12, 15, 27, 30]. In all studies high level of pro-ADM was correlated with other severity indicators (high level of CRP, LDH, D-dimer, lymphocytopenia) and high scores of APACHE II и SOFA scales.

In some studies, other markers investigated such as γ-interferon [27], copeptin [26], proendothelin [9], C-terminal proendothelin-1[13], methemoglobin and carboxyhemoglobin [22]. In reviewed studies pro-ADM mortality prognostic value with ROC-analysis were demonstrated the highest sensitivity and specificity among other predictors (AUC varied 0,73 to 0,95).

Some authors recommended the inclusion pro-ADM measurement in the required diagnostic complex when a

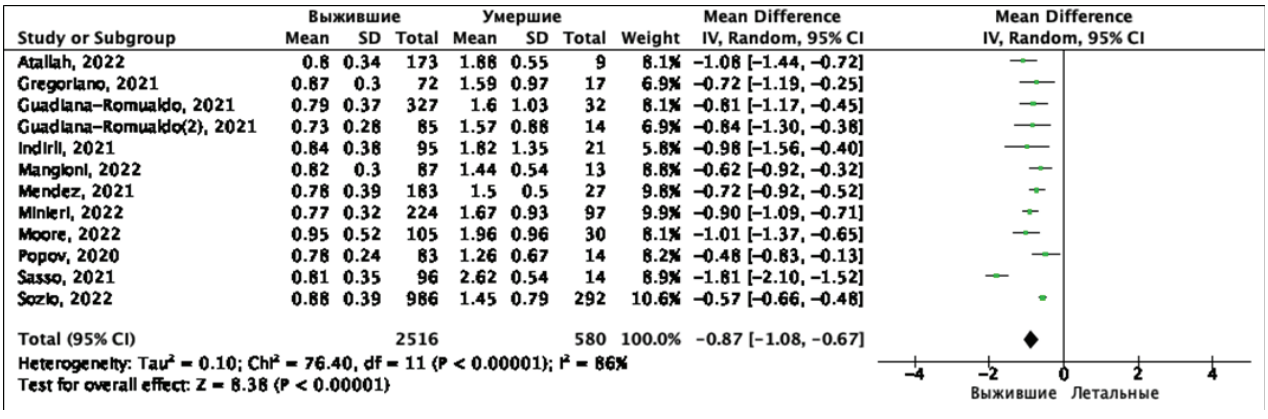

Fig. 2. Meta-analysis results and Forest Plot, general department patients.

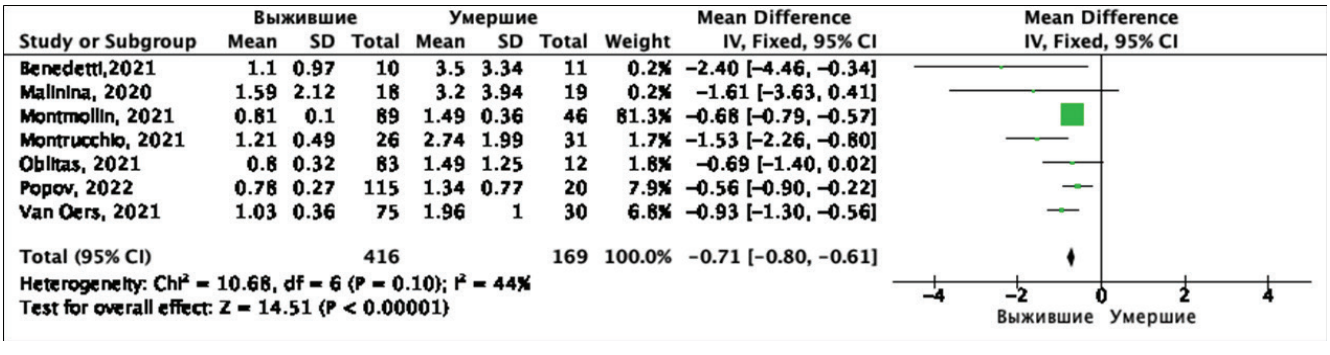

Fig. 3. Meta-analysis results and Forest Plot, ICU patients

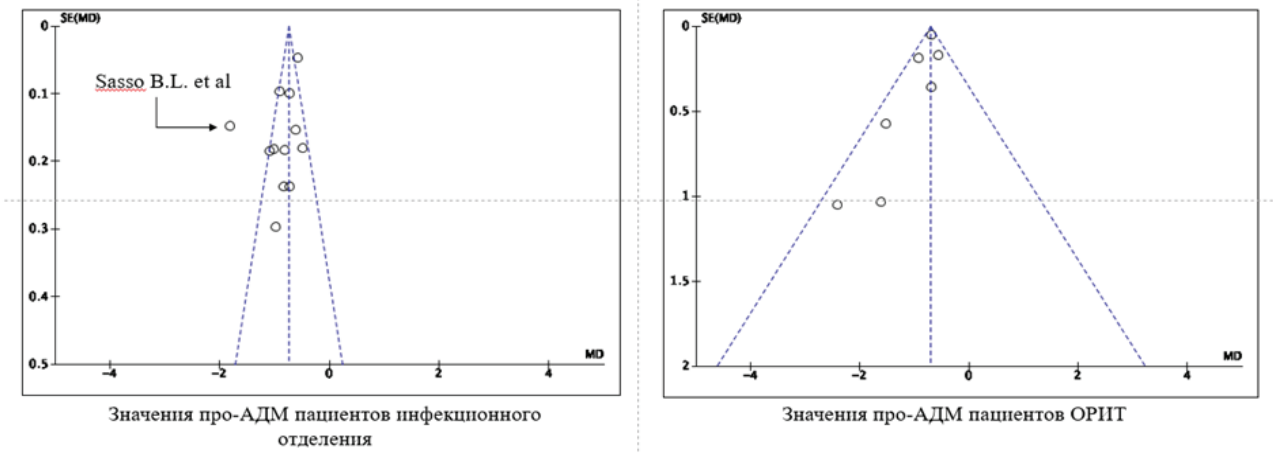

Fig. 4. Funnel Plot of the meta-analysis for assess publication bias

patient is admitted to the hospital. Thus, Sozio et al. found the high prognostic significance of pro-ADM in predicting outcome and making a decision about hospitalization in the infectious department, they proposed to count pro-ADM blood level [17]. Note that there was other opinions. For example, Zaninotto et al. demonstrated no noticeable increase in prognostic informativeness with pro-ADM addition: the prognostic significance of criteria such as age and the index of neutrophils to lymphocytes ratio amounted to AUC was 0.916 (95% CI 0.853-0.979), but pro-ADM AUC was 0.900 (95% CI 0.827-0.974) [14].

Currently, despite the first positive results about the high prognostic informativeness of pro-ADM as an early marker of an unfavorable outcome in COVID-19 compared with other laboratory indicators, the question of it use as a single or additional marker remains open.

Conclusion. Results of our meta-analysis indicate prognostic efficiency of pro-ADM as an early predictor of the unfavorable outcome of COVID-19. Determination the level of pro-ADM as a promising biomarker with high sensitivity and specificity in severity and mortality prediction seems to be optimal at the early stages preferably at the emergency department for patients' stratification according to their severity, making a decision of hospitalization and differentiated approach of medical care.

Of course, the attractiveness of patients's stratification by only one highly sensitive and specific biomarker is obvi-

ous, it will improve the quality and effectiveness of diagnosis and treatment, as well as ensure the economic feasibility of the entire treatment process. However, further studies are required to select such markers in diseases and particular in COVID-19. At the same time, it's necessary to conduct further trials, to compare pro-ADM with other biomarkers, to determine the level of its threshold values accounting comorbidity, pregnancy and other groups of patients.

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