Expert Review of Molecular Diagnostics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iero20

Mid-regional pro-adrenomedullin as a supplementary tool to clinical parameters in cases of suspicion of infection in the emergency department

Kordo Saeed, Jacopo M. Legramante, Silvia Angeletti, Francesco Curcio, Iria Miguens, Stephen Poole, Carlo Tascini, Emanuela Sozio & Juan González Del Castillo

To cite this article: Kordo Saeed, Jacopo M. Legramante, Silvia Angeletti, Francesco Curcio, Iria Miguens, Stephen Poole, Carlo Tascini, Emanuela Sozio & Juan González Del Castillo (2021): Mid-regional pro-adrenomedullin as a supplementary tool to clinical parameters in cases of suspicion of infection in the emergency department, Expert Review of Molecular Diagnostics, DOI: 10.1080/14737159.2021.1902312

To link to this article: https://doi.org/10.1080/14737159.2021.1902312

Published online: 29 Mar 2021.

EXPERT REVIEW OF MOLECULAR DIAGNOSTICS
https://doi.org/10.1080/14737159.2021.1902312

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

Mid-regional pro-adrenomedullin as a supplementary tool to clinical parameters in cases of suspicion of infection in the emergency department

Kordo Saeed[a,b], Jacopo M. Legramante[c], Silvia Angeletti[d], Francesco Curcio[e], Iria Miguens[f], Stephen Poole[g], Carlo Tascini [h], Emanuela Sozio[h] and Juan González Del Castillo[i]

[a]Microbiology Innovation and Research UNIT, Department of Infection, University Hospitals Southampton NHS Foundation Trust, Southampton, UK; [b]School of Medicine, University of Southampton, Southampton, UK; [c]Emergency Department, University Hospital Tor Vergata, Rome, Italy; [d]Clinical Pathology, University Hospital Campus Bio-Medico of Rome Science Unit, University Campus Bio-Medico of Rome, Faculty of Medicine University Campus Bio-Medico of Rome, Italy; [e]Department of Medicine (DAME), University of Udine, Udine, Italy; [f]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [g]NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK; [h]Infectious Diseases Clinic, Udine University Hospital, Udine, Italy; [i]Emergency Department, Hospital Clínico San Carlos, Madrid, Spain

ABSTRACT

Introduction: Mid-regional proadrenomedullin (MR-proADM), a novel biomarker, has recently gained interest particularly with regards to its potential in assisting clinicians' decision making in patients with suspicion of infection in the emergency department (ED). A group of international experts, with research and experience in MR-proADM applications, produced this review based on their own experience and the currently available literature.

Areas covered: The review provides evidence related to MR-proADM as a triaging tool in avoiding unnecessary admissions to hospital and/or inadequate discharge, and identifying patients most at risk of deterioration. It also covers the use of MR-proADM in the context of COVID-19. Moreover, the authors provide a proposal on how to incorporate MR-proADM into patients' clinical pathways in an ED setting.

Expert opinion: The data we have so far on the application of MR-proADM in the ED is promising. Incorporating it into clinical scoring systems may aid the clinician's decision making and recognizing the 'ill looking well' and the 'well looking ill' sooner. However there are still many gaps in our knowledge especially during the ongoing COVID-19 waves. There is also a need for cost-effectiveness analysis studies especially in the era of increasing cost pressures on health systems globally.

ARTICLE HISTORY
Received 8 January 2021
Accepted 9 March 2021

KEYWORDS
MR-proADM; emergency department; triage tool; admission; ICU

1. Introduction

Adrenomedullin (ADM), a 52 amino acid peptide, is a member of the calcitonin peptide family [1] and is widely expressed in many tissues and organs. In healthy subjects, ADM circulates at low picomolar concentrations, but during pathological events, plasma concentrations are significantly up-regulated. Plasma concentration changes are proportional to disease severity [2].The increased stability of its precursor molecule, mid-regional proadrenomedullin (MR-proADM), allows a reliable measurement as a surrogate biomarker for the unstable ADM in a 1:1 ratio [3]. The assays can be performed on routine blood samples, and generally it takes around 30 minutes to get a result from the receipt of the sample in diagnostic laboratories.

Complications leading up to initial organ dysfunction in sepsis include factors such as impaired microcirculation, enhanced microvascular permeability, decreased numbers of perfused capillaries, endothelial cell apoptosis, and abnormal systemic blood flow to organ systems. During the pathophysiology and progression of sepsis, ADM levels are increased, leading to a reduction in vascular resistance and a significantly increased microvascular blood flow in many organs and systems such as the liver, small intestine, kidneys, and spleen [4]. The production of ADM has been shown to have beneficial properties in sepsis. These include having protection against endothelial permeability and consequent organ damage, protective effects in organs in response to bacterial induced shock, the ability to stabilize the microcirculation in inflammation, and the ability to restore endothelial stability in infected organs due to prevention of undesired inflammatory decompartmentalisation [5]. The body can facilitate localized cellular production and release of ADM in order to meet the specific perfusion requirements of individual organs which can be crucial in maintaining blood supply [6].

Whilst current benchmarks of sepsis, which include lactate and sequential organ failure (SOFA) scores, can accurately assess the degree of tissue hypoxia and organ dysfunction at any given time point, animal studies have shown that elevated MR-proADM levels can accurately reflect the early microvascular changes that occur in the build up to subsequent organ damage and dysfunction [7], the majority of which are extremely difficult to detect using standard clinical techniques, biomarkers or severity scores.

CONTACT Kordo Saeed kordosaeed@nhs.net Microbiology Innovation and Research UNIT, Department of Infection, University Hospitals Southampton NHS Foundation Trust, Tremona Road; Southampton SO16 6YD UK

Article highlights

- Mid-regional proadrenomedullin (MR-proADM) is a novel biomarker Animal studies have shown that elevated MR-proADM levels can accurately reflect the early microvascular changes that occur in the build-up to subsequent organ damage and dysfunction during sepsis.
- Studies have shown the MR-proAD can be incorporated into clinical scoring systems, and other markers to accurately differentiate the 'ill looking well' from the 'well looking ill'.
- It may assist clinicians decision making with regards to; A) triaging patient care at the outset, B) avoiding unnecessary admissions to hospital or inadequate discharges, and C) identifying patients most at risk of deterioration or poor outcome for early escalation of their management including antibiotic treatment or admission to higher level care.
- Limited data available for patients with COVID-19 and findings of these studies are promising however more studies are required to maximize our knowledge with regards to the full potential of MR-proADM in these patients.

Generally in the emergency department (ED), clinical scores and investigations are used to assist clinicians in their decision making. Although these can be helpful, they can also be misleading since patient factors such as age, comorbidities, and prior health status can play an important role in disease progression, outcome and mortality [8]. It is therefore also important to consider additional tools, such as blood biomarkers, that can better predict disease progression and mortality, that can be incorporated into clinical scoring systems, and other markers that can accurately differentiate the 'ill looking well' from the 'well looking ill'. With this in mind, there are three main potential benefits of using MR-proADM in a continuously busy ED, which include; A) triaging patient care at the outset, B) avoiding unnecessary admissions to hospital or inadequate discharges, and C) identifying patients most at risk of deterioration or poor outcome for early escalation of their management including antibiotic treatment or admission to higher level care [9–11].

During the 2020 COVID-19 pandemic, the pressure on hospital EDs, Intensive Care Units (ICU), and healthcare systems became more apparent globally. Hence a biomarker that can assist in easing off that pressure would be extremely valuable in clinical settings.

Accordingly, a group of international experts with research and experience in the applying MR-proADM to their clinical practice produced this review and aimed to:

(1) *Review literature on Mid-regional pro*-adrenomedullin (MR-proADM) in the emergency department (ED) and impact on clinical decision making in the emergency department
(2) Present current evidence and personal opinion from experts, including those related to COVID-19
(3) Agree to an algorithm or proposal on how to incorporate MR-proADM into patient clinical pathways and how to measure impacts of MR-proAM in EDs
(4) Propose conclusions and highlighting areas of future research and direction

2. Methodology

A multidisciplinary group of clinical experts from three countries met virtually during July 2020 to discuss topics related to MR-proADM applications in the ED, where key topics were agreed and selected for review.

A PubMed literature search was performed from inception to 15 July 2020, using the following search criteria [(proadrenomedullin OR proADM OR MR-proADM) AND (Emergency Department OR Emergency Room OR ED OR ER)) AND (infection)].

Each subtopic was assigned to at least two of the coauthors to draft the original articles related to each subtopic. Additionally, following the initial review, the number of papers have been published relating to MR-proADM in COVID-19 patients, these have been included as well as authors own anecdotal experience where applicable to the final discussion.

These were forwarded to the lead author for critical review and an initial manuscript was compiled. All the authors had the chance to review and agree to the final submitted version of the article.

3. Results

The literature search yielded 34 papers, including three papers in Spanish, six reviews and meta-analyses which were all included in the review. The following themes were identified within these papers and were agreed by the authors who formed the main points of the discussion for the review:

(1) Current evidence related to MR-proADM as a triaging tool in cases with suspicion of infection (assisting in admission or avoid admission decisions) or as a disease progression tool including ICU admission and mortality in the ED
(2) MR-proADM as an antibiotic stewardship tool in the ED
(3) MR-proADM in the context of COVID-19 in ED: does it help to identify those at risk of disease progression

3.4Incorporating MR-proADM into patient clinical pathways or algorithms

3.1. Current evidence related to MR-proADM as a tool in cases with suspicion of infection in the ED as A) a triaging tool assisting in admission or avoid admission decisions or B) as a disease progression tool including ICU admission and C) as prognostic tool and predictor of mortality

Emergency departments are increasingly under immense pressure; with huge throughput causing prolonged waiting times for the patients. A safe and rapid triaging of patients with low risk of deterioration, that can be treated as outpatients is essential to improve the workflow within the ED without reducing patient safety and comfort, and alleviating any unnecessary financial burden from the healthcare provider. Additionally, a tool that can aid ED clinicians to early identify those at risk of disease progression could be immensely

Table 1. Summary of current literature related to MR-proADM as a tool in the ED as A) a triaging tool (assisting in admission or avoiding admission decisions) or B) as a disease progression tool including ICU admission and C) as prognostic tool and predictor of mortality.

MR-proADM as a triaging tool (assisting in admission or avoid admission decisions)	Ref	MR-proADMas a disease progression tool including, ICU admission	Ref	MR-proADMas a prognostic tool and predictor of mortality	Ref
A large multicentre study of over 2000 patients with suspicion of infection, low MR-proADM values (< 0.87 nmol/L) could have potentially identified patients with low disease severity that could have been sent home safely (almost double the number of patients that were discharged conventionally in the same patient cohort) without increase in readmission and mortality rates for up to 28 days post their discharges. Another prospective study, focused on urinary tract infection (UTI), showed that a level of MR-proADM< 0.80 identified patient who could be safely managed as outpatients with only 2% of outpatient re-presentation to the ED without higher mortality rates within the next 30 days or requiring ICU admission. The results of this study suggested that MR-proADM may play a significant role in the triage of febrile UTI patients Similarly based on the evaluation of a group of patients who attended ED with respiratory symptoms and fever, MR-proADM proved to be a useful tool for risk stratification of community acquired pneumonia (CAP) patients, as its levels correlated with indicators linked to the complications of pneumonia and outcome. Additionally MR-proADM could have provided an early risk stratification in patients affected by pneumonia in term of promptly determining the eventual admission to the hospital and also to the right level of care.	[1,11,12]	Saeed K et al also shown that Higher MR-proADM (≥ 1.54 nmol/L) also showed greater precision in predicting mortality at 28 days and hospitalization requirements and admission to the ICU regardless of low biomarker values (PCT <0.25 ng/ml, lactate <2.0 mmol/L or CRP <67 mg/L) or clinical score values (SOFA <2 points, qSOFA<2 points, NEWS <4 points or CRB-65 < 2 points) ($p < 0.001$). Recently, MR-proADM has been extensively evaluated and incorporated to clinical scoring systems (e.g. SOFA score) as prognostic marker in different critical conditions, e.g. sepsis or acute heart failure & predict higher 30-day mortality risk. A study on serial MR-proADM measurements among a panel of markers used for diagnosis and prognosis of critically ill septic patents or in patients admitted to ICU. Its clearance on 2^{nd} and 5^{th}-day of admission was significantly higher in surviving patients compared to non-surviving patients. A level of MR-proADM higher than 2.5 nmol/L and a clearance lower than 30% on 5^{th}-day identified and predicted non-surviving patients more reliably. MR-proADM could most accurately identify low and high disease severity populations compared to other biomarkers or scores upon presentation. Patients with low NEWS and high MR-proADM values had a significantly higher risk of overall as well as delayed ICU admission compared to corresponding patients with low MR-proADM concentrations. Buendgens and colleagues investigated the potential role of MR-proADM as a diagnostic and prognostic biomarker in critical patients in ICU. They measured MR-proADM in 203 ICU patients and 66 healthy controls. MR-proADM levels were significantly increased in critically ill patients with sepsis compared to healthy controls. But, the diagnostic value of MR-proADM for identifying sepsis was numerically lower than that of other established markers (eg, interleukin-6, C-reactive protein, and procalcitonin.	[1,13–23]	The prognostic assessment of CAP includes several clinical severity scores, such as pneumonia severity index (PSI) and CURB-65 plus several biochemical markers, each of which integrate and support the clinical evaluation. Those most currently in use are CRP and PCT, in virtue of their high predictive capacity. However, in the last years, new attention is being focused on MR-pro-ADM, which has demonstrated to be the most reliable biomarker available in mortality and prognosis prediction for pneumonia Similarly, MR-proADM at a cutoff of 1.77 nmol/L, showed the greatest association with mortality upon presentation and 72 h [22] Additionally, MR-proADM at presentation, with a cutoff of > 2.07 nmol/l, have also shown to be the best accuracy for 30-day mortality risk compared in elderly infected patients compare with qSOFA score, systemic inflammatory response syndrome (SIRS), lactate, PCT, suPAR, and CRP. Baldiró et al, carried out a study at the Hospital Valld'Hebron, Spain, with 148 patients. Of these, 130 (87.8%) had a confirmed diagnosis of infection after retrospective evaluation. MR-proADM and SOFA performed well in predicting mortality at 28 and 90 days within the total population of infected patients of any origin. MR-proADM also showed a high association with the requirement of admission to the ICU after presentation to the emergency department [OR (95% CI) 8.18 (1.75–28.33)] or during ward treatment [OR (95% CI) 3.64 (1.43–9.29)]. A recent study concluded that MR-proADM improved the mortality risk stratification in patients with infection presenting to the ED beyond SOFA score alone and may further improve initial therapeutic site-of-care decisions. The study was a secondary analysis in > 650 patients with infection., MR-proADM and SOFA score were measured at time of admission. While the SOFA score alone revealed an AUC of 0.81, adding MR-proADM further improved discrimination (AUC 0.87). An admission MR-proADM threshold of 1.75 nmol/L provided the best prognostic accuracy for 30-day mortality; with a sensitivity of 81% and a specificity of 75%, and a negative predictive value of 98%.	[19,24–26]

valuable in planning escalations of level of care soon after patients' presentation. Findings from the review are presented in (Table 1) [1,11–26].

Incorporating MR-proADM into clinical scoring as a guide to avoid admission and a triaging tool in the ED could safely increase the number of outpatients compared to standard practice; overcome over-crowded situations in the ED and redirect the ED resources to the severely ill patients. Additionally, the prognostic value of MR-proADM as marker of organ dysfunction is in agreement with clinical scores and early sepsis identification is critical to begin appropriate management and improve the clinical outcomes [12,19,20,22,27,28] More studies and prospective pragmatic trials are required to confirm these original experiences and data.

3.2. MR-proADM as an antibiotic stewardship tool inED

The early administration of antibiotics in patients presenting to ED with a suspected infection is a challenge for clinicians, who must balance the necessary early administration of antibiotics in severe cases against the over prescription and misuse of antibiotics that derive increasing antibiotic resistance and can have detrimental effects on the microbiota.

Biomarkers, e.g., MRproADM, PCT, and C-reactive protein (CRP), can aid clinicians in their antibiotic decision-making. A prospective study consecutively enrolled patients presenting with a suspected infection to the EDs of three large tertiary level university hospitals in Spain [22], found that patients with a low National Early Warning Score (NEWS) but high pro-ADM had worse outcomes if they were not treated with antibiotics. This included higher rates of ICU admission (27.3% vs 4.8%, $p < 0.001$) and infection-related hospital readmission (54.5% vs 14.3%, $p < 0.001$). Therefore, an early administration of antibiotics must be considered in patients with suspected infection especially with high MR-proADM concentrations.

A recent study [9] highlighted a greater association with the requirement for antibiotic administration using NEWS and MR-proADM, as opposed to more commonly used parameters such as CRP and PCT. The rapid kinetics of MR-proADM, which is released significantly earlier than many other cytokines in response to microbial infection, could be useful to identify high-risk patients in which early antibiotics are genuinely indicated. The results suggest that delayed antibiotic administration in patients with low MR-proADM concentrations (<1.27 nmol/L) may result in fewer adverse effects, potentially allowing for a more detailed clinical assessment and investigations prior to any subsequent antimicrobial initiation without negative impact on patients [9]. Hence MR-proADM could represent an interesting antibiotic stewardship tool, however again more studies are required to confirm this hypothesis.

3.3. MR-proADM and COVID-19 cases in ED does it help to identify those at risk of disease progression?

The new Coronavirus disease 2019 (COVID-19), a disease caused by the severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) infection - continues to represent a major threat to global health [29].

COVID-19 is a systemic disease characterized by widespread endothelial damage with multiple organ dysfunction syndrome, when infection evolves causing severe clinical conditions, pneumonia and death [29]. Recently, to investigate the pathophysiological bases of organ failure development during COVID-19 disease, the involvement of endothelial cells at the interface between blood and parenchymal cells was evaluated [30]. COVID-19 related damage could resemble alterations observed during sepsis, and also in this case alteration of MR-proADM release could be suggested during SARS-CoV2 infection [30–32].

In COVID-19 infections, patients' clinical condition can worsen abruptly and unpredictably with many patients seemingly improving before deteriorating. As a result, the workload in ED, general wards, and ICUs has dramatically increased almost everywhere, creating a pressing need to optimize resources through risk stratification for critically ill COVID-19 patients. Interestingly, Li H. et al. [33] recently hypothesized that in critical patients with COVID-19-related pneumonia, the integrity of the epithelial-endothelial barrier was severely interrupted, describing a particular syndrome denominated 'viral sepsis'. MR-proADM may prove to be effective in risk stratification for patients affected by viral sepsis.

Recent studies have highlighted the value of PCT as a useful tool for antibiotic stewardship in COVID-19 patients in the intensive care unit. Patients in the first week of admission with a low PCT had 2 days less exposure to antibiotics with comparable outcomes [34]. A study tested the effectiveness of MR-proADM in comparison to C-reactive protein (CRP), procalcitonin (PCT), D-dimer, and lactate dehydrogenase (LDH) in predicting disease progression and mortality in 57 COVID-19 ICU-patients. MR-proADM, clinical and other routine laboratory tests were measured within 48 hours from ICU admission, on day 3, 7 and 14. Survival curves difference with MR-proADM cutoff set to 1.8 nmol/L were tested using log-rank test. ICU and overall mortality were 54.4%. MR-proADM was higher in dying patients (2.65 + 2.33 vs 1.18 + 0.47, p = 0.0001) and a higher mortality characterized patients with MR-proADM exceeding 1.8 nmol/L (p = 0.0157) [35].

An observational study investigated the association of MR-proADM levels with in-hospital mortality. The study included 89 critically ill COVID-19 patients, 19% (n = 17) died while in the hospital. Median admission MR-proADM levels were increased almost 1.5-fold in non-survivors compared to survivors (1.3 (IQR 1.1 to 2.3) vs. 0.8 (IQR 0.7 to 1.1) difference, P value) and showed good discrimination (AUC 0.78). An increase of 1 nmol/L of admission MR-proADM was independently associated with a more than fivefold increase in in-hospital mortality (adjusted odds ratio (OR) of 5.5, 95%CI 1.4 to 21.4, p = 0.015). An admission MR-proADM threshold of 0.93 nmol/L showed the best prognostic accuracy for in-hospital mortality with a sensitivity of 93%, a specificity of 60%, and a negative predictive value of 97%. Kinetics of follow-up MR-proADM provided further prognostic information for in-hospital treatment. The study concluded that increased levels of MR-proADM on admission and during hospital stay were independently associated with in-hospital mortality and may allow a better risk stratification, and particularly rule-out of fatal outcome in COVID-19 patients [36].

In another prospective observational study among 99 adult patients hospitalized with confirmed COVID-19. Twenty-five (25.3%) cases progressed to severe disease (defined as a composite of admission to Intensive Care Unit and/or need for mechanical ventilation and/or 28-day mortality) and the 28-day mortality rate was of 14.1%. MR-proADM showed the highest AUC to predict 28-day mortality (0.905; [CI] 95%: 0.829–0.955; P < 0.001) and progression to severe disease (0.829; [CI] 95%: 0.740–0.897; p < 0.001), respectively. MR-proADM plasma levels above optimal cutoff (1.01 nmol/L) showed the strongest independent association with 28-day mortality risk (hazard ratio [HR]: 10.470, 95% CI: 2.066–53.049; p < 0.005) and with progression to severe disease (HR: 6.803, 95% CI: 1.458–31.750; p = 0.015) [37].

Furthermore, results from a pragmatic retrospective including 111 patients, admitted to Udine University Hospital due SARS-CoV-2 pneumonia, showed an association between MR-proADM levels and the severity of COVID-19: high MR-proADM levels were significantly associated with combined events of death or orotracheal intubation (OR 4.284 [95%CI 1.893–11.413]). AUROC analysis showed a good discriminative performance of MR-proADM (AUROC: 0.849 [95% CI 0.771–0.730]; p < 0.0001). Additionally the identified that the optimal value of MR-proADM, associated with negative outcome, was 0.895 nmol/l (sensitivity 0.857 [95% CI 0.728–0.987]; specificity of 0.687 [95% CI 0.587–0.787]) [38]. This cutoff value is almost identical to the value previously found to be a good level to safely discharge patients with other infections from ED [1].

Extrapolating results from bacterial infection and sepsis to COVID-19 is a major limitation, while results on these small-scale COVID-19 studies are promising, larger and randomized trials are urgently required to assess MR-proADM use in the diagnosis and prognosis of COVID-19 patients, particularly when the impact of steroids and tocilizumab on the outcome of COVID-19 and impact on MR-proADM in COVID-19 patients.

3.4. Incorporating MR-proADM to patients clinical pathways or algorithms

Despite increasing numbers of publications and studies, the uptake of MR-proADM in clinical practice has been generally low. This is likely to be due to many reasons including lack of guidance on how to best integrate MR-proADM test results into the clinical management of patients attending EDs, and lack of national or international bodies to support its use, which is again due to lack of clinical trials, sufficient clinical data, large numbers of studies, and cost effectiveness analysis.

The main point from a recent med-tech innovation briefing by the National Institute for Health and Care Excellence (NICE) [10] suggested that the available studies, at the time of the review, show that MR-proADM can improve accuracy of infection diagnosis and can predict the infection's severity. However, there is a lack of prospective studies showing how MR-proADM results influence clinical decisions. Following this review a randomized-controlled 2-arms study demonstrated 20% more patients could be managed in the outpatient setting safely [22].

While we agree with NICE's finding, we would like to propose the following algorithms which can be considered for future clinical evaluations and/or studies. The proforma allows for comparing data among studies, local reports, and real-life publications (Table 2). Again we must emphasize that no biomarker can replace clinician experience and this will always override any diagnostic results.

4. Discussion and further research

Misdiagnosis is one of the most common errors in the ED settings, and diagnosis of bacterial infection can be very challenging during the initial assessment of patients or in certain patient groups, e.g., in elderly patients where classical features of infection or sepsis could be absent. Indeed, the confusion between cardiovascular events and infections is the most common misdiagnosis in studies that evaluate discrepancies between clinical diagnosis and autopsy findings [39].

In patients with suspicion of infection, MR-proADM levels can provide clinicians with a more accurate reflection of abnormalities in the microcirculation before the patient develops any form of organ dysfunction or adverse clinical signs become apparent. Limited number of studies which are mostly observational have shown that MR-proADM could represent one of the most valuable tools in identifying infected patients at risk of disease progression and poor clinical outcomes. High levels of MR-proADM despite low clinical scores in patients are associated with greater risk of disease progression, ICU admission, and mortality, as well as a higher readmission rates for EDs. However, published studies have concentrated on bacterial infection; viral infections have been poorly investigated even before COVID-19 with regards to the impact of MR-proADM on their management and outcome. Therefore, pragmatic clinical trials and studies are required to maximize our knowledge regarding the potential of MR-proADM and its clinical implications in making-decisions and impact on patients outcomes and health economics as well as studies and trials specifically with regards to COVID-19 −19 pandemic as it looks like SARS-CoV-2 is going to stay with us for a protracted period.

5. Expert opinion

There are still big gaps in our knowledge with regards to novel biomarkers and their application in clinical practice. MR-proADM is one of these novel markers that recently gained much interest in clinicians and researchers particularly with regards to its ability to support or be incorporated into clinical scoring systems and aiding clinicians to recognize deteriorating patients who appear to be well looking and vice versa as well as in predating who requires higher levels of care and outcomes.

The data summarized in this review represent mostly what is available and from experts that have used MR-proADM in their practice. Although what we know now is very promising, we are still in need of larger studies and evaluations to maximize our knowledge and recognize the full potential of MR-

Table 2. An action table that may be considered for future evaluations and/or clinical studies following MR-rroADM results (could be modified according to local needs).

	Pro-ADM levels nmol / L and potential ACTIONS◊		
	<0.87	>0.87-1.5	>= 1.5
Patients clinically well (Defined by setting specific scores, e.g. SOFA <2, qSOFA<2, NEWS2 < 5) *	Discharge with safety net**	Ward based admission Repeat MR-proADM in 12-24 hours to assess progress and potential discharge depending on clinical scoring and the trend of MR-proADM levels	Admit to acute admissions Closely monitor clinical scoring and picture Secondary examinations and review Monitor daily MR-proADM to assess progress and plan escalation or de-escalation of therapy based on combinations of these findings
Patients is clinically unwell OR clinican concern (Defined by setting specific scores, e.g. SOFA ≥2, qSOFA ≥ 2, NEWS ≥5)	Potentially discharge patients with safety net**		Admit to acute admissions, consider ICU/ HDU outreach depending on senior review Closely monitor clinical scoring and picture Secondary examinations and review Monitor daily MR-proADM to assess progress and plan escalation or de-escalation of therapy based on combinations of these findings

* Please consider other local scoring systems; clinician's decision could override the test result at any time based on their clinical assessment
**advice patient to come back if noticed clinical deterioration
◊ The following are some examples on what impacts need to be accounted or measured to further assess the impact of MR-proADM:
1) The number of admissions and discharges that were influenced by measuring MR-proADM levels, vs total number of admissions and discharges in the EDs
2) The number of admissions to HDU and ICU that were influenced by measuring MR-proADM levels, vs total number of admissions and discharges to these areas
3) Impact of the above decisions on subsequent mortality within 30 days of that decision
4) Impact of those decisions on earlier discharges and subsequent readmission rates (within 30 days)

proADM. Although MR-proADM can be measured easily through a blood test and results could be available within 30 minutes from receiving a sample in a diagnostic laboratory, the marker itself hasn't universally taken off, yet, due to a number of reasons. These could be, lack of large randomized multicentre studies, availability of suitable wide range platforms in diagnostic laboratories; lack of diagnostic point of care test that could be used by the bed-site, outside research; lack of wide experience by clinicians; lack of cost effectiveness analysis studies and lack of international consensus or guidance on how to use and what cut offs should be adopted, e.g., in emergency settings. All these are questions requiring answers and answers can be obtained through systematic, randomized studies and evaluations.

Additionally using MR-proADM, alone and in combination with other biomarkers, has not yet fully appreciated in the emergency departments during COVID-19 waves and how it may assist in triaging patients, admission avoidance, and prognostication. There are limited real-life reports and retrospective studies highlighting the potential that MR-proADM could have, but these findings need confirmation in larger studies, especially in the era of increasing demand for hospital beds and cost pressures on health systems globally.

There are now, and in many corners of the world, point of care diagnostics that are being used in various settings including home settings and virtual wards. Examples of these include point of care COVID-19 tests. We think. In the future, affordable point of care measurements of MR-proADM from a single blood drop with other biomarkers will be immensely helpful in settings like home settings, outpatients and virtual wards, emergency rooms, general practice, and even inside ambulances.

Availability of this marker with others as well as a diagnostic test for, e.g., COVID-19 will help not only clinicians and health care providers, but also individuals to make more informed decisions whether to seek further medical advice or even attend a hospital for further evaluation. Or these diagnostic could be linked to a mobile phone application, linked to an artificial intelligence system, the net outcome of it will be an instruction to the user of what the best action is.

Additionally for clinicians in the above settings, incorporating MR-proADM levels into clinical scoring systems and other biomarkers could make their decision around patients triaging more individualized, e.g., safe discharge or avoid admissions or rapid escalation of treatment to high dependency or intensive care which overall will be beneficial to both healthcare systems and patient outcomes. Furthermore a meta-analysis of the existing studies on the proposed cutoffs of risk prediction with MR-proADM for bacterial sepsis based on publications before COVID-19 and comparing it to findings from COVID-19 studies is required.

Until then we encourage collaboration between healthcare providers, industries, and funding agencies to assist in studies that provide answers to the gaps highlighted above.

Funding

This paper was not funded.

Declaration of interest

K Saeed received Research Grants from Pfizer and Thermofisher. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers in this manuscript have no relevant financial or other relationships to disclose.

ORCID

Carlo Tascini http://orcid.org/0000-0001-9625-6024

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Saeed K, Wilson DC, Bloos F, et al. The early identification of disease progression in patients with suspected infection presenting to the emergency department: a multi-centre derivation and validation study. Crit Care. 2019;23(1):40. .
   - **A large multicenter study invloving two cohorts over 2000 patients showed the value of MR-proADM in assisitng clinicans in traiging patients and recognising disease progression.**
2. Schuetz P, Wolbers M, Christ-Crain M, et al. Prohormones for prediction of adverse medical outcome in community-acquired pneumonia and lower respiratory tract infections. Crit Care. 2010;14(3):R106.
3. Struck J, Tao C, Morgenthaler NG, et al. Identification of an Adrenomedullin precursor fragment in plasma of sepsis patients. Peptides. 2004;25(8):1369–1372.
4. Wang P, Ba ZF, Cioffi WG, et al. The pivotal role of adrenomedullin in producing hyperdynamic circulation during the early stage of sepsis. Arch Surg. 1998;133(12):1298–1304.
5. Pugin J. Adrenomedullin: a vasodilator to treat sepsis? Crit Care. 2014;18(3):152.
6. Elsasser TH, Kahl S. Adrenomedullin has multiple roles in disease stress: development and remission of the inflammatory response. Microsc Res Tech. 2002;57(2):120–129.
7. Temmesfeld-Wollbrück B, Brell B, Dávid I, et al. Adrenomedullin reduces vascular hyperpermeability and improves survival in rat septic shock. Intensive Care Med. 2007;33(4):703–710.
8. Research on sepsis biomarkers in the emergency department: what now, what next? - PubMed n.d. https://pubmed.ncbi.nlm.nih.gov/31625300/(accessed 2020 Oct 15).
9. Rosenqvist M, Wilson DC, Tegnér L, et al. Biomarkers to guide antibiotic timing and administration in infected patients presenting to the emergency department. Crit Care. 2019;23(1):141.
10. Overview | MR-proADM test for use with clinical deterioration scores in cases of suspected infection | advice | NICE n.d. https://www.nice.org.uk/advice/mib195 (accessed 2020 Oct 15).
11. Legramante JM, Mastropasqua M, Susi B, et al. Prognostic performance of MR-proadrenomedullin in patients with community acquired pneumonia in the emergency department compared to clinical severity scores PSI and CURB. PLoS One. 2017;12(11):e0187702. .
   - **Observational prospective, single-center study in patients with suspected community acquired pneumonia (CAP). MR-pro-ADM levels with other biomarkers and scoring should be further studied to determine its full potential with regards to prognostic accuracy and clinical severity classification.**
12. Stalenhoef JE, Van Nieuwkoop C, Wilson DC, et al. Biomarker guided triage can reduce hospitalization rate in community acquired febrile urinary tract infection. J Infect. 2018;77(1):18–24.
13. Dschietzig T, Azad HA, Asswad L, et al. The adrenomedullin receptor acts as clearance receptor in pulmonary circulation. Biochem Biophys Res Commun. 2002;294(2):315–318.
14. Voors AA, Kremer D, Geven C, et al. Adrenomedullin in heart failure: pathophysiology and therapeutic application. Eur J Heart Fail. 2019;21(2):163–171.
15. Viaggi B, Poole D, Tujjar O, et al. Mid regional pro-adrenomedullin for the prediction of organ failure in infection. results from a single centre study. PLoS One. 2018;13(8):e0201491.
16. Angeletti S, Spoto S, Fogolari M, et al. Diagnostic and prognostic role of procalcitonin (PCT) and MR-pro-Adrenomedullin (MR-proADM) in bacterial infections. APMIS. 2015;123(9):740–748.
17. Spoto S, Fogolari M, De Florio L, et al. Procalcitonin and MR-proAdrenomedullin combination in the etiological diagnosis and prognosis of sepsis and septic shock. Microb Pathog. 2019;137:103763.
18. Angeletti S, Dicuonzo G, Fioravanti M, et al. Procalcitonin, MR-Proadrenomedullin, and cytokines measurement in sepsis diagnosis: advantages from test combination. Dis Markers. 2015;2015:1–14. .
   - **A study evaluated combined measurement of procalcitonin (PCT), MR-proADM, and cytokines over 200 patients (sepsis vs control). PCT, MR-proADM, IL-6, IL-10, TNF-*α*, and MCP-1 were considered applicant for sepsis diagnosis. A composite score of PCT, MR-proADM, and TNF-*α* showed the best ROC curve in the early diagnosis of sepsis.**
19. Angeletti S, Ciccozzi M, Fogolari M, et al. Procalcitonin and MR-proAdrenomedullin combined score in the diagnosis and prognosis of systemic and localized bacterial infections. J Infect. 2016;25(3):1369–1372.
20. Spoto S, Cella E, De Cesaris M, et al. Procalcitonin and MR-Proadrenomedullin combination with SOFA and qSOFA scores for sepsis diagnosis and prognosis: a diagnostic algorithm. SHOCK. 2018;50(1):44–52.
21. Valenzuela-Sánchez F, Valenzuela-Méndez B, Rodríguez-Gutiérrez JF, et al. New role of biomarkers: mid-regional pro-adrenomedullin, the biomarker of organ failure. Ann Transl Med. 2016;4(17):6.
22. Gonzalez Del Castillo J, Wilson DC, Clemente-Callejo C, et al. Biomarkers and clinical scores to identify patient populations at risk of delayed antibiotic administration or intensive care admission. Crit Care. 2019;23(1):335. .
   - **Prospective multicentre study, confirming findings from previous studies, highlighting the ability of MR-proADM to identify patients with a high potential for subsequent disease progression. Additionally it showed patients with low presenting symptoms and high MR-proADM concentrations had an increased risk of a less intensive treatment despite high subsequent mortality rates, characterised by a withheld or delayed antibiotic therapeutic response, a delayed admission onto the ICU, and a high readmission rate due to the reoccurrence of an infection-related complication.**
23. Buendgens L, Yagmur E, Ginsberg A, et al. Midregional Proadrenomedullin (MRproADM) serum levels in critically Ill patients are associated with short-term and overall mortality during a two-year follow-up. Mediators Inflamm. 2020;2020:2020.
24. Julián-Jiménez A, Yañez MC, González-del Castillo J, et al. Prognostic power of biomarkers for short-term mortality in the elderly patients seen in emergency departments due to infections. Enferm Infecc Microbiol Clin. 2019;37(1):11–18.
25. Baldirà J, Ruiz-Rodríguez JC, Wilson DC, et al. Biomarkers and clinical scores to aid the identification of disease severity and intensive care requirement following activation of an in-hospital sepsis code. Ann Intensive Care. 2020;10(1):7.
26. Haag E, Gregoriano C, Molitor A, et al. Does mid-regional pro-adrenomedullin (MR-proADM) improve the sequential organ failure assessment-score (SOFA score) for mortality-prediction in patients with acute infections? Results of a prospective observational study. Clin Chem Lab Med. published ahead of print 2021. DOI: 10.1515/cclm-2020-1566
27. Valenzuela Sanchez F, Valenzuela Mendez B, Rodríguez Gutierrez J, et al. Initial levels of mr-proadrenomedullin: a predictor of severity in patients with influenza a virus pneumonia. Intensive Care Med Exp. 2015;3(S1). DOI:10.1186/2197-425x-3-s1-a832
28. Sepsis in the emergency department: key points, controversies, and proposals for improvements in Latin America - PubMed n.d. https://pubmed.ncbi.nlm.nih.gov/30963741/(accessed 2020 Oct 15).
29. Potere N, Valeriani E, Candeloro M, et al. Acute complications and mortality in hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. Crit Care. 2020;24(1):389.

30. Ince C, Mayeux PR, Nguyen T, et al. The endothelium in sepsis. Shock. 2016;45(3):259–270.
31. Elena T, Rosanna DP, Emanuela M, et al. Anti-inflammatory effects of adrenomedullin on acute lung injury induced by carrageenan in mice. Mediators Inflamm. 2012;2012:13.
32. Wilson DC, Schefold JC, Baldirà J, et al. Adrenomedullin in COVID-19 induced endotheliitis. Crit Care. 2020;24(1):411.
33. Li H, Liu L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet. 2020;395(10235):1517–1520.
34. Heesom L, Rehnberg L, Nasim-Mohi M, et al. Procalcitonin as an antibiotic stewardship tool in COVID-19 patients in the intensive care unit. J Glob Antimicrob Resist. 2020;22:782–784.
35. Montrucchio G, Sales G, Rumbolo F, et al. Effectiveness of Mid-Regional Pro-Adrenomedullin (MR-proADM) as prognostic marker in COVID-19 critically Ill patients: an observational prospective study. PLoS One. 2021;16(2):e0246771. Published online 2021 Feb 8. doi: 10.1371/journal.pone.0246771.
36. Gregoriano C, Koch D, Kutz A, et al. The vasoactive peptide MR-pro-adrenomedullin in COVID-19 patients: an observational study. Clin Chem Lab Med. Internet 2021. Available from https://www.degruyter.com/document/doi/10.1515/cclm-2020-1295/html
- **Observational study, highlighting the prognostic ability of serial MR-proADM measurements among COVID-19 patients admitted to the ICU.**
37. ALuis García de Guadiana Romualdo María Dolores Calvo Nieves María Dolores Rodríguez Mulero Ismael Calcerrada Alises Marta Hernández Olivo Wysali Trapiello Fernández Mercedes González Morales Cristina Bolado Jiménez María Dolores Albaladejo Otón Hilda Fer LG de GRMDCNMDRMICAMHOWTFMGMCBJMDAOHF. MR-proADM as marker of endotheliitis predicts COVID-19 severity. Eur J Clin Invest. [Internet]. 2021; Available from:]. . : https://onlinelibrary.wiley.com/doi/10.1111/eci.13511
38. Sozio E, Tascini C, Fabris M, et al. MR-proADM as prognostic factor of outcome in COVID-19 patients. Sci Rep. 2021;11(1). in Press. DOI: 10.1038/s41598-021-84478-1.
- **A recently accepted study on MR-proADM and COVID-19 confirming previously published cut offs prior to the SARS-CoV-2 pandemic.**
39. [Discrepancies between clinical diagnoses and autopsy findings] - PubMed n.d. https://pubmed.ncbi.nlm.nih.gov/21550929/ (accessed 2020 Oct 15).