

# Clinical scores and blood biomarkers for early risk assessment of patients presenting to the emergency department

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## Abstract

### Introduction

The use of an accurate and well-validated triage system in the emergency department is pivotal for early risk stratification of medical patients. For this purpose different clinical scores, such as the Manchester Triage Score, are widely propagated. Prognostic blood biomarkers mirroring physiopathological changes in different organ systems and severity of disease provide additional prognostic information. Also, nursing scores have been developed for early prediction of post-acute care needs. Still, there is no well-validated initial triage score integrating this information on clinical status, biomarker, prognosis and nursing care needs for a more overall assessment of patients. Such an integral score will help to estimate early initial treatment priority, decide site of care and predict post-acute care needs, and thereby optimise management of undifferentiated patients. The aim of this current review is to critically summarise potential and limitations of present clinical risk scores and blood biomarkers that have been used in recent studies in the emergency department setting for early patient assessment. Particularly, we focused on the following biomarkers from different organ systems: proadrenomedullin, C-reactive protein and procalcitonin as markers of infection/vasodilation; high-sensitivity

troponin T assay and natriuretic peptides as cardiac dysfunction markers; copeptin and cortisol as markers of stress; plasma neutrophil gelatinase-associated lipocalin, the soluble form of urokinase-type plasminogen activator and urea as markers of kidney dysfunction; thyroid hormones and proEndothelin-1 as a marker of endothelial activation and lactate as a marker of organ dysfunction.

### Conclusion

Despite the promising role of clinical scores and biomarkers from different pathophysiological concepts, no conclusive clinical trial has yet looked at different biomarkers in a large and comprehensive patient population. In addition, it remains unclear whether the use of scores and biomarkers has the potential to improve clinical outcome of patients as randomised trials are largely lacking.

### Introduction

Emergency departments (ED) are progressively overwhelmed by patients with both urgent and non-urgent problems<sup>1,2</sup>. This leads to overfilled ED waiting rooms with long waiting times, detrimental outcomes and unsatisfied patients. As a result, patients needing urgent care may not be treated in time, whereas patients with non-urgent problems may unnecessarily receive expensive and dispensable treatments. Time to effective treatment is among the key predictors for outcomes across different medical conditions ('time is cure'), including patients with septicemia<sup>3</sup>, pneumonia<sup>4</sup>, stroke ('time is brain')<sup>5</sup> and myocardial infarction ('time is heart')<sup>6</sup>. For these reasons, a well-validated risk stratification

system in the ED is essential for an optimal initial triage of medical patients. Furthermore, precise ED triage should not only focus on treatment priority but also on site-of-care decisions (i.e. outpatient vs. inpatient management) and early identification and organisation of post-acute care needs. For this purpose different tools have been propagated, namely standardised triage scores for the ED, biomarkers thought to mirror pathophysiological changes and severity of disease, and nursing scores to predict post-acute care needs. This might help identifying patients at risk and individualise treatment and patient management decisions safely.

The aim of this current review is to critically summarise potential and limitations of current clinical risk scores and blood biomarkers that have been used in recent studies in the ED setting for early patient assessment.

### Discussion

The authors have referenced some of their own studies in this critical review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

### Clinical scores of early patient triage

To prioritise patients in EDs, triage systems are commonly used. Different initial triage systems have

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been proposed including the Manchester Triage System (MTS), the Australasian Triage Scale, the Canadian Triage and Acuity Scale and the Emergency Severity Index<sup>7,8</sup>. Among these scores, the MTS is the most widely used score in European and North-American health care settings<sup>7</sup>. The MTS allocates patients to one of 52 flowchart diagrams, each representing an independent medical complaint. A triage nurse categorises the patient into an algorithm and determines which flow chart should be followed. Each flow chart is based on a five-step decision process that uses key discriminators, for example, pain or dyspnoea, at each step to assign patients to one of the five priority groups. These groups are represented by five different colours<sup>9</sup>. These colours indicate the level of urgency and the recommended maximum waiting time for physician assessment: patient has to be seen immediately (0 min, red), very urgent (<10 min, orange), urgent (<30 min, yellow), not urgent (<90 min, green) and not at all urgent (<120 min, blue).

Surprisingly, no rigorous clinical outcome study has yet investigated the impact of these triage scores on patient outcomes<sup>10</sup>. In fact, a literature review published in 2010<sup>7</sup> found only four observational studies that have been published by then in adult patients, with low number of patients included (ranging from 50 to 167 patients) in each of them. Indeed, the accuracy of the MTS instrument was suboptimal with only 67% of high-risk patients being correctly identified as high-priority patients.

Thus, there is urgent need for scientific validation of these scores in a large, unselected and international cohort of medical ED patients. Also, due to the suboptimal performance, the MTS should further be refined to increase its accuracy before a more widespread implementation into clinical routine. Importantly, initial triage is not only important to assign

treatment priorities but should also assist in estimating the medical risk of patients influencing site-of-care decisions and post-acute care needs to optimise early planning of post-acute care/nursing support. For certain medical diagnoses, such as in patients with pneumonia<sup>11</sup>, specific medical risk scores have been developed and are propagated by international guidelines to improve initial site-of-care decisions. Yet, there is a need for a pragmatic multi-professional risk assessment system to better predict the risk of unselected medical patients in routine care and, thus, a need for in-hospital management, as well as post-acute care needs at an early stage of ED admission.

#### **Clinical scores for initial severity assessment which may assist in site-of-care decisions**

Accurate assessment of disease severity, risk stratification and prediction of outcome are prerequisites for safe decision making on the need for hospitalisation and identifying patients at low risk of complications and thus suitable for outpatient management. Despite their widespread use in clinical routine, traditional markers such as severity of disease self-estimation by the patient, fever, white blood cells and C-reactive protein (CRP), different studies have found these not to be reliable to assess disease severity and mortality risk<sup>12</sup>. For specific medical diagnoses, such as pneumonia, organisations have developed prediction rules and disseminated guidelines to stratify management of patients based on predicted mortalities in order to optimise hospital referral and lower hospital admission rates<sup>13,14</sup>. The pneumonia severity index is an extensively validated and widely propagated American scoring system that assesses the risk of death in a two-step algorithm<sup>11</sup>. Other prognostic scores in the emergency setting are found for cardiac conditions, such

as the Killip classification to estimate the mortality risk of patients with myocardial infarction<sup>15</sup>. Yet, no such scores exist for undifferentiated medical patients at the most proximal time point of ED admission.

In this context, new rapidly measurable blood biomarkers mirroring distinct pathogenetic mechanisms to predict severity and outcome may improve prognostication of patients. Importantly, the utility of a blood biomarker in this context is defined by the degree it improves clinical decision making and adds timely information beyond that of readily available information from clinical examination<sup>16</sup>.

#### **Scores for early predicting nursing needs**

Discharge planning has to begin on admission. In addition to early prediction of medical risk for mortality and complications, post-acute care discharge (PACD) needs is an important variable which may influence the discharge process. It is therefore crucial to assist physicians and nurses to make more rational decisions about PACD needs for early involvement of care givers and social workers. This may result in a decrease in length of stay (LOS) with important cost implications. However, cost issues should not be the most relevant driver to reduce LOS. Even more importantly, hospital-acquired disability is an emerging issue especially in older, frail medical patients at high risk for premature referral to a nursing home with consecutive depression and further deterioration of mental and physical independence<sup>17</sup>.

For this purpose, a promising tool was recently developed in Geneva (Switzerland) to predict post-acute institutional care needs and thus assess biopsychosocial risk of patients. As a scoring system on admission and day 3 the PACD score facilitates early discharge planning<sup>18</sup>. The PACD compiles information on nursing needs before hospital admission and

the amount of initial medical diagnoses (on admission) to a score. Observational data from a validation study showed a significant relation between biopsychosocial risk and discharge to a post-acute care facility<sup>19</sup>.

Another nursing score that is used in different German-speaking countries is the 'Selbstpflegeindex' (SPI). This simple nursing and geriatric tool assesses the functional dependence in activities of daily life. An SPI score of <32 points indicates a risk for post-acute care deficit<sup>20</sup>.

As a limitation, these scores have not been tested in a rigorous intervention study to ultimately assess the clinical and financial impact of early prediction of nursing needs.

### Prognostic biomarkers for triage and risk assessment

Recently, several promising blood biomarkers have been investigated for their ability for early severity assessment and risk stratification. As a big advantage, blood biomarkers are objective, dynamic and easily measurable, and may improve clinical decision making if used in the right context. Several blood biomarkers have been investigated in different patient populations, such as patients presenting to the ED with lower respiratory tract infections, pneumonia, chronic obstructive pulmonary disease, sepsis, acute heart failure and myocardial infarction<sup>21</sup> among others. Table 1 gives an overview about selected ED studies investigating biomarkers from different organ systems for improved prognostic and diagnostic patient assessment.

Because biomarkers and clinical scoring systems may reflect different aspects of the host response, an improved prognostic accuracy may be achieved when combining both<sup>22</sup>. This has been demonstrated for several markers and risk scores for selected patient populations. Yet, for undifferentiated medical patients, as of today there is no validated clinical scoring system which integrates prognostic

biomarkers for prediction of triage needs and risk of complications. In the following section, we discuss selected biomarkers from different pathophysiological concepts, which have high potential for improving early risk assessment of undifferentiated patients presenting to the ED (Figure 1).

### Markers of inflammation, infection and vasodilation

Acute disease often leads to an inflammatory host response in patients characterised by the release of different active cytokines and hormone-like peptides into the blood stream. Among them, proadrenomedullin (ProADM) is the most potent vasodilator and becomes up-regulated in inflammatory and infectious conditions. It belongs to the calcitonin peptide superfamily and is ubiquitously expressed in the body including sepsis, respiratory infections and pneumonia, and also heart failure and myocardial infarction. Importantly, ProADM has been shown to improve clinical pneumonia risk scores<sup>23</sup>, and in a pilot intervention study, tended to decrease in LOS without increased risk for readmissions by improving physicians admission and early discharge decisions<sup>22</sup>.

CRP is an inflammatory marker that is used in many hospitals across Europe as a screening tool for inflammation and infection. Among others, a Spanish study compared procalcitonin (PCT) and CRP levels in febrile patients admitted to a medical ward and found CRP not able to discriminate between infections and inflammatory diseases<sup>24</sup>. Also, its prognostic accuracy has been found to be inferior to other commonly used markers of infection<sup>25</sup>.

PCT has emerged as an inflammatory blood marker more specific to bacterial infections and apt to steward antibiotic therapy. A combination of elevated PCT levels and systemic inflammatory response syndrome criteria seems to be more accurate for the diagnosis of early, uncomplicated sepsis in patients presenting

to the ED than either measure taken alone<sup>26</sup>.

### Markers of cardiac dysfunction

Arguably, cardiac dysfunction due to several reasons is a main driver of morbidity and mortality in emergency patients. Cardiac troponins are well-known as diagnostic markers for cardiac injury in acute coronary syndrome. It also has a prognostic value in stable coronary disease and correlates with mortality and risk for re-events. Recently, elevated high-sensitivity troponin T assay has also been found to be a strong marker of mortality in consecutive general hospitalised patients aged > 40 years<sup>27</sup>. In addition, natriuretic peptides (NPs), such as B-type NP or N-terminal pro-B-type NP correlate with cardiac (dys-) function and aid in the diagnosis of acute heart failure in patients presenting at the ED with acute dyspnoea. NPs are also increased in septic conditions where they have a prognostic value.

### Markers of stress

During conditions of stress, the body reacts with an activation of the hypothalamus-pituitary adrenal axis with the up-regulation of different 'stress hormones'. Among them, serum cortisol has been found to be elevated in different severe conditions such as sepsis, pneumonia and also cardiac conditions. Studies in pneumonia patients found that cortisol has a close correlation with severity and is an important predictor for mortality independent of clinical scores and other markers of inflammation<sup>28</sup>. Another important stress hormone is vasopressin and its precursor, copeptin, which also closely correlates with severity of illness. Recent studies found a diagnostic value of copeptin when combined with troponin for rule out of myocardial infarction<sup>29</sup>.

### Markers of kidney dysfunction

Severe diseases can lead to organ failure including dysfunction of the

Table 1 Selected emergency department studies investigating biomarkers from different organ systems for improved prognostic and diagnostic patient assessment						
Biomarker (s)	Author, year	Setting, patient population	n	Main findings	Limitations	
<b>Proadrenomedullin, PCT, copeptin</b>	Schuetz et al. <sup>21</sup>	Medical patients, ED, prospective, observational, cohort study	Around 4500	Study ongoing, preliminary results suggest a high-predictive ability of all markers for 30 day mortality as well as complications and treatment priority	(1) Treatment priority is as adjudicated by the attending physicians (gold standard) and (2) no blinding for physicians and nurses	
<b>Copeptin, troponin</b>	Balmelli et al. <sup>29</sup>	Patients presenting to the ED with symptoms suggestive of AMI of < 12 h	1247 (34% female, 66% male)	(1) Important gender differences regarding the final diagnoses underlying acute chest pain; (2) no significant difference in the diagnostic accuracy of cTnT, hs-cTnT and copeptin, alone or in combination, in women vs. men; (3) increased risk of death to a similar extent in both genders having elevated versus normal concentration of cTnT, hs-cTnT or copeptin and (4) similar prognostic accuracy by cTnT, hs-cTnT and copeptin in both genders	(1) Only patients with chest pain as predominate symptoms enrolled and (2) three limited number of markers under investigation	
<b>Troponin</b>	Iversen et al. <sup>27</sup>	Consecutive medical and surgical patients aged > 40 years	1176 patients (59,2% female)	Elevated hs-TnT in 57.1% of the entire cohort and in 52.3% of patients with non-cardiac diagnoses. Hs-TnT above the median was associated in univariate analysis with a 3-fold higher mortality in the entire population. In patients without past or present ischaemic heart disease hs-TnT in the upper quartile was associated in univariate analysis with a 5-fold higher mortality risk	(1) No serial measurements of troponin, for further characterisation of the cause of elevation and (2) blood samples were stored for 12 years	

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Table 1 (Continued)						
Biomarker (s)	Author, year	Setting, patient population	n	Main findings	Limitations	
<b>Cortisol</b>	Kolditz et al. <sup>28</sup>	Hospitalised CAP-patients	984	Cortisol levels were significantly elevated in both adverse outcomes ( $P < 0.001$ ) and predicted mortality (Area under the curve (AUC) 0.70, cut off 795 nmol/L) and critical pneumonia (AUC 0.71) independently of all other measured variables after logistic regression analysis. Prognostic accuracy of CRB-65 was significantly improved by adding cortisol levels (combined AUC 0.81 for both endpoints)	(1) No correction for concomitant steroid medication; (2) no controlling for the time point of blood sampling and (3) no testing for adrenal insufficiency	
<b>SupAR</b>	Uusitalo-Seppälä et al. <sup>31</sup>	Patients in the ED with suspected infection	539	The supAR concentrations in all five groups were 4.7, 5.0, 4.4, 4.8 and 7.9 ng mL <sup>-1</sup> , respectively ( $P < 0.001$ ). The levels were significantly higher in non-survivors compared with survivors (8.3 vs. 4.9 ng mL <sup>-1</sup> , $P < 0.001$ ) and in patients with severe sepsis (group 5) compared with those in the other groups (7.9 vs. 4.8 ng mL <sup>-1</sup> , $P < 0.001$ )	Only sepsis patients included	
<b>Triiodothyronine (T3), thyroxine (T4)</b>	Meyer et al. <sup>33</sup>	Critically ill patients in the medical ICU of an University hospital	103	Plasma T3 levels were lower in patients with sepsis as compared with patients with SIRS; circulating thyroid hormone levels measured on admission were not different in survivors and non-survivors and thus, did not give helpful prognostic information	(1) Secondary analysis; (2) no measurement of TSH levels and (3) small sample	
<b>NGAL</b>	Soto et al. <sup>30</sup>	Prospective cohort study, patients admitted from the ED	616	Plasma NGAL is an accurate biomarker for prediction of AKI in patients admitted from the ED. Proposal of a three-grade classification of AKI risk based on plasma NGAL levels	No measurement of other kidney markers	

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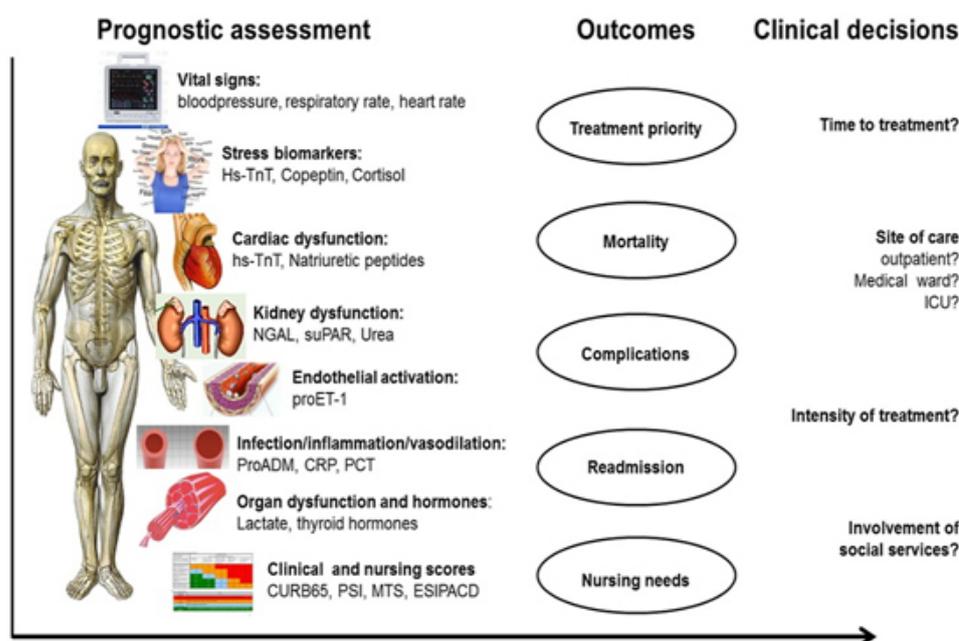
Table 1 (Continued)					
Biomarker (s)	Author, year	Setting, patient population	n	Main findings	Limitations
<b>ProET-1</b>	Schuetz et al. <sup>35</sup>	Consecutive patients with definite diagnosis of CAP	925	ProET-1 levels on admission and changes from baseline to day 3 were significant mortality predictors with adjusted hazard ratios of 10.5 and 28.4. Initial proET-1 levels improved the PSI in reclassification statistics and in c-statistics	(1) Exclusion of some patients with limiting diseases and (2) no assessment of pulmonary artery pressure, which may cause an increase in proET-1 levels independent from sepsis
<b>Lactate</b>	Trzeciak et al. <sup>36</sup>	Consecutive patients with primary or secondary diagnosis of infection and serum lactate	1177	Acute-phase deaths and in-hospital deaths increased linearly with lactate. Initial lactate $\geq 4$ mmol/L was associated with 6-fold higher odds of acute-phase death; however, a lactate level less than 4 mmol/L had little impact on probability of death	(1) Timing of measuring lactate in relation to time that a clinician first identified the presence of an acute infection not available for all; (2) lactate measured by a clinician; (3) no comprehensive clinical information and (4) no estimations of clinicians for probability of death prior to obtaining the lactate measurement
<b>PCT, CRP</b>	Ruiz-Esteban et al. <sup>24</sup>	Patients admitted to a general internal medicine ward, > 18 and < 85 years of age, admitted for less than a week, temperature > 38°C the day before their inclusion	62	Neither PCT nor CRP was able to discriminate infectious (or bacterial) diseases from the other aetiologies as a group, with an AUC of 0.63 (95% CI 0.47–0.79, $P = 0.15$ ) for PCT and 0.61, (95% CI 0.44–0.78, $P = 0.23$ ) for CRP	(1) Issues concerning the cut-off point; (2) low-prognostic value in sepsis; (3) specifically selection of febrile patients and (4) small sample size
<b>PCT</b>	Hicks et al. <sup>26</sup>	Convenience sample, >18-years-old, signs and symptoms of infection, >38°C or blood culture acquisition	66	Higher PCT levels in patients with uncomplicated sepsis compared with patients with no sepsis. Better association with final diagnosis of sepsis when combination of SIRS criteria and PCT levels	(1) Low-risk sepsis cohort and (2) small sample size

ED, emergency department; PCT, procalcitonin; suPAR, soluble urokinase plasminogen activator receptor; AMI, acute myocardial infarction; hs-cTnT, high-sensitivity cardiac troponin T; cTnT, cardiac troponin T; hs-TnT, high-sensitivity troponin T; CAP, community-acquired pneumonia; TSH, thyroid stimulating hormone; NGAL, neutrophil gelatinase-associated lipocalin; AKI, acute kidney injury; PSI, pneumonia severity index; proET-1, proEndothelin-1; CRP, C-reactive protein; SIRS, systemic inflammatory response syndrome.

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**Figure 1:** Multi-functional prognostic assessment including prognostic biomarkers. proADM, proadrenomedullin; PCT, procalcitonin; suPAR, soluble urokinase plasminogen activator receptor; hs-TnT, high-sensitivity troponin T; NGAL, neutrophil gelatinase-associated lipocalin; PSI, pneumonia severity index; proET-1, proEndothelin-1; CRP, C-reactive protein; MTS, Manchester Triage Score; ESI Emergency Severity Index; PACD, post-acute care discharge.

kidney. Different markers have been found to correlate with kidney injury and kidney failure including creatinine, urea and plasma neutrophil gelatinase-associated lipocalin (NGAL). In a recent study, NGAL was able to discriminate patients admitted from the ED into three different categories of acute kidney injury, normal function and transient azotaemia, respectively<sup>30</sup>. Another novel marker of kidney dysfunction is the soluble form of urokinase-type plasminogen activator (suPAR). In patients presenting at the ED with suspected infection, a high suPAR level predicts case fatality and severe sepsis<sup>31</sup>.

Urea is a more traditional marker of kidney dysfunction and an important component of well-established risk scores such as the pneumonia CURB-65 score<sup>32</sup>.

#### Thyroid hormones

During acute disease, the body reacts with the up- and deregulation of the different hormonal systems. Thereby,

it reduces the active thyroid hormones (T3) by blocking the conversion from the less active T4 hormones. This constellation of low T3 and higher T4 hormones is called the low T3 (or low thyroid sick) syndrome and mirrors severity of disease. In an intensive care unit (ICU) study, T3 levels inversely correlated with sepsis severity and in-hospital mortality<sup>33</sup>.

#### Markers of endothelial activation and dysfunction

The endothelium is an important component for the host reaction to acute disease. Different endothelial markers have been found to correlate with severity of disease and outcome. ProEndothelin-1 (proET-1) is one of the precursor hormones of endothelin and a potent vasoconstrictor and vasopressor<sup>34</sup>. In pneumonia patients, proET-1 levels on admission and changes from baseline to day 3 were independent predictors for mortality and ICU admission, and significantly improved the clinical risk scores<sup>35</sup>.

#### Other markers of organ dysfunction

The prognostic value of lactate as a marker for organ dysfunction has been known for a long time. Recently, lactate has emerged as an important sepsis marker which directs early fluid resuscitation (early goal directed therapy)<sup>36</sup>.

#### Conclusion

Despite the promising role of clinical scores and biomarkers from different pathophysiological concepts, no conclusive clinical trial has yet looked at different biomarkers in a large and comprehensive patient population. In addition, it remains unclear whether the use of scores and biomarkers has the potential to improve clinical outcome of patients as randomised trials are largely lacking.

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### Abbreviations list

CRP, C-reactive protein; ED, emergency department; LOS, length of stay; MTS, Manchester Triage Score; NGAL, neutrophil gelatinase-associated lipocalin; NP, natriuretic peptides; PACD, post-acute care discharge; PCT, procalcitonin; proADM, proadrenomedullin; proET-1, proEndothelin-1; SPI, Selbstpflegeindex; suPAR, soluble urokinase plasminogen activator receptor.

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