PART II
ADDITIONAL BIOMARKER STRATEGIES

CHAPTER 8

EARLY IDENTIFICATION OF DISEASE SEVERITY USING BIOMARKERS IN THE EMERGENCY DEPARTMENT

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ABSTRACT

Objective

In the emergency department(ED), it is important to identify patients with sepsis early, in order to start optimal treatment. Risk stratification in the ED is performed with clinical scores SIRS and qSOFA. The objective of this study is to compare the predictive values of SIRS and qSOFA with biomarkers C-reactive protein(CRP), procalcitonin(PCT), proadrenomedullin(proADM), pro-endothelin-1(proET-1) and soluble urokinase-type plasminogen activator receptor(suPAR) for prediction of intensive care unit(ICU) admission and 30-days and 90-days mortality.

Methods

Post-hoc analysis of the HiTEMP study, a multicenter study in a general ED population with fever. Patients were followed-up for 90 days. In all patients, blood samples for biomarker analysis were obtained in the ED. Single-center study, Erasmus University Medical Center, Rotterdam, the Netherlands. All adult patients who visited the ED with fever were eligible. Exclusion criteria were: no written informed consent, pregnancy, solid organ transplant, severe neutropenia, or current chemotherapy, post-operative patients, and moribund patients. Only patients with complete 90-days follow-up were included in analysis.

Results

A total of 353 patients were included in the study. Nine patients were admitted to the ICU, 9 patients died within 30 days, and a total of 13 within 90 days. For ICU admission, clinical scores had similar predictive values as biomarkers, (AUC(95%CI) of SIRS 0.727 (0.542-0.912), qSOFA 0.688 (0.499-0.876), CRP 0.528 (0.322-0.734),PCT 0.570 (0.352 - 0.788), proADM 0.730 (0.614-0.846), proET-1 0.773 (0.660-0.886), suPAR 0.672(0.488-0.857), respectively). For both 30-days and 90-days mortality, biomarkers outperformed clinical scores, (AUC(95%CI) for 30-days mortality: SIRS 0.522 (0.317-0.726), qSOFA 0.518 (0.312-0.723), CRP 0.742 (0.610-0.873), PCT 0.668 (0.481-0.855), proADM 0.836 (0.743-0.930), proET-1 0.945 (0.896-0.993), suPAR 0.842(0.685-1.000), respectively).

Conclusion

Biomarkers proADM, proET-1 and suPAR, and to a lesser extent CRP and PCT were more accurate in predicting mortality than clinical scores SIRS and qSOFA. ProADM, proET-1 and suPAR and clinical scores predicted ICU admission with comparable accuracy. Biomarkers can be used for timely diagnosis of a severe course of disease in sepsis.

INTRODUCTION

Sepsis is a global health problem causing high rates of intensive care unit (ICU) admissions and mortality[1,2].
In the emergency department (ED), patients who are at risk for developing a severe course of disease need to be identified early, so timely treatment can be initiated, and patients will receive optimal sepsis care[3,4].
Sepsis is a multi-system disease, with involvement of different inflammatory pathways, the coagulation system and the endothelial system[5,6]. Currently, physicians in the ED classify disease severity with clinical scores, such as the systemic inflammatory response syndrome (SIRS) criteria and with the quickSOFA (qSOFA) score[3,7]. These clinical scores have fair accuracy for adverse outcome prediction8. However, these clinical scores mainly include vital signs, and have limited predictive value in specific patient groups, such as the elderly[9].
Biomarkers can predict disease severity by indicating the state of activation of pathways in different systems, even before patients have abnormal vital parameters. Procalcitonin (PCT) can be used as a prognostic marker for severity of sepsis in the ED and ICU[10,11]. Indicators of activation of the microvascular system and endothelial dysfunction, mid-regional proadrenomedullin (proADM), pro-endothelin-1 (proET-1) and soluble urokinase-type plasminogen activator receptor (suPAR), a biomarker for activation of inflammatory systems, can predict mortality in patients with community acquired pneumonia and in patients with sepsis[12-16].
Despite the multi-system involvement in sepsis, a comparison of the predictive value of clinical scores and biomarkers of both inflammatory activity and endothelial dysfunction has not been studied extensively in a general ED population.

The aim of this study is to determine and compare the predictive value of clinical scores with single measurements of biomarkers CRP, PCT, proADM, proET-1 and suPAR on ICU admission and all-cause 30-days and 90-days mortality in a general ED population.

METHODS

This study was a post-hoc study of the HiTEMP (Higher diagnostic accuracy and cost-effectiveness using procalcitonin in the treatment of emergency medicine patients with fever) study cohort, which has been described previously[11,17]. In brief, the cohort of this study consists of adult patients who visited the ED of the Erasmus University Medical Center between August 2014 and June 2016 with a temperature of ≥38.2 ˚C/ ≥100.7 ˚F in ED triage.

Study population

All adult febrile patients were eligible for inclusion. All patients gave written informed consent. Pregnant patients, patients with a solid organ transplant, severe neutropenia, or current chemotherapy, post-operative patients (up to 72 hours), and patients with a confirmed surgical diagnosis before ED triage and patients with a life expectancy of less than 24 hours were excluded. In this post-hoc analysis only patients with a complete follow-up were included, to ensure validity of data on mortality.

Study design

In the ED, blood samples were obtained for clinical use and for additional research purposes. Patients were followed up after 30 days by a telephone interview, after 90 days by contacting their general practitioner and with medical chart review.

Outcomes

The primary outcomes of the study were ICU admission within 30 days after ED visit, and mortality within 30 and 90 days after ED visit.

Measurements

In all patients, we calculated a SIRS and qSOFA score. In case of missing values in vital parameters, we set the missing values to a non-divergent value, so the patients would not score an extra point on the clinical score. The assumption was that the triage nurse would have reported all vital parameters if an abnormal value was expected. Furthermore, in all patients, CRP, PCT, proADM, proET-1 and suPAR levels were measured from blood samples obtained in the ED. CRP and PCT measurements were performed on the routine analyzer of the clinical chemistry laboratory (using an electro-chemiluminiscent immunoassay (ECLIA) (Roche diagnostics, Brahms, Henningsdorf, Germany). ProADM and proET-1 measurements were performed on a Kryptor Compact Plus in Thermofisher laboratories, Henningsdorf, Germany. ELISA SuPAR measurements (Virogates, Denmark) were performed in NUTOPI laboratories, Poznan, Poland.

Data analysis

Using vital parameters measured at ED admission, we calculated the SIRS and qSOFA clinical scores. For the primary outcomes, baseline differences and differences in qSOFA, SIRS and biomarkers were analyzed using the Fisher's exact test for dichotomous variables, with the independent T-test for normally distributed continuous variables, and with the Mann-Whitney U test for non-normally distributed variables. For the outcomes ICU admission and 30-days and 90-days mortality, receiver operator characteristic (ROC) curves were used to calculate the area under the curve (AUC) for each biomarker and the SIRS and qSOFA severity scores. We calculated the optimal cut-off for each biomarker with Youden's index[18]. The optimal cut-offs were used to calculate sensitivity and specificity for the primary outcomes, binomial proportion confidence intervals (CIs) were calculated using the using the Clopper-Pearson method. All statistical tests were two-sided with a significance level of 0.05, unless otherwise specified. Data-analysis was performed with the statistical package for the social sciences (SPSS), version 23, IBM cooperation.

RESULTS

Of a total of 449 patients who were included, 9 patients did not give consent for additional studies, there were insufficient additional blood samples to determine all biomarkers from 68 patients, and 19 patients did not have complete 90-days follow-up. This resulted in a total number of 353 patients who were included in the analysis. Of the total cohort, 9 (3%) patients were admitted to the ICU within 30 days, of whom 8 within 72 hours after ED visit. Nine patients (3%) died within 30 days of their ED visit. Four patients died within the period of 31 and 90 days after ED visit, making the total of patients who died within 90 days 13(4%).

Baseline characteristics

Baseline characteristics are reported in table 1. In 108 patients, no respiratory rate was available, and in 2 patients no blood pressure was available because these data were not recorded in ED triage. Between patients who were admitted to the ICU, there were statistically significant differences in baseline characteristics for age ($p = 0.03$), diabetes as comorbidity ($p = 0.05$) and respiratory rate ($n = 237$) ($p < 0.001$). Between 30-days survivors and non-survivors, there were statistically significant differences in age, ($p = 0.01$), sex ($p = 0.04$), malignancy as comorbidity ($p = 0.02$) and respiratory rate ($n = 237$) ($p = 0.00$). Between 90-days survivors and non-survivors, there were statistically significant differences in age ($p = 0.01$), sex ($p = 0.03$) and malignancy as comorbidity ($p = 0.01$) (supplement 1).

Table 1. Baseline characteristics

		All (n = 353)	ICU admissions (n = 9)	30-days non-survivors (n = 9)	90-days non-survivors (n = 13)
Demographic characteristics					
Age	median [IQR]	59 [41 - 69]	68 [60 - 76]	75 [61 - 77]	72 [54 - 77]
Female sex	n (%)	163 (46)	6 (67)	1 (11)	2 (15)
Vital signs at presentation					
Temperature	median [IQR]	38.8 [38.4 - 39.2]	38.8 [38.4 - 39.5]	38.6 [38.5 - 39.0]	38.6 [38.4 - 38.9]
Heart rate	median [IQR]	105 [92 - 120]	113 [98 - 122]	110 [89 - 126]	110 [95 - 126]
Systolic bloodpressure	median [IQR] n = 351	130 [119 - 145]	127 [107 - 146]	121 [114 - 126]	121 [113 - 139]
Diastolic bloodpressure	median [IQR] n = 351	76 [67 - 85]	85 [60 - 94]	80 [72 - 86]	78 [64 - 84]
Respiratory rate	median [IQR] n = 245	20 [16 - 25]	28 [23 - 40] (n = 8)	32 [21 - 40] (n = 5)	25 [19 - 38](n = 8)
Comorbidity					
Malignancy	n (%)	73 (21)	3 (33)	5 (56)	7 (54)
Diabetes mellitus	n (%)	59 (17)	4 (44)	2 (22)	2 (15)
HIV	n (%)	11 (3)	0 (0)	0 (0)	0 (0)
Clinical scores					
SIRS	median [IQR]	3 [2 -3]	3 [3 - 4]	3 [2 - 3]	3 [2 - 3]
qSOFA	median [IQR]	0 [0-1]	1 [0 - 1]	0 [0 - 1]	0 [0 - 1]
Biomarkers					
CRP in mg/L	median [IQR]	61 [18 - 143]	101 [17 - 155]	129 [96 - 229]	122 [79 - 198]
PCT in mcg/L	median [IQR]	0.23 [0.09 - 0.82]	0.31 [0.08 - 10.09]	1.21 [0.25 - 1.76]	1.21 [0.47 - 2.33]
ProADM in nmol/L	median [IQR]	0.99 [0.70 - 1.49]	1.41 [1.20 - 2.00]	2.04 [1.42 - 3.26]	2.21 [1.65 - 3.26]
ProET-1 in pmol/L	median [IQR]	90.6 [63.6 - 127.4]	139.2 [100.5 - 239.3]	301.9 [179.1 - 573.0]	255.1 [177.0 - 485.9]
suPAR in ng/mL	median [IQR]	3.73 [2.91 - 5.46]	5.02 [3.21 - 10.39]	9.77 [5.96 - 13.69]	9.77 [5.04 - 13.69]
Etiology of fever					
Confirmed bacterial infection	n (%)	122 (35)	4 (44)	3 (33)	6 (46)
Confirmed viral infection	n (%)	28 (8)	1 (11)	0 (0)	0 (0)
Confirmed bacteremia	n (%)	64 (18)	3 (33)	1 (11)	3 (23)
Initial ED treatment					
Antibiotics in ED because of SIRS	n (%)	167 (47)	7 (78)	6 (67)	8 (62)
Antibiotic therapy started	n (%)	252 (72)	7 (78)	8 (89)	12 (92)
Disposition					
Hospital admission	n (%)	259 (73)	9 (100)	8 (89)	12 (92)
ICU admission	n (%)	9 (3)	9 (100)	3 (33)	3 (23)
30-days mortality	n (%)	9 (3)	3 (33)	9 (100)	9 (69)
90-days mortality	n (%)	13 (4)	3 (33)	9 (100)	13 (100)

CRP: C-reactive protein, ED: emergency department, HIV: human immunodeficiency virus, ICU: intensive care unit, IQR: interquartile range, PCT: procalcitonin, proADM: proadrenomedullin, proET-1: pro-endothelin-1, qSOFA: quick SOFA, SIRS: systemic inflammatory response syndrome, suPAR: soluble urokinase-type plasminogen activator receptor.

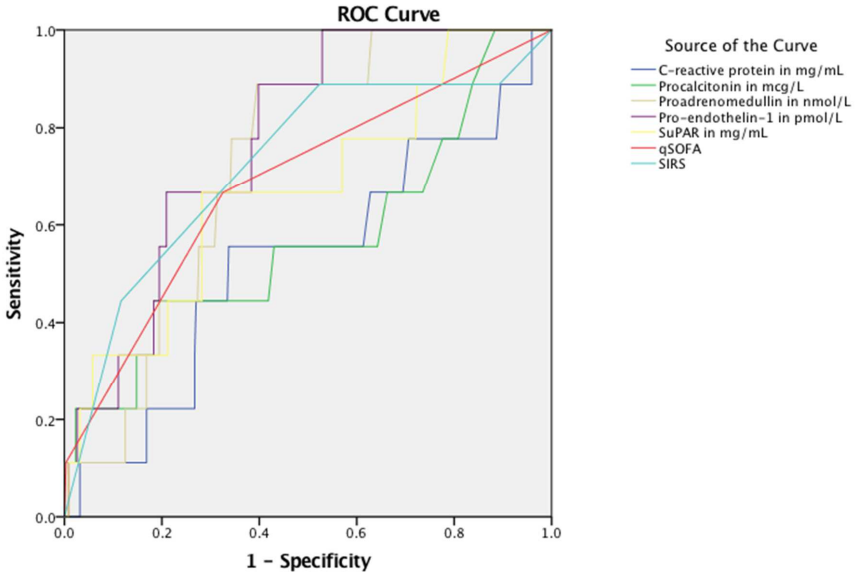
Biomarkers

Patients who were admitted to the ICU had significantly higher levels of proADM, proET-1, SIRS score, and a qSOFA score in the ED than patients who were not admitted to the ICU (proADM ($p = 0.02$), proET-1 ($p = 0.02$), SIRS (0.01), qSOFA ($p = 0.01$)). Patients who died within 30 days after ED visit, had significantly higher levels of CRP, proADM, proET-1 and suPAR than survivors (CRP ($p = 0.02$), proADM ($p = 0.01$), proET-1 ($p < 0.001$), suPAR ($p < 0.001$)).

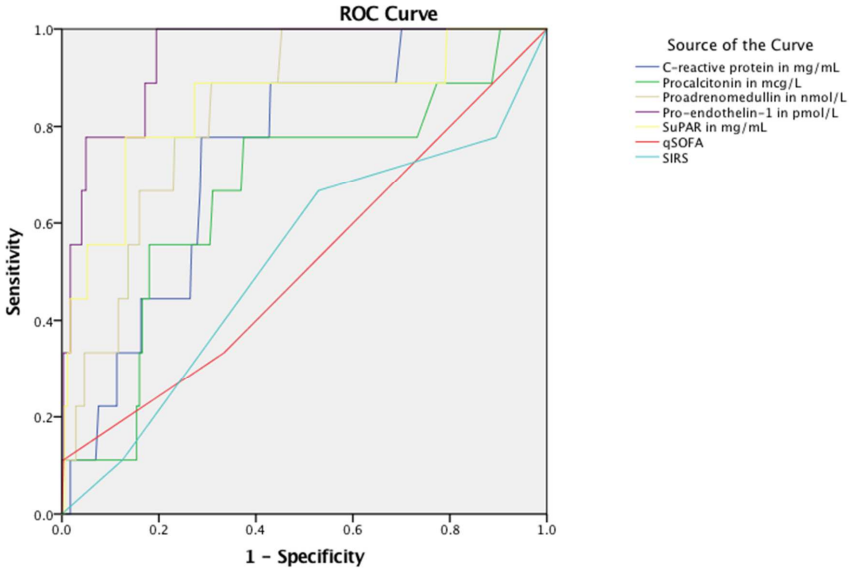
Patients who died within 90 days after ED visit, had significantly higher levels of PCT, proADM, proET-1 and suPAR than survivors (CRP ($p = 0.05$), PCT ($p = 0.01$), proADM ($p < 0.001$), proET-1 ($p < 0.001$), suPAR ($p < 0.001$) (supplement 1)). The ROC curves of the primary endpoints are reported in figure 1. For ICU admission, proADM, proET-1, and SIRS and qSOFA scores had statistically significant predictive values. For both 30-days and 90-days mortality, CRP, PCT, proADM, proET-1 and suPAR had statistically significant predictive values. The AUCs of biomarkers and clinical scores are reported in table 2.

Figure 1. ROC curves of clinical scores and biomarkers for primary outcomes

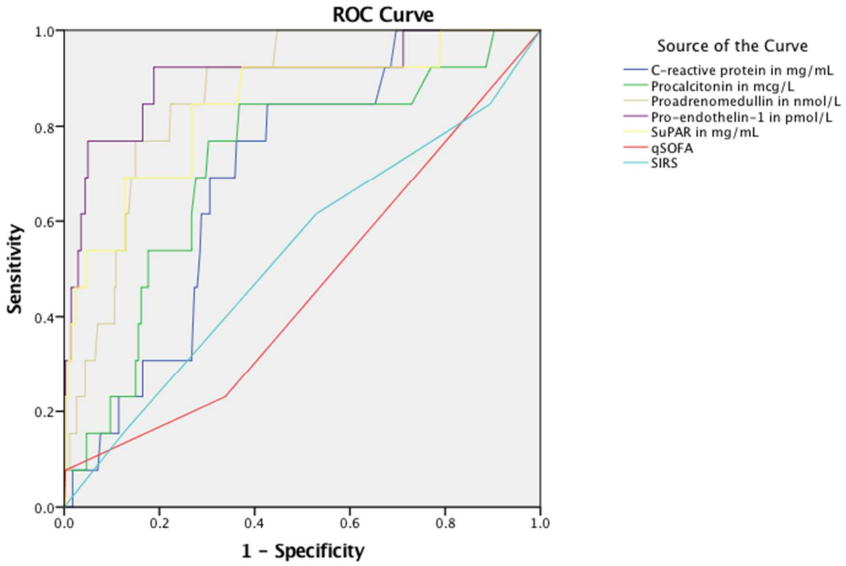
a. ROC curve of clinical scores and biomarkers for intensive care unit admission



b. ROC curve of clinical scores and biomarkers for 30-days mortality



c. ROC curve of clinical scores and biomarkers for 90-days mortality



Areas under curve are reported in table 2.

qSOFA: quick SOFA, ROC: Receiver operator curve, SIRS: systemic inflammatory response syndrome, ROC curve: Receiver operator characteristic curve, suPAR: soluble urokinase-type plasminogen activator receptor.

Optimal cut-offs and Youden's index for ICU admission, 30-days and 90-days mortality of CRP, PCT, proADM, proET-1, suPAR and SIRS and qSOFA criteria are reported in table 2.

Sensitivity and specificity of clinical scores and biomarkers for primary outcomes are reported in table 2. For ICU admission within 30 days after ED visit, clinical scores had predictive values that were comparable to the predictive values of biomarkers proADM, proET-1 and suPAR, and to a lesser extent CRP and PCT. For both 30-days and 90-days mortality, all biomarkers had higher predictive values than clinical scores.

Table 2. Analyses of predictive values of biomarkers and clinical scores for primary outcomes

ICU admission within 30 days (n = 353)									
Predictors	AUC	(95% CI)	Youden's index	Optimal cut-off		Sensitivity	(95% CI)	Specificity	(95% CI)
Biomarkers									
CRP	0.528	(0.322 - 0.734)	0.22	101	mg/ml	0.56	(0.21 - 0.86)	0.66	(0.61 - 0.71)
PCT	0.570	(0.352 - 0.788)	0.26	1.21	mg/ml	0.44	(0.14 - 0.79)	0.82	(0.77 - 0.86)
proADM	0.730	(0.614 - 0.846)	0.49	1.12	mg/ml	0.89	(0.52 - 1.00)	0.60	(0.55 - 0.66)
proET-1	0.773	(0.660 - 0.886)	0.49	99.6	mg/ml	0.89	(0.52 - 1.00)	0.60	(0.55 - 0.65)
suPAR	0.672	(0.488 - 0.857)	0.39	4.96	mg/ml	0.67	(0.30 - 0.93)	0.72	(0.67 - 0.77)
Clinical scores									
SIRS	0.727	(0.542 - 0.912)	0.37	3	criteria	0.89	(0.52 - 1.00)	0.48	(0.43 - 0.53)
qSOFA	0.688	(0.499 - 0.876)	0.34	1	criterion	0.67	(0.30 - 0.93)	0.67	(0.62 - 0.72)
30-days mortality (n = 353)									
Predictors	AUC	(95% CI)	Youden's index	Optimal cut-off		Sensitivity	(95% CI)	Specificity	(95% CI)
Biomarkers									
CRP	0.742	(0.610 - 0.873)	0.49	120	mg/ml	0.78	(0.40 - 0.97)	0.71	(0.66 - 0.76)
PCT	0.668	(0.481 - 0.855)	0.40	0.41	mg/ml	0.78	(0.40 - 0.97)	0.63	(0.57 - 0.68)
proADM	0.836	(0.743 - 0.930)	0.58	1.33	mg/ml	0.89	(0.52 - 1.00)	0.69	(0.64 - 0.74)
proET-1	0.945	(0.896 - 0.993)	0.81	136.3	mg/ml	1.00	(0.66)*	0.81	(0.76 - 0.85)
suPAR	0.842	(0.685 - 1.000)	0.65	6.90	mg/ml	0.78	(0.40 - 0.97)	0.87	(0.83 - 0.90)
Clinical scores									
SIRS	0.522	(0.317 - 0.726)	0.11	3	criteria	0.67	(0.30 - 0.93)	0.47	(0.42 - 0.52)
qSOFA	0.518	(0.312 - 0.723)	0.14	2	criteria	0.11	(0.00 - 0.48)	0.99	(0.98 - 1.00)
90-days mortality (n = 353)									
Predictors	AUC	(95% CI)	Youden's index	Optimal cut-off		Sensitivity	(95% CI)	Specificity	(95% CI)
Biomarkers									
CRP	0.698	(0.587 - 0.809)	0.42	71	mg/ml	0.85	(0.55 - 0.98)	0.57	(0.52 - 0.63)
PCT	0.720	(0.580 - 0.861)	0.48	0.41	mg/ml	0.85	(0.55 - 0.98)	0.63	(0.58 - 0.68)
proADM	0.866	(0.796 - 0.936)	0.62	1.33	mg/ml	0.92	(0.64 - 1.00)	0.70	(0.65 - 0.75)
proET-1	0.903	(0.800 - 1.000)	0.74	136.3	mg/ml	0.92	(0.64 - 1.00)	0.81	(0.77 - 0.85)
suPAR	0.842	(0.722 - 0.962)	0.58	5.00	mg/ml	0.85	(0.55 - 0.98)	0.73	(0.68 - 0.78)
Clinical scores									
SIRS	0.530	(0.361 - 0.698)	0.09	3	criteria	0.62	(0.32 - 0.86)	0.47	(0.42 - 0.53)
qSOFA	0.459	(0.297 - 0.621)	0.07	2	criteria	0.08	(0.00 - 0.36)	1.00	(0.98 - 1.00)

* one-sided 97.5% confidence interval. AUC: area under curve, CI: confidence interval, CRP: C-reactive protein, ICU: Intensive care unit, PCT: procalcitonin, proADM: proadrenomedullin, proET-1: proendothelin-1, qSOFA: quick SOFA score, SIRS: systemic inflammatory response syndrome, suPAR: soluble urokinase-type plasminogen activator receptor

DISCUSSION

The results of our study show that biomarkers proADM, proET-1 and suPAR predicted ICU admission, 30-days and 90-days mortality with good to excellent accuracy in a general ED population of patients with fever, and outperformed clinical scores in predicting mortality.

Our findings are in line with several studies on the biomarkers PCT, proADM, proET-1 and suPAR, that showed fair prognostic accuracy for ICU admission and in-hospital or 30-days mortality[10,12,16]. A meta-analysis of the predictive value of proADM in ED patients with community acquired pneumonia yielded a combined AUC of 0.76 (95 % CI, 0.72-0.80)19.

For both clinical scores SIRS and qSOFA, we found a lower predictive value for both 30-days and 90-days mortality than a recent study by Seymour et al. In the study by Seymour et al., the qSOFA score and SIRS score identified in-hospital mortality in patients with a suspected infection with an AUC of 0.76 (0.75 – 0.77) for SIRS and 0.81 (95% CI 0.80 – 0.82) for qSOFA, respectively8. Singer et al reported an AUC of qSOFA for in-hospital mortality of 0.76 (95% CI 0.73 – 0.78), in a retrospective study of a general ED population20. Contrary to these studies, our results showed that SIRS and qSOFA did not predict mortality, with a AUC for 30-days mortality for SIRS of 0.522 (95% CI 0.317 – 0.726) and for qSOFA of 0.518 (95% CI 0.312 – 0.723). These differences may be attributable to a selection bias in our study; severely ill patients who could not give written informed consent were not included. Yet, lower accuracy of qSOFA was also found in geriatric patients with suspected fever[9]. In our study, the accuracy of both SIRS and qSOFA for ICU admission was higher than the accuracy for 30-days and 90-days mortality. However, abnormal clinical scores may have prompted physicians to admit specific patients to the ICU. Because this potential influence on clinical decision making, clinical scores may have had a confounding role in the prediction of ICU admission in this study.

The difference between clinical scores and biomarkers is that biomarkers are indicators of specific activated systems and inflammatory pathways in sepsis, contrary to clinical scores, which only represent the combined end-organ effects of all activated systems in sepsis. End-organ effects, such as increased respiratory rate, tachycardia and hypotension are compensatory mechanisms, which are activated to counter organ dysfunction. Patients with sepsis who still have normal vital parameters cannot be identified using a clinical score. However, because activation of specific activated systems and inflammatory pathways can be measured using biomarkers, patients with severe course of disease can be detected earlier. In short, clinical scores are lagging behind in identifying critically ill patients. This is a crucial difference. When patients with severe disease are identified earlier, interventions can be started earlier, and end-organ failure and subsequent adverse events may be prevented.

Sepsis is a complex syndrome, and has no uniform manifestation[7]. Therefore, bio-

marker guided treatment in sepsis can be effective in selected groups of patients, but inaccurate and ineffective in a general, real-life population. In cardiology, myocardial infarction is ruled out based on measurements of a single biomarker, high sensitive troponin T, with an accuracy of >99%[21]. Consequently, troponin guided risk assessment and treatment is incorporated in international treatment guidelines[22,23]. Likewise, using the biomarkers in this study, the activity of specific pathophysiologic pathways can be identified with high accuracy. To effectively treat patients based on risk stratification tools, the accuracy of these tools needs to be unequivocal. The findings in this study are based on a small number of patients with adverse events. Hence, these findings have to be validated in a larger cohort in order to start biomarker-guided interventions.
We hypothesize that combining both biomarkers for severity of disease with clinical scores in a combined prediction model will yield a higher accuracy for predicting disease severity than individual biomarkers or clinical scores. Therefore, we suggest a combined prediction model of both the qSOFA clinical score and biomarkers CRP, PCT, proADM, proET-1 and suPAR for identifying patients who are at risk for both ICU admission and 30-days and 90-days mortality. This model needs to be validated in larger populations to determine if interventional studies are feasible. If feasible, implementation of this strategy can result in timely and accurate identification of patients who are at risk for adverse events. Consequently, end-organ failure and subsequent adverse events can be prevented, unnecessary hospital admissions and ICU admissions can be reduced, and critically ill patients receive optimal care.

Limitations
Fever as inclusion criterion was used to select patients with a suspected infection objectively, and to make the results generalizable for a real-life ED population. However, not all patients with suspected infectious diseases who visit the ED have fever. Additionally, patients in this study were required to give written informed consent in the ED. Severely ill patients with reduced consciousness were therefore not included. Hence, these factors created a selection bias in our cohort, and consequently, results of this study cannot be generalized to all ED patients with suspected infections. The respiratory rate was not reported in several patients. Because this variable is part of both the qSOFA and SIRS scores, we made the assumption that these parameters were non-divergent in the patients with missing values. If there were abnormal variables in these patients, the accuracy of the clinical scores could deviate from our results. Our population had a low number of patients who were admitted to the ICU and who had 30-days and 90-days mortality. Therefore, our results may be an overestimation of the predictive value due to the small number of patients. This study is therefore intended as a proof of concept that biomarkers can be used as early predictive indicators for mortality in a general ED population. Validation of the accuracy of the proposed model is required.

CONCLUSION

In our study, we showed that in a general ED population, biomarkers proADM, pro-ET-1 and suPAR, and to a lesser extent CRP and PCT were more accurate in predicting 30-days and 90-days mortality than clinical scores SIRS and qSOFA. ProADM, proET-1 and suPAR and clinical scores predicted ICU admission with comparable accuracy. Biomarkers can be used for timely diagnosis of a severe course of disease in sepsis.

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Supplement 1. Analysis of differences between baseline and predictor variables between groups per primary outcome

		ICU admission			30-days mortality			90-days mortality		
		Non-ICU admissions (n = 344)	ICU admissions (n = 9)	p-value	30-days survivors (n = 344)	30-days non-survivors (n = 9)	p-value	90-days survivors (n = 340)	90-days non-survivors (n = 13)	p-value
Demographic characteristics										
Age	median [IQR]	58 [40 - 69]	68 [60 - 76]	p = 0.03*	58 [40 - 69]	75 [61 - 77]	p = 0.01*	58 [39 - 69]	72 [54 - 77]	p = 0.01*
Female sex	n (%)	157 (46)	6 (67)	p = 0.31	162 (47)	1 (11)	p = 0.04	161 (47)	2 (15)	p = 0.03
Vital signs at presentation										
Temperature	median [IQR]	38.8 [38.4 - 39.2]	38.8 [38.4 - 39.5]	p = 0.81	38.8 [38.4 - 39.2]	38.6 [38.5 - 39.0]	p = 0.51*	38.8 [38.4 - 39.2]	38.6 [38.4 - 38.9]	p = 0.12*
Heart rate	median [IQR]	105 [92 - 120]	113 [98 - 122]	p = 0.61	105 [92 - 119]	110 [89 - 126]	p = 0.57	105 [92 - 119]	110 [95 - 126]	p = 0.47
Systolic bloodpressu	median [IQR]	130 [119 - 145] (n = 342)	127 [107 - 146]	p = 0.43	130 [119 - 145] (n = 342)	121 [114 - 126]	p = 0.44*	130 [120 - 146] (n = 338)	121 [113 - 139]	p = 0.64
Diastolic bloodpressu	median [IQR]	76 [67 - 85] (n = 342)	85 [60 - 94]	p = 0.57	76 [67 - 85] (n = 342)	80 [72 - 86]	p = 0.13	76 [67 - 85] (n = 338)	78 [64 - 84]	p = 0.83
Respiratory rate	median [IQR]	20 [16 - 24] (n = 237)	28 [23 - 40] (n = 8)	p < 0.001	20 [16 - 25] (n = 240)	32 [21 - 40] (n = 5)	p = 0.00	20 [16 - 25] (n = 237)	25 [19 - 38](n = 8)	p = 0.07*
Comorbidity										
Malignancy	n (%)	70 (20)	3 (33)	p = 0.40	68 (20)	5 (56)	p = 0.02	66 (19)	7 (54)	p = 0.01
Diabetes mellitus	n (%)	55 (16)	4 (44)	p = 0.05	57 (17)	2 (22)	p = 0.65	57 (17)	2 (15)	p = 1.00
HIV	n (%)	11 (3)	0 (0)	p = 1.00	11 (3)	0 (0)	p = 1.00	11 (3)	0 (0)	p = 1.00
Clinical scores										
SIRS	median [IQR]	3 [2 - 3]	3 [3 - 4]	p = 0.02	3 [2 - 3]	3 [2 - 3]	p = 0.98	3 [2 - 3]	3 [2 - 3]	p = 0.78
qSOFA	median [IQR]	1 [0 - 1]	1 [0 - 1]	p = 0.01	0 [0 -1]	0 [0 - 1]	p = 0.83*	0 [0 - 1]	0 [0 - 1]	p = 0.81
Biomarkers										
CRP in mg/L	median [IQR]	61 [18 - 143]	101 [17 - 155]	p = 0.68	59 [17 - 141]	129 [96 - 229]	p = 0.02	59 [17 - 142]	122 [79 - 198]	p = 0.05
PCT in mcg/L	median [IQR]	0.23 [0.09 - 0.77]	0.31 [0.08 - 10.09]	p = 0.47*	0.22 [0.09 - 0.75]	1.21 [0.25 - 1.76]	p = 0.09*	0.22 [0.09 - 0.74]	1.21 [0.47 - 2.33]	p = 0.01*
ProADM in nmol/L	median [IQR]	0.97 [0.68 - 1.48]	1.41 [1.20 - 2.00]	p = 0.02*	0.97 [0.68 - 1.44]	2.04 [1.42 - 3.26]	p = 0.01*	0.96 [0.68 - 1.42]	2.21 [1.65 - 3.26]	p < 0.001*
ProET-1 in pmol/L	median [IQR]	89.3 [63.0 - 124.4]	139.2 [100.5 - 239.3]	p = 0.02	89.1 [63.0 - 122.2]	301.9 [179.1 - 573.0]	p <0.001*	89.0 [62.7 - 121.1]	255.1 [177.0 - 485.9]	p < 0.001*
suPAR in ng/mL	median [IQR]	3.73 [2.89 - 5.43]	5.02 [3.21 - 10.39]	p = 0.08*	3.71 [2.89 - 5.29]	9.77 [5.96 - 13.69]	p <0.001*	3.69 [2.89 - 5.24]	9.77 [5.04 - 13.69]	p < 0.001*

P-values were calculated using the Fisher's exact test for dichotomous variables and using independent sample T-test for continouos variables, when a Mann-WIthney U test was used because variables were not normally distributed, this was indicated with an *.