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Are admission procalcitonin levels universal mortality predictors across different medical emergency patient populations? Results from the multi-national, prospective, observational TRIAGE study

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Abstract

Background: Procalcitonin (PCT), an inflammatory blood biomarker, is well studied in infectious diseases. Its prognostic value in unselected emergency department (ED) patients remains yet undefined. Herein, we investigated association of admission PCT levels and mortality in a large, international-multicenter ED patient cohort.
Methods: We prospectively enrolled 6970 unselected, consecutive, adult, medical patients seeking ED care in three tertiary-care hospitals in Switzerland, France and the USA. We used multivariable logistic regression models to examine association of admission PCT levels (as a continuous predictor and across cut-offs) and 30-day mortality. We also investigated subgroup effects by main diagnosis, comorbidities and clinical features at presentation.
Results: During the 30-day follow-up, 328 (4.7%) participants died. Mortality increased stepwise within higher PCT cut-offs (0.05, 0.1, 0.25, 0.5 ng/mL) from 1%, 3%, 7%, 13% to 15%, respectively. This association was also confirmed in a fully-adjusted model including age, gender, main symptom, main diagnosis and vital parameters on admission. Receiver operating characteristic (ROC) curve analysis showed that PCT differentiated well between survivors and non-survivors in the overall cohort (area under ROC curve [AUC] 0.75) with best results for patient with metabolic (AUC: 0.85) and cardiovascular disease (AUC: 0.82). Addition of PCT also improved the prognostic accuracy of the quick sequential organ failure assessment (qSOFA) score from an AUC of from 0.61 to 0.76 ($p < 0.001$). Results were similar for other secondary endpoints including intensive care unit (ICU) admission and hospital readmission.
Conclusions: In this large and heterogenous medical ED patient cohort, admission PCT was a strong and independent outcome predictor for 30-day mortality across different medical diagnoses independent of underlying infection. PCT may help to improve risk stratification in unselected medical ED patients.

Keywords: emergency department; outcome; procalcitonin; risk stratification.

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Introduction

Early risk stratification in the emergency department (ED) becomes a higher priority as crowding increases due to higher number of patient visits. To focus on patients with highest urgency may have a positive impact on patient outcomes. Conversely, identification of low risk patients who can potentially be treated as outpatients in the general physician office may also help to reduce costs and overcrowding. Although the clinical presentation of patients may help to assess risk, accurate prediction based on clinical grounds only is challenging. Prognostic biomarkers

have been studied as predictor of adverse clinical outcome including cardiac markers, renal markers and inflammatory markers among others. The advantage of such biomarkers is a fast and objective information about a patients prognosis which may add to clinical parameters in the risk stratification of patients [1, 2].

Among these inflammatory markers, procalcitonin (PCT) is helpful for the diagnosis of infections and to guide antibiotic therapy [3–8]. PCT increases markedly within 6 h in response to bacterial sepsis and decreases once a patient recovers from infection. Also, PCT remains relatively low in viral infections. Milder elevations of PCT may be observed in non-infectious diseases such as congestive heart failure, cardiogenic shock, myocardial infarction, or stroke [9–13]. In these diseases, more pronounced elevations were associated with adverse prognosis in patients and PCT was therefore suggested to be a prognostic marker of cardiovascular disease. However, there is insufficient data to support the use of PCT in general medical emergency patients.

Herein, we investigated association of admission PCT levels with mortality and other adverse outcomes in a large, international multicenter ED patient cohort.

Materials and methods

Research aim and outcome measures

The aim of this analysis was to investigate the association of admission PCT level and adverse clinical outcome in ED patients depending on their main diagnosis and comorbidities.

The primary endpoint for this analysis was 30-day mortality. Secondary endpoints were intensive care unit (ICU) admission, in-hospital mortality (defined as not surviving to hospital discharge) and rehospitalization for any reason.

Study design

This analysis includes all patients from a previous multi-national, prospective, observational cohort study (TRIAGE study) [2]. In brief, from March 2013 to October 2014, we prospectively included consecutive medical patients presenting with a medical urgency at three tertiary care hospital in Aarau (Switzerland), Paris (France), and Clearwater (Florida, USA). We tested the hypothesis that the addition of prognostic blood markers from distinct biological pathways would improve risk stratification and initial triage of patients at an early stage of hospital admission, namely in the ED. As an observational quality control study, the Institutional Review Boards of the three hospitals approved the study and waived the need for individual informed consent (Ethikkommission Kanton Aargau, EK 2012/059). The study was registered (http://www.clinicaltrials.gov/ct2/show/NCT01768494). A study protocol and more detailed information about design have been published previously [14].

Patient sample

Inclusion criteria were adult medical patients in whom an initial blood draw was done as part of the routine ED assessment. We excluded surgical and pediatric patients, but had no other exclusion criteria. All patients seeking ED care for medical health issues that did meet our inclusion criteria at one of the participating hospital EDs were consecutively included. A total of 78.2% (n = 5577) of all included patients were finally admitted to the hospital.

Data collection and processing

Upon ED admission, all participants provided a thorough medical history and underwent a physical examination with measurement of vital signs and laboratory assessment with collection of left over blood samples. The admission PCT levels were measured as part of the study protocol in all patients in retrospect (batch analysis). We also recorded main presenting clinical symptoms and complaints, socio-demographics and comorbidities. Signs of organ failure or sepsis was assessed by the quick sepsis-related organ failure score in retrospect (qSOFA) [15]. All information was entered into a case report form and stored in a centralized, password secured databank (SecuTrial).

Throughout the hospital stay, physicians, nurses and social care workers managed patients in accordance to hospital guidelines according to the underlying medical condition and independent of the research team. All hospital survivors were contacted by telephone interview 30 days after hospital admission using a predefined questionnaire to assess vital and functional status, and clinical outcomes.

Statistical analysis

We used descriptive statistics including mean with standard deviation (SD), median with interquartile range (IQR) and frequencies to describe the populations, as appropriate. Based on the initial PCT concentration we calculated the risk for five individual groups within different cut-offs similar to the cut-offs proposed by Muller et al. [16] with cut-offs of 0.05, 0.1, 0.25 and 0.5 ng/mL. We investigated the association of PCT levels and primary and secondary endpoints in multivariate logistic regression analyses and report odds ratios (OR) and 95% confidence intervals (CI) for each group. We adjusted the model for age, gender, main symptom at admission, main diagnosis at discharge and vital parameters at admission. We assessed discrimination by using area under the receiver operating characteristics curve analysis (AUC) for the whole cohort and for selected subgroups. Particularly, we repeated analyses in predefined subgroups stratified by main medical diagnoses, younger and older patients, temperature and signs of organ failure or sepsis assessed by quick sepsis related organ failure score (qSOFA) and performed forest plot.

Tests were two-tailed and carried out at 5% significance levels. Analyses were performed with Stata 12.1 (Stata Corp., College Station, TX, USA).

Results

Patient population

We included 6970 patients (Switzerland, n = 4553; France, n = 1418; USA, n = 999) with completed 30-day follow-up information regarding primary and secondary endpoints. There were 53.4% male patients and the median age was 62 years (interquartile range: 46–76). Main acute medical conditions, causing ED admission, were cardiovascular diseases in 23.5%, neurological diseases in 22.1%, acute infections in 14.7%, gastrointestinal diseases in 13.8% and metabolic disease in 2.7%. There was a high burden of comorbidities in the overall cohort. Patient characteristics overall and stratified by PCT group are shown in Table 1.

Primary outcome: association of PCT and mortality

In the cohort, a total of 328 patients died within 30 days of admission. A stepwise increase in mortality rate from 0.9% to 14.7% was observed with increasing PCT levels across predefined cut-off ranges (0.00–0.05, 0.05–0.1, 0.01–0.25 and above 0.5 ng/mL) (Table 2). This was also confirmed in univariate and multivariate logistic regression in the fully adjusted logistic regression model including age, gender, main diagnosis, comorbidities and vital signs. Association of higher PCT levels and 30-day mortality remained significant with an OR of 7.31 (95% CI: 3.62–14.75, $p < 0.001$) for the highest PCT group (>0.5 ng/mL) as compared to the reference group (<0.05 ng/mL). We found an acceptable goodness of fit for our model with a Hosmer-Lemeshow χ^2 of 9.05.

Kaplan-Meier curves show a stepwise increase in mortality with PCT levels (Figure 1). We further investigated the association of PCT and mortality using higher cut-offs of <1, 1–2, 2–10, >10 ng/mL and found again a stepwise increase in mortality (Supplemental Data, Figure 1). The concentration of PCT among survivors and non-survivors across different medical conditions are shown in the Supplemental Data, Figure 2.

PCT also showed good discrimination of survivors and non-survivors with an AUC of 0.75 for 30-day mortality in the total cohort. We further explored whether the prognostic accuracy of PCT would change across different subgroups in regard to AUCs. We found highest discriminatory values in patients with metabolic disease (AUC: 0.85) and in those with cardiovascular disease as main diagnosis (AUC: 0.82), followed by patients with infectious diseases (ACU: 0.72) (Figure 2). Further analysis revealed better discrimination in younger patients (<70 years of age) (AUC of 0.76 vs. 0.71 for older patients), in patients with no fever at ED admission (AUC: 0.76 vs. 0.71) and in patients without signs of organ failure/sepsis defined by the qSOFA score <2 points (AUC: 0.76 vs. 0.65).

We also investigated whether additiona of PCT to qSOFA would increase the prognostic potential of qSOFA in this patient population by calculating a combined logistic regression model. Addition of PCT improved the AUC of qSOFA from 0.61 to 0.76 ($p < 0.001$).

Association of PCT and secondary outcome

Similar results were found for secondary outcomes within 30 days: 186 (2.7%) patients died during the hospital stay, 449 (6.4%) were admitted to the ICU and 580 (8.3%) were hospitalized after hospital discharge within 30 days. The numbers of primary and secondary outcomes by main diagnosis are shown in the Supplemental Data, Table 1.

PCT showed a significant association in the fully adjusted logistic regression model for inhospital mortality with an OR of 10.34 (95% CI: 3.59–29.8, $p < 0.001$) for patients with an admission PCT of >0.5 ng/mL. Similar results were found for ICU admission with an OR of 2.33 (95% CI: 1.5–3.63, $p < 0.001$) for patients with PCT >0.5 ng/mL. For rehospitalization after hospital discharge, associations were only significant in the univariable model, but not in multivariable analysis (OR: 1.4, 95% CI: 0.94–2.1, $p = 0.098$, see Table 2).

Discussion

This first study investigating the prognostic value of PCT for risk stratification in an unselected medical ED patient cohort has three key findings. First, we found a strong association of PCT and adverse clinical outcome, particularly mortality within 30 days and within the hospital stay. Second, this association was independent of other clinical parameters available upon ED presentation of patients including age, gender, main symptom, main diagnosis, comorbidities and vital parameters. Third, we found a high discriminative power for 30-day mortality of PCT for the total cohort with best performance values for metabolic and cardiovascular disease. This study thus proposes PCT as a general prognostic marker in unselected ED patients independent of underlying infections.

Table 1: Patient characteristics overall and stratified by PCT group.

	Total cohort	By PCT group, ng/mL					p-Value
		0–0.05	0.05–0.1	0.1–0.25	0.25–0.5	>0.5	
Number of patients	**n=6970**	**n=1095**	**n=3418**	**n=1508**	**n=393**	**n=556**	
Socio-demographic							
Age, median (IQR)	62 (46, 76)	49 (33, 67)	61 (46, 76)	67 (53, 79)	69 (56, 78)	68 (54, 78)	<0.001
Male gender, n (%)	3715 (53.4%)	450 (%)	1816 (%)	883 (%)	252 (%)	314 (%)	<0.001
Vital signs							
Respiratory rate, median (IQR)	18 (18, 20)	18 (16, 20)	18 (18, 20)	18 (18, 21)	18 (18, 20)	19 (18, 22)	0.059
Oxygen saturation, median (IQR)	97 (94, 98)	97 (95, 98)	97 (95, 98)	96 (94, 98)	96 (93, 98)	96 (93, 98)	<0.001
Blood pressure systolic, median (IQR)	137 (121, 154)	138 (124, 154)	141 (125, 157)	135 (119, 153)	130 (114, 146)	124 (109, 140)	<0.001
Blood pressure diastolic, median (IQR)	80 (70, 90)	82 (74, 91)	83 (72, 93)	78 (68, 89)	75 (65, 83)	70 (61, 80)	<0.001
Pulse rate, median (IQR)	83 (71, 97)	80 (70, 92)	81 (70, 94)	85 (72, 100)	87 (74, 104)	91 (78, 105)	<0.001
Temperature, °C, mean (IQR)	36.8 (36.4, 37.2)	36.8 (36.4, 37.1)	36.8 (36.4, 37.1)	36.8 (36.5, 37.3)	36.9 (36.5, 37.8)	37.2 (36.6, 38.3)	<0.001
Confusion, n (%)	518 (7.4%)	74 (6.8%)	231 (6.8%)	114 (7.6%)	36 (9.2%)	63 (11.3%)	0.002
Main symptoms at admission, n (%)							
Non-thoracic pain	1190 (17.1%)	221 (20.2%)	594 (17.4%)	243 (16.1%)	53 (13.5%)	79 (14.2%)	
Thoracic pain	1022 (14.7%)	181 (16.5%)	610 (17.8%)	170 (11.3%)	37 (9.4%)	24 (4.3%)	
Neurological symptoms	1359 (19.5%)	283 (25.8%)	760 (22.2%)	236 (15.6%)	34 (8.7%)	46 (8.3%)	
Respiratory symptoms	937 (13.4%)	83 (7.6%)	431 (12.6%)	265 (17.6%)	72 (18.3%)	86 (15.5%)	
General worsening	826 (11.9%)	91 (8.3%)	353 (10.3%)	232 (15.4%)	68 (17.3%)	82 (14.7%)	
Blood loss	196 (2.8%)	12 (1.1%)	98 (2.9%)	54 (3.6%)	15 (3.8%)	17 (3.1%)	
Diarrhea, vomitus, dysuria	488 (7.0%)	60 (5.5%)	194 (5.7%)	116 (7.7%)	47 (12.0%)	71 (12.8%)	
Fever	338 (4.8%)	21 (1.9%)	78 (2.3%)	83 (5.5%)	46 (11.7%)	110 (19.8%)	
Other	614 (8.8%)	143 (13.1%)	300 (8.8%)	109 (7.2%)	21 (5.3%)	41 (7.4%)	
Main diagnosis, n (%)							
Infection	1027 (14.7%)	77 (7.0%)	347 (10.2%)	245 (16.2%)	116 (29.5%)	242 (43.5%)	
Cardiovascular	1639 (23.5%)	258 (23.6%)	948 (27.7%)	322 (21.4%)	63 (16.0%)	48 (8.6%)	
Metabolic	189 (2.7%)	13 (1.2%)	82 (2.4%)	59 (3.9%)	12 (3.1%)	23 (4.1%)	
Cancer	337 (4.8%)	21 (1.9%)	112 (3.3%)	113 (7.5%)	40 (10.2%)	51 (9.2%)	
Neurological	1543 (22.1%)	344 (31.4%)	869 (25.4%)	251 (16.6%)	37 (9.4%)	42 (7.6%)	
Gastrointestinal	962 (13.8%)	121 (11.1%)	441 (12.9%)	234 (15.5%)	70 (17.8%)	96 (17.3%)	
Pulmonary	292 (4.2%)	35 (3.2%)	136 (4.0%)	91 (6.0%)	19 (4.8%)	11 (2.0%)	
Other	981 (14.1%)	226 (20.6%)	483 (14.1%)	193 (12.8%)	36 (9.2%)	43 (7.7%)	
Co-morbidities, n (%)							
Congestive heart failure	480 (6.9%)	26 (2.4%)	207 (6.1%)	158 (10.5%)	41 (10.4%)	48 (8.6%)	<0.001
Coronary artery disease	824 (11.8%)	71 (6.5%)	444 (13.0%)	205 (13.6%)	47 (12.0%)	57 (10.3%)	<0.001
COPD	352 (5.1%)	18 (1.6%)	155 (4.5%)	119 (7.9%)	22 (5.6%)	38 (6.8%)	<0.001
Dementia	221 (3.2%)	20 (1.8%)	107 (3.1%)	58 (3.8%)	9 (2.3%)	27 (4.9%)	0.005
Diabetes	1072 (15.4%)	70 (6.4%)	483 (14.1%)	341 (22.6%)	86 (21.9%)	92 (16.5%)	<0.001
History of stroke	554 (7.9%)	71 (6.5%)	333 (9.7%)	115 (7.6%)	22 (5.6%)	13 (2.3%)	<0.001
Substance abuse	456 (6.5%)	87 (7.9%)	213 (6.2%)	97 (6.4%)	27 (6.9%)	32 (5.8%)	0.32
Cancer	952 (13.7%)	90 (8.2%)	338 (9.9%)	287 (19.0%)	89 (22.6%)	148 (26.6%)	<0.001
Chronic renal failure	867 (12.4%)	23 (%)	251 (%)	300 (%)	119 (%)	174 (%)	<0.001

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

Table 2: Association of admission PCT levels and adverse clinical outcome in univariate and multivariate logistic regression models.

	Number of events	Unadjusted model	Fully adjusted model[a]
30-day mortality			
PCT (continuous)	328 (4.7%)	2.75 (2.38–3.17), p < 0.001	2.13 (1.77–2.55), p < 0.001
PCT over cut-offs			
Ref. <0.05 ng/mL	10 (0.9%)	1	1
0.05–0.1 ng/mL	85 (2.5%)	2.77 (1.43–5.35), p = 0.002	1.71 (0.87–3.34), p = 0.119
0.1–0.25 ng/mL	102 (6.8%)	7.87 (4.09–15.14), p < 0.001	3.28 (1.67–6.44), p < 0.001
0.25–0.5 ng/mL	49 (12.5%)	15.45 (7.75–30.84), p < 0.001	6.48 (3.15–13.36), p < 0.001
>0.5 ng/mL	82 (14.7%)	18.77 (9.65–36.51), p < 0.001	7.31 (3.62–14.75), p < 0.001
In-hospital death			
PCT (continuous)	186 (2.6%)	2.94 (2.48–3.49), p < 0.001	2.24 (1.8–2.79), p < 0.001
PCT over cut-offs			
Ref. <0.05 ng/mL	4 (0.4%)	1	1
0.05–0.1 ng/mL	44 (1.3%)	3.56 (1.28–9.92), p = 0.015	2.02 (0.72–5.71), p = 0.184
0.1–0.25 ng/mL	59 (3.9%)	11.11 (4.02–30.67), p < 0.001	4.28 (1.52–12.06), p = 0.006
0.25–0.5 ng/mL	24 (6.1%)	17.74 (6.12–51.46), p < 0.001	6.45 (2.15–19.35), p < 0.001
>0.5 ng/mL	55 (9.9%)	29.94 (10.79–83.08), p < 0.001	10.34 (3.59–29.8), p < 0.001
ICU admission			
PCT (continuous)	449 (6.4%)	1.86 (1.61–2.14), p < 0.001	1.58 (1.33–1.88), p < 0.001
PCT over cut-offs			
Ref. <0.05 ng/mL	41 (3.7%)	1	1
0.05–0.1 ng/mL	182 (5.3%)	1.45 (1.02–2.04), p = 0.037	1.15 (0.8–1.64), p = 0.447
0.1–0.25 ng/mL	108 (7.2%)	1.98 (1.37–2.87), p < 0.001	1.34 (0.91–1.98), p = 0.135
0.25–0.5 ng/mL	51 (13.0%)	3.83 (2.5–5.89), p < 0.001	2.52 (1.59–3.99), p < 0.001
>0.5 ng/mL	67 (12.1%)	3.52 (2.35–5.27), p < 0.001	2.33 (1.5–3.63), p < 0.001
Rehospitalization			
PCT (continuous)	580 (8.3%)	1.24 (1.06–1.44), p = 0.007	1.12 (0.94–1.34), p = 0.195
PCT over cut-offs			
Ref. <0.05 ng/mL	64 (5.8%)	1	1
0.05–0.1 ng/mL	281 (8.2%)	1.44 (1.09–1.91), p = 0.01	1.31 (0.99–1.74), p = 0.063
0.1–0.25 ng/mL	144 (9.5%)	1.7 (1.25–2.31), p < 0.001	1.4 (1.02–1.92), p = 0.039
0.25–0.5 ng/mL	37 (9.4%)	1.67 (1.1–2.55), p < 0.001	1.34 (0.86–2.08), p = 0.195
>0.5 ng/mL	54 (9.7%)	1.73 (1.19–2.53), p < 0.001	1.4 (0.94–2.1), p = 0.098

[a]Full model analysis includes adjusting for age, gender, main symptoms, main diagnosis, comorbidities and vital signs. ICU, intensive care unit; Log PCT, logarithm of procalcitonin concentration; Ref., reference.

Although PCT is an established marker of bacterial infection and antibiotic stewardship [6, 17], we found PCT to be a strong predictor of mortality in non-infectious disease, mainly in metabolic and cardiovascular diseases. Of note, even subtle increases in PCT indicated a higher risk for mortality despite the fact that PCT concentrations in these non-infectious conditions were much lower as compared to those levels seen in sepsis syndromes. There are several potential explanations for this finding. First, PCT levels per se could have detrimental effects on a patients' medical condition. As shown in animal models, PCT negatively influenced the course of disease and exogenous injection of PCT in septic hamsters increased their mortality [18]. Conversely, neutralization of PCT reduced mortality in septic hamsters and pigs [19]. However, due to the relatively low levels in morbid non-infectious diseases, it seems unlikely that PCT per se explains the higher mortality. Alternatively, bacterial translocation triggered across the gut wall by gastrointestinal malperfusion may trigger a deadly cascade [20, 21]. Finally, PCT could also slightly be increased as part of the general immunological response to illness and thus mirror the severity of illness in our patient population. This hypothesis is further supported by the fact, that prediction of mortality was best in patients without fever and patients without signs of organ dysfunction and sepsis as defined by the qSOFA score. To disentangle these different hypotheses, we performed multivariate regression models adjusting for medical parameters (main diagnosis and main symptom), patient characteristics (age, gender, comorbidities) and vital signs. In these models, associations of PCT and adverse outcome were somewhat weaker but still significant and relevant as shown by the high ORs. This suggests that the relationship of PCT and outcome is partly explained by

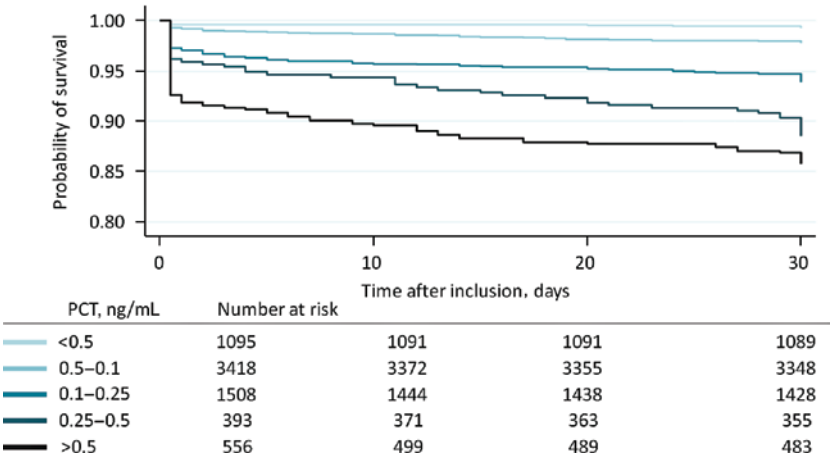

Figure 1: Kaplan-Meier curve for procalcitonin and 30-day mortality.

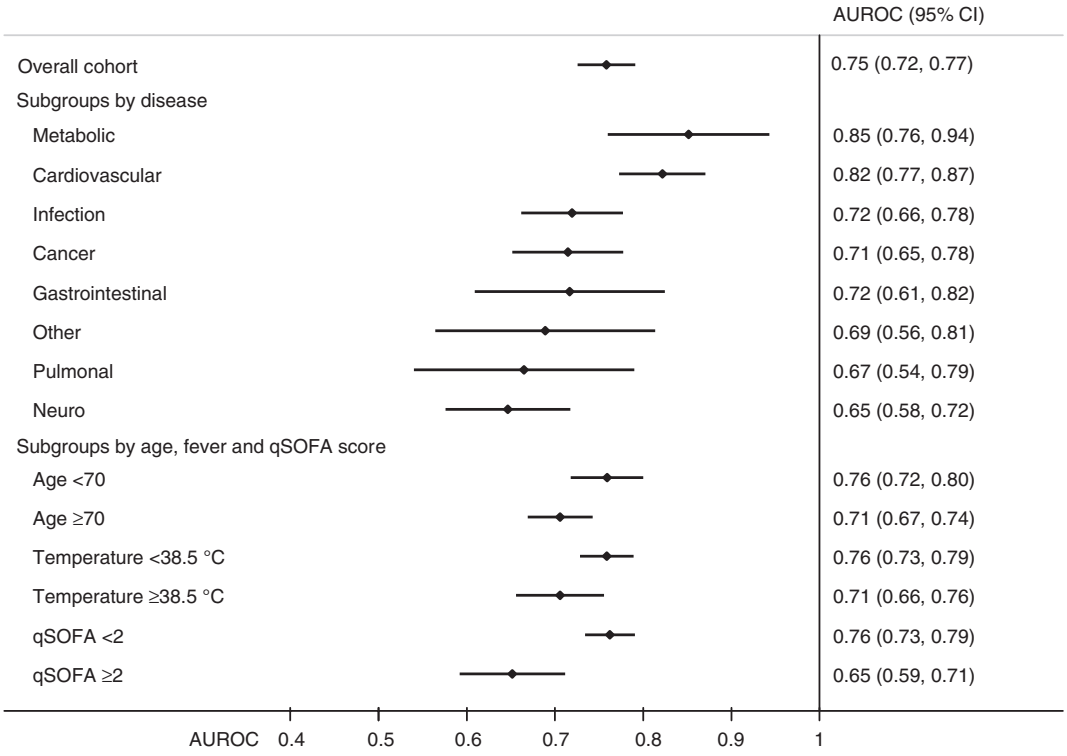

Figure 2: Forest plot of AUCs for the discrimination of PCT and 30-day mortality stratified by different criteria and main diagnosis. X-axis, AUROC, area under the receiver operating curve; CI, confidence interval; qSOFA, quick sepsis related organ failure score.

disease factors but adds further prognostic information to the clinical picture. It is important that future research focuses on the role of PCT in this non-infectious patient population to better understand the physiophathological mechanisms explaining these results.

We are aware of several limitations. First, we did not assess the cause of death, and therefore, it is unclear, whether infection was present or not. Especially for infectious patients we did not separately investigate bacterial and viral causes mainly due to lack of "gold standard" diagnostic criteria. Therefore, it remains unclear if concentrations of PCT positively correlate with mortality in patients with a primary diagnosis of viral origin. Second, the physiopathology of PCT upregulation is not fully understood and possible explanations cannot be answered by this observational clinical study. As PCT levels change over the course of a patients disease (particularly in bacterial infectious diseases), the one-point measurement at

hospital admission might not always capture the highest PCT level. Finally, from an observational study, we cannot conclude that risk stratification with PCT would lead to better patient care and to a lowering of adverse outcome.

Conclusions

In the ED setting, PCT could be helpful in risk stratification as it has independent association for adverse outcome, especially for mortality, and it has a high discriminative power to identify patients at high risk for 30-day mortality. Discrimination was best in metabolic and cardiovascular disease, as well as in young patients, without fever and no signs of organ failure or sepsis. Physiopathological mechanisms in these patients should be further investigated.

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