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Plasma soluble suppression of tumorigenesis 2 measured in the emergency department for diagnosis and outcome prediction of sepsis: A single-center prospective study

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ABSTRACT

Background and aims: The diagnostic and prognostic performance of soluble Suppression of Tumorigenicity 2 (sST2) in suspected septic patients presenting to the Emergency Department (ED) is largely unknown.
Materials and methods: Patients were included in this prospective study if there was high suspicion of sepsis. The plasma level of sST2 was measured during initial ED evaluation. Outcomes were the evaluation of (1) sST2 diagnostic performance (alone and in combination with procalcitonin [PCT]), and (2) sST2 ability to predict 30-day and 90-day all-cause mortality.
Results: Among 569 patients included, 481 (84.5 %) had sepsis or septic shock. Plasma sST2 levels were more elevated in septic patients (159 [71–331] vs 50 [31–103] ng/mL, $P < 0.001$). The AUC of sST2 for sepsis diagnosis was lower than the AUC of PCT (0.76 vs 0.85, $P = 0.03$). The best cut-off for sST2 was 61.7 ng/mL, with a sensitivity of 79.9 % and a specificity of 70.6 %. sST2 was able to correctly reclassify septic patients with PCT <0.5 (NRI 28.9 % [$P = 0.02$]). sST2 level was an independent predictor of 30-day mortality in a model including clinical variables (aHR 2.03 [1.24–3.33], C-index 0.69).
Conclusion: sST2 could be a useful adjunct in diagnosing sepsis and in all-cause mortality prediction.

1. Introduction

Sepsis is a clinical syndrome characterized by end-organ dysfunction caused by host reaction to an infection, with increasing incidence and high mortality [1]. Diagnosing sepsis is difficult, especially in the Emergency Department (ED), since it can have a multifaceted presentation and no specific biomarker is accurate enough to reliably detect it, particularly in its early stages [2]. Nonetheless, to improve outcome, early sepsis recognition is crucial to initiate proper treatment (resuscitation, antibiotics and source control) and to decide the appropriate intensity of care (e.g. intensive care or high-dependency unit versus normal ward) without delay [3].

Soluble Suppression of Tumorigenicity 2 (sST2) is the circulating form of ST2 created through alternative splicing and acts as an IL-33 decoy receptor, preventing IL-33 from binding to its transmembrane, and thus active, receptor. IL-33 exhibits pleiotropic effects, both inducing Th-1 and Th-2 immune response, depending on the timing, site, involved immune cells and stimuli. It seems to support bacterial clearance in the early phases of sepsis, but also to induce immunosuppression in the late phases [4]. In addition, it has been demonstrated that sST2 promotes atherosclerosis, cardiac fibrosis and heart remodeling and could be a useful biomarker for prognosis prediction in heart failure and

Abbreviations: ED, Emergency Department; PCT, Procalcitonin; PE, Pulmonary Embolism; sST2, soluble Suppression of Tumorigenicity 2.

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for diagnosing acute aortic syndromes [5–8].

Preliminary studies have shown that blood-culture positive septic children have higher levels of sST2 than healthy controls and that sST2 levels in septic adults and critically-ill patients correlate with mortality, although not unequivocally [9–12] More recently, it has been demonstrated that sST2 levels correlate with COVID-19 severity [13]. However, the diagnostic accuracy and prognostic utility of sST2 in patients presenting to the ED with suspected sepsis is largely unknown. This study aimed to evaluate the diagnostic performance of sST2 in patients presenting to the ED with suspected sepsis, alone and in combination with PCT, and to investigate the prognostic utility of sST2 on top of clinical variables and severity scores.

2. Methods

2.1. Study design and patients

This was a prospective monocenter study conducted in the Emergency Department of Molinette Hospital, a tertiary care university referral hospital in Torino, Italy, from January 2017 to December 2019. All participants signed a written informed consent. The study complied with the Declaration of Helsinki and was approved by the local ethics committee (CEI-419 approved on Jan 23, 2012). The reporting of this study was done according to the STROBE Checklist (Supplemental Table I) [14].

Adult (age ≥18 years) patients were enrolled if they presented with infective signs and symptoms and their attending physician had a suspicion of sepsis, defined according to the Sepsis-3 criteria (i.e.: with end-organ dysfunction and/or presence of shock) [1]. Patients were excluded if they were <18 years old, denied consent to participate, had an evident alternative diagnosis to sepsis or septic shock during the index visit, or sST2 was not measured at presentation. Patients satisfying inclusion criteria and without exclusion criteria were used for further analyses (Fig. 1). Clinical management was done irrespective of patient's participation in the present study, in adherence with local and international guidelines. The attending physician was blinded only to the sST2 results.

2.2. sST2 measurement

During the index visit, during the routine blood draw to determine laboratory parameters (including those shown in Table 1), an additional probe was collected to measure sST2 and transferred to the hospital central biochemistry laboratory. Plasma specimens obtained after centrifugation were stored at −20 °C. To allow for expedite centrifugation and freezing of plasma, enrolment was limited from 8 a.m. to 6 p.m., Monday to Friday. The concentrations of sST2 were measured using the Critical Diagnostics Presage® ST2, a quantitative sandwich-type ELISA which uses monoclonal antibodies. Human endogenous ST2 demonstrated stability in all the following conditions: storage at 20 °C for 48 h, at 4 °C for 7 days, at −20 °C and −80 °C for 18 months [15]. The assay precision assessment was performed according to the CLSI (Clinical and Laboratory Standards Institute) EP5-A standards. Intra-series coefficient of variation (CVa) and total CVa were 6.5 % and 9.1 %, respectively, at an average concentration of 16.9 ng/mL, 3.4 % and 5.5 % at a mean concentration of 33.1 ng/mL, 3.8 % and 6.3 % at an average concentration of 68.7 ng/mL, 2.4 % and 4.8 % at an average concentration of 159.1 ng/mL. The limit of quantification is 2.4 ng/mL. There are no significant interferences with total proteins, triglycerides, hemoglobin, cholesterol, bilirubin [16].

2.3. Clinical variables

During the index ED visit, patients' demographic and clinical data were collected in a standardized electronic case report form. These included blood pressure, heart rate, respiratory rate, oxygen saturation and body temperature, laboratory tests (including procalcitonin, PCT) as ordered by the attending physicians according to their clinical gestalt. Cultures of biological fluids were ordered whenever appropriate. Clinical severity scores (SOFA and APACHEII) were calculated retrospectively by the study investigators [17,18].

2.4. Final diagnosis and follow-up

The final diagnosis was adjudicated based on all available medical records by an expert ED physician not involved in the study design and

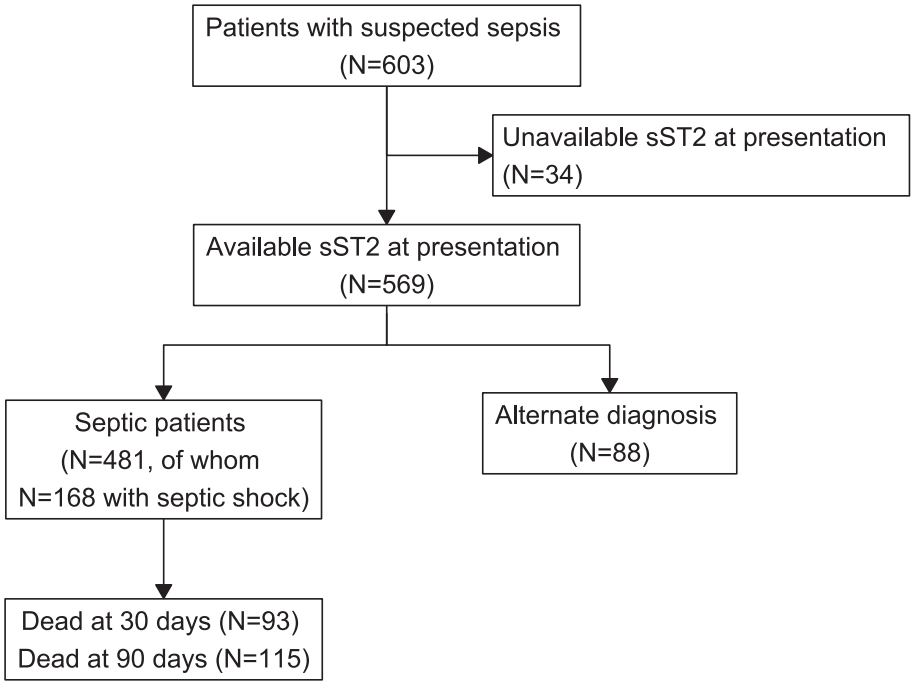

Fig. 1. Patient flowchart.

Table 1
Patient characteristics at Emergency Department presentation.

Characteristic	Overall (N = 569)	Alternative diagnosis (N = 88)	Sepsis or septic shock (N = 481)	P-value
Demographics				
Age (years)	73.0 (62.0, 81.0)	67.5 (53.8, 78.2)	74.0 (64.0, 81.0)	<0.001
Sex (Female)	229 (40 %)	40 (45 %)	189 (39 %)	0.3
Comorbidities				
Hypertension	299 (53 %)	30 (34 %)	269 (56 %)	<0.001
Diabetes	148 (26 %)	14 (16 %)	134 (28 %)	0.019
Coronary artery disease	112 (20 %)	5 (5.7 %)	107 (22 %)	<0.001
Chronic obstructive pulmonary disease	86 (15 %)	8 (9.1 %)	78 (16 %)	0.086
Cancer	181 (32 %)	21 (24 %)	160 (33 %)	0.082
Immunosuppression	110 (19 %)	3 (3.4 %)	107 (22 %)	<0.001
Chronic kidney disease	80 (14 %)	2 (2.3 %)	78 (16 %)	<0.001
Vital signs at presentation				
SBP (mmHg)	120 (100, 130)	130 (115, 145)	115 (95, 130)	<0.001
DBP (mmHg)	70 (60, 80)	80 (70, 80)	70 (60, 80)	<0.001
HR (bpm)	100 (80, 110)	100 (80, 110)	100 (82, 112)	0.2
RR (bpm)	20 (14, 24)	20 (16, 24)	20 (14, 24)	0.8
SpO2 (%)	95.0 (91.0, 97.0)	96.0 (93.0, 98.0)	94.0 (90.0, 97.0)	0.007
P/F ratio	276 (222, 338)	324 (257, 381)	273 (215, 333)	<0.001
Temperature (°C)	37.6 (36.5, 38.5)	36.8 (36.0, 37.6)	37.7 (36.7, 38.6)	<0.001
Glasgow Coma Scale	15 (15, 15)	15 (15, 15)	15 (15, 15)	0.4
Selected laboratory values at presentation				
White blood cells (10^9/L)	11.9 (7.7, 17.3)	11.1 (8.8, 14.1)	12.0 (7.2, 18.2)	0.4
Hemoglobin (g/dL)	11.8 (9.9, 13.4)	13.1 (11.5, 14.0)	11.6 (9.8, 13.2)	<0.001
Platelets (10^9/L)	195 (128, 271)	216 (168, 310)	191 (120, 263)	0.002
International Normalized Ratio (INR)	1.2 (1.1, 1.4)	1.1 (1.0, 1.2)	1.3 (1.1, 1.5)	<0.001
Activated partial thromboplastin time (aPTT) ratio	1.0 (0.9, 1.1)	1.0 (0.9, 1.0)	1.0 (0.9, 1.1)	0.010
AST (U/L)	25 (17, 40)	23 (16, 33)	25 (17, 41)	0.3
ALT (U/L)	21 (12, 37)	25 (17, 36)	20 (12, 37)	0.10
Creatinine (mg/dL)	1.2 (0.9, 1.9)	0.9 (0.8, 1.1)	1.3 (0.9, 2.0)	<0.001
eGFR (2021 CDK-EPI, ml/min)	57.4 (31.7, 86.4)	83.8 (67.6, 100.0)	50.7 (29.2, 83.7)	<0.001
Lactate (mmol/L)	2.0 (1.3, 3.4)	1.5 (1.0, 2.0)	2.1 (1.3, 3.7)	0.002
Ventilatory and circulatory support started during ED visit				
Vasopressors	77 (14 %)	5 (5.7 %)	72 (15 %)	0.019
Invasive or non-invasive ventilation	21 (3.7 %)	2 (2.3 %)	19 (4.0 %)	0.8
Severity scores at presentation				
APACHE II	12.0 (9.0, 17.0)	7.0 (4.5, 10.0)	13.0 (10.0, 17.0)	<0.001
SOFA	4.0 (2.0, 6.0)	1.0 (1.0, 3.0)	4.0 (3.0, 6.0)	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; RR: respiratory rate; SpO2: peripheral oxygen saturation; AST: aspartate transaminase; ALT: alanine transaminase; eGFR: estimated glomerular filtration rate; P/F: partial oxygen pressure (pO_2) / Fraction of inspired oxygen (FiO_2).

data analysis, blinded to sST2 levels. Sepsis was defined according to the Sepsis-3 guidelines, i.e. evidence of infection plus organ dysfunction defined by an increase in the Sequential Organ Failure Assessment (SOFA) score of ≥2 points [1]. Septic shock was defined by vasopressor therapy to maintain mean arterial pressure ≥65 mmHg and serum lactate level ≥2 mmol/L [1].

After 90 days from index visit, an automatic query on the death registry was carried out to check for a death event.

2.5. Outcomes

This study aimed to: (1) evaluate the performance of sST2 levels for the diagnosis of sepsis in suspected septic patients presenting to the ED (alone and in combination with PCT), and (2) quantify the prognostic ability of sST2 on top of clinical variables and severity scores to predict 30-day and 90-day all-cause mortality. For the diagnostic endpoint, PCT was taken as the "gold standard" biomarker for the diagnosis of sepsis, given its widespread use and availability coupled to well-known diagnostic accuracy characteristics outperforming C-reactive protein (CRP) and lactate, even though [2,3,19,20]. Although no definite cut-off has been established for PCT and the last Surviving Sepsis Campaign guidelines did not recommend its use to start antibiotic therapy, in this study we considered a cut-off of ≥0.5 ng/mL for sepsis diagnosis [21–23].

2.6. Sample size calculation

It was estimated that a total sample size of 538 patients would be needed for the 95 % confidence interval (95 %CI) width for the sensitivity not to exceed 10 %, assuming a sensitivity of 70 % and a prevalence of sepsis of 85 % [24].

2.7. Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR) and were compared using the Mann–Whitney *U* test. Categorical variables were expressed as absolute number (percentage) and compared with the Chi-squared or the Fisher's exact test as appropriate.

To evaluate the diagnostic accuracy of plasma sST2 levels for sepsis, a receiver operating characteristic (ROC) curve was built and its area under the curve (AUC) was compared to that of PCT using the DeLong's test. Subgroup analysis of predefined characteristics (sex, age groups, renal dysfunction, immunosuppression, cancer, diabetes and infective focus) was carried out to evaluate consistency of the diagnostic accuracy findings. The Youden index was used to find the optimal cut-off value for sST2, defined as the maximum value of sensitivity + specificity − 1. Diagnostic performance measures (sensitivity, specificity, positive and negative likelihood ratios, LR) were calculated and compared with those of PCT [25]. Logistic regression analysis was used to explore the diagnostic value of combining PCT and sST2. The C-index of the two models (PCT alone vs PCT and sST2) was compared with the DeLong's test and

the additional diagnostic information provided by sST2 was quantified according to Harrel [26].

The clinical utility of sST2 in PCT-negative sepsis patients was evaluated using diagnostic performance measures and net reclassification improvement (NRI), as a summary estimate and for either events (NRI+) or non-events (NRI−) [27].

To evaluate the prognostic performance, Kaplan-Meier estimator and Cox regression analysis were carried out to evaluate if sST2 was an independent predictor of mortality in univariate or multivariate models. Two multivariate models were built: one with clinical variables (age, sex, CAD, diabetes, hypertension, presence of septic shock and immunosuppression, cancer and serum lactate levels) and one with SOFA score. The choice of the included clinical variables was made upon their known importance in sepsis prognosis and their role as confounders of sST2 levels (CAD, diabetes and hypertension to account for cardiac disease). sST2 was modelled as a continuous variable using cubic splines [28]. The C-index of the multivariate models with and without sST2 were compared using the DeLong's test. The additional prognostic information provided by sST2 was quantified according to Harrel [26]. Dose-response plots were drawn to show the predicted all-cause mortality probability across sST2 levels at arrival.

All hypothesis testing was two-tailed and P-values were considered statistically significant if <0.05. All statistical analysis were performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

During the study period, 603 patients with suspected sepsis were enrolled; of those, 569 patients had sST2 measured at ED presentation and were further analyzed (Fig. 1). A final diagnosis of sepsis or septic shock was adjudicated in 481 (84.5 %) patients, while an alternative diagnosis was adjudicated in 88 (15.5 %) patients. Patient characteristics according to final diagnosis are presented in Table 1. Patients with sepsis or septic shock were significantly older, had significantly more comorbidities (such as diabetes, coronary artery disease, immunosuppression and chronic kidney disease), had significantly lower systolic and diastolic blood pressure, peripheral oxygen saturation, pO_2/FiO_2 ratio, and glomerular filtration rate, and statistically higher serum lactate levels.

Among patients with sepsis, blood cultures were drawn in 246 (51.1 %) patients and were positive in 125 of them. The most prevalent infective foci were the lungs (38 %), the urinary tract (25 %) and the abdomen (15 %, Supplemental Table II). Among patients without sepsis, the most common diagnosis was pulmonary embolism (PE, 70 %) followed by infection without sepsis (21 %, Supplemental Table III).

3.2. sST2 concentration at ED presentation

Plasma sST2 levels at ED presentation were more elevated in patients with vs patients without sepsis/septic shock (159 [71–331] vs 50 [31–103] ng/mL, P < 0.001), with the highest levels in patients with septic shock (Fig. 2). Also CRP and PCT concentrations at ED presentation were significantly higher in patients with sepsis (Supplemental Table IV).

3.3. Diagnostic performance

The AUC of sST2 for sepsis diagnosis was 0.76 (95 %CI 0.71–0.81) and was significantly lower than the AUC of PCT (0.85 [95 %CI 0.79–0.91], P = 0.03; Fig. 3). The AUC of CRP was 0.69 ([95 % CI 0.62–0.75], P = 0.04 vs sST2) and was not further analyzed. The AUC of sST2 was consistent in all subgroups analyzed, except for immunosuppression where it showed a lower AUC (point estimate 0.48,

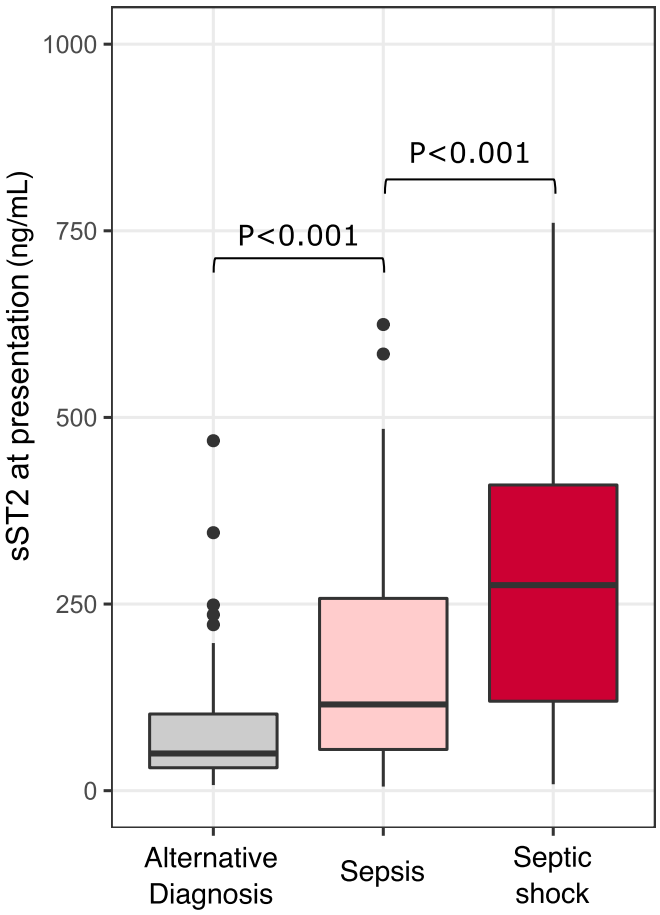

Fig. 2. Plasma sST2 levels in patients with sepsis, septic shock and alternative diagnosis at Emergency Department presentation.

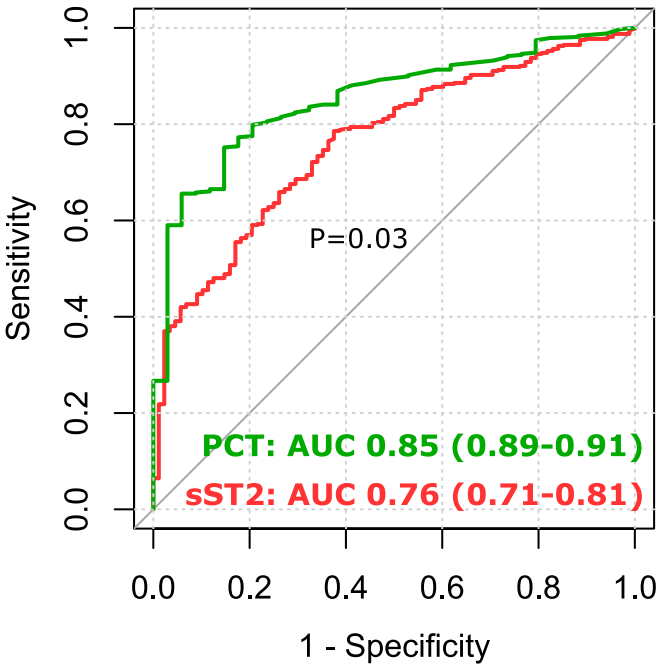

Fig. 3. ROC curve analysis of sST2 and PCT for diagnosis of sepsis/septic shock.

Supplemental Fig. I, panel A). On the other hand, the AUC of PCT was lower in patients with chronic kidney disease and cardiac artery disease (point estimates 0.60 and 0.68 respectively, Supplemental Fig. I, panel B). Using the Youden index, the best cut-off for sST2 was 61.7 ng/mL, with a sensitivity of 79.9 % (95 %CI 76.1–83.7) and a specificity of 70.6 % (95 %CI 55.3–85.9). Compared to PCT ≥0.5 ng/mL (sensitivity 73.1 % [68.9–77.3], specificity 85.3 % [73.4–97.2]), the sensitivity of sST2 was significantly higher (P = 0.005), while the specificity was lower though not significant (P = 0.23, Supplemental Table V).

3.4. Reclassification of PCT-negative patients with sST2

The general characteristics of PCT-negative patients (compared to PCT-positive patients) are shown in Supplemental Table VI. PCT-negative patients had significantly lower prevalence of sepsis or septic shock (80 % vs 98 %), lower severity scores (SOFA score 3.0 [2.0–4.0] vs 5.0 [3.0–7.0]), lower frequency of treatment with vasopressors (7.6 % vs 20 %), higher prevalence of pulmonary infection (49 % vs 35 %) and lower prevalence of urinary tract infection (15 % vs 28 %).

In 144 PCT-negative patients (25.3 %), sST2 ≥ 61.7 ng/mL correctly reclassified 65 patients with sepsis or septic shock and incorrectly classified 8 patients without sepsis (28.9 % [P = 0.02], NRI + 56.5 % [P < 0.001], NRI- −27.6 % [P = 0.005]). In this patient subgroup, sST2 ≥ 61.7 ng/mL had a sensitivity of 56.5 % (47.0–65.7) and a specificity of 72.4 % (52.8–87.3).

3.5. Combined use of sST2 and PCT

A bivariate logistic regression model for the diagnosis of sepsis using levels of PCT and sST2 (modelled as continuous) had a C-index of 0.86 vs 0.85 (P = 0.80) for the univariate model with PCT only, with the addition of sST2 to PCT providing 23 % of new diagnostic information.

A diagnostic strategy for sepsis combining PCT ≥0.5 ng/mL or sST2 ≥ 61.7 ng/mL would have a sensitivity of 88.3 % (85.2–91.3, P < 0.001 vs PCT alone), a specificity of 61.7 % (45.4–78.0, P = 0.008) and an overall accuracy of 86.3 % (82.9–89.3).

Table 2
General characteristics of septic patients according to vital status at 30 and 90 days.

Characteristic	30-day all-cause mortality			90-day all-cause mortality		
	Alive N = 388	Dead N = 93	P-value	Alive N = 366	Dead N = 115	P-value
Demographics						
Age (years)	73.0 (63.0, 81.0)	79.0 (68.0, 83.0)	0.001	73.0 (62.5, 80.0)	78.0 (68.0, 83.0)	<0.001
Sex (Female)	149 (38 %)	40 (43 %)	0.4	144 (39 %)	45 (39 %)	>0.9
Comorbidities						
Hypertension	217 (56 %)	52 (56 %)	>0.9	204 (56 %)	65 (57 %)	0.9
Diabetes	109 (28 %)	25 (27 %)	0.8	102 (28 %)	32 (28 %)	>0.9
Coronary artery disease	88 (23 %)	19 (20 %)	0.6	85 (23 %)	22 (19 %)	0.4
Chronic obstructive pulmonary disease	65 (17 %)	13 (14 %)	0.5	62 (17 %)	16 (14 %)	0.4
Cancer	118 (30 %)	42 (45 %)	0.007	110 (30 %)	50 (43 %)	0.008
Immunosuppression	73 (19 %)	34 (37 %)	<0.001	68 (19 %)	39 (34 %)	<0.001
Chronic kidney disease	61 (16 %)	17 (18 %)	0.5	56 (15 %)	22 (19 %)	0.3
Vital signs at presentation						
SBP (mmHg)	120 (100, 130)	110 (90, 129)	0.008	120 (100, 130)	110 (90, 130)	0.011
DBP (mmHg)	70 (60, 80)	60 (50, 75)	0.008	70 (60, 80)	61 (55, 75)	0.008
HR (bpm)	100 (80, 110)	105 (86, 121)	0.007	99 (80, 110)	100 (85, 120)	0.013
RR (bpm)	19 (14, 24)	20 (16, 24)	0.5	19 (14, 24)	20 (14, 24)	0.4
SpO2 (%)	95 (91, 97)	93 (88, 96)	0.007	95 (92, 97)	92 (88, 96)	<0.001
P/F ratio	280 (229, 338)	240 (177, 295)	0.003	281 (232, 342)	241 (176, 302)	<0.001
Temperature (°C)	37.8 (36.7, 38.6)	37.5 (36.7, 38.2)	0.12	37.8 (36.7, 38.7)	37.5 (36.7, 38.1)	0.046
Glasgow Coma Scale	15 (15, 15)	15 (14, 15)	<0.001	15 (15, 15)	15 (14, 15)	<0.001
Severity scores at presentation						
SOFA	3.0 (2.0, 5.0)	6.0 (4.0, 7.0)	<0.001	3.0 (2.0, 5.0)	5.0 (3.5, 7.0)	<0.001
APACHE II	12.0 (9.0, 16.0)	17.0 (14.0, 22.0)	<0.001	12.0 (8.5, 16.0)	17.0 (13.5, 21.5)	<0.001
Selected laboratory values at presentation						
White blood cells (10^9/L)	11.7 (7.6, 17.2)	14.4 (6.0, 21.8)	0.2	11.7 (7.6, 17.6)	13.9 (6.0, 20.3)	0.3
Hemoglobin (g/dL)	11.8 (10.1, 13.3)	10.4 (9.1, 12.5)	<0.001	11.9 (10.1, 13.3)	10.6 (9.2, 12.6)	<0.001
Platelets (10^9/L)	194.0 (130, 267)	166 (69, 243)	0.004	199.0 (137, 269)	168 (72, 240)	0.001
International Normalized Ration (INR)	1.2 (1.1, 1.5)	1.3 (1.2, 1.6)	0.003	1.2 (1.1, 1.5)	1.3 (1.2, 1.6)	0.004
Activated partial thromboplastin time (aPTT) ratio	1.0 (0.9, 1.1)	1.1 (0.9, 1.3)	0.022	1.0 (0.9, 1.1)	1.0 (0.9, 1.2)	0.1
AST (U/L)	25 (17, 39)	25 (17, 51)	0.5	25 (17, 40)	25 (16, 45)	>0.9
ALT (U/L)	20 (12, 36)	21 (13, 41)	0.3	20 (12, 36)	21 (12, 40)	0.6
Creatinine (mg/dL)	1.3 (0.9, 2.0)	1.4 (1.0, 2.2)	0.2	1.3 (0.9, 2.0)	1.5 (1.0, 2.2)	0.1
eGFR (2021 CDK-EPI, ml/min)	53.0 (30.0, 84.1)	42.8 (26.4, 66.2)	0.084	53.8 (30.0, 85.5)	42.8 (27.0, 66.3)	0.038
Lactate (mmol/L)	1.9 (1.3, 3.3)	2.8 (1.9, 5.3)	<0.001	1.9 (1.3, 3.3)	2.5 (1.6, 5.0)	0.001
Ventilatory and circulatory support at ED presentation						
Vasopressor use	51 (13 %)	21 (23 %)	0.022	6 (13 %)	26 (23 %)	0.008
Invasive or non-invasive ventilation	14 (3.6 %)	5 (5.4 %)	0.4	10 (2.7 %)	9 (7.8 %)	0.024
Microbiology						
Pulmonary focus	135 (39 %)	38 (45 %)	0.3	130 (39 %)	43 (43 %)	0.5
Urinary focus	95 (27 %)	14 (17 %)	0.047	89 (27 %)	20 (20 %)	0.2
Abdominal focus	52 (15 %)	12 (14 %)	0.9	51 (15 %)	13 (13 %)	0.5
Culture positivity	249 (64 %)	57 (61 %)	0.6	236 (64 %)	70 (61 %)	0.5
Biomarkers at ED presentation						
sST2 (ng/mL)	141.5 (62.5, 320.0)	264.2 (121.3, 405.3)	<0.001	137.6 (60.8, 320.4)	253.7 (114.9, 369.4)	<0.001
PCT (ug/mL)	2.2 (0.4, 14.6)	5.5 (0.7, 20.1)	0.03	2.2 (0.3, 14.7)	4.1 (0.8, 16.1)	0.047

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; RR: respiratory rate; SpO2: peripheral oxygen saturation; SOFA: sequential organ failure assessment; APACHEII: acute physiology and chronic health evaluation; AST: aspartate transaminase; ALT: alanine transaminase; eGFR: estimated glomerular filtration rate.

3.6. Prognosis prediction in patients with sepsis

In patients with sepsis or septic shock, 30-day all-cause mortality was 19.3 % and 90-day all-cause mortality was 23.9 %. The characteristics of patients who died and who were alive at 30 and 90 days from index visit are summarized in Table 2. sST2 values at presentation were higher in patients who died at 30 days (264 [121–405] vs 142 [63–320] ng/mL; P < 0.001) and at 90 days (254 [115–369] vs 138 [61–320]; P < 0.001).

Kaplan-Meier curves for sST2 and PCT are shown in Fig. 4 panels A and B, respectively. In univariate Cox regression analysis, the HR of sST2 for 30-day mortality was 2.59 (1.63–4.12) and the HR of PCT was 1.29 (0.85–1.96). The C-index of sST2 was 0.63 (0.57–0.70) while the C-index of PCT was 0.57 (0.51–0.64, P = 0.05).

Adding sST2 as a predictor for 30-day mortality to a multivariate Cox model including age, sex, CAD, diabetes, hypertension, presence of septic shock and immunosuppression, cancer and lactate levels, led to a C-index of 0.75 (0.70–0.81), significantly higher than the C-index of the model without sST2 (0.70 [0.65–0.76], P = 0.009). sST2 had an adjusted hazard ratio (aHR) of 4.77 (1.42–16.0) and its addition provided 59 % of new prognostic information, with respect to the model without sST2. On the other hand, a model with SOFA score with and without sST2 levels at ED presentation had comparable C-indexes (0.69 [0.63–0.75] vs 0.68 [0.63–0.74], respectively, P = 0.44). sST2 had an aHR of 2.03 (1.24–3.33) and provided 13 % of new prognostic information. The dose–response plot for 30-day all-cause mortality, showing the probability of death at 30-day as predicted by sST2 levels at ED presentation in the multivariate (clinical variables) regression model, is depicted in Fig. 4, panel C. Similar results were found also for the prediction of 90-day all-cause mortality.

4. Discussion

In this study, we evaluated the diagnostic and prognostic utility of sST2 in a monocentric cohort of patients with a high clinical suspicion of sepsis in the ED. We report several findings. The AUC of sST2 for the diagnosis of sepsis in the ED was 0.76, thus showing acceptable accuracy [29]. However, the AUC of sST2 proved to be lower than the AUC of PCT (0.85 [95 %CI 0.89–0.91]), whose estimate was concordant to previous research [19]. However, the diagnostic performance of PCT could be overestimated as its levels were available during the final diagnosis adjudication process. On the other hand, the diagnostic performance of sST2 could be underestimated given the high prevalence of PE in the non-septic group and the fact that sST2 levels are increased in this disease [30]. In the subgroup analysis, sST2 maintained its accuracy in patients with chronic kidney disease, while that of PCT was reduced. Previous studies have shown that sST2 levels are not influenced by renal function; instead, the influence of acute and chronic renal dysfunction on PCT levels are still a matter of debate, although it seems that its diagnostic accuracy is lower [31–34]. Hence, sST2 could be particularly useful in clinical practice with the increasing prevalence of chronic kidney disease in an aging population. On the other hand, sST2 accuracy decreased in immunosuppressed patients, possibly indicating that ST2 expression is enhanced not only by cardiovascular stress, but also immunity, e.g. through a NF-κB-dependent mechanism [35]. Gender did not significantly impact on sST2 accuracy, differently from what was expected according to studies defining normal ranges, which were higher in men [31].

We found that the best sST2 cut-off for sepsis diagnosis was 61.7 ng/mL, which had a sensitivity of 79.9 % and a specificity of 70.6 %. The cut-off found in this analysis is greater than the 99th percentile (56.5 ng/mL), derived from the lognormal distribution of a self-reported healthy cohort, indicated by the manufacturer [36]. The relatively low specificity could correlate with the fact that in our study sepsis prevalence was very high (85 %), according to the inclusion criterion based on clinical suspicion. To the best of our knowledge, this is the first study to identify a cut-off for diagnosing sepsis in an ED cohort, although this finding must be replicated in other studies before being introduced in clinical practice. In addition, the diagnostic value of sST2 should be compared to that of other biomarkers in development [2]. In previous studies performed on small patient groups, sST2 levels at admission could differentiate between septic and cardiogenic shock (AUC 0.81) and sST2 levels were significantly higher in septic patients compared to patients with trauma or who underwent abdominal surgery [12,37].

We showed that sST2 ≥ 61.7 ng/mL could be clinically most useful in PCT negative patients, in whom it can correctly identify more than 50 % of patients with sepsis with a very good sensitivity and good accuracy. This could be particularly useful in clinical practice in case of high suspicion of sepsis despite a PCT level <0.5 ng/mL. The combined use of sST2 and PCT is also supported by the fact that it brings 23 % of new diagnostic information over PCT alone. Nonetheless, this diagnostic strategy would reduce specificity and the best way to combine the two biomarkers is yet to be identified.

In this study, sST2 proved to be superior to PCT in predicting 30-day and 90-day mortality, although the C-index of 0.63 reflected only fair accuracy. These results are consistent with a previous study, where sST2 had a C-index of 0.67, similar to that of SOFA score (0.69), and PCT was not a predictor of mortality [38]. The relationship with sST2 and all-cause mortality was non-linear, as shown by the dose–response plots. sST2 was found to be an independent predictor of mortality over a model with clinical variables alone, providing 59 % of new prognostic information and showing good accuracy and calibration. Further studies are needed to test sST2 over other prognostic biomarkers, such as proadrenomedullin and galectin-3, and to explore its potential in predicting treatment failure with serial testing over time [39]. In the cited study by Kim et al, galectin-3 had a C-index for 30-day all-cause mortality of 0.77 [38]. Hoogerwerf et al. also demonstrated that sST2 levels remain higher throughout the stay in the in the intensive care unit in non-survivors [10]. Unfortunately, comparisons among studies are hampered by differences in the assay used to measure sST2 levels, in addition to various study designs and “control” populations.

This study has several limitations. Due to its monocentric nature, its external generalizability is low, although the diagnostic characteristics of PCT were analogous to previous studies reflecting a good case-mix. The high prevalence of sepsis found in this cohort could overestimate sensitivity and underestimate specificity of sST2; nonetheless, it reflects the “real-life” nature of this study, where patients were included only if there was a significant clinical suspicion of sepsis. Unfortunately, we did not record cardiac function at presentation nor the prevalence of heart failure in our cohort. From a diagnostic perspective, while the higher prevalence of hypertension, CAD and diabetes in the sepsis group could have led to an overestimation of sST2 diagnostic performance, the very high prevalence of PE in the non-septic group could counterbalance this effect. From a prognostic perspective, adjusting for CAD, hypertension and diabetes could help mitigate the confounding effect of cardiac function and sepsis-induced cardiac dysfunction for its prognostication ability in sepsis.

5. Conclusions

sST2 could be a useful biomarker in the diagnosis of sepsis in the ED, above all in patients with a negative PCT, with a potential to further boost sensitivity. In addition, sST2 proved to be an independent predictor of 30-day and 90-day all-cause mortality. Further studies are needed to implement sST2 in disposition decisions and to evaluate the additive value of serial sST2 measurements during hospitalization, to monitor treatment response.

Ethics approval and consent to participate

The study received ethics approval by the competent local ethics committee and all study participants gave written informed consent.

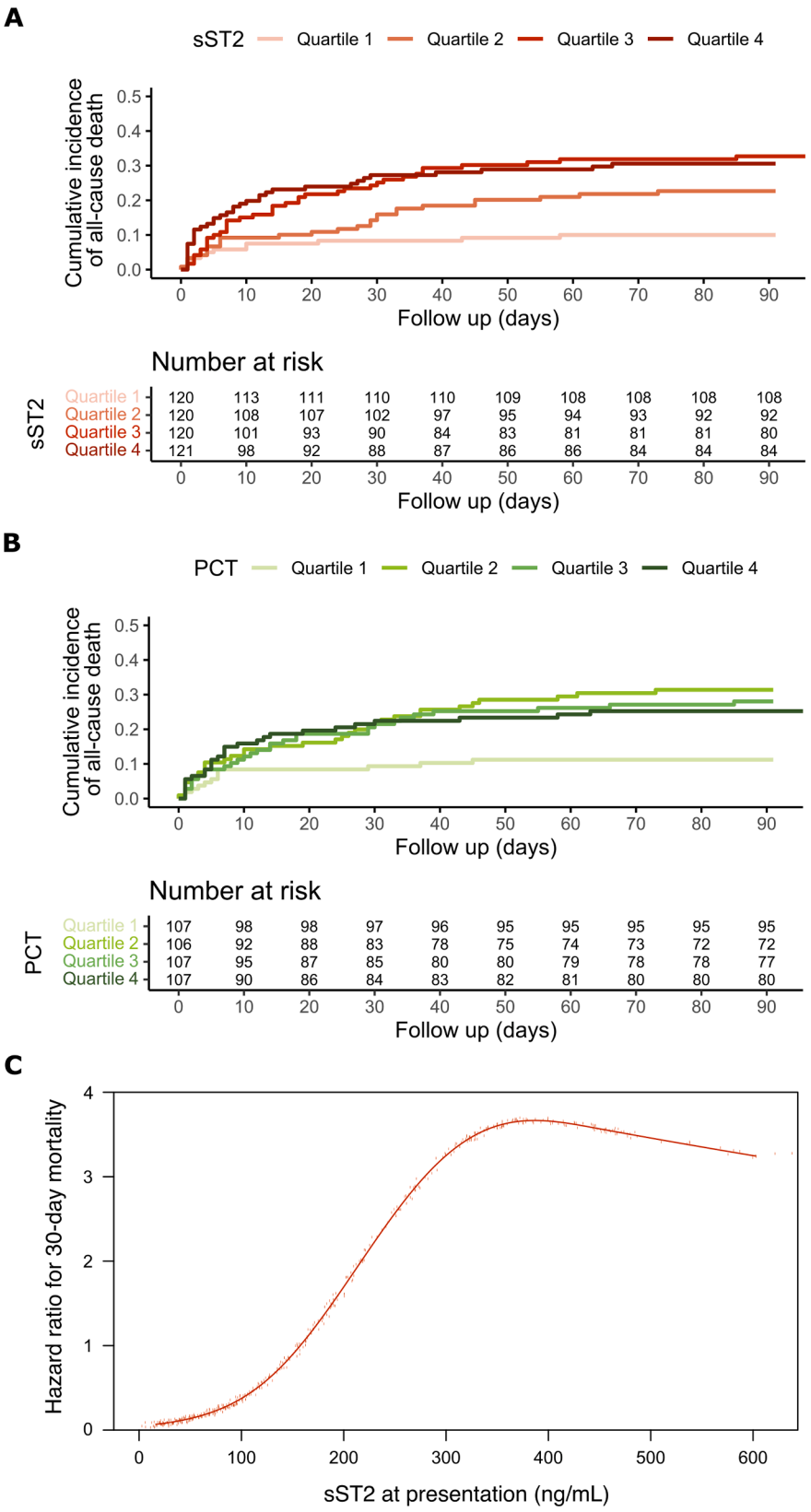

Fig. 4. Kaplan-Meier curves of sST2 (panel A) and procalcitonin (PCT, panel B) quartiles. In panel B, the total number at risk is lower due to missing PCT measurements. Panel C shows a dose–response plot depicting predicted hazard ratios for 30-day mortality according to plasma sST2 levels at Emergency Department presentation, as predicted by the multivariate (clinical variables) Cox regression model.

Consent for publication

All authors consented to publication of this manuscript.

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CRediT authorship contribution statement

Stefania Battista: Conceptualization, Writing – review & editing. **Paolo Bima:** Data curation, Formal analysis, Writing – original draft. **Daniela Forno:** Data curation, Investigation. **Demetrio Luzzi:** Data curation, Investigation. **Elisa Pizzolato:** Data curation, Investigation. **Alice Ianniello:** Data curation, Investigation. **Federico Ponzetto:** Data curation, Investigation. **Francesca Rumbolo:** Data curation, Investigation. **Fabio Settanni:** Data curation, Investigation. **Giulio Mengozzi:** Data curation, Investigation, Supervision, Writing – review & editing. **Fulvio Morello:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Enrico Lupia:** Supervision, Writing – review & editing.

Data availability

Data are available upon reasonable request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2023.117710.

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