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Prognostic value of sepsis-induced coagulation abnormalities: an early assessment in the emergency department

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Abstract
To evaluate if the assessment of coagulation abnormalities at ED admission could improve prognostic assessment of septic patients. This report utilizes a portion of the data collected in a prospective study, with the aim to identify reliable biomarkers for an early sepsis diagnosis. In the period November 2011–December 2016, we enrolled 268 patients, admitted to our High-Dependency Unit with a diagnosis severe sepsis/septic shock. Study-related blood samplings were performed at ED-HDU admission (T0), after 6 h (T6) and 24 h (T24): D-dimer, thrombin–antithrombin complex (TAT) and prothrombin fragment F1 + 2 levels were analyzed. The primary end-points were day-7 and in-hospital mortality. Day-7 mortality rate was 16%. D-dimer (T0: 4661 ± 4562 µg/ml vs 3190 ± 7188 µg/ml; T6: 4498 ± 4931 µg/ml vs 2822 ± 5623 µg/ml; T24 2905 ± 2823 µg/ml vs 2465 ± 4988 µg/ml, all $p < 0.05$) and TAT levels (T0 29 ± 45 vs 22 ± 83; T6 21 ± 22 vs 15 ± 35; T24 16 ± 19 vs 13 ± 30, all $p < 0.05$) were higher among non-survivors compared to survivors. We defined an abnormal coagulation activation (COAG+) as D-dimer > 500 µg/ml and TAT > 8 ng/ml (for both, twice the upper normal value). Compared to COAG−, COAG+ patients showed higher lactate levels at the earliest evaluations (T0: 3.3 ± 2.7 vs 2.5 ± 2.3, p = 0.041; T6: 2.8 ± 3.4 vs 1.8 ± 1.6, $p = 0.015$); SOFA score was higher after 24 h (T24: 6.7 ± 3.1 vs 5.4 ± 2.9, $p = 0.008$). At T0, COAG+ patients showed a higher day-7 mortality rate (HR 2.64; 95% CI 1.14–6.11, $p = 0.023$), after adjustment for SOFA score and lactate level. Presence of abnormal coagulation at ED admission shows an independent association with an increased short-term mortality rate.

Keywords Sepsis · Coagulation abnormalities · Prognostic stratification

Introduction

Coagulation abnormalities are frequent in patients with sepsis [1, 2]. Deviations range from modest activation of coagulation that can only be recognized by highly sensitive assays, to stronger haemostatic activation and overt disseminated intravascular coagulation (DIC) [3]. Coagulation activation is one part of the host defense against infectious agents, but during sepsis its derangement can contribute to multiple organ failure (MOF), as a result of microvascular thrombosis. Postmortem findings in septic patients with DIC include the presence of microthrombi in small blood vessels and also thrombi in mid-size and larger veins and arteries [4].

However, the presence of coagulopathy or DIC, assessed by readily available routine laboratory tests or more comprehensive assays, may be helpful to determine disease severity. Several papers report an increased mortality rate in patients with a more pronounced coagulation dysfunction: most of these papers include septic patients admitted to the Intensive Care Unit (ICU), who are followed through their early ICU course, to evaluate if coagulation abnormalities assessment might improve prognostic stratification [5–7]. The prognostic role of coagulation parameters measured in the first 24 h, after emergency department (ED) admission, hasn't been thoroughly analyzed.

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The aim of the following study is to assess whether the evaluation of coagulation parameters throughout the first 24 h after ED admission might add prognostic information to the routine assessment of septic patients.

Materials and methods

Study design and settings

This report utilizes a portion of the data collected as part of a prospective study, which was conducted at the Emergency Department High-Dependency Unit (ED-HDU) of the University Hospital Careggi, Florence. The aim of the study is to identify reliable biomarkers, which might confirm the diagnosis of sepsis at an early stage in the course of the disease; in this paper, we report only the data regarding coagulation parameters. The study protocol was approved by the local Ethics Committee, and all subjects provided oral and written informed consent. The study was conducted in compliance with the Declaration of Helsinki at the Careggi University Hospital (Florence, Italy), a 1600 bed tertiary care facility, with 82,000 ED visits per year from November 2011 to December 2016. The ED-HDU is a sub-intensive care unit, with availability of advanced monitoring, managed by emergency physicians; all patients are admitted from the ED, according to bed availability. Within 48 h from ED admission, the ED-HDU physicians must decide the optimal patients' disposition, choosing between the ordinary ward and the intensive or sub-intensive care facilities. Because our ED-HDU does not have invasive mechanical ventilators, intubated patients or those potentially requiring intubation within 24 h are directly admitted into the ICU. In a previous analysis of a population of septic patients, we demonstrate that ED-HDU allows a significant reduction in ICU admissions, leading to a relevant cost reduction [8].

Selection of participants and outcomes

We include all subjects with a diagnosis of severe sepsis or septic shock according to the 2001 SCCM/ESICM/ACCP/ATS/SIS criteria [9]: as the most proportion of patients was enrolled before the publication of Sepsis-3, we maintained the previous diagnostic criteria. Exclusion criteria are: (1) age < 18 years; (2) severe bone marrow aplasia induced by recent chemotherapy; (3) dementia complicated by immobilization syndrome lasting at least 3 months; (4) refusal to participate. By a standardized template, we prospectively collected anamnestic data, vital signs, and routine laboratory data and bold samples, which were stored to be analyzed at a later time. Survival status was collected at hospital discharge; the primary outcomes were day-7 and in-hospital mortality rate.

Measurements

The Sequential Organ Failure Assessment (SOFA) scoring system was used to evaluate organ dysfunction during the first 24 h of ED-HDU stay. Study-related blood samplings were performed immediately after ED-HDU admission (T0), after 6 h (T6) and after 24 h (T24). D-dimer (DD), thrombin–antithrombin complex (TAT) and prothrombin fragment F1 + 2 (F1 + 2) were analyzed to determine the relationships between their values at sequential evaluations and survival. The first 3 ml blood was discarded and the next was drawn into a Vacutainer containing 0.109 mol/l buffered trisodium citrate (1:10) in Vacutainer plastic tubes (Becton–Dickinson, Plymouth, England). After centrifuging the citrated blood samples at 1500×*g* for 15 min at a temperature of 4 °C, the plasma samples were aliquoted and frozen at − 80 °C until the time of the different determinations. F1 + 2, and TAT plasma levels were assayed by enzyme-linked immunosorbent test with commercial kits (Enzygnost® F1 + 2 micro, Siemens Healthcare Diagnostics Products GmbH, Germany; Enzygnost® TAT micro, Siemens Healthcare Diagnostics Products GmbH, Germany; normal range for F1 + 2 < 285 pmol/l and for TAT < 4.1 µg/l). DD plasma levels were evaluated by immunoturbidimetric assays with commercial kit (D-Dimer HS, HemosIL, USA, normal range < 250 ng/ml). Disseminated intravascular coagulation was diagnosed according to International Society on Thrombosis and Hemostasis score [10].

Statistical analysis

The sample size was calculated, based on the levels of several biomarkers in survivors and non-survivors [11, 12]; if we consider D-dimer levels [6], a population of 44 patients was needed. As there was a marked difference between different markers, we finally decided to enroll 250 patients.

Continuous variables were reported as mean ± standard deviation; categorical data were analyzed using contingency tables and performing χ^2 test. Between-group comparisons of continuous variables were calculated using the Mann–Whitney *U* test for data with a non-normal distribution (laboratory data) and with the Student's *t* test for unpaired data with normal distribution.

To evaluate differences in trend among different scores we employed Analysis of Variance (ANOVA) for repeated measures. The area under the ROC curves (AUC) was used to evaluate the discriminatory power of the parameters of interest (SOFA score, Lactate, D-dimer and TAT); ROC curves comparison was performed by mean of the DeLong methodology. To evaluate independent prognostic value of

a variable expressing coagulation activation, we employed multivariable logistic regression, with backward method (likelihood ratio method, with variable in by $p < 0.05$ and out $p > 0.10$ to avoid biases due to colinearity). p values < 0.05 were considered as significant. All statistical analyses were carried out using SPSS version 21 (SPSS Statistics Inc, Armonk, New York, USA).

Results

During the study period, 369 patients were admitted to the ED-HDU because of sepsis; 94 patients were excluded according to study criteria (20 for patients' refusal, 33 for bone marrow aplasia induced by chemotherapy and 41 demented bed-ridden patients). Seven more patients were not included due to technical problems with blood sampling. Therefore, in the end we enrolled 268 patients; similar to the participants, excluded patients show a similar age (76 ± 13 vs 75 ± 13 years, p = NS) and T0 SOFA score (5.6 ± 3.0 vs 6.0 ± 3.0, p = NS). The in-hospital mortality rate is similar between participants and non-participants (35 vs 40%, p = NS). The mean of the door-to ED-HDU admission time is 4 ± 2 h.

In Table 1, we show the baseline characteristics, previous medical conditions and vital signs, collected in sequential evaluations. Day-7 mortality rate is 16%, while in-hospital mortality rate is 35%. Compared to survivors, non-survivors show worse vital signs, a more pronounced hypoperfusion and a more severe organ damage, expressed by a higher SOFA score.

In Table 2, we report on the coagulation parameters collected in sequential evaluations, according to day-7 and in-hospital outcome: D-dimer and TAT levels are significantly higher in non-survivors than in survivors at all the evaluations (T0, T6 and T24), while coagulation parameters usually measured in clinical practice (PT, aPTT, fibrinogen and platelets) do not show any significant difference no matter the outcome. Baseline D-dimer (median 1824 vs 1232) and TAT levels (median 8.0 vs 8.6, all p = NS) are comparable between patients who are admitted to the ICU within the first 24 h and those who are not. In Fig. 1, we show the D-dimer and TAT values distribution based on day-7 mortality rate: only a minority of our patients demonstrate values in the normal range (respectively, < 250 ng/ml and < 4.1 ng/ml) during the first 24 h from the moment of admission to the ED. A normal D-dimer (T0: 8% in survivors and non-survivors; T6: 7 vs 3%; T24: 7 vs 4%, all p = not significant) is present in a minority of patients at all evaluations, regardless of the outcome. The proportion of patients with a normal TAT value (T0: 13 vs 3%, p = 0.182; T6: 21 vs 0%, p = 0.019; T24: 24 vs 5%, p = 0.069) increases at T6 and T24 evaluations, and is marginally higher among survivors compared with non-survivors. D-dimer and TAT values remain stable during the first 6 h, while they show a more marked, although non-significant, decrease after 24 h. An Analysis for Repeated Measures (between T0 and T24 evaluations) does not show different trends for D-dimer and TAT in survivors and non-survivors, or a significant parameters variation within patients.

We evaluate a short-term prognostic discriminative power of coagulation parameters alongside sepsis severity indexes by mean of ROC curves. At T0 (Table 3), all the variables show a fair prognostic stratification ability, without significant differences between each other (Fig. 2, Top). At T24 evaluation, SOFA score significantly outperform the coagulation parameters (Table 3 and Fig. 2, Bottom).

We dichotomize D-dimer and TAT values, and we define the cut-off as twice the upper normal limit (≤ or > 500 ng/ml for D-dimer and ≤ or > 8 µg/l for TAT). Compared to survivors, non-survivors more frequently show a T0 D-dimer and TAT value above the median (Table 2). An overt DIC was present in a minority of patients in the first 24 h (10 patients, 4%): despite the low number, patients with DIC show an increased day-7 mortality rate (T0: 13 vs 3%, p = 0.011).

We divide our population in two subgroups: patients with an abnormal coagulation activation (COAG+), who show both D-dimer and TAT abnormal values, and patients in whom one or both parameters are in the lower range (COAG−). The proportion of COAG+ patients decreases in sequential evaluations (43% at T0, 31% at T6 and 24% at T24). Compared to COAG- patients, COAG+ patients show higher lactate levels at the earliest evaluations (T0: 3.3 ± 2.7 vs 2.5 ± 2.3, p = 0.041; T6: 2.8 ± 3.4 vs 1.8 ± 1.6, p = 0.015; T24: 2.4 ± 3.2 vs 1.6 ± 2.0, p = NS), while the SOFA score is significantly higher only after 24 h (T0: 5.5 ± 2.8 vs 4.9 ± 2.5, p = NS; T6: 6.6 ± 3.3 vs 6.0 ± 2.7, p = NS; T24: 6.7 ± 3.1 vs 5.4 ± 2.9, p = 0.008). Finally, day-7 and in-hospital mortality rate are significantly higher in T0 COAG+ patients (respectively 22 vs 9% and 34 vs 16%, all $p < 0.05$); at the following evaluations, the presence of an abnormal coagulation is not associated with a worst day-7 (T6: 19 vs 12%; T24: 20 vs 10%, all p = NS) and in-hospital (T6: 28 vs 23%; T24 33 vs 19%, all p = NS) prognosis. T0 COAG+ patients do not show an increased admission rate in ICU (21 vs 22%) or a more frequent treatment with vasoactive medications (T6: 35 vs 26%, T24: 20 vs 17%, all p = NS).

In a regression analysis, presence of coagulopathy at T0, adjusted for SOFA score and lactate level, maintain an independent association with an increased day-7 mortality rate (HR 2.64; 95% CI 1.14–6.11, p = 0.023) altogether with a high lactate level (HR 1.13; 95% CI 1.03–1.25, p = 0.015); at T6 and T24, only a high SOFA score is independently associated with an increased mortality rate (T6: HR 1.22; 95% CI 1.05–1.41, p = 0.010; T24: HR 1.44; 95% CI 1.23–1.68, $p < 0.001$). Baseline coagulopathy is also associated with an

Table 1 Clinical characteristics in the whole study population and according to day-7 outcome

	All patients ($n=268$)	Survivors ($n=224$)	Non-survivors ($n=44$)	p
Age (years)	74 ± 14	72 ± 14	78 ± 13	0.003
Male sex (%)	157 (59%)	126 (56%)	31 (71%)	NS
PMC				
Arterial hypertension (%)	153 (60%)	130 (60%)	23(56%)	NS
Diabetes (%)	83 (32%)	67 (31%)	16 (39%)	NS
Arterial disease (%)	91 (35%)	73 (34%)	18 (44%)	NS
COPD (%)	54 (21%)	48 (22%)	6 (15%)	NS
CKD (%)	59 (23%)	48 (22%)	11 (27%)	NS
Solid tumor (%)	41 (16%)	31 (14%)	10 (24%)	NS
Hematologic malignancy (%)	18 (7%)	12 (6%)	6 (15%)	NS
Anticoagulant treatment (%)	16 (6%)	14 (6%)	2 (5%)	NS
Antiplatelet therapy (%)	48 (18%)	37 (16%)	11 (25%)	NS
Source of infection				NS
Pulmonary (%)	119 (46%)	95 (44%)	24 (55%)	
Urinary tract (%)	45 (17%)	41 (19%)	4 (9%)	
Abdominal (%)	36 (14%)	31 (14%)	5 (11%)	
Skin (%)	9 (4%)	9 (4%)	0 (0%)	
Unknown (%)	35 (14%)	25 (12%)	10 (23%)	
Other (%)	16 (6%)	15 (7%)	1 (2%)	
Parameters at ED admission				
HR (b/min)	96 ± 20	94 ± 20	104 ± 21	0.006
MAP (mmHg)	76 ± 16	77 ± 16	71 ± 14	0.019
Lactate (mmol/l)	3.0 ± 3.1	2.8 ± 2.7	4.2 ± 4.5	NS
SOFA score	5.3 ± 2.7	5.0 ± 2.5	6.6 ± 3.1	0.004
Parameters after 6 h				
HR (b/min)	90 ± 18	89 ± 17	100 ± 19	0.001
MAP (mmHg)	76 ± 13	76 ± 13	71 ± 12	0.019
Lactate (mmol/l)	2.2 ± 2.4	1.9 ± 1.7	3.9 ± 4.4	0.013
SOFA score	6.3 ± 3.0	6.0 ± 2.8	8.5 ± 3.3	< 0.001
Parameters after 24 h				
HR (b/min)	88 ± 18	88 ± 18	95 ± 17	0.043
MAP (mmHg)	81 ± 14	82 ± 14	78 ± 15	NS
Lactate (mmol/l)	2.2 ± 3.2	1.7 ± 2.1	4.9 ± 6.5	0.021
SOFA score	5.9 ± 3.1	5.4 ± 2.5	9.4 ± 4.0	< 0.001
Septic shock (%)	114 (43%)	88 (39%)	26 (59%)	0.024

PMC previous medical conditions, *COPD* chronic obstructive pulmonary disease, *CKD* Chronic kidney disease, *HR* heart rate, *MAP* mean arterial pressure, *WBC* white blood cells

increased in-hospital mortality (HR 2.54; 95% CI 1.29–5.01, $p=0.007$), altogether with a higher SOFA score (HR 1.16; 95% CI 1.03–1.31, $p=0.015$).

Discussion

Our study presents three major findings: (1) upon ED-HDU admission, most septic patients show significantly abnormal indexes of coagulation activation, which was are not apparent in routine coagulation tests, and tend to improve within the first hours; (2) patients with an abnormally activated coagulation, develop a more marked organ dysfunction, suggested by a higher SOFA score, and show a more severe hypoperfusion, as indicated by higher lactate levels, compared with patients with a less pronounced coagulation derangement; (3) upon admission, the presence of an abnormal coagulation activation shows an independent prognostic association with an increased short- and medium-term mortality rate.

An abnormal coagulation activation is a mechanism, known to contribute to multiple organ damage in the

Table 2 Coagulation parameters in the first 24 h according to day-7 and in-hospital outcome

	Day-7 mortality		In-hospital mortality	
	Survivors ($n=224$)	Non-survivors ($n=44$)	Survivors ($n=198$)	Non-survivors ($n=70$)
T0 evaluation				
DD (ng/ml)	1296 (601–3147)	2962 (968–7464)°	1182 (500–2607)	2437 (954–5030)°
DD > 500 ng/ml (%)	166 (74%)	36 (82%)*	144 (73%)	58 (83%)*
F1 + 2 (pmol/l)	291 (151–531)	343 (137–701)	276 (152–495)	369 (142–701)
TAT (µg/l)	8.4 (5.3–17.0)	13.3 (7.9–32.0)°	7.7 (4.8–14.2)	13.5 (7.6–31.8)°
TAT > 8 µg/l (%)	99 (44%)	26 (59%)*	85 (43%)	40 (57%)°
PT-INR	1.4 (1.3–1.9)	1.4 (1.2–1.8)	1.4 (1.3–1.9)	1.5 (1.3–1.9)
aPTT (s)	31 (27–40)	31 (28–40)	31 (27–40)	31 (27–38)
Fibrinogen (g/l)	490 (410–452)	452 (384–537)	497 (428–562)	466 (403–539)
PLT ($\times 10^3$/µl)	161 (106–229)	166 (96–232)	161 (109–228)	167 (99–232)
T6 evaluation				
DD (ng/ml)	1301(641–3261)	2871 (952–6964)°	1151 (566–2690)	2417 (884–4884)°
DD > 500 ng/ml (%)	151 (67%)	30 (68%)	132 (67%)	49 (70%)
F1 + 2 (pmol/l)	268 (140–541)	317 (151–690)	246 (135–493)	309 (179–655)
TAT (µg/l)	7.9 (4.8–14.3)	11.6 (6.9–20.5)°	7.3 (4.3–12.2)	11.4 (5.8–19.6)°
TAT > 8 µg/l (%)	76 (34%)	18 (41%)	78 (39%)	26 (37%)
PT-INR	1.5 (1.3–2.0)	1.5 (1.2–1.9)	1.5 (1.3–2.0)	1.5 (1.3–2.1)
aPTT (s)	33 (29–41)	31 (28–40)	32 (29–41)	33 (29–40)
Fibrinogen (g/l)	493 (431–564)	470 (398–551)	503 (437–567)	464 (399–503)*
PLT ($\times 10^3$/µl)	152 (100–218)	148 (94–211)	151 (100–221)	159 (97–216)
T24 evaluation				
DD (ng/ml)	1165 (628–2719)	1390 (779–4298)	1053 (587–2498)	1437 (948–3064)*
DD > 500 ng/ml (%)	142 (63%)	24 (55%)	125 (63%)	41 (59%)
F1 + 2 (pmol/l)	222 (128–385)	334 (157–603)	212 (114–342)	249 (162–538)*
TAT (µg/l)	6.5 (4.3–10.3)	8.9 (4.8–17.4)*	5.7 (3.9–9.5)	8.5 (5.2–14.5)°
TAT > 8 µg/l (%)	59 (26%)	14 (32%)	49 (25%)	24 (34%)*
PT-INR	1.5 (1.3–2.0)	1.3 (1.2–2.3)	1.5 (1.3–2.0)	1.4 (1.2–2.1)
aPTT (s)	32 (28–39)	32 (28–42)	31 (28–39)	33 (29–41)
Fibrinogen (g/l)	501 (440–570)	506 (471–527)	501 (435–573)	496 (444–528)
PLT ($\times 10^3$/µl)	143 (95–211)	150 (69–221)	143 (97–209)	141 (69–238)

DD D-dimer, *F1 + 2* prothrombin fragment F1 + 2, *TAT* thrombin–antithrombin complex, *APTT* activated partial thromboplastin time, *PLT* platelets

*$p < 0.05$; °$p < 0.01$. Data are expressed as median level (25th–75th percentile)

presence of sepsis [4, 13]. Pathological coagulation derangement is mainly caused by circulating cytokines, which along side other mediators are responsible for activating the coagulation system and downregulating important physiological anticoagulant pathways, such as protein C and fibrinolytic systems. Increased fibrin formation and its impaired removal lead to microvascular thrombosis, which may result in tissue ischemia and subsequent organ damage [14].

Several observational studies have demonstrated the association between a more marked abnormality of different coagulation parameters and an increased mortality rate in ICU patients [1, 6, 15, 16]. In this study, for the first time, we include a large population of patients cared for in the emergency department, and evaluate coagulation abnormalities over the first 24 h from sepsis diagnosis, to determine the potential of coagulation assessment to improve prognostic stratification. In Emergency Medicine, identifying patients at risk for an early adverse prognosis is of utmost importance; therefore, we decided to explore the short-term (7 day interval) prognostic value of these parameters, alongside in-hospital mortality. Coagulation parameters commonly measured in clinical practice and used in SOFA score calculation do not provide us with any useful prognostic information. Conversely, D-dimer and TAT levels, measured in sequential evaluations, are significantly higher in non-survivors, compared with survivors. Upon ED-HDU admission, the individual parameters show a fair prognostic accuracy; however, a combined increase of these indexes shows a significant

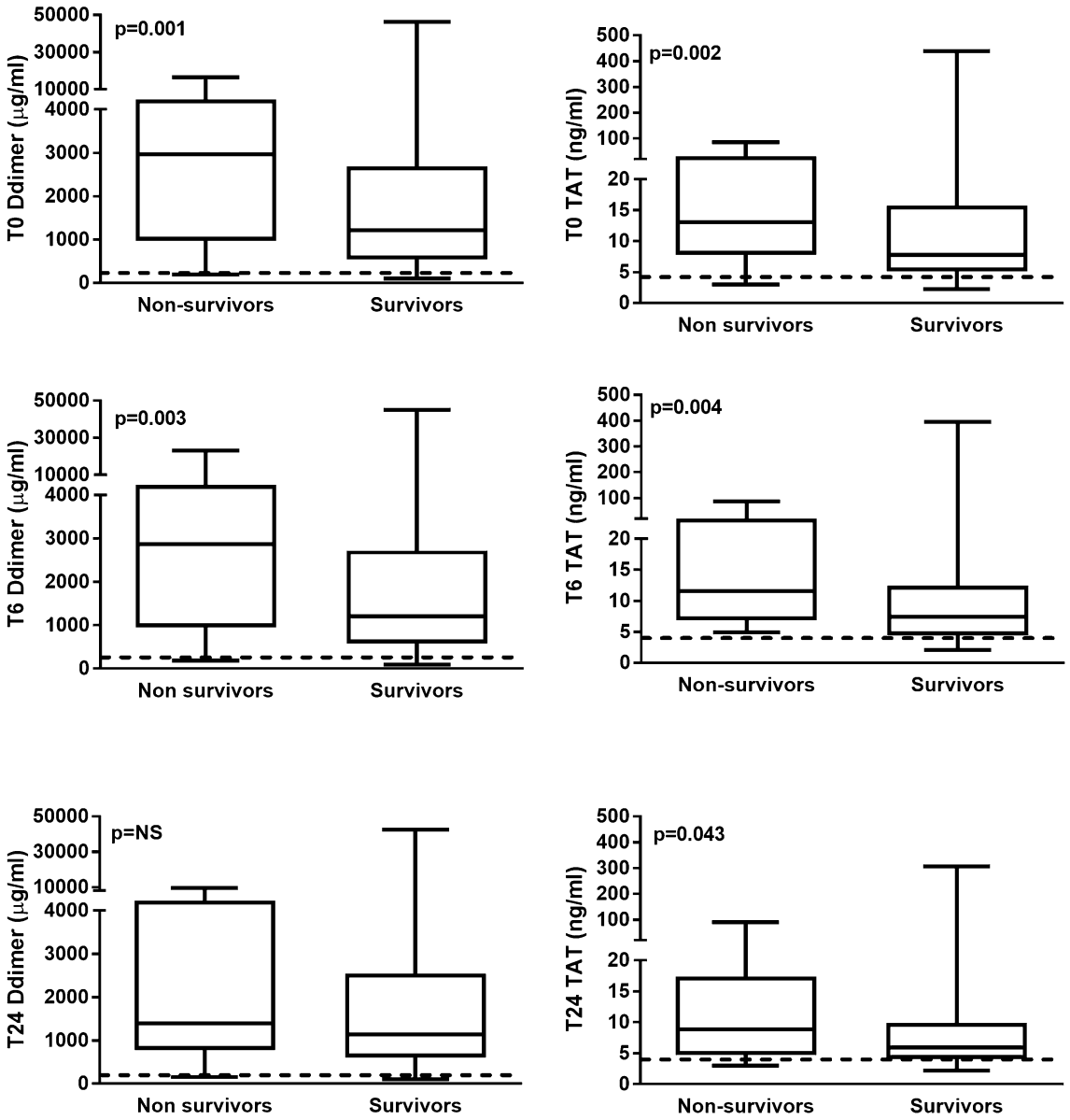

Fig. 1 D-dimer and TAT values distribution according to day-7 mortality at T0, T6 and T24 evaluations. The continuous lines represent the median values in survivors and non-survivors, while the dotted lines represent the upper normal limit

Table 3 Analysis of the prognostic discriminative power of the coagulation and sepsis severity parameter at T0 and T24

	Day-7 mortality			In-hospital mortality		
	AUC	95% CI	*p*	AUC	95% CI	*p*
T0 evaluation						
D-dimer	0.67	0.57–0.77	0.001	0.65	0.57–0.72	< 0.001
TAT	0.66	0.57–0.76	0.002	0.67	0.60–0.75	< 0.001
SOFA	0.65	0.55–0.75	0.003	0.64	0.55–0.72	0.001
Lactate	0.63	0.54–0.71	0.013	0.59	0.51–0.57	0.026
T24 evaluation						
D-dimer	0.62	0.55–0.69	0.042	0.60	0.53–0.67	0.026
TAT	0.64	0.56–0.71	0.028	0.64	0.56–0.71	0.005
SOFA	0.80	0.74–0.85	< 0.001	0.77	0.70–0.82	< 0.001
Lactate	0.72	0.65–0.78	< 0.001	0.69	0.63–0.76	< 0.001

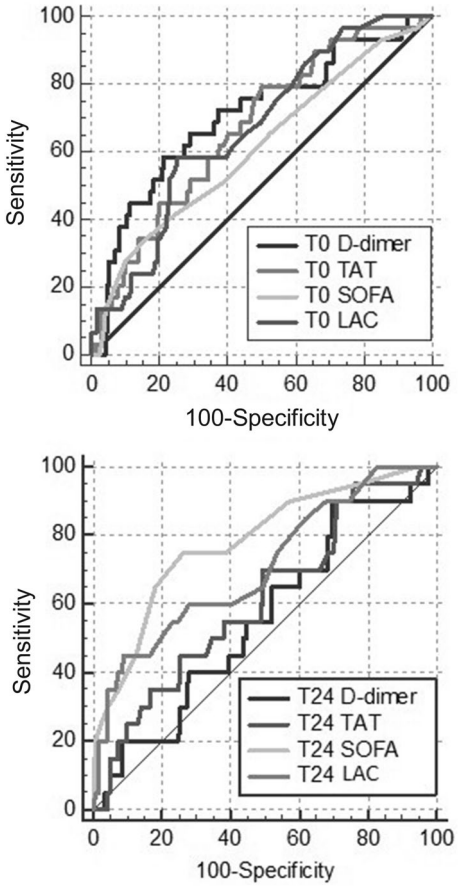

Fig. 2 Comparison of T0 (top) and T24 (bottom) D-dimer, TAT, SOFA and Lac prognostic performance by day-7 mortality. No significant difference at T0; at T24, $p < 0.05$, respectively, between SOFA and D-dimer and SOFA and TAT

association with an increased short- and medium-term mortality rate, independent of lactate level and SOFA score. At T6 and T24 evaluations, the SOFA score becomes the only independent prognostic determinant, which shows the severity of the global organ damage [17–20]. We are aware that the SOFA score is less expensive and more feasible than coagulation parameters. However, in this paper and in the previous ones, its prognostic discrimination ability is not optimal, especially during the very early evaluations; the cut-off value, to identify patients at high risk of an adverse prognosis, has never been identified and prospectively validated. The presence of a coagulation abnormality might represent an adjunctive parameter to integrate and improve SOFA score performance, especially at the time of the earliest prognostic assessment.

There are some limitations in this report. The single center study design and the clinical setting of the ED-HDU could limit the applicability of our results because it is not common, especially outside of European countries. Moreover since all our patients were admitted to ED-HDU, they were not intubated: we must keep in mind that a different selection criteria could have had different results. Another problem is that while we analyzed the prognostic value of an increased coagulation activation, we did not examine the presence of an impaired fibrinolysis. A previous study [1], which evaluated a large population, already demonstrates that in the early phase of the disease, almost all septic patients have an activated coagulation, while only a minority of them show an impaired fibrinolysis. For this reason, we decided to analyze these coagulation parameters. We have taken into account that patients had only spent a few hours in the ED before being admitted to the HDU, and had already begun treatment: however, at that time, we observed a very slight change in the level of coagulation parameters during the first 6 h of their ED-HDU stay. We can, therefore, assume that our T0 evaluation represented the coagulation parameters at the very early stage of the septic process. Finally, as we had already explained, we added the day-7 mortality endpoint: by the seventh day, the number of events was low, but we are still able to show that a very short-term mortality rate depends on several parameters, such as a high SOFA score and lactate levels, as well as a more pronounced coagulation derangement. More extensive studies are needed to confirm this very short-term prognostic stratification, which appears to be of utmost importance in Emergency Medicine.

To summarize, in this series of consecutive, non-intubated, septic patients admitted to the HDU from the ED, coagulation abnormalities are very common. In early sequential evaluations, D-dimer and TAT levels are higher in non-survivors compared to survivors; upon admission, the presence of abnormal coagulation shows an independent association with an increased short- and medium-term mortality rate. Further multi-institutional collaborative studies are needed to confirm our results; these new parameters could improve the early identification of septic patients at risk of an unfavorable prognosis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights The study was conducted in compliance with the Declaration of Helsinki at the Careggi University Hospital.

Informed consent The study protocol was approved by the local Ethics Committee, and all subjects provided oral.

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