Prognostic indexes of septic syndrome in the emergency department

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Objective. **Sepsis is a frequent and often lethal condition. Rapid identification and aggressive therapy in the emergency department (ED) are essential for outcome. Several indexes were found to be significantly related to short-term clinical outcome, but only bedside, rapidly available tests are thought to be useful in the ED. To define the prevalence and mortality of patients with severe sepsis presenting to the ED of a tertiary care hospital in Italy, we furthermore investigated the ability of bedside, non-invasive prognostic indexes to identify patients with adverse short-term clinical outcome.**

Methods. **All patients admitted to the ED with a diagnosis of severe sepsis or septic shock were included. Retrospective data were collected by a dedicated software program using predefined searching criteria including clinical data, vital sign parameters, sepsis-related organ failure assessment (SOFA) score, and blood tests. The relationship between prognostic indexes and 24-h or 28-day mortality was evaluated by multivariate logistic regression analysis.**

Results. **Ninety patients were enrolled from June 2004 to June 2005 (0.2% of all incoming patients to ED and 0.7% of all critical patients). Mean age was 77 ± 15 years, 54.4% were women. During follow-up (28 days) 46 patients died (51.1%), 21 patients (23.3%) within 24 h. At multivariate analyses, age > 80 (odds ratio [OR] 4.10; 95% confidence intervals [CI] 1.39-11.90, p = 0.01), serum lactate > 5 mmol/l (OR 3.40; 95% CI 1.21-9.60, p = 0.02) and acute renal failure (OR 18.90; 95% CI 1.80-200, p = 0.02) were independent predictors of 28-day mortality.**

Conclusions. **Among critical patients admitted to an Italian ED, those with severe sepsis/septic shock represent about 1%, with a very high mortality rate. Bedside non-invasive prognostic indexes are able to identify with high accuracy patients with adverse short-term clinical outcome.**

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Key words: **emergency medicine, lactic acid, septic shock, septic syndrome, severity of illness index**

Introduction

Sepsis is a frequent, and potentially reversible, severe syndrome with high mortality[1,2]; it is the second cause of death in non-cardiovascular intensive care units and the 10th cause of mortality in the world[3]. Rapid identification and aggressive therapy are essential for outcome of patients with septic syndrome[4-6].

Standard criteria for sepsis identify a very heterogeneous population in relation to severity and prognosis. Previous data show that patients with severe sepsis septic shock have to be treated as soon as possible in the emergency department (ED)[5,7-9]. Moreover, to better identify patients needing an aggressive approach, several prognostic indexes have been proposed in different clinical settings[5,10-17]. However, few data are available about prognostic indicators for sepsis in the ED[2,4,17]. In addition, some of the indexes investigated require invasive procedures or time-consuming computations and are difficult to obtain in a busy ED.

The present study was planned to investigate the prevalence of patients with severe sepsis/septic shock in a tertiary care Italian ED, and to estimate the accuracy of several bedside indexes in predicting early all-cause mortality.

Methods

Subjects investigated

All patients entering the ED of Careggi Hospital (Florence, Italy) between June 2004 and June 2005 matching inclusion criteria were eligible for the study. Study inclusion criteria were: a) clinical suggestion of infection; b) two or more systemic inflammatory response syndrome criteria (tachycardia [heart rate of ≥ 90 bpm]), tachypnoea [respiratory rate of > 20 bpm]) or < 90% oxygen saturation, hyperthermia of > 38°C, or hypothermia of < 35.5°C, white blood cell count of ≥ 12 000 or < 4000 cells/mm^3); and c) either an elevated lactate level (> 4 mmol/l) or systolic blood pressure of < 90 mmHg. Patients selected with such criteria well represent the group of all septic syndrome patients needing an immediate and aggressive treatment in the ED[5]. No exclusion criteria were considered. Clinical data were retrospectively obtained from a dedicated software program (PSB 4.2.2.0 version, First Aid, Sago, Florence, Italy). The study complied with

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the Declaration of Helsinki, and all patients enrolled in the study gave their consent to the use of medical information for research purposes.

Prognostic indexes

We conducted an electronic search using the National Library of Medicine web site (PubMed) using the following key words: sepsis, severe sepsis, septic shock, prognosis, prognostic index, outcome, and ED. We excluded indexes relative to laboratory data not routinely available in the ED, or indexes not available because of the retrospective nature of the study (poor socio-economic status, reduced muscular mass, nosocomial nature of infections, under-nourishment, very low weight). We also examined the prognostic value of semi-invasive/invasive procedures practiced in the ED.

For searching purposes, we classified prognostic indexes into three different categories (Table 1)[10,12,13,15,18-27]: anamnestic indexes, including data obtained by clinical history; presentation indexes, including all the clinical and laboratory parameters on admission in the ED; procedure indexes, including semi-invasive/invasive procedures performed in the ED.

Statistical analysis

Data are expressed as means ± SD. The unpaired Student's *t*-test or one-way analysis of variance were used to compare normally distributed data. Fisher's exact test was used for the comparison of non-continuous variables expressed as proportions. Logistic regression analysis was performed to investigate the accuracy of the prognostic indexes for predicting 24-h or 28-day all-cause mortality. Odds ratios (OR) and 95% confidence intervals (CI) were calculated with both univariate and multivariate analysis, the last using a stepwise forward regression model, in which each variable with a $p \leq 0.05$ was entered into the model. P values are two-sided, and a $p \leq 0.05$ was considered to indicate statistical significance. Calculations were performed with use of a SPSS statistical package (version 8.0, SPSS Inc., Chicago, IL, USA).

Table 1. Prognostic indexes.

Anamnestic prognostic indexes
Male sex[18]
Older age[15]
Co-morbidities: chronic obstructive pulmonary disease, heart failure, preexisting renal failure, diabetes, arterial hypertension, cirrhosis, recent stroke, malignancy, dementia[10,19]
Peripheral skin injuries indicative of compromised circulation (ulcers, blisters, gangrene)[10]
History of recurrent infections[20]
Invasive procedures in the last 3 days (central venous catheter, artificial ventilation, endoscopy, intubation, drains, bladder catheter, etc.)[12]
Hospital admission in the last 72 h[10]
Surgery in the last 2 months[13]
Congenital or acquired immunodepression (corticosteroids, chemotherapics, immunodepressor or cytotoxic drugs, haematological neoplasms, severe autoimmune disease, leukopaenia, splenectomy, transplantation)[21,22]
Mono/polymicrobic origin of infection[23]
Adequate home antibiotic therapy[24]
Home insulin therapy
Forced bed rest
Institutionalisation[15]
Prognostic indexes at presentation
Acute renal failure[25]
Disseminated intravascular coagulation[15]
Leukopaenia[26]
Vital parameters (body temperature, heart and respiratory rate, systolic and diastolic blood pressure)
SOFA score (describing functional alteration of cardiovascular, respiratory, nervous, hepatic, haematological, renal system)[27]
Haemogasanalytic parameters (pH, oxygen and carbon monoxide pressure, oxygen saturation, anion gap, carbonates, simple basis excess, serum lactate, methaemoglobin, carboxyhaemoglobin, electrolytes, glucose)
Laboratory parameters available in the first hours (ALT, AST, CK-MB, troponin I, myoglobin, urea, creatinine, total bilirubin, CPK, LDH, amylases, white and red cells, haemoglobin, packed cell volume, platelets, PT, APTT, INR, fibrinogen)
Procedural prognostic indexes
Non-invasive ventilation, adequate antibiotic therapy, oro-tracheal intubation, others (venous and arterial catheterisation, bladder catheterisation, fiberscope techniques, drains, tracheotomy, suction drainages, nasogastric tube, angiography)

ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate transaminase; CK, creatine kinase; CPK, creatine phosphokinase; INR, international normalised ratio; LDH, lactic dehydrogenase; PT, prothrombin time; SOFA, sepsis-related organ failure assessment.

Results

Ninety patients matched the inclusion criteria (Table 2). They represented 0.2% of all patients entering our ED, 0.6% of overall hospital admissions, and 0.7% of high priority codes (yellow and red). Forty-nine were women (54.4%) and the mean age was 77 ± 15 years. Co-morbidities were found in a very high percentage of patients (94.4%). The most frequent site of infection was pulmonary (52.5%), followed by the genitourinary tract (8.5%) and soft tissues (6.7%). Of note, 25.6% of patients had an unknown infective source.

The mean ED stay for severe sepsis/septic shock patients was 5.15 h vs 3.6 h of overall high priority codes ($p < 0.001$). Four patients (4.4%) died in the ED, 5 (5.5%) were admitted to intensive care units, and 71 (78.8%) were admitted to the general ward.

During follow-up (28 days), 46 patients died (51.1%), 21 patients (23.3%) within 24 h.

Table 2. Patients investigated.

No. patients	90
Age (years)	77 ± 15 (range 28-98)
Female	49 (54.4%)
Infective source	
Lung	47 (52.5%)
Urinary tract	8 (8.5%)
Intra-abdominal	5 (5.6%)
Skin/subcutis	6 (6.7%)
Meningitis	1 (1.1%)
Unknown	23 (25.6%)
HR (bpm)	118.2 ± 25.2 (range 66-194)
SBP (mmHg)	85.9 ± 15 (range 50-140)
Body temperature (°C)	37.4 ± 1.9 (range 30.8-39.9)
Co-morbidity	85 (94.4%)

HR, heart rate; SBP, systolic blood pressure.

Several studied parameters were found significantly related to all-cause mortality at univariate logistic regression analysis (Table 3). Multivariate analysis showed that age > 80 years (OR 4.10; 95% CI 1.39-11.90, p = 0.01), serum lactate > 5 mmol/l (OR 3.40; 95% CI 1.21-9.60, p = 0.02) and acute renal failure (OR 18.90; 95% CI 1.80-200, p = 0.02) were independent predictors of 28-day mortality. Home therapy with insulin was the only variable related to a lower risk of death during follow-up (OR 0.02; 95% CI 0.00-0.30, p < 0.01). From this model a patient with all the adverse prognostic indexes has a risk of death of 99%, whereas a patient without any of those has a risk of death of about 1%. The global accuracy of the model is 83%.

Age > 80 years (OR 5.73; 95% CI 1.24-26.42, p = 0.025) and serum lactate > 5 mmol/l (OR 3.92; 95% CI 0.86-17.94, p = 0.078) were found to be significantly related at multivariate analysis, as well as to death within 24 h of admission (Table 4). In addition, sepsis-related organ failure assessment (SOFA) score > 7 (OR 15.86; 95% CI 1.40-179.32, p = 0.026), a history of chronic obstructive pulmonary disease (OR 9.26; 95% CI 1.76-48.67, p = 0.009), disseminated intravascular coagulation on ED admission (OR 41.99; 95% CI 2.01-875.64, p = 0.016) and the need for non-invasive positive pression ventilation in the ED (OR 54.03; 95% CI 2.40-1216.75, p = 0.012) were independently related to adverse outcome at 24 h but not at 28 days (Table 4).

Table 3. Multivariate logistic regression analysis at 28 days.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Anamnestic indexes				
Age > 80 years	3.00 (1.27-7.10)	0.012	4.10 (1.39-11.90)	0.01
Diabetes	0.31 (0.11-0.89)	0.03	–	0.81
Insulin	0.11 (0.02-0.54)	< 0.01	0.02 (0.00-0.30)	< 0.01
Presentation indexes				
ARF	7.81 (1.63-37.33)	0.01	18.90 (1.80-200)	0.02
SOFA score > 7	4.5 (1.46-13.90)	< 0.01	–	0.157
pH	0.01 (0.00-0.29)	< 0.01	–	0.47
Serum lactate > 5 mmol/l	3.62 (1.52-8.65)	< 0.01	3.40 (1.21-9.60)	0.02

ARF, acute renal failure; CI, confidence intervals; OR, odds ratio; SOFA, sepsis-related organ failure assessment.

Table 4. Multivariate logistic regression analysis at 24 h.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Anamnestic indexes				
Age > 80 years	3.50 (1.20-10.19)	0.022	5.73 (1.24-26.42)	0.025
COPD	3.14 (1.11-8.90)	0.027	9.26 (1.76-48.67)	0.009
Presentation indexes				
ARF	4.84 (1.45-16.19)	0.007	–	0.326
DIC	12.18 (1.2-124.5)	0.009	41.99 (2.01-875.64)	0.016
SOFA score > 7	3.37 (0.64-17.74)	0.009	15.86 (1.40-179.32)	0.026
SO_2	0.94 (0.89-0.99)	0.003	–	0.415
Serum lactate > 5 mmol/l	5.99 (1.81-19.83)	0.002	3.92 (0.86-17.94)	0.078
Procedural indexes				
NPPV	5.58 (1.13-27.46)	0.021	54.03 (2.40-1216.75)	0.012

ARF, acute renal failure; COPD, chronic obstructive pulmonary disease; DIC, disseminated intravascular coagulation; NPPV, non-invasive positive pressure ventilation; SO_2, oxygen saturation; SOFA, sepsis-related organ failure assessment.

Discussion

This study shows that patients with severe sepsis or septic shock represent 0.2% of all incoming patients to a tertiary care European ED, showing a 51% mortality rate at 28-day follow-up. Bedside prognostic indexes, readily available on admission, accurately recognise patients at high risk of adverse short-term outcome.

To our knowledge no data are available about incidence and prognosis of severe sepsis/septic shock in European EDs. Two large cohort studies performed in the United States found an incidence of severe sepsis/septic shock of 0.1%[4] and 0.3%[5] respectively, very similar to that we found in our study that shows some relevant insights: patients with severe sepsis/septic shock are about 1% of all high priority codes, and their mean stay in the ED is significantly longer (+69%) than overall high priority codes. In our series the rate of intensive care unit admission is 5.5%, markedly lower than previously reported in studies conducted in the United States (from 30 to 100%)[3,28-30]. This higher proportion is not justified by differences in inclusion criteria because in our study only patients with a worse clinical profile were enrolled. A low availability of high dependent unit beds in a public health system with limited resources, as that present in Italy, probably might be the best explanation. Might a different management have changed the outcome of severe sepsis/septic shock patients? Although the retrospective nature of our study cannot allow a definitive answer, the mortality rate in our population was considerably higher (51.1%) than previously reported in studies performed in the ED, and including patient with severe sepsis/septic shock (from about 4 to 40%)[2,3,5,28,31]. On the other hand, we did not exclude patients with terminal conditions, our patients were older (mean age 77 vs about 60 years) and more often affected by co-morbidites (94 vs about 60%), thus a rough comparison of mortality data is not possible.

Many prognostic indexes are shown by the vast bibliography available about sepsis[2,10,13,14,16,25,26]. The aim of the present study was also to test the utility of bedside and rapidly available indexes in the ED. We find that a model based on four simple prognostic parameters is able to correctly predict the 28-day mortality in 83% of the cases. Age > 80 years, high serum lactate, and the presence of acute renal failure are found to be strongly related to adverse short-term outcome in previous studies[10,32-34]. At univariate analysis, surprisingly, we find that a history of diabetes predicts a favourable outcome. Multivariate analysis reveals that the protective effect of diabetes is due to the co-presence of insulin therapy started before admission (Table 3). We could not have information about glycaemic control before and during all hospital stays; however, considering that the vast majority of patients were admitted to a general ward, we can suppose that diabetic patients treated with insulin before hospital admission, were subjected to a more careful glycaemic control than patients without a history of insulin treatment. This observation agrees with previous large studies that demonstrate a 3.7% absolute mortality reduction through an intensive insulin therapy[35,36]. Moreover, although diabetes, through its effect on the immunological system, has been shown to have a negative prognostic value in a general population with sepsis[10], the high level of immunological impairment present in our population with severe septic disease probably conceals the prognostic role of diabetes[37].

A very high mortality rate was found in the first 24 h. Twenty one patients died within 24 h of admission in the ED (23.3%). They represent about 46% of all deaths that occurred in the follow-up. At multivariate analysis, the presence of disseminated intravascular coagulation and high SOFA scores (> 7 points) are found to be independently related to adverse outcome at 24 h but not at 28 days indicating their relevance in the very early clinical course. In addition, the history of chronic obstructive pulmonary disease and the need for non-invasive positive pression ventilation in the ED were significantly related to an adverse outcome at 24 h, suggesting an important role for impaired respiratory function in very early mortality.

In conclusion, the incidence of patients with severe septic disease in a tertiary care Italian ED is only 0.2%. However, these patients represent about 1% of all high priority codes, and their management in the ED was longer than patients with other critical illnesses. Very simple, ready available bedside prognostic indexes are able to predict with high accuracy an adverse short-term clinical outcome.

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