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Severe sepsis mortality prediction with logistic regression over latent factors

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ABSTRACT

Sepsis is one of the main causes of death for non-coronary ICU (Intensive Care Unit) patients and has become the 10th most common cause of death in western societies. This is a transversal condition affecting immunocompromised patients, critically ill patients, post-surgery patients, patients with AIDS, and the elderly. In western countries, septic patients account for as much as 25% of ICU bed utilization and the pathology affects 1–2% of all hospitalizations. Its mortality rates range from 12.8% for sepsis to 45.7% for septic shock.

The prediction of mortality caused by sepsis is, therefore, a relevant research challenge from a medical viewpoint. The clinical indicators currently in use for this type of prediction have been criticized for their poor prognostic significance. In this study, we redescribe sepsis indicators through latent model-based feature extraction, using factor analysis. These extracted indicators are then applied to the prediction of mortality caused by sepsis. The reported results show that the proposed method improves on the results obtained with the current standard mortality predictor, which is based on the APACHE II score.

1. Introduction

Sepsis is a clinical syndrome defined by the presence of both infection and Systemic Inflammatory Response Syndrome (SIRS). This condition can lead to severe sepsis, which implies organ dysfunction, or to an even more severe state: septic shock (severe sepsis with hypotension refractory to fluid administration) and multiorganic failure (American College of Chest Physicians, 1992; Levy et al., 2003).

In western countries, septic patients account for as much as 25% of ICU bed utilization and the pathology occurs in 1–2% of all hospitalizations. The mortality rates of sepsis range from 12.8% for sepsis and 20.7% for severe sepsis, to up to 45.7% for septic shock (Esteban et al., 2007).

This pathology has followed a clear upwards trend over the last 20 years, reaching 300,000 cases per year only in the United States. The number of sepsis cases in this country is projected to grow at a yearly rate between 1.5% and 8% as the population ages and treatment becomes more aggressive (Angus et al., 2001; Martin, Mannino, Eaton, & Ross, 2003).

The medical management of sepsis is therefore a serious challenge to healthcare systems as a whole. Recently, doubts have been raised about the usefulness of current diagnostic methods for this pathology (Vincent, 1997). This is due to their poor specificity and sensitivity results, as well as to their lack of prognostic significance. Raising to this challenge, the aim of this paper is to investigate new sets of descriptors that improve on current standards in terms of mortality prediction accuracy.

Here, we propose the use of a latent model-based feature extraction approach to obtain such new sets of descriptors, or prognostic factors. The experimental results reported in this study show them to be readily interpretable. Interpretability is, needless to say, a sensitive issue in the medical ambit, and one that should not be underestimated: lack of translation of the prognostic factors into usable clinical knowledge might render the proposed approach useless (Lisboa, Vellido, & Martín, 2010).

In the experiments of this study, the extracted factors are used to predict mortality through standard logistic regression (LR), a method commonly used in medical applications (Kurt, Ture, & Kurum, 2008; Paliwal & Kumar, 2009) and widely trusted by clinicians. The prediction accuracy results herein reported improve on those obtained with current standard data descriptors and therefore provide support for the use of these new factors as risk-of-death predictors in ICU environments.

2. Related work

The SIRS pathology is known to be a quite sensitive indicator of sepsis (Rangel-Frausto et al., 1995), but also one of poor specificity.

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Different studies have shown that the incidence of SIRS is quite high in critical patients in general. For example, Pittet et al. (1995) present a SIRS incidence of up to 93% in critical care patients, while Rangel et al. show an incidence of 68% (Rangel-Frausto et al., 1995). The latter study also shows that 25% of patients with SIRS developed a sepsis, 18% presented severe sepsis, and 4% of them, septic shock. Regardless of these incidence ratios, the early detection of patients with a higher risk of death remains a challenge.

The MEDS (Mortality in Emergency Department Sepsis) score is a collection of variables routinely recorded in the emergency departments (terminal illness, tachypnea/hypoxemia, septic shock, platelet count, age, lower respiration infection, bands, nursing home resident and mental status). It was shown in Sankoff et al. (2008) to yield an area under the ROC curve (AUC) of 0.88 for the population under study: patients at the emergency department with SIRS (not taking into account those septic patients admitted in the emergency department who were not critical enough to be admitted in the ICU).

Since the publication in 1985 of the Organ System Failure (OSF) score by Knaus, Draper, Wagner, and Zimmerman (1985), which is a prognosis scale to evaluate and quantify the Multiple Organ Dysfunction Syndrome (MODS), alternative prognostic scores have been developed. They include the APACHE II (Acute Physiology and Chronic Health Evaluation II) score (Knaus, Draper, Wagner, & Zimmerman, 1985), the Multiple Organ Dysfunction Score (MODS) (Marshall et al., 1995) and the SOFA (Sequential Organ Failure Assessment) score (Vincent et al., 1996), and the LODS (Logistic Organ Dysfunction System) (Le Gall, Klar, & Lemeshow, 1997). Two prognostic scores based on the PIRO model (Predisposition, insult/infection, response and organ dysfunction) have also been recently proposed: the SAPS3 PIRO score (Moreno et al., 2008: AUC 0.77) and the PIRO score (Rubulotta et al., 2009: AUC 0.70).

Machine learning methods have been used with varying success for the prediction of mortality caused by sepsis. A diagnostic system for septic shock based on ANNs (Radial Basis Functions and supervised Growing Neural Gas) was presented in Brause, Hamker, Paetz, and Jain (2001), reporting an overall correct classification rate of 67.84%, with a specificity of 91.61% and an extremely poor sensitivity of 24.94%. Support Vector Machines (SVM) have also been used in this context. Tang et al. (2010) presented a SVM-based system for sepsis and SIRS prediction from non-invasive cardiovascular spectrum analysis, reporting an accuracy of 84.62%, with a rather low specificity of 62.50% and a high sensitivity of 94.44%.

3. Materials

This work is based on a prospective study approved by the Clinical Investigation Ethical Committee of the *Hospital Universitari del Vall d'Hebron* in Barcelona, Spain, and is based on a prospective database collected by the Research Group on Shock, Organic Disfunction and Ressuscitation of Vall d' Hebron's Intensive Care Unit. The database consisted of data collected in the ICU at this hospital between June 2007 and November 2008. During this period of time, 156 patients were admitted to the ICU (including medical and surgical patients) with severe sepsis.

The mean age of the patients in the analyzed database was 57.24 (with standard deviation ±15.25) years, 41.03% of patients were female and the diagnosis on admission was 64.10% *medical* and 35.90% *surgical*. The origin of primary infection for the cases on the database was 49.36% pulmonary, 14.74% abdominal, 10.26% urinary, 7.05% skin/muscle, 2.56% central nervous system (CNS), 1.28% catheter related, 0.64% endovascular, 5.13% biliar, 2.56% mediastinum and 6.41% unknown.

The collected data show the worst values for all variables during the first 24 h of evolution for severe sepsis. Organ dysfunction was evaluated by means of the SOFA score (Vincent et al., 1996), which quantifies the dysfunction and failure of six organs/systems (Cardiovascular, Respiratory, CNS, Hepathic, Renal and Haematologic), as shown in Table 1, and scored from 0 (normal function) to 4 points (maximum failure). Severity was evaluated by means of the APACHE II score (for further reference, see Knaus et al., 1985).

Table 1
List of SOFA scores, with their corresponding mean and (standard deviation) values.

Cardiovascular (CV)	2.980 (1.496)
Respiratory (RESP)	2.413 (1.062)
Central Nerv. Sys. (CNS)	0.419 (0.859)
Hepatic (HEPA)	0.387 (0.863)
Renal (REN)	0.968 (1.159)
Haematologic (HAEMATO)	0.877 (1.164)
Global SOFA score	7.948 (3.671)
Dysf. Organs (SOFA 1-2)	1.729 (1.124)
Failure Organs (SOFA 3-4)	1.152 (0.892)
Total Dysf. Organs	3.200 (1.406)

In the population under study, 56.41% received mechanical ventilation with a PaO_2/FiO_2 of 166 ± 100, 73% received vasoactive drugs, the platelet count was $1.84 \cdot 10^5/L \pm 1.36 \cdot 10^5/L$, the Lactate Levels were 3.40 ± 3.60 mmol/L, and the APACHE II score was 22.73 ± 8.53.

In 2004, the Surviving Sepsis Campaign (SSC) defined a set of guidelines for the management of severe sepsis and septic shock (Dellinger et al., 2004). More specifically, these set of guidelines were proposed for both the first 6 hours of evolution and for the first 24 h. Therefore, the compliance of the SSC bundles for the first 6 h was 31.41%, out of which 77.56% had Haemocultures performed, 85.90% received antibiotics, 57.05% had their lactate monitored, 69.87% received volume (i.e. Fluid Resuscitation) 18.59% received transfusions and 4.89% received Dobutamine. The $SVCO_2$

Table 2
List of variables used in this study.

Variable	Description
v1	Age
v2	Gender
v3	Sepsis focus
v4	Germ class
v5	Polimicrobial infection
v6	Base pathology
v7	Cardiovascular SOFA score
v8	Respiratory SOFA score
v9	CNS SOFA score
v10	Hepathic SOFA score
v11	Renal SOFA score
v12	Haematologic SOFA score
v13	Total SOFA score
v14	Dysfunctioning Organs for SOFA 1-2
v15	Dysfunctioning Organs for SOFA 3-4
v16	Total number of Dysfunctioning Organs
v17	Mechanical ventilation
v18	Oxygenation index PaO_2/FiO_2
v19	Vasoactive drugs
v20	Platelet count
v21	APACHE II score
v22	Surviving sepsis campaign bundles 6 h
v23	Haemocultures 6 h
v24	Antibiotics 6 h
v25	Volume 6 h
v26	O_2 central venous saturation 6 h
v27	Haematocrit 6 h
v28	Transfussions 6 h
v29	Dobutamine 6 h
v30	Surviving sepsis campaign bundles 24 h
v31	Glycaemia 24 h
v32	PPlateau
v33	Worst lactate
v34	O_2 central venous saturation