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A computational approach to early sepsis detection

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ABSTRACT

Objective: To develop high-performance early sepsis prediction technology for the general patient population.
Methods: Retrospective analysis of adult patients admitted to the intensive care unit (from the MIMIC II dataset) who were not septic at the time of admission.
Results: A sepsis early warning algorithm, *InSight*, was developed and applied to the prediction of sepsis up to three hours prior to a patient's first five hour Systemic Inflammatory Response Syndrome (SIRS) episode. When applied to a never-before-seen set of test patients, *InSight* predictions demonstrated a sensitivity of 0.90 (95% CI: 0.89–0.91) and a specificity of 0.81 (95% CI: 0.80–0.82), exceeding or rivaling that of existing biomarker detection methods. Across predictive times up to three hours before a sustained SIRS event, *InSight* maintained an average area under the ROC curve of 0.83 (95% CI: 0.80–0.86). Analysis of patient sepsis risk showed that contributions from the coevolution of multiple risk factors were more important than the contributions from isolated individual risk factors when making predictions further in advance.
Conclusions: Sepsis can be predicted at least three hours in advance of onset of the first five hour SIRS episode, using only nine commonly available vital signs, with better performance than methods in standard practice today. High-order correlations of vital sign measurements are key to this prediction, which improves the likelihood of early identification of at-risk patients.

1. Introduction

Severe sepsis and septic shock are among the leading causes of death in the United States [1,2]. Sepsis is most frequently caused by a systemic bacterial infection, but can also be caused by fungal, viral, and microbial endotoxin infections [3,4]. A nonspecific indicator of risk for developing sepsis is Systemic Inflammatory Response Syndrome (SIRS) [5]. SIRS is defined as two or more of the following variables: temperature of more than 38 °C or less than 36 °C, heart rate of more than 90 beats per minute, respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension of less than 32 mm Hg, or abnormal white blood cell count ($>12{,}000/\mu L$ or $<4000/\mu L$ or $>10\%$ immature band forms) [5]. Sepsis is defined as SIRS with the addition of a known or suspected infection. Severe sepsis is sepsis with associated organ dysfunction, and septic shock additionally includes refractory hypotension [5,6]. Approximately 750,000 patients are diagnosed with severe sepsis annually, and roughly one third of them die [6,7]. The cost of treating sepsis is estimated to be $16.7 billion per year, making sepsis one of the most expensive conditions to diagnose and treat [7,8].

Despite this, sepsis detection methods have changed little since 1991 and include screening labs, which may be slow or inaccurate. Multiple studies have shown that early diagnosis and treatment, such as Early Goal-Directed Therapy (EGDT), can reduce the risk of adverse patient outcome from severe sepsis and septic shock [9–11], though recent studies have questioned the effectiveness of existing treatment methods [12–14]. Regardless, earlier and more accurate diagnosis of patients at high risk of developing severe sepsis or septic shock would provide a valuable window for identifying the most effective sepsis treatments or preventative measures. To fill the need for earlier and higher performance sepsis screening technology, we have developed a machine learning workflow for sepsis prediction, called *InSight*. *InSight* computes, in real-time, the risk that a patient will develop sepsis. The goal of *InSight* is to provide clinicians with accurate advance

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notice that a patient is "trending septic".

The increasing availability of Electronic Health Records (EHR) in clinical settings has inspired several attempts to identify patient conditions and trends through the automated analysis of medical records, with varying success. Alarm indicators for sepsis and septic shock have been shown to reduce mortality in hospital settings [15]. Several systems have been validated against the detection of existing severe sepsis or septic shock, but lack predictive value [16–19]. In this study, we assess the sensitivity and specificity of the *InSight* algorithm in the prediction of sepsis, three hours prior to an extended SIRS episode. This prediction is achieved through the analysis of correlations between nine common vital sign measurements.

2. Materials and methods

2.1. Data collection and inclusion criteria

This is a retrospective study using the Multiparameter Intelligent Monitoring in Intensive Care (MIMIC) II Clinical Database (Version 3) [20]. The MIMIC II database is composed of anonymized clinical documentation from approximately 32,000 patients at the Beth Israel Deaconess Medical Center (BIDMC) collected between 2001 and 2008. The BIDMC and the Massachusetts Institute of Technology Institutional Review Boards waived individual patient consent requirements, as the study did not affect clinical care and all data were anonymized.

Inclusion criteria for this study were (Fig. 1):

I. Adult patient (i.e. age $\geq$ 18 years) admitted to the medical Intensive Care Unit (ICU).
II. Patient does not meet SIRS criteria at time of admission to the ICU or within first four hours of stay.
III. Documented measurements available for (i) systolic blood pressure, (ii) pulse pressure, (iii) heart rate, (iv) temperature, (v) respiration rate, (vi) white blood cell count, (vii) pH, (viii) blood oxygen saturation and (ix) age [21].

In order to analyze time series data more easily, beginning with ICU admission, the patient ICU stay was divided into one-hour intervals and measurement timestamps were rounded up to the nearest hour. For intervals without observations for all nine measurements, missing values were taken to be the most recent available observation.

2.2. Gold standard

After selection of the patients in the retrospective dataset for inclusion, each of the patients underwent a binary classification process to designate them as positive or negative for having acquired in-hospital sepsis. This classification was made based on the patient meeting both of the following criteria:

(1) The patient record contains an ICD9 code (995.9) indicating in-hospital contraction of sepsis.
(2) The patient meets the 1991 Systemic Inflammatory Response Syndrome (SIRS) criteria for sepsis for a persistent 5-hour period of time [21]. The beginning of the patient's first 5-hour SIRS event is defined as the zero hour.

2.3. Training and testing

1394 patients satisfied inclusion criteria I–III, of which 159 (11.4%) also met gold standard criteria (1) and (2). The 1394 patients were partitioned into mutually exclusive sets for training and testing the prediction algorithm. In order to ensure that training and testing set selections did not erroneously influence results, 4-fold cross validation was used. The 4-fold cross validation was done with a built-in MATLAB (MathWorks, Natick, MA, R2014a) function, which randomized the patients being placed in each group based on their anonymized medical record number (AMRN) provided in MIMIC II.

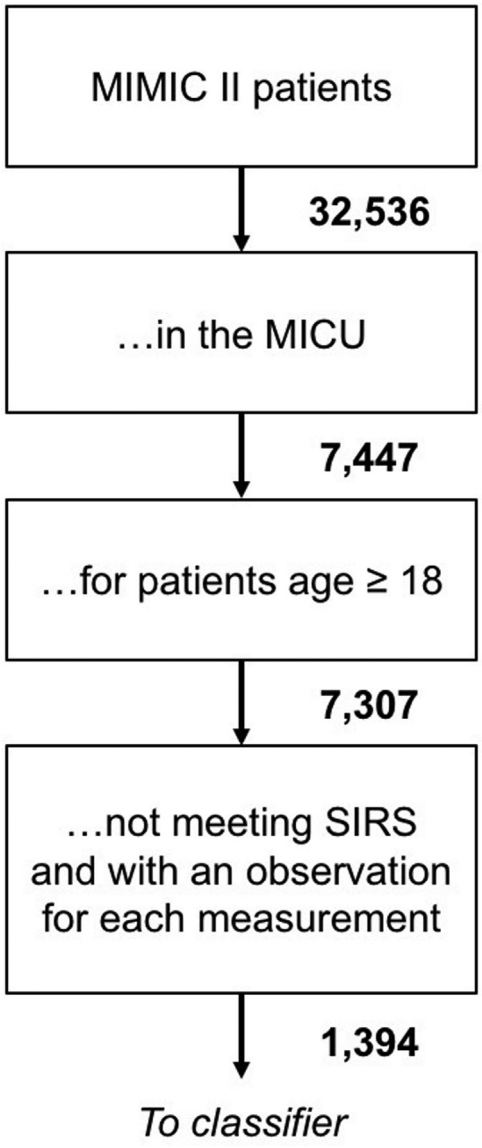

Fig. 1. Patient inclusion flow chart.

2.4. Analysis of patient time-series data

In order to capture trends in patient measurements and to emulate the analysis that would be performed for a prospective study, patient data were analyzed as a causal time-series. In particular, correlations between the following nine measurements (labeled as ***i*** below) – systolic blood pressure, pulse pressure, heart rate, temperature, respiration rate, white blood cell count, pH, blood oxygen saturation, and age – were classified within a sliding, 5-h observation window. These nine measurements were selected for their standard availability, medical relevance to sepsis, and the reliable likelihood of their frequent determination in a clinical setting.