www.sciencetranslationalmedicine.org/cgi/content/full/7/299/299ra122/DC1

Supplementary Materials for

A targeted real-time early warning score (TREWScore) for septic shock

Katharine E. Henry, David N. Hager, Peter J. Pronovost, Suchi Saria*

*Corresponding author. E-mail: ssaria@cs.jhu.edu

Published 5 August 2015, *Sci. Transl. Med.* **7**, 299ra122 (2015)
DOI: 10.1126/scitranslmed.aab3719

The PDF file includes:

SUPPLEMENTARY MATERIALS

MATERIALS & METHODS

Organ dysfunction criteria

As specified in the SSC guidelines (45), we defined organ dysfunction caused by sepsis as the presence of any of the following: systolic blood pressure <90 mmHg; lactate > 2.0 mmol/L; urine output < 0.5 mL/kg over the preceding two hours despite adequate fluid resuscitation; creatinine > 2.0 mg/dL without the presence of chronic dialysis or renal insufficiency as indicated by an ICD-9 code of V45.11 or 585.9; bilirubin > 2 mg/dL without the presence of chronic liver disease and cirrhosis as indicated by an ICD-9 code of 571 and any of the subcodes; platelet count < 100,000 μL; international normalized ratio (INR) > 1.5; acute lung injury with PaO_2/FiO_2 < 200 in the presence of pneumonia indicated by an ICD-9 code of 486; or acute lung injury with PaO_2/FiO_2 < 250 in the absence of pneumonia indicated by the absence of an ICD-9 code of 486.

Feature computation

The following groups of routinely collected measurements were processed to compute candidate features: age, vital signs (respiratory rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, SpO_2, FiO_2, Glasgow Coma Score (GCS), Riker sedation-agitation score, urine output, fluid input), laboratory test results (blood urea nitrogen, creatinine, white blood cell count, hematocrit, hemoglobin, potassium, bicarbonate, arterial pH, PaO_2, $PaCO_2$), and clinical history (HIV, chronic liver disease, chronic heart failure, chronic organ insufficiency, immunocompromised state, hematologic malignancy, current type of care unit) (**Table S1**). Trend features (mean, slope) were computed over six and three hour intervals but did not contribute to predictive performance and therefore were not included in our reported experiments. The poor predictive performance of these trend features could be due to their infrequent measurement in the EHR, which prevented reliable computation of trends. Importantly, by not using trend features, the system could make predictions without the delays needed to obtain serial observations.

For vital signs and laboratory measurements, we used the last observed measurement value within a window specified by the typical duration between consecutive measurements (45). For example, since creatinine is typically measured daily, we used the creatinine value last observed within the previous 24-hour period. As in previous studies with EHR data, if no measurement existed within that window, we imputed the measurement using the population mean observed in the development set (37,58). These data were then used to assess organ-specific SOFA scores (16), individual SIRS criteria, and the commonly used clinical measurements of shock index, BUN to creatinine ratio, and urine output normalized by weight over the preceding six hours (46,47,48,49). The time since a patient first received antibiotics and the time since the first organ failure—acute or chronic and not necessarily due to sepsis—were also computed. The motivation for the time since event features is that an individual's risk of shock may increase if they have previously experienced organ failure. Antibiotic use could similarly modify risk. Vital signs, laboratory measurements, clinical observations, and demographics were used along with the computed features as candidate risk factors for the model.

Table S1. Sample feature coefficients learned by TREWScore for a single imputation of the development data set.

Category	Feature name	Feature description	Weight
Vital	Shock index*	HR/SBP	3.66

Vital	SBP	Systolic blood pressure	-1.36
Clinical	Time since first antibiotics*	Minutes since the patient first received antibiotics in the ICU	1.28
Clinical	Urine 6hr*	Total urine output over the past 6 hours	-1.17
Laboratory	BUN/CR*	BUN/creatinine ratio	1.16
Vital	GCS	Glasgow coma score	-0.78
Laboratory	Arterial pH	Blood pH as measured by an arterial line	-0.61
Vital	RR	Respiratory rate	0.57
Laboratory	PaO2	Partial pressure of arterial oxygen	-0.56
Laboratory	BUN	Blood urea nitrogen	0.50
Clinical	Chronic liver disease and cirrhosis	Presence of chronic liver disease and cirrhosis as indicated by ICD-9 571	0.42
Vital	HR	Heart rate	0.40
Laboratory	Hepatic SOFA*	Hepatic SOFA score computed based on the bilirubin concentration	0.49
Vital	FiO2	Fraction of inspired oxygen	0.38
Clinical	Cardiac surgery patient	Patient currently in the cardiac surgery recovery unit	-0.32
Clinical	Immunocompromised	Immunocompromised (patient has received past therapy that suppresses resistance to infection) as indicated by presence of any ICD-9 in V58.65, V58.0, V58.1, 042, 208.0, 202	0.32
Clinical	SIRS*	Presence of at least two of the SIRS criteria at the current time	0.30
Laboratory	WBC	White blood cell count	0.30
Clinical	Hematological malignancy	Presence of hematologic malignancy as indicated by any ICD-9 code in 200-208	0.20
Clinical	Chronic heart failure	Presence of heart failure as indicated by ICD-9 code 428	0.17
Clinical	Chronic organ insufficiency	Severe organ insufficiency (chronic liver disease, chronic heart failure, chronic respiratory failure, receiving chronic dialysis) as indicated by one of the ICD-9 codes 571, 585.6, 428.22, 428.32, 428.42, 518.83	0.11

Clinical	Diabetes	Presence of diabetes as indicated by ICD-9 code 250	-0.10
Laboratory	Renal SOFA*	Renal SOFA score computed on the basis of creatinine concentration	0.08
Vital	Neurologic SOFA*	Neurologic SOFA score computed on the basis of GCS	0.07
Laboratory	Platelets	Platelet count in the bloodstream	-0.06
Clinical	Metastatic carcinoma	Metastatic carcinoma as indicated by presence of any ICD-9 codes in 140-165, 170-175, 179-199	0.05

* Feature computed automatically in the EHR

If not specified, ICD-9 codes XXX include all subcodes XXX.XX.

Features considered, but not included in the presented model were: the highest SOFA score, sodium, SpO_2, $PaCO_2$, respiratory SOFA score, hematologic SOFA score, patient on dialysis, presence of chronic renal insufficiency, creatinine, potassium, admission weight, current care unit, hematocrit, hemoglobin, hypotension, temperature, mean arterial pressure, current weight, Riker Sedation-Agitation Scale, presence of HIV, diastolic BP, urine output over the past 6 hours per kg, SIRS criteria for abnormal heart rate, SIRS criteria for abnormal temperature, SIRS criteria for abnormal respiratory rate, SIRS criteria for abnormal white blood cell count, time since first organ dysfunction (chronic or acute), and age

Table S2. Patient characteristics.

Patient demographics	Number of patients	16,234
	Age, mean (SD)	65 (21)
	Female, %	40.9
	Male, %	59.0
	Unknown, %	0.1
ICU to which patient was admitted**, %**	Medical ICU	24.3
	Surgical ICU	5.8
	Finard ICU (a medical and surgical ICU)	6.3
	Cardiac Care Unit	22.9
	Cardiac Surgery Recovery Unit	41.7

Sepsis stages, %	Ever meet SIRS criteria	90.2
	Sustain SIRS for at least 5 hours	60.9
	Sepsis	47.6
	Severe sepsis	31.3
	Septic shock	14.1
In hospital mortality, %	All patients	13.3
	Patients with septic shock only	39.3
	Patients without septic shock only	7.7
ICU length of stay, median days	All patients	2.8
	Patients with septic shock only	8.8
	Patients without septic shock only	2.3
Chronic conditions, %	Stage V chronic kidney disease or renal insufficiency	8.0
	Chronic liver disease and cirrhosis	4.6
	Hematologic malignancy	2.8
	Metastatic carcinoma	7.8
	Heart failure	35.4
Treatments, %	Ever received pressors	51.2
	Ever received mechanical ventilation	68.6