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Prediction of Bacteraemia and of 30-day Mortality Among Patients with Suspected Infection using a CPN Model of Systemic Inflammation

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Abstract: Prediction of both the likelihood of bacteraemia and of death within 30 days allows for prudent decisions to be made regarding the diagnostic workup and therapy of patients with suspected sepsis. In this paper, we combine two predictive models and perform machine learning to tune the new model's ability to predict both bacteraemia and 30-day mortality. The model was then validated on three independent datasets. There was no difference in the discriminatory ability of the model compared to each of the predecessors. For bacteraemia prediction, the new model had an AUC = 0.71 for the training data, and AUC = 0.73, 0.74 and 0.79 for the validation data. For mortality prediction, the model had an AUC = 0.81 for the training data and AUC = 0.76, 0.84 and 0.80 for the validation data.

Keywords: Decision support and control; Identification and validation; Model formulation, experiment design; Bayesian methods; Machine Learning

1. INTRODUCTION

Sepsis is the body's systemic response to severe infection. It is a major healthcare problem with high mortality, ranging from approximately 15% in less severe cases to over 60% in cases with multiple organ dysfunction (Angus et al., 2001; Martin, Mannino, Eaton, & Moss, 2003; J.-L. Vincent et al., 2006).

The ability to predict mortality allows for expedited diagnosis and improved treatment for those patients most in need. Sepsis definitions also reflect this, with the current consensus definitions designed to grade severity according to risk of death; the clinical criteria were chosen based on their performance in predicting in-hospital mortality and/or ICU stay (Seymour et al., 2016; Singer et al., 2016). Attempts have been made to design algorithms and clinical scores for mortality prediction among patients with suspected sepsis, such as SOFA (J. L. Vincent et al., 1996) (now part of the sepsis definitions) and MEDS (Shapiro et al., 2003).

The diagnostic workup of a patient may additionally be guided by the likelihood of a clinically significant positive blood culture (bacteraemia); knowing the pre-test probability of bacteraemia allows prudent decisions to be made on the use of rapid diagnostics. Algorithms and clinical scores have been developed to predict bacteraemia, but none of these are in routine clinical use (Eliakim-Raz, Bates, & Leibovici, 2015).

We have previously developed two models, Sepsis-B (L. M. Ward, 2016) and Sepsis-M (originally: L_A-Sepsis CPN) (L. Ward, Paul, & Andreassen, 2017), capable of predicting bacteraemia and 30-day mortality, respectively. Compared with traditional scores, these models have the advantage that they can handle missing data, and give an explicit representation of the probability.

The aim of this paper is to combine the two models in an attempt to improve the predictions by allowing the model to learn from both bacteraemia and mortality.

2. MATERIALS AND METHODS

In this paper, we describe the formation of the SepsisFinder CPN (Causal Probabilistic Network), tuning by machine learning, and validation on external datasets.

2.1 Predictive model

Model Construction

The Sepsis-B (L. M. Ward, 2016) and Sepsis-M (L. Ward et al., 2017) models were merged. Figure 1 shows the merged model, with both 30-day mortality and bacteraemia as output variables. The Sepsis-B model used neutrophil fraction (the ratio between neutrophil and leucocyte counts) as an input variable, while the Sepsis-M model used leukocyte count as an input variable.

In the merged model, neutrophil fraction was kept instead of leukocyte count due to its superior predictive performance on the training data (for both 30-day mortality and bacteraemia).

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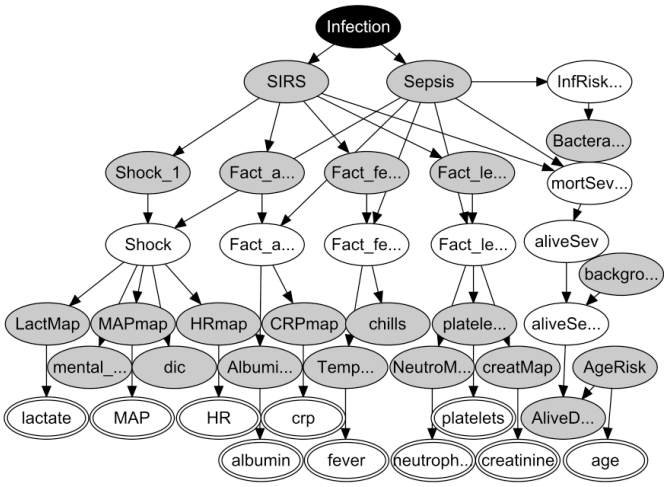

Figure 1: SepsisFinder CPN. The nodes where learning took place are coloured grey (stage 1) and black (stage 2).

Training

The model was trained using the Expectation-Maximisation (EM) method (Lauritzen, 1995). EM learning is a maximum likelihood method, and is offered as a tool for training CPNs in the commercial software Hugin (Hugin Expert A/S, Aalborg, Denmark).

We used the same learning process as for the individual original models (L. Ward et al., 2017). First, the "mapping nodes", "factor mapping nodes", NSIRS, Sepsis, BackgroundMort, AgeRisk, AliveDay30 and Bacteraemia were learned (shaded grey in Figure 1). As a second step, "Infection" (shaded black in Figure 1) was learned to allow for cases where both NSIRS and Sepsis are present. NSIRS and Sepsis were not available in the annotated data.

2.2 Datasets

Training data: 2357 patients with suspected community-acquired infection at Beilinson Hospital, Petah Tiqva, Israel from November 2014 to June 2016. Data were collected during routine clinical use of the clinical decision support system, TREAT (Andreassen et al., 2005; L Leibovici, Paul, & Andreassen, 2010; Leonard Leibovici, Paul, Nielsen, Tacconelli, & Andreassen, 2007; Paul et al., 2006). The following variables were used in training the model: presence of bacteraemia (yes/no), death within 30 days (yes/no), infectious diagnosis (yes/no), neutrophil fraction, lactate, C-reactive protein, temperature, chills (yes/no), albumin, creatinine, calculated mean arterial pressure, heart rate, platelets, age, mental status (normal/confused/comatose).

Three validation datasets were available, these will be referred to as HvH, SLB and TREAT04. Two of the datasets are from hospitals in Denmark (HvH and SLB), and one from the same hospital from which training data were gathered (TREAT04).

HvH: 263 patients with suspected sepsis at Hvidovre Hospital, Hvidovre, Denmark; November 2011 – April 2012 (Arboe, Laub, Kronborg, & Knudsen, 2014).

SLB: 199 patients with suspected sepsis at Lillebælt Hospital, Vejle, Denmark; July – August 2012 (L. M. Ward et al., 2013).

TREAT04: From patients included in an interventional study of TREAT from May to November 2004 (Paul et al., 2006), the 1354 patients with community acquired infections were selected.

2.3 Outcomes

Outcomes were clinically significant bacteraemia, and 30-day mortality. Clinically significant bacteraemia is defined as blood culture positive for a clinically relevant pathogen. *Aerococcus spp., Bacillus spp. (*not *B. anthracis),* coagulase-negative staphylococci*, Corynebacterium spp., Micrococcus spp., Proprionibacterium acnes,* and *viridans* streptococci were considered contaminants.

To calculate the 30-day mortality, only the final episode was included for patients who were included multiple times within 30 days.

2.4 Statistical Analysis

Differences between continuous variables were assessed using the independent samples Mann-Whitney U Test and categorical variables were assessed using the Pearson Chi-squared statistic. EM learning was performed using Hugin (Version 8.5 (x64), Hugin Expert A/S), commercially available software for constructing and analysing CPNs. Discriminatory ability was assessed by the area under the receiver-operating characteristic (ROC) curve. Calibration assessed using the Hosmer-Lemeshow chi-squared statistic. Statistical analyses carried out in Matlab R2016a (The MathWorks, Inc).

3. RESULTS

The structure of the SepsisFinder CPN is shown in Figure 1. Table 1 presents descriptive statistics for the model input variables included in the training data. Table 2 presents the discriminatory performance of the individual variables included in the model and their ability to predict bacteraemia and mortality. This table presents the general performance profile of the variables in the univariate case. However, this is not fully representative of the performance as part of the model; for example, for some of the variables, both very high and very low values are considered pathological (fever/hypothermia, high/low platelet count). Despite this, we can see that some variables are better predictors of bacteraemia (e.g. neutrophil fraction or temperature) and others are better predictors of mortality (e.g. mean arterial pressure (MAP) or age).

Following the learning process, we first tested the performance of the model on the training data itself. The Area under the ROC curve (AUC) was 0.81 (95% CI 0.79 – 0.84) for the model's prediction of death within 30 days and 0.71 (95% CI 0.67 – 0.75) for the model's prediction of bacteraemia (Figure 2, A and B).

Table 1: Descriptive statistics for variables in the training data

Variable	All	Bacteraemia			Alive Day 30		
	Median (IQR)/n (%)	Median (IQR)/n (%)			Median (IQR)/n (%)		
		yes	no	p*	no	yes	p*
Neutrophil fraction	0.82 (0.74-0.88)	0.87 (0.81-0.92)	0.81 (0.73-0.87)	<0.001	0.84 (0.78-0.90)	0.81 (0.73-0.87)	<0.001
Lactate	2.0 (1.4-2.8)	2.6 (1.9-3.8)	2.0 (1.4-2.7)	<0.001	2.3 (1.8-3.4)	2.0 (1.4-2.7)	<0.001
CRP	76.7 (30.4-158.5)	119.5 (70.9-214.2)	72.6 (28.5-151.6)	<0.001	105.9 (43.6-191.3)	74.3 (28.8-153.3)	<0.001
Temperature	37.8 (37.0-38.6)	38.3 (37.5-39.1)	37.7 (37.0-38.5)	<0.001	37.6 (36.8-38.4)	37.8 (37.0-38.6)	0.002
Chills	283 (14.6%)	34 (23.3%)	249 (13.9%)	0.008	16 (7.2%)	267 (15.6%)	0.001
Albumin	37 (32-41)	34 (30-48)	37 (33-41)	<0.001	32 (27-36)	37 (33-41)	<0.001
Creatinine	1.04 (0.79-1.48)	1.26 (0.89-1.76)	1.03 (0.77-1.45)	<0.001	1.42 (0.90-2.35)	1.01 (0.77-1.41)	<0.001
MAP	80 (70-90)	78 (65-86)	80 (70-90)	0.001	72 (62-82)	81 (71-91)	<0.001
Heart rate	95 (83-110)	100 (88-113)	95 (83-110)	0.005	100 (86-116)	95 (83-110)	0.001
Platelets	220 (162-301)	195 (149-292)	220 (162-301)	0.026	225 (153-346)	219 (162-294)	0.217
Age	76 (64-85)	77 (66-84)	76 (64-85)	0.504	84 (75-89)	75 (63-84)	<0.001
Mental status				0.429			<0.001
Normal	1858 (93.6%)	134 (91.2%)	1724 (93.8%)		184 (83.6%)	1674 (94.8%)	
Confused	120 (6.0%)	13 (8.8%)	107 (5.8%)		30 (13.6%)	90 (5.1%)	
Comatose	7 (0.4%)	0 (0%)	7 (0.4%)		6 (2.8%)	1 (0.1%)	

* Independent-samples Mann-Whitney U Test, distributions are not the same where p<0.05

Table 2: Discriminatory performance of individual variables included in the model

Variable	Recorded (%)	AUC bacteraemia (95% CI)	AUC mortality (95% CI)
Neutrophil fraction↑	98.3%	0.67 (0.63-0.71) *	0.60 (0.56-0.63) *
Lactate↑	61.6%	0.65 (0.59-0.70) *	0.61 (0.57-0.66) *
CRP↑	77.2%	0.64 (0.59-0.68) *	0.58 (0.54-0.62) *
Temperature↑	99.2%	0.64 (0.59-0.68) *	0.44 (0.40-0.48)
Albumin↓	74.5%	0.62 (0.57-0.66) *	0.74 (0.70-0.77) *
Creatinine↑	97.5%	0.61 (0.56-0.65) *	0.65 (0.61-0.69) *
MAP↓	98.3%	0.58 (0.53-0.62) *	0.67 (0.63-0.70) *
Heart rate↑	98.2%	0.56 (0.52-0.61) *	0.56 (0.53-0.60) *
Platelets↓	98.3%	0.55 (0.51-0.60) *	0.48 (0.44-0.52)
Age↑	99.6%	0.52 (0.47-0.56)	0.68 (0.65-0.71) *

↑: higher value predicts positive outcome (e.g. bacteraemia)
↓: lower value predicts positive outcome (e.g. bacteraemia)
*: significant predictor, p<0.05 (univariate analysis)

In the calibration curves (Figure 2, C and D), cases are split into deciles based on the predicted probability, and observed and predicted rates of the outcome are plotted against each other. A perfectly calibrated model would plot as a y=x line. The Hosmer-Lemeshow statistic was 13.3 (8 degrees of freedom, p = 0.10) for the mortality predictions and 3.6 (8 d.f., p = 0.89) for the bacteraemia predictions, which suggests that the model is well calibrated for both sets of model predictions. Overall, the model predicted 7.5% bacteraemia; the actual bacteraemia rate was 7.6%. The model slightly overpredicted 30-day mortality, with 13.6% predicted compared with 11.9% present in the dataset.

The model performed well on all three validation datasets in terms of its predictive ability for both 30-day mortality and bacteraemia (Figure 3, A and B). There were no significant differences between the AUC for the training set and any of the validation sets.

In addition, we compared the performance of the mortality predictions with those of the Sepsis-M CPN, and the bacteraemia predictions with those of the Sepsis-B CPN, performance statistics are given in Table 3. There were no significant differences for any of these comparisions.

Table 3: Predictive performance of the SepsisFinder CPN vs. the Sepsis-B and Sepsis-M CPNs

Dataset	Bacteraemia Prediction	
	Sepsis-B	SF
Training	0.72 (0.68-0.76)	0.71 (0.67-0.75)
HvH	0.72 (0.62-0.82)	0.73 (0.69-0.78)
SLB	0.80 (0.70-0.90)	0.79 (0.64-0.94)
TREAT04	0.76 (0.72-0.81)	0.74 (0.69-0.78)
Dataset	Mortality Prediction	
	Sepsis-M	SF
Training	0.81 (0.78-0.83)	0.81 (0.79-0.84)
HvH	0.77 (0.67-0.88)	0.84 (0.77-0.90)
SLB	0.83 (0.73-0.92)	0.80 (0.68-0.93)
TREAT04	0.76 (0.72-0.80)	0.76 (0.72-0.80)

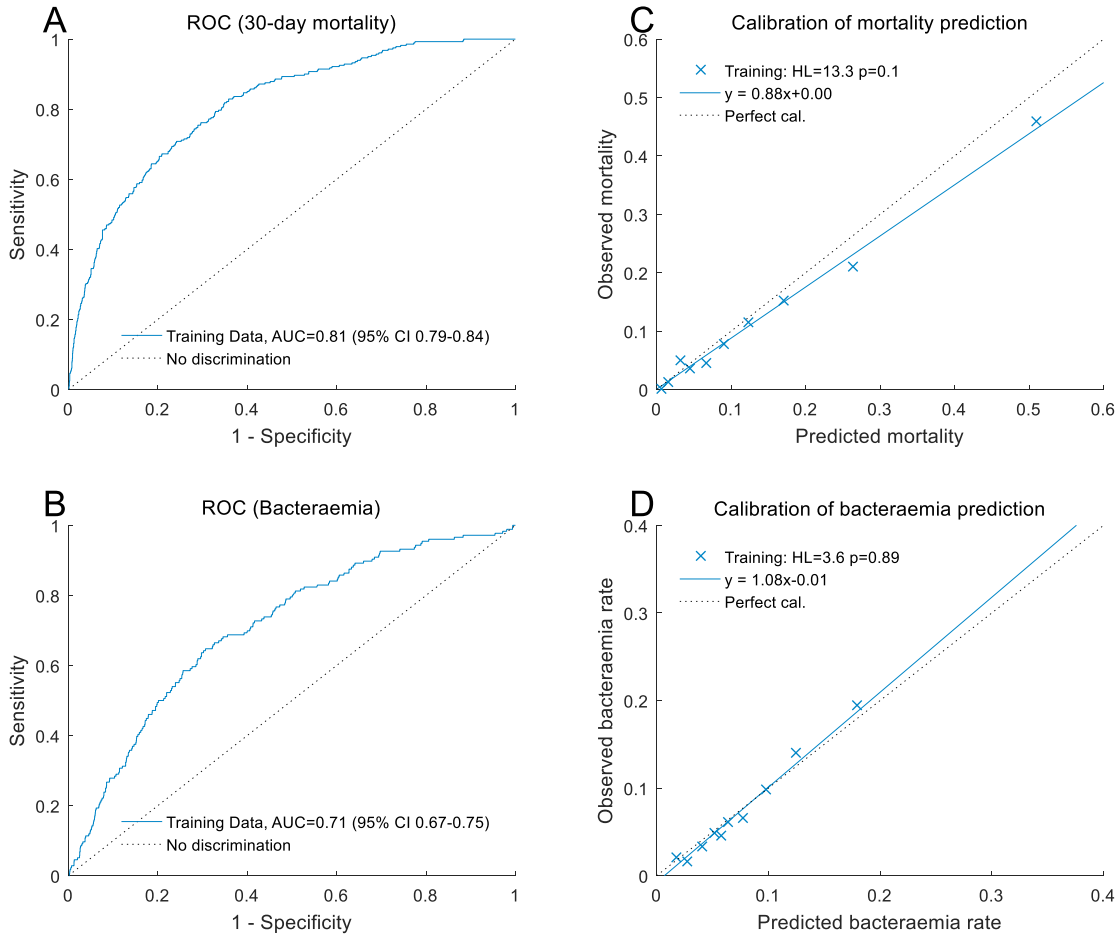

Figure 2: Performance of the model on the training data. A: ROC curve for model predicted probability of death within 30 days. B: ROC curve for model predicted probability of bacteraemia. C: Calibration curves for observed vs. model predicted probability of death within 30 days. D: Calibration curves for observed vs. model predicted probability of bacteraemia. HL = Hosmer-Lemeshow statistic, p>0.05 indicates no significant deviation.

According to the Hosmer-Lemeshow statistic, the model predicted probabilities of 30-day mortality and bacteraemia were well calibrated (p>0.24 for all) for both the HvH and SLB datasets (Figure 3, C and D). This is also seen in the overall predictions matching the observations. For the HvH dataset, the model predicted 6.2% bacteraemia and 10.9% mortality where the observed rates were 6.8% and 8.8%. For the SLB dataset, the model predicted 5.5% bacteraemia and 6.3% mortality; the observed rates were 6.0% and 6.5%. However, for the TREAT04 dataset, the deviations were significant ($p = 3x10^{-5}$). with under-prediction of mortality: overall predicted mortality was 9.1% vs. an observed mortality of 11.5%. Bacteraemia was also under-predicted with a predicted probability of 7.4% vs. an observed probability of 9.3%.

4. DISCUSSION

We combined two CPN models and trained them to provide predictions of the probability of bacteraemia and of death within 30 days. Models performed well on the training data and external validation both in terms of discriminatory performance and generally in terms of calibration. The combined model performed better than all individual finding, both for mortality and bacteraemia predictions. The model performed as well as the two original models.

The model was trained using data from a hospital in Israel, and validated using datasets from two hospitals in Denmark, and an additional dataset from the hospital at which training data were collected. The four datasets in this study were collected over different time periods (ranging from 2004 to 2016), and had different rates and types of missing data (data not shown). The model appears to be robust, with no evidence of overfitting; no degradation in performance relative to the training dataset was observed for any of the validation datasets. One limitation of this study was the small size of the SLB and HvH datasets.

At the time that the TREAT04 data were collected, fewer lab tests were run per patient. This dataset had fewer data per patient overall, and in particular fewer of the 'good' data i.e. CRP for bacteraemia prediction, and albumin for prediction of death within 30 days.

The mortality predictions for the TREAT04 dataset appeared to have a systematic offset in mortality prediction. The gradient of the calibration curve was 0.98, and the offset was +0.03. This could potentially be explained as a higher background mortality in this cohort not accounted for by the model.

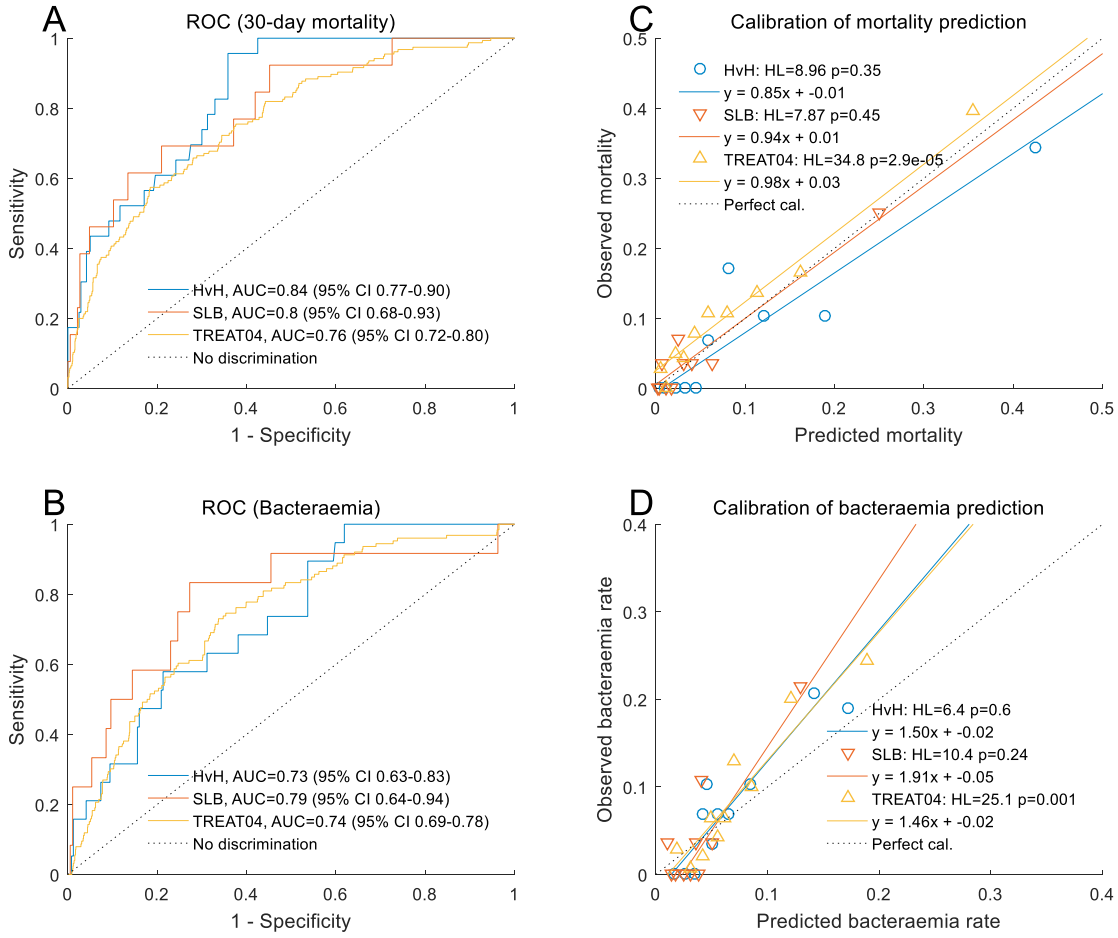

Figure 3: Performance of the model on the three validation datasets. A: ROC curve for model predicted probability of death within 30 days. B: ROC curve for model predicted probability of bacteraemia. C: Calibration curves for observed vs. model predicted probability of death within 30 days. D: Calibration curves for observed vs. model predicted probability of bacteraemia. HL = Hosmer-Lemeshow statistic, p>0.05 indicates no significant deviation.

There are a number of confounding factors for bacteraemia, which can be either laboratory- or patient-specific. Typically, we expect higher likelihood of bacteraemia in more severe infections, but it is also dependent on the type of infection (i.e. whether there is an easy path to the bloodstream in e.g. endocarditis) and also if blood was drawn before antibiotics were administered. Differences between microbiology labs in terms of their blood culture procedures may also affect the probability of detecting microbes in the blood cultures.

CPN models possess some advantages over other forms of predictive model, notably their inherent ability to handle missing data. This ability is particularly useful in the medical domain, where both the quality and amount of data recorded for a given patient can vary significantly between and even within healthcare centres.

The predictive performance of the model described in this study are in line with other models described in the literature. The current sepsis definition uses the SOFA score, in particular for ICU patients, while also recommending the use of qSOFA (or "quick SOFA") for patients outside the ICU (Singer et al., 2016). The study describing the clinical criteria for sepsis shows good performance for both these scores in predicting in-hospital mortality in a large validation dataset, with AUC = 0.74 (all) and 0.79 (non-ICU) for SOFA and for 0.66 (all) and 0.81 (non-ICU) for qSOFA (Seymour et al., 2016). Despite these results, there has been significant debate surrounding the use of qSOFA and SOFA for sepsis screening, with mixed results reported in the literature (Askim et al., 2017; Carneiro, Póvoa, & Gomes, 2017; Franchini & Duca, 2016; Freund et al., 2017; Hwang et al., 2017; Kim et al., 2017). A recent review described a number of efforts made to develop models to predict bacteraemia, none of which were in routine clinical use (Eliakim-Raz et al., 2015). AUCs for the predictive models ranged from 0.62-0.79, similar to what we found in this study.

One possible application of this model is as part of a decision support system for the microbiology laboratory. Expensive, rapid diagnostics can be suggested for patients with a high likelihood of returning an actionable positive result (high probability of bacteraemia) and/or greater need for rapid appropriate therapy (high probability of mortality).

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