British Journal of General Practice

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Loots, Feike; Smits, Marleen; Hopstaken, Rogier; Jenniskens, Kevin; Schroeten, Fleur; Van den Bruel, Ann; van de Pol, Alma C; Oosterheert, Jan-Jelrik; Bouma, Hjalmar; Little, Paul; Moore, Michael; van Delft, Sanne; Rijpsma, Douwe; Holkenborg, Joris; van Bussel, Bas; Laven, Ralph; Bergmans, Dennis; Hoogerwerf, Jacobien; Latten, Gideon; de Bont, Eefje; Giesen, Paul; den Harder, Annemarie; Kusters, Ron; van Zanten, Arthur; Verheij, Theo

DOI: <https://doi.org/10.3399/BJGP.2021.0520>

To access the most recent version of this article, please click the DOI URL in the line above.

Received 08 September 2021

Revised 15 November 2021

Accepted 04 January 2022

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Author Accepted Manuscript

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Development and external validation of a new clinical prediction model for early recognition of sepsis in adult patients in primary care: a diagnostic study

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Word count: 3298

Abstract

Background

Recognising patients who need immediate hospital treatment for sepsis while simultaneously limiting unnecessary referrals is challenging for GPs.

Aim

Develop and validate a sepsis prediction model for adult patients in primary care.

Design and setting

Prospective cohort study in four out-of-hours primary care services in the Netherlands, between June 2018 and March 2020.

Method

Acutely ill adult patients who received home visits were included. Nine clinical variables were candidate predictors, next to the biomarkers C-reactive protein, procalcitonin, and lactate. The primary endpoint was sepsis within 72 hours of inclusion, as established by an expert panel. Multivariable logistic regression with backwards selection was used to design an optimal model with continuous clinical variables. The added value of the biomarkers was evaluated. Subsequently, a simple model using single cutoff points of continuous variables was developed and externally validated in two emergency department populations.

Results

357 patients were included with a median age of 80 years, of which 151 (42%) were diagnosed with sepsis. A model based on a simple count of one point for each of six variables (age > 65 years; temperature > 38°C; systolic blood pressure ≤ 110 mmHg; heart rate > 110/min; saturation ≤ 95%; altered mental status) had good discrimination and calibration (C statistic of 0.80 [95% CI 0.75-0.84]; Brier score 0.175). Biomarkers did not improve the performance of the model and were therefore not included. The model was robust during external validation.

Conclusion

Based on this GP out-of-hours population, a simple model can accurately predict sepsis in acutely ill adult patients using readily available clinical parameters.

Keywords: Sepsis; Clinical Prediction Rule; General Practice; After-Hours Care; Diagnosis; Vital Signs

How this fits in

Early recognition and treatment of sepsis are essential to improve patient outcomes. Scoring systems such as SIRS, qSOFA and NEWS are used in the hospital setting for suspected sepsis but are not validated in the primary care setting. A newly developed simple score-based model may help to predict sepsis in adult primary care patients. Biomarkers (lactate, C reactive protein, procalcitonin) and the respiratory rate were not incorporated in this model, as the added value was not clinically relevant.

Introduction

Early recognition of sepsis is the critical factor influencing patient outcome.¹⁻⁴ Protocols for the early identification of sepsis to trigger the administration of intravenous antibiotics successfully decreased sepsis-related mortality in emergency departments (EDs).^{5,6} In patients with community-acquired sepsis, general practitioners (GPs) are often the first responding healthcare providers assessing patients.^{7,8} GPs' recognition of sepsis and decision to refer a patient to the hospital is essential for adequate treatment. At the same time, GPs have an essential role in preventing unnecessary referrals, as hospital admission in itself can have a negative impact, especially in older, frail patients.

Currently, GPs' decision to refer patients with severe infections to the hospital is based on an intuitive interpretation of signs, symptoms and general impression of a patient.^{9,10} For primary care, up until now, there is no diagnostic model available to support decisions to diagnose and manage sepsis. Clinical scores used in hospitals, like the quick Sequential Organ Failure Assessment (qSOFA) score,¹¹ Systemic Inflammatory Response Syndrome (SIRS)¹² or National Early Warning Score (NEWS),¹³ are not validated in primary care.

This study aimed to develop and validate a first diagnostic clinical model for the early recognition of sepsis in adults presenting in primary care. Ideally, patients with sepsis are identified early in the course of the disease, and therefore the model will be designed to predict sepsis to be present within 72 hours. In these patients, immediate hospital referral is expected to improve outcome. Clinical signs and symptoms and biomarkers potentially available at the bedside were investigated.

Methods

Setting

Patients were enrolled between June 2018 and March 2020 at four participating out-of-hours primary care services in the central and south of the Netherlands. The combined area covers ~800,000 inhabitants in a mixed urban, suburban and rural area. In the Netherlands, out-of-hours primary care is organised in large-scale primary care services serving between 50,000 and 400,000 inhabitants.¹⁴ Telephone triage is used to decide who needs to come to the clinic and who is visited at home. Only patients who received home visits were included in the study as these patients are usually more severely ill than other primary care populations. All participants (or legally authorised representatives of incapacitated patients) gave written informed consent for the study. The protocol for this study has been previously published¹⁵ and can be consulted for further details.

Patients

Acutely ill adult (≥ 18 years) patients with fever, confusion, general deterioration or otherwise suspected severe infection were eligible for inclusion. Patients were excluded if any of the following criteria were present: 1) non-infectious diagnosis suspected as the cause of the acute complaints (e.g. myocardial infarction or stroke); 2) hospitalisation within seven days before the home visit; 3) a condition present requiring secondary care assessment regardless of the severity of infection (e.g. neutropenic fever); 4) terminal illness or other reason not to be referred to the hospital, despite the presence of a life-threatening condition.

Candidate predictors

Nine clinical parameters were selected as candidate predictors based on other prediction models, sepsis guidelines and triage protocols.^{11-13,16,17} These included: age; tympanic temperature; systolic blood pressure; peripheral oxygen saturation; heart rate; respiratory rate; mental status (normal or altered); rapid progression of illness (yes/no) and rigors (yes/no). Furthermore, three biomarkers were selected: lactate, C-reactive protein (CRP), and procalcitonin (PCT).

Procedures

The GP assessed eligibility for inclusion at the home visit. Drivers who accompanied the GPs during the home visit were equipped with portable monitoring devices (Philips Intellivue MP2 or X2) to measure blood pressure, peripheral oxygen saturation, heart rate, and respiratory rate. All vital signs and other clinical candidate predictors were registered in a case report form on site. The GP also rated the perceived likelihood of sepsis on a scale from 0-10. Either the GP or an on-call laboratory assistant obtained venous blood samples directly after inclusion. Lactate was measured by point-of-care testing (StatStrip Xpress lactate, Nova Biomedical), as lactate cannot be measured reliably from stored blood samples.¹⁸ The venous blood samples were stored at -70°C for later measurements of CRP and PCT. All patients received care as usual.

Outcome definitions and assessment

Three expert panels were created, each consisting of one GP, one emergency physician and one intensivist (or acute care internist). These expert panels established the primary outcome "sepsis within 72 hours of inclusion", using all relevant information from medical records, per Sepsis-3 definition.¹⁹ Cases were divided among the three panels, with 10% of all cases being

evaluated by all three panels for inter-rater and inter-panel reliability. If panel members could not reach a consensus on the presence or absence of sepsis, the case was discussed in a face-to-face meeting until consensus was reached.

Secondary outcomes assessed by the expert panel included whether the infection was the cause of acute complaints (yes/no) and the need for hospital treatment (on a scale from 0-10). Furthermore, the presence or absence of an "adverse outcome" - defined as an intensive care unit (ICU) admission within 72 hours or death within 30 days of inclusion - was determined.

Statistical analysis

Baseline characteristics of the study population were described using the mean and standard deviation for continuous variables with a normal distribution and the median and interquartile range (IQR) for variables with a skewed distribution. Inter-rater and inter-panel reliability were assessed using Cohen's Kappa for the primary outcome of sepsis.

Multiple imputations using Multivariate Imputation by Chained Equations (MICE) procedure^{21,22} was used to account for missing data. These imputed datasets' regression coefficients and performance measures were pooled using Rubin's rules²³ and the total covariance matrix, respectively.

Firstly, a multivariable logistic regression model was developed using all clinical parameters. Subsequently, lactate, CRP and PCT were added to this clinical model. The linearity of the relationship between continuous variables and the log odds of sepsis was assessed. For non-

linear relationships, a restricted cubic spline was used. Backward selection with $p < 0.157$ as selection criterion (based on Akaike's information criterion)^{24,25} was used to remove any non-informative clinical parameters and biomarkers. Subsequently, performance measures of the model with and without biomarkers were compared using predictors as continuous variables (hereafter referred to as "continuous model"). Variables included in this model were then dichotomised, creating a simplified model based on a simple count of the number of predictors. All cutoff points of vital signs used in the NEWS were considered for the simplified model and chose the model with the highest C statistic.

Combined with previously described methods for imputing missing data and variable selection,²⁶ optimism was calculated to adjust for C statistics of the continuous models using 10-fold cross-validation. The calibration slope was used as a shrinkage factor for model regression coefficients and subsequently re-estimating the intercept.

Discrimination was evaluated using the area under the receiver-operating curve (C statistic). Calibration was assessed by visual inspection of the calibration plots and evaluating the calibration slope and Brier score. In addition, the calibration of external datasets was also assessed using the O/E ratio as a measure for calibration in the large. Percentiles of bootstrapped samples were used to calculate 95% confidence intervals (CI) for performance measures. Performance measures of the continuous and simplified model were compared to each other, as well as to the performance of existing scoring systems (i.e., SIRS, qSOFA, and NEWS), and to the likelihood of sepsis (on a scale from 0-10) according to GP on site.

R v4.0.5 package was used for the analyses.

Sensitivity analyses

To evaluate potential incorporation bias resulting from the use of the SOFA score (by the expert panel) as part of the sepsis definition, model performance for secondary outcomes was assessed, as well as for a more conservative calculation of the SOFA score (fewer SOFA points for decreased oxygen saturation and altered mental status).

External validation

To test the external validity of both the continuous and simplified model, datasets from patients with suspected infections assessed in two EDs in the Netherlands were used. The C statistic discrimination was assessed, and the continuous and simplified models were compared with the NEWS. The calibration was assessed using calibration plots, as well as calibration in the large and slope. A more detailed description can be found in Supplementary Methods S1.

Results

Study population and outcome

In total, 357 patients were included for analysis (Figure 1). The median age was 80 years (IQR 71-86), and 61% was male. The GPs referred 199 patients (56%) to the ED directly after inclusion, of which 188 (94%) were subsequently admitted to the hospital. Of the 158 patients not referred immediately, 22 (14%) were admitted to the hospital within the first 72 hours after inclusion. Twelve patients (3.4%) were admitted to the ICU within 72 hours after inclusion, and overall 30-day mortality was 5.6%. The proportion of missing values was low for all candidate predictors, with the highest being 3.6% for PCT. A total of 151 patients (42%)

had sepsis, according to the expert panel. Cohen's kappa indicating the inter-rater reliability for the individual members of the same panel ranged between 0.55 and 0.85 (mean 0.66), and Cohen's kappa for inter-panel reliability ranged between 0.69 and 0.95 (mean 0.79) (Supplementary Table S2). Table 1 shows a summary of the characteristics of patients with and without sepsis.

Prediction model development

Of the nine clinical candidate predictors, six were included in the continuous model after backward selection: age, temperature, systolic blood pressure, respiratory rate, peripheral oxygen saturation and mental status. Age was included as a restricted cubic spline with three knots. After correction for optimism, the continuous model without biomarkers had a C statistic of 0.80 (95% CI 0.75 to 0.84), a calibration slope of 0.86, and a Brier score of 0.181 (See Supplementary Table S3 for the regression coefficients). The addition of the three biomarkers to this model resulted in lactate and PCT remaining after backward selection. However, the optimism corrected C statistic of 0.80 was identical to the model without biomarkers. Therefore, no biomarkers were included in the final continuous model. Analyses of individual biomarkers are shown in Supplementary Figure S4.

A simplified model was created through the dichotomisation of variables included in the continuous model (Box 1). Models without respiratory rate were also evaluated, as the respiratory rate is less feasible for GPs to perform. Heart rate showed collinearity with respiratory rate, and model performance did not decrease after substitution. Consequently, heart rate was used instead of respiratory rate in the final simplified model.

Discrimination of the simplified model (C statistic of 0.80, 95% CI 0.76 to 0.83) was nearly identical to the continuous model (Figure 2). Diagnostic accuracy measures for the simplified model at different cutoff scores are presented in Table 2. The calibration of the simplified model was also similar to the continuous model (Supplementary Figure S5). The use of multiple cutoff points for individual variables in the model, or grouping score categories, did not significantly improve performance.

Comparison with existing models

Performance of the continuous and simplified models was compared to SIRS, qSOFA and NEWS. (Table 3) NEWS showed similar performance compared to the simplified model with a C statistic of 0.79 (95% CI 0.75 to 0.83). SIRS and qSOFA had lower C statistics of 0.66 (95% CI 0.61 to 0.70) and 0.71 (95% CI 0.66 to 0.75). The perceived probability of sepsis within 72 hours by the GP on site resulted in a C statistic of 0.73 (95% CI 0.67 to 0.78). Brier scores for continuous and simplified models were lower (i.e. better) than SIRS, qSOFA and NEWS.

Sensitivity analyses

The prediction of secondary endpoints (including alternative sepsis definition using more restrictive calculation of the SOFA score) resulted in comparable performance results for the continuous model, simplified model and NEWS for all analyses. C statistics ranged between 0.7 and 0.8 for all outcomes, except for prediction of "adverse outcome" (ICU admission <72 hours or 30-day mortality), where a C statistic of 0.58 (95% CI 0.51 to 0.66) was found for the continuous model, compared to 0.62 (95% CI 0.53 to 0.69) for both the simplified model and NEWS (Supplementary Table S6).

External validation

The first validation dataset (Dataset 1) was from a teaching hospital in the south of the Netherlands and previously published by Latten *et al.*⁷ The population consisted of 440 patients with a median age of 71 years, of whom 163 (37%) were diagnosed with sepsis (severe sepsis or septic shock according to the sepsis-2 definitions).²⁶ A C statistic of 0.80 (95% 0.77 to 0.83) was found for the simplified model and 0.84 (95% CI 0.80 to 0.87) for the

continuous model. Calibration showed an O/E ratio of 1.4 for the simplified model and 1.5 for the continuous model.

The second dataset (Dataset 2) from an academic medical centre in the north of the Netherlands consisted of 1340 patients, with a median age of 65 years, of whom 342 (26%) were diagnosed with sepsis (sepsis-3 criteria). In this dataset, the C statistic was 0.70 for both the simplified and the continuous models. The O/E ratio was 1.4 for the simplified model and 1.7 for the continuous model (see Supplementary Tables and Figures S7-S11 for complete external validation results).

Discussion

Summary

In this observational cohort study, a new and easy-to-use prediction model was developed for the early recognition of sepsis in primary care. Biomarkers provided no significant improvement in prediction performance when added to the model. The respiratory rate could be replaced with the more accessible and more reliable measure heart rate without decreasing the prediction performance of the simplified model. The performance of the simplified model was significantly better than SIRS and qSOFA. The outcomes of our simplified model were comparable to NEWS.

The validity of the simplified model was confirmed in the external validation, although some differences were found in discrimination and calibration compared to the development data. Three different aspects may have contributed to these discrepancies. Firstly, the outcome "sepsis" was defined differently in the external datasets. The SIRS-based sepsis definition may

have introduced incorporation bias in the first external dataset (Dataset 1), resulting in better NEWS predictions. Secondly, the variable "altered mental status" was registered differently. Any empirical change in mental status was sufficient in our cohort, while a decrease in the Glasgow Coma Score was used in the validation cohorts. This score is probably less sensitive to subtle changes in mental status. Finally, resuscitation, admission of intravenous fluids, and supplemental oxygen by ambulance personnel of septic patients have likely occurred. Consequently, vital signs may have normalised once patients arrived at the ED and were included in the study.²⁸

Strengths and limitations

This study is the first to include patients in their home situation, where the decision to refer the patient had yet to be made. This is a major strength, as the potential impact on patient care is larger in these patients than in patients already in, or in transit to the hospital. Another strength of the study is the prospective design, specifically tailored to developing a clinical prediction rule. As only very few data on the candidate predictors were missing, the study was sufficiently powered according to prevailing sample size calculation methods.^{25,29, 30} Furthermore, the newly developed models were internally and externally validated and compared to existing scoring systems.

Several limitations of this study should be taken into account. Firstly, using an expert panel as a reference standard for sepsis may have resulted in biased results. Verification bias may have occurred, as patients referred to the hospital received more diagnostic tests than non-referred patients did. Secondly, as some candidate predictors were also part of the SOFA score, this may have resulted in incorporation bias. Therefore sensitivity analyses were

performed, using a more strict calculation of the SOFA score and alternative outcomes (i.e. adverse outcomes and need for hospital treatment according to the expert panel). These analyses did not suggest significant bias. Furthermore, not all eligible patients have been included in the study. However, the most common reasons not to include eligible patients were not based on patient factors but rather on a too busy shift, which is unlikely to have resulted in selection bias. Finally, the external validations were performed in patients assessed in the accident and emergency department due to suspected infection. Ideally, validation of the model would have been performed in a primary care population in whom the decision to refer a patient to the hospital was not yet made. These data were not available to the authors. However, the fact that the model also performed well in other domains underscores the robustness.

Comparison with existing literature

Other clinical prediction rules have been proposed for either sepsis or critically ill patients in the prehospital setting. These were mostly derived from retrospective data retrieved from patients transported by ambulance and used SIRS-based sepsis definitions.³¹ Only one prospective cohort study using the Sepsis-3 outcome definition was found in the prehospital setting, which included 551 patients with suspected infection in the ambulance.³² This study showed blood pressure ≤ 100 mmHg, temperature > 38.5 °C, lactate > 4 mmol/L, gastrointestinal symptoms, and altered mental status to be most predictive of sepsis. These findings mainly align with our results and support the decision not to include respiratory rate in the simplified model. In our data, only three patients showed a lactate > 4 mmol/L, which might explain lactate was not found to be a useful predictor in the primary care setting. Two

studies were found in which vital signs were measured in acutely ill adult patients in a primary care setting.^{32,33} However, both studies only included patients who were referred to a hospital or acute care clinic, and both did not report sepsis as an outcome measure.

The simplified prediction model developed in the current study was comparable to the NEWS score. NEWS was initially developed for the early detection of clinical deterioration of adult patients admitted to the hospital.³⁵ Recent studies in the ED setting showed NEWS superior to SIRS and qSOFA to predict sepsis,^{36,37} which was confirmed in our study for the primary care setting. An implementation study of the NEWS in the prehospital setting in England showed promising results,³⁸ but NEWS was only performed in 30% and 63% of cases by GP support teams and ambulance personnel, respectively.³⁴

Implications for research and practice

Although the difference between empirical clinical assessment by the GP and performance of our model was modest, it can help support clinicians during the busy daily routine, reduce variation in the quality of primary care and improve collaboration between primary and secondary care for this potentially life-threatening condition. The model is not intended to overrule the GP's overall judgement but rather to inform the GP on the probability of the outcome sepsis. The GP can subsequently use this information to decide whether or not to refer the patient to the hospital. The presented simplified model is easy to use in daily practice. Compared to the NEWS score, our model does not include respiratory rate and does not have a complex scoring matrix. The results do not mean that respiratory rate should not be measured in severely ill patients, and the minority of the GPs who are currently using the NEWS score are using a valid and useful model, as our results showed. Our simplified model

showed similar diagnostic properties and could be easier to implement in the primary care setting. After the decision to refer a patient due to suspected sepsis, ambulance personnel can score the NEWS depending on local protocols. Before widely advocating the new model, effects on referrals and patient outcomes should also be prospectively evaluated in a pragmatic trial in primary care.

Conclusion

A simple score-based model can accurately predict sepsis in adult primary care patients with suspected severe infections at home. Biomarkers do not improve the model's predictive performance. The score does not replace clinical judgement, and further research will have to demonstrate how GPs can best use the score to improve the management of patients with possible sepsis.

Funding

This study was funded by ZonMw (grant number 843001811). Star-shl provided additional funding. The following manufacturers provided in-kind funding of materials: Philips, Nova Biomedical, ThermoFisher. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Ethical approval

The study received ethical approval from the medical research ethics committee Utrecht (reference number 18-169).

Competing interests

Dr Hopstaken declares to have received honoraria from Lumiradx, Photondelta, and Abbott for advisory board meetings and lecturing. Prof. Dr Van Zanten reported receiving honoraria for advisory board meetings, lectures, research, and travel expenses from Baxter, Cardinal Health, Danone-Nutricia, DIM3, Fresenius Kabi, Mermaid, Lyric, and Nestlé-Novartis. Prof. Dr Verheij participated in studies that were funded by the EU and partly by Biomerieux, Becton Dickinson, Janssen Pharmaceuticals and Abbott (IMI projects). The remaining authors have declared no competing interests.

Acknowledgements

We thank all site personnel of the GP cooperatives and the patients for participating in this study. Also, we thank Idelette Nutma for her valuable input as a patient representative throughout the study and Eugenie Gemen of the Laboratory of Clinical Chemistry and Hematology of the Jeroen Bosch Hospital for assistance with analyses of the blood samples.

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Box 1. Simplified model of 6 variables, resulting in a score ranging between 0-6 points

Age > 65 years	1 point
Tympanic temperature >38 °C	1 point
Systolic blood pressure ≤ 110mmHg	1 point
Heart rate > 110 beats/minute	1 point
Peripheral oxygen saturation ≤ 95%	1 point
Altered mental status	1 point

Table 1. Patient characteristics, by sepsis diagnosis.

	Sepsis (n = 151)	No sepsis (n=206)
Demographics		
Age, median (IQR), y	80 (74-85)	79 (67-86)
Sex, No. (%)		
Men	93 (62)	123 (60)
Women	58 (38)	83 (40)
Comorbidities, No. (%)		
Diabetes	55 (36)	49 (24)
COPD	22 (15)	40 (19)
Cardiac disease	76 (50)	70 (34)
Cerebrovascular accident	33 (22)	39 (19)
Malignancy	19 (13)	30 (15)
Chronic kidney disease	43 (28)	49 (24)
Dementia	25 (17)	18 (9)
Immunosuppressive use	6 (4)	7 (3)
Final diagnosis, No. (%)		
Respiratory tract infection	61 (40)	74 (36)
Urinary tract infection	45 (30)	47 (23)
Abdominal infection	12 (8)	7 (3)
Skin/soft tissue infection	11 (7)	17 (8)
Infection with unknown source	11 (7)	25 (12)
Other source of infection	11 (7)	8 (4)
Non-infectious diagnosis	-	28 (14)
Candidate predictors		
Tympanic temperature, mean (SD), °C	39.0 (0.7)	38.5 (1.0)
Systolic blood pressure ^a , mean (SD), mmHg	135 (25)	139 (24)
Heart rate, mean (SD), /min	100 (20)	96 (20)
Respiratory rate ^a , mean (SD), /min	26 (6)	23 (7)
Peripheral oxygen saturation ^b median (IQR), %	93 (90-95)	95 (93-97)
Altered mental status, No. (%)	81 (54)	46 (22)
Rigors, No. (%)	100 (66)	123 (60)
Rapid illness progression (yes), No. (%)	127 (84)	144 (70)
Lactate ^a , median (IQR), mmol/L	1.6 (1.1-2.1)	1.3 (0.9-1.7)
C-reactive protein ^c , median (IQR), mg/L	85 (34-146)	57 (20-115)
Procalcitonin ^d , median (IQR), ng/mL	0.25 (0.09-1.20)	0.08 (0.03-0.22)
Time to blood collection, median (IQR), minutes	50 (25-65)	45 (15-65)
Secondary outcomes, No. (%)		
Hospital admission	134 (89)	76 (37)
Length of stay, median days (IQR)	5.4 (3.4-9.5)	4.6 (2.5-7.9)
ICU admission within 72 hours	11 (7.3)	1 (0.5)
30-day mortality	13 (8.6)	8 (3.9)

Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; SD, standard deviation. ^a 1 missing value ^b 2 missing values ^c 6 missing values ^d 13 missing values

Table 2. Diagnostic accuracy measures with 95% confidence intervals of the simplified prediction model for predicting sepsis at different score thresholds in the development data (n=357).

Cutoff point	Sensitivity	Specificity	LR+	LR-	PPV	NPV
≥1 (n=352)	100 (98-100)	2 (1-6)	1.02 (1.00-1.05)	0.00	43 (38-48)	100
≥2 (n=324)	99 (96-100)	16 (11-21)	1.18 (1.11-1.25)	0.04 (0.01-0.31)	46 (41-52)	97 (84-100)
≥3 (n=251)	92 (87-96)	46 (39-53)	1.69 (1.48-1.93)	0.17 (0.10-0.31)	55 (49-62)	89 (81-94)
≥4 (n=118)	60 (51-68)	86 (81-91)	4.39 (3.03-6.34)	0.47 (0.38-0.57)	76 (68-84)	74 (68-80)
≥5 (n=32)	18 (12-25)	98 (94-99)	7.37 (2.90-18.7)	0.84 (0.78-0.91)	84 (67-95)	62 (56-67)

Abbreviations: LR+, positive likelihood ratio; LR-, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

Table 3. Optimism corrected performance measures in the development data (n=357) of the multivariable model consisting of clinical parameters as continuous variables (continuous model), with the addition of lactate and procalcitonin (continuous model + biomarkers), simplified model, SIRS, qSOFA, and NEWS.

Prediction model	C statistic (95% CI)	Calibration slope	Brier score
Continuous model	0.80 (0.75-0.84)	0.86	0.181
Continuous model + biomarkers	0.80 (0.74-0.84)	0.83	0.176
Simplified model	0.80 (0.76-0.83)	1.00	0.175
NEWS	0.79 (0.75-0.83)	1.01	0.182
qSOFA	0.71 (0.66-0.75)	1.02	0.207
SIRS	0.66 (0.61-0.70)	1.03	0.224

Abbreviations: NEWS, National Early Warning Score; qSOFA, quick Sepsis Related Organ Failure Assessment Score; SIRS, Systemic Inflammatory Response Syndrome (based on criteria: temperature <36 or >38°C, respiratory rate >20/min, heart rate >90/min)

Figure 1. Patient flow diagram

Figure 2. A. Receiver-operating curves of the continuous model, continuous model + biomarkers (lactate and PCT), and simplified model for sepsis outcome. B. Receiver-operating curves of the simplified model, NEWS, qSOFA and SIRS for the outcome sepsis. C. Number of patients with and without sepsis for all scores on the simplified model. D. Predicted rate of sepsis with 95% confidence intervals for all scores on the simplified model.

Abbreviations: NEWS, National Early Warning Score; qSOFA, quick Sepsis Related Organ Failure Assessment Score; SIRS, Systemic Inflammatory Response Syndrome (based on criteria: temperature <36 or >38°C, respiratory rate >20/min, heart rate >90/min)

Figure 1. Patient flow diagram

134x96mm (300 x 300 DPI)

Figure 2. A. Receiver-operating curves of the continuous model, continuous model + biomarkers (lactate and PCT) and simplified model for the outcome sepsis. B. Receiver-operating curves of the simplified model, NEWS, qSOFA and SIRS for the outcome sepsis. C. Number of patients with and without sepsis for all scores on the simplified model. D. Predicted rate of sepsis with 95% confidence intervals, for all scores on the simplified model.

Legend: Abbreviations: NEWS, National Early Warning Score; qSOFA, quick Sepsis Related Organ Failure Assessment Score; SIRS, Systemic Inflammatory Response Syndrome (based on criteria: temperature <36 or $>38^{\circ}\text{C}$, respiratory rate $>20/\text{min}$, heart rate $>90/\text{min}$)

157x222mm (600 x 600 DPI)