# Added Diagnostic Value of Biomarkers in Patients with Suspected Sepsis: A Prospective Cohort Study in Out-Of-Hours Primary Care

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**Background:** Point-of-care testing (POCT) has shown promising results in the primary care setting to improve antibiotic therapy in respiratory tract infections and it might also aid general practitioners (GPs) to decide if patients should be referred to a hospital in cases of suspected sepsis. We aimed to assess whether biomarkers with possible POCT use can improve the recognition of sepsis in adults in the primary care setting.

**Methods:** We prospectively included adult patients with suspected severe infections during out-of-hours home visits. Relevant clinical signs and symptoms were recorded, as well as the biomarkers C-reactive protein, lactate, procalcitonin, high-sensitive troponin I, N-terminal pro b-type natriuretic peptide, creatinine, urea, and pancreatic stone protein. We used a POCT device for lactate only, and the remaining biomarkers were measured in a laboratory from stored blood samples. The primary outcome was sepsis within 72 h of inclusion. The potential of biomarkers to either rule in or rule out sepsis was tested for individual biomarkers combined with a model consisting of signs and symptoms. Net reclassification indices were also calculated.

**Results:** In total, 336 patients, with a median age of 80 years, were included. One hundred forty-one patients (42%) were diagnosed with sepsis. The C statistic for the model with clinical symptoms and signs was 0.84 (95% CI 0.79–0.88). Both lactate and procalcitonin increased the C statistic to 0.85, but none of the biomarkers significantly changed the net reclassification index.

**Conclusions:** We do not advocate the routine use of POCT in general practice for any of the tested biomarkers of suspected sepsis.

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**IMPACT STATEMENT**

General practitioners increasingly use point-of-care testing to guide management in patients with acute conditions. In this study, we assessed the added diagnostic value of 8 biomarkers to clinical symptoms and signs to diagnose sepsis in adult patients. We found that none of these biomarkers added clinically relevant diagnostic information, leading to the conclusion that point-of-care testing for the evaluated biomarkers is not useful in adult patients with suspected sepsis.

## INTRODUCTION

Sepsis is a life-threatening complication from infection, characterized by organ dysfunction resulting from a dysregulated host response (1). In 2017, the global incidence was estimated at 49 million cases and 11 million deaths per year (2). Timely recognition and treatment of sepsis are essential to reduce mortality and morbidity (3). General practitioners (GPs) are mostly the first healthcare providers assessing patients with acute infections (4), and they have to decide which patients need immediate hospital referral and which patients can be safely treated at home. In a recently published study, we developed and validated a model based on age, tympanic temperature, systolic blood pressure, heart rate, oxygen saturation, and mental status that was shown to be helpful in predicting sepsis in acutely ill adult patients visited at home by a GP (5). Three biomarkers, C-reactive protein (CRP), lactate, and procalcitonin (PCT), showed no added value. However, several other biomarkers feasibly measured with point-of-care testing (POCT) could well have added value in predicting sepsis in an early stage outside hospital, and could therefore have high clinical relevance (5–10).

POCT is increasingly used in the primary care setting, as the rapid availability of the test result during the patient encounter increases the potential to decide on management jointly. For example, CRP POCT has successfully been implemented to better diagnose pneumonia and improve antibiotic prescribing in acute respiratory tract infections in various countries (11). To ensure feasibility of biomarker measurement by GPs, results should be available within 10 to 20 min at the bedside, using blood from a finger prick.

This study aims to assess the potential value of various biomarkers in improving GPs' recognition of sepsis in suspected adult patients in a primary care setting.

## MATERIALS AND METHODS

We prospectively collected data for the TeSD-IT study (12, 13), and performed a sub-analysis of the data from patients who provided additional informed consent to analyze stored blood samples. The methods have been described previously (13) and are summarized here. In addition to CRP, lactate, and PCT, high-sensitivity troponin I (hs-TnI), N-terminal pro b-type natriuretic peptide (NT-proBNP), creatinine, urea, and pancreatic stone protein (PSP) were measured from the stored blood samples. PSP is a protein secreted by the pancreas, which is increased during systemic infection and sepsis (10).

### Inclusion and Exclusion Criteria

Patients were consecutively recruited during out-of-hours home visits by GPs at 4 out-of-hours GP cooperatives in the Netherlands between June

2018 and March 2020. All acutely ill adult patients (≥18 years old) with fever, confusion, general deterioration, or being otherwise suspected of severe infection were eligible for inclusion. We excluded patients if one or more of the following criteria were present: (*a*) non-infectious cause of the acute complaints (e.g., stroke or myocardial infarction); (*b*) hospitalization within 7 days before the home visit; (*c*) condition that requires secondary care assessment if there are any signs of systemic infection (e.g., chemotherapy with possible neutropenia); (*d*) terminal illness or other reason not to refer the patient to a hospital despite the presence of a life-threatening condition.

### Data Collection and Blood Analysis

The following clinical signs and symptoms were recorded on the case report form by the GP: tympanic temperature; blood pressure; heart rate; respiratory rate; peripheral oxygen saturation; altered mental status (yes/no); rapid progression of illness (yes/no); rigors (yes/no); and duration since the onset of the acute complaints. Venous blood samples were obtained immediately by the GP, or soon afterwards by an on-call laboratory assistant.

Lactate was tested at the patient site for quality reasons (StatStrip Xpress Lactate, Nova Biomedical). All other biomarkers were measured at the Jeroen Bosch Hospital, Laboratory for Clinical Chemistry and Haematology, 's-Hertogenbosch, the Netherlands, from serum of the venous blood samples stored at −70 °C. CRP, PCT, Hs-TnI, NT-proBNP, creatinine, and urea were measured on ADVIA XPT systems (Siemens Healthcare Diagnostics). PSP was measured on the abioSCOPE® (Abionic). All laboratory analyses were performed between August 2020 and October 2020, with standard quality control procedures including testing for hemolysis, icterus, and lipemia. The investigators assessing the biomarkers were blinded to the patients' outcomes. Also, GPs who initially assessed and included patients in the study were blinded to the blood analyses and did not assess any of the investigated biomarkers during standard care.

### Follow-up

The total follow-up of the study was 30 days for all patients. The medical follow-up information on the patients included in the study was retrieved from the electronic medical record of their own GP and from the hospital in cases of the patient having been admitted to the hospital during the follow-up period. This information included discharge letters from the emergency department and hospital, and all relevant vital signs and laboratory findings in the first 72 h after inclusion to determine the presence or absence of sepsis.

### Primary and Secondary Outcomes

The primary outcome was sepsis within 72 h of inclusion, as established by an expert panel. The panel consisted of one GP, one emergency physician, and one intensivist/acute care internist. All relevant medical information was provided to the panelists and they were instructed to base their judgment on the presence of sepsis according to the Sepsis-3 definition. This implies an increase from baseline by 2 or more points on the SOFA score due to an acute infection (1). The expert panel was blinded to the results of laboratory analyses of the study samples. Secondary outcomes were "adverse outcome" (defined as a composite outcome of either intensive care unit [ICU] admission within 72 h or 30-day mortality) and positive blood cultures. If there was no consensus on the primary outcome between the panelists, the case was discussed in a meeting until consensus was reached. The secondary outcomes were based on the majority vote (or average score) during the first round of panel assessment.

In addition to the secondary endpoints, we performed a subgroup analysis based on the duration of the acute complaints before inclusion. As there can be a delay in the increase of biomarkers after

the onset of sepsis, we performed a subgroup analysis based on the duration of the acute complaints before inclusion (less or more than 24 h).

### Statistical Analyses

Mean values with standard deviation are presented for normally distributed continuous variables and median values with interquartile range (IQR) for skewed distributed variables. Missing data were imputed using Multiple Imputation by Chained Equations (MICE), creating 10 imputed datasets. Differences in the mean test results of the biomarkers between patients with and without sepsis were assessed using independent sample *t*-tests. As the distributions of all biomarkers were positively skewed, we performed a log transformation. The assumption of equal variances was assessed using F-tests.

We assessed discrimination of individual biomarkers using receiver operating characteristic (ROC) curves and calculating the C statistic (area under the ROC curve). Furthermore, we calculated sensitivity, specificity, positive predicted value (PPV), and negative predicted value (NPV) for different cutoff points to assess the feasibility of biomarkers to rule out sepsis in clinical practice.

Subsequently, we used multivariable logistic regression analysis to assess the added value of biomarkers in combination with clinical signs and symptoms. To that extent, individual biomarkers were added to the model developed in the TeSD-IT study (12). This model includes age, tympanic temperature, systolic blood pressure, respiratory rate, peripheral oxygen saturation, and altered mental status (yes/no). Interactions between biomarkers were not assessed, as the study was insufficiently powered to allow for these analyses.

The 2 best performing multivariable prediction models with biomarkers were compared to the model without that biomarker concerning the potential impact on treatment decisions based on risk categories. Predicted probabilities from these models were used to classify patients into low risk (<10%) and high risk (>50%) of having sepsis. Discrepancies between classifications by these models were evaluated using the net reclassification index (NRI) and integrated discrimination index (IDI). The NRI was calculated by adding the proportion of more favorable classifications in patients with sepsis (i.e., higher risk category classification) to the proportion of more favorable classifications in patients without sepsis (i.e., lower risk category classification) (14). The IDI is complementary to the C statistic, but uses only the predefined classification cutoffs of 10% and 50%. It is calculated by taking the difference in area under the curve (AUC) of sensitivity between the model with and without biomarker, and subtracting the difference in AUC of specificity (15).

The 95% confidence intervals (CI) were estimated using bootstrapping. Statistical significance was defined as a two-tailed *P* value <0.05. All analyses were performed using R version 4.0.3.

### Ethical Approval

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

## RESULTS

We analyzed the data of 336 patients, with a median age of 80 years (IQR 71 to 86) and 58% males. A flowchart of the patients included is shown in online Supplemental Fig. 1. According to the expert panel, the primary outcome "sepsis within 72 h of inclusion" was reached by 141 (42%) patients. Respiratory tract and urinary tract infections were most common in sepsis and non-sepsis patients (see Table 1). According to the expert panel, 14% of the patients without sepsis did not have an infectious

**Table 1. Background characteristics by sepsis diagnosis and for the total population.[a]**

| Characteristic | Sepsis (n = 141) | No sepsis (n = 195) | Total population (n = 336) |
|---|---|---|---|
| Demographics | | | |
| Age, median (IQR), y | 80 (74–85) | 80 (71–86) | 79 (68–86) |
| Sex, No. (%) | | | |
| Men | 202 (60) | 93 (62) | 123 (60) |
| Women | 134 (40) | 58 (38) | 83 (40) |
| Source of infection, No. (%) | | | |
| Respiratory tract | 58 (41) | 127 (38) | 69 (35) |
| Urinary tract | 42 (30) | 88 (26) | 46 (24) |
| Abdominal | 10 (7.1) | 17 (5.1) | 7 (3.6) |
| Skin/soft tissue | 11 (8.2) | 27 (8.0) | 16 (8.2) |
| Unknown source | 10 (7.1) | 33 (9.8) | 23 (12) |
| Other | 10 (7.1) | 18 (5.4) | 8 (4.1) |
| No infection | 0 (0) | 26 (7.7) | 26 (13) |
| Time to blood collection, median (IQR), min | 50 (25–65) | 45 (15–65) | 45 (18–65) |
| Hospital admission, No. (%) | 124 (88) | 71 (36) | 195 (58) |
| Length of hospital stay, median (IQR), days | 4.7 (3.0–8.2) | 4.5 (2.5–7.0) | 4.7 (2.8–8.1) |
| ICU admission, No. (%) | 10 (7.1) | 1 (0.5) | 11 (3.3) |
| 30-day mortality, No. (%) | 13 (9.2) | 8 (4.1) | 21 (6.2) |

[a]Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease.

condition as the cause of the acute complaints. Of the patients referred to the emergency department immediately after inclusion, 180/190 (95%) were admitted to the hospital and 18/146 (12%) of the initially non-referred patients were admitted to the hospital within 72 h of inclusion. The average length of stay (hospital admission) was 5.4 days for the sepsis patients and 4.6 days for the non-sepsis patients. Admission to the ICU within 72 h occurred in 11 sepsis patients and 1 non-sepsis patient, and the overall 30-day mortality was 6.2%. Missing data on biomarkers ranged from 0.3% for lactate to 3.9% for hs-TnI.

All tested biomarkers showed significantly higher concentrations in patients with sepsis (Table 2). Univariable analysis of the predictive value of the biomarkers for the outcome sepsis showed the highest C statistic for PCT (C statistic 0.72 [95% CI, 0.66–0.77]) (see Fig. 1). In online Supplemental Table 1, diagnostic accuracy measures are presented for different cutoff points of the biomarkers. The highest PPV was found for PCT at a cutoff point of >2 μg/L (PPV 74%). The sensitivity of PCT at this cutoff point was 22%, with a specificity of 94%. The highest NPVs were found for CRP <10 mg/L and NT-proBNP <150 pg/mL, both resulting in an NPV of 80%. For CRP <10 mg/L the sensitivity was 94% with a specificity of 17% and for NT-proBNP <150 pg/mL the sensitivity and specificity were, respectively, 93% and 20%.

The multivariable model of clinical symptoms and signs without biomarkers showed a C statistic of 0.83 (95% CI, 0.79–0.88). After the addition of individual biomarkers, the C statistic increased to 0.84 for both lactate and PCT. The C statistics of the models with the other biomarkers remained 0.83. Reclassification tables for the comparison of the model without

**Table 2. Biomarkers by sepsis diagnosis, with the number of patients in which the biomarkers were analyzed (*N*) and *P* value in imputed data.[a,b]**

| Biomarker | *N* | Sepsis (n = 141) | No sepsis (n = 195) | *P* value |
|---|---|---|---|---|
| CRP, mg/L | 331 | 85 (34–141) | 58 (20–117) | <0.001 |
| Lactate, mmol/L | 335 | 1.6 (1.2–2.1) | 1.3 (0.9–1.7) | <0.001 |
| PCT, ng/mL | 324 | 0.26 (0.10–1.4) | 0.08 (0.03–0.21) | <0.001 |
| Hs-TnI, ng/L | 323 | 21 (10–51) | 10 (6–23) | <0.001 |
| NT-proBNP, ng/L | 326 | 1604 (640–4315) | 495 (179–2302) | <0.001 |
| Creatinine, umol/L | 328 | 98 (73–121) | 84 (67–104) | 0.006 |
| Urea, mmol/L | 328 | 8.9 (6.8–12.2) | 7.2 (5.9–9.8) | <0.001 |
| PSP, ng/mL | 330 | 156 (90–286) | 131 (83–205) | 0.016 |

[a]Abbreviations: CRP, C-reactive protein; PCT, Procalcitonin; Hs-TnI, high sensitivity troponin I; NT-proBNP, N-terminal pro b-type natriuretic peptide; PSP, pancreatic stone protein.
[b]Values of the biomarkers are presented as median (interquartile range).

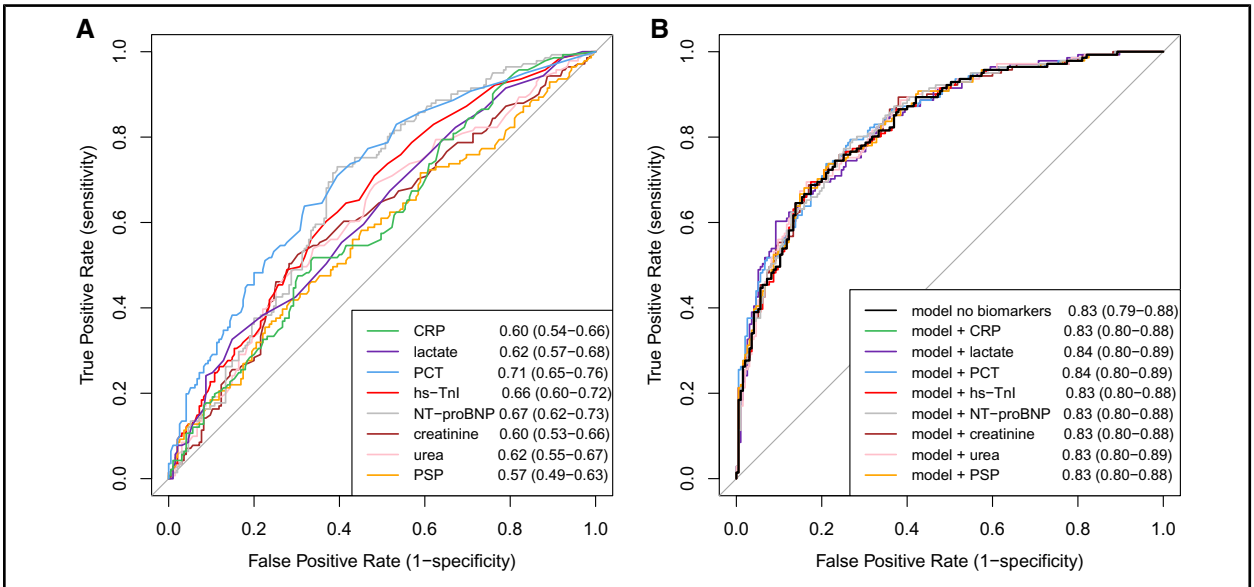


**Fig. 1. Receiver operating curves (ROC) of the individual biomarkers with the C statistic (95% confidence intervals) (A) and ROC of the symptoms and signs model compared to the model with the addition of the individual biomarkers (B).**

biomarkers compared to the model with addition of lactate and the model with addition of PCT are shown in Table 3. NRIs did not change significantly after the addition of either lactate or PCT. IDIs did show a statistically significant change for lactate (0.01 [95% CI, 0.00–0.03], $P = 0.04$) and PCT (0.02 [95% CI, 0.00–0.04], $P = 0.03$) when compared to the model without biomarkers, though this is not considered a clinically meaningful difference.

**Table 3. Reclassification tables for comparing a clinical signs and symptom-based model to the same model with lactate (A) or procalcitonin (B) added to it.[a]**

**A**

| Symptoms and signs model | Symptoms and signs model with the addition of lactate | | | |
|---|---|---|---|---|
| **Frequency** | **<10%** | **10% to 50%** | **>50%** | **Total** |
| *Patients with sepsis* | | | | |
| <10% | 3 | 1 | 0 | 4 |
| 10% to 50% | 0 | 38 | 7 | 45 |
| >50% | 0 | 5 | 87 | 92 |
| Total | 3 | 44 | 94 | 141 |
| *Patients without sepsis* | | | | |
| <10% | 43 | 4 | 0 | 47 |
| 10% to 50% | 5 | 105 | 8 | 118 |
| >50% | 0 | 4 | 26 | 30 |
| Total | 48 | 113 | 34 | 195 |

**B**

| Symptoms and signs model | Symptoms and signs model with the addition of procalcitonin | | | |
|---|---|---|---|---|
| **Frequency** | **<10%** | **10% to 50%** | **>50%** | **Total** |
| *Patients with sepsis* | | | | |
| <10% | 4 | 0 | 0 | 4 |
| 10% to 50% | 0 | 43 | 3 | 46 |
| >50% | 0 | 4 | 87 | 91 |
| Total | 4 | 47 | 90 | 141 |
| *Patients without sepsis* | | | | |
| <10% | 47 | 0 | 0 | 47 |
| 1% to 80% | 3 | 111 | 4 | 118 |
| >80% | 0 | 3 | 27 | 30 |
| Total | 50 | 114 | 31 | 195 |

[a]Red fields indicate a less favorable reclassification; green fields indicate a more favorable reclassification, when adding the biomarker.

## Secondary Analyses

For the outcome "positive blood culture," PCT resulted in the highest C statistic (0.80 [95% CI, 0.73–0.87]). The other biomarkers showed C statistics ranging between 0.59 and 0.70 (see online Supplemental Fig. 2). For the outcome "adverse event" (ICU admission <72 h or 30-day mortality), NT-proBNP showed a C statistic of 0.74 (95% CI, 0.63–0.83). In online Supplemental Table 2, the results of the analyses that compare biomarker levels in patients with sepsis with acute onset of illness (<24 h before inclusion) to those without acute onset (>24 h after inclusion) are shown. In patients with sepsis with acute onset of illness, lactate levels were higher compared to patients without acute onset. Conversely, CRP levels were higher in patients with the onset of complaints more than 24 h before inclusion. For the remaining biomarkers, no statistically significant differences were found.

## DISCUSSION

In this prospective observational study of 336 acutely ill, adult patients in the setting of out-of-hours primary care, we assessed the added value of biomarkers feasible for POCT for sepsis recognition, as compared to our optimal clinical model. The best performance was found for PCT, resulting in a C statistic of 0.71 (95% CI, 0.65–0.76) as a standalone test, and a C statistic of 0.84 (95% CI, 0.80–0.89) when combined with clinical parameters. PCT also showed the best discrimination for positive blood cultures (C statistic 0.80). However, the model of clinical parameters without biomarkers showed a C statistic of 0.83 for the outcome sepsis, and reclassification indexes did not show statistically significant improvement. Furthermore, PCT and all other biomarkers could not rule out sepsis at any cutoff value in this population, as the chance of a false-negative result was at least 20%.

### Comparison with Literature

Brant and colleagues published the results of a study in which the added value of biomarkers was evaluated in combination with a clinical risk score in 452 patients transported by emergency medical services (16). CRP increased the C statistic for sepsis prediction from 0.59 to 0.79, and smaller increases in discrimination were found for lactate, PCT, troponin, tumor necrosis factor, interleukin-6, and interleukin-10. However, the clinical risk score was developed to predict critical illness in a heterogeneous population of non-trauma patients and was not validated for use as a sepsis prediction model. In a prospective study performed in patients transported by ambulance in Sweden, the value of clinical parameters and several biomarkers (glucose, lactate, soluble urokinase Plasminogen Activator Receptor [suPAR], and heparin-binding protein) were assessed for developing a sepsis prediction tool (17). Only lactate at a cutoff point of >4 mmol/L was found to improve prediction in a multivariable regression model statistically. In our study, a lactate >4 mmol/L was observed in 3 patients, of which only one was diagnosed with sepsis.

### Strengths and Limitations

We have successfully collected complete sets of vital signs and blood samples in patients with possible sepsis in primary care. To our knowledge, this has never been done in a primary care setting previously. This achievement enabled us to assess the potential added value of POCT in patients for whom the decision to refer to a hospital had yet to be made. Data collected in the emergency department or ambulance setting are not representative for primary care populations as all patients are assessed at the hospital. In addition, the prospective design resulted in very few missing data. Another strength is use of an expert panel to assess the outcome of sepsis, as a subjective interpretation of medical records is needed, especially in patients not admitted to the hospital.

Several limitations of the study should be taken into account. We only tested a limited number of biomarkers. We focused on feasible tests for use in the primary care setting, using POCT that could be analyzed from the stored blood samples. For example, white blood cell count could not be performed from the stored serum and plasma samples. Of the tested biomarkers, only lactate was measured using a POCT device. We chose laboratory measurements for the sake of blinding health care professionals and patients, and for efficiency. The diagnostic accuracy of the biomarkers is unlikely to be superior when measured with a POCT device compared to our presented results based on laboratory analyses. Due to the limited sample size, we could not assess all possible combinations, interactions, and non-linear associations between the different biomarkers in our study. It should be taken into account that the patients included in this study

were already suspected of having a severe infection from the first impression of the GP. Patients were also recruited in a mainly elderly population during out-of-hours home visits, resulting in a high percentage of patients meeting the sepsis criteria. Therefore, the results may not be valid for all patients with suspected (milder) infections presenting in primary care.

### Implications for Further Research and Practice

POCT is increasingly available in general practice and can improve diagnostic accuracy in the primary care setting. However, it is essential that GPs understand the limitations of diagnostic tests and only use a test in a specific population and for a specific outcome. For example, CRP can safely reduce antibiotic prescribing in patients with acute cough and exacerbations of chronic obstructive pulmonary disease (18, 19). However, our study showed that a CRP <20 mg/L could not rule out sepsis in a high-risk population at home. Vital signs can be easily measured by GPs and can predict sepsis accurately. Including biomarkers in a defined clinical model does not markedly improve prediction.

Further research should therefore focus on optimal use of vital signs in the primary care setting. Also, validation in other primary care populations, and in other countries where out-of-hours care is often organized differently, is needed. Any biomarkers that were not evaluated in our study, with particular consideration for newly developed biomarkers, should be considered in future assessment of the added value of biomarkers.

## CONCLUSION

In patients with possible sepsis visited at home by GPs, we did not find any diagnostic added value in the biomarkers we evaluated compared to a diagnostic model with clinical signs and symptoms. Therefore, based on this study, we cannot advocate the routine use of these point-of-care tests for sepsis in general practice.

## SUPPLEMENTAL MATERIAL

Supplemental material is available at *The Journal of Applied Laboratory Medicine* online.

**Nonstandard Abbreviations:** POCT, point-of-care testing; PCT, procalcitonin; GP, general practitioner; CRP, C-reactive protein; NT-proBNP, N-terminal pro b-type natriuretic peptide; Hs-TnI, high sensitivity troponin I; PSP, pancreatic stone protein.

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