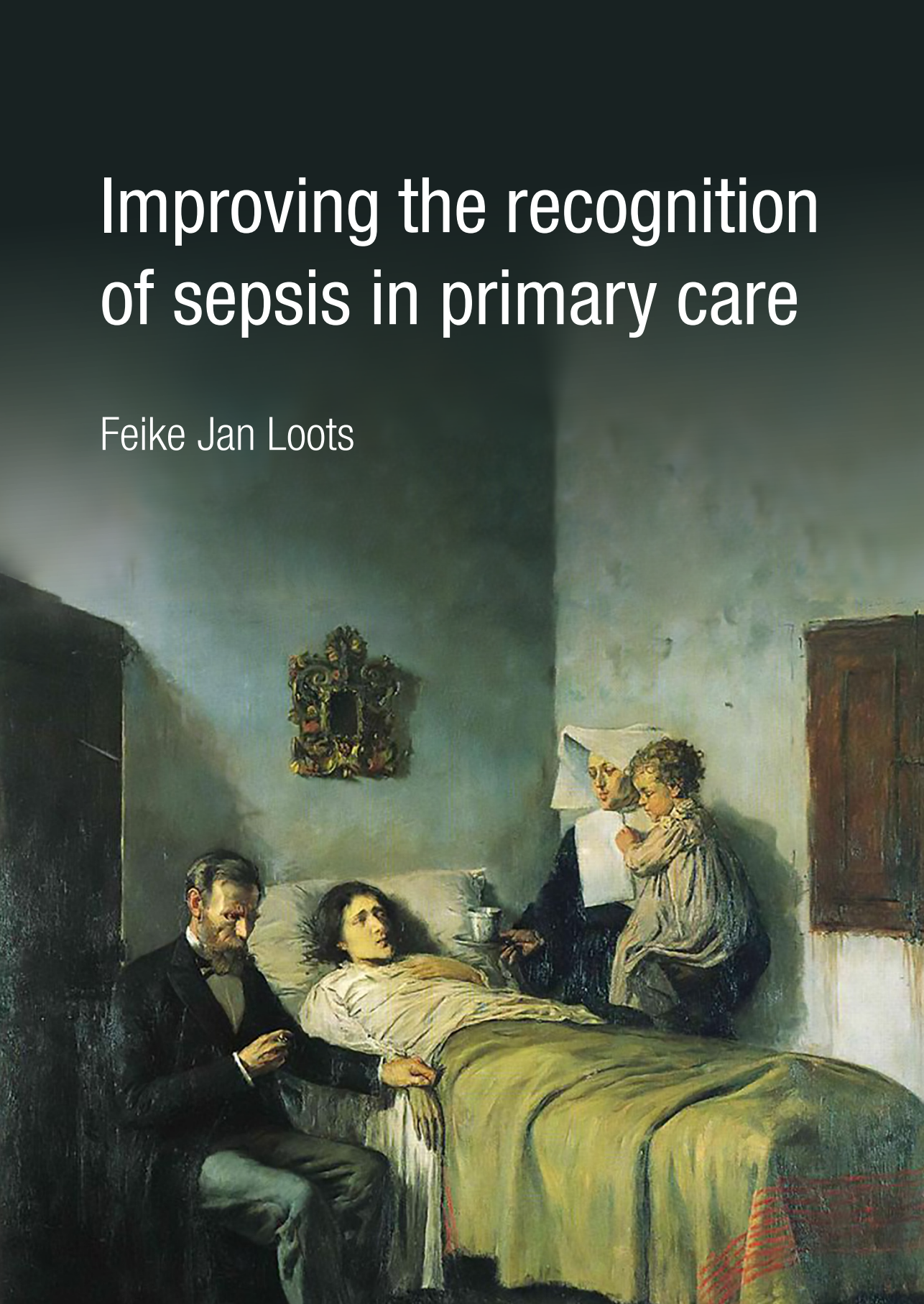
Improving the recognition of sepsis in primary care

Feike Jan Loots



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Printing: ProefschriftMaken || www.proefschriftmaken.nl

ISBN: 978-94-6423-859-4

The TeSD-IT study was funded by ZonMw (grant number 843001811), with additional (in kind) funding by Saltro, Star-shl, Philips, ThermoFisher and Nova Biomedical. Financial support for the printing of this thesis was provided by the Julius Center, UMC Utrecht.

TeSD-IT
TESTING FOR SEPSIS IN PRIMARY CARE

Improving the recognition of sepsis in primary care

Verbeteren van de herkenning van sepsis in de eerste lijn
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor
promoties in het openbaar te verdedigen op

donderdag 23 juni 2022 des ochtends te 10.15 uur

door

Feike Jan Loots

geboren op datum 6 september 1977 te Amersfoort

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CHAPTER 1

Introduction

The term sepsis (σῆψις) dates back to 2700 years ago when in ancient Greece, Homer mentioned it in one of his poems.[1] The word is derived from "sepo"(σήπω), which means "I rot". Hippocrates (c. 460 - c. 370 BC) was the first to mention sepsis in a medical context in his Corpus Hippocratum, viewing it as a dangerous biological decay in the body [2]. However, it was not until the nineteenth century that the understanding was gained that germs are the causative agent in sepsis.[3] Moreover, it was only in 1991 when the first definition of sepsis was formulated by the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) during a consensus conference in Northbrook in the United States.[4] During this conference, definitions for sepsis, severe sepsis and septic shock were formulated. The Systemic Inflammatory Response Syndrome (SIRS) was introduced to define sepsis in patients with a suspected infection. Severe sepsis was defined as sepsis in combination with signs of organ failure. In 2001 a second international consensus conference was held in which more diagnostic criteria for sepsis were proposed than just the four components of SIRS.[5] However, it would take until the current consensus definition of sepsis (Sepsis-3), published in 2016, to entirely abandon the concept of SIRS as part of the sepsis definition. Sepsis is since then defined as "as life-threatening organ dysfunction caused by a dysregulated host response to infection".[6] Severe sepsis is no longer separately defined. The Sequential Organ Failure Assessment (SOFA) score is used to assess the presence of organ dysfunction (see Box 1). To meet the sepsis criteria, an increase of at least two points on the SOFA score consequent to the infection should be present. Unfortunately, Sepsis-3 is not the end of the debate regarding the definition of sepsis. During the formulation of Sepsis-3, it was recognised that it is still "work in progress", and a new update on the definition may be necessary in the future.[6] In this thesis, we will only focus on sepsis in adult patients. Although the pathophysiology is essentially the same, risk factors and clinical presentations differ significantly, making it more appropriate to investigate sepsis in children and adults separately.[7]

Box 1. Sequential Organ Failure Assessment (SOFA) score[a]

System		Score 1	2	3	4
Respiration					
	PaO_2/FiO_2, mmHg	300-440	> 440	<200 with respiratory support	< 100 with respiratory support
Coagulation					
	Platelets, $x10^3/\mu L$	<150	<100	<50	<20
Liver					
	Bilirubin, µmol/L	20-32	33-101	102-204	>204
Cardiovascular					
	Hypotension	MAP < 70 mmHg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system					
	Glasgow Coma Score	13-14	10-12	6-9	<6
Renal					
	Creatinine, µmol/L	110-170	171-299	300-440	> 440
	Urine output, mL/d			<500	<200

[a] Adapted from Vincent et al. [8]
[b] Adrenergic agents administered for at least one hour (doses given in µg/kg/min).
PaO_2, partial pressure of arterial oxygen. FiO_2, fraction of inspired oxygen. MAP, mean arterial pressure.

Epidemiology and mortality

The global incidence of sepsis is estimated at 49 million, resulting in 11 million deaths annually. Sepsis accounts for one in five of all deaths globally.[9] Almost 90% of the sepsis cases originate outside the hospital (community-onset sepsis).[10] The remaining 10% result from hospital-acquired infections, often after surgery.[11, 12] Best estimates of the incidence of community-onset sepsis in western countries range between 0.4-4.5 per 1000 person-years.[13] This concerns only patients admitted to the hospital due to community-onset sepsis and therefore does not include patients who die from sepsis at home or in nursery homes. Converted to an average general practice of about 2100 patients, this would be 1-10 sepsis cases per year. This range is comparable to the incidence of pulmonary embolism (0.6/ 1000 person-years)[14] and stroke (5/1000 person-years).[15] Age is a significant risk factor for sepsis. In adults, the risk of sepsis increases exponentially above the age of 50 years, doubling the incidence every ten years.[16] Also, men are also at increased risk for sepsis.[16] Other risk factors are comorbidities such as chronic respiratory diseases, cardiovascular diseases, and diabetes. The use of immunosuppressive medication and alcohol abuse

also increases sepsis's risk[17]. Furthermore, recent surgery and invasive devices (e.g. central lines or urinary catheters) can be a port of entry for bacteria that may lead to subsequent sepsis[18].

Pathophysiology and clinical manifestations

In sepsis, both pro-inflammatory and anti-inflammatory responses occur. In the first phase, when the patients' immune system does not adequately control an infection, pro-inflammatory mechanisms dominate after leucocytes are activated, and cytokines are released[19]. The inflammatory process can cause tissue damage, triggering further immune system activation, resulting in a cytokine storm condition.[20, 21] The over-activated immune response causes damage to the endothelium and activation of the coagulation cascade. This results in impaired microcirculation through capillary leakage and microthrombi. As a consequence, oxygen delivery is decreased, leading to tissue hypoxia. Organ failure and lactate acidosis arise when the condition progresses to septic shock. Initially, the blood pressure is maintained through increased cardiac output.[22] In the early phase of septic shock, vasodilatation can result in a hyperdynamic state with preserved peripheral circulation ("warm shock"). In later stages of sepsis, myocardial dysfunction and decreased intravascular volume are compensated through vasoconstriction to maintain arterial blood pressure. This results in decreased peripheral circulation ("cold shock"). Anti-inflammatory mechanisms can get the upper hand in patients who survive the initial pro-inflammatory phase. This can result in a condition called "immune paralysis", which makes the patient vulnerable to secondary infections.[19]

Most sepsis cases result from bacterial infections, but viruses, fungi and parasites can also cause sepsis. The COVID-19 pandemic is the most striking example of the possibility of sepsis resulting from a viral infection. The most common sources of infection in sepsis are respiratory tract infections, accounting for about half of the sepsis cases, followed by abdominal infections and urinary tract infections.[16, 23] Also, skin and soft tissue infections are common, as is sepsis with unknown origin. Infections such as meningitis and endocarditis are known for the high risk of sepsis but are relatively rare and represent only 1-2% of all sepsis cases.[16] Clinical manifestations of sepsis can vary widely due to different symptomology during progression from infection to septic shock, and due to symptoms caused by local inflammation at the site of infection.[19, 23] SIRS reflects the initial pro-inflammatory response to infection. Decreased peripheral circulation, hypotension, oliguria, hypoxia, and changed mental status can occur due to subsequent impaired (micro) circulation. Depending on the source of infection, other clinical symptoms can be present, for example, shortness of breath, coughing, abdominal pain or other localised complaints at the site of infection.

Importance of early recognition of sepsis

In 2001 Emanuel Rivers and colleagues published the paper "Early goal-directed therapy in the treatment of severe sepsis and septic shock", which showed mortality was reduced by 16% after immediate protocolled sepsis care, compared to standard care.[24] Although the exact "goals" which are targeted during the initial resuscitation of patients with sepsis are still heavily debated,[25] immediate and adequate treatment with antibiotics is crucial for the prognosis.[26, 27] The Surviving Sepsis Campaign (SSC) was launched in 2002 as an international effort to improve outcomes of patients with sepsis using protocolled care. The key elements are screening for possible sepsis and immediate treatment according to an "Hour-1 bundle" [28].

If the patient's condition demands intensive care unit (ICU) treatment after initial resuscitation, optimal supportive care (e.g. vasopressors and mechanical ventilation) and source control are essential.[19] Extensive research has been performed in the past decades to improve the outcome of patients with sepsis admitted to the ICU, but nearly all experimental treatments have failed to show benefit in randomised controlled trials.[29] The most crucial factor determining the outcome is the early recognition and initiation of adequate treatment. For general practitioners (GPs), this implies that patients with sepsis should be referred to the hospital immediately. Prescribing oral antibiotics only and reassessing the patient the following day can result in severe consequences for patients with sepsis.

Diagnostic strategies

In the early 2000s, when the guidelines of the SSC were implemented in the Netherlands, the SIRS criteria were used to identify sepsis in all patients with suspected infection after arrival at an emergency department (ED). As the leucocyte count and partial CO_2 pressure are not readily available during initial triage, often just the body temperature, heart rate and respiratory rate were used for the first screening. In 2016, simultaneously with the new definitions of Sepsis-3, the qSOFA (quick SOFA) was introduced as a bedside tool for assessing patients with suspected sepsis.[30] The qSOFA is scored positive if two of the following three criteria are present: 1) systolic blood pressure ≤100 mmHg; 2) respiratory rate ≥22/min; 3) altered mental status. The qSOFA was intended to predict increased mortality risk in a patient suspected of sepsis.

Box 2. Quick Sequential Organ Failure Assessment (qSOFA) score

Suspected infection and 2 or more of the following:

- Respiratory rate ≥ 22/min
- Altered mental status
- Systolic blood pressure ≤ 100 mmHg

Shortly after introducing the qSOFA, the debate started whether the qSOFA should replace SIRS as a sepsis screening tool in the ED. Research comparing SIRS of qSOFA showed that SIRS has superior sensitivity and qSOFA is more specific for sepsis.[31] As a result, a large proportion (30-50%) of the sepsis cases are missed using the qSOFA. Early warning scores (EWS) and later modified scores, NEWS and MEWS, are increasingly used in the hospital setting in the last five to ten years. The NEWS was initially proposed to detect patients at risk for cardiac arrest or ICU admission in patients admitted on hospital wards,[32] but are also increasingly used in the ED.[33] In the Netherlands, current national sepsis guidelines advise using the NEWS or MEWS over SIRS and qSOFA.[34] Although the NEWS and MEWS are more complicated to calculate than SIRS and qSOFA, only vital signs are used, and other clinical signs and risk factors are not considered. In the UK, more detailed guidelines are formulated, in which a list of high risk and moderate to high-risk criteria are formulated.[35] These guidelines are tailored to different age groups and settings. Separate guidelines are formulated for in- and outside the hospital setting, and for use during telephonic triage. These guidelines are based on expert opinion and not prospectively validated, and observational data suggest the diagnostic performance of the NICE criteria are inferior to NEWS and SIRS.[36]

Box 3. National Early Warning Score (NEWS) 2.[37]

Physiological parameter	Score						
	3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9-11	12-20		21-24	≥25
SpO_2 Scale 1(%)	≤91	92-93	94-95	≥96			
SpO_2 Scale 2(%)	≤83	84-85	86-87	88-92 ≥93 on air	93-94 on oxygen	95-96 on oxygen	≥97
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91-100	101-110	111-219			≥220
Pulse (per minute)	≤40		41-50	51-90	91-110	111-130	≥131
Consciousness							
Temperature (° C)	≤35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	

Biomarkers in sepsis

Laboratory analyses of blood samples can provide important information in patients with (suspected) sepsis.[38] Blood testing in the ED usually includes markers of inflammation such as the leucocyte count and C-reactive protein (CRP) and markers of organ failure such as creatinine and liver function tests. The hour-1 bundle, as advised by the SSC, included the measurement of lactate as the first step in the protocol.[28] Lactate > 2 mmol/L can be a sign of (occult) shock, and in case of a level >4 mmol/L, fluid resuscitation should be initiated immediately, similar as in patients with hypotension. Numerous other biomarkers have

been proposed as a "sepsis marker", of which the most investigated is procalcitonin. Procalcitonin has shown to be helpful in the ICU setting to guide antibiotic therapy,[39] but the role in the diagnostic workup in the initial phase remains unclear.[40]

Recognition of sepsis in primary care

Before 2017, when the research project presented in this thesis started, no studies had been performed assessing the recognition and treatment of patients with sepsis by GPs. In the Netherlands, several studies in the ambulance setting showed that prehospital sepsis was present in only 10-15% of the patients,[41,42] which was similar in patients that were-, or were not referred by a GP.[41] For GPs, the recognition of sepsis is complex due to a large number of patients with acute infections in general practice compared to the incidence of sepsis.

Patients with acute infections are usually assessed by a GP. Most infections are self-limiting or can be treated at home with oral antibiotics. As only a minority of the patients with acute infections are at risk of sepsis, patients should not be referred to the hospital without a good reason. The early stages of sepsis are hard to distinguish from presentations of less severe illnesses such as influenza. Also, elderly patients who are most at risk of sepsis often present with subtle or atypical symptoms. Therefore, GPs face a dilemma: referring all patients with acute complaints that could indicate sepsis will lead to many unnecessary referrals while waiting how the symptoms progress over time may delay adequate treatment in case of sepsis. Delay of hospital treatment may result in sepsis-related mortality or morbidity. In addition to history taking and physical examination, GPs are increasingly using point-of-care testing (POCT) to support the diagnostic process in patients presenting with acute illness. For example, in patients with acute cough, point-of-care CRP testing can guide antibiotic treatment for pneumonia.[43] However, the diagnostic value of CRP in suspected sepsis in general practice is not known, and CRP may not be as valid to safely rule out sepsis as it is to rule out pneumonia in patients with acute cough who are not severely ill.

Out-of-hours GP cooperatives

As sepsis is an acute illness, a large proportion of the patients with (early stages) of sepsis present during out-of-hours. In the Netherlands, primary care during out-of-hours is organised predominantly by large scale GP cooperatives serving between 100,000 and 500,000 inhabitants.[44] A total of 112 GP cooperatives serve 99% of the population, and more than half of these cooperatives are co-located with an emergency department in the hospital. In 2020, a total of 3.5 million contacts with GP cooperatives were registered.[45] Patients call the GP cooperative to make an appointment, after which telephonic triage is performed by a trained doctors assistant, supervised by a GP. Patients receive a medical urgency category, ranging from U0 to U5. The most appropriate subsequent management is chosen, depending on the urgency and other contextual factors,. About 50% of the patient receive telephonic advice, a GP assesses 40% during a clinic consultation, and

10% receive a home visit. In about 1-2%, an ambulance is directly deployed in case of acute life-threatening conditions.[46] The most common reasons for immediate ambulance deployment are suspicion of myocardial infarction or stroke. An evaluation of reported adverse events at GP cooperatives listed sepsis as the fourth leading missed diagnosis after myocardial infarction, stroke and ruptured abdominal aortic aneurism.[47] A study in Denmark showed that more than two-third of patients with sepsis initially contacted a GP cooperative, about 25% an ambulance service and about 10% both.[48] More than half directly contacted an ambulance service in patients with myocardial infarction or stroke. However, the mortality of patients with sepsis was substantially higher than patients with myocardial infarction or stroke.

Knowledge gaps

The lack of research into the recognition of sepsis in primary care is striking, considering the extent of sepsis-related mortality and morbidity and the importance of immediate hospital referral. First, more insight is needed into the current clinical decision making of GPs in patients with possible sepsis. Also, the delay in treating patients with sepsis after contact with a GP is unknown. To recognise sepsis, SIRS, qSOFA and NEWS scoring systems can potentially all be used in primary care, but none of these scores are validated for use in this setting. Advice to GPs on using these scores - or any other guideline - is not possible without more research. A sensitive approach aimed not to miss any patients with sepsis might cause a significant increase in unnecessary hospital referrals. Conversely, if sepsis is only considered in patients with suspected infection showing signs of organ failure (such as qSOFA), the window of opportunity to prevent a complicated course may already have passed. Therefore, it is crucial to investigate what clinical information that is assessable for GPs at the bedside (including POCT) can be used best to predict sepsis at an early stage.

Aim and outline of the thesis

The general aim of this thesis is to improve the recognition of sepsis in general practice. First, in several preliminary studies, the current management of patients with (suspected) sepsis is explored. This includes the clinical decision–making process of GPs in patients with acute infections, the feasibility and accuracy of the measurement of the respiratory rate by GPs, the prevalence of SIRS criteria in adult patients with suspected infection presenting at OOH GP cooperative, and the diagnosis and management at the out-of-hours GP cooperative of patients who were subsequently admitted to ICU for community-onset sepsis. The primary study presented in this thesis is the TeSD-IT study (**Te**sting for **S**epsis in primary care: **D**iagnostic and prognostic study **I**nvestigating the potential benefits of point-of-care **T**esting). The study's goal is to assess the value of clinical information and additional tests to develop a new diagnostic model to support early diagnosis and management of sepsis by GPs. Additional analyses include external validation, an early economic evaluation, and analyses of additional biomarkers that can potentially be measured by GPs using point-of-care testing.

In **chapter 2**, we explore the current clinical decision-making process of GPs during the assessment of patients with acute infections and establish how GPs use the measurement of vital signs in the decision to refer a patient to the hospital.

Chapter 3 assesses the prevalence of SIRS criteria in adult patients with suspected infections presenting at GP cooperatives and the association with hospital referral.

Chapter 4 describes a retrospective analysis of patients admitted to the ICU due to community-onset sepsis. We obtained records from the GP cooperative from a 72-hour time window prior to hospital admission to assess the presence and type of GP cooperative contact and the delay between GP contact and hospital entrance.

In **chapter 5**, we assess the feasibility and accuracy of the respiratory rate measurement by GPs. Observations during home visits were performed to compare GP measurement with a reference count. Also, semi-structured interviews with GPs were performed.

In **chapter 6**, the study design of the TeSD-IT study is presented.

The main results of the TeSD-IT study are presented in **chapter 7.** We developed a new clinical diagnostic model for GPs, which can be easily scored at the bedside of acutely ill patients. This model was internally and externally validated.

In **chapter 8,** we assess the added value of biomarkers in addition to a model of clinical signs and symptoms for the diagnosis of sepsis. In addition to CRP, PCT, and lactate, which were candidate predictors for the model developed in the TeSD-IT study, we also evaluate other biomarkers that are feasible to measure with POCT.

Chapter 9 describes an early economic evaluation of the model developed in the TeSD-IT study. Costs are estimated for referral scenarios by the GP, based on different cut-off points on the models' scores.

Finally, in **chapter 10,** a general discussion of all results presented in this thesis is presented. This chapter puts the research in a broader context, and implications for further research are formulated.

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CHAPTER 2

2

Recognition of sepsis in primary care: a survey among general practitioners

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BJGP Open 2017

ABSTRACT

Background Early recognition and treatment of sepsis are important to reduce morbidity and mortality. Screening tools using vital signs are effective in emergency departments. It is not known how the decision to refer a patient to the hospital with a possible serious infection is made in primary care.

Aim To gain insight into the clinical decision-making process of GPs in patients with possible sepsis infections.

Design and setting Survey among a random sample of 800 GPs in the Netherlands.

Method Quantitative questionnaire using Likert scales.

Results 160 (20.3%) questionnaires were eligible for analysis. Bases on self-reported cases of possible serious infections, the factors most often indicated as important for the decision to refer patients were: general appearance (94.1%), gut feeling (92.1%), history (92.0%), and physical examination (89.3%). Temperature (88.7%), heart rate (88.7%) and blood pressure (82.1%), were the most frequently measured vital signs. In general, GPs more likely referred patients in case of: altered mental status (98.7%), systolic blood pressure <100 mmHg (93.7%), unable to stand on feet (89.3%), insufficient effect of previous antibiotic treatment (87.4%), and respiratory rate ≥22/min (86.1%).

Conclusions The GPs' assessment of patients with possible serious infection is a complex process, in which besides checking vital signs, many other aspects of the consultation guide the decision to refer a patient to the hospital. To improve care for patients with sepsis, the diagnostic and prognostic value of signs, symptoms, GPs' gut feeling, and additional diagnostic tests, should be prospectively studied in the primary care setting.

INTRODUCTION

Reducing morbidity and mortality from sepsis is a major healthcare challenge.[1] Millions of people are suffering from sepsis each year worldwide,[2] and one in every twenty of all deaths in England is sepsis related.[3] Extensive efforts have been made in hospital settings, most prominently by the launching of the Surviving Sepsis Campaign (SSC) in 2004.[4,5] Early recognition and initiation of adequate treatment are the crucial factors for successful treatment of sepsis[6], and screening all patients with suspected infection for "sepsis-criteria" is important for the success of the SSC.[4,5] In the hospital, vital signs are measured in all patients with suspected infections and these measurements determine whether or not the patient is included in a sepsis protocol.[7] Frequently measured vital signs in the hospital setting are the ones that are included in the systemic inflammatory response syndrome (SIRS): body temperature <36 or >38 °C, heart rate >90/min and respiratory rate >20/min.[7] Recently, new consensus sepsis definitions were published, in which a new clinical decision tool was launched for bedside evaluation of patients with suspected infections: the quick Sequential Organ Failure Assessment (qSOFA).[8] This scoring system indicates increased risk of mortality from sepsis and is positive if two out of the following three items are present: altered mental status, a respiratory rate of ≥22/min and a systolic blood pressure <100 mmHg.

In patients transported to an emergency department by ambulance, sepsis is frequently not detected and this is associated with increased mortality.[9-11]More complete assessment of vital signs can improve the detection of sepsis in this setting.[9] GPs are also encouraged to measure full sets of vital signs, to guide the decision to refer a patient to the hospital with suspected sepsis.[12-14] However, acute infections are very common in primary care, and only a small minority progress to sepsis. Screening all patients with an infection with a full set of vital signs might not be feasible, and the diagnostic and prognostic value of vital signs in this setting is unknown.

The objective of this study is to get more insight into the current clinical decision-making process of GPs in patients with acute infections, and establish how GPs use the measurement of vital signs in the decision to refer a patient to the hospital.

METHOD

Design and population

A cross-sectional questionnaire survey was conducted among GPs in the Netherlands. A random sample of 800 Dutch GPs was provided by the Netherlands Institute for Health Services Research (NIVEL).

Questionnaire

The questionnaire was developed by the research team with the input from semi-structured face-to-face interviews with nine GPs, one infectiologist, one intensivist and three emergency physicians. The preparation of these interviews included a review of literature for clinical signs diagnostic for sepsis and the creation of fictitious patient cases with equivocal signs and symptoms of sepsis. The different factors influencing the clinical decision-making process named by the interviewed professionals were categorised and included in the questionnaire. The interviews also resulted in the decision not to use the term sepsis in the questionnaire. The interpretation of the definition of sepsis was different between GPs and the interviewed specialists. GPs frequently mentioned hypotension as diagnostic for sepsis, in contrast to the other interviewed specialists who all used the SIRS criteria to diagnose sepsis. Therefore, the term "possible serious infection" was used instead of "suspected sepsis" to prevent misinterpretation. The questionnaire was tested in three rounds by three GPs, and feedback was obtained from the nine interviewed GPs.

In the first part of the questionnaire (see appendix 1 for translated version) the GP had to think of two adult patients from their own experience: the last patient with an acute infection that the GP had referred, and the last patient with an acute infection for whom the GP prescribed oral antibiotics. In both cases, the respondents were asked whether they had measured the following vital signs: blood pressure, respiratory rate, heart rate, peripheral oxygen saturation, capillary refill time, and body temperature. Following the first case, GPs had to respond to questions concerning the importance of several aspects of the history, clinical examination and 'gut feeling' in the decision to refer the patient to the hospital. The second part of the questionnaire contained 30 general questions about the importance of history and physical examination for the decision whether or not to refer patients with a possible serious infection to the hospital. All questions were answered on a five-point scale of importance or agreement except the questions asking for objective information (for example whether a certain vital sign was measured). In these cases 'yes' or 'no' options were given. Outcomes in the result section were never based on free text questions.

Procedure

The survey was sent to 800 GPs in March 2016. GPs could return the questionnaire in print, or use a link to an electronic questionnaire in LimeSurvey (an online survey tool). A reminder was sent two weeks later and data collection ended after 10 weeks. Questionnaires were excluded if the background questions were not answered or if the questionnaire was not filled in by the intended GP. Incorrect (two options ticked in the paper version) or unanswered questions were missing data in the analyses. If a case did not meet the inclusion criteria (such as age < 18 years), all questions concerning this

case were missing data. If questionnaires were undeliverable, these questionnaires were considered as not sent instead of non-response.

Data analysis
Data were analysed using descriptive statistics. For the clarity of the tables, the two most positive answering categories (e.g. 'agree' and 'strongly agree') were combined into one category. A non-response analysis was performed based on age, sex, working area and working hours. 95% confidence intervals (CI) and two-sample z-tests were used to study differences between responders and the total sample. The analyses were performed using the Statistical Package for the Social Sciences version 22.0. Results were considered significant at $P<0.05$.

RESULTS

Response
Of the 800 questionnaires sent, 11 were found incorrectly addressed. A total of 163 of the remaining 789 were completed, of which 160 (20.3%) were included and three were excluded due to incompleteness. The average age of the respondents was 46.5 years and 59.4% was female. A non-response analysis showed that respondents did not differ from the total sample in age, gender, and fulltime-equivalent status. Respondents from strongly urban areas were slightly underrepresented (Table 1).

Table 1. Characteristics of the responding GPs and total sample.

Background characteristic	Respondents (n=160) % (95% CI)	Total sample (n=800) % (95% CI)
Age ≥ 50 years	38.1 (31.0 - 45.8)	46.3 (42.8 – 49.7)
Female	59.4 (51.6 - 66.7)	51.8 (48.3 – 55.2)
Working area[a]		
Strongly urban*	41.1 (33.8 – 48.9)	52.3 (48.8 – 55.7)
Moderately urban**	26.6 (20.3 - 34.0)	17.6 (15.1 – 20.4)
Little to non-urban	32.3 (25.5 – 39.9)	30.1 (27.0 – 33.4)
Full time equivalent (FTE)[b]		
≥ 0.8 FTE	53.1 (45.4 – 60.7)	50.0 (46.4 – 53.6)

* p <.05; ** p<.01; [a] n=158 for respondents; [b] n=732 for total sample

Cases
In the self-reported cases of referred patients, the patients had an average age of 64.3 years, and patients were mostly seen during home visits (59.2%). In the cases of patients treated with oral antibiotics, the mean age was 50.4 years and 88.3% concerned regular consultations. The respiratory tract was the most common site of infection in both the referred patients (60.3%) as well as the patients treated with antibiotics (53.9%).

Aspects of the history and physical examination that were considered most important in the cases of patients who were referred were 'general appearance' (94.1%), 'gut feeling' (92.1%), 'history' (92.0%) and 'physical examination' (89.3%) (Table 2).

Table 2. Importance of aspects of the history and physical examination for the clinical decision making in the self-reported cases of referred patients.

Aspect of consultation	Considered (very) important % (n)
General appearance	94.1 (143)
Gut feeling	92.1 (140)
History	92.0 (138)
Physical examination	89.3 (134)
Past illness	67.6 (102)
Age	36.2 (55)
Desire of the patient or relatives	33.8 (51)
Diagnostic tests	19.2 (29)

The vital sign measurements most frequently performed, were body temperature (88.7% in referred patients and 76.6% in patients treated with antibiotics), and heart rate (respectively 88.7% and 53.2%) (Table 3). Capillary refill time was least frequently measured (21.9% and 7.1% respectively). All vital signs were measured more frequently in the referred patients.

Table 3. Frequency of performed vital signs measurements in the self-reported cases of referred patients and patients treated with oral antibiotics.

Vital sign measurement	Referred patients % (n)	Patients treated with antibiotics % (n)
Body temperature	88.7 (134)	76.6 (118)
Heart rate	88.7 (134)	53.2 (82)
Blood pressure	82.1 (124)	31.2 (48)
Peripheral oxygen saturation	76.8 (116)	42.2 (65)
Respiratory rate	66.2 (100)	37.0 (57)
Capillairy refill time	21.9 (33)	7.1 (11)

Approximately one-quarter of the GPs expressed doubt whether or not to refer the patient in the cases where they had referred, and 5.8% were unsure whether to refer patients where they started antibiotic treatment. C-reactive protein (CRP) was available as a point-of-care test in 34.4% of the cases who were referred and in 57.1% of the cases treated with antibiotics. If point-of-care (POC) CRP was available, it was used in 45.5% of the patients who were referred for a suspected respiratory tract infection and in 36.8% of the patients who were referred due to other infections. This corresponds to the higher prevalence of home visits in the referred group; a setting in which CRP tests are not available. In patients treated with antibiotics, the POC CRP was used in 63.3% of respiratory tract infections and 12.8% in other infections when available.

Factors influencing referral in general

Regarding the questions whether specific premorbid conditions influenced the decision to refer a patient with a possible serious infection in general, respondents agreed most on 'chronic use of immunosuppressive medication' (96.8%) and 'multimorbidity' (83.6%) (Table 4). The aspects of the history that were mentioned by > 80% to be important were: 'not able to stand on feet', 'insufficient effect of previous antibiotic treatment', 'rapid progression of illness' and 'decreased urinary output'. The three most mentioned aspects of the physical examination were 'altered mental status'(98.7%), 'systolic blood pressure <100 mmHg' (93.7%) and 'respiratory rate ≥22/min' (86.1%).

Table 4. Importance of premorbid conditions and aspects of the history and physical examination for the decision to refer a patient with a possible serious infection.

Condition	% Important (N)
Premorbid conditions	
Chronic use of immunosuppressive medication	96.8 (154)
Multimorbidity	83.6 (133)
Diabetes	72.1 (114)
Previous hospitalisation due to infection	70.9 (112)
Congestive heart failure	68.5 (109)
Age > 80 years	67.1 (106)
Lack of social support	66.7 (106)
COPD	62.2 (99)
Malignancy	55.1 (86)
Chronic use of antibiotics	52.2 (83)
Renal disease	37.1 (59)
Other heart or vascular disease	24.5 (39)
Alcohol abuse	22.6 (36)
Age > 65 years	21.4 (33)
Psychiatric disorder	11.4 (18)
History	
Not able to stand on feet	89.3 (142)
Insufficient effect of previous antibiotic treatment	87.4 (139)
Rapid progression of illness	83.7 (133)
Decreased urinary output	82.3 (131)
Dyspnoea	79.2 (126)
Rigors	71.1 (113)
Patient feels very ill	45.3 (71)
Decreased oral intake	28.4 (45)
Physical examination	
Altered mental status[a]	98.7 (157)
Systolic blood pressure < 100 mmHg[a]	93.7 (148)
Respiratory rate ≥ 22/min[a,b]	86.1 (136)
Sweating or clammy skin	51.3 (81)
Heart rate > 90/min[b]	47.8 (75)
Body temperature < 36 ˚C[b]	31.0 (49)
Body temperature >38 ˚C[b]	28.3 (45)

[a] qSOFA criterium
[b] SIRS criterium (cut-off point for respiratory rate in SIRS criteria is >20/min)

DISCUSSION

Summary

In self-reported cases of patients referred due to a possible serious infection, body temperature, heart rate, blood pressure and peripheral oxygen saturation were measured in the majority of the patients, but were not perceived as more important for clinical decision making than the history, general appearance and gut feeling. In general, GPs consider the use of immunosuppressive medication, multimorbidity and diabetes as important reasons to refer a patient to hospital with a possible serious infection. 'Unable to stand on feet' and 'insufficient effect of previous antibiotic treatment' were the two most important aspects of the history for the decision to refer a patient. The individual signs of the qSOFA (altered mental status, systolic blood pressure < 100mmHg and respiratory rate ≥ 22/min), were all scored (very) important for referral by the vast majority of the respondents. The other signs from the SIRS criteria (body temperature < 36 ˚C or > 38˚, and heart rate >90/min) were (very) important for less than half of the respondents.

Strengths and limitations

To the authors knowledge, this is the first study into the clinical decision making of GPs in adult patients with possible serious infections, performed in a balanced, random sample of Dutch GPs across the country. The questionnaire was thoroughly designed using information from literature as well as interviews with GPs, and hospital specialists.

A limitation of the study is the rather low response rate, just above 20%. This could be due to the requested time investment of 15 minutes. Another possible explanation is that respondents who started the questionnaire could not (accurately) recall the last patient they referred due to an infection and did not complete the questionnaire. The non-response analysis, however, showed that the background characteristics of the respondents did not differ from the total sample, except for the degree of urbanisation.

The frequency and relative importance of measurements of vital signs were measured, based on the last patient the responding GP had referred due to a suspected serious infection, and the last patient that the respondent had treated with oral antibiotics. Thus, a sample was obtained of the two clinical scenarios and the vital signs that were measured in practice, which provides more representative results than use of written case scenarios. However, several forms of bias could have influenced the results. Firstly, recollection of the assessment and relevance of the vital signs might not be accurate, especially when the case occurred longer than a few days before filling in the questionnaire. Secondly, recall bias of respondents may have caused them not to have picked the very last case. More severely sick patients are remembered better, and more vital signs might have been assessed in these cases. Finally, GPs who perform more measurements of vital signs in general, could be more likely to complete the questionnaire. These possible forms of bias are likely to result in an overestimation of the measured vital signs. However, the relative differences between the measured vital signs will probably not be influenced by this.

Comparison with existing literature

Although no previous research was performed on referrals by GPs of adult patients with serious infections in general, two studies were found on the clinical decision-making process in case of suspected pneumonia. Schaberg and colleagues conducted a survey among GPs, and found that in case of the clinical diagnosis of pneumonia, the presence of dyspnea and hypotension were correlated with referral.[15] In an observational study, Bont and colleagues investigated the prognostic accuracy of the CRB-65 score in the primary care setting.[16] In this scoring tool, points are attributed for confusion (C), respiratory rate ≥30/min (R), systolic blood pressure <90 mmHg or diastolic <60 mmHg (B), and age ≥65 years. In secondary care, this scoring system also includes the serum urea (CURB-65), and is used to guide hospital admission. Bont and colleagues found that the number of points correlated with the severity of the pneumonia, but the decision to refer could not solely be based on these signs. These results are in line with the findings in the present study that hypotension, increased respiratory rate, and altered mental status are not the only important factors in the decision to refer a patient: more factors than vital signs are needed for this decision.

The results from our questionnaire containing the relative importance of comorbidity and age, can be compared to epidemiologic data from patients with sepsis reported by Henriksen and colleagues.[17] This study showed the highest odds ratios for advanced age, immunosuppressive medication, alcohol-related conditions and psychotic disorders. In the present study, GPs mentioned immunosuppressive medication most frequently to be important, but they seem to underestimate advanced age, alcohol-related conditions and psychotic disorders as risk factors for sepsis.

Implications for further research

As timely recognition and referral of patients with sepsis is crucial, and patients are often primarily assessed in primary care, more research into the epidemiology and diagnostic strategies are needed. Identifying high risk populations is important for targeted assessment for possible sepsis. The results of this study indicate the qSOFA score is more in line with the clinical reasoning of GPs than the SIRS criteria. However, these findings cannot be used as evidence for the validity of the qSOFA for the guidance of referral. Patients who meet these criteria might not always need hospital treatment, as well as the possibility that patients with early stages of sepsis assessed by GPs might not (yet) score positive on the qSOFA.

POC testing may also provide an opportunity for improvement of the (early) detection of sepsis. CRP is a marker of infection, and is widely used as POC test by GPs to guide antibiotic prescription in patients with symptoms of respiratory tract infections.[18] However, there is no research to support the ruling out or ruling in of sepsis with CRP, or any other biomarker in the primary care setting.

Prospective research investigating the diagnostic and prognostic value of vital signs and biomarkers should be studied in the primary care setting to guide the development of improved diagnostic algorithms. Adopting diagnostic algorithms from secondary care populations in primary care adheres the risk of overdiagnosis and unnecessary referrals,

with potential adverse effects. Algorithms may focus on patients with suspected infections or on signs of acute illness in a broader sense, and the need for hospital treatment might be more relevant than the presence of sepsis.

The GPs' assessment of patients with possible serious infection is a complex process, in which in addition to the measurement of vital signs, many other aspects of the consultation guide the decision to refer a patient or not to hospital. Although better use of the assessment of vital signs might improve the detection of sepsis, adoption of a clinical decision rule in the primary care setting only based on vital signs will disregard other valuable clinical information. To improve care for patients with sepsis, the diagnostic and prognostic value of signs, symptoms, GPs' gut feeling, and additional diagnostic tests should be prospectively studied in the primary care setting.

Funding
The study was funded in part by an unrestricted research grant by Philips Handheld Diagnostics (reference number 715657932). Philips Handheld Diagnostics had no role in the study design, data collection, analysis, interpretation, or writing of the manuscript.

Ethical approval
The Ethical Research Committee of the Radboud university medical center Nijmegen was consulted and concluded that this study did not require ethical approval (file number 2016-2523).

Acknowledgements
The authors thank all GPs and hospital specialists who participated in this study.

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CHAPTER 3

3

Vital signs of the systemic inflammatory response syndrome in adult patients with acute infections presenting in out-of-hours primary care: a cross-sectional study

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Eur J Gen Pract 2021

Abstract

Background Signs of the systemic inflammatory response syndrome (SIRS) –fever (or hypothermia), tachycardia and tachypnoea- are used in the hospital setting to identify patients with possible sepsis.

Objectives To determine how frequently abnormalities in the vital signs of SIRS are present in adult out-of-hours (OOH) primary care patients with suspected infections and assess the association with acute hospital referral.

Methods We conducted a cross-sectional study at the OOH GP cooperative in Nijmegen, the Netherlands between August and October 2015. GPs were instructed to record the body temperature, heart rate and respiratory rate of all patients with suspected acute infections. Vital signs of SIRS, other relevant signs and symptoms, and referral state were extracted from the electronic registration system of the OOH GP cooperative retrospectively. Logistic regression analysis was used to evaluate the association between clinical signs and hospital referral.

Results A total of 558 patients with suspected infections were included. At least two SIRS vital signs were abnormal in 35/409 (8.6%) of the clinic consultations and 60/149 (40.3%) of the home visits. Referral rate increased from 13% when no SIRS vital sign was abnormal to 68% when all three SIRS vital signs were abnormal. Independent associations for referral were found for decreased oxygen saturation, hypotension and rapid illness progression, but not for individual SIRS vital signs.

Conclusion Although patients with abnormal vital signs of SIRS were referred more often, decreased oxygen saturation, hypotension and rapid illness progression seem to be most important for GPs to guide further management.

Introduction

Sepsis is a major cause for critical illness, with a global incidence of almost 50 million patients, resulting in 11 million deaths per year.[1] Early administration of intravenous antibiotics is a central element, as mortality and morbidity resulting from sepsis increase after delayed treatment.[2-4]

Most patients with acute infections are assessed in primary care initially, and timely referral of patients with sepsis to the emergency department (ED) by the general practitioner (GP) is essential to prevent unnecessary delay in treatment. A previous study by the authors' research group has shown that one in three patients admitted to the intensive care unit due to community acquired sepsis were not referred to a hospital by the GP after the first contact.[5] Furthermore, it has been found that sepsis was suspected in only a minority of patients who are referred, leading to non-urgent ambulance transports even in patients with septic shock.[6,7]

In the past decades, systemic inflammatory response syndrome (SIRS) has been widely used to identify patients with sepsis.[8] SIRS is a syndrome characterised by two or more of the following symptoms: fever or hypothermia, tachycardia, tachypnoea and abnormal leucocyte count. Although in a new international consensus definition of sepsis (Sepsis-3) was published in 2016[9] in which SIRS is no longer conditional for sepsis, screening for SIRS is still considered useful to identify patients at risk for sepsis.[10,11] Screening for symptoms of SIRS might also improve the recognition of sepsis in primary care. Although the leucocyte count is not readily available in primary care, the three vital signs of SIRS can be assessed during ambulance transport or triage in the ED.

As sepsis is an acute illness, patients often present during out-of-hours (OOH). In the Netherlands, GPs are organised in GP cooperatives during OOH. These are often co-located with hospitals and usually serve catchment areas between 100,000 and 400,000 inhabitants. In total, 119 GP cooperatives provide care almost the entire Dutch population. Yearly about 250 contacts per 1000 inhabitants are performed, consisting of approximately 50% clinic consultations, 10% home visits and 40% telephone consultations.[12]

The objectives of this study were to measure the presence of abnormalities in the vital signs of SIRS in adult patients with suspected infectious conditions who are assessed by GPs at OOH GP cooperatives, and assess the association with hospital referral.

Methods

Study design and setting

We conducted a cross-sectional study at one large GP cooperative, located in Nijmegen, the Netherlands. This GP cooperative delivers out-of-hours primary care to approximately 327,000 inhabitants of whom about half live in the city of Nijmegen and half in the surrounding suburban to rural area. In 2015, 133,844 contacts were registered, consisting of 41% telephone consultations, 49% clinic consultations and 10% home visits.[13]

Procedure

During an eight-week period between 30 August and 24 October 2015, a medical intern (DS) instructed attending GPs to measure the tympanic temperature, heart rate and respiratory rate in all patients in whom they had any suspicion of infection as cause of the acute complaints and register the findings in the medical record. Although these measurements are standard care for patients with infections, not all GPs perform and record these in the patient file. Our efforts were therefore focused on motivating the GPs to minimize missing data on the SIRS parameters. The member of the research team personally explained the study to the attending GPs, but did not assist the GPs during patient contacts. Small reminder cards and desktop clocks were also provided in all consultation rooms. In addition, chauffeurs assisting the GPs during the home visits were instructed to remind the GP and help with the measurement of the vital signs. All patients received care as usual. The researcher was present to instruct the GPs in 28/40 weekday evenings and nights and 5/16 weekend days, accounting for 45.7% of the clinic consultations and home visits during the study period.

Data collection

Anonymised patient files of all clinic consultations and home visits in the study period were extracted from the GP cooperative registration system. Adult patients with a suspected infection were eligible for inclusion. This concerned all acute infections, such as respiratory tract infections, abdominal infections, fever of unknown origin, and localized infections (e.g. otitis or local abscess). Only contacts of GPs who received instruction (corresponding to the 45.7% of the clinic consultations and home visits as mentioned above), were included. Patients with more than one contact during the study period were analysed as separate index cases. ICPC (International Classification of Primary Care) codes that did not match (possible) infections were excluded during the extraction based on the codes listed in Supplemental Appendix 1. Next, all anonymised medical records were screened manually. Patients in whom the GP did not suspect an infection according to the differential diagnosis in the free text were excluded (e.g. trauma or renal colic). Other exclusion criteria were pregnant or terminally ill patients and records that were insufficiently documented to assess. Figure 1 shows a flowchart of included patients.

Variables

The following variables were digitally extracted from the medical records: age and sex as background characteristics and (probable) diagnosis based on the ICPC code. We divided the included patients in the following groups, based on the ICPC codes (Supplemental Appendix 1): upper respiratory tract infections, lower respiratory tract infections, urogenital infections, abdominal infections, skin and soft tissue infections, fever of unknown origin and other infections. Other variables were manually retrieved from the free text of the medical records by a medical intern (DS). Firstly, the vital signs of SIRS: temperature, heart rate and respiratory rate. SIRS criteria were defined as a temperature <36 or >38°C, heartrate >90 beats/minute and respiratory rate >20 breaths/minute. Second, we also retrieved recording of the other relevant clinical signs and symptoms: systolic blood pressure, peripheral oxygen saturation (SpO_2), shivering (yes/no), rapid illness progression (yes/no), unable to walk normally (yes/no), altered mental status (yes/no). If a clinical symptom was not mentioned in the medical records, we considered it

absent. In case the free text in the medical record was equivocal, the final decision on the presence or absence of a symptom was discussed with a general practitioner (PG) and an emergency physician (FL). Furthermore, antibiotic prescription (yes/no), hospital referral (yes/no) and 30-day mortality were retrieved from the GP cooperative registration system. We did not have access to data from patients' own GP or hospital data, as informed consent would be required.

Data analyses

We used descriptive statistics for the background characteristics and clinical parameters of the study population. Mean and standard deviation (SD) were used for the description of normally distributed variables; median and interquartile range (IQR) for non-normal distributions. We performed univariable and multivariable logistic regression analysis to examine the association of clinical signs and symptoms with hospital referral. Missing data of vital signs were assumed to be normal values. Still, for the analysis of the association between clinical signs and symptoms and hospital referral rate, we also performed a sensitivity analysis after imputing missing data using multiple imputation by chained equations (MICE).[14] Rubin's rules were used to pool the results of 30 imputed datasets.[15] We used SPSS (IBM SPSS, version 25) for all data analyses.

Ethical considerations

We conducted the study in compliance with the declaration of Helsinki. The Ethical Research Committee of the Radboud university medical center Nijmegen concluded that this study does not fall within the remit of the Dutch Medical Research Involving Human Subjects Act [Wet Mensgebonden Onderzoek) (file number 2016-2697).

Results

A total of 2838 electronic medical records of clinic consultations and home visits in adult patients were retrieved. We selected 1056 patient records on relevant ICPC codes, which we screened manually for eligibility (Figure 1). In total 558 patient records were included for analyses: 409 clinic consultations and 149 home visits.

Of the clinic consultations, 75/409 patients (18.3%) were referred to the hospital, and 45/149 (30.2%) of the patients receiving home visits were referred. Patients who received a home visit were older and more often presented themselves with lower respiratory tract infections than patients who received a clinic consultation. Temperature was the SIRS vital sign measured most often (84%). Heart rate and respiratory rate were measured, respectively, in 66% and 50% of the 558 included patients. In 95/558 (17%) of all patients at least two SIRS vital signs were abnormal: 35/409 (8.6%) of the clinic consultations and 60/149 (40.3%) of the home visits. In total, five patients were recorded as deceased within 30 days after the initial contact with the GP cooperative. All five patients were visited at home, of whom three patients were not referred to the hospital (Table 1).

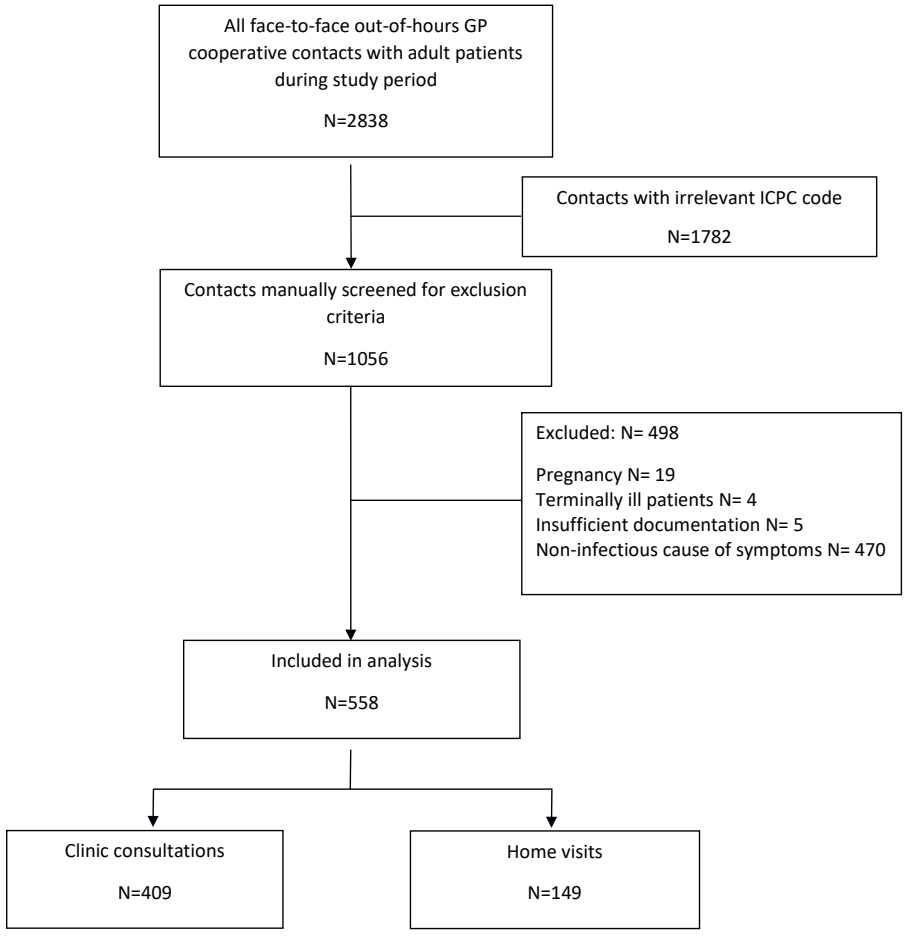

Figure 1. Flowchart of included patients

Table 1. Patient characteristics of the total study population, and divided by contact type and by hospital referral.

Patient characteristic	All patients (n=558)	Clinic consultations			Home visits		
		Not referred to hospital (n=334)	Referred to hospital (n=75)	Total (n=409)	Not referred to hospital (n=104)	Referred to hospital (n=45)	Total (n=149)
Background characteristics							
Age, median (IQR[a]),y	50 (31-71)	41 (27-55)	44 (27-61)	41 (27-56)	79 (68-84)	75(59-84)	78 (67-84)
Female, N (%)	315 (56.5)	196 (58.7)	40 (53.3)	236 (57.7)	57 (52.8)	22 (48.9)	79 (53.0)
Source of infection, N (%)							
Lower respiratory tract infection	102 (18.3)	47 (14.1)	3 (4.0)	50 (12.2)	36 (34.6)	16 (35.6)	52 (34.9)
Upper respiratory tract infection	78 (14.0)	65 (19.5)	7 (9.3)	72 (17.6)	6 (5.8)	0 (0.0)	6 (4.0)
Urogenital infection	107 (19.2)	73 (21.9)	3 (4.0)	76 (18.6)	26 (25.0)	5 (11.1)	31 (20.8)
Abdominal infection	95 (17.0)	38 (11.4)	39 (52.2)	77 (18.8)	8 (7.7)	9 (20.0)	18 (12.1)
Skin or soft tissue infection	103 (6.9)	89 (26.6)	5 (6.7)	94 (23.0)	8 (7.7)	1 (2.2)	9 (6.0)
Fever of unknown origin	48 (8.6)	8 (2.4)	14 (18.7)	22 (5.4)	16 (15.4)	10 (22.2)	26 (17.4)
Other	25 (4.5)	14 (4.2)	4 (5.3)	18 (4.4)	3 (2.9)	4 (8.9)	7 (4.7)
Vital signs of SIRS							
Body temperature measurement, N (%)	471 (84.4)	275 (82.3)	61 (81.3)	336 (82.2)	92 (88.5)	43 (95.6)	135 (90.7)
Body temperature, mean(SD[b]), ℃	37.5 (0.9)	37.2 (0.7)	37.8 (1.0)	37.3 (0.8)	37.7 (1.0)	38.3 (1.1)	37.9 (1.1)
Respiratory rate measurement, N (%)	279 (50.0)	142 (42.5)	35 (46.7)	177 (43.3)	63 (60.6)	39 (88.7)	102 (68.5)
Respiratory rate, mean(SD), breaths/min	20 (6.9)	17 (4.7)	19 (6.0)	17 (5.1)	22 (6.5)	27 (7.5)	24 (7.3)
Heart rate measurement, N (%)	368 (65.9)	186 (55.7)	45 (60.0)	231 (56.5)	92 (88.5)	45 (100)	137 (91.9)
Heart rate, mean(SD), beats/min	87 (18.3)	83 (16.6)	91 (19.1)	85 (17.4)	87 (16.7)	100 (20.9)	92 (19.1)
≥ 2 SIRS vital sign abnormalities[c], N (%)	95 (17.0)	22 (6.6)	13 (17.3)	35 (8.6)	28 (26.9)	32 (71.1)	60 (40.3)
Antibiotics, N (%)	244 (43.7)	177 (53.0)	0 (0.0)	177 (43.3)	67 (64.4)	0 (0.0)	67 (45.0)
30-day mortality, N (%)	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.9)	2 (4.4)	5 (3.4)

[a] Interquartile range
[b] Standard deviation
[c] Defined as body temperature <36 or >38°C; tachycardia >90/min; tachypnoea >20/min.

In table 2, the differences in SIRS vital signs and other clinical signs and symptoms between patients who were and were not referred to the hospital are shown. With an increasing number of abnormalities of SIRS vital signs, the referral rate increased from 46/343 (13%) if none of the SIRS vital signs were abnormal, to 29/120 (24%) in cases with one, 22/61 (36%) with two, and 23/34 (68%) if all three SIRS vital signs were abnormal. However, none of the individual three SIRS vital signs showed a statistically significant independent association with hospital referral (Table 3). Age, shivering, altered mental status, and inability to walk normally did not show an independent association with referral. For a rapid illness progression and SpO_2 <94% the association was highly significant (p<0.001) with adjusted odds ratio (OR) of 3.75 (95% CI 2.26-6.20) for rapid illness progression and 5.23 (95% CI 2.40-11.4) for peripheral oxygen saturation. For hypotension (systolic blood pressure ≤100 mmHg), the adjusted OR was 4.07 (95% CI 1.16-14.3). A sensitivity analysis using multiple imputed data in which all vital signs were entered as continuous variables showed almost similar results. The only differences were for temperature (now independently associated with referral) and blood pressure (no independent association) (see Supplemental Table 2).

Table 2. Differences in patient characteristics between referred patients and patients not referred to the hospital.

Patient characteristic	Referred (n=120)	Not referred (n=438)
Age, median (IQR[a]), y	55 (35-75)	48 (31-69)
Vital signs of SIRS, n (%)		
Temperature <36 or >38°C	48 (40)	66 (15)
Respiratory rate >20/min	44 (37)	55 (13)
Heart rate >90/min	50 (42)	81 (18)
Number of SIRS vital sign abnormalities ,n (%)		
0 (n=343)	46 (38)	297 (68)
1 (n=120)	29 (24)	91 (21)
2 (n=61)	22 (18)	39 (9)
3 (n=34)	23 (19)	11 (3)
Other clinical signs and symptoms, n (%)		
Hypotension[b]	10 (8)	6 (1)
Peripheral oxygen saturation <94%	27 (23)	18 (4)
Shivering	37 (31)	68 (16)
Unable to walk normally	18 (15)	28 (6)
Rapid illness progression	62 (52)	77 (18)
Altered mental status	9 (8)	12 (3)

[a] Interquartile range.
[b] Defined as systolic blood pressure ≤100mmHg.

Table 3. Logistic regression analyses for association of patient characteristics with hospital referral: univariable and multivariable analyses.

	Univariable analyses		Multivariable analyses	
Patient characteristic	**Odds ratio (95% CI[a])**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age (per year)	1.01 (1.00-1.02)	0.04	0.99 (0.98-1.00)	0.09
Vital signs of SIRS				
Temperature <36 or >38°C	3.76 (2.40-5.89)	<0.001	1.68 (0.94-2.99)	0.08
Respiratory rate >20/min	4.03 (2.53-6.43)	<0.001	1.76 (0.94-3.30)	0.08
Heart rate >90/min	3.15 (2.04-4.87)	<0.001	1.36 (0.78-2.37)	0.3
Other clinical signs and symptoms (yes/no)				
Hypotension[b]	6.54 (2.33-18.4)	<0.001	4.07 (1.16-14.3)	0.03
Peripheral oxygen saturation <94%	6.77 (3.58-12.8)	<0.001	5.23 (2.40-11.4)	<0.001
Shivering	2.43 (1.52-3.87)	<0.001	1.12 (0.62-2.06)	0.7
Unable to walk normally	2.58 (1.38-4.96)	0.003	1.03 (0.46-2.28)	0.9
Rapid illness progression	5.0 (3.25-7.74)	<0.001	3.75 (2.26-6.20)	<0.001
Altered mental status	2.88 (1.18-7.00)	0.02	1.50 (0.48-4.70)	0.5

[a] Confidence Interval.
[b] Defined as systolic blood pressure ≤100mmHg.

Discussion

Main findings

In adult patients with suspected infection assessed In OOH primary care, we observed the vital signs of SIRS after instructing GPs to record the temperature, heart rate and respiratory rate systematically in these patients. In 40% of patients assessed during a home visit at least two SIRS vital signs were abnormal compared to 9% of clinic consultations. With an increasing number of abnormal SIRS vital signs, the referral rate increased from 13% if none were abnormal, up to 68% if all three SIRS vital signs were abnormal. However, in this population, associations of the three individual SIRS criteria and hospital referral were not statistically significant. Of the other clinical signs and symptoms, only peripheral oxygen saturation was unequivocally associated with hospital referral. Furthermore, rapid illness progression was associated independently with hospital referral, but not age, shivering, inability to walk normally or altered mental status.

Strengths and limitations

A strength of the study is that all contacts were analysed during a study period, in which GPs were instructed to measure the body temperature, respiratory rate and heart rate in all patients with suspected infection. Using this method, we obtained a complete count of all patients with suspected infections presenting in OOH primary care, and the abnormal SIRS vital signs in these patients. However, still, in more than half of the patients at least one of these measurements was missing. This implies that the true presence of abnormalities in the SIRS vital signs could be more frequent than shown in the data. We did not impute missing data for the primary analysis as missing data are more likely to be normal values (for example, in cases temperature was not recorded by the GP, patients were unlikely to be febrile). Furthermore, GPs do not make their decision to refer patients based on

unmeasured vital signs. However, the sensitivity analyses using multiple imputed data showed similar results, concluding that a significant bias has occurred due to missing data less likely.

Other limitations of the study are the data collection at a single GP cooperative in The Netherlands, and the relatively short study period in the months September-October. Results may differ in other locations or seasons. The findings of this study are not representative for the setting of primary care during office hours, as contacts are usually less urgent than in OOH.

Comparison with existing literature

To the best of our knowledge, no previous research has been published assessing the presence of abnormalities in the SIRS vital signs in the primary care setting or relation with the referral rate. Tusgul *et al* investigated the sensitivity of SIRS for adverse outcomes in patients with infections during ambulance transportation and at triage in the ED.[16] SIRS status was based on vital signs only and not on the leucocyte count. The reported rate of SIRS in the ambulance was 49% compared to 42% during triage in the ED in the same population. As the mortality rate was relatively low in patients with SIRS abnormalities who were referred after a home visit (30-day mortality of 4.4%), we do not suspect the patients in the current study to be more severely ill than the patients included in that paper (mortality of 3.7% at 48 h). In this study, SIRS was compared to the quick Sequential Organ Failure Assessment (qSOFA) score.[17] A qSOFA score ≥2 (of the items respiratory rate ≥22, systolic blood pressure <100 mmHg and altered mental status), showed a poor sensitivity for adverse outcome and was present in only 19% of the study population during ambulance transport. We did not instruct GPs to record blood pressure and mental status in all patients, but retrieved this information if mentioned in the medical records. Both hypotension and altered mental status were present in only 8% of the referred patients.

Implications for research and practice

In the Netherlands, guidelines for the management of sepsis by GPs are currently lacking. We do not advise implementing the SIRS screening tool to diagnose sepsis in primary care based of the current findings. Rather, the results should be interpreted as an indication how often GPs are confronted with possible sepsis. This study shows this is relatively common, especially during OOH home visits to patients with suspected infections. Complete measurement of all vital signs during home visits of elderly patients with suspected infection can help GPs to identify patients in early stages of sepsis who do not appear critically ill otherwise. Not every patient who has abnormal SIRS vital signs needs hospital treatment. On the other hand, other clinical signs and symptoms - especially peripheral oxygen saturation and rapid illness progression - appear to be more important for GPs than SIRS vital signs in subsequent referral. More research is needed to determine which vital signs are the most predictive of progression to sepsis and what clinically relevant cut-off values of vital signs are in the primary care setting to design a simple and effective screening tool. Rapid diagnostic tests such as CRP testing might add to the clinical decision-making process. Currently, our study group is performing a full,

diagnostic study to develop a clinical decision rule with clinical signs and symptoms and including additional blood tests available at the point of care.[18]

Conclusion
Abnormalities in the SIRS vital signs in patients with suspected infections are relatively common in OOH primary care, especially in patients assessed during home visits. Although patients with abnormal vital signs of SIRS were more frequently referred to the hospital, decreased peripheral oxygen saturation, hypotension, and rapid illness progression seem to be the most important clinical signs for GPs to guide further management.

Funding
None.

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Supplemental Appendix 1.

Codes of the International Classification of Primary Care (2nd Edition) extracted for further manual review.

A01 Pain general/multiple sites
A02 Chills
A03 Fever
A04 Weakness/tiredness general
A05 Feeling ill
A06 Fainting/syncope
A29 General symptom/complaint other
A75 Infectious mononucleosis
A76 Viral exanthem other
A77 Viral disease other/NOS
A78 Infectious disease other/NOS
A99 General disease NOS
B02 Lymph gland(s) enlarged/painful
B70 Lymphadenitis acute
B99 Blood/lymph/spleen disease other
D01 Abdominal pain/cramps general
D02 Abdominal pain epigastric
D06 Abdominal pain localized other
D09 Nausea
D10 Vomiting
D11 Diarrhoea
D18 Change faeces/bowel movements
D25 Abdominal distension
D29 Digestive symptom/complaint other
D70 Gastrointestinal infection
D73 Gastroenteritis presumed infection
D83 Mouth/tongue/lip disease
D88 Appendicitis
D92 Diverticular disease
D95 Anal fissure/perianal abscess
D98 Cholecystitis/cholelithiasis
D99 Disease digestive system, other
H70 Otitis externa
H71 Acute otitis media/myringitis
H72 Serous otitis media
K70 Infection of circulatory system
K94 Phlebitis/thrombophlebitis
L04 Chest symptom/complaint
L05 Flank/axilla symptom/complaint
L12 Hand/finger symptom/complaint
L14 Leg/thigh symptom/complaint
L20 Joint symptom/complaint NOS
L29 Sympt/complt. Musculoskeletal other
L70 Infections musculoskeletal system
L99 Musculoskeletal disease, other
N01 Headache
N18 Paralysis/weakness
N71 Meningitis/encephalitis
N73 Neurological infection other
R01 Pain respiratory system
R02 Shortness of breath/dyspnoea
R04 Breathing problem, other
R05 Cough
R09 Sinus symptom/complaint
R21 Throat symptom/complaint
R24 Haemoptysis
R25 Sputum/phlegm abnormal
R29 Respiratory symptom/complaint oth.
R71 Whooping cough
R72 Strep throat
R74 Upper respiratory infection acute
R75 Sinusitis acute/chronic
R76 Tonsillitis acute
R77 Laryngitis/tracheitis acute
R78 Acute bronchitis/bronchiolitis
R80 Influenza
R81 Pneumonia
R82 Pleurisy/pleural effusion
R83 Respiratory infection other
R95 Chronic obstructive pulmonary dis
R99 Respiratory disease other
S01 Pain/tenderness of skin
S06 Rash localized
S07 Rash generalized
S08 Skin colour change
S09 Infected finger/toe
S10 Boil/carbuncle
S11 Skin infection post-traumatic
S76 Skin infection other
T11 Dehydration
T70 Endocrine infection
U01 Dysuria/painful urination
U02 Urinary frequency/urgency
U14 Kidney symptom/complaint
U70 Pyelonephritis/pyelitis
U71 Cystitis/urinary infection other
U72 Urethritis
U98 Abnormal urine test NOS
U99 Urinary disease, other
W70 Puerperal infection/sepsis
W94 Puerperal mastitis
X01 Genital pain female
X04 Painful intercourse female
X14 Vaginal discharge
X17 Pelvis symptom/complaint female
X71 Gonorrhoea female
X74 Pelvic inflammatory disease
X84 Vaginitis/vulvitis NOS
X85 Cervical disease NOS
Y06 Prostate symptom/complaint
Y71 Gonorrhoea male
Y73 Prostatitis/seminal vesiculitis
Y74 Orchitis/epididymitis
Y75 Balanitis

Supplemental Table 2.

Logistic regression analysis based on multiple imputed data with vital signs as continuous variables. Univariable and multivariable association with hospital referral.

	Univariable analyses		Multivariable analyses	
Patient characteristic	**Odds ratio (95% CI[a])**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age (per year)	1.01 (1.00-1.02)	0.043	0.99 (0.97-1.00)	0.04
Vital signs of SIRS				
Temperature (per °C)	2.12 (1.68-2.69)	<0.001	1.53 (1.11-2.11)	0.01
Respiratory rate(per breath/min)	1.09 (1.05-1.13)	<0.001	1.04 (0.98-1.09)	0.2
Heart rate (per beat/min)	1.03 (1.02-1.04)	<0.001	1.01 (0.99-1.03)	0.4
Other clinical signs and symptoms				
Systolic blood pressure (per mmHg)	0.99 (0.98-1.00)	0.08	0.99 (0.98-1.01)	0.3
SpO_2[b] (per %)	0.81 (0.74-0.88)	<0.001	0.82 (0.72-0.92)	0.001
Shivering	2.42 (1.52-3.87)	<0.001	1.20 (0.65-2.22)	0.6
Unable to walk normally	2.58 (1.38-4.86)	0.003	1.24 (0.56-2.73)	0.6
Rapid illness progression	5.01 (3.27-7.74)	<0.001	3.57 (2.10-6.06)	<0.001
Altered mental status	2.88 (1.19-7.00)	0.02	1.57 (0.50-4.91)	0.4

[a] Confidence Interval. [b] Peripheral oxygen saturation.

CHAPTER 4

Management of sepsis in out-of-hours primary care: a retrospective study of patients admitted to the intensive care unit

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BMJ Open 2018

ABSTRACT

Objectives Timely recognition and treatment of sepsis is essential to reduce mortality and morbidity. Acutely ill patients often consult a general practitioner (GP) as the first healthcare provider. During out-of-hours, GP cooperatives deliver this care in the Netherlands. The aim of this study is to explore the role of these GP cooperatives in the care for patients with sepsis.

Design Retrospective study of patient records from both the hospital and the GP cooperative.

Setting An intensive care unit (ICU) of a general hospital in the Netherlands, and the co-located GP cooperative serving 260,000 inhabitants.

Participants We used data from 263 patients who were admitted to the ICU due to community-acquired sepsis between January 2011 and December 2015.

Main outcome measures Contact with the GP cooperative within 72 hours prior to hospital admission, type of contact, delay from the contact until hospital arrival, GP diagnosis, initial vital signs and laboratory values, and hospital mortality.

Results Of 263 patients admitted to the ICU, 127 (48.3%) had prior GP cooperative contacts. These contacts concerned home visits (59.1%), clinic consultations (18.1%), direct ambulance deployment (12.6%) or telephone advice (10.2%). Patients assessed by a GP were referred in 64% after the first contact. The median delay to hospital arrival was 1.7 hours. The GP had not suspected an infection in 43% of the patients. In this group the in-hospital mortality rate was significantly higher compared with patients with suspected infections (41.9% versus 15.8%). Mortality difference remained significant after correction for confounders.

Conclusion GP cooperatives play an important role in prehospital management of sepsis and recognition of sepsis in this setting proved difficult. Efforts to improve management of sepsis in out-of-hours primary care should not be limited to patients with a suspected infection, but also include severely ill patients without clear signs of infection.

Introduction

Sepsis is a life-threatening complication from infection requiring urgent hospital treatment.[1,2] One in four patients with sepsis die during hospitalisation, and sepsis survivors often suffer from long-term functional and cognitive impairment.[2,3] Sepsis is one of the most common reasons for ICU admission, and is associated with high healthcare costs.[4] Estimations of the incidence of community-acquired sepsis range between 40-455 per 100,000.[5] Over the last decades epidemiological data show a rising incidence of sepsis.[6,7] Due to the ageing population, a further increase of the sepsis incidence is expected.[8]

In 2004 the Surviving Sepsis Campaign (SSC) was launched internationally.[9] Mainly owing to the implementation of screening tools for early recognition of sepsis in the emergency department (ED), the SSC succeeded to reduce in-hospital mortality by 17% in the Netherlands.[10] Research in patients transported by ambulance shows that recognition of sepsis in the prehospital setting is low.[11,12] Most patients with sepsis initially contact a general practitioner (GP), and the assessment by the GP, including the decision whether or not to refer a patient to secondary care, is crucial for timely initiation of hospital treatment. Recording of vital signs is essential, but, compared to secondary care doctors, GPs generally use more factors such as clinical impression and gut feeling in their diagnostic work-up.[13] However, rigorous data on diagnostic accuracy and appropriateness of sepsis management in primary care is not available.

In the Netherlands, out-of-hours primary care is delivered by large scale GP cooperatives that are in about 65% colocated with hospital ED.[14] A total of 120 GP cooperatives provide out-of-hours primary care for all inhabitants of the Netherlands.[15] As sepsis typically presents as an acute illness in which assessment cannot wait until the next day, we expect a large proportion of all patients with sepsis contacting a GP cooperative prior to hospital admission.The aim of this study is to investigate the diagnosis and management at the out-of-hours GP cooperative of patients who were subsequently admitted to ICU for community-acquired sepsis. This information is needed to better target interventions and further research to improve the management of sepsis in primary care.

Methods

Design and setting

A retrospective study of medical records of patients admitted to the ICU of Gelderse Vallei Hospital, Ede, The Netherlands, for community-onset sepsis was conducted. Data were retrieved from patients admitted between 1 January 2011 and 31 December 2015. Gelderse Vallei Hospital is a general hospital with 605 hospital beds and a 17 beds level 3 ICU, to serve a mainly suburban population of 260,000 inhabitants. Over 22,000 patients visit the ED annually. A large GP cooperative for out-of-hours primary care is colocated adjacent to the hospitals' ED and serves a similar catchment area as the hospital. Patients contact the GP cooperative by telephone. Subsequently, a triage nurse supervised by a GP decides whether a telephone advice, clinic consultation, home visit or immediate ambulance deployment is needed, and with which urgency.

Patients

Patients were selected using the following inclusion criteria: age ≥18 years; admitted to the ICU within 24 hours from hospital arrival; sepsis diagnosis during ICU stay. In the hospital, all patients admitted to the ICU are screened with an electronic tool to assess the presence of sepsis. These data are recorded in the patient data management system (PDMS). The presence of sepsis in this registration system is based on the ACCP/SCCM sepsis consensus definitions.[16]

The medical records of the included patients were subsequently screened (by FJL and ARHZ) for the following exclusion criteria: sepsis not the primary reason for ICU admission; readmissions after hospitalisation < 7 days earlier; patients referred to the ED by the GP cooperative, but not admitted after initial ED assessment (as delay to hospital treatment is not caused by the GP in these patients); medical treatment with close secondary care follow-up (for example chemotherapy with possible neutropenia, as typically these patients bypass the GP by consulting secondary care directly); transfer from or to another hospital; home address outside the catchment area of the GP cooperative at the time of admission.

Data collection

We digitally collected the following routine registration data from the electronic medical records of the ICU: age, sex, Sepsis-related Organ Failure Assessment (SOFA) score, Acute Physiology And Chronic Health Evaluation (APACHE) II score, immunosuppressive status, length of ICU stay, length of hospital stay, and in-hospital mortality. Additional data from the electronic hospital records were retrieved by manual search (by FJL): comorbidities, vital signs (tympanic temperature, systolic blood pressure, heart rate, respiratory rate and mental status), laboratory values (C-reactive protein (CRP), lactate and creatinine), presence of septic shock, and final diagnosis. For both vital signs and laboratory values the first recorded values in the first 24 hours after ED arrival were used. If a parameter was not recorded in the first 24 hours after ED arrival, this was entered as missing data. Mental status was considered as altered in case of a Glasgow Coma Scale <15 or an otherwise recorded altered mental status in the medical records. The final diagnosis regarding the presence of sepsis and site of infection were based on review of all available medical records. In case of equivocal diagnosis in the medical records, a consulted intensivist made the final decision.

Septic shock was defined as the prolonged use of vasopressors to maintain a mean arterial pressure of ≥65 mmHg after fluid resuscitation. The comorbidities were recorded as documented in the discharge letter of the ED. Cardiovascular disease was present in case coronary artery disease, heart failure or stroke was noted. Malignancy was reported in case any malignancy was noted, except for basalioma or if curative treatment had taken place > 5 years ago. Multimorbidity was defined as the presence of two or more recorded comorbidities.

Subsequently, we retrieved data from the included patients from the electronic medical records of the GP cooperative. All contacts from the last 72 hours before hospital admission were analysed. The time of the first telephone contact was recorded, as well as the urgency

category after telephone triage, type of consultation, clinical signs, diagnosis and referral. Suspected infection was defined as the diagnosis of an infectious disease or mentioning of an infectious cause in one of the first three differential diagnoses in the free text.

Statistical analysis

Analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) version 22. Descriptive analyses were used for frequencies, time intervals and outcome. For normal distributions means and standard deviations (SD) were used, while median and interquartile ranges (IQR) were used in case of skewed distributions. For comparison of continuous variables, Student's t-tests were used for normal distributions and Mann-Whitney U tests for skewed distributions. Pearson's chi-squared test was used for nominal variables. After univariate regression analyses, all variables with a p-value < 0.1 were subsequently tested in a multivariable logistic regression model to explore associations with mortality. Results were considered significant at $p<0.05$.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. The results of this study are used for the planning of further research in which patients are involved and of which the results will be disseminated in the relevant patient community.

Results

A total of 480 patients with sepsis were identified using an automated search of the PDMS. After reviewing the medical records, 217 patients were excluded (Figure 1). Of the included 263 patients, 127 patients (48.2%) had previous contact(s) with the GP cooperative in the 72 hours before hospital admission. In total, 97/127 patients (76.4%) had one contact with the GP cooperative prior to the hospital admission, 23/127 (18.1%) had two contacts, and 7/127 (5.5%) more than two. There were no statistically significant differences between the characteristics of the patients with and without prior GP cooperative contact (Table 1). Of all included patients, 140/263 (53.2%) arrived at the ED during out-of-hours. Of the patients arriving out-of-hours at the ED, 75.7% had contacted the GP cooperative in the previous 72 hours, compared to 17.1% of the patients arriving in hours (data not shown in table).

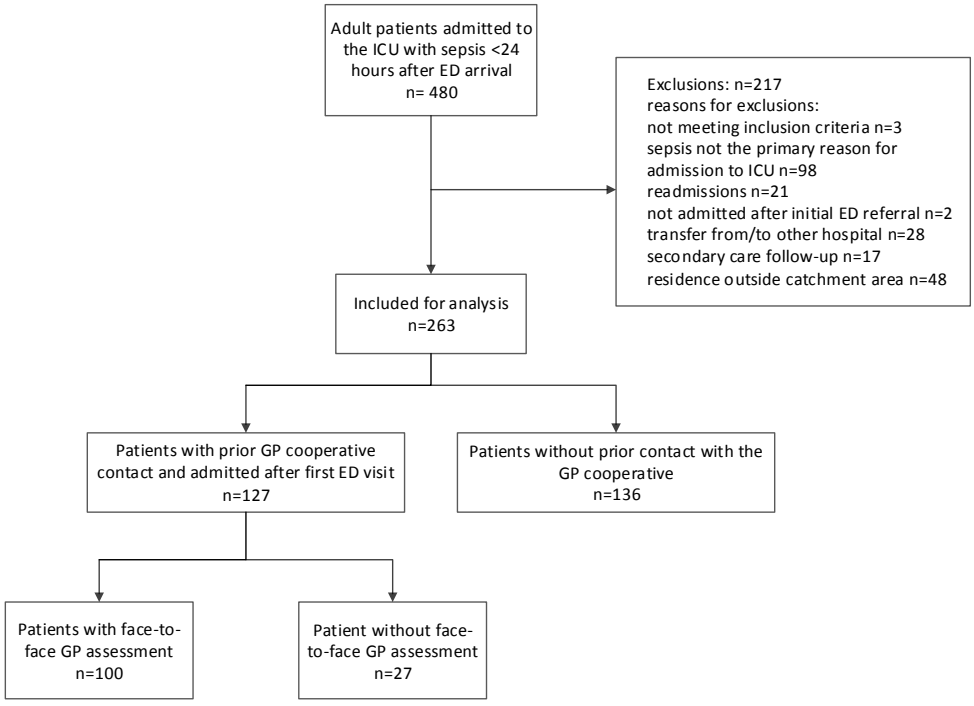

Figure 1. Flowchart of study population
ICU= intensive care unit, ED= emergency department, GP= general practitioner

Table 1. Patient characteristics and outcomes of patients with sepsis with and without prior GP cooperative contact.

	Prior GP cooperative contact	
	No (n=136) n (%)	Yes (n=127) n (%)
Age (years), median (IQR)	68 (60-78)	70 (58-78)
Female	60 (44.1)	54 (42.5)
Source of infection		
Respiratory tract	71 (52.2)	54 (42.5)
Urinary tract	16 (11.8)	24 (18.9)
Abdominal	20 (14.7)	26 (20.5)
Skin/ soft tissue	9 (6.6)	10 (7.9)
Other	20 (14.7)	13 (10.3)
Comorbidities		
Cardiovascular disease	32 (23.5)	41 (32.3)
Diabetes	39 (28.7)	42 (33.1)
COPD	40 (29.4)	32 (25.2)
Kidney disease	11 (8.1)	17 (13.4)
Malignancy	14 (10.3)	10 (7.9)
Immunosuppression	15 (11.0)	10 (7.9)
Multimorbidity	48 (35.3)	50 (39.4)
APACHE II score, mean (SD)	22.7 (7.8)	22.1 (7.5)

	Prior GP cooperative contact	
	No (n=136)	Yes (n=127)
	n (%)	n (%)
SOFA score, mean (SD)	7.8 (3.0)	7.4 (3.4)
Positive blood culture	41 (30.1)	45 (35.4)
Clinical signs on admission		
Body temperature > 38.0 °C	65 (47.8)	63 (49.6)
Body temperature < 36.0 °C	10 (7.4)	16 (12.6)
Heart rate >90/min	103 (75.7)	84 (66.1)
Systolic blood pressure <100 mmHg	36 (26.5)	40 (31.5)
Respiratory rate ≥ 22/min	103 (75.7)	103 (81.1)
Altered mental status	53 (39.0)	38 (29.9)
qSOFAscore ≥2, %	61 (44.9)	52 (40.9)
Laboratory findings on admission		
CRP (mg/L), mean (SD)	189 (142)	186 (158)
Creatinine (µmol/L), mean (SD)	147 (95)	183 (154)
Lactate (mmol/L) mean (SD)	3.5 (2.6)	3.6 (2.8)
Outcome parameters		
Septic shock	114 (83.8)	100 (78.7)
Length of ICU stay in days, median (IQR)	4.9 (2.2-11.9)	5.8 (2.8-12.6)
Length of hospital stay, median (IQR)	13.4 (7.8-22.6)	13.6 (9.6-22.5)
Hospital mortality	31 (22.8)	32 (25.2)

IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. SD = standard deviation. SOFA = Sepsis-related organ failure assessment. qSOFA = quick SOFA[17]. CRP = C-reactive protein.

The 127 patients who had prior contact with the GP cooperative were further analysed (Table 2). In 16 cases (12.6%), the patient was directly transferred to the hospital by an ambulance, after telephone triage, and without face-to-face GP assessment. In 76 cases (59.8%), a home visit followed after telephone triage, and in 24 cases (18.9%) a face-to-face consultation at the GP cooperative was performed (clinic consultation). The remaining 11 cases (8.7%) received telephone advice. Sixty-three per cent of the patients received a highly urgent triage category (U1 or U2) after telephone triage. In patients assessed during a home visit, 50/76 (65.8%) were referred to the hospital after this initial contact, compared to 14/24 (58.3%) of the patients receiving a clinic consultation. The median delay to hospital arrival was 1.7 hours for the total cohort. As expected, the median delay in case of immediate ambulance deployment was shorter (median 1.0 hour), and longer after only telephone advice (median 15.1 hours). Mortality rates in the different subgroups had a wide range (0.0-38.1%), but the subgroups were too small to reach statistically significant differences.

One hundred patients (76 home visits and 24 clinic consultations) received a face-to-face assessment by a GP (Table 3). In 57/100 cases an infection was either diagnosed or suspected, and in only six cases this was documented as sepsis or possible sepsis (not shown in table). In case that infection was not suspected after the initial GP assessment, the mortality rate was higher compared with patients with suspected infection (41.9% versus

15.8%). The patients without suspicion of infection were older (mean age 71 years, versus 65 years). In this group, respiratory rate and temperature were less frequently recorded, as well as the total number of vital signs (1.6 compared to 2.4). Fever (temperature > 38˚C) was recorded more frequently when infection was suspected (54.4% compared with 11.6% in patients without suspected infection). There was no association between delay and hospital mortality. In the multivariable logistic regression model (Table 4), the increased mortality when infection was not suspected remained statistically significant after corrections for the possible confounders age, multimorbidity, APACHE II score and SOFA score.

Table 2. Hospital referral, prehospital time delay and hospital mortality of patients with sepsis who had contacted the GP cooperative (n=127), according to type of contact and triage urgency category after telephone triage[a]

	n (%)	Hospital referral, n (%)	Delay in hours, median (IQR)	Hospital mortality % (95% CI)
Total cohort	127	80 (63.0)	1.7 (1.2-10.2)	25.2 (18.5-33.4)
Type of contact				
Ambulance	16 (12.6)	16 (100.0)	1.0 (0.8-1.2)***	18.8 (6.6-43.0)
Clinic consultation	24 (18.9)	14 (58.3)	1.7 (0.9-14.5)	16.7 (6.7-35.9)
Home visit	76 (59.8)	50 (65.8)	1.8 (1.2-9.2)	30.3 (21.1-41.3)
Telephone advice	11 (8.7)	0 (0.0)	15.1 (2.7-38.0)*	18.2 (5.1-47.7)
Urgency after telephone triage				
U1 – Life threatening	21 (16.5)	21 (100.0)	1.1 (0.9-1.2)*	38.1 (20.8-59.1)
U2 - Emergent	59 (46.5)	39 (66.1)	1.6 (1.2-9.6)	32.2 (21.7-44.9)
U3 - Urgent	36 (28.3)	19 (52.8)	2.4 (1.5-13.0)	11.1 (4.4-25.3)
U4 – Non-urgent	6 (4.7)	1 (16.7)	20.1 (11.5-38.0)**	0.0 (0.0-39.0)
U5 - Advice	5 (3.9)	0 (0.0)	15.1 (2.4-37.6)*	20.0 (3.6-62.4)

[a] Statistical differences between subgroups were tested for delay (reference group home visit for type of contact and U3 for urgency after triage), and hospital mortality. * p<0.05. **p<0.01. ***p<0.001. IQR = interquartile range. CI = confidence interval.

In patients who were referred to the ED after the first GP assessment, the mortality rate of patients in whom infection was suspected was 12.5%, compared to 56.0% when the GP did not suspect infection. In patients not referred after the first contact, hospital mortality was 22.2% in both groups (data not show in table).

Table 3. Characteristics and clinical findings of patients with sepsis who had face-to-face GP assessment (n=100), in whom infection was suspected or not suspected.

	Infection suspected by GP[a]	
	Yes (n=57) n (%)	No (n=43) n (%)
Age (years), median (IQR)	66 (58-77)	71 (61-81)*
Female	25 (43.9)	16 (37.2)
Multimorbidity	24 (42.1)	14 (32.6)
Source of infection		
Respiratory tract	25 (43.9)	17 (39.5)
Urinary tract	11 (19.3)	7 (16.3)
Abdominal	11 (19.3)	10 (23.3)
Skin/ soft tissue	5 (8.8)	2 (4.7)
Other	5 (8.8)	7 (16.3)
Clinical assessment GP		
Recorded vital signs, mean (SD)	2.4 (1.0)	1.6 (1.3)**
Temperature recorded	42 (73.7)	18 (41.9)*
Temperature >38.0°C	31 (54.4)	5 (11.6)**
Blood pressure recorded	39 (68.4)	26 (60.5)
Systolic blood pressure <100mmHg	11 (19.3)	6 (14.0)
Heart rate recorded	42 (73.7)	24 (55.8)
Heart rate >130/minute	10 (17.5)	2 (4.7)
Respiratory rate recorded	13 (22.8)	2 (4.7)*
Respiratory rate >25/minute	9 (15.8)	2 (4.7)
Altered mental status	9 (15.8)	9 (20.9)
Rigors	10 (17.5)	4 (9.3)
Not able to stand	8 (14.0)	6 (14.0)
Rapid illness progression	12 (21.1)	9 (20.9)
Hospital data		
CRP (mg/L), mean (SD)	192 (149)	197 (178)
APACHE II score, mean (SD)	20.5 (7.3)	24.3 (8.1)
SOFA score, mean (SD)	6.9 (3.6)	8.1 (3.3)
qSOFA score ≥2	18 (31.6)	24 (55.6)
Management and outcome		
Referred to hospital	39 (68.4)	25 (58.1)
Delay in hours, median (IQR)	1.8 (1.3-10.2)	1.6 (1.2-10.7)
Hospital mortality	9 (15.8)	18 (41.9)**

[a] GP recorded an infections diagnosis, or mentioned an infectious diagnosis in the first three differential diagnoses. * $p<0.05$. ** $p< 0.01$. IQR = interquartile range. SD = standard deviation. CRP = C-reactive protein. APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = Sepsis-related organ failure assessment.

Table 4. Multivariable logistic regression model for in-hospital mortality of patients with sepsis who received face-to-face GP assessment (n=100)[a]

	adjusted OR (95% CI)	p-value
Age, per year	1.11 (1.04 to 1.18)	0.001
Multimorbidity	2.64 (0.84 to 8.33)	0.097
SOFA score, per point	1.28 (1.03 to 1.58)	0.025
APACHE II score, per point	0.97 (0.88 to 1.07)	0.57
Suspected infection[b]	0.30 (0.10 to0.94)	0.038

[a] Sex, lactate, qSOFA and delay had a p-value >0.1 in univariate logistic regression analysis. [b] GP recorded an infections diagnosis, or mentioned an infectious diagnosis in the first three differential diagnoses. OR = odds ratio. CI = confidence intervals. SOFA = Sepsis-related organ failure assessment. APACHE = Acute Physiology and Chronic Health Evaluation.

Discussion

We found that 48% of the patients admitted to the ICU for community-acquired sepsis had contacted the GP cooperative for out-of-hours primary care prior to admission. The most important new finding is that in 43% of these patients the GP did not suspect an infection, and mortality rates were almost three times higher in this group compared to patients with sepsis in whom the GP suspected infection during the initial contact.

The patients with sepsis in whom infection was not suspected by the GP were on average five years older. This may indicate that infections are more difficult to identify in the elderly. As sepsis related mortality increases with age, this can partially explain the difference in mortality between the two groups, but the difference remained statistically significant after adjustment for age and other possible confounders. The failure to suspect infection in a patient with sepsis might delay adequate treatment, even if the GP decides to refer the patient. For example, several patients in our cohort were referred to a cardiologist with suspicion of acute decompensated heart failure and initially treated with furosemide. Roest et al found similar results in a retrospective cohort of patient with sepsis transported to hospital by ambulance.[12] In 42% of the transported patients, sepsis was not documented and mortality was significantly higher in this group (26% in non-documented sepsis versus 13% in patients with documented sepsis).

However, patients without clear signs of infection might also have a worse prognosis regardless the treatment. In a large retrospective study in patients with community-acquired sepsis admitted to 1 of 30 ICUs in Sweden, an inverse correlation was found between body temperature at presentation in the ED, and mortality.[17] Not only hypothermic, but also normothermic patients showed higher mortality compared with febrile patients who could not be attributed to other risk factors or treatment. We cannot predict the effect on mortality should the GP recognise sepsis in all patients correctly, but the subgroup of patients in whom infection was not suspected seems to be the most severely ill group of patients which cannot be ignored in efforts to decrease sepsis-related mortality.

In our study approximately two-thirds of the patients were referred after the initial GP consultation. Other studies investigating the management of sepsis in general practice were not found, though the recognition and management of meningococcal disease in children by GPs has been reported.[18] In about half of these cases the GP referred the patient to the hospital after the first assessment, which is slightly lower than in our study. These findings suggest that serious infections can be difficult to recognise in general practice, even within hours before the infection is imminent life threatening.

Implications for practice and further research

The out-of-hours home visit should be considered as a high-risk setting for the prevalence of sepsis, as one in three patients admitted to the ICU with sepsis was assessed during a home visit of the GP cooperative prior to the hospital admission. Patients with sepsis are therefore heavily over-represented in this setting, as out-of-hours home visits only account for around 0.5% of all GP contacts and 10% of GP cooperative contacts.[14] As early initiation of adequate treatment of sepsis is crucial to improve outcome, prehospital delay should be minimised. Ideally, every patient needing ICU treatment for sepsis should be directly transported by ambulance to the ED. The lack of association between delay and mortality in this study does not imply delay is irrelevant for the outcome. More severely ill patients are generally transported to the hospital more quickly. Therefore, it was expected that patients with short delay presented high mortality rates. The finding that the most severely ill patients, who were directly transported to the ED by ambulance presented relatively low mortality rates (19%), suggest immediate ambulance deployment is beneficial for these patients.

On the other hand, unnecessary referrals should be prevented. Therefore, quick assessment by a GP is warranted in case the need for hospital treatment is equivocal after telephone triage. Comprehensive measurements of relevant vital signs might facilitate detection of sepsis. As in almost half of the patients infection was not suspected, sepsis should also be considered in patients who are acutely ill without obvious signs of infection, especially among elderly patients. As only 30% of the patients presented with fever, point-of-care (POC) testing can possibly identify infection better than physical examination alone. CRP values were strongly elevated in most patients who were not considered as having an infection. POC-CRP testing is increasingly available in primary care, and it is feasible to implement this during home visits. However, not all patients with sepsis have (strongly) elevated CRP levels, and not all patients with elevated CRP levels need hospital treatment. Procalcitonin is possibly superior to CRP for the diagnosis of sepsis and should also be investigated, as also recommended in the NICE guidelines for the diagnosis and management of sepsis published in 2016.[19] Prospective research in the primary care setting is needed to investigate the diagnostic and prognostic value of both clinical findings as well as biomarkers available as rapid bedside tests.

Strengths and limitations

The major strength of the study is the linking of data from the electronic medical records from the ICU and the GP cooperative, resulting in complete data for the main outcome measures of all included patients. Manual retrieval of additional data from the hospital medical records provided more contextual information. However, several limitations have

to be mentioned. The study was performed in one large general hospital. Results may not be the same for other areas in the Netherlands or other countries. Another limitation of the study is the retrospective design and selection of patients requiring ICU treatment for sepsis. Patients with sepsis who were promptly recognised and urgently referred to the ED by a GP may have been treated successfully in regular wards, and therefore did not receive ICU treatment. This may have resulted in a selection of patients who were treated less adequately in the prehospital phase. However, this would then also imply that ICU admissions could be prevented if detection by the GP is improved.

Conclusions

GPs' clinical detection of sepsis in primary care proves to be difficult. More than one third of ICU admitted patients with sepsis initially assessed by GPs in out-of-hours primary care were not referred to a hospital. In almost half of the patients the GP had not suspected an infection. The highest mortality rates were observed in those patients in whom GPs had not suspected an infection. Efforts to improve identification and management of sepsis in the primary care setting should not be limited to patients with obvious signs of infection, but also include acutely ill patients without a clear diagnosis.

Ethical Approval

The medical ethics committee of the Radboud university medical center Nijmegen approved the study (file number 2015-2209). Written informed consent was waived.

Funding

None

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CHAPTER 5

5

The accuracy and feasibility of respiratory rate measurements in acutely ill adult patients by general practitioners: a mixed-methods study

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Accepted for publication in BJGP Open

ABSTRACT

Background Tachypnoea in acutely ill patients can be an early sign of a life-threatening condition such as sepsis. General practitioners (GPs) are often the first healthcare providers assessing acutely ill patients. Routine measurement of the respiratory rate by GPs might improve the recognition of sepsis.

Aim To assess the accuracy and feasibility of respiratory rate measurements by GPs.

Methods We performed an observational cross-sectional mixed-methods study in the setting of out-of-hours home visits at three GP cooperatives in the Netherlands. GPs were observed during the assessment of acutely ill patients, and semi-structured interviews were performed in a sample of the GPs. The GP-assessed respiratory rate was compared to a 60-seconds-counting reference measurement by the observing researcher. The interviewed GPs were asked to estimate the rate to be ≥22 breaths per minute or not, in case the respiratory rate was not counted,

Results Observations of 130 acutely ill patients were included and 14 GPs were interviewed. In 33 patients (25%), the GP counted the respiratory rate. We found a mean difference of 0.27 breaths per minute (95% CI -5.7 to 6.3) with the reference measurement. At a cut-off point of ≥22 breaths per minute, a sensitivity of 86% (95% CI 57-98%) was found when the GP counted the rate compared to a sensitivity of 43% (95% CI 22-66%) when GPs estimated respiratory rates. Many GPs reported that they do not use the respiratory rate for patient management and rely more on oxygen saturation to assess potential respiratory failure. Practical problems mentioned were that the measurement could be hindered by the clothing or movements of the patient and the time required for the measurement.

Conclusion GPs are aware of the importance of assessing the respiratory rate of acutely ill adult patients, and counted measurements are accurate. However, in most patients the respiratory rate was not counted, and the rate was often underestimated when estimated.

INTRODUCTION

The respiratory rate is an important sign to identify seriously ill patients early in the course of the disease.[1-3] According to the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach, the respiratory rate should be measured as part of the assessment of 'Breathing".[4] The ABCDE approach is widely used in acute care settings and increasingly taught in general practitioners' (GPs) training programs.[5,6] The respiratory rate is deemed important for the early recognition of sepsis. In the early stage of sepsis, cytokines and endotoxins increase the respiratory drive leading to hyperventilation beyond the metabolic needs. In later stages, metabolic acidosis and lung injury induced by sepsis further increase the respiratory drive.[7] Both the Systemic Inflammatory Response Syndrome (SIRS), and the quick Sequential Organ Failure Assessment (qSOFA) score use the respiratory rate as one of the variables in the score.[8,9] The cut-off points in the SIRS and qSOFA are respectively >20 breaths per minute and ≥22 breaths per minute. Also, the respiratory rate is included in warning scores such as the National Early Warning Score (NEWS) and Modified Early Warning Score (MEWS), which are used to recognise critically ill patients, including sepsis patients.[10] Besides for suspected sepsis, the respiratory rate can be used to assess the likelihood and/or severity of acute conditions such as pulmonary embolism, heart failure, pneumonia and COPD exacerbations.

Currently, it is not known if GPs can measure the respiratory rate reliably and in which clinical scenarios GPs assess it. This study aims to examine the accuracy of the respiratory rate measurement by GPs and evaluate barriers and facilitators for measuring it in acutely ill adult patients.

METHODS

The study consisted of observations of respiratory rate measurements during the assessment of acutely ill adult patients . Semi-structured interviews with GPs were held during the shift of the GP in which the home visits were conducted. Informed consent was obtained from the participating GPs. The need for informed consent from the patients was waived as all patients received care as usual. Patients were asked if they agreed with the presence of a member of the research team during the GP assessment.

Setting

We conducted the study between May 2018 and June 2019 at three out-of-hours (OOH) GP cooperatives located in Ede, Den Bosch and Uden, serving about 700,000 inhabitants in a mixed urban and rural area. In Dutch OOH GP cooperatives, each patient contact is preceded by telephonic triage by a trained triage nurse supervised by a GP. If possible, telephonic advice is given, or patients are asked to come to the OOH GP cooperative for a GP consultation. If this is not feasible, a GP visits the patient at home. If an acute life-threatening condition, such as myocardial infarction, is suspected, an ambulance is directly deployed to transport the patient to a hospital.[11] At all participating GP cooperatives, contacts with acutely ill adult patients who received a home visit were included in the study to observe respiratory rate measurements. These contacts mainly concerned frail elderly patients with urgent medical complaints for whom assessment could not be postponed to the next working day. Therefore, all patients were considered acutely ill unless a clear other reason for the home visit was present (e.g. determination of death, palliative care or psychiatric emergencies). At the GP cooperative in Ede only, semi-structured interviews with the GP were performed.

Patient observations

During home visits of acutely ill adult patients, a member of the research team (medical intern) was present during GP assessment of the patient. GPs were asked to measure the respiratory rate when medically indicated, without specific instruction in which patients and how to perform the measurement. During the home visit, the research team member counted the respiratory rate as a reference value by observing the thorax excursions for 60 seconds while the patient was not talking or moving. The reference measurement was usually performed during the physical examination by the GP, but the exact timing and result were concealed for the GP, as the observing researcher was positioned behind the GP and did not provide any information about the measurement to the GP.

Directly after the patient consultation, we asked the GP if he or she measured the respiratory rate and, if so, what the value and method of measurement were. If the GP counted the respiratory rate for at least 15 seconds, the value was recorded as a counted value. In case the GP assessed the respiratory rate without counting the exact rate for at least 15 seconds, we only recorded whether the estimated rate was ≥22 breaths per minute (cut-off value of the qSOFA). At the GP cooperative where GPs were also interviewed for the study, we asked GPs after each contact with an acutely ill patient to estimate the value (≥22 breaths per minute or not), in case the rate was not counted.

Qualitative research among GPs

The research team member performed a semi-structured interview with the GP at the beginning of or during the shift. This interview lasted about 10 minutes in total. The interviews were continued until data saturation was observed. The main topics of the interview were 1) the frequency and method of the respiratory rate measurement during patient assessments, 2) the clinical scenarios in which they usually measure the respiratory rate, and 3) the perceived relevance of the measurement.

Data analyses

The quantitative data were analysed using SPSS version 25. Descriptive analyses were used for the background characteristics of the included patients and GPs. Mean values with standard deviation (SD) were used for normally distributed continuous variables and median with interquartile range (IQR) for skewed distributions. Pearson's correlation coefficient assessed the correlation between the counted respiratory rate measurements and reference measurement. A Bland-Altman plot was used to assess systematic differences between the GP and reference measurements. 2x2 contingency tables were calculated at the cut-off value of ≥22 breaths per minute for both the counted and estimated respiratory rate measurements.

The interviews were summarised based on notes taken during the interview, and illustrative quotes were written down in full. Subsequently, the interviews were coded in AtlasTi version 8.2.29.0. The codes were organised based on the topics of the interview.

RESULTS

We included observations of 35 different GPs, of whom 14 were also interviewed. 18/35 (51%) of the GPs were female, and the mean working experience was 16 years. In total, 164 home visits for any medical reason were performed by the 35 GPs. Of these home visits, 130 observations of acutely ill adult patients were included in the analyses (range of one to seven observations per GP). The excluded contacts concerned determination of death (17), children (3) and patients who were not acutely ill (14).

In total, in 33/130 (25%) of the included patient contacts, the respiratory rate was counted for at least 15 seconds by the GP. At the GP cooperative in Ede, the respiratory rate was counted in 12/56 (21%) of the patients. Of the remaining 44 patient observations, an estimated respiratory rate (≥22 breaths per minute or not) was recorded. At the GP cooperatives in Den Bosch and Uden, in 21/74 (28%) of the patient contacts, the GP had counted the respiratory rate, and in 4 cases an estimation was recorded. Table 2 shows the patients' background characteristics in whom the respiratory rate was counted for at least 15 seconds, compared to the remaining included patients. The median age was 79 years in both groups, with respiratory complaints as the most common reason for the home visit. According to the reference measurement, the mean respiratory rate in the group in which the GP counted the respiratory rate was 21 breaths per minute, compared to 20 breaths per minute in the remaining patients.

Table 1. Background characteristics of the included acutely ill patients (n=130), divided by patients in whom the GP did or did not count the respiratory rate for at least 15 seconds.

Variable	Respiratory rate counted	
	Yes (n=33)	No (n=97)
Age, median years (IQR[a])	79 (68-86)	79 (69-85)
Sex, No (%)		
Male	15 (45)	50 (52)
Female	18 (55)	47 (48)
Type of complaint, No (%)		
Respiratory	12 (36)	16 (16)
Infectious	6 (18)	11 (11)
General malaise	2 (6)	12 (12)
Cardiovascular	4 (12)	9 (9)
Gastro-intestinal	4 (12)	14 (14)
Trauma	2 (6)	14 (14)
Neurologic	2 (6)	6 (6)
Other	1 (3)	15 (15)
Urgency at triage, No (%)		
U1: response immediately	2 (6)	2 (2)
U2: response as quickly as possible	17 (52)	41 (42)
U3: response in a few hours	13 (39)	53 (55)
U4: response in 24 hours	1 (3)	1 (1)
Respiratory rate, mean (SD[b])	21 (7.3)	20 (6.4)
GP characteristics, No (%)		
Female sex	14 (42)	43 (44)
>10 years working experience	25 (76)	74 (76)

[a]interquartile range; [b]standard deviation

Accuracy of the respiratory rate measurement

In Figure 1, the correlation of the counted respiratory rate measurements of the GPs and the reference measurement are shown. The Pearson's correlation coefficient was 0.91. There was no significant systematic difference between the GP- and reference measurement, as shown in the Bland-Altman plot in Figure 2. A mean difference of 0.27 (95% CI -5.7 to 6.3) breaths per minute was found, and 28/33 (85%) of the observations were within a margin of error of ≤ 2 breaths per min. Contingency tables of both the counted and estimated respiratory rates at a cut-off point of 22 breaths per minute are shown in Table 2. Compared to the reference measurement, the sensitivity for the observation of a respiratory rate ≥22 breaths per minute was 86% (95% CI, 57-98%) in patients for whom GPs counted the respiratory rate and 43% (95% CI, 23-66%) in patients for whom GPs estimated the respiratory rate. We found a specificity of 100% (95% CI 83-100%) for the counted observations and 96% (95% CI 81-100%) for the estimated observations.

Results of the interviews

All 14 interviewed GPs reported assessing the respiratory rate in practice, although some of them reported this as (very) infrequent. None of the GPs performed the measurements

routinely in all acutely ill patients. A reported method used to count the respiratory rate was observing thorax excursions for 15-30 seconds, with or without simultaneous palpation of the pulse. Other methods reported by the GPs are lung sound auscultation or palpation of the thorax. Mentioned clinical scenarios to measure the respiratory rate were adult patients with respiratory complaints, suspected infection, and acutely ill children. Other mentioned reasons to measure the respiratory rate were the clinical handover concerning patients referred to the hospital, to objectify shortness of breath, and to complete the overall clinical assessment.

> *"You often measure the respiratory rate in really sick patients or patients with dyspnea."* [GP8, F, 14y experience)

> *"It is improbable that the respiration rate influences patient management. In children, on the other hand, I do assess the respiratory rate sometimes."* [GP7, F, 18y experience)

Most GPs use the respiratory rate with other clinical findings in their final assessment. Reasons not to measure the respiratory rate in all patients can be divided into medical and practical concerns. Most GPs find other vital signs more helpful in their assessment. Especially the peripheral oxygen saturation is often found sufficient for assessing breathing. Other medical reasons not to measure the respiratory rate are the chance of an abnormal finding without clinical relevance or the feeling it will not change patient management.

> *"I combine the respiratory rate with other vital signs and use that to decide how I treat the patient."* [GP5, M, 38y experience)

> *"Since I use a pulse oximeter, I seldom measure the respiratory rate anymore, as this [the oxygen saturation) provides me with the information I need."* [GP6, M, 30y experience)

Practical concerns are the difficulty of counting the respiratory rate in patients who keep talking or are moving or wear hindering clothes. Also, the needed investment of time was mentioned to play a role in the decision deciding whether to count the respiratory rate.

> *"It can be difficult to measure the respiratory rate accurately. You should invest the time for it, and that is not always possible."* [GP1, F, 12y experience)

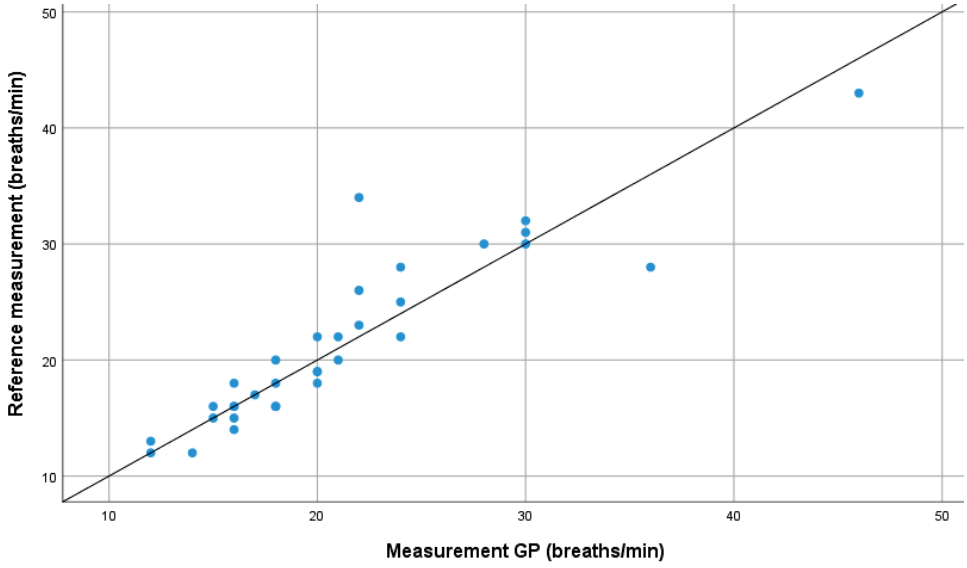

Figure 1. Correlation between the respiratory rate measurements of the GP (counted during at least 15 seconds) and the reference measurement.

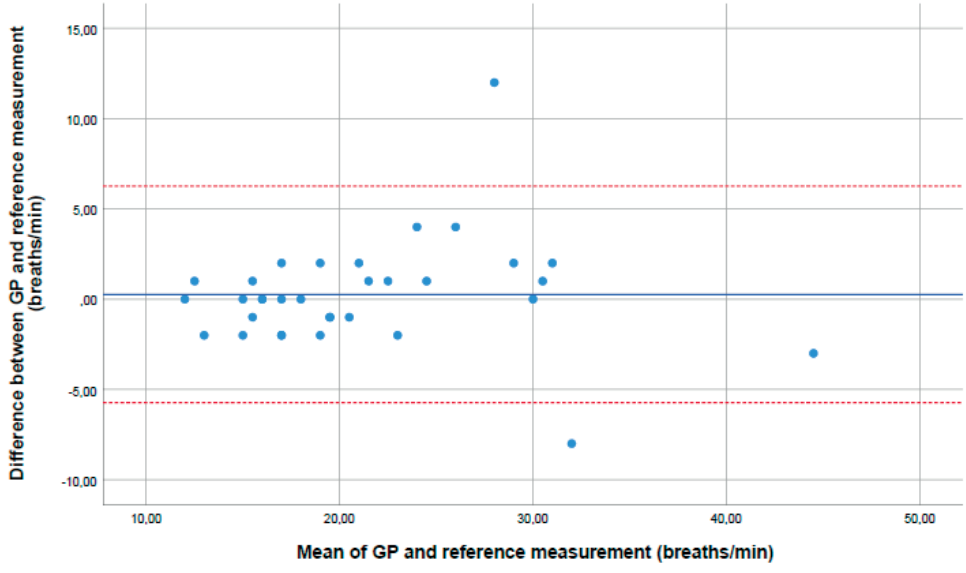

Figure 2. Bland-Altman plot of the differences between the GP measurement of the respiratory rate and the reference measurement.

Table 2. Contingency tables of the assessment of the respiratory rate of the GP compared to the reference measurement at a cut-off of 22 breaths per minute. A. GP counted respiratory rate at least 15 seconds, and B. Estimated respiratory rate by the GP.

A

		Reference measurement		
		≥22/min	<22/min	Total
Counted by GP	≥22/min	12	0	12
	<22/min	2	19	21
	Total	14	19	33

B

		Reference measurement		
		≥22/min	<22/min	Total
Estimated by GP	≥22/min	9	1	10
	<22/min	12	26	38
	Total	21	27	48

DISCUSSION

Main findings

In the setting of out of-hours home visits of acutely ill adult patients, GPs counted the respiratory rate during one in four consultations. These counted measurements were found to be accurate. In cases where the respiratory rate was not counted, the rate was often underestimated. A respiratory rate of ≥22 breaths per minute, as used in the qSOFA score, was not noticed in about half of the cases in which the GP did not count the respiratory rate. Based on the GP interviews, respiratory complaints and fever were the most important reasons GPs assess the respiratory rate. The preferred method was to count thorax excursions for 30 seconds (with or without taking the pulse). Reasons not to count the respiratory rate were medical (e.g., believed to be less relevant for patient management than other vital signs) and practical (e.g., time investment, hindering clothes).

Comparison with literature

We could not find any previous studies on the accuracy of respiratory rate measurements in general practice. Latten and colleagues, however, assessed the accuracy of the respiratory rate assessment by medical professionals, including GPs, based on video observations.[12] Overall, 78% of the observations were within a margin of error of 4 breaths per min, and the accuracy of the GP measurement was comparable to other healthcare professionals. The overall misclassification for the qSOFA was 8.9%. We found a somewhat lower misclassification in 2/33 (6%) of the patients for the qSOFA when the GP counted the respiratory rate.

In a study conducted in the ED in the Netherlands, assessments of adult medical patients were observed to assess how the ABCDE approach was applied in practice. The ABCDE approach was used in 26% of the patients. In case the ABCDE approach was used, this included measuring the respiratory rate in 92%. These study results are comparable to the results we found, but it should be noted that in the ED, vital signs were already measured during triage prior to the physician's assessment. Also, the respiratory rate might be measured by the physician, not as part of the ABCDE assessment.

Several GPs interviewed in the study reasoned that the respiratory rate measurement could be replaced by oxygen saturation. However, increased metabolic need, acidosis and inflammation are the main drivers of the respiratory rate in sepsis and not decreased oxygenation.[13] Several questionnaire studies have been performed among clinicians working in the hospital setting, assessing the knowledge of nurses and physicians about pulse oximetry.[14] The limitations of reading of the peripheral oxygen saturation are poorly understood and 7-42% of the clinicians believed it provides information about the ventilation of the patient. Measurement of respiratory rate and oxygen saturation are complementary and should not be substituted by one another.[15]

Strengths and limitations

The most important strength of this study is that we observed GPs during the actual assessment of acutely ill patients in their homes. This study design enabled us to obtain real-world data on the accuracy of the respiratory rate measurement in practice. Another strength is the simultaneous qualitative research, which provided more insight into the feasibility for GPs to count the respiratory rate. Several limitations of the study should also be mentioned. First, the Hawthorn effect may have played an important role during the study. The frequency of measurement of the respiratory rate is probably not representative of the typical situation without the presence of a researcher. As the GPs agreed to participate in a study where the respiratory rate measurement was observed, we expect to have overestimated the frequency in which GPs count the respiratory rate. We believe our findings should be interpreted as indicating how often (and how accurate) the respiratory rate is measured at best. Also, we only focused on the respiratory rate measurements during out-of-hours home visits. This timeframe may not be representative of other primary care settings. However, while all GPs participating in the study also work in office hours, and it is likely assessment of patients in this setting will be done comparable to OOH. Secondly, results may differ between countries as local GP training programs probably influence the attitude towards the respiratory rate measurement. Furthermore, we used a 60 second count of a single researcher as reference measurement, which may differ from the true respiratory rate. However, this is not likely to have influenced the results, as differences between the reference measurement and GP counted rates were small. Finally, the number of patient observations was small, leading to wide confidence intervals of the estimated sensitivity of counted and estimated measurements. However, the finding of the low sensitivity for the estimated measurements is robust as the upper limit of the 95% CI is still low at 66%.

Implications for practice and research
The finding that only in a minority of the undifferentiated acutely ill patients, GPs in the Netherlands currently measure the respiratory rate has several implications. Firstly, the potential signalling function of an increased respiratory rate as an early sign of shock or sepsis is not fully utilised. Secondly, implementing a sepsis score such as the qSOFA may be difficult, and scores of the qSOFA may not be accurate in the respiratory rate is estimated instead of counted. Education and training of GPs may improve the measurement of the respiratory rate. However, before more extensive efforts are undertaken to encourage respiratory rate measurement by all GPs, it should be proven beneficial. More research should be performed in the primary care setting to show the added value of recognising critically ill patients or improving outcomes.

Conclusion
GPs are aware of the importance of assessing the respiratory rate of acutely ill adult patients and can accurately count the frequency. However, the respiratory rate is not counted in most patients, and the rate is often underestimated in these cases, with important loss of sensitivity to detect a high respiratory rate.

Funding
None.

Ethical approval
The Ethical Research Committee of the Radboud University Medical Center Nijmegen was consulted and concluded that this study did not require ethical approval (file number 2018-4178).

Acknowledgements
The authors thank all GPs who participated in this study.

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CHAPTER 6

6

Development of a clinical prediction rule for sepsis in primary care: protocol for the TeSD-IT study

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Diagnostic and Prognostic Research 2020

Abstract

Background Early recognition and treatment of sepsis is crucial to prevent detrimental outcomes. General practitioners (GPs) are often the first healthcare providers to encounter seriously-ill patients. The aim of this study is to assess the value of clinical information and additional tests to develop a clinical prediction rule to support early diagnosis and management of sepsis by GPs.

Methods We will perform a diagnostic study in the setting of out-of-hours home visits in four GP cooperatives in the Netherlands. Acutely ill adult patients suspected of a serious infection are screened for eligibility by the GP. The following candidate predictors are prospectively recorded: 1) age; 2) body temperature; 3) systolic blood pressure; 4) heart rate; 5) respiratory rate; 6) peripheral oxygen saturation; 7) altered mental status; 8) rigors and 9) rapid illness progression. After the clinical assessment of the GP, blood samples will be collected in all patients to measure C-reactive protein, lactate and procalcitonin. All patients receive care as usual. The primary outcome is presence or absence of sepsis within 72 hours after inclusion, according to an expert panel. The need for hospital treatment for any indication will be assessed by the expert panel as a secondary outcome. Multivariable logistic regression will be used to design an optimal prediction model first, and subsequently derive a simplified clinical prediction rule that enhances feasibility of using the model in daily clinical practice. Bootstrapping will be performed for internal validation of both the optimal model and simplified prediction rule. Performance of both models will be compared to existing clinical prediction rules for sepsis.

Discussion This study will enable us to develop a clinical prediction rule for the recognition of sepsis in a high-risk primary care setting to aid in the decision which patients have to be immediately referred to a hospital and who can be safely treated at home. As clinical signs and blood samples will be obtained prospectively in all participants, near complete data will be available for analyses. External validation will be needed before implementation in routine care and to determine in which prehospital settings care can be improved using the prediction rule.

Background

Sepsis is a life-threatening complication of an infection. Early detection and initiation of adequate treatment is the key factor influencing outcome.[1-4] It is estimated that annually 49 million people suffer from sepsis worldwide, of which 11 million do not survive.[5] In 2017, the WHO declared sepsis a global healthcare priority and urged member states to improve recognition and treatment of sepsis.[6] Global efforts to reduce mortality and morbidity from sepsis have focused on hospital settings, but patients often present in primary care in the early stages of sepsis. General practitioners (GPs) are confronted with acutely ill patients with a variety of symptoms, signs and potential diagnoses. Within minutes they have to decide whether a patients can safely be treated at home or should be referred to a hospital for further assessment.

In the Netherlands, out-of-hours primary care is provided by large GP cooperatives.[7] Patients are only assessed by a GP if the medical complaint cannot wait until the following working day. In contrast to other common time-critical conditions such as stroke and myocardial infarction, patients with sepsis are more likely to contact a GP cooperative instead of an emergency medical service prior to hospital treatment.[8] Data from our preliminary research on patients admitted to an intensive care unit (ICU) due to community acquired sepsis, showed that about half of the patients had prior contact with a GP cooperative. Two thirds of these patients were referred to the hospital after the first contact.[9] The majority of the patients were assessed during a home visit.

In the hospital setting, vital signs are used to screen for sepsis in patient with suspected infections. The Systemic Inflammatory Response Syndrome (SIRS) was introduced in 1992 to define sepsis.[10] Besides the white blood count, the SIRS criteria are a heart rate <90/min, respiratory rate >20/min, and a body temperature <36°C or >38°C. As SIRS criteria are often present in patients without serious infections and one in eight patients admitted to the ICU with sepsis were found to lack positive SIRS criteria, a new consensus definition was formulated in 2016. In the "Sepsis-3" definition, the Sequential Organ Failure Assessment (SOFA) score was proposed to diagnose sepsis.[1] As this score is not easy to apply outside the ICU, the quick SOFA (qSOFA) was introduced for rapid bedside assessment. The criteria used in the qSOFA are an altered mental status, systolic blood pressure ≤100 mmHg, and a respiratory rate ≥ 22/min. A positive score on two or more parameters predicts an increased risk of mortality. However, the qSOFA is not suitable as a screening tool as it lacks sensitivity.[11-12] C-reactive protein (CRP), lactate and procalcitonin (PCT) have all been shown to increase the sensitivity and overall diagnostic performance of the qSOFA.[13-15] To our knowledge, no study has assessed the contribution to the accurate early detection of sepsis in primary care of factors such as symptoms, signs, and biomarkers potentially available as point-of-care tests (POCT) such as CRP, lactate and PCT.

The aim of the TeSD-IT study (**Te**sting for **S**epsis in primary care: **D**iagnostic and prognostic study **I**nvestigating the potential benefits of point of care **T**esting) is to develop a clinical prediction rule to improve the detection of sepsis while limiting unnecessary referrals in acutely ill patients presenting at the GP cooperative home visits. Clinical signs and symptoms as well as blood tests are considered as candidate variables.

Methods

Setting, and design

We will perform a prospective diagnostic cohort study in the Netherlands in four GP cooperatives (Ede, Den Bosch, Uden and Oss) for out-of-hours primary care. The cooperatives serve a total of approximately 830,000 inhabitants in a mixed urban, suburban and rural area. The cooperatives are based in or adjacent to regional hospitals.

Patients

Patients will be recruited during out-of-hours home visits by GPs. Patients only receive home visits when they have acute medical complaints that cannot wait until the next working day and they are not able to visit the GP cooperative location for a clinic consultation. This is decided after telephone assessment by a triage nurse based on the Netherlands Triage System (NTS).[16] All acutely ill adult patients (≥18 years) with fever, confusion or general deterioration or otherwise suspected of a serious infection are eligible for inclusion. Exclusion criteria are: 1) Non-infectious cause of the acute complaints (*e.g.* stroke or myocardial infarction); 2) Hospitalisation within seven days before the home visit; 3) Condition that requires secondary care assessment if there are any signs of systemic infection (*e.g.* chemotherapy with possible neutropenia); 4) Terminal illness or other reason not to refer the patient to a hospital despite presence of a life-threatening condition.

Candidate predictors

We selected nine clinical features and three blood tests as candidate predictors for the development of the clinical prediction model (Table 1). Parameters of widely used scoring systems such as the SIRS, qSOFA and National Early Warning Score (NEWS)[17] were considered, as well as clinical features used in guidelines such as the Netherlands Triage Standard (NTS) and NICE Sepsis guideline.[18] Candidate predictors were selected if there was evidence to suggest that they might usefully contribute to the diagnosis of sepsis, and if they can be easily and objectively measured by GPs.

Candidate blood tests had to be currently used in the hospital setting for the diagnosis and/or prognosis of sepsis, and, preferably, to be available as a point-of-care test for reasons of implementation. CRP and lactate measurement are part of the standard care in patients with suspected sepsis during assessment in the Emergency Department (ED) in the Netherlands. Procalcitonin (PCT) is not routinely measured in most hospitals, but we decided to include PCT as a candidate predictor as PCT might be superior to CRP,[19] and the NICE sepsis guideline recommends research to further evaluate the use of PCT POCT for diagnosing serious bacterial infection and initiating antibiotic therapy. CRP, lactate, and PCT are currently available as POCT tests.

Table 1. Candidate predictors eligible for the selection in the prediction model

Type of predictor	Candidate predictor	Measurement method	Measurement unit	Used in
Clinical feature	Age	Inclusion date minus date of birth	years	NICE guideline[18]
	Body temperature	Tympanic measurement	°C	SIRS,[10] NEWS,[17] NICE guideline
	Heart rate	IntelliVue MP2/ X2	beats/min	SIRS, NEWS, NICE guideline
	Respiratory rate	IntelliVue MP2/ X2 or GP assessment	breaths/min	SIRS, qSOFA, NICE guideline, NEWS
	Systolic blood pressure	IntelliVue MP2/ X2	mmHg	qSOFA, NEWS, NICE guideline
	Peripheral oxygen saturation	IntelliVue MP2/ X2	%	NEWS, NICE guideline
	Mental status	GP assessment	normal/altered	qSOFA, NEWS, NICE guideline
	Rapid illness progression in last 24h	GP assessment	yes/no	NICE guideline
	(History of) rigors in last 24h	GP assessment	yes/no	NTS[16]
Blood test	C-reactive protein (CRP)	Siemens, ADVIA Chemistry XPT	mg/l	
	Lactate	StatStrip Xpress	mmol/l	
	Procalcitonin (PCT)	Siemens, ADVIA Centaur XPT	ng/ml	

Outcome measures

The primary outcome measure is sepsis within 72 hours after inclusion. This will be determined by an expert panel using the Sepsis-3 criteria.[1] The operational definition of sepsis is the presence of infection and a SOFA score (Table 2) of at least two above the baseline (which can be assumed to be zero in patients not known to have preexisting organ dysfunction).To limit the workload for the experts, we will appoint three expert panels, each comprising a GP, an emergency physician, and an internist(-intensivist). Each case will be assessed by one panel. All relevant information from medical records from the GP and the hospital when applicable will be presented to the panel (see Additional file 1). If there is no consensus on the primary outcome, the case will be discussed in a face-to-face consensus meeting with all three experts to determine the final outcome. Interobserver agreement between the three panels will be assessed in a selection of 10% of the cases that will be assessed by all panels. Besides the dichotomous primary outcome "sepsis within 72 hours", the likelihood of sepsis will be assigned a numerical score between 0 and 10. This gives information on remaining uncertainty regarding sepsis classification, providing insight in the degree of bias that may be introduced when calculating diagnostic accuracy measures using dichotomous sepsis classification.[20] Furthermore, the need for hospital treatment is scored between 0 and 10 by the expert panel as a secondary outcome. An average score above 5 will be regarded as a patient that should best be referred to the hospital immediately by the GP and a score ≤ 5 as a patient that does not have to be referred immediately.

Other outcome measures are hospitalisation (length of stay and type of care: ICU or regular ward), maximum SOFA score in the first 72 hours, 30 day all-cause mortality, final diagnosis, and medical costs.

Table 2. Sequential Organ Failure Assessment (SOFA) score[a]

	Score			
System	**1**	**2**	**3**	**4**
Respiration				
PaO_2/FiO_2, mmHg	300-440	> 440	<200 with respiratory support	< 100 with respiratory support
Coagulation				
Platelets, $x10^3/\mu L$	<150	<100	<50	<20
Liver				
Bilirubin, µmol/L	20-32	33-101	102-204	>204
Cardiovascular				
Hypotension	MAP < 70 mmHg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system				
Glasgow Coma Score	13-14	10-12	6-9	<6
Renal				
Creatinine, µmol/L	110-170	171-299	300-440	> 440
Urine output, mL/d			<500	<200

[a] Adapted from Vincent et al.[21]
[b] Adrenergic agents administered for at least one hour (doses given in µg/kg/min).
PaO_2, partial pressure of arterial oxygen. FiO_2, fraction of inspired oxygen. MAP, mean arterial pressure.

Study procedures

Study period

The inclusion period is from June 2018 until April 2020. If in April 2020 the required sample size is not reached, patients will continued to be recruited until the minimum required number of events has been reached. Follow-up of the patients is 30 days.

Procedure during home visit

All patients receive usual care. Patients will be screened for eligibility during home visits by the attending GP of the GP cooperative. Verbal informed consent is obtained from the patient or his legal representative. The GP is (routinely) accompanied by a chauffeur during the home visit. The chauffeurs are used to practically assist the GP during the visit. Portable monitors (Philips intelliVue MP2 or X2) will be available to record peripheral oxygen saturation, automated blood pressure and heart- and respiratory rate by three lead electrodes on the chest.

The GP records the assessment of the candidate predictors in a case report form. In addition, the GP records if he/she has a gut feeling that "something is wrong" and provides the likelihood of presence of sepsis at inclusion on a scale from 0 to 10.

All study materials will be taken to the patient's home in a study bag. The venous samples will be collected by either the GP or an on-call laboratory assistant or nurse within one hour after inclusion, with a maximum of eight hours. Written informed consent is obtained prior to the collection of the blood samples. In case the patient is referred to the hospital and the blood samples are not collected by the GP, the study bag will be transported with the patient to the ED. Subsequently, the laboratory assistant on call will visit the patient in the hospital and collect the blood samples. Three blood tubes will be collected: 10 ml for serum, 10 ml for EDTA plasma and a 2 ml heparin tube. Lactate will be measured immediately afterwards from a single drop of blood taken from the heparin tube, using the StatStrip Xpress (Nova Biomedical) point-of-care test. The remaining blood samples will be taken to the hospital laboratory and divided into six samples of serum and six samples of EDTA plasma. The aliquots will be temporarily stored at the local laboratory at < -70°C. Two samples (1 ml serum and 1 ml EDTA plasma) will be transported to the Jeroen Bosch Hospital for CRP and PCT analyses, and the remaining samples (5x 0.5 ml serum and 5x 0.5 ml EDTA plasma) will be stored for 15 years at < -80°C at the UMC Utrecht for potential future testing.

Training and remuneration of personnel

Chauffeurs of the GP cooperatives are trained in using portable monitors for vital sign measurement and other study procedures. At the GP cooperative in Ede the chauffeurs will also be trained in the measurement of POC-lactate, as GPs will collect the venous blood samples themselves occasionally. The laboratory assistants and nurses who will be on call for the collection of the blood samples will also be trained in the POC–lactate measurement and other study procedures including the obtaining of written informed consent. Attending GPs are informed by an information letter by mail and hard copy at the GP cooperative. Leaflets with a summary of the study procedures will also be available.

Follow-up

The total follow-up time is 30 days (see Figure 1). Patients will be asked to complete the EQ5D-5L questionnaire[22] at the end of follow-up to report on their health status: (1) at the day of completion of the questionnaire; (2) before the onset of the recent disease episode (i.e. their health status of at least one month ago); and (3) for the worst day they remember from their recent disease episode. Furthermore, patients will be asked to report on consumption of medical resources during the 30-day follow-up period. Productivity losses are not considered, as most patients are elderly and not doing paid work. In case of no response to the questionnaire after one week, patients are contacted once by telephone as a reminder.

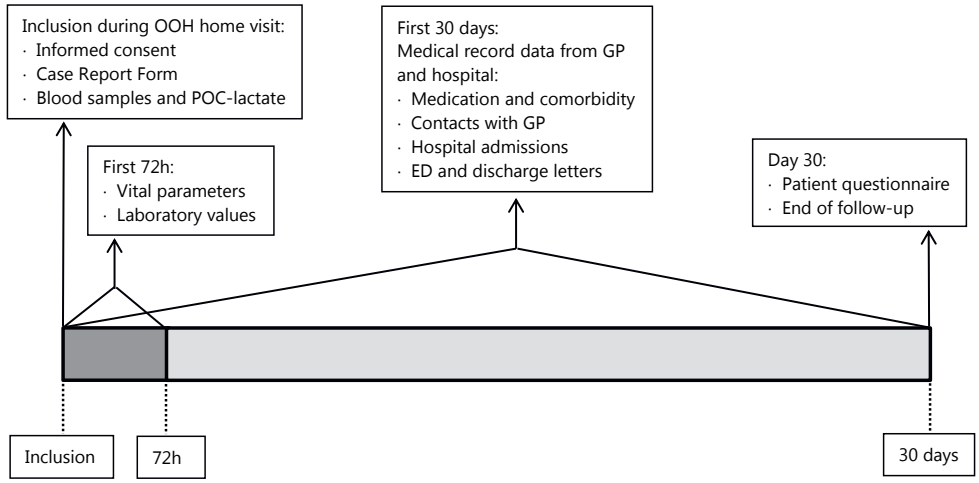

Figure 1. Summary of study procedures

Data-extraction

Relevant medical information will be obtained from the patient's (regular) GP, the GP cooperative, and the hospital. Medication use and comorbidities before inclusion are retrieved from GP electronic records, as well as information on any subsequent contacts. The medical record of the assessment at the time of inclusion is retrieved from the GP cooperative. The following data from the electronic medical record of the hospital will be collected: full reports from ED and hospital discharge; date and time of ED visit, hospital admittance and discharge (including type of ward); vital signs, EMV score, leucocyte count, thrombocyte count, creatinine, bilirubin, CRP and lactate measured in the first 72 hours after inclusion; cultures taken in the first 72 hours after inclusion; radiodiagnostic procedures in the first seven days after inclusion; antibiotic prescriptions during hospitalisation; intravenous volume therapy in the first 72 hours (defined as more than 1.5 litres of fluids in 24 hours).

Sample size

In total, 12 candidate predictors are chosen for the development of the prediction model (table 1). Using the rule of thumb of 10 events per variable,[23] we need 120 patients reaching the primary outcome "sepsis within 72 hours after inclusion" in the final dataset. Prior to the start, the prevalence of sepsis based on previous research and literature was estimated to be around 12%. However, preliminary data analysis from the patients included in the study so far, indicates the prevalence of sepsis in the study cohort to be around 30-40%. After the first 100 cases will be assessed by the expert panel, we will determine the final target sample size.

Statistical analyses

Descriptive statistics

We will use a combination of IBM SPSS Statistics and R Statistical Software for all analyses. We will start with descriptive analyses on baseline characteristics (age, sex, comorbidities, vital sign measurements and other clinical features, blood tests results, baseline EQ5D-5L score), final diagnosis, hospital admission, ICU admission, length of stay, EQ5D-5L compared to baseline, and 30-day mortality. Results will be stratified based on whether patients do or do not meet the primary outcome sepsis.

Data cleaning

Range and distribution of all continuous variables will be graphically inspected, and any outliers (more than three standard deviations from the mean) will be discussed and corrected or removed in case of a data recording error. Any missing data on clinical features or blood tests, will be accounted for by applying multiple imputation techniques. Prediction model development and performance will be analysed using the imputed datasets.

Development of the prediction model

A multivariable penalized logistic regression model will be developed, based on the variables listed in Table 1, for predicting the primary outcome (sepsis within 72 hours after inclusion). We will use a two-stepped approach entering and selecting clinical features first, and blood tests second. In both steps the selection of predictors will be based on a stepwise backward selection, using change in Akaike information criterion (AIC) for selecting the preferred model.[24] The goal is to generate an efficient model by eliminating variables that contribute little to the model's performance, requiring only measurement of the most important variables in clinical practice.

Continuous predictors in the model will be assessed for linear relationship with the logit of the primary outcome. Transformation of the data and splines will be used if deemed appropriate based on distribution of the data.

The resulting prediction model that will be the most accurate prediction model, by making use of continuous measurements of predictors and reflecting non-linear relationships by transformations or splines (optimal model). To make this model workable in daily clinical practice without electronic aids, a second model will be derived (clinical practice model) by categorising or stratifying predictors. Cut-offs for categorisation will be based on a combination of known and commonly used thresholds in clinical practice and optimal thresholds based on the data. This model simplification is likely to induce a performance drop with regard to the full model, which will be assessed during the analysis.

The above procedures will result in the following three models: 1) Optimal model with clinical features only; 2) Optimal model with clinical features and blood tests; 3) Simplified model (with clinical features and blood tests).

Performance of the prediction model

The performance of all three models will be determined based on their discrimination and calibration. Discrimination will be evaluated based on the area under the receiver-operator characteristic (AUROC). Calibration will be assessed by plotting observed and expected probabilities and inspecting this plot graphically. Measures of calibration will include calibration slope, calibration in the large, observed/expected (O/E) ratio, and the Brier score.[25] We will perform internal validation for all three models by using a bootstrap simulation. The resulting distribution will reflect optimism and the degree of overfitting.[26]

The SIRS criteria, NEWS score, and qSOFA score will be calculated for all individuals in the TeSD-IT study. Diagnostic performance of the existing models will be determined by calculating the same measures of discrimination and calibration as described in the sections above, and comparing these with the three models that were developed.

To assess the added value of the prediction models on top of usual care, other outcomes than sepsis will be considered. This is crucial for gaining insight in the net benefit of using the clinical prediction rule in daily practice. For example, when a patient is predicted as non-sepsis by the model, but the patient was referred by the GP, improvement compared to care as usual is only the case if hospital treatment was not needed according to the expert panel. To assess the added value, the proportion of reclassifications within the original contingency tables will be presented for the following outcomes: 1) the gut feeling of the visiting GP that "something is wrong" 2) the assessment of the visiting GP for the likelihood of sepsis, and 3) the decision of the visiting GP whether or not to refer the patient to the hospital.

Cost-effectiveness and budget impact analysis

We will measure costs from a societal perspective, including health care costs and patient costs within and outside the hospital (see additional file 2 for detailed information). Productivity costs will be ignored as the average age of patients participating will exceed the age of pensioning in the Netherlands. The patient questionnaire as well as follow-up data from hospital and GP medical records will be used for the calculation of total and per patient costs. The EQ5D-5L scores retrieved from the questionnaire will be used to calculate QALYs. Our patient outcome analysis will generate QALYs for different health states that will be used in health economic modelling, such as a complicated sepsis case (including ICU admission), hospital admittance for a suspicion of sepsis, and an infectious disease episode without hospital admission. Different scenarios with different levels of implementation of POCT for sepsis in general practice will be analysed and compared to standard of care: 100% use of the best performing testing strategy; 70%, 30% and 0% use of POCT for suspicion of sepsis (the latter representing usual care). The budget impact will be assessed using the health economic model that will be built for the economic evaluation and results will be analysed in a probabilistic way.

Discussion

The TeSD-IT study is a diagnostic and prognostic study, designed for the development of a clinical prediction rule for the early recognition of sepsis in primary care. A limited number of nine clinical parameters and three blood tests were selected. This will enable us to construct the model using multivariable logistic regression techniques with 120 events included in the dataset. We realise the validity of rule of thumb of 10 event per variable is debated.[27] However, using an alternative sample size calculation suggested by van Smeden,[28] results in a similar identical sample size of about 350 patients in case of 12 variables, an outcome rate of 0.35 and rMPSE set at 0.09. We have chosen to recruit patients in the setting of out-of-hours home visits performed by a GP. In this setting GPs frequently encounter seriously ill patients in whom they instantly have to decide whether or not to refer the patient (immediately) to the hospital. A methodological advantage is that the required sample size is substantially lower than in other primary care settings with a lower incidence of sepsis. However, external validation in other settings and populations will be needed before implementing the clinical prediction rule more broadly.

The diagnosis of sepsis is not straightforward. In 2016, new consensus definitions for sepsis were published, which we try to implement as well as possible. As both the presence of infection as well as organ failure can be equivocal, we will use expert panels to determine the final outcome. The outcome should be clinically relevant for the GP. The rationale of the timeframe of 72 hours is that patients who are found septic within this period after GP assessment would likely benefit from immediate hospital referral. Not all patients with organ failure need hospital treatment to recover, and not all patients with severe infections that are treated with intravenous antibiotic therapy have signs of organ failure. However, we believe the diagnosis of sepsis based on the Sepsis-3 definitions is the most relevant endpoint for GPs to differentiate between patients who are likely to benefit from immediate hospital treatment and patients who might be treated at home successfully. The expert panel will also rate the need for hospital treatment for every patient, regardless of the diagnosis. This will enable us to evaluate the effect of the new clinical prediction rule on medically unnecessary referrals.

The expert panels will be instructed to use the SOFA score (increase, due to infection, of ≥2 points from baseline) to define the primary outcome "sepsis within 72 hours after inclusion". This is consistent with the Sepsis-3 consensus definition and leads to an objective and reproducible endpoint in absence of a gold standard. However, this approach introduces the risk of incorporation bias. Parameters included in the SOFA score are more likely to be predictive of sepsis in our model. However, the blood tests (CRP, lactate and procalcitonin) are not included in the SOFA score, which limits the risk of incorporation bias for these tests. Furthermore, vital signs measured in the first 72 hours will be used to calculate the SOFA score and not only at the time of inclusion.

Patients will receive a questionnaire at day 30 measuring EQ5D-5L. The results may be biased due to selective response and poor recall due to sepsis- or age-related cognitive impairment. Imputation of the missing answers on the questionnaires will reduce this form of bias as much as possible. Furthermore, the development of the clinical prediction rule

is not affected, as the patient questionnaires will only be used for the cost-effectiveness analyses.

To compare the performance of the new clinical prediction rule with usual care, not only the decision to refer the patient to the ED, but also the assessment of the GP of the likelihood of sepsis on a scale from 0-10 and the presence of a "gut-feeling something is wrong" will be used. We will examine if the prediction rule will outperform those assessments of the GP in order to likely improve the usual care.

Only three candidate blood tests were selected for the development of the prediction rule. Various other biomarkers have promising diagnostic and/or prognostic properties in patients with suspected sepsis.[29-30] At the start of this study, sufficient evidence of the additional diagnostic and/or prognostic value above lactate, CRP and PCT was lacking. However, sufficient blood samples will be stored for retrospective testing of multiple additional biomarkers.

Although to our best knowledge no clinical prediction rules for sepsis in primary care were previously developed, several sepsis screening tools were published for the ambulance setting.[31] However, none of those have adequate inclusion criteria, data collection and clinically relevant endpoints for use in the primary care setting.

Funding
The study was financially supported by ZonMw, grant number 843001811. In kind support for material costs were provided by ThermoFischer (procalcitonin analyses), Nova Biomedical (POC lactate measurement) and Philips (portable monitoring devices). Neither funding party had a role in the design of this study, interpretation of the data, or decision to submit results.

Ethics approval and consent to participate
The study was approved by the METC Utrecht, and is registered under number 18/169. Written informed consent will be obtained before the collection of blood samples and after initial verbal informed consent. In mentally incapacitated patients, consent will be provided by the legal representative. In case written informed consent is not feasible prior to the collection of blood samples due to an acute life-threatening condition, the written consent will be asked as soon as possible afterwards. All collected data - including the blood results - will be stored without identifying information under a study number. Personal details of the patient which are needed for the data collection will be store in an secured online environment until the data collection is completed. The data and excess blood samples will be stored for 15 years afterwards. Additional test of stored blood samples will only be done in patients who opted in in the written informed consent.

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Additional file 1

Expert panel assessment
All members of the expert panel use a secure online tool (Sharepoint) for the assessment of the cases. All relevant medical information from the hospital and GP is presented in this online tool without any personal information of the patients or other persons such as healthcare providers (pseudo-anonymised).

The experts have to answer 5 questions:

1. Is an infection the cause of the acute complaints the patients presented at inclusion? (Yes/No)

2. Is there an pre-existing condition causing a baseline SOFA-score >0?

3. Does the patient meet the criteria for sepsis within 72 hours of inclusion? (Yes/No)

4. What is the likelihood of sepsis on a scale from 0-10?

5. How certain are you of the need for hospital treatment on a scale from 0-10?

The information presented to the experts is the following:

- Letter from the GP visits during with the patient was included in the study.
- Discharge letters form ED visits within 72 hours.
- Discharge letters form hospitalisation starting within 72 hours.
- Medical record from GP contacts in the first 72 hours.
- Microbiology reports from cultures taken in the first 72 hours.
- Radiology reports of all instigations in the first 7days after inclusion.
- Antibiotic treatment during hospitalisation.
- All relevant vital signs and laboratory values of the first 72 hours. The most abnormal value for every calendar day is presented in a table as shown below. The first calendar day starts at the time of inclusion and the fourth calendar day ends exactly 72 hours after inclusion.

	Day 1		Day 2		Day 3		Day 4	
Parameter SOFA-score	Value	SOFA	Value	SOFA	Value	SOFA	Value	SOFA
Mental status, EMV	12	2	15	0	15	0	15	0
Blood pressure, mmHg	100/50	1	120/61	0	117/53	0	138/75	0
Saturation (Supplemental O2)	96%,3 Ltr	2	93%,0 Ltr	1	95%,0 Ltr	1	95%,0 Ltr	1
Creatinine, µmol/L	67	0	57	0		0	66	0
Thrombocytes, × 10^9/L	153	0						
Bilirubin, µmol/L	13	0						
SOFA-score total		**5**		**1**		**1**		**1**
Other parameters								
Temperature, °C	40.1		39.6		38.6		37.8	
Hart rate, /min	60		71		81		88	
Respiratory rate, /min	25		24		20		20	
Leukocytes, × 10^9/L	8.6							
CRP, mg/L	18		67		72		48	
Lactate, mmol/L	2.4							

All vital signs and laboratory values that can be digitally extracted from the electronic medical records are used, as well as the vital signs recorded on the case report form at inclusion. Analyses of the blood samples collected for the study are not used to inform the experts.

The experts are instructed to use the Sepsis-3 criteria for the determination of the primary outcome "sepsis within 72 hours". This means that sepsis is present if an infection is the cause of the complaints in combination with an increase of the SOFA score of ≥ 2 from baseline, within 72 hours. The experts are instructed to take pre-existing conditions into account to estimate what the baseline SOFA score of the patient most likely was.

Handling of missing SOFA points:
Missing SOFA points are only imputed using direct information of the missing parameter. In the absence of direct information, the missing parameters are considered normal.

In case blood results needed for the calculation of SOFA points (platelets, creatinine and/or bilirubin) are not available on one or more of the four calendar days in the first 72 hours, no points are given to that part of the SOFA score. The only exception is in case the missing value is between two days on which the blood values are available. In that case the blood result is imputed with the assumption there was a linear trend between the two measured values. For example, if on Day 1 the creatinine is 130 and on Day 3 100, the imputed value for Day 2 is 115 (Day 4 is not imputed). If the creatinine is 130 on Day 1 and 100 on Day 4, a value of 120 is imputed on Day 2 and 110 on Day 3. Only blood results from the hospital within the first 72 hours are used.

Peripheral oxygen saturation (SpO2) and supplemented oxygen are used to estimate respectively the PaO2 and FiO2 for calculation of the PaO2/FiO2 ratio. Results from blood gas analyses are (outside the ICU) are not taken into account as the amount of oxygen supplied at the time of blood collection is unknown. For the estimation of the PaO2 and FiO2, the following conversion tables are used:

SpO_2 (%)	PaO_2 (mmHg)
≤80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145
100	200

O_2 flow (l/min)	FiO_2 (%)
0	21
1	24
2	28
3	32
4	36
5	40
≥6	44

Mean arterial blood pressure (MAP) is calculated using the formula: (2 x diastolic blood pressure + systolic blood pressure)/3.

The AVPU scale (an acronym for "alert, verbal, pain, unresponsive") is used to impute the Glasgow Coma Score. For "A" a score of 15 is imputed, for "V" a score of 12, for "P" a score of 8 and for "U" a Glasgow Coma Score of 3. In case the AVPU scale is extended with "D" for "delirium", a score of 14 is imputed. In case on the case report form the mental status is recorded as "altered", a Glasgow Coma Score of 14 is imputed.

In case patients were admitted in the ICU on a specific day within 72 hours of inclusion, SOFA points are obtained from the electronic medical records from the ICU.

Additional file 2

Cost-effectiveness analysis

Cost analysis

We propose to measure costs from a societal perspective, including health care costs and patient costs. Productivity costs will be ignored in this study as the average age of patients participating will exceed the age of pensioning in the Netherlands. All costs during follow up will be monitored on an individual basis. Main categories of health care use will be retrieved from both hospital and GP records. In addition, patients will be asked to complete a questionnaire after the follow-up period of 30 days to monitor all health care use that could not be observed from medical records. This mainly relates to professional home care, physical therapy and use of care from relatives. Furthermore, we will ask for type and amount of out-of-pocket payments, e.g. for travel costs and over the counter drugs. We anticipate that most cost categories will have standard unit prices available from the Dutch guidelines on costing research. For the different POCT, we will estimate costs using a bottom up costing approach, including handling of costs of the device (analyser) as proposed in the Dutch guidelines for costing research. Our cost analysis will generate costs for different health states that will be used in health economic modelling, such as costs of a complicated sepsis case (including ICU admission), costs of hospital admittance for a suspicion of sepsis and costs for an infectious disease episode without hospital admission. Patient outcome analysis Following earlier correct diagnosis of sepsis and the avoidance of unnecessary hospital admissions, quality of life will possibly be better with improved diagnosis of sepsis. However, the measurement of quality of life in patients with severe conditions is hampered by their sometimes devastating health status. Analogous to procedures that were followed in hospitalized pneumonia patients,1 we propose to measure quality of life with a so-called then-test once patients are recovered. At the end of follow-up at 30 days, patients will be asked to complete the EQ5D-5L questionnaire thrice. First, for their current health status at the day of completion of questionnaire. Second, for their health status before onset of the recent disease episode (i.e. their health status of 1 month ago) and third, for the worst day they remember from their recent disease episode. This enables us to calculate QALY losses over this 1 month period. The EQ5D-5L version enables the expression of health status in a single index value for quality of life, necessary for QALY calculations. We will calculate index values according to the algorithm published by Versteegh et al.2 Our patient outcome analysis will generate QALYs for different health states that will be used in health economic modelling, such as a complicated sepsis case (including ICU admission), hospital admittance for a suspicion of sepsis, and an infectious disease episode without hospital admission.

Budget impact analysis (BIA): general considerations

The design of the budget impact analysis (BIA) will be a study of different scenarios of either or not introducing POCT for the diagnosis of sepsis in general practice. The BIA will be based on data collected alongside this diagnostic study. It will allow estimation of the financial consequences of introduction of POCT measurements in general practice from the perspective of different stakeholders involved. All cost items needed for the BIA will be derived directly from our diagnostic study, the valuation of those items depends on the perspective taken for the budget impact analysis. The aim of the BIA is to study costs

of different scenarios for the nationwide introduction of POCT measurements in general practice to diagnose sepsis in severely ill elderly. We will perform budget impact analyses from two different perspectives. The perspectives to be included in the BIA are:

1. The perspective from the Health care budgetary framework (net-BKZ or government perspective): this will only include direct medical costs reimbursed by basic health insurance coverage. In our study this will include the analysis of the costs of different POCT, of GPs (both regular consultations and out-of-hours consultations), the costs of drugs, of referral to the hospital, the costs of professional homecare and of physical therapy. In the net BKZ perspective only the changes in costs within the basic package of care will be taken into account, including substitution effects when usual care shifts as a result from improved diagnosis of sepsis in elderly. At present, POCT for sepsis are not yet reimbursed for. Positive findings from our diagnostic study, once confirmed in prospective studies, would open a case for reimbursement of POCT diagnostics in this target group, with possible shifts in patient care following from improved diagnosis. Results for the net BKZ perspective will be expressed as potential cost-savings within the health care budget of the ministry of VWS. Results from the net BKZ perspective will be expressed in M€ (millions of Euros).

2. The perspective of health care insurance companies, including all reimbursed health care. Results for the health care insurance companies perspective will be expressed in M€ (millions of Euros). As all sepsis related health care use is most likely also covered in the net BKZ perspective, the cost items to be valued will mainly be similar to those in the net BKZ perspective. However, valuation of costs is different in both perspectives (see below). Different scenarios with different levels of implementation of POCT for sepsis in general practice will be analysed and compared: 100 % use of the best performing testing strategy; 70%, 30% and 0 % use of POCT for suspicion of sepsis (the latter representing usual care). Moreover, the scenario will be analysed that POCT is outsourced by laboratories to GPs, which alters directions and magnitude of costs and reimbursement. Considering that more POC tests are becoming available and popular lately (D-dimer for deep venous thrombosis for example) and that insurance companies will probably require more strict protocols for measurement, such cooperations between laboratories and GPs are becoming more common.

Sensitivity analyses will include variances in costs of POCT and of prevalence of suspicion of sepsis in elderly. The range of the effects to be included in the sensitivity analyses will depend on the results of our proposed trial. As episodes of sepsis usually do not exceed a 30-day period, the time horizon for the BIA will be four years. BIA results will be reported separately for each year within the time horizon and indexation will be applied. The budget impact will be assessed using the health economic model that will be built for the economic evaluation and results will be analysed in a probabilistic way.

Budget impact analysis: cost analysis

Different perspectives for the BIA merit different valuation of resource use. The total number of patients eligible for the intervention will be estimated based on data collected in this diagnostic study and extrapolation to national level. Resource utilisation is calculated by multiplying the number of eligible patients with the resource utilisation patterns obtained from our data collection. Different prices will be used to value resource use depending on the perspective of the analysis: actual NZA tariffs for the government perspective, and average tariffs NZA for the insurer perspective. Both resource use and annual costs will be presented over a 4 year period for all perspectives. Different implementation scenarios will be evaluated (implementation rate will be varied between 0% and 100%). Aggregated and disaggregated (e.g. GP care, secondary care) total costs per year will be presented for the different perspectives and scenarios.

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CHAPTER 7

7

New clinical prediction model for early recognition of sepsis in adult primary care patients: a prospective diagnostic cohort study of development and external validation

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BJGP 2022

Abstract

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

Aim To develop and validate a sepsis prediction model for adult patients in primary care.

Design and setting This was a prospective cohort study in four out-of-hours primary care services in the Netherlands, conducted between June 2018 and March 2020.

Method Adult patients who were acutely and received home visits were included. A total of nine clinical variables were selected as 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 cut-off points of continuous variables was developed and externally validated in two emergency department populations.

Results A total of 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-ours population, a simple model can accurately predict sepsis in acutely ill adult patients using readily available clinical parameters.

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, primary care physicians (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 patients who are older or frail.

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. Immediate hospital referral is expected to improve outcome in these patients. This study investigated clinical signs, symptoms and biomarkers potentially available at the bedside.

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 (Ede, Den Bosch, Uden and Oss). The combined area covers roughly 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 published[15] 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, for example 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, for example 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

Based on other prediction models, sepsis guidelines and triage protocols,[11-13,16,17] nine clinical parameters were selected as candidate predictors. 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^{0}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] The operational definition of sepsis is the presence of infection and a SOFA score[20] of at least two points above the baseline. 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] were used to account for missing data. The regression coefficients and performance measures of the imputed datasets were pooled using Rubin's rules[23] and the total covariance matrix, respectively.

First, 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 the '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 cut-off points of vital signs used in NEWS were considered for the simplified model and the model with the highest C-statistic (equal to the area under the receiver operating curve) was chosen as the final model.

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 tenfold 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 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 observed-to-expected (O/E) ratio as a measure for mean calibration. 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, that is, SIRS, qSOFA, and NEWS, and to the likelihood of sepsis (on a scale from 0-10) according to GP on site. R (version4.0.5) package was used for the analyses.

Sensitivity analyses

Model performance for secondary outcomes was assessed to evaluate potential incorporation bias resulting from the use of the SOFA score (by the expert panel) as part of the sepsis definition, 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

Datasets from patients with suspected infections assessed in two EDs in the Netherlands were used to test the external validity of both the continuous and simplified model. 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 mean calibration and calibration slope. A more detailed description can be found in Supplementary Appendix 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% were 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. Of the 357 patients included in the study 12 (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 interrater reliability between members within the same panel, ranged between 0.57 and 0.76 (mean 0.68), 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.

Table 1. Patient characteristics, by sepsis diagnosis.

	Sepsis (n = 151)	No sepsis (n=206)
Demographics		
Age, median (IQR), y	80 (74-85)	79 (68-86)
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	63 (42)	59 (29)
Cerebrovascular accident	33 (22)	39 (19)
Malignancy	19 (13)	30 (15)
Chronic kidney disease	43 (28)	49 (24)
Dementia	25 (17)	18 (8.7)
Immunosuppressive use	6 (4.0)	7 (3.4)
Final diagnosis, No. (%)		
Respiratory tract infection	61 (40)	74 (36)
Urinary tract infection	45 (30)	47 (23)
Abdominal infection	12 (7.9)	7 (3.4)
Skin/soft tissue infection	11 (7.3)	17 (8.3)
Infection with unknown source	11 (7.3)	25 (12)
Other source of infection	11 (7.3)	8 (3.9)
Non-infectious diagnosis	-	28 (14)
Candidate predictors		
Tympanic temperature, mean (SD), ^{o}C	39.0 (0.7)	38.5 (1.0)

	Sepsis (n = 151)	No sepsis (n=206)
Systolic blood pressure[a], mean (SD), mmHg	135 (25)	139 (24)
Heart rate, mean (SD), beats/min	100 (20)	96 (20)
Respiratory rate[a], mean (SD), breaths/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 (34-145)	56 (20-114)
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 (26-65)	45 (15-65)
Secondary outcomes, No. (%)		
Hospital admission	134 (89)	76 (37)
Length of stay, median days (IQR)	5.2 (3.1-8.3)	4.5 (2.5-6.5)
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

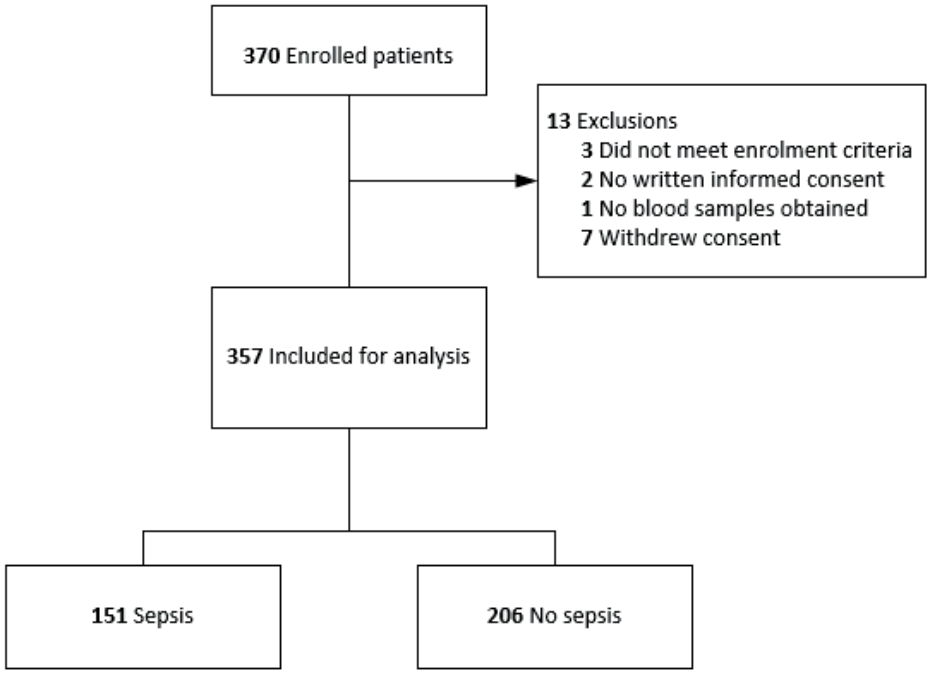


Figure 1. Patient flow diagram

Prediction model development

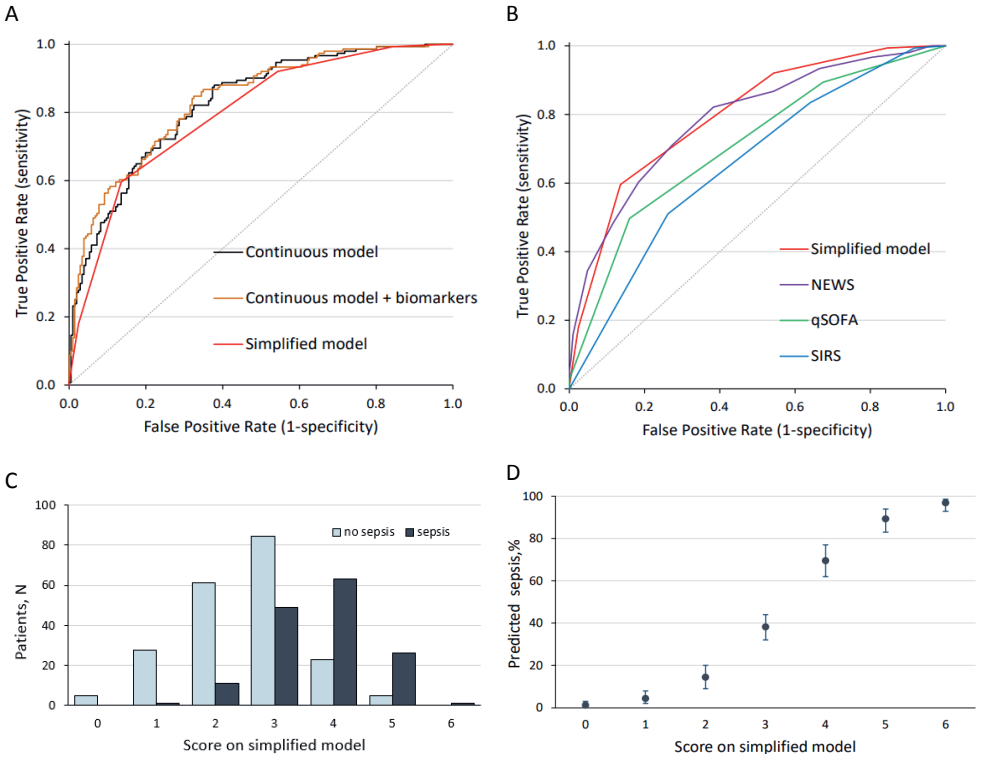
Of the nine clinical candidate predictors, six were included in the continuous model after backward selection: age, temperature, systolic blood pressure, respiratory rate, peripheral oxygen saturation and mental status. Age was included as a restricted cubic spline with three knots. After correction 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 cut-off 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 cut-off points for individual variables in the model, or grouping score categories, did not significantly improve performance.

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

Age > 65 years	1 point
Tympanic temperature >38 ^{0}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



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 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.

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).

Cut-off point	Sensitivity	Specificity	LR+	LR-	PPV	NPV
≥1 (n=352)	100 (98-100)	2.4 (0.8 to 5.6)	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.

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, that is, better than SIRS, qSOFA and NEWS.

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 breaths/min, heart rate >90 beats/min)

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).[27] 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, admission of intravenous fluids, and supplemental oxygen by ambulance personnel of patients with sepsis 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

To the authors' knowledge, 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. First, 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. Second, as some candidate predictors were also part of the

SOFA score, this may have resulted in incorporation bias. Therefore sensitivity analyses were performed, using stricter calculation of the SOFA score and alternative outcomes, that is, 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 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 NEWS. NEWS was initially developed for the early detection of clinical deterioration of adult patients admitted to the hospital.[34] Recent studies in the ED setting showed NEWS superior to SIRS and qSOFA to predict sepsis,[35,36] 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,[37] but NEWS was only performed in 30% and 63% of cases by GP support teams and ambulance personnel, respectively.[38]

Implications for research and practice

Though 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 sepsis outcome. 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 perform 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 GPs who are currently using the NEWS score is using a valid and useful model, as the present results showed. The simplified model presented here 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).

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Supplementary data

Methods S1. External validation

Dataset 1

Patients and setting

From the first dataset used for external validation, we used data from 440 adult patients prospectively included in 4 weeks (2017) at the emergency department of the Zuyderland Medical Centre, a large teaching hospital located in Heerlen, the Netherlands. Methods of the data collection were previously published by Latten *et al.* [Latten 2019). All adult patients (≥18 years) with suspected infection were included.

Outcome definition

Sepsis was defined as "severe sepsis" or "septic shock" according to the Sepsis-2 definitions [Levy 2003). This implies that at least 2 SIRS criteria and signs of organ failure are needed to meet the outcome of sepsis. This is in contrast to the development data where the Sepsis-3 definition was used. Also, the diagnosis of sepsis was at the time of ED assessment, compared to the 72 hours timeframe used in the development data.

Dataset 2

Study design

We performed a post-hoc analysis on selecting patients from a prospective observational database study of adult patients visiting the emergency department of the University Medical Center Groningen (UMCG), a tertiary medical centre. The Dutch Medical Research Involving Human Subjects Act is not applicable for this study, as ruled by the Institutional Review Board of the University Medical Center Groningen, and a waiver was granted (METc 2015/164). Written informed consent was obtained from all patients included in this study.

Population

Adult patients (≥18 years of age) visiting the emergency department of the UMCG) who presented with suspected infection (as determined by the treating physician upon initial contact) and/or fever (≥38°C) between 8:00 – 23:00 h between March 2016 till July 2020 were included by a trained medical student team. In total, 39,719 adult patients visited the ED for internal medicine, gastro-enterology or pulmonology. Of these, 1,838 were prospectively enrolled in the UMCG sepsis-database. In total, 8,388 could not be included due to a visit outside the research team's working hours (21%). Further, 29,493 patients were excluded because of lack of consent to participate, patients not meeting inclusion criteria, research staff was unavailable or occupied (n = 29,493, 75.25%). For this external validation of the prediction models for the primary care setting, we also excluded patients with organ- or bone marrow transplants (n= 417) and neutropenic patients (absolute neutrophil count< 1000 cells/μL) (n=81), as we do not propose to use the decision model in these patients.

Data collection

Collected data included demographic characteristics, vital parameters, clinical impression score of physician and nurse, laboratory measurements at admission, and hospitalisation. Patient characteristics consisted of age, sex, history of diabetes, COPD, chronic kidney disease, kidney transplantation, cardiovascular disease (defined as chronic heart failure and/or ischemic heart disease) and active cancer (defined as radiotherapy or chemotherapy treatment received up to two years before the current hospitalisation). Additionally, logistic data were collected, describing the referral, transport, number of patients in the waiting room, and ER. Data were collected from the electronic patient files, and in case the electronic patient file did not contain the necessary data, in addition, by interviewing patients and physicians.

Outcome definition

Sepsis was defined as a combination of an infection (final diagnosis) and an increase of 2 or more SOFA score points from baseline within 72 hours from ED arrival. SOFA score at baseline was assumed to be 0 unless patients had a history of COPD or chronic kidney disease. In the case of a history of COPD, 1 point was subtracted on the SOFA score, unless one of the measurements of the respiratory item of the SOFA score in the first 72 hours did not result in at least one SOFA score point.

Statistical analyses (Dataset 1 and 2)

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. In case supplemental oxygen was given in the ED, the peripheral oxygen saturation (SpO2) was lowered by five percentage points to estimate the SpO2 without supplemental oxygen. In both datasets only the Glasgow Coma Scale (GCS) was recorded a as measure of mental status, and consequently a score below the maxima score of 15 was used as the definition for "altered mental status". Multiple imputations using the Multivariate Imputation by Chained Equations (MICE) procedure [vBuuren 2011, Perkins 2018) was used to account for missing data. Performance measures of these imputed datasets were pooled using Rubin's rules [Rubin 1989). Discrimination was evaluated using the area under the receiver-operating curve (C-statistic). Calibration was assessed by visual inspection of the calibration plots, O/E ratio as a measure for calibration in the large and Brier score. Percentiles of bootstrapped samples were used to calculate 95% confidence intervals (CI) for performance measures.

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Table S2. Inter-rater reliability of expert panels

Table S2a. Cohen's Kappa values between members of the same panel

	Panel 1 (n=159)	Panel 2 (n=138)	Panel 3 (n=140)
GP vs EP	0.69	0.71	0.67
EP vs INT	0.66	0.74	0.57
INT vs GP	0.69	0.76	0.63

Table S2b. Cohen's Kappa values between GPs of different panels

	GP panel 1 (n=40)	GP panel 2 (n=40)	GP panel 3 (n=40)
GP panel 1	1	0.55	0.60
GP panel 2	0.55	1	0.85
GP panel 3	0.60	0.85	1

Table S2c. Cohen's Kappa values between EM physicians (EPs) of different panels

	EP panel 1 (n=40)	EP panel 2 (n=40)	EP panel 3 (n=40)
EP panel 1	1	0.64	0.54
EP panel 2	0.64	1	0.58
EP panel 3	0.54	0.58	1

Table S2d. Cohen's Kappa values between intensivist /acute internists of different panels

	INT panel 1 (n=40)	INT panel 2 (n=40)	INT panel 3 (n=40)
INT panel 1	1	0.74	0.74
INT panel 2	0.74	1	0.57
INT panel 3	0.74	0.57	1

Table S2e. Cohen's Kappa values between the different panels

	Panel 1 (n=40)	Panel 2 (n=40)	Panel 3 (n=40)
Panel 1	1	0.95	0.74
Panel 2	0.95	1	0.69
Panel 3	0.74	0.69	1

GP, general practitioner; EP, emergency physician; INT, intensivist /acute internist

Table S3a. Univariable and multivariable regression analyses of all candidate predictors in the development data (n=357)

	Univariable analysis		Multivariable analysis	
Variable	**Odds (95% CI)**	**P-value**	**Odds (95% CI)**	**P-value**
Age, per year	1.03 (1.01 -1.05)	0.002	1.03 (1.01-1.06)	0.01
Tympanic temperature, per °C	2.00 (1.56 -2.68)	<0.001	2.41 (1.65-3.52)	<0.001
Syst. blood pressure, per mmHg	0.99 (0.99 -1.00)	0.19	0.99 (0.98-1.00)	0.081
Heart rate, per beat/min	1.01 (1.00 -1.02)	0.068	1.00 (0.99-1.02)	0.74
Respiratory rate, per breath/min	1.09 (1.05 -1.12)	<0.001	1.02 (0.98-1.06)	0.35
Peripheral oxygen saturation, per %	0.85 (0.80 -0.91)	<0.001	0.87 (0.81-0.94)	<0.001
Altered mental status (yes/no)	4.02 (2.55 -6.36)	<0.001	4.06 (2.35-7.02)	<0.001
Rigors (yes/no)	1.32 (0.85 -2.05)	0.21	0.97 (0.54-1.73)	0.92
Rapid illness progression (yes/no)	2.28 (1.34 -3.86)	0.002	1.32 (0.69-2.51)	0.40
Lactate, per mmol/L	1.81 (1.31 -2.50)	<0.001	1.52 (1.01-2.27)	0.043
C-reactive protein, per mg/L	1.00 (1.00 -1.01)	0.001	1.00 (1.00-1.01)	0.22
Procalcitonin, per ng/mL	1.10 (1.03 -1.16)	0.002	1.06 (0.99-1.12)	0.081

CI, Confidence interval

Table S3b. Final variables included in the multivariable logistic regression model for predicting sepsis after backward selection.

Predictor	**Beta (SE)**	**Odds Ratio (95% CI)**	**p-value**
Intercept	-28.29 (7.97)		
Age, per year	0.10 (0.029)	1.1 (1.04-1.17)	<0.001
Age', per year[a]	-0.084(0.028)	0.9 (0.87-0.97)	0.002
Tympanic temperature, per ^{o}C	0.88 (0.177)	2.42 (1.71-3.42)	<0.001
Systolic blood pressure, per mmHg	-0.015 (0.005)	0.99 (0.98-1.00)	0.020
Respiratory rate, per breath/min	0.044 (0.020)	1.04 (1.00-1.09)	0.032
Peripheral oxygen saturation, per %	-0.13 (0.038)	0.87 (0.81-0.94)	<0.001
Altered mental status (yes/no)	1.43 (0.277)	4.18 (2.43-7.21)	<0.001

Abbreviations: SE, standard error; CI, confidence interval; SpO^2 Peripheral oxygen saturation
[a] Age is entered in the regression model as a cubic restricted spline with 3 knots, and therefore 2 regression coefficients for age are calculated.

Regression formula continuous model unadjusted for optimism

Linear Predictor = -28.29 + 0.10 *(Age) – $0.89*10^{-5}$ *pmax(Age-59.6, 0)^3 + 0.00026*pmax(Age-79.6, 0)^3 - 0.00017*pmax(Age-90.2, 0)^3 + 0.88*(Tympanic temperature) – 0.015 *(Systolic blood pressure) + 0.044* (Respiratory rate) - 0.13*(SpO^2) + 1.43 * (Altered mental status)

Regression formula continuous model adjusted for optimism (shrinkage factor 0.86)

Linear Predictor = -24.36 + 0.10 *(Age) – $0.86*10^{-5}$ *pmax(Age-59.6, 0)^3 + 0.00022*pmax(Age-79.6, 0)^3 - 0.00014*pmax(Age-90.2, 0)^3 + 0.76*(Tympanic temperature) – 0.013 *(Systolic blood pressure) + 0.038* (Respiratory rate) - 0.12*(SpO^2) + 1.23 * (Altered mental status)

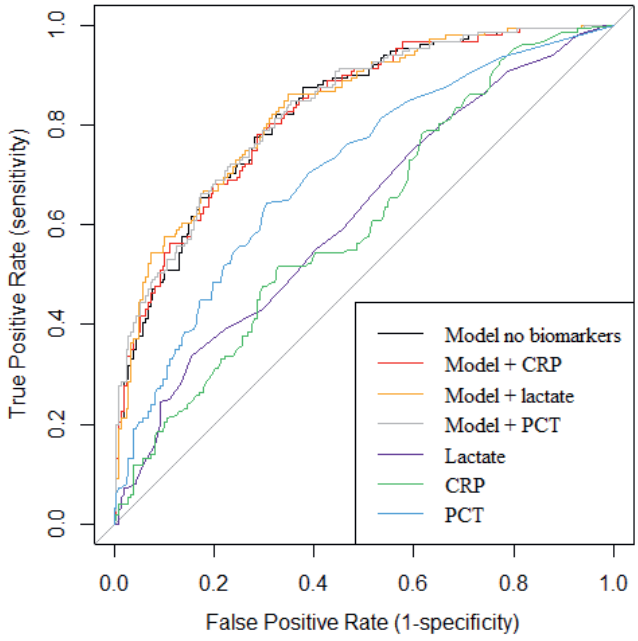


Figure S4. ROC curves of biomarkers
Receiver operating characteristic (ROC) curves of the biomarkers lactate, C-reactive protein (CRP) and procalcitonin (PCT), both univariable and in addition to clinical parameters in a multivariable regression model (continuous model).

Model	C-statistic (95% CI)[a]
Model no biomarkers	0.80 (0.75-0.84)
Model + CRP	0.80 (0.74-0.84)
Model + Lactate	0.80 (0.75-0.85)
Model + PCT	0.80 (0.75-0.84)
Lactate	0.62 (0.56-0.68)
CRP	0.61 (0.55-0.67)
PCT	0.69 (0.63-0.74)

[a]Corrected for optimism

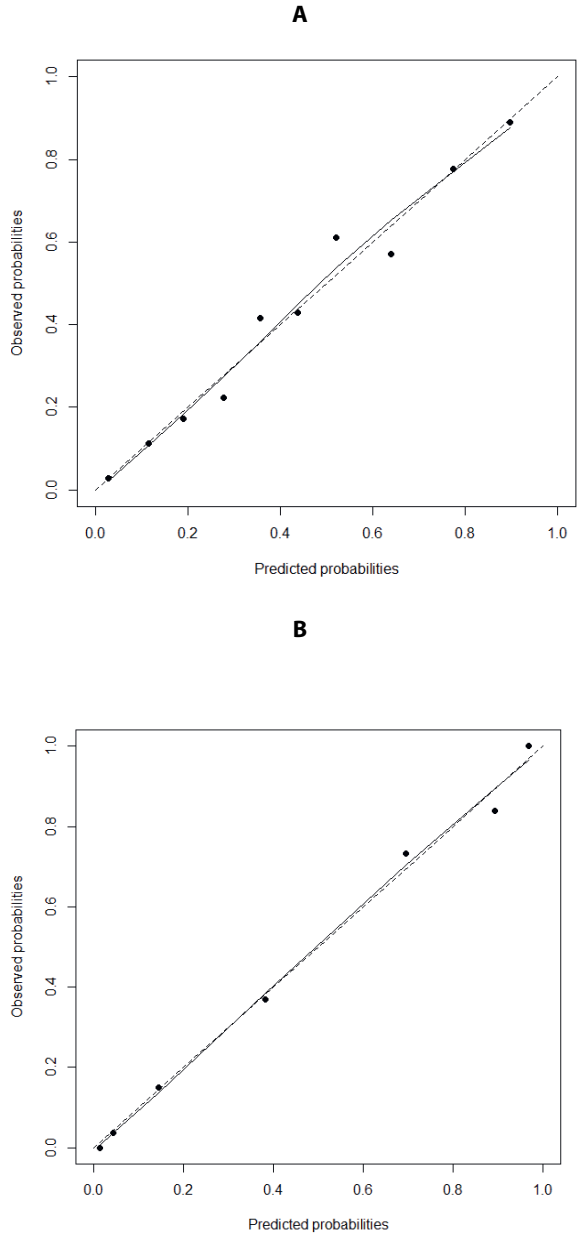


Figure S5. Calibration plot of the continuous model (A) and simplified model (B) in the development data (n= 357)

Table S6. Sensitivity analyses

Table S6a. Performance measures of the continuous model, simplified model and NEWS for the primary outcome "sepsis within 72 hours after inclusion" (151 outcomes).

Model	C-statistic (95% CI)	Brier score
Continuous model	0.80 (0.75-0.84)	0.181
Simplified model	0.80 (0.76-0.83)	0.175
NEWS	0.79 (0.75-0.83)	0.182

Table S6b. Sepsis, in combination with a need for hospital treatment, scored as 8/10 or above by the expert panel (115 outcomes).

Model	C-statistic (95% CI)	Brier score
Continuous model	0.78 (0.74 -0.82)	0.184
Simplified model	0.76 (0.72 -0.80)	0.188
NEWS	0.75 (0.70 -0.79)	0.194

Table S6c. Infection combined with a need for hospital treatment scored as 8/10 or above by the expert panel (134 outcomes).

Model	C-statistic (95% CI)	Brier score
Continuous model	0.73 (0.68 -0.77)	0.204
Simplified model	0.72 (0.68 -0.77)	0.206
NEWS	0.73 (0.68 -0.77)	0.202

Table S6d. Adverse outcome (ICU treatment <72 hours or 30-day mortality) (31 outcomes).

Model	C-statistic (95% CI)	Brier score
Continuous model	0.58 (0.51-0.66)	0.249
Simplified model	0.62 (0.53-0.69)	0.243
NEWS	0.62 (0.53-0.69)	0.239

Table S6e. Need for hospital treatment according to the expert panel (score >5/10) (199 outcomes).

Model	C-statistic (95% CI)	Brier score
Continuous model	0.74 (0.69 -0.78)	0.226
Simplified model	0.71 (0.67 -0.75)	0.236
NEWS	0.74 (0.70 -0.78)	0.223

Table S6f. Sepsis according to Sepsis-3 criteria, but restricted SOFA points for the respiratory tract. Saturation <92% is 1 SOFA point (118 outcomes).

Model	C-statistic (95% CI)	Brier score
Continuous model	0.80 (0.75 -0.83)	0.177
Simplified model	0.77 (0.73 -0.81)	0.184
NEWS	0.77 (0.73 -0.82)	0.184

Table S6g. Sepsis according to Sepsis-3 criteria, but recorded mental status at inclusion not taken into account in SOFA score (139 outcomes).

Model	C-statistic (95% CI)	Brier score
Continuous model	0.80 (0.76 -0.84)	0.178
Simplified model	0.77 (0.73 -0.81)	0.184
NEWS	0.77 (0.72 -0.80)	0.189

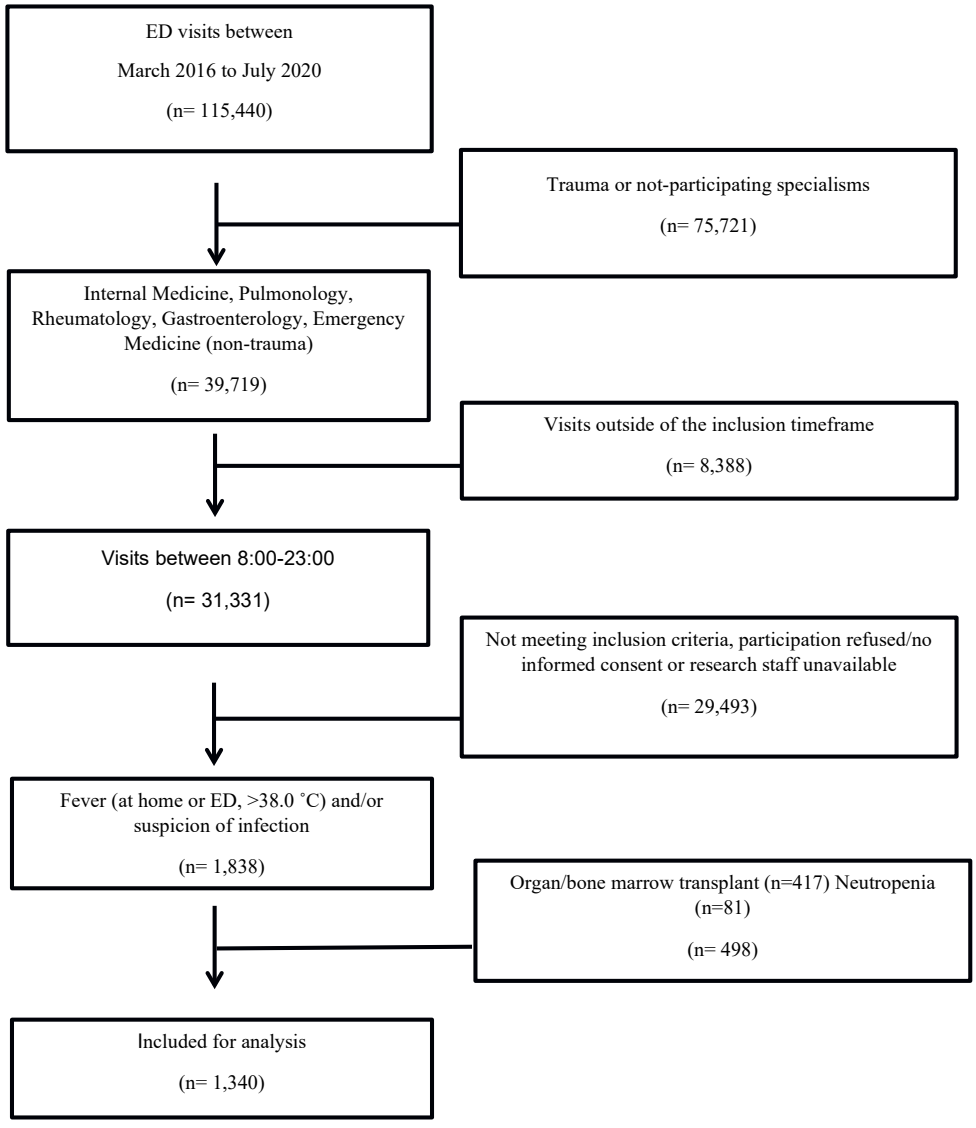


Figure S7. Flow chart of patient selection Dataset 2.

Table S8. Patient characteristics of validation Dataset 1 and Dataset 2

Characteristic	Dataset 1 (n=440)	Dataset 2 (n=1340)
Age, median (IQR), y	71 (57-81)	65 (51-73)
Sex, No. %		
Male	218 (49.5)	765 (57)
Female	222 (50.5)	575 (43)
Charlson Comorbidity Index, median (IQR)	2 (1-3)	2 (1-5)
Vital signs		
Body temperature, mean (SD), ^{o}C	37.7 (1.1)	37.5 (1.1)
Missing body temperature, No. (%)	8 (1.8)	49 (2.6)
Systolic blood pressure, mean (SD), mmHg	135 (27.7)	128 (21.9)
Missing systolic blood pressure, No. (%)	30 (6.8)	35 (2.6)
Heart rate, mean (SD), /min	97 (22.6)	95 (19.9)
Missing heart rate, No. (%)	11 (2.5)	33 (2.5)
Respiratory rate, mean (SD), /min	21 (6.0)	20 (5.8)
Missing respiratory rate, No. (%)	6 (1.4)	141 (10.5)
Peripheral oxygen saturation median (IQR), %	95 (92-97)	97 (95-98)
Missing peripheral oxygen saturation, No. (%)	14 (3.2)	35 (2.6)
Glasgow Coma Score <15, No. (%)	51 (11.6)	64 (4.8)
Missing Glasgow Coma Score	0 (0)	57 (4.3)
Outcomes, No. (%)		
Infection	429 (97.5)	1293 (96.5)
Sepsis	163 (37.0)	342 (25.5)
30-day mortality	10 (2.3)	52 (3.9)

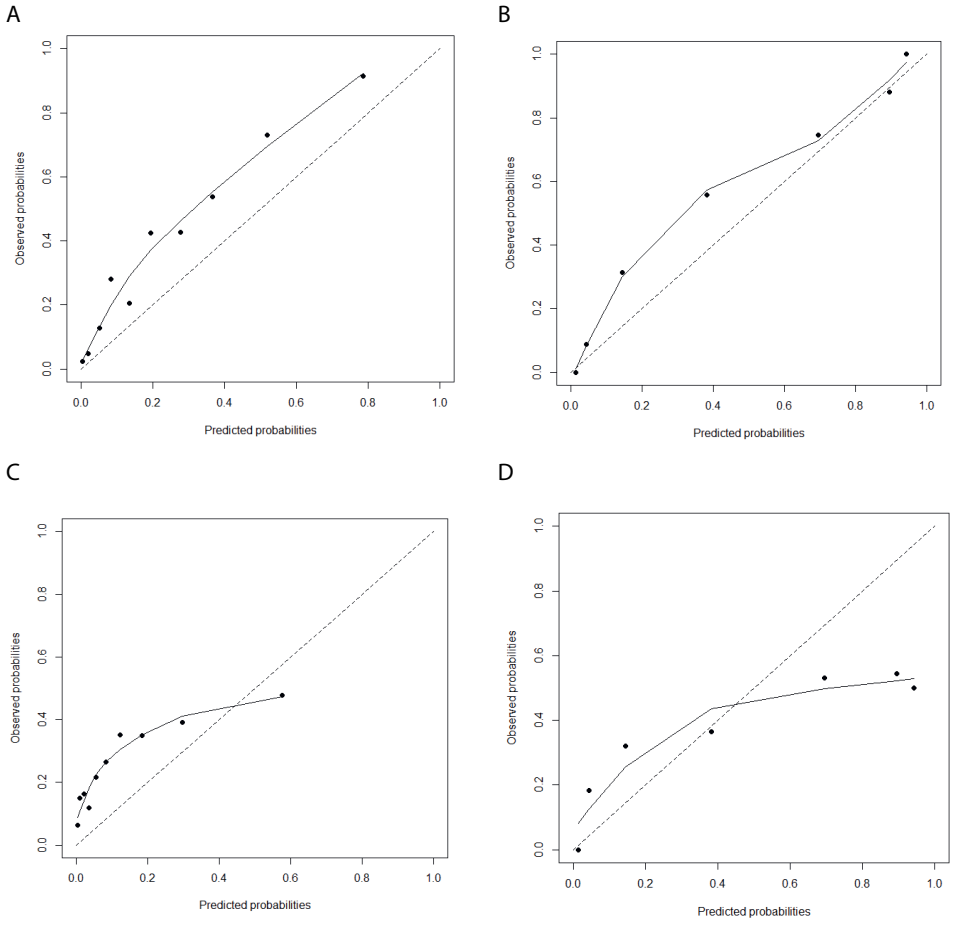


Figure S9. Calibration plots of external validations. A. Continuous model in Dataset 1 B. Simplified model in Dataset 1 C. Continuous model in Dataset 2 D. Simplified model in Dataset 2

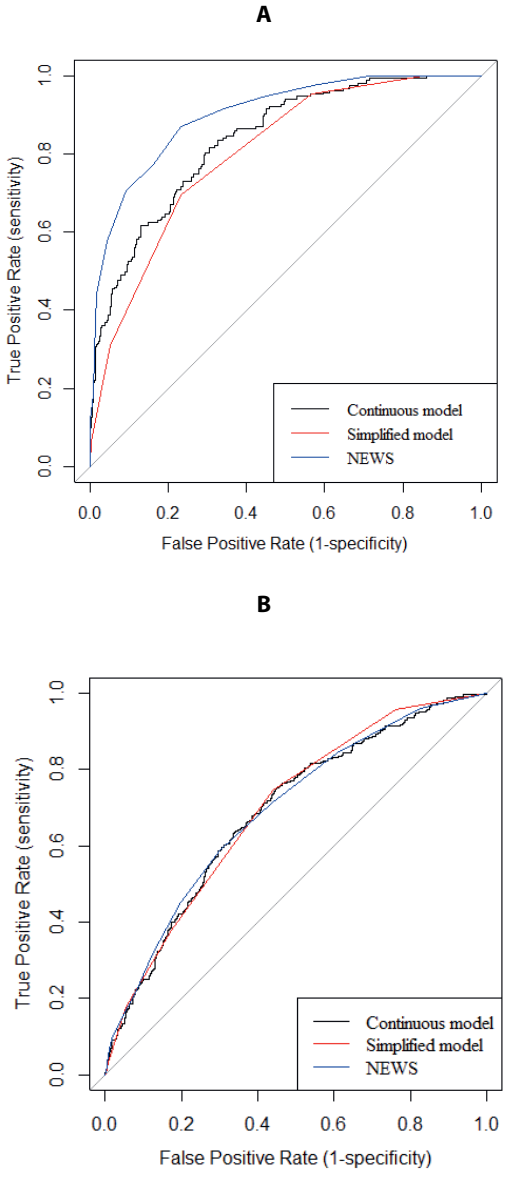


Figure S10. Receiver operating characteristic curves of continuous model, simplified model and NEWS for sepsis in Dataset 1 (n=440) (A), and Dataset 2 (n=1340) (B)

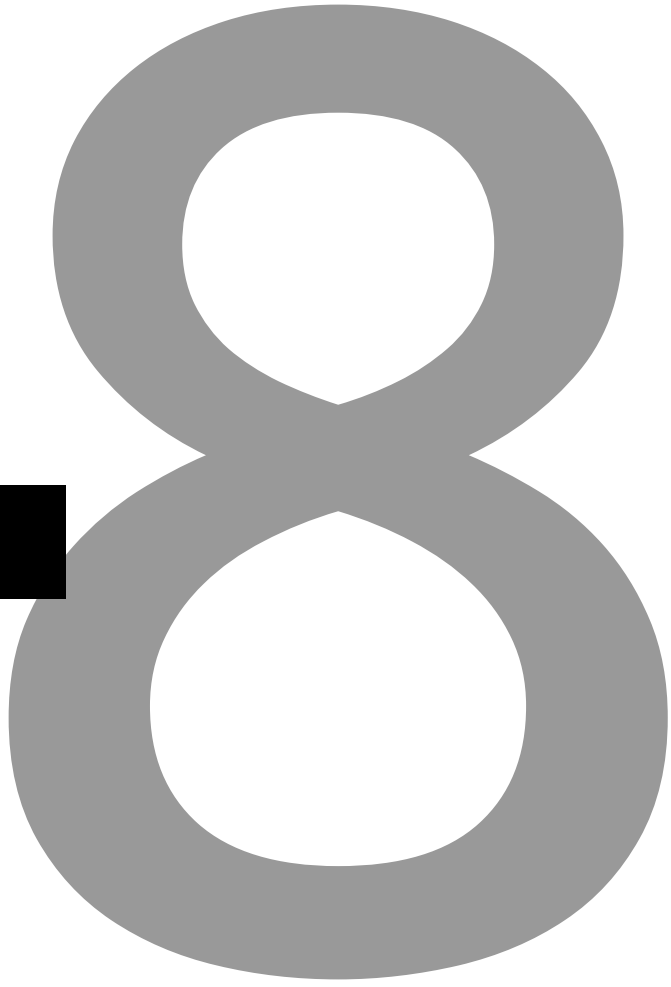
Table S11a. Performance measures of the continuous model, simplified model and NEWS in Dataset 1 (n=440)

Model	C-statistic (95% CI)	Brier score
Continuous model	0.84 (0.80 -0.87)	0.177
Simplified model	0.80 (0.77 -0.83)	0.188
NEWS	0.90 (0.87 -0.92)	0.143

Table S11b. Performance measures of the continuous model, simplified model and NEWS in Dataset 2 (n=1340)

Model	C-statistic (95% CI)	Brier score
Continuous model	0.70 (0.67 -0.73)	0.191
Simplified model	0.70 (0.67 -0.72)	0.188
NEWS	0.71 (0.68 -0.74)	0.201

CHAPTER 8



Added diagnostic value of biomarkers in patients with suspected sepsis: a prospective cohort study in out-of-hours primary care

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Accepted for publication in JALM

Abstract

Background Point-of-care testing (POCT) has shown promising results in the primary care setting to improve antibiotic therapy in respiratory tract infections and might also aid general practitioners (GPs) to decide if patients should be referred to a hospital in case 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, NT-proBNP, 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 hours 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. Also, net reclassification indices were calculated.

Results In total, 336 patients were included with a median age of 80 years. 141 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 of any of the tested biomarkers for suspected sepsis in general practice.

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 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 showed to be helpful in predicting sepsis in acutely ill adult patients visited at home by a GP.[9] Three biomarkers, C-reactive protein (CRP), lactate and procalcitonin (PCT), showed to have no added value. However several other biomarkers feasible to measure 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 diagnose pneumonia better 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 10-20 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.

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 analyse 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 four 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 otherwise suspected of severe infection were eligible for inclusion. We excluded patients if one or more of the following criteria were present: 1) Non-infectious cause of the acute complaints (e.g. stroke or myocardial infarction); 2) Hospitalisation within seven days before the home visit; 3) Condition that requires secondary care assessment if there are

any signs of systemic infection (e.g. chemotherapy with possible neutropenia); 4) Terminal illness or other reason not to refer the patient to a hospital despite the presence of a life-threatening condition.

Data collection and (POCT) 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, from serum of the venous blood samples stored at minus 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 for the patients' outcomes. Also, GPs who initially assessed and included patients in the study were blinded for 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 of the included patients was retrieved from the electronic medical record of the own GP and from the hospital in case the patient had 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 hours after inclusion to determine the presence or absence of sepsis.

Primary and secondary outcomes
The primary outcome was sepsis within 72 hours 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 two or more points on the SOFA score due to an acute infection (1). The expert panel was blinded for the results of laboratory analyses of the study samples. Secondary outcomes were "adverse outcome" (defined as a composite outcome of either ICU admission within 72 hours 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 hours).

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 ten 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 cut-off 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 two 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 cut-offs 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 <.05. All analyses were performed using R version 4.0.3.

Results

We analysed data of 336 patients, with a median age of 80 years (IQR 71-86) and 58% males. A flowchart of included patients is shown in Supplemental Figure 1. According to the expert panel, the primary outcome "sepsis within 72 hours 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, fourteen percent of the patients without sepsis did not have an infectious condition as the cause of the acute complaints. 180/190 (95%) of the patients referred to the emergency department immediately after inclusion were admitted to the hospital. 18/146 (12%) of the initially non-referred patients were admitted to the hospital within 72 hours of inclusion. The average length of stay (hospital admission) was 5.4 days for the patients with sepsis and 4.6 days for the non-sepsis patients. Admission to the ICU within 72 hours occurred in 11 patients with sepsis and one 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.

Table 1. Background characteristics by sepsis diagnosis and for the total population

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), minutes	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)

Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; SD, standard deviation

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 Figure 1). In Supplemental Table 1, diagnostic accuracy measures are presented for different cut-off points of the biomarkers. The highest PPV was found for PCT at a cut-off point of >2 µg/L (PPV 74%). The sensitivity of PCT at this cut-off 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%.

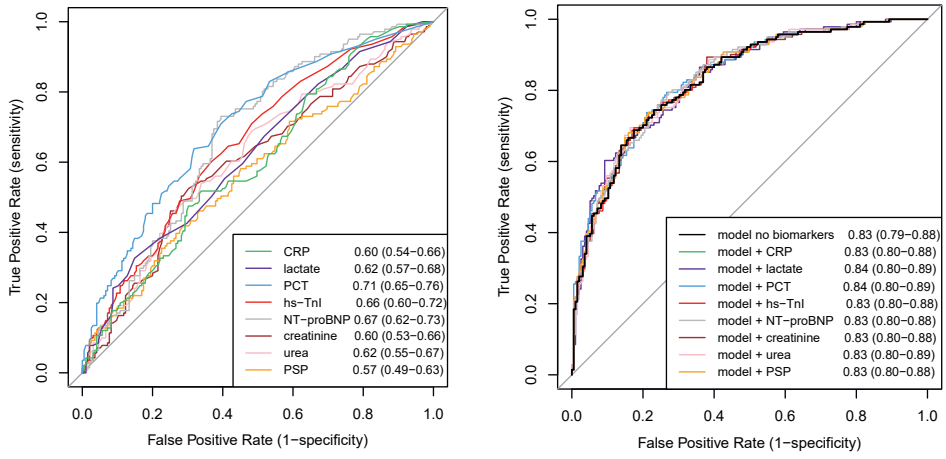

Figure 1. Receiver operating curves (ROC) of the individual biomarkers with the C-statistic (95% confidence intervals)(A) and ROC of the symptoms and signs model compared to the model with the addition of the individual biomarkers (B).

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 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.

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 Supplemental Figure 2). For the outcome "adverse event" (ICU admission <72 hours or 30-

day mortality), NT-proBNP showed a C-statistic of 0.74 (95% CI 0.63-0.83). In Supplemental Table 2, the results of the analyses are shown that compare biomarker levels in patients with sepsis with acute onset of illness (<24 hours before inclusion) to those without acute onset (>24 hours after inclusion). 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 hours before inclusion. For the remaining biomarkers, no statistically significant differences were found.

Table 2. Biomarkers by sepsis diagnosis with the number of patients in which the biomarkers were analysed (N) and P-value in imputed data.

Biomarker	N	Sepsis (n = 141) median (IQR)	No sepsis (n=195) median (IQR)	P-value
CRP, mg/L	331	85 (34-141)	58 (20-117)	<.001
Lactate, mmol/L	335	1.6 (1.2-2.1)	1.3 (0.9-1.7)	<.001
PCT, ng/mL	324	0.26 (0.10-1.4)	0.08 (0.03-0.21)	<.001
Hs-TnI , ng/L	323	21 (10-51)	10 (6-23)	<.001
NT-proBNP, ng/L	326	1604 (640-4315)	495 (179-2302)	<.001
Creatinine, umol/L	328	98 (73-121)	84 (67-104)	.006
Urea, mmol/L	328	8.9 (6.8-12.2)	7.2 (5.9-9.8)	<.001
PSP, ng/mL	330	156 (90-286)	131 (83-205)	.016

Abbreviations: IQR, interquartile range; CRP, C-reactive protein; PCT, Procalcitonin; H s-TnI, high sensitivity troponin I; NT-proBNP; N-terminal pro b-type natriuretic peptide PSP, Pancreatic stone protein.

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 as 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 cut-off value in this population, as the chance of a false-negative result was at least 20%.

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

A

Symptoms and signs model	Symptoms and signs model with the addition of lactate			
Frequency	**<10%**	**10-50%**	**>50%**	**Total**
Patients with sepsis				
<10%	3	1	0	**4**
10-50%	0	38	7	**45**
>50%	0	5	87	**92**
Total	**3**	**44**	**94**	**141**
Patients without sepsis				
<10%	43	4	0	**47**
10-50%	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%**	**10-50%**	**>50%**	**Total**
Patients with sepsis				
<10%	4	0	0	**4**
10-50%	0	43	3	**46**
>50%	0	4	87	**91**
Total	**4**	**47**	**90**	**141**
Patients without sepsis				
<10%	47	0	0	**47**
10-80%	3	111	4	**118**
>80%	0	3	27	**30**
Total	**50**	**114**	**31**	**195**

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) for developing a sepsis prediction tool were assessed.[17] Only lactate at a cut-off 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 three 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 in 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 using 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 to use in the primary care setting as POCT which could be analysed 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 for 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 by 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 COPD.[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 relevantly 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 is needed, and in other countries where out-of-hours care is often organized differently. 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 of 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.

Funding

This study was funded by ZonMw (grant number 843001811). Abionic and 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).

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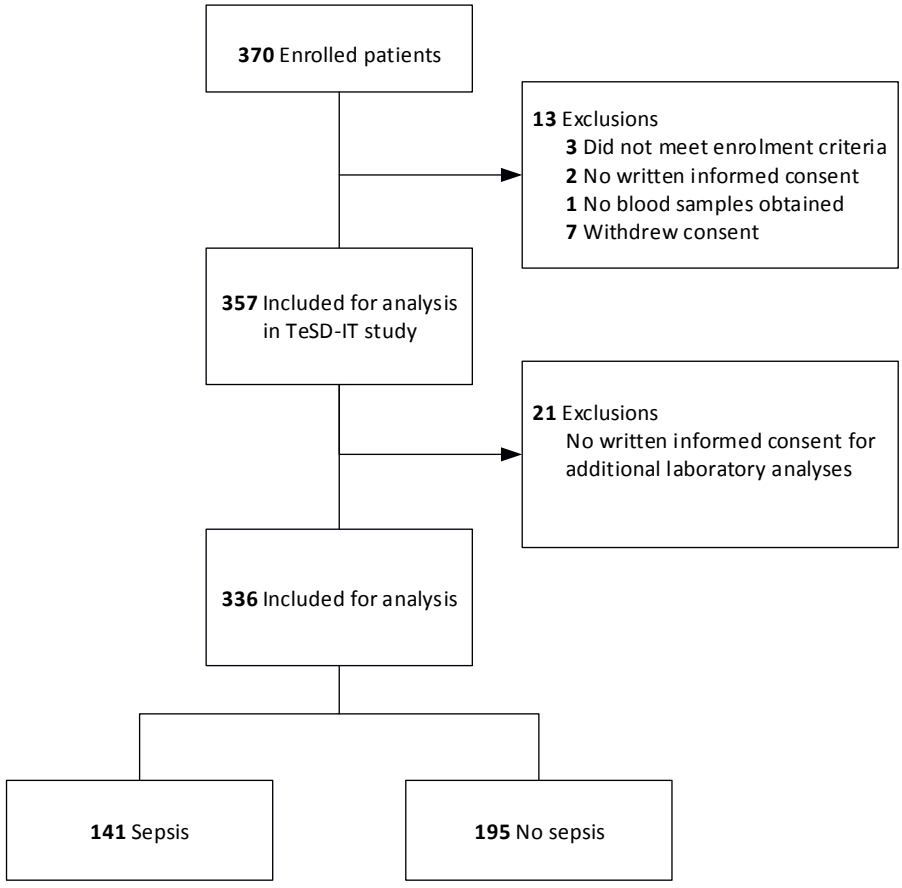
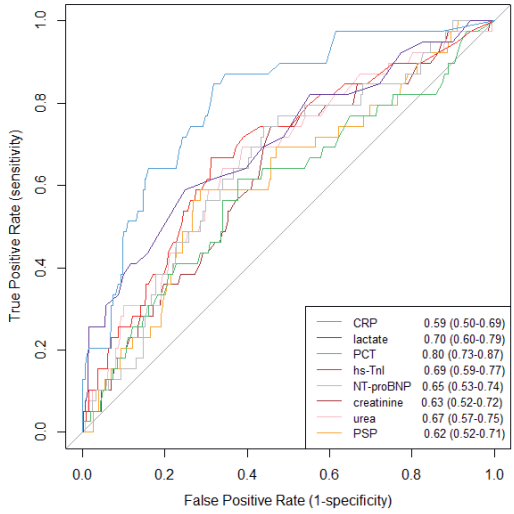
Supplemental files

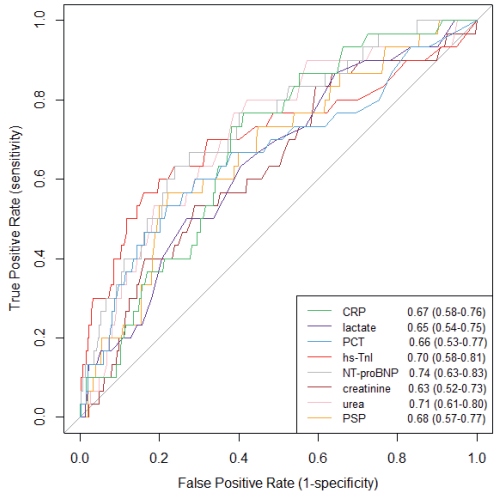


Supplemental Figure 1. Patient flow diagram.

Supplemental Figure 2.



A. ROC curves of biomarkers for prediction of positive blood cultures collected within 72 hours of inclusion



B. ROC curves of biomarkers for prediction of adverse outcome (ICU admission within 72 hours or 300day mortality)

Supplemental Table 1. Sensitivity, specificity, PPV and NPV for different cut-off values of the biomarkers.

Biomarker	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CRP <10 mg/L	94	17	45	80
CRP <20 mg/L	87	25	46	72
CRP >100 mg/L	40	72	51	63
CRP >150 mg/L	21	87	54	60
Lactate <1 mmol/L	87	27	46	73
Lactate <1.5 mmol/L	55	60	50	65
Lactate >2 mmol/L	28	87	61	63
Lactate >4 mmol/L	0.7	99	33	58
Procalcitonin, <0.1ng/mL	73	57	55	75
Procalcitonin, >0.25ng/mL	51	79	64	69
Procalcitonin, >0.5ng/mL	36	87	66	65
Procalcitonin, >2ng/mL	22	94	74	63
Hs-TnI <10 ng/L	74	49	51	72
Hs-TnI <20 ng/L	49	72	56	66
Hs-TnI >100 ng/L	13	95	64	60
NT-proBNP <150 ng/mL	93	20	46	80
NT-proBNP >1000 ng/mL	63	64	56	70
Creatinine <100 umol/L	47	72	55	65
Creatinine >150 umol/L	12	92	52	59
Creatinine >200 umol/L	3.5	96	42	58
Urea < 7.5 mmol/L	65	54	51	68
Urea >10 mmol/L	39	77	55	64
Urea >15 mmol/L	16	92	59	60
PSP <100 ng/mL	71	37	45	64
PSP >500 ng/mL	8.5	97	71	60

Supplemental Table 2. Differences of biomarkers between patients with sepsis with the onset of illness <24 and >24 hours before inclusion.

Biomarker	Onset of illness <24 h n=91 Median (IQR)	Onset of illness>24 h n=50 Median (IQR)	P-value
C-reactive protein, mg/L	58 (31-113)	128 (39-169)	<.001
Lactate, mmol/L	1.7 (1.2-2.3)	1.4 (1.1-1.7)	.004
Procalcitonin, ng/mL	0.25 (0.09-2.1)	0.34 (0.11-1.1)	NS
Hs-TnI , ng/L	17 (9.3-36)	31 (11-59)	NS
NT-proBNP, ng/L	1576 (633-4143)	1890 (812-4429)	NS
Creatinine, umol/L	99 (74-123)	94 (72-119)	NS
Urea, mmol/L	9.2 (7.0-12)	8.1 (6.7-12)	NS
PSP, ng/mL	162 (11-291)	150 (79-275)	NS

Abbreviations: IQR, interquartile range; NS, not significant; Hs-TnI, high sensitivity troponin I; PSP, Pancreatic stone protein

CHAPTER 9

9

Economic evaluation of a new sepsis prediction model for the primary care setting

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ABSTRACT

Background Early recognition of sepsis by general practitioners (GPs) is essential to improve outcome. Recently, we developed a prediction model that potentially can improve hospital referral of adult patients with sepsis without increasing unnecessary referrals.

Aim To estimate the potential referral rate and cost impact at different cut-off points of this sepsis prediction model in the primary care setting.

Methods In the TeSD-IT study 357 acutely ill adult patients were prospectively included during home visits at four out-of-hours GP services in the Netherlands. Health care resource use of these patients was collected using hospital registries and healthcare consumption questionnaires. The potential impact of direct referral of patients with sepsis on mortality and hospital admission was estimated by an expert panel. Using these study data, a decision tree with a time horizon of one month was built to estimate the referral rate and costs impact, in case the model would be implemented.

Results Referral rates at a low cut-off (score 2 or 3 on a scale from 0-6) of the prediction model were higher than observed for patients with sepsis (99% and 91% respectively, compared to 88% observed). Then however, referral was also substantially higher for patients who did not need hospitalisation. As a consequence, cost-savings due to direct referral of patients with sepsis was offset by increased costs due to unnecessary referral for all cut-offs of the prediction model.

Implications Guidance for referral of adult patients with suspected sepsis in the primary care setting using any cut-off point of the sepsis prediction model is not likely to save costs. The model may help GPs to improve the recognition of sepsis, but improvement of care should be observed in an implementation trial before incorporation of the model in sepsis guidelines for GPs.

INTRODUCTION

Sepsis is a life-threatening complication from infection with high mortality and morbidity. The global incidence of sepsis is estimated at 48 million cases per year, resulting in 11 million deaths.[1] For the Netherlands the same study estimated about 59,000 cases and 9,400 deaths annually. Patients are often treated in the Intensive Care Unit (ICU), and the average costs for adult patients admitted to the ICU with sepsis is estimated at €30,000 per patient in the Netherlands.[2]

Early identification of sepsis is the key factor to improve outcome.[3, 4] In the hospital setting, protocolised care for patients with suspected sepsis is increasingly implemented to reduce time to adequate treatment. However, the current prehospital recognition of sepsis is suboptimal.[5-8]

Recognition of sepsis can potentially be improved by a clinical prediction model consisting of vital signs and other readily available clinical information. Our research group recently showed a simple diagnostic sepsis model enables GPs to estimate the risk of sepsis in adult patients immediately at the bedside.[9] Ideally, all patients with sepsis are referred to the hospital directly after GP assessment. However, such a strategy aiming not to miss cases of sepsis will also lead to more unnecessary hospital referrals, and can potentially increase medical costs. The primary aim of this study was to assess the potential impact on the rate of referral and subsequent costs at different cut-off levels of the prediction model in the primary care setting in a so-called early economic evaluation. Secondary, we assessed room for improvement in costs if referral decisions would have been perfect.

METHODS

We performed the analyses using data of a cohort of 357 patients included in a previously described diagnostic study.[9, 10] These data were used as input for a decision tree to perform an early economic evaluation. The analyses were performed from a third-party payer/ healthcare perspective with a time horizon of one month. Due to the short time horizon, discounting was deemed unnecessary.

The primary outcome of this study was the estimation of the potential impact of the prediction model on referral rates, mortality and costs, the secondary outcome was to estimate the "room for improvement", calculated as the maximum reduction in costs and mortality in case patients are directly referred according to their need for hospitalisation. To be able to estimate this impact, we estimated the observed resource use in patients, grouped by their necessity of hospitalisation and final diagnosis category and the impact of direct referral on mortality and healthcare costs of patients with sepsis.

Utility loss was also measured, but not taken into account in the modeling of different scenarios for referral, as it was not deemed possible to accurately estimate utility loss of alternative scenarios.

Study population

In the TeSD-IT study, 357 patients were included during out-of-hours home visits by GPs at four GP cooperatives in the Netherlands. All acutely ill, adult patients ≥18 years with fever, confusion or general deterioration or otherwise suspected of a serious infection were eligible for inclusion. We excluded patients if one or more of the following criteria were present: 1) Non-infectious cause of the acute complaints (e.g. stroke or myocardial infarction); 2) Hospitalisation within seven days before the home visit; 3) Condition that requires secondary care assessment if there are any signs of systemic infection (e.g. chemotherapy with possible neutropenia); 4) Terminal illness or other reason not to refer the patient to a hospital despite presence of a life-threatening condition. All patients (or their legal representatives in case of mental incapacitation) provided informed consent. The study was approved by the METC Utrecht, and is registered under number 18/169. Other details of the methods of this study were published previously.[9] Candidate predictors for the decision model were collected prospectively by the GPs who included the patients. Sepsis diagnosis and need for hospitalisation of patients (regardless of the final diagnosis) were judged by three expert panels. Each panel consisted of one GP, one emergency physician and one intensivist/acute care internist. The final diagnosis "sepsis within 72 hours of inclusion" was established by the expert panels based on relevant medical health records. Besides the presence of sepsis, the panellists also scored the need for hospital treatment on a scale of 0-10, a mean score above 5 defined the need for hospitalisation.

Previously developed sepsis prediction model

The developed prediction model consisted of six dichotomous variables, each accounting for one point when present: age>65 years; temperature>38°C; systolic blood pressure≤110 mmHg; heart rate>110/min; saturation≤95%; altered mental status. The total score ranges from 0 to 6 points. This model showed a C-statistic of 0.80 for the prediction of the outcome "sepsis within 72 hours" according to the Sepsis-3 definition.[11]

Decision tree

A decision tree was developed to estimate the impact of a change in (direct) referral due to the prediction model on resource use (Figure 1). The decision tree has branches for the need of hospitalisation, final diagnosis (sepsis, infection without sepsis or no infection) and for patients who were directly referred or not directly referred. Implementation of the prediction model was modeled by adjusting the probability to be (directly) referred in each branch. Costs as observed in the trial were used to estimate the costs of each branch. The costs of being in a branch were the same, but the total costs of all the branches were influenced by the differing probability. Because referral was not randomised and the probability for referral can be influenced by patient mix and severity of disease, an exception was made for the branch for patients with sepsis needing hospitalisation, as is described in section "Expert opinion impact of direct referral patients with sepsis". For patients needing hospitalisation for other infection or other cause (without infection), we assumed that direct referral did not influence their hospital costs.

Input parameters

Probabilities

The proportion of patients that required hospitalisation, and the proportion that had sepsis, infection without sepsis or no infection were used as probabilities in the decision tree (Table 1).

Costs

Healthcare costs were estimated for different groups of patients, divided by their need of hospitalisation, final diagnosis (sepsis, infection without sepsis or no infection) and whether or not they were directly referred.

After 30 days, patients were sent a healthcare consumption questionnaire (iMCQ)[12] to report health related costs for homecare and family care in the previous 30 days. Furthermore, data on the number of consultations, rehabilitation or nursery homes were retrieved retrospectively from the patients' own GP. In addition, all hospital procedures were collected from the hospital registries. Total costs were calculated by multiplying the procedures with unit costs from the Dutch Healthcare Authority (NZa) or the Dutch costing manual.[13] For 10 patients hospital registry data were missing because they were referred to a hospital outside the region. However, ICU and ward admission days were known in the CRF. Average hospital costs per admission days of other patients were used to impute other hospital procedures in these patients. Multiple imputation was performed with Multiple Imputation by Chained Equations (MICE) for missing data on home care and family care creating 40 imputed datasets since 34.4% of responses were missing. The variables age, sex, all other variables included in the sepsis model, medication use, variables related to medical history and hospital costs were used as predictors.

Impact of direct referral on mortality and costs of patients with sepsis

The timing of referral in patients with sepsis is likely to influence hospital costs. However, due to the observational study design, observed costs in directly referred and not directly referred patients could reflect a difference in patient mix and severity of disease instead of timing in referral. Therefore, expert panel opinion was used to assess the impact of direct referral on costs and mortality for the patients diagnosed with sepsis. The panel experts estimated the change in admission days, ICU admission and probability of death in patients in the study who could change from "direct hospital referral" to "no direct referral" or vice versa. Based on the score of the new sepsis model, the referral advice for 44 patients who were directly referred, and for 16 patients who were not (directly) referred could change in the different modeled scenarios. The experts were presented 1) 16 cases of patients who were not directly referred but eventually needed sepsis treatment in the hospital and 2) 9 cases of patients who were directly referred to the hospital. Details on selection of the patients presented to the expert panel can be found in the Supplemental Methods. They were asked specific questions on their estimations on hospital duration, ICU admission duration and probability of death if they 1) would have been directly referred or, 2) would have not directly been referred. Referred patients are assumed to be transported by ambulance in all scenario's, as this was also observed in the vast majority of referrals during the TeSD-IT study.

Measurement of quality of life
In the follow-up questionnaire at 30 days, patients were asked to fill in the EQ-5D-3L for three different moments: 1) for the situation before start of the acute complaints (T0); 2) for the situation when the patients was most servery ill during the 30 day follow-up period (T1); 3) at the end of the 30 day follow-up (T2). For patients who died before the end of follow-up, utility at T2 was assumed to be 0. Other missing data for utilities were imputed using MICE. The handling of inconsistencies in the reported utilities and the calculation of the utility loss is described in the Supplemental Methods.

Analysis
Room for improvement analysis
To estimate the maximum costs that could be saved, a room for improvement analysis was performed. In this analysis we assumed that none of the patients without a need for hospitalisation would have been referred, while all patients with sepsis with a need for hospitalisation would have been directly referred.

Impact of prediction model on referral rates and costs
The costs and effects of current care were compared with scenarios in which referral corresponded with the score of the prediction model. The four scenarios differed in the cut-off of the score of the model: 1) a cut-off score of 2 (no referral at a score <2, and referral at ≥2), 2) a cut-off score of 3 ,3) a cut-off score of 4, and 4) a mixed scenario: patients below a score of 2 were not referred, while patients with a score of 4 or higher were referred. In case of a score of 2 or 3, referral remained unchanged. For each scenario, the costs of all branches were summed and compared to each other.

Sensitivity analysis
To estimate the uncertainty around the outcome, we performed deterministic and probabilistic sensitivity analyses. Uncertainty ranges of costs for the branches with more than 30 patients were estimated with bootstrapping and were assumed to be normally distributed, while ranges of costs for the branches with less than 30 patients were assumed to range from the cheapest to the most expensive patient with a gamma distribution. Probabilistic sensitivity analysis was performed with 1000 runs on the most positive scenario of the prediction model compared to current care. The outcome of these runs were displayed in violin plots.

RESULTS

The impact of direct referral and final diagnosis on resource use

Resource use collected during the study
Table 1 shows the healthcare costs in the trial for all groups divided by their need of hospitalisation, final diagnosis and whether or not they were directly referred. As mentioned in the methods, only costs of the patients in whom hospitalisation was not necessary were completely used in the calculation of the impact of the prediction model.

Costs of patients in whom hospitalisation was not necessary were higher for directly referred patients compared to not directly referred patients. This increase was due to ambulance and hospital costs. Referral led to an increase in total costs from €1373 to €2515 in patients with sepsis, €1379 to €4838 in patients with infection without sepsis and from €2029 to €6209 in patients without infection.

Costs of patients in whom hospitalisation was necessary consisted primarily of hospital costs (€4937 to €7938 over the different groups), while family and homecare added less to the total costs. In patients with sepsis in whom hospitalisation was necessary, the costs of the directly referred patients were lower with €9298 compared to €9687 in not directly referred patients. In patients without sepsis, costs were higher in the directly referred patients. To estimate the impact of referral on costs of patients with sepsis these observed costs were not used, but instead expert opinion outcomes were used.

Expert opinion outcomes

The experts expected that 25% of the directly referred cases with a standard disease pattern (did not die, had an ICU admission or rare complication) could have died if they were not directly referred. In addition, an increase of 38% in hospital days was estimated by the experts should these patients not have been referred. Of the cases that were not directly referred and did not die nor were admitted the ICU, a decrease in hospital days of 25% was assumed by the experts. The expert panel assessed two patients with sepsis that were not directly referred and died within 30 days, but none of the experts expected death could have been prevented by direct referral. Corresponding mortality and hospital costs at different cut-offs of the prediction model are shown in the supplemental file, Table S1 and TableS2.

Room for improvement analysis

Hospitalisation was deemed necessary in 136 of the 357 patients with sepsis in the primary study. A total of €53,796 could have been saved in case all these patients would have been directly referred according to the expert panel judgement. If all 158 patients for whom hospitalisation was not necessary would not have been referred to the hospital, this could have saved €84,086. In total, perfect referral could save €137,882 out of €1,583,732 in these 357 patients (mean €386).

Impact of prediction model on referral rates and costs

Observed referral of patients who needed hospitalisation was 88% for patients with sepsis (120/136) and 15% for patients who did not need hospitalisation (see supplemental file Table S3). Referral rates at a low cut-off (2 or 3) of the prediction model were higher for patients with sepsis (99% and 91%, respectively). However, referral was also substantially higher for patients who did not need hospitalisation. At a high cut-off score of 4, referral rates for patients who did not need hospitalisation were still higher than the observed referral rate, while at the same time referral in patients with sepsis that needed hospitalisation was lower (60%).

In the mixed scenario, where referral was based on the prediction model below a score of 2 and equal to or above a score of 4 and partly on the GPs opinion (referral as observed if

score was 2 or 3), referral of patients with sepsis in whom hospitalisation was necessary increased to 91%. However, referral of patients in which hospitalisation was not necessary was also increased to 26%.

The decision tree analysis shows that the observed probabilities of referral led to the lowest costs with average patient costs of €5890. The average costs of referral based on the prediction model ranged between €5954 and €6742)(Table 2). At higher prediction model cut-offs (score 3 and 4), sepsis mortality will increase according to the expert opinion analysis. At a cut-off of 2 and the mixed scenario, a benefit in costs of increased referral of patients with sepsis is offset by the increased costs of unnecessary referral. However the mixed scenario had the lowest costs of the prediction model scenarios resulting in mean costs of €5954 per patient.

Sensitivity analyses

In a one-way sensitivity analysis, the costs of all different patient groups were varied using both bootstrapped standard deviations and mean costs (from a minimum of 2 standard deviations below and above the bootstrapped mean costs). The impact was greatest for patients with sepsis who were not previously referred and for the costs of patients who did not need hospital treatment and had an infection without sepsis (Figure 2). This is mainly because the modelled uncertainty was also the largest in these parameters. With maximum costs of €16,614 instead of €9697 per patient, direct referral of sepsis save more costs even leading to cost-savings of the prediction model in these extreme assumptions. If the costs of patients who did not need hospital treatment and had an infection without sepsis only added an ambulance ride and ED visit (and no hospital days), referral based on the prediction model could save €23 compared than usual care. In the probabilistic sensitivity analyses, costs for the prediction model were higher than usual care in 83% of the runs (Figure 3).

Utility loss

We observed a median utility at baseline of 0.78 (IQR 0.59-0.89) in the total population and 0.74 (IQR 0.54-0.86) for patients with sepsis who required hospital treatment. Mean utility loss in the first month was 0.36 for these patients, compared to 0.34 in the total population. More detailed results of the utility loss can be found in the supplemental file Table S4 and Figure S1.

		Probability	
Hospitalisation necessary	Sepsis	0.38	Referred
			Not referred
	Other infection	0.14	Referred
			Not referred
	No infection	0.03	Referred
			Not referred
	Total	0.56	
Hospitalisation not necessary	Sepsis	0.04	Referred
			Not referred
	Other infection	0.35	Referred
			Not referred
	No infection	0.05	Referred
			Not referred
	Total	0.44	

Figure 1. Structure of the branches and corresponding probabilities of the decision tree

Table 1. Observed healthcare costs in the TeST-ID study of referred and non-referred patients, divided by diagnosis and need for hospital treatment.

			Costs							
			Ambulance	Hospital	GP	Nursing home	Home care & family care	Total	Min*	Max*
Hospitalisation necessary	Sepsis (n=136)	**Referred** (n=120)	€ 613	€ 6,950	€ 44	€ 239	€ 1,453	€ 9,298	€ 8,097	€ 10,500
		Not referred (n=16)	€ 0	€ 7,488	€ 57	€ 460	€ 1,682	€ 9,687	€ 2,760	€ 16,614
	Other infection (n=51)	**Referred** (n=45)	€ 613	€ 4,937	€ 35	€ 153	€ 1,558	€ 7,297	na	na
		Not referred (n= 6)	€ 0	€ 6,272	€ 25	€ 0	€ 894	€ 7,191	na	na
	No infection (n=12)	**Referred** (n= 10)	€ 613	€ 7,938	€ 27	€2,899	€ 1,660	€ 13,137	na	na
		Not referred (n= 2)	€ 0	€ 6,969	€ 34	€ 0	€ 977	€ 7,980	na	na
Hospitalisation not necessary	Sepsis (n=15)	**Referred** (n=2)	€ 613	€ 1,326	€ 17	€ 0	€ 559	€ 2,515	€ 1,557	€ 6,050
		Not referred (n=13)	€ 0	€ 161	€ 51	€ 0	€ 1,160	€ 1,373	€ 277	€ 2,468
	Other infection (n=126)	**Referred** (n=13)	€ 613	€ 3,081	€ 29	€ 0	€ 1,115	€ 4,838	€ 2,492	€ 7,184
		Not referred (n=116)	€ 0	€ 359	€ 73	€ 37	€ 911	€ 1,379	€ 1,007	€ 1,752
	No infection (n=17)	**Referred** (n=10)	€ 613	€2,913	€ 80	€ 299	€ 2,304	€ 6,209	€ 3,628	€ 8,790
		Not referred (n=7)	€ 0	€ 875	€ 59	€ 0	€ 1,096	€ 2,029	€ 363	€ 3,695

*Minimum and maximum values as used in the deterministic and probabilistic sensitivity analyses.

Table 2. The total percentage of patients referred, sepsis mortality as estimated with expert opinion and healthcare costs as observed and as modelled using expert opinion at the different prediction model cut-offs.

	Observed	According to prediction model			cut-off 2-4 according to GP
		cut-off 2	cut-off 3	cut-off 2	
% Referred sepsis cases[a]	88%	99%	91%	60%	91%
% Referred without necessity for hospitalisation	15%	85%	56%	15%	26%
Sepsis mortality cases	9	9	12	18	9
Cost for sepsis cases[b]	€ 1,270,760	€ 1,222,325	€ 1,229,761	€ 1,347,172	€ 1,251,438
Cost for patient without necessity for hospitalisation	€ 312,972	€ 665,885	€ 505,075	€ 293,107	€ 355,442
Total costs	€ 1,583,732	€ 1,888,210	€ 1,734,836	€ 1,640,280	€ 1,606,880
Total cost per patient[b]	€ 5,890	€ 6,742	€ 6,313	€ 6,048	€ 5,954

[a] With necessity for hospitalisation
[b] Including patient with necessity for hospitalisation without sepsis

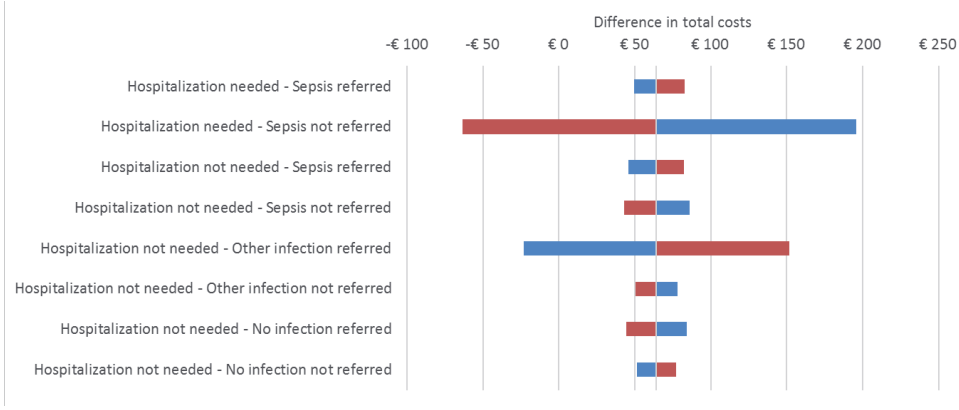

Figure 2. Plots of one-way sensitivity analysis; costs for health states were varied independently, and the cost difference, by using the prediction model, is compared to usual care.

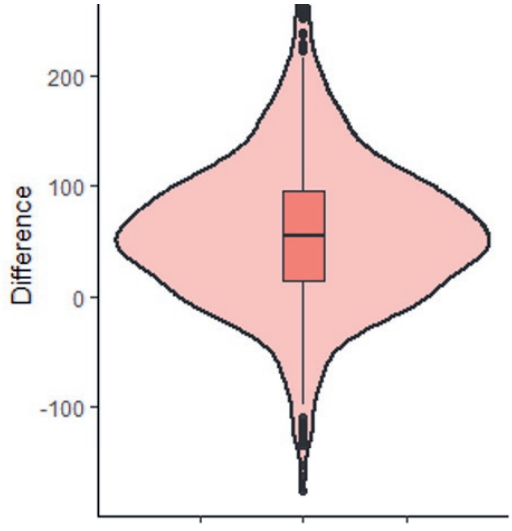

Figure 3. Violin plot of probabilistic sensitivity analysis; differences in costs of 1000 runs of implementation of the prediction model costs for health states were varied independently, and the cost difference, by using the prediction model, is compared to usual care.

DISCUSSION

In this early economic evaluation, we estimated the potential rate of referral and cost-impact of the implementation of a new clinical prediction model for adult patients with possible sepsis in the primary care setting. We saw that, when using the model, cost-savings due to direct referral of patients with sepsis was offset by increased costs due to unnecessary referral for all cut-offs of the prediction model. With "perfect" referral, it is estimated that €137,882 could be saved in the 357 study patients.

It was expected that direct referral of patients with sepsis previously not (directly) referred would have large beneficial effects. However, during expert opinion 16 of these patients were judged and the impact on hospitalisation the experts gave was smaller than expected. In addition, the impact of direct referral of patients that did not need hospitalisation on costs was larger than expected. The one-way sensitivity analyses showed that if these costs would only compromise an ambulance ride and emergency department visit, costs of the prediction model and usual care would almost be equal. Together, these costs are crucial for the conclusion of the analysis and should be studied in a randomised setting.

Comparison with literature

Several cost-effectiveness analysis on sepsis prediction models or diagnostics at a hospital level exist,[14-16] but we were not able to find other cost-effectiveness analysis of sepsis prediction models in general practice. However, evaluations of prediction models for other acute medical conditions in the primary care setting do exist. A cost-utility analyses of point-of-care troponin testing in patients consulting a GP with chest pain showed a decreased referral rate and cost-savings of €77.25/patient).[17] A cost-effectiveness analysis of a new strategy to rule out DVT in the primary care setting in the Netherlands, showed that €138 per patients could be saved at the expense of a very small heath loss (0.002 QALYs)[18]. In both studies, the new strategies could safely reduce the number of referrals and decrease hospital costs. In our study population the proportion unnecessary referrals is substantially lower, making it more difficult to safe costs by decreasing the total number of referrals.

Strengths and limitations

A strength of our study is that costs from different sources were used to gain a broad oversight on different cost components. Another strength is that an extensive expert opinion was used on detailed patient cases to evaluate the potential impact of direct referral on patients with sepsis, instead of using observed data that could be prone to bias due to the observational design of the study. For instance, directly referred patients could differ in severity of illness and fragility from patients who also needed hospitalisation, but were not directly referred. Because the impact of direct referral is also not known in literature, our expert opinion was the most accurate estimation to our opinion, but could have biased results towards the observed management. For example, intravenous antibiotics are appropriate in case of positive blood cultures, but blood cultures were only obtained in referred patients. Possibly some patients that were successfully treated at home with oral antibiotics would have shown positive blood cultures if they had been collected. In addition, the added value of the model to usual care could be greater than

observed during the study as the requirement of the study protocol to measure all vital signs might have improved the recognition of sepsis by the GPs.

The aim of the study was to perform an early economic evaluation, which is in line with the observational design of the study. However, using this observational design as input for the decision tree did result in another two challenges. Firstly, the probability of referral when implementing the sepsis prediction model was based on a hypothetical scenario that could have been different from the actual management of the GP during the study. Secondly, costs of patients without need for hospitalisation might also not be interchangeable between the directly and not-directly referred patients. For instance, a more frail patient could have a higher probability to be (unnecessarily) referred, but this might also result in other additional resource use that might be omitted if a younger vital patient would be (unnecessarily) referred.

Implication for research and clinical practice

As we showed a reduction in costs is not likely if GPs use only the prediction model to refer patient to the hospital, more research is needed into the effects of our model in routine care comparing with a usual care group in which measurements are up to the GP to perform. As explained in the previous paragraph, beneficial effects of the model may have been underestimated in this study. Also, a reduction in costs is not a precondition for a new intervention, but additional costs per QALY gained should be acceptable. To more accurately measure the effects on health outcomes and costs, a large prospective randomised trial should be performed, in which the effects of the new sepsis model are evaluated in practice. Given the results of the current study, we do not propose for GPs to use strict cut-off points of the model to decide to refer a patient, but rather to use the score to estimate the risk of sepsis and incorporate this information in their overall judgment.

In conclusion, guidance for referral of adult patients with suspected sepsis in the primary care setting using a single cut-off point of the sepsis prediction model is not likely to save costs. The model may help GPs to improve the recognition of sepsis, but improvement of care should be observed in an implementation trial before incorporation of the model in sepsis guidelines for GPs.

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Supplement

Supplemental Methods

Selection of patients presented to the expert panel

The experts were presented 1) 16 cases of patients who were not directly referred but eventually needed sepsis treatment in the hospital and 2) 9 cases of patients who were directly referred to the hospital. All patients who died, were admitted to the ICU or had a deviant disease pattern were included. For example, all patients with an uncommon source of infection (e.g. endocarditis) or who needed invasive procedures were assessed by the expert panel. Of the other patients, cases were selected based on representative age and length of hospital stay, and results were extrapolated to similar patients. For patients who were initially not referred, but were referred to the hospital shortly after the index contact and did not need ICU treatment, no change in outcome was assumed. This was also assumed for patients who were referred, but who were only treated with oral antibiotics in the hospital with an uncomplicated course.

Corrections of inconsistencies in EQ-5D-5L scores.

Patients were asked to fill in the EQ-5D-5L for three different moments in time: 1) Before onset of the acute complaints (T0); 2) At the time patients were most severely ill during the last 30 days (T1), and 3) At the time the questionnaire was filled in (30-days after inclusion) (T2). Utility loss was calculated for one month by subtracting the area under the curve during this month from the baseline value for one month. Corrections were made for errors of patients in the time points: T0 was corrected to the highest value as filled in, T1 was recoded if T0 was lower than T1. T2 was never corrected.

Table S1. Number of patients for whom hospitalisation was necessary or not necessary, subdivided in groups with sepsis, another infection or no infection and the percentages referred as in the trial and according to the prediction model at different cut-offs.

Hospitalisation necessary	Cause	% immediate referral				
		Observed	According to prediction model			
			cut-off 2	cut-off 3	cut-off 3	cut-off 2-4
Yes (n=199)	Sepsis (n=136)	88%	99%	91%	60%	91%
	Other infection (n=51)	88%	88%	63%	22%	78%
	No infection (n=12)	83%	83%	50%	8%	67%
No (n=158)	Sepsis (n=15)	13%	100%	93%	47%	60%
	Other infection (n=126)	10%	85%	56%	13%	20%
	No infection (n=17)	56%	67%	20%	0%	40%

Table S2. Admission costs and sepsis mortality of patients with sepsis that were directly referred in the study as estimated with help of expert opinion.

Prediction score	N	Observed		Estimated					
				Cut-off 2		Cut-off 3		Cut-off 4	
		Mortality	Admission costs	Mortality	Admission costs	Mortality	Admission costs	Mortality	Admission costs
0 or 1	1	0	€2,428	0.0	€5,397	0.0	€5,397	0.0	€5,397
2	8	1	€56,567	1.0	€56,567	3.6	€55,443	3.6	€55,443
3	35	2	€205,322	2.0	€205,322	2.0	€205,322	8.1	€299,740
4	53	4	€415,125	4.0	€415,125	4.0	€415,125	4.0	€415,125
5 or 6	23	0	€154,499	0.0	€154,499	0.0	€154,499	0.0	€154,499
Total	120	7	€833,941	7.0	€836,909	9.6	€835,785	15.7	€930,203

Table S3. Admission costs and sepsis mortality of patients with sepsis that were not directly referred in the study as estimated with help of expert opinion.

Prediction score	N	Observed		Estimated					
				Cut-off 2		Cut-off 3		Cut-off 4	
		Mortality	Admission costs	Mortality	Admission costs	Mortality	Admission costs	Mortality	Admission costs
0 or 1	0	0	€0	0	€0	0	€0	0	€0
2	3	0	€17,621	0	€9,060	0	€17,621	0	€17,621
3	8	0	€44,065	0	€21,072	0	€21,072	0	€44,065
4	3	1	€53,568	1	€31,326	1	€31,326	1	€31,326
5 or 6	2	1	€4,556	1	€4,556	1	€4,556	1	€4,556
Total	16	2	€119,810	2	€66,014	2	€74,574	2	€97,568

Table S4. Utility of the included patients at baseline (T0), at the time of most severe illness (T1) and at the end of the 30 day follow-up (T2). Utility loss is calculated over the first 30 days.

	T0	T1	T2	Utility loss
Hospital treatment necessary				
Sepsis	0.74	0.07	0.61	0.36
Other infections	0.74	0.15	0.59	0.33
No infection	0.74	0.00	0.37	0.46
Hospital treatment not necessary				
Sepsis	0.81	0.23	0.70	0.33
Other infections	0.81	0.21	0.74	0.30
No infection	0.81	0.14	0.54	0.36

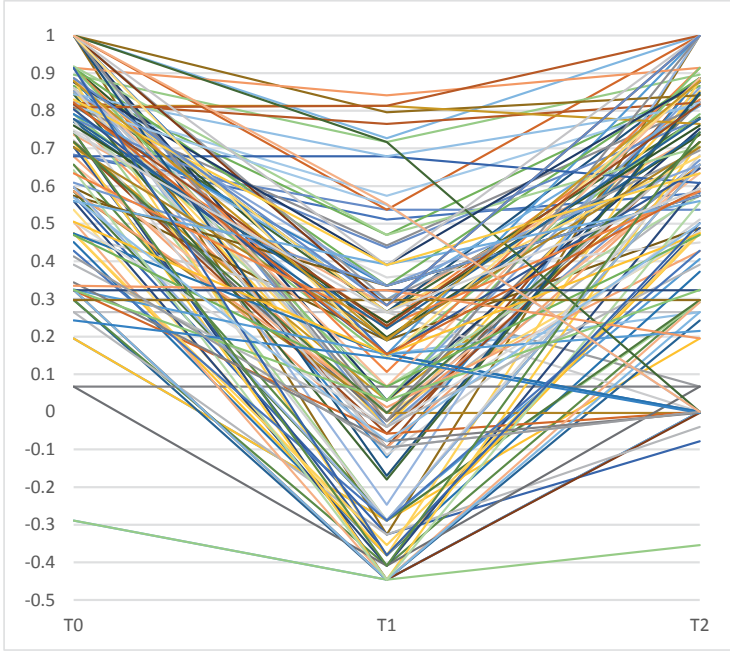

Figure S1. Plot of all individual utility scores of the patients with sepsis with need for hospital treatment at baseline (T0), at the time of most severe illness (T1) and at the end of the 30 day follow-up (T2).

CHAPTER 10

10

General discussion

Considering the importance of the role of the GP in the management of sepsis, the lack of studies in this particular field is striking. The studies presented in this thesis can be regarded as an essential first step to fill this knowledge gap. Our research group continues to initiate new studies as described at the end of this chapter. The aim is to provide more definitive answers for GPs facing a diagnostic dilemma in patients with possible sepsis. Hopefully, other research groups will join this effort.

How big is the sepsis problem?

Sepsis-related mortality accounts for one in five deaths globally.[1] Sepsis was found to be the most important cause of death in hospitals in the US, accounting for one in every two to three in-hospital deaths.[2] In most of these patients, sepsis was present at hospital admission. In 2017, the World Health Organization adopted a resolution declaring sepsis a global health priority in which member states were urged to improve prevention, diagnosis and management of sepsis.[3] A study performed in Denmark showed that two-thirds of patients with sepsis contacted an out-of-hours (OOH) primary care service, whereas in myocardial infarction and stroke, more than half of the patients contacted emergency medical services directly.[4] This underscores the importance of the role of OOH GP cooperatives, and general practice in general, in the prehospital management of sepsis.

As described in chapter 4, we have found that one in three patients admitted to the ICU due to sepsis was not referred to the hospital after the first contact with an OOH GP cooperative.

In this study, 32 sepsis-related deaths were observed after OOH GP cooperative contact. This study included patients admitted to the ICU in the Gelderse Vallei Hospital (serving a population of 260,000 inhabitants) over five years. Assuming one in three of these 32 deaths is potentially preventable by GPs (as this proportion was not immediately referred to the hospital), extrapolation to the Netherlands results in 143 potentially preventable deaths annually. However, this number only includes patients admitted to the ICU. The data from the TeSD-IT study suggests mortality from sepsis outside the ICU is substantially more prominent, as only 2/21 (10%) of the deceased patients were admitted to the ICU. Therefore, the total number of potentially preventable sepsis-related deaths could be up to tenfold greater. It should, however, be acknowledged that the proportion of sepsis-related deaths in patients who are not admitted to the ICU and that are preventable is highly uncertain.

Perceived importance of sepsis in general practice

The question can be raised why so little sepsis research has been initiated in general practice previously. An important factor may be that the relation between diagnosis and outcome in patients with sepsis is often less evident than with conditions such as myocardial infarction and pulmonary embolism. In these conditions, a missed diagnosis will, in some

cases, result in sudden death shortly after GP assessment. The causal association between the missed diagnosis and death is apparent and may confront the treating physician. In a patient who dies from pneumonia, the causality between initial management and outcome is often less clear. For example, a patient is diagnosed with pneumonia by a GP, after which oral antibiotics are prescribed. After 24 hours of treatment, the patient is referred to the hospital due to clinical deterioration. The patient develops a septic shock and eventually dies after one week of intensive care treatment. If the patient had been referred directly after the first presentation, the patient might have recovered quickly. The GP who initially assessed the patient might not feel a case of sepsis was missed. According to the GP, the patient presented as a case of pneumonia without alarming symptoms, and after all, not all patients with pneumonia should be referred to the hospital. This lack of an apparent relation between delayed treatment and outcome is especially true for patients assessed at the OOH GP cooperative. GPs treat patients that are not part of their own patient population, and the GP is usually not informed about the outcome.

Another reason for the paucity of research may be related to the presentation of sepsis as an acute illness, often during OOH. Research is more difficult to perform in an acute setting, especially when informed consent of the patient is required. In the Netherlands OOH primary care is well organised, and uniform across the country by large scale OOH GP cooperatives.[5] In other European countries, OOH care is less uniformly organised,[6] which may be a complicating factor. Furthermore, outside Europe, acutely ill patients are often not assessed by GPs during OOH.[7]

Is sepsis a relevant entity for GPs?

Patients diagnosed with sepsis are usually diagnosed with underlying infections, such as pneumonia or a urinary tract infection. Is it necessary for GPs to consider the diagnosis of sepsis, or is it more beneficial to consider hospital referral based on the severity of a specific infection? The current guidelines for GPs are concurrent with this last approach. Separate guidelines are formulated for acute cough, urinary tract infections, bacterial skin infections and diverticulitis.[8-11] In each guideline, specific symptoms are listed as reasons to refer to the hospital, which are not the same in the different guidelines. However, there are important arguments for why a general approach - not based on a specific diagnosis - is essential to reduce sepsis-related mortality. Chapter 4, showed that the GP did not suspect infection in about half of the patients who were subsequently admitted to the ICU due to sepsis. An important finding was that mortality in patients without suspected infection was about three times higher compared to patients in whom infection was suspected. Therefore, more than half of the sepsis-related mortality will not be influenced by guidelines targeting patients with specific infectious conditions. Furthermore, misdiagnosis or uncertainty in differential diagnosis by the GP was common in patients included in the TeSD-IT study. For example, some patients were diagnosed with a differential diagnosis of "pneumonia or urinary tract infection" or "fever of unknown origin".

Other research also shows that the absence of fever in sepsis is associated with an increased mortality risk.[12-14] Two factors can attribute to this association. Firstly, fever is a result of the patients' immune response. The absence of fever in severe infections can signify that the patients' immune response is inadequate. Secondly, adequate treatment for sepsis may be delayed in patients without fever if an infection is not considered. Therefore, it is essential that the starting point of any sepsis guideline is "acutely ill patients" and not "patients with a suspected infection". In patients with clear signs of infection, GPs should look for signs of organ dysfunction. Conversely, in patients with clear signs of organ dysfunction, GPs should consider an infectious cause. In both cases, the question "Could this be sepsis?" may be essential for successful treatment. In the TeSD-IT study, we formulated inclusion criteria such that nearly all patients with sepsis were eligible for inclusion, not only patients with clear signs of infection. This was formulated as: "acutely ill adult patient with fever, confusion or general deterioration or otherwise suspected of a serious infection". Still, patients with sepsis presenting without fever or other clear signs of infection may have been underrepresented in the study. If the GP did not think sepsis was a possible diagnosis in these patients, it was less likely they would include these patients in our sepsis study. This is, however, similar to how the sepsis model will be used in practice. If sepsis is not considered by the GP, the model will not be used. Therefore, it is also important GPs are aware of the broad clinical spectrum of sepsis.

Implications of the absence of a gold standard in sepsis diagnosis

The Sepsis-3 criteria have been widely accepted since its publication in 2016.[15, 16] However, these criteria are not unequivocal and are challenging to implement in clinical research.[17] In patients without comorbidity admitted to the ICU due to an acute infection, the SOFA score can be used to assess the presence of organ failure and subsequently diagnose sepsis in case the SOFA score is ≥2 points. However, outside the ICU, not all variables to calculate the SOFA score may be available (especially outside the hospital). Also, preexisting conditions may cause chronic organ dysfunction, which may or may not result in a SOFA score >0 at baseline. Moreover, the diagnosis of an underlying infection is not always unequivocal in patients with organ dysfunction. In the TeSD-IT study, we used an expert panel to interpret all available medical records to determine if the sepsis definition was met. Other studies performed since the publication of the Sepsis-3 definition in 2016 have used different approaches.[17-21] These studies did not use expert panels, and SOFA score at baseline and missing items of the SOFA score were handled differently. This difference is problematic for the comparison of the results of these studies.

The approach used in the TeSD-IT study, which included the use of an expert panel, may not be feasible in other studies in case of a large sample size or unavailability of detailed medical records. However, this approach resulted in several advantages. Firstly, as three independent experts judged each case, the final diagnosis is more accurate and objective compared to the judgement of a single researcher of the study. Also, we gained insight into the interobserver agreement, which was satisfactory. Finally, using an expert panel enabled us also to obtain a score for the need for hospital treatment. This secondary outcome was used to assess the accuracy of the diagnostic model for a clinically relevant

outcome not dependent on specific cut-off points of clinical information. This secondary outcome is, therefore, less at risk for incorporation bias. Incorporation bias can occur when variables used as predictors are also part of the outcome measure. Blood pressure, oxygen saturation and mental status are variables in the newly developed model that can also result in points on the SOFA score. However, no essential differences were shown to predict the need or hospital treatment and in sensitivity analyses where we defined sepsis based on more conservative calculations of the SOFA score.

Complexity of the model: accuracy versus usability

In the TeSD-IT study, both a complex and a simplified model were developed. The complex model uses predictors as continuous variables (therefore referred to as continuous models), accounting for non-linear relationships with the outcome. The simplified model uses single cut-off points, adding 0 or 1 point to the total score. Simplifying a diagnostic model is usually at the expense of accuracy as less information is used in the model. Therefore, it is generally advised not to simplify a diagnostic model by dichotomising predictors.[22] Online calculators can be used to calculate predicted probabilities regardless of the complexity of the model. However, we proposed the simplified model as the final model. The main reason for this decision is the expected better uptake in the daily practice of a model that can be easily calculated without any additional resources. GPs do not assess patients with possible sepsis daily, and the need to use a computer or smartphone to calculate a score in the setting of home visits will probably deter a proportion of the GPs from using the model. Therefore, we simplified the model as far as possible without losing too much accuracy to ensure no additional time investment is needed to calculate the score. The diagnostic accuracy of the simplified model was only slightly lower than the continuous model. The cut-off points were chosen as used in the NEWS and not at optimal cut-off points based on the study data to prevent overfitting. More importantly, two external validations confirmed the slight difference between the continuous and simplified model (see chapter 7).

Besides reducing the score's complexity, we also decided to replace respiratory rate with heart rate in the simplified model. In chapters 2 and 3 is shown that the respiratory rate is measured less frequently than other vital signs, and in chapter 5 we showed many GPs experienced practical difficulties counting the respiratory rate. Chapter 5 also showed that the rate is often underestimated when the respiratory rate is estimated instead of counted. The multivariable regression analysis with a backward selection of all candidate predictors resulted in respiratory rate, but not heart rate remained in the model. However, collinearity of the variables was observed, and predictions remained almost identical after replacement of the respiratory rate by heart rate. The simplified model is easy for every GP to assess, as both the measurements and the score calculation is straightforward. Another advantage of the simplified model may be that the score is not a "black box". The future may well be that machine learning algorithms using all available data provide far better predictions of the need for hospital treatment in patients with possible sepsis than simple models or experienced clinicians.[23, 24] If used in the primary care setting, this will take many

years to develop, validate and implement. A simple tool that then can be implemented without additional resources in the primary care setting seems the most logical first step.

Why a new score?

The SIRS, qSOFA and NEWS scores are extensively investigated for the diagnosis of sepsis in the hospital setting, and it can be argued that GPs should instead use an existing validated score rather than a new score. The TeSD-IT study showed that the NEWS score resulted in similar diagnostic accuracy as our newly developed model. SIRS and qSOFA provided lower diagnostic accuracy, in line with previous research performing a head-to-head comparison in the ED setting.[25] The NEWS score may well be a valuable tool for the primary care setting, but its complexity may deter GPs to calculate the complete score in patients who are not apparently severely ill. Especially the respiratory rate measurement may be problematic, as shown in chapter 5. Our data showed that the respiratory rate did not add clinically relevant information to the model. Without the need for respiratory rate measurement, a simple model can be quickly assessed in all acutely ill patients by GPs.

POCT in suspected sepsis

In chapters 7 and 8, we showed that none of the tested biomarkers added clinically relevantly to a model of only clinical symptoms and signs in acutely ill adult patients in the primary care setting. We, therefore, did not include any biomarkers in the new model and did not advise GPs to use these POCT in patients suspected of sepsis. CRP is currently often used by GPs in patients with lower respiratory tract infections to diagnose pneumonia and decide on antibiotic treatment.[26, 27, 28] POCT enables the GP to assess the CRP level accurately from a finger prick in a few minutes. Given the accessibility, GPs may be tempted to use POCT in other clinical scenario's to assess the severity of an infection or to distinguish infections from other diagnoses. GPs should be aware of the limitations of CRP testing in patients with suspected sepsis. Not all patients with high CRP levels need hospital treatment, and, maybe, more importantly, CRP can be normal in patients with sepsis. In the TeSD-IT study, a CRP <20 mg/L resulted in a sensitivity of 87% and a negative predicted value of 72% for sepsis. Therefore, sepsis cannot be safely excluded using CRP in the primary care setting. A possible explanation is that it takes about 6-8 hours for CRP levels to rise after the onset of infection.[29] In sepsis, the progression of infection to organ dysfunction can develop within several hours. Especially in infections with rapid illness progression, delay in treatment can be detrimental.

In chapter 8, we assessed several available biomarkers, of which none showed additional diagnostic value in combination with a model of clinical signs and symptoms. New biomarkers may be discovered in the future, which may be helpful to identify patients with (increased risk) of sepsis. However, with the currently available evidence, it seems better to improve the recognition of sepsis in the primary care setting using signs and symptoms. If new biomarkers are proven to be helpful in the hospital setting in diagnostic strategies of patients with possible sepsis, it may be appropriate to investigate the benefits

in the prehospital setting. A further condition is a possible application using POCT, and results being available within a few minutes.

Consequences of the COVID-19 pandemic

The data collection of the TeSD-IT study was performed between June 2018 and March 2020. The first COVID-19 case was diagnosed in February 2020 in the Netherlands, and none of the participants in the study were tested positive for COVID-19. The validity of the developed diagnostic sepsis model may differ in a pandemic situation, either if this is SARS-CoV-2 or another highly infectious virus. During epidemic waves of COVID-19 a substantial proportion of the acutely ill patients presenting in primary care may be suffering from COVID-19. However, several factors may limit the impact on the model's validity. Firstly, the model is advised to determine the need for hospital referral due to suspected sepsis regardless of whether the source of infection is bacterial or viral. Prediction models for assessing the severity of COVID-19 often consist of the same predictors as used in the TeSD-IT model,[30] suggesting the model is likely to be valid in the case of COVID-19. Secondly, the diagnosis of COVID-19 is often known before hospital referral is considered due to extensive testing of Sars-CoV-2 with either PCR or antigen tests. GPs can therefore take this into account when using the model. Finally, the prevalence and pathogenicity are likely to decrease in the coming years to increase immunity in the population resulting from vaccinations and infections. At the moment of publication of this thesis, predictions of the future impact of COVID-19 remains highly uncertain, but a plausible scenario is SARS-CoV-2 to become one of the endemic viruses causing a flu-like illness.[31] In the study population of the TeSD-IT study, several patients were diagnosed with viral infections. Depending on the development of the COVID-19 pandemic, it may be necessary to validate our new developed model in a population which includes patients with COVID-19.

Impact of the model in practice

In chapter 9, an early economic evaluation is described, in which the effects of several referral strategies based on the model's score are assessed in the population of patients included in the TeSD-IT study. This chapter suggests that no gains in QALYs or healthcare costs are expected after implementing the prediction model. This may turn out to be accurate, but as no other known sepsis score or other diagnostic strategy is likely to give better results, it may be worthwhile to investigate the effects in real life. Two critical factors could have biased the analysis presented in chapter 9, and relevant improvement in recognition of sepsis is still possible due to the implementation of the new sepsis model. Firstly, all patients were included by GPs who already considered the diagnosis sepsis. The GP had to assess eligibility and ask the patients' consent to participate in a sepsis study. Secondly, a complete set of vital signs was measured in all patients. The study protocol instructed the GP to report the tympanic temperature, blood pressure, peripheral oxygen saturation, heart rate, respiratory rate and mental status on the case report form. The vital signs were reported almost without missing values. This was primarily due to the drivers' assistance who accompanied the GP during the home visits, but it is unlikely the GP would

not have taken notice of the measurements. Therefore, the newly developed prediction model's clinical information was available to the GP. In everyday clinical practice, vital signs are often measured incompletely.[32] Not considering the diagnosis of sepsis and incomplete measurement of vital signs may be important reasons why cases of sepsis are not recognised and contribute to poor outcomes. Both factors could result in a more considerable improvement in the recognition of sepsis than suggested in chapter 9.

How to use the model in practice

Chapter 9 showed that the model is not likely to improve usual care if the decision to refer a patient is based solely on the score of the model. However, we did show in chapter 7 that the prediction of the score was more accurate than the overall judgement of the GP. As discussed in chapter 9, the model should therefore not overrule the opinion of the GP, but should be incorporated in the overall judgement. The following advice based on the model's score may be appropriate. In case the model's score is low (total points 0 or 1), the risk of sepsis is low, and referral is only warranted if a specific diagnosis requiring hospital treatment is considered (e.g. appendicitis). In intermediate scores (total score of 2 or 3 points), sepsis should be considered, and patients who are not immediately referred may need reassessment. In case of a high score on the model (total score of 4 to 6 points), sepsis is likely, and patients should be immediately referred unless there is a good reason not to (for instance, a patient's preference to stay at home).

Proposals for future research

So, what is the best way to go forward from here? Is the model developed in the TeSD-IT study ready to be implemented in daily clinical practice? In general, validation studies are advised before implementation. Chapter 7 also described the external validation in two populations of patients with suspected infections in the ED. Ideally, the model is externally validated in the primary care setting in patients where the decision to refer a patient to the hospital has yet to be made. However, this would take a new prospective diagnostic study as no adequate datasets are currently available from the primary care setting. Relevant prehospital data is only available from patients transported by ambulance. Wallgren and colleagues performed a diagnostic study in the ambulance setting in Sweden in which both the relevant predictors as the outcome sepsis (according to Sepsis-3 criteria) were collected.[19] If our new model shows good diagnostic performance during external validation in this study population (superior or comparable to NEWS), it will make it reasonable to also consider the new model in the ambulance setting. However, the weaker performance of our model in the ambulance setting does not prove the model is not valid in the primary care setting. All patients in the ambulance setting are transported to the hospital, and this difference in case-mix may cause a decrease in the performance of the model.

The best way to test if the new model improves the current management of patients with suspected sepsis by GPs is to perform an implementation study in which GPs are

instructed to use the model. A pragmatic trial performed at several GP cooperatives can subsequently be performed to show the effect of the implementation in real life. Hospital costs and patient outcomes should be measured in all patients at risk. Ideally, sepsis-related mortality is reduced as well as hospital costs. Total costs may increase due to an increase in hospital referrals. In that case, the model should only be implemented in GP guidelines if the costs per QALY gained are acceptable.

OOH home visits is the setting in primary care in which the model is most likely to improve care. Our research group currently performs a retrospective study in cooperation with Nivel, in which GP cooperative contacts from about 1 million inhabitants of the Netherlands in the period 2017-2019 are analysed. This study aims to identify high-risk sepsis groups based on information available during telephonic triage. Preliminary results from this study confirm that patients receiving home visits are most at risk of sepsis compared to patients assessed during a clinic consultation. In case implementation of the model in patients receiving home visits shows to improve care, broadening of the use to other primary care populations should be considered. If no detrimental effects are observed in low-risk populations, GPs should use a similar approach both in OOH and daily practice.

In conclusion, the new model developed in the TeSD-IT study is a promising new tool for general practitioners to improve the recognition of sepsis. The model consists of clinical signs and symptoms that are easy to assess by GPs in all acutely ill patients. Biomarkers and the respiratory rate did not add to the model performance, making it easier to implement in practice. However, effects on patient outcomes and costs when used in practice should be evaluated carefully. Guidelines for managing sepsis in primary care should be formulated as soon as sufficient evidence is obtained. However, even then, research should continue to keep improving diagnostic strategies for sepsis.

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Appendices

Summary

Sepsis is one of the most common causes of mortality accounting for 11 million annual deaths globally. Early initiation of adequate therapy is the key factor to improve outcome and prevent unnecessary mortality. Therefore, it is crucial for general practitioners (GPs) to recognise sepsis in the early stages, and refer patients to the hospital timely. Definitions of sepsis have changed in the past decades. In 1991, the first international consensus definition of sepsis was formulated. The Systemic Inflammatory Response Syndrome (SIRS) was used to define sepsis in patients with suspected infections, and severe sepsis was defined as a combination of sepsis and organ failure. In 2016, the latest consensus definitions (Sepsis-3) abandoned the SIRS criteria as part of the sepsis definition. Now sepsis is defined as "a life threatening organ dysfunction as result of a dysregulated host response to infection". The Sequential Organ Failure Assessment (SOFA) score is used as a measure for organ dysfunction. A minimum increase of two points on the SOFA score from baseline is conditional for sepsis. GPs are often confronted with patients with acute infections and have to decide which patients are at risk of sepsis and need immediate hospital care, and who can be treated safely at home. Sepsis can be hard to distinguish from presentations of less severe illnesses such as influenza. Also, elderly patients who are most at risk of sepsis often present with subtle or atypical symptoms. Currently, no guidelines for the recognition of sepsis in primary care are used in the Netherlands. Several scores are used in the hospital setting. SIRS criteria are highly sensitive for sepsis, and although no longer part of the sepsis definition, still valuable as screening tool to identify patients with possible sepsis. The quick SOFA (qSOFA) score is a new score introduced simultaneously with the Sepsis-3 definition as a bedside screening tool to identify patients with high risk for sepsis related mortality. Also, the National Early Warning Score (NEWS) or comparable warning scores are used in the hospital setting to identify patients who need further diagnostic test and treatment for possible sepsis. None of these sepsis scoring systems have been validated in the primary care setting. Diagnostic strategies in the primary care setting should not only focus on correctly identifying patient with sepsis, but should also limit unnecessary hospital referrals. Therefore, it is important to collect data of the target (primary care) population. We will only focus on sepsis in adult patients. Although the pathophysiology is essentially the same as in children, risk factors and clinical presentations differ significantly, making it more appropriate to investigate sepsis in children and adults separately. This thesis aims to explore the current prevalence and management of sepsis in the primary care setting, and develop an optimal strategy for guidance of hospital referral of adult patients with possible sepsis for GPs.

In **chapter 2**, we present the results of a questionnaire study among GPs in the Netherlands, in which we explored the clinical decision making process in patients with suspected severe infections. In the questionnaire, GPs were asked questions about the last patient referred to the hospital due to an acute infection, and the last patient with an infection treated with oral antibiotics. The factors most often indicated by GPs to be important for the decision to refer a patient to the hospital, were general appearance, gut feeling, history, and physical examination. For both the referred patients, and the patients treated with oral antibiotics the temperature and heart rate were the most frequently

measured vital signs. The respiratory rate was reported to be measured in 66% of the referred patients, and 37% of the patients treated with antibiotics. We also asked the GPs to rate the importance for the decision to refer a patient to the hospital for different premorbid conditions, and aspects of the history and physical examination. Chronic use of immunosuppressive medication and multimorbidity were the premorbid conditions most often rated as (very) important. Of the history, unable to stand, insufficient effect of previous antibiotic treatment and rapid progression of illness were most frequently rated as (very) important. Regarding the physical examination, altered mental status, systolic blood pressure, and a respiratory rate ≥22/minute were most often rated as (very) important. We concluded that the assessment of a patient with a possible serious infection is a complex process, in which GPs use many different aspects to decide whether or not to refer the patient to the hospital. Vital signs are important, but other valuable clinical information should not be disregarded.

In **chapter 3**, we investigated how often GPs encounter adult patients with suspected infections who meet the SIRS criteria at out-of-hours (OOH) GP cooperatives, and how these criteria are associated with hospital referral. The vital signs of SIRS (temperature <36 or >38 °C, heart rate >90/min and respiratory rate > 20/min), are – although no longer part of the sepsis definition - still used in the hospital setting to screen for possible sepsis. During an eight week period, we instructed GPs to record the respiratory rate, heart rate and temperature in the electronic medical records of all patients with possible infections. Subsequently, anonymised medical records of all adult patients with possible infections were extracted. In total, 558 patients were included in the analyses. In 35/409 (9%) clinical consultations and 60/109 (40%) home visits, two or more SIRS criteria were present. Referral rate increased from 13% when no SIRS vital signs were abnormal to 68% when all three SIRS vital signs were abnormal. We also analysed the association between the individual vital signs of SIRS and other clinical signs with hospital referral. Independent associations for referral were found for decreased oxygen saturation, hypotension and rapid illness progression, but not for individual SIRS vital signs. An important finding in this study is the high prevalence of SIRS criteria in patients receiving home visits for possible infections. However, although patients with signs of SIRS are referred to the hospital more often, decreased oxygen saturation, hypotension and rapid illness progression seem to be most important for GPs to guide further management.

In **chapter 4**, we explored the role of OOH GP cooperatives in the care for patients with community-onset sepsis. We conducted a retrospective study in a population of adult patients who were admitted to the ICU of the Gelderse Vallei Hospital for the treatment of community onset sepsis in a period of five years. Subsequently, all contacts with the GP cooperative in the previous 72 hours were analysed. In total, 263 patients were included in the study, of which 127 (48%) had prior GP cooperative contacts. The median age of these patients was 70 years, and 43% were female. The type of contacts mostly concerned home visits (59%), followed by clinic consultations (18%), direct ambulance deployment (13%) and telephone advice (10%). Patients assessed by a GP were referred in 64% after the first contact. The median delay to hospital arrival was 1.7 hours. The GP had not considered an infectious diagnosis in 43% of the patients. In these patients, the in-hospital mortality rate was significantly higher compared with patients with suspected infections (42%

versus 16%). The results of this study show that GP cooperatives play an important role in the prehospital management of sepsis, and about one in three patients admitted to the ICU with community-onset sepsis is assessed during a home visit in the 72 hours prior to admission. The recognition of sepsis is suboptimal as only two thirds of the patients were referred to the hospital after the first contact, and an infection was not considered as the cause of the acute complaints in almost half of the cases. The highest mortality rates were observed in those patients in whom GPs had not suspected an infection. Efforts to improve the identification and management of sepsis in the primary care setting should therefore not be limited to patients with obvious signs of infection, but also include acutely ill patients without a clear diagnosis.

In **chapter 5**, we describe a study in which the accuracy and feasibility of the respiratory rate measurement by GPs is assessed. Tachypnoea can be an early sign of sepsis and is used as one of the variables in the SIRS, qSOFA and NEWS. The respiratory rate should be counted in every patient suspected of critical illness according to the ABCDE-approach, which is currently also part of the GP training program in the Netherlands. However, the respiratory rate is measured less frequently than other vital signs, and the accuracy of the measurement by GPs has not been studied previously. We performed semi-structured interviews with GPs, and observed the respiratory rate measurement during assessments of acutely ill adult patients during home visits by OOH GP cooperatives. The accuracy of the GP measurement was assessed by comparing the reported rate with a 60-second reference measurement by a member of the research team who was present during the home visit. We analysed results of 130 home visits and interviews with 14 GPs. The respiratory rate was counted during at least 15 seconds in 33/123 (25%) of the patients. A mean difference of 0.27 breaths per minute was found with the reference measurement. This resulted in a sensitivity 86% and a specificity of 100% at a cut-off point of ≥ 22 breaths per minute (as used in the qSOFA score). In 48 home visits during which the respiratory rate was not counted, GP were asked afterwards if the rate was estimated to be ≥ 22 breaths per minute or not. These estimated values resulted in a sensitivity of 43% and a specificity of 96%. All GPs reported to measure the respiratory rate, although some (very) infrequently. Many GPs reported that they do not use the respiratory rate for patient management and rely more on oxygen saturation to assess potential respiratory failure. Practical problems mentioned, were that the measurement could be hindered by the clothing or movements of the patient, and the time required for the measurement. Based on these results, we concluded that counted respiratory rate measurements by GPs are accurate. However, the respiratory rate is not counted in most patients, and the rate is often underestimated when estimated, with important loss of sensitivity to detect a high respiratory rate.

In **chapter 6**, we describe the study methods of the TeSD-IT study (**Te**sting for **S**epsis in primary care: **D**iagnostic and prognostic study **I**nvestigating the potential benefits of point-of-care **T**esting). The aim of this study was to develop a clinical prediction model to support early diagnosis and management of sepsis by GPs. In this study, clinical information and biomarkers that can be assessed at the bedside were considered as predictors in the model. Patients were recruited at OOH GP cooperatives during home visits. All acutely ill adult patients (≥18 years) with fever, confusion or general deterioration or otherwise suspected of a serious infection were eligible for inclusion. Written informed consent were

obtained from the patient or legal representative in case of mental incapacitation. The following candidate predictors were recorded prospectively: 1) age; 2) body temperature; 3) systolic blood pressure; 4) heart rate; 5) respiratory rate; 6) peripheral oxygen saturation; 7) altered mental status; 8) rigors and 9) rapid illness progression. After the clinical assessment of the GP, blood samples were collected in all patients to measure C-reactive protein, lactate and procalcitonin. All patients received care as usual. The primary outcome was presence or absence of sepsis within 72 hours after inclusion. An expert panel of three members were used to determine the primary outcome, and the secondary outcome "need for hospital treatment". The expert were instructed to apply the Sepsis-3 criteria. The required sample size had to consist of at least 120 outcomes using the rule of thumb of at least 10 outcomes per variable. As the proportion of outcomes could not be estimated accurately before the study, the final target sample size was determined after expert panel assessment of the first 100 included patients. For the development of the model, first an optimal model of only clinical predictors was designed using multivariable logistic regression analyses with backwards selection. Missing data were imputed using Multivariate Imputation by Chained Equations (MICE) and spline transformations were be used for continuous variables without a linear relationship with the logit of the outcome. Subsequently, the added value of the biomarkers to the model of clinical predictors was assessed. Finally, a simplified model was constructed that enhances feasibility of using the model in daily clinical practice. The developed models were internally validated and were also compared to SIRS, qSOFA and NEWS.

In **chapter 7**, we reported the main results of the TeSD-IT study. The new developed clinical prediction model for the recognition of sepsis in the primary care setting was externally validated in two datasets of adult patients with suspected infections in the emergency department. Between June 2018 and March 2020, a total of 357 patients were included in the study at four GP cooperatives central to south in the Netherlands. The median age was 80 years and 61% of the patients were male. According to the expert panel judgement, 151/357 (42%) of the patients met the primary outcome "sepsis within 72 hours of inclusion". The GPs referred 199 patients (56%) to the ED directly after inclusion. Twelve patients (3.4%) were admitted to the ICU within 72 hours after inclusion, and overall 30-day mortality was 5.6%. In both the sepsis group and the non-sepsis group, the most frequent diagnoses were respectively respiratory tract infections and urinary tract infections. 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. After correction for optimism, the continuous model without biomarkers had a C statistic of 0.80 (95% CI 0.75 to 0.84). The biomarkers CRP, procalcitonin and lactate did not result in a clinically relevant improvement of the performance of the model. In the simplified model, we substituted the respiratory rate for the heart rate as this resulted in similar performance and is easier to measure by GPs. The final model consisted of a simple count of one point for each of the following six variables: age>65 years, temperature>38°C, systolic blood pressure≤110 mmHg, heart rate>110/min, saturation≤95% and altered mental status. This model resulted in a C statistic of 0.80. NEWS showed similar prediction (C statistic 0.79). SIRS and qSOFA showed a C statistic of respectively 0.66 and 0.71. The simplified model was deemed robust during sensitivity analysis and external validation. We concluded that a simple score-based model can

accurately predict sepsis in adult primary care patients with suspected severe infections. However, 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.

In **chapter 8**, we presented the results of additional testing of biomarkers from blood samples obtained during the TeSD-IT study. As described in the previous two chapters, we selected the biomarkers lactate, CRP and procalcitonin as candidate predictors during the development of the new sepsis prediction model. These biomarkers are feasible to measure with a POCT device and shown to have potential to predict sepsis in the hospital setting, but were not included in the final model. In this chapter, we presented the complete analyses of these three biomarkers, but also other biomarkers feasible to measure in the primary care setting with POCT. We used the data of 336 patients included in the TeSD-IT study who also provided additional written informed consent for the use of stored blood samples for research purposes. The biomarkers high-sensitive-troponin, NT-proBNP, creatinine, urea and pancreatic stone protein were additionally measured from the samples stored at ≤-70 ° C. The diagnostic performance of the biomarkers for the outcome "sepsis within 72 hours" was analysed as a standalone test, and in addition to a model of clinical signs and symptoms. For all biomarkers, statistically significant higher values were found in the patients with sepsis compared to the non-sepsis group. The C statistic for the model with clinical symptoms and signs was 0.83 (95% CI 0.79-0.88). Both lactate and procalcitonin increased the C statistic to 0.84, but, none of the biomarkers significantly changed the net reclassification index. Furthermore, procalcitonin or any other tested biomarkers could not rule out sepsis at any cut-off value in this population, as the chance of a false-negative result was at least 20%. Therefore, we concluded that POCT of any of the biomarkers tested in this study is not helpful for the recognition of sepsis in the primary care setting.

In **chapter 9**, we present an early economic evaluation of the model developed in the TeSD-IT study. Before introduction of a new diagnostic strategy in clinical practice, it should be likely that the intervention is cost-effective. The use of the model by GPs in itself does not result in additional costs, but increased healthcare costs can occur as a result of an increase of unnecessary hospital referrals even if the recognition of sepsis is improved compared to usual care. In this study, we evaluated the expected effects on health outcomes and costs, if hospital referral of the study population of the TeSD-IT study would be based on the score of the simplified model. We tested four different scenarios: 1) a cut-off score of 2 (no referral at a score <2, and referral at ≥2), 2) a cut-off score of 3 ,3) a cut-off score of 4, and 4) a mixed scenario: patients below a score of 2 are not referred, while patients with a score of 4 or higher are referred. In case of a score of 2 or 3, referral remained unchanged. A decision tree with a time horizon of one month was built to estimate the referral rate and costs impact, in case the model would be implemented. The potential impact of direct referral of sepsis patients on mortality and hospital admission was estimated by an expert panel. Also, the room for improvement was calculated by comparing the observed costs with a hypothetical scenario in which all patients requiring hospital referral are directly referred to the hospital by the GP. We found that, when using the model, cost-savings due to direct referral of sepsis patients

was offset by increased costs due to unnecessary referral for all cut-offs of the prediction model. With "perfect" referral, it is estimated that €137,882 could be saved in the 357 study patients. We concluded that guidance for referral of adult patients with suspected sepsis in the primary care setting using any cut-off point of the sepsis prediction model is not likely to save costs. The model may help GPs to improve the recognition of sepsis, but improvement of care should be observed in an implementation trial before incorporation of the model in sepsis guidelines for GPs.

In **chapter 10**, we discuss the main findings, reflect on the relevance of early detection of sepsis in the primary care setting, how the new developed sepsis prediction model may be used to improve care, and further research needed. Studies in the primary care setting concerning (severe) infections are almost all focused on specific diagnoses such as pneumonia of urinary tract infections. Although sepsis is a complication of an underlying infection, we discuss why a more general approach in case of possible sepsis is needed. The research presented in this thesis provides insight into the prevalence of patients with (suspected) sepsis, the current management, and a simple prediction model which can be easily used by GPs during assessment of acutely ill patients. The fact that biomarkers and the respiratory rate did not contribute relevantly to the model was unexpected, but makes the implementation in practice more easy. The diagnostic accuracy combined with simplicity makes us believe that our new developed model is more suited for the implementation in primary care than existing sepsis scores. However, it is important to show improvement compared to usual care before formulating new GP guidelines for suspected sepsis.

Nederlandse samenvatting

Sepsis is één van de belangrijkste doodsoorzaken. Jaarlijks sterven er wereldwijd 11 miljoen mensen aan sepsis. Snel starten met behandeling is de belangrijkste factor om onnodige sterfte te voorkomen. Daarom is het voor huisartsen cruciaal om sepsis in een vroeg stadium te herkennen en patiënten tijdig door te verwijzen naar het ziekenhuis. Definities van sepsis zijn de afgelopen decennia veranderd. In 1991 werd de eerste internationale consensusdefinitie van sepsis geformuleerd. Sepsis werd destijds gedefinieerd als de combinatie van de klinische verdenking op een infectie en de aanwezigheid van SIRS (Systemic Inflammatory Response Syndrome). Er is sprake van SIRS bij minimaal twee van de volgende vier criteria: temperatuur >38 of <36 °C; hartfrequentie >90 slagen per minuut; ademhalingsfrequentie >20 ademhalingen per minuut; leukocyten >12 of <4 x 10^9/L. Ernstige sepsis werd gedefinieerd als een combinatie van sepsis en orgaanfalen. De huidige consensusdefinitie die in 2016 is gepubliceerd (Sepsis-3), heeft de SIRS-criteria verlaten als onderdeel van de sepsisdefinitie. Nu wordt sepsis gedefinieerd als "een levensbedreigende orgaandisfunctie als gevolg van een ontregelde reactie van de gastheer op een infectie". Hierbij wordt de Sequential Organ Failure Assessment (SOFA)-score gebruikt als een maat voor orgaandisfunctie. Er dient minimaal een toename van twee punten op de SOFA-score te zijn ten opzichte van de situatie voor de infectie.

Huisartsen zien vaak patiënten met acute infecties en moeten beslissen welke patiënten ze wegens (verdenking op) sepsis direct naar het ziekenhuis verwijzen en welke patiënten veilig thuis kunnen worden behandeld. Sepsis kan soms lastig te onderscheiden zijn van minder ernstige infecties zoals influenza. Ook hebben oudere patiënten die het meeste risico lopen op sepsis, vaak subtiele of atypische symptomen. Op dit moment zijn er geen specifieke richtlijnen voor de herkenning van sepsis door huisartsen. In het ziekenhuis worden verschillende scores gebruikt voor de vroege herkenning van sepsis. Ondanks dat de SIRS-criteria geen onderdeel meer uitmaken van de sepsisdefinitie, zijn deze nog steeds waardevol als screeningsinstrument om patiënten met mogelijke sepsis te identificeren. De quick SOFA (qSOFA)-score is een nieuwe score die gelijktijdig met de Sepsis-3-definitie is geïntroduceerd. Hiermee kan aan het bed een inschatting worden gemaakt of er een verhoogd risico is op een ernstig beloop waarvoor IC opname noodzakelijk is. De National Early Warning Score (NEWS) of hiermee vergelijkbare scores, worden ook steeds meer gebruikt in het ziekenhuis om vast te stellen welke patiënten baat hebben bij verdere onderzoeken en behandeling wegens mogelijke sepsis. Geen van deze scores is echter gevalideerd in de eerstelijnszorg. In de eerste lijn is het niet alleen belangrijk om alle patiënten met sepsis tijdig te herkennen, maar ook om het aantal onnodige verwijzingen naar het ziekenhuis te beperken. Het is daarom belangrijk om onderzoeksgegevens te verzamelen in de eerste lijn. We richten ons in dit proefschrift alleen op sepsis bij volwassenen. Hoewel het om hetzelfde ziektebeeld gaat, verschillen de risicofactoren en klinische presentaties aanzienlijk, waardoor het beter is om sepsis bij kinderen en volwassenen afzonderlijk te onderzoeken. De doelstelling van dit proefschrift is het onderzoeken van de huidige prevalentie en behandeling van sepsis in de eerstelijnszorg en het ontwikkelen van een optimale strategie voor huisartsen, om te bepalen welke patiënten naar het ziekenhuis dienen te worden verwezen vanwege een verdenking op sepsis.

In **hoofdstuk 2** presenteren we de resultaten van een vragenlijstonderzoek onder huisartsen in Nederland, waarin we het klinische besluitvormingsproces bij patiënten met verdenking op ernstige infecties hebben onderzocht. In de vragenlijst zijn aan de huisartsen vragen gesteld over de meest recente patiënt die zij vanwege een acute infectie naar het ziekenhuis hadden verwezen en de meest recente patiënt die zij met orale antibiotica hadden behandeld. De factoren die huisartsen het vaakst aangaven als belangrijk voor de beslissing om een patiënt naar het ziekenhuis te verwijzen, waren algemene indruk, niet-pluisgevoel, anamnese en lichamelijk onderzoek. Voor zowel de verwezen patiënten als de patiënten die werden behandeld met orale antibiotica waren temperatuur en hartfrequentie de meest gemeten vitale functies. De ademhalingsfrequentie werd gemeten bij 66% van de verwezen patiënten en bij 37% van de patiënten die werden behandeld met antibiotica. We vroegen de huisartsen ook om in het algemeen een inschatting te maken van het belang van specifieke aandoeningen in de voorgeschiedenis en aspecten van de anamnese en lichamelijk onderzoek voor de beslissing om een patiënt naar het ziekenhuis te verwijzen. Chronisch gebruik van immunosuppressieve medicatie en multimorbiditeit waren de aspecten in de voorgeschiedenis die het vaakst als (zeer) belangrijk werden beoordeeld. Van de anamnese waren de belangrijkste aspecten "niet meer goed op de benen kunnen staan", "onvoldoende effect van eerder gestarte antibiotica", en "snelle toename van klachten" het vaakst als (zeer) belangrijk beoordeeld. Van de onderdelen van het lichamelijk onderzoek werden veranderd bewustzijn, systolische bloeddruk en een ademhalingsfrequentie ≥ 22/min het vaakst als (zeer) belangrijk beoordeeld. We concludeerden hieruit dat de beoordeling van een patiënt met een mogelijk ernstige infectie een complex proces is, waarbij huisartsen veel verschillende aspecten van het consult gebruiken om te beslissen om de patiënt al dan niet door te verwijzen naar het ziekenhuis. Vitale parameters spelen een belangrijke rol bij de beoordeling, maar andere klinische informatie kan een belangrijke toegevoegde waarde hebben en moet niet worden genegeerd.

In **hoofdstuk 3** hebben we onderzocht hoe vaak huisartsen volwassen patiënten met een vermoedelijke infectie die voldoen aan de SIRS-criteria beoordelen op de huisartsenpost, en hoe deze criteria samenhangen met verwijzing naar het ziekenhuis. De vitale functies van SIRS (temperatuur <36 of >38 °C, hartfrequentie >90/min en ademhalingsfrequentie > 20/min) worden – hoewel niet langer onderdeel van de sepsisdefinitie – nog steeds gebruikt in de ziekenhuisomgeving om te screenen op mogelijke sepsis. Gedurende een periode van acht weken hebben we huisartsen gevraagd om de ademhalingsfrequentie, hartfrequentie en temperatuur vast te leggen in het elektronisch medisch dossier van alle patiënten die ze verdachten van een infectie. Vervolgens werden geanonimiseerde medische dossiers van alle volwassen patiënten met mogelijke infecties geanalyseerd. In totaal werden 558 patiënten in het onderzoek geïncludeerd. Bij 35/409 (9%) van de consulten en 60/109 (40%) van de huisbezoeken waren twee of meer SIRS-criteria aanwezig. Het percentage ziekenhuisverwijzingen nam toe van 13% wanneer geen enkele SIRS-parameter afwijkend was tot 68% wanneer alle drie de SIRS-parameters afwijkend waren. Naast de individuele SIRS-parameters onderzochten we ook de associatie tussen andere klinische kenmerken en ziekenhuisverwijzing. Onafhankelijke associaties met verwijzing werden gevonden voor verlaagde zuurstofsaturatie, hypotensie en snelle ziekteprogressie, maar niet voor de individuele SIRS-parameters. Een belangrijke

bevinding in deze studie is de hoge prevalentie van positieve SIRS-criteria bij patiënten die een huisvisite krijgen wegens infecties. Echter, hoewel patiënten met tekenen van SIRS vaker naar het ziekenhuis worden verwezen, lijken verminderde zuurstofsaturatie, hypotensie en snelle ziekteprogressie de belangrijkste klinische kenmerken te zijn voor huisartsen om te beslissen of een patiënt naar het ziekenhuis moet worden verwezen.

In **hoofdstuk 4** hebben we de rol van huisartsenposten in de zorg voor patiënten met sepsis onderzocht. We voerden een retrospectief onderzoek uit in een populatie van volwassen patiënten die binnen een periode van vijf jaar waren opgenomen op de IC van Ziekenhuis Gelderse Vallei voor de behandeling van sepsis die buiten het ziekenhuis was ontstaan. Vervolgens zijn alle contacten met de huisartsenpost in de voorafgaande 72 uur geanalyseerd. In totaal werden 263 patiënten geïncludeerd, van wie 127 (48%) voorafgaand contact met de huisartsenpost hadden. De mediane leeftijd van deze patiënten was 70 jaar en 43% was vrouw. Het type contact betrof vooral huisvisites (59%), gevolgd door consulten (18%), directe inzet van een ambulance (13%) en telefonisch consult (10%). Van de patiënten die door een huisarts werden beoordeeld, werd 64% direct verwezen naar het ziekenhuis. De mediane tijd tot aankomst in het ziekenhuis bedroeg 1,7 uur. Bij 43% van de patiënten had de huisarts geen verdenking op een infectieuze oorzaak van de klachten. Bij deze patiënten was de mortaliteit in het ziekenhuis significant hoger in vergelijking met patiënten die wel werden verdacht van een infectie (42% versus 16%). De resultaten van deze studie laten zien dat huisartsenposten een belangrijke rol spelen bij de prehospitale behandeling van sepsis. Ongeveer één op de drie patiënten die op de IC worden opgenomen met sepsis die buiten het ziekenhuis is ontstaan, wordt voorafgaand tijdens een huisvisite beoordeeld. De herkenning van sepsis is suboptimaal aangezien slechts tweederde van de patiënten na het eerste contact naar het ziekenhuis wordt verwezen en in bijna de helft van de gevallen een infectie niet als oorzaak van de acute klachten werd overwogen. De hoogste sterftecijfers werden juist waargenomen bij patiënten zonder dat de huisarts verdenking op een infectie had. Pogingen om de herkenning van sepsis in de eerstelijnszorg te verbeteren moeten daarom niet beperkt blijven tot patiënten met duidelijke tekenen van infectie, maar ook gericht zijn op acuut zieke patiënten zonder een duidelijke diagnose.

In **hoofdstuk 5** beschrijven we een onderzoek naar de betrouwbaarheid en bruikbaarheid van de meting van de ademhalingsfrequentie door huisartsen. Tachypnoe kan een vroeg teken van sepsis zijn en maakt onderdeel uit van zowel de SIRS, qSOFA als NEWS. Bij elke (mogelijk) kritiek zieke patiënt dient de ademhalingsfrequentie te worden geteld volgens de ABCDE-methodiek. De ABCDE-methodiek maakt momenteel ook onderdeel uit van de huisartsenopleiding in Nederland. De ademhalingsfrequentie wordt echter minder vaak gemeten dan andere vitale functies en de nauwkeurigheid van de meting door huisartsen is niet eerder onderzocht. We hielden semigestructureerde interviews met huisartsen en observeerden de ademhalingsfrequentiemeting tijdens beoordelingen van acuut zieke volwassen patiënten tijdens huisvisites van een huisartsenpost. De nauwkeurigheid van de meting door de huisarts werd beoordeeld door te vergelijken met een referentiemeting van 60 seconden door een onderzoeker die tijdens de visite aanwezig was. We analyseerden in totaal resultaten van 130 huisvisites en interviews met 14 huisartsen. De ademhalingsfrequentie werd bij 33/123 (25%) van de patiënten gemeten

door gedurende ten minste 15 seconden te tellen. In vergelijking met de referentiemeting werd een gemiddeld verschil van 0,27 ademhalingen per minuut gevonden. Dit resulteerde in een sensitiviteit van 86% en een specificiteit van 100% bij een afkappunt van ≥ 22 ademhalingen per minuut (zoals gebruikt in de qSOFA-score). Bij 48 huisbezoeken waarbij de ademhalingsfrequentie niet werd geteld, werd de huisarts achteraf gevraagd of de frequentie ≥ 22 ademhalingen per minuut werd geschat of niet. Deze geschatte waarden resulteerden in een sensitiviteit van 43% en een specificiteit van 96%. Tijdens de interviews gaven alle huisartsen aan de ademfrequentie te meten, hoewel sommige (zeer) zelden. Veel huisartsen vermeldden dat ze meer vertrouwen op de saturatiemeter om mogelijke respiratoire insufficiëntie vast te stellen. Praktische problemen die genoemd werden, waren onder meer dat de meting belemmerd kan worden door de kleding of bewegingen van de patiënt en de tijdsinvestering die nodig is voor de meting. Op basis van deze resultaten concludeerden we dat getelde ademhalingsfrequentiemetingen door huisartsen betrouwbaar zijn. De ademhalingsfrequentie wordt bij de meeste patiënten echter niet geteld en een geschatte waarde is vaak te laag, waardoor tachypnoe in een belangrijk deel van de patiënten onopgemerkt kan blijven.

In **hoofdstuk 6** beschrijven we de methoden van de TeSD-IT studie (**Te**sting for **S**epsis in primary care: **D**iagnostic and prognostic study **I**nvestigating the potential benefits of point-of-care **T**esting). Het doel van deze studie was om een klinisch predictiemodel te ontwikkelen ter ondersteuning van vroege diagnose en behandeling van sepsis door huisartsen. Zowel klinische gegevens als bloedwaarden die aan het bed van de patiënt kunnen worden bepaald werden als variabelen in het predictiemodel overwogen. Patiënten werden geïncludeerd op huisartsenposten tijdens huisvisites. Alle acuut zieke volwassen patiënten (≥ 18 jaar) met koorts, verwardheid of algehele achteruitgang, of anderszins verdacht van een ernstige infectie kwamen in aanmerking voor inclusie. Schriftelijke toestemming werd verkregen van de patiënt of de wettelijke vertegenwoordiger van wilsonbekwame patiënten. De volgende gegevens werden geregistreerd: 1) leeftijd; 2) lichaamstemperatuur; 3) systolische bloeddruk; 4) hartfrequentie; 5) ademhalingsfrequentie; 6) saturatie; 7) veranderd bewustzijn; 8) koude rilling 9) snelle klinische achteruitgang. Na de beoordeling door de huisarts werden bij alle patiënten bloedmonsters afgenomen om daaruit CRP, lactaat en procalcitonine te meten. Alle patiënten werden verder behandeld zoals gebruikelijk. De primaire uitkomstmaat was sepsis binnen 72 uur na inclusie. Een expertpanel van drie leden werd gebruikt om de primaire uitkomstmaat en de secundaire uitkomst 'noodzaak voor ziekenhuisbehandeling' te bepalen. Het expertpanel werd geïnstrueerd de Sepsis-3 criteria toe te passen bij het vaststellen van de primaire uitkomst. Voor de berekening van de minimale omvang van de onderzoekspopulatie, werd gebruik gemaakt van de vuistregel dat er minimaal 10 uitkomsten per variabele nodig zijn. Bij het totaal van 12 variabelen komt dit neer op minimaal 120 uitkomsten. Omdat de proportie van patiënten dat de uitkomsten haalt niet nauwkeurig kon worden geschat voorafgaand aan het onderzoek, werd de uiteindelijke steekproefomvang bepaald na beoordeling door het expertpanel van de eerste 100 geïncludeerde patiënten. Voor de ontwikkeling van het model is eerst een optimaal model van alleen klinische variabelen ontworpen met behulp van multivariabele logistische regressieanalyse. Ontbrekende gegevens werden geïmputeerd en er werden transformaties overwogen van continue variabelen die geen lineaire relatie met de

uitkomst toonden. Vervolgens werd de toegevoegde waarde van de bloedwaarden ten opzichte van het model met alleen klinische variabelen beoordeeld. Ten slotte werd een vereenvoudigd model ontwikkeld dat eenvoudig in de dagelijkse klinische praktijk is toe te passen. De ontwikkelde modellen werden intern gevalideerd en tevens vergeleken met SIRS, qSOFA en NEWS.

In **hoofdstuk 7** hebben we de belangrijkste resultaten van de TeSD-IT studie beschreven. Het nieuw ontwikkelde predictiemodelmodel voor de herkenning van sepsis in de eerste lijn werd tevens extern gevalideerd in twee datasets van volwassen patiënten met verdenking op een infectie op de SEH. Tussen juni 2018 en maart 2020 werden in totaal 357 patiënten geïncludeerd op vier huisartsenposten in Nederland. De mediane leeftijd was 80 jaar en 61% van de patiënten was man. Volgens het oordeel van het expertpanel voldeden 151/357 (42%) van de patiënten aan de primaire uitkomstmaat "sepsis binnen 72 uur na inclusie". De huisartsen verwezen 199 patiënten (56%) direct na inclusie naar de SEH. Twaalf patiënten (3,4%) werden binnen 72 uur na inclusie op de IC opgenomen en de totale mortaliteit na 30 dagen was 5,6%. Bij zowel de patiënten met sepsis als de overige patiënten waren de meest voorkomende diagnoses luchtweginfecties, gevolgd door urineweginfecties. Van de negen klinische variabelen werden er zes opgenomen in het model met continue variabelen: leeftijd, temperatuur, systolische bloeddruk, ademhalingsfrequentie, saturatie en bewustzijn. Na correctie voor optimisme had het continue model zonder bloedwaarden een C-statistiek van 0,80 (95% BI 0,75 tot 0,84). De bloedwaarden CRP, procalcitonine en lactaat resulteerden niet in een klinisch relevante verbetering van het model. Bij het vereenvoudigden van het model werd besloten de ademhalingsfrequentie te vervangen door de hartfrequentie, omdat dit vergelijkbare prestaties opleverde en dit gemakkelijker te meten is door huisartsen. Het uiteindelijke model bestond uit een optelling van één punt voor elk van de volgende zes variabelen: leeftijd>65 jaar, temperatuur>38°C, systolische bloeddruk ≤110 mmHg, hartfrequentie >110/min, saturatie ≤95% en veranderd bewustzijn. Dit model resulteerde in een C-statistiek van 0,80. NEWS liet een vergelijkbare voorspelling zien (C-statistiek 0,79). SIRS en qSOFA lieten een C-statistiek zien van respectievelijk 0,66 en 0,71. Het vereenvoudigde model was robuust tijdens sensitiviteitsanalyse en externe validatie. We concludeerden dat een eenvoudige score sepsis nauwkeurig kan voorspellen bij volwassen patiënten met verdenking op ernstige infecties in de eerste lijn. De score vervangt echter niet het klinische oordeel van de huisarts en verder onderzoek zal moeten uitwijzen hoe huisartsen de score het beste kunnen gebruiken om de behandeling van patiënten met mogelijke sepsis te verbeteren.

In **hoofdstuk 8** presenteren we de resultaten van aanvullende testen van bloedwaarden uit veneuze bloedmonsters verkregen tijdens de TeSD-IT studie. Zoals beschreven in de vorige twee hoofdstukken, hebben we de bloedwaarden CRP, lactaat en procalcitonine geselecteerd als mogelijke voorspellers tijdens de ontwikkeling van het nieuwe sepsis predictiemodel. Deze bloedwaarden zijn makkelijk te meten met point-of-care testing (POCT) en voor deze bloedwaarden is in onderzoek in de tweede lijn de voorspellende waarde voor sepsis aangetoond. Wegens gebrek aan toegevoegde waarde ten opzichte van het model met alleen klinische variabelen, werden deze echter niet opgenomen in het uiteindelijke model. In dit hoofdstuk hebben we de volledige analyses van CRP, lactaat en

procalcitonine gepresenteerd, maar ook andere bloedwaarden die potentieel in de eerste lijn kunnen worden gemeten met POCT. We gebruikten de gegevens van 336 patiënten die deelnamen aan de TeSD-IT studie die ook schriftelijke toestemming hadden gegeven voor aanvullend onderzoek van de opgeslagen bloedmonsters. De bloedwaarden hs-troponine, NT-proBNP, creatinine, ureum en PSP (pancreatic stone protein) werden gemeten uit de bloedmonsters die waren bewaard bij -70 °C. De voorspellende waarden van de bloedwaarden voor de uitkomst "sepsis binnen 72 uur" werden zowel geanalyseerd als een op zichzelf staande test, als in aanvulling op een model van klinische variabelen. Voor alle bloedwaarden werden statistisch significant hogere waarden gevonden bij de patiënten met sepsis in vergelijking met patiënten zonder sepsis. De C-statistiek voor het model met klinische variabelen was 0,83 (95%-BI 0,79-0,88). Zowel lactaat als procalcitonine verhoogde de C-statistiek tot 0,84, maar geen van de bloedwaarden veranderde de netto reclassificatie-index significant. Bovendien konden procalcitonine of andere geteste bloedwaarden sepsis bij geen enkele afkapwaarde in deze populatie uitsluiten, aangezien de kans op een fout-negatief resultaat minimaal 20% was. We concluderen daarom dat POCT van de in dit onderzoek geteste bloedwaarden niet bijdragend is aan de herkenning van sepsis in de eerste lijn.

In **hoofdstuk 9** presenteren we een vroege economische evaluatie van het model dat we ontwikkelden in de TeSD-IT studie. Voordat een nieuwe diagnostische strategie in de praktijk wordt geïntroduceerd, moet het aannemelijk zijn dat deze interventie kosteneffectief is. Het toepassen van het model zelf gaat niet gepaard met extra kosten, maar door een toename van onnodige ziekenhuisverwijzingen kunnen wel hogere zorgkosten ontstaan, zelfs als de herkenning van sepsis is verbeterd ten opzichte van de gebruikelijke zorg. In deze studie evalueerden we de effecten op gezondheidsuitkomsten en kosten, in het geval ziekenhuisverwijzing van de onderzoekspopulatie van de TeSD-IT studie zou worden gebaseerd op de score van het vereenvoudigde model. We hebben vier verschillende scenario's getest: 1) een afkapwaarde van 2 (geen verwijzing bij een score <2 en wel verwijzing bij ≥2 punten), 2) een afkapwaarde van 3 ,3) een afkapwaarde van 4 , en 4) een scenario met twee afkapwaardes: patiënten onder een score van 2 worden niet verwezen, terwijl patiënten met een score van 4 of hoger worden verwezen. Bij een score van 2 of 3 bleef de verwijzing ongewijzigd ten opzichte van het beleid van de huisarts zoals werd geobserveerd. Er is een beslisboom gemaakt met een tijdshorizon van één maand om het aantal verwijzingen en effect op de kosten in te schatten. De potentiële impact van directe verwijzing ongewijzigd ten opzichte van het beleid van de huisarts zoals werd geobserveerd van patiënten met sepsis op mortaliteit en ziekenhuisopname werd geschat door een expertpanel. Ook is de maximale kostenbesparing berekend door de geobserveerde kosten te vergelijken met een hypothetisch scenario waarin alle patiënten die een ziekenhuisverwijzing nodig hebben ook direct door de huisarts naar het ziekenhuis worden verwezen. De resultaten van het onderzoek toonden aan dat bij gebruik van het model, de kostenbesparingen ten gevolge van terechte verwijzingen van patiënten met sepsis, werden tenietgedaan door hogere kosten als gevolg van onnodige verwijzingen. Dit was het geval voor alle afkapwaarden van model. Met een "perfecte" verwijzing zou naar schatting €137.882 bespaard kunnen worden bij de onderzoekspopulatie van 357 patiënten. We concludeerden dat verwijzing van volwassen patiënten met verdenking op sepsis in de eerste lijn met behulp van een afkappunt van het sepsis-voorspellingsmodel

waarschijnlijk niet kostenbesparend is. Het model kan huisartsen mogelijk helpen de herkenning van sepsis te verbeteren, maar positieve effecten op de kwaliteit van zorg dienen in een implementatieonderzoek te worden aangetoond voordat het model wordt opgenomen in richtlijnen voor huisartsen.

In **hoofdstuk 10** bespreken we de belangrijkste bevindingen, reflecteren we op de relevantie van vroege detectie van sepsis door huisartsen, hoe de nieuw ontwikkelde sepsis score kan worden gebruikt om de zorg te verbeteren en welk onderzoek er verder nodig is. Eerdere studies in de eerste lijn naar (ernstige) infecties zijn vrijwel allemaal gericht op specifieke diagnoses zoals longontsteking of urineweginfecties. Hoewel sepsis een complicatie is van een onderliggende infectie, bespreken we waarom een meer algemene aanpak bij sepsis nodig is. Het onderzoek in dit proefschrift geeft inzicht in de prevalentie van patiënten met (vermoedelijke) sepsis, de huidige behandeling en een eenvoudig voorspellingsmodel dat gemakkelijk door huisartsen kan worden gebruikt bij de beoordeling van acuut zieke patiënten. Dat bloedwaarden en de ademhalingsfrequentie geen relevante bijdrage hadden aan het model was onverwacht, maar maakt de implementatie in de praktijk wel makkelijker. De diagnostische nauwkeurigheid gecombineerd met eenvoud doet ons geloven dat ons nieuw ontwikkelde sepsis score geschikter is voor implementatie in de eerste lijn dan bestaande scores. Het is echter belangrijk om in verder onderzoek verbetering aan te tonen ten opzichte van de huidige zorg, voordat nieuwe huisartsrichtlijnen voor de herkenning van sepsis worden opgesteld.

Dankwoord

Begin 2015 begon ik met een eerste onderzoeksidee. Hier is zeven jaar later dan het tastbare resultaat van de succesvolle uitvoering hiervan. Naast dat ik heel trots ben op dit proefschrift, ben ik ook erg dankbaar voor alle hulp en steun die ik tijdens dit traject heb mogen ontvangen. Ik kan met recht zeggen dat er veel mensen een onmisbare rol hebben gespeeld om dit eindresultaat te kunnen bereiken. In het begin voelde het soms als een trein die ik eigenhandig op gang moest duwen en direct stil zou vallen als ik zou ophouden met duwen. In de afgelopen jaren is de trein steeds harder gaan rijden en voelt het geleidelijk meer als sturen in plaats van duwen.

Geachte prof. dr. T.J.M. Verheij, beste Theo, jij bent degene geweest die het risico aan heeft gedurfd veel tijd en energie te steken in het opzetten van de TeSD-IT studie, om later als eindverantwoordelijke en mijn eerste promotor leiding aan dit project te kunnen geven. Niet alleen was het uiterst onzeker of het überhaupt zou lukken financiering te vinden, ook was het op voorhand al duidelijk dat het een "logistiek uitdagend" project zou worden. Bovendien was sepsis een nieuw onderzoeksgebied binnen de huisartsgeneeskunde van het Julius Centrum. Zelf had ik als beginnende onderzoeker natuurlijk de neiging alles te optimistisch in te schatten. Jouw enorme ervaring en realisme in het uitvoeren van complexe onderzoeksprojecten waren essentieel om het tot een goed einde te kunnen brengen. Je hebt me vanaf het begin gewaarschuwd dat het includeren van patiënten door huisartsen tegen zou gaan vallen. Dit heeft zeker geholpen het niet te veel als een persoonlijk falen te zien, toen dit inderdaad het geval bleek. Wat ik verder enorm heb gewaardeerd is dat je op belangrijke momenten altijd direct beschikbaar was voor overleg. Ongeacht de omvang van het probleem was je altijd in staat direct met een goede oplossing te komen. Het snel knopen doorhakken maakte overleg ook erg efficiënt. Een half uur was altijd ruim voldoende om alles te bespreken, ongeacht hoe lang de lijst met punten was waar ik mee kwam.

Geachte prof. dr. A.R.H. van Zanten, beste Arthur, wat voelt het als een voorrecht samen met jou onderzoek te mogen doen. Ondanks je meer dan volle agenda reageerde je direct op mijn eerste mail om mee te werken aan retrospectief onderzoek onder IC patiënten naar de rol van de huisartsenpost. Je expertise op het gebied van sepsis als intensivist was onmisbaar, maar zeker ook je visie dat er in het traject voor de IC opname mogelijk veel winst is te behalen. Wat ik het meest bewonder en heb gewaardeerd is je onuitputtelijke energie en je vermogen dit op anderen over te dragen. Voorafgaand aan een afspraak voelde ik altijd al de motivatie en goede zin toenemen en na afloop kon ik er weer een tijdje tegen aan. Verder wil ik je nog bedanken dat je altijd tijd vrij hebt gemaakt op momenten dat het nodig was, vooral natuurlijk in de fase dat het onderzoek niet goed liep.

Geachte dr. Smits, beste Marleen, als dagelijkse begeleider heb je een heel belangrijk aandeel gehad in dit proefschrift. Maar belangrijker nog is je aandeel in mijn ontwikkeling als wetenschapper. In alle onderdelen van het wetenschappelijk onderzoek kan perfectionisme een belangrijke eigenschap zijn om kwaliteit te leveren, maar ook

belemmerend werken. Door jou heb ik de afgelopen jaren steeds beter geleerd om kwalitatief goed werk af te leveren zonder vast te lopen op punten die in mijn ogen beter kunnen. Schrijven is voor mij wellicht de grootste uitdaging binnen het onderzoek. Het kwam mijn productiviteit buitengewoon ten goede dat ik altijd stukken tekst (al dan niet met fouten) op kon sturen en erop kon vertrouwen dat ik het in afzienbare tijd terug had. Dat het een productieve samenwerking is geweest de afgelopen jaren blijkt niet alleen uit het aantal publicaties in dit proefschrift, maar ook uit de succesvolle subsidieaanvraag in 2020 voor de PRESHAPE studie en het indienen van een subsidieaanvraag voor een implementatiestudie het afgelopen jaar. Verder wil ik je op deze plaats natuurlijk ook bedanken voor de fijne samenwerking. Helaas hadden we door coronabeperkingen de laatste 2 jaar vooral telefonisch of online vergaderingen, maar daar hebben we ons toch ook weer vrij makkelijk aan aangepast.

Geachte dr. Hopstaken, beste Rogier, wat heb ik veel aan jou te danken en wat was het een avontuur dat we zijn aangegaan, toen je besloot mijn ambities voor een complex onderzoek vol te ondersteunen. Soms heb je iemand nodig die meer vertrouwen in je kunnen heeft dan jezelf hebt. Voor mij was het daar destijds precies het goede moment voor. Je hebt er voor gezorgd dat ik steeds meer in mezelf en in het project ging geloven. Bovendien opende het deuren bij andere mensen als ze wisten dat jij erbij betrokken was. Ik ben steeds meer gaan beseffen hoe bijzonder het is dat jij met de onderzoeksresultaten van je eigen promotieonderzoek vervolgstappen hebt gezet, totdat de CRP sneltest door de huisarts uiteindelijk in de dagelijkse praktijk is geïmplementeerd. Dit is voor mij een belangrijke inspiratie geweest en is dat nog altijd om mijn onderzoek voort te zetten. Jouw vaardigheden in presenteren en schrijven kan ik helaas nog lang niet benaderen, maar ik heb toch wel stappen gezet door bij jou de kunst af te kijken. Verder heb ik erg goede herinneringen aan de trips die we naar het buitenland hebben gemaakt en hopelijk komt het er ooit nog een keer van ergens een mooie ronde te fietsen.

Geachte dr. Giesen, beste Paul, hoewel je rol in het onderzoeksproject dat heeft geleid tot dit proefschrift zich vooral voor de start van mijn formele promotietraject heeft afgespeeld, is dit wel een cruciale rol geweest. Ik liep begin 2015 al enkele maanden in mijn hoofd met het idee om onderzoek te doen naar de toegevoegde waarde van lactaatmeting door huisartsen om sepsis beter te herkennen. Door het lezen van jouw stukken in Medisch Contact over innovaties in de huisartsenspoedzorg, ben ik geïnspireerd geraakt om hier ook echt werk van te maken. Ons eerste gesprek op de afdeling IQ healthcare van het Radboudumc zal ik niet snel vergeten en dit gaf een enorme energie om aan de slag te gaan. Als ik toen had geweten hoe moeilijk het is een onderzoek gefinancierd te krijgen, was ik er waarschijnlijk nooit aan begonnen, maar achteraf ben ik natuurlijk blij dat jij die naïviteit niet direct de kop hebt ingedrukt. Ik ben dankbaar voor de mogelijkheden die je bood om de eerste vooronderzoeken samen met stagestudenten uit te voeren en heb erg goede herinneringen aan de manier waarop we toen samenwerkten. Je bracht me al snel in contact met Rogier en Marleen die uiteindelijk mijn beide copromotoren zouden worden. Tijdens de uitvoering van de TeSD-IT studie bleef je betrokken, met name doordat we samen nog enkele wetenschappelijke stages begeleidden vanuit IQ healthcare. In de fase waarin de studie in een neerwaartse spiraal dreigde te belanden, was dit doorslaggevend om het tij te keren.

Geachte leden van de beoordelingscommissie, prof. dr. A.W. Hoes, prof. dr. O.L. Cremer, prof. dr. H.A.H. Kaasjager, prof. dr. J.W.L. Cals en dr. J.Y.J. Verbakel, hierbij wil ik u allen hartelijk danken voor de beoordeling van dit proefschrift.

Beste Daan, Roeland, Rick, Carlijn, Lieke, Ruochen, Irma, Marieke, Robin, Muriel, Fleur en Marlie, veel dank voor jullie inzet in het onderzoeksproject tijdens jullie wetenschappelijke stages tijdens de geneeskunde opleiding. Niet alleen hebben jullie allen erg hard gewerkt om onderzoeksdata te verzamelen en te analyseren, het was ook leuk, leerzaam en motiverend om jullie te begeleiden.

Verder dank ik alle overige coauteurs van de publicaties die onderdeel zijn van dit proefschrift voor hun bijdrage. Het was een genoegen om gedurende het project met zo veel goede onderzoekers samen te mogen werken. In het bijzonder dank aan Jan Jelrik Oosterheert en Ann van den Bruel voor jullie bijdrage aan de subsidieaanvraag voor de TeSD-IT, Alma van de Pol voor je begeleiding in het eerste jaar van de studie studie en Kevin Jenniskens voor je rol als begeleider bij mijn epidemiologie masteropleiding. Idelette Nutma, dank voor je rol als patiëntvertegenwoordiger in het onderzoek en je toewijding om de zorg voor patiënten met sepsis te verbeteren.

Bij de uitvoering van de TeSD-IT studie was de ondersteuning vanuit de betrokken huisartsenposten heel belangrijk. Vooral Monique Kuunders van de HAP Gelderse Vallei en Geert-Jan van Holten van Huisartsenposten Oost-Brabant wil ik graag hartelijk danken voor de prettige samenwerking en ondersteuning van de studie. Ook dank ik alle huisartsen die zich in hebben gezet voor het onderzoek door patiënten te includeren. Voor de verzameling van de onderzoeksgegevens waren de chauffeurs van de huisartsenposten en een pool vrijwillige laboratorium medewerkers onmisbaar. Beste chauffeurs, wat hebben jullie goed geholpen tijdens het onderzoek. Het meenemen van alle studiematerialen en huisartsen motiveren mee te doen was geen makkelijke taak en door jullie inzet hebben we het onderzoek tot een succes kunnen maken. Ook is het fantastisch hoe volledig alle onderzoekformulieren door jullie hulp zijn ingevuld. Beste laboratorium medewerkers, jullie bereidheid om in de avond en weekend-uren beschikbaar te zijn om bloed af te nemen van de patiënten die net toestemming hadden gegeven voor deelname aan het onderzoek was geweldig. Het afnemen van enkele buisjes bloed en verrichten van de lactaatmeting was de grootste logistieke uitdaging van het onderzoek. Er moest op elke locatie altijd iemand telefonisch bereikbaar zijn om direct op pad te gaan om het bloed af te nemen. Jullie hebben je geweldig ingezet om altijd op tijd ter plaatse te zijn en met elkaar te ruilen om het rooster dekkend te houden.

Ook alle betrokken laboratoria wil ik graag danken voor de ondersteuning van het onderzoek. Saltro voor ondersteuning van het hele project vanaf de beginfase, Star-shl voor aanvullende financiële ondersteuning, het Klinisch-chemisch en hematologisch laboratorium van het ZGV voor hulp bij de validatie van de lactaatmeters en opslag van bloedmonsters, het Klinisch Chemisch Laboratorium Bernhoven voor opslag van bloedmonsters en het Laboratorium Klinische Chemie en Hematologie van het JBZ voor het uitvoeren van alle laboratorium analyses door Eugenie Gemen onder leiding van Ron Kusters.

De fabrikanten Philips, ThermoFisher, Nova Biomedical en Abionic dank ik voor de ondersteuning van het onderzoek. In het bijzonder ook veel dank aan Menarini voor het verzorgen van de trainingen voor het gebruik van de lactaatmeters aan betrokken chauffeurs en laboratorium medewerkers.

Beste kamergenoten van 5.122, wat heb ik het getroffen om in het Julius Centrum op zo'n fijne kamer te mogen werken. De balans tussen hard werken en gezelligheid was precies goed. Het was wel even wennen om alleen thuis te werken vanaf de eerste lockdown.

Beste Esther, ondanks dat je primaire werkplek in Amsterdam lag, was je toch een volwaardige kamergenoot en het meest bij mijn onderzoek betrokken doordat je deel uitmaakte van de infectieziekten onderzoeksgroep. De trip naar het GRIN congres in Leuven was erg geslaagd en nog dank voor de hulp met het schaven aan mijn presentatie ter plaatse. Ook volgde je net als ik de master epidemiologie aan de VU en hebben we het laatste vak eind 2021 nog samen fysiek kunnen volgen. Ik ben dan ook erg blij met jou als paranimf tijdens mijn promotie.

Beste Joost, ook jou dank ik voor je rol als paranimf. Onze vriendschap gaat terug tot het begin van de middelbare school en het is bijzonder te merken dat er aan deze vriendschap na al die jaren eigenlijk niets is veranderd. Het was samen met jou dat ik voor het eerst enkele onderzoekjes deed voor het vak biologie. Hoewel er op de uitvoering het een en ander viel af te dingen, staat me nog helder voor de geest hoeveel voldoening het gaf zelf een onderzoeksopzet te bedenken en vervolgens uit te voeren. Jij bent vervolgens veel eerder in je loopbaan gepromoveerd in de theoretische natuurkunde. In vergelijking daarmee is mijn onderzoek wel erg eenvoudige kost en ik moet eerlijk bekennen dat ik ondanks je verwoede pogingen destijds geen flauw idee had wat je onderzoek precies inhield.

Beste Haye, jouw oprechte interesse en wijsheid tijdens onze gesprekken hebben veel indruk op me gemaakt. Het heeft geholpen meer inzicht in mezelf te krijgen, maar zeker ook om te voelen dat ik een goede afslag was ingeslagen met dit onderzoek.

Beste Olaf, dank voor het luisterend oor en het reflecteren op het proces tijdens een kop koffie of een biertje. Vooral tijdens fases waarin het project dreigde vast te lopen hielp het wat afstand te nemen om vervolgens weer de motivatie te voelen om er mee door te gaan.

Beste Aukje, dank je voor het mooie ontwerp van het studielogo van de TeSD-IT studie. Een professioneel bureau had het niet beter gekund en in mijn herinnering had je het ontwerp binnen een paar dagen klaar. Vooral op de studietassen stond het erg goed. Ik heb overigens nog goede herinneringen aan het bijwonen van jouw promotie in Verona 11 jaar geleden, maar ik kon toen niet vermoeden dat ik ooit zelf nog zou promoveren.

Lieve Jaike, Olaf, Jurre en Duco, een stevige en liefdevolle thuisbasis is onmisbaar geweest en heel veel dank voor het meeleven en geduld afgelopen jaren. Ik hou zielsveel van jullie alle vier en wat zijn we nu op onze plek in ons nieuwe huis in Renkum waar

we in 2019 naartoe zijn verhuisd. Een goede balans vinden tussen werk en gezin was soms een uitdaging en vooral in de zomervakanties van 2018 en 2019 hebben we de vakantieplannen toch behoorlijk moeten aanpassen aan het onderzoek. Deze flexibiliteit heb ik erg gewaardeerd, maar nog belangrijker waren de momenten van ontspanning. Juist door ook tijd te maken om met elkaar leuke dingen te doen, geeft dat weer veel energie. Het was ook fijn samen mijlpalen van het aantal inclusies te vieren. Het meetellen werd symbolisch uitgebeeld door een foto van de hand van Jaike in elke nieuwsbrief, die een ronde teller vasthield met het aantal inclusies erop. Een nieuwsbrief waar je overigens de rest van de opmaak van verzorgde. In de toekomst liggen weer nieuwe uitdagingen, maar eerst is het tijd om deze mijlpaal samen te vieren!

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About the Author

Feike Jan Loots was born on the 6th of September in 1977 in Amersfoort, the Netherlands. In 1995 he graduated from the Zernicke College in Haren, and started his study Medicine at the Vrije Universiteit Amsterdam. After obtaining his medical degree in March 2003, he worked as a physician in the OLVG, department of cardio-thoracic surgery until October 2004, and in the BovenIJ Hospital, department of general surgery until July 2006. Subsequently, he started working in Tilburg (STZ-St Elisabeth Hospital) at the emergency department, were he followed his Emergency Medicine residency between 2008 and 20011. Thereafter, he worked for one year as an emergency physician in the Rijnstate Hospital in Arnhem. Between June 2012 and March 2014 he worked as a physician for Pluryn (Kemnade and Groesbeekse Tehuizen), and performed medical repatriations.

In March 2014 he started General Practitioner training, which he terminated after one year, and switched to research work. In 2015 he initiated the research project into the recognition of sepsis in primary care, which ultimately resulted in this thesis. First under supervision of dr. P. Giesen at IQ healthcare, Radboudumc. In December 2017 he started his PhD programme at the Julius Center, UMC Utrecht under supervision of prof. dr. T.J.M. Verheij, prof. dr. A.R.H. van Zanten, dr. M. Smits and dr. R.M. Hopstaken. He combined his PhD research project with part-time clinical work in the emergency department of the Gelderse Vallei Hospital and the Postgradual Master of Epidemiology at the VUmc, the latter for which he obtained his degree in February 2022. Besides the clinical work in the Gelderse Vallei Hospital, he is currently working on a sepsis research project into the triage at GP cooperatives (the PRESHAPE study) and preparing the start of a large implementation study of the sepsis prediction model presented in this thesis study, under supervision of dr. R. Venekamp.

Feike is happily married to Jaike Loots-de Graaf with whom he has three children: Olaf (2009), Jurre (2011) and Duco (2015). In his free time he enjoys playing cards or board games with his family and he has a passion for sport, especially cycling in the mountains. As a medical student, he started with rowing and later also competed in speed skating and cycling. He was national champion wintertriathlon in 2005 and won several cyclosportive events. Currently he is preparing for the long distance triathlon at Alpe d'Huez.