DISSERTATION

Sepsis Screening according to International Sepsis Guidelines
–
Relevance and Challenges for Emergency Medical Services in Germany

Sepsis-Screening gemäß internationaler Sepsis-Leitlinie
–
Relevanz und Herausforderungen für den Rettungsdienst in Deutschland

zur Erlangung des akademischen Grades

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Table of contents

List of tables

List of figures

List of abbreviations

(in alphabetic order)

AI: Artificial intelligence

AUROC: Area under the receiver operating characteristic curve

CI: Confidence Interval

CIP: Critical Illness Prediction

ED: Emergency Department

EMS: Emergency Medical Service

EP: Emergency physicians

GCS: Glasgow Coma Scale

ICD: International Statistical Classification of Diseases and Related Health Problems

ICU: Intensive Care Unit

LR-: Negative Likelihood Ratio

LR+: Positive Likelihood Ratio

MEWS: Modified Early Warning Score

NEWS2: National Early Warning Score-2

NPV: Negative predictive value

PM: Paramedics

PPV: Positive predictive value

qSOFA: Quick Sequential [Sepsis-related] Organ Failure Assessment

RD: Rettungsdienst (German for: Emergency Medical Services)

Se: Sensitivity

SIRS: Systemic Inflammatory Response Syndrome

Sp: Specificity

SSC: Surviving Sepsis Campaign

Abstract

Background: Sepsis is characterized as a life-threatening organ dysfunction caused by a self-damaging host response to an infection. If Emergency Medical Services (EMS) suspect sepsis, improved survival rates have been observed. The international sepsis guidelines name four sepsis screening tools. In EMS, two of them can usually only be used with a reduced number of parameters (e.g., without information on leukocytes).

This dissertation examined which screening tool should be preferred to improve EMS' quality of sepsis suspicions. As nation-wide analyses on sepsis incidence and case fatality for EMS users were missing, it also aimed to elaborate sepsis' relevance in German EMS.

Method: This German retrospective cohort study draws on EMS cases recorded in

a) claims data from ten health insurance companies (n=221,420 cases) and
b) documentations by paramedics and prehospital emergency physicians (n=110,419 cases).

Incidence and case fatality of sepsis were compared to those of stroke and myocardial infarction. Analyses also included documentation rates for vital signs and sepsis suspicions, and intersection analysis on which case screens positive with which tool. Linking the data sets allowed analysis of n=4,503 adult EMS cases regarding the tools' ability to predict an inpatient sepsis diagnosis.

Results: Among 221,420 cases, incidence of sepsis (1.6%) was similar to stroke (2.7%) and myocardial infarction (2.6%). Case fatality 30 days past EMS use was about three times higher for sepsis compared to stroke or myocardial infarction (31.6% versus 11.8% and 13.4%). In absolute numbers, more cases died of sepsis.

Of all cases documented by EMS (n=110,419), 8.2% had all screening-relevant parameters filled that could have been measured by EMS. Paramedics never documented any sepsis suspicion, emergency physicians coded "septic shock" in 0.1% of their cases.

Depending on the screening tool retrospectively applied to the linked data (n=4,503), 3.7 to 19.4% of all cases screened positive; 0.8% in all tools simultaneously. NEWS2 had a superior sensitivity (73.1%), AUROC (0.773) and negative predictive value

(99.4%). qSOFA achieved the highest specificity (96.6%) and positive predictive value (10.7 %). Yet, qSOFA missed the most – 76.9% – of all septic cases.

Conclusion: Paramedics and emergency physicians should document vital signs and conduct screenings more frequently: Even when vital signs were documented, EMS did not sufficiently interpret critical values as potential indicators of sepsis. Those low suspicion rates were in contrast to sepsis incidence and fatality. NEWS2 was best at predicting most cases' inpatient sepsis diagnosis and with the best trade-off between sensitivity and specificity. Due to its comparably high sensitivity, it may also be an indicator to prioritize other preliminary diagnoses in NEWS2-negative patients. For EMS, future sepsis guidelines may omit recommendations to screen with MEWS or SIRS.

Zusammenfassung

Hintergrund: Sepsis ist eine lebensbedrohliche Organdysfunktion, die durch eine selbst-schädigende Wirtsantwort auf eine Infektion gekennzeichnet ist. Stellten Rettungsdienste (RD) einen Sepsis-Verdacht, führte dies nachweislich zu verbesserten Überlebenschancen. Die internationale Sepsis-Leitlinien nennen vier Sepsis-Screening-Instrumente. Zwei davon können im RD gewöhnlich nur mit einer reduzierten Anzahl an Parametern genutzt werden (z.B. ohne Informationen zu den Leukozyten).

Daher wurde analysiert, welches Instrument zu bevorzugen ist, um die Qualität des rettungsdienstlichen Sepsis-Verdachts zu erhöhen. Da bundesweite Analysen zur Sepsis-Inzidenz und -Fallsterblichkeit bei RD-Nutzern fehlten, sollte zusätzlich die Relevanz der Sepsis im deutschen RD herausgearbeitet werden.

Methode: Diese deutsche retrospektive Kohortenstudie basiert auf dokumentierten Rettungsdienstfällen in

a) Abrechnungsdaten von zehn Krankenkassen (n=221.420 Fälle) und
b) RD-Dokumentationen durch nicht-ärztliches und ärztliches Rettungsdienstpersonal (n=110.419 Fälle).

Inzidenz und Fallsterblichkeit der Sepsis wurden mit denen von Schlaganfall und Myokardinfarkt verglichen.

Es wurden auch die Dokumentationsquoten für Vitalparameter und für den Sepsis-Verdacht sowie Schnittmengen ausgewertet, welche Fälle mit welchen Instrumenten ein positives Screening-Ergebnis erhalten.

Durch die Verknüpfung der Datensätze konnte für n=4.503 Fälle erwachsener RD-Nutzer überprüft werden, wie gut die Instrumente eine stationäre Sepsis-Diagnose vorhersagen.

Ergebnis: Unter den 221.420 Abrechnungsfällen war die Inzidenz der Sepsis (1,6%) vergleichbar zu Schlaganfall (2,7%) und Myokardinfarkt (2,6%). Die 30-Tage-Fallsterblichkeit nach RD-Nutzung war rund dreimal höher für Sepsis als für Schlaganfall oder Myokardinfarkt (31,6% versus 11,8% und 13,4%). Auch in absoluten Zahlen starben mehr Fälle mit Sepsis.

Von den 110.419 vom RD dokumentierten Einsätzen hatten 8,2% eine vollständige Dokumentation der Vitalparameter, die der RD für die Screening-Instrumente erheben hätte können. Nicht-ärztliches Personal dokumentierte nie einen Sepsis-Verdacht, Notärzte einen “septischen Schock” in 0,1% ihrer Fälle. Abhängig vom Screening-Instrument, das retrospektiv an den verknüpften Datensatz angewandt wurde (n=4.503), waren 3,7 bis 19,4% aller Fälle positiv; 0,8% bei allen Instrumenten gleichzeitig. Der NEWS2 war hinsichtlich der Sensitivität (73,1%), AUROC (0,773) und des negativen prädiktiven Werts (99,4%) überlegen. qSOFA hatte die höchste Spezifität (96,6%) und den höchsten positiven prädiktiven Wert (10,7 %). Zugleich übersieht der qSOFA am häufigsten septische Fälle (76,9% unerkannt).

Conclusio: Nicht-ärztliches und ärztliches Personal sollte Vitalparameter häufiger dokumentieren und regelmäßig Screenings durchführen. Sofern Vitalparameter erhoben wurden, führten auffällige Werte zu selten zu einem dokumentiertem Sepsis-Verdacht. Diese niedrigen Sepsis-Verdachtsquoten standen im Kontrast zu Sepsis-Inzidenz und -Fallsterblichkeit. NEWS2 erwies sich als am besten geeignet, um die meisten Fälle mit einer stationären Sepsis-Diagnose vorherzusagen und mit dem besten Kompromiss zwischen Sensitivität und Spezifität. Auf Grund seiner vergleichsweisen hohen Sensitivität kann NEWS2 auch ein guter Indikator sein, um für NEWS2-negative Patienten andere Verdachtsdiagnosen zu priorisieren. Zukünftige Leitlinien könnten für den RD auf Screening-Empfehlungen mit MEWS und SIRS verzichten.

1 Introduction

Sepsis is a life-threatening syndrome which the current international guidelines define as an *"organ dysfunction caused by a dysregulated host response to infection"* ([1], p. 801). This host response does not only cause organ dysfunction(s), but can progress to failure of one or multiple organs, causing an estimated 20% of all global deaths [2]. Apart from its high case fatality rate, sepsis often results in longtime burden for sepsis survivors and high overall costs, e.g. by complications such as amputations or sequel in other medical, psychological and cognitive domains [2-4]. There is a great potential to save lives and maintain patients' quality of life if sepsis was recognized and treated earlier [5-8].

In 2016, a German expert-based consensus statement for emergency medical care judged sepsis as one out of six time-critical emergencies, emphasizing its urgency in-line with stroke, ST-elevation myocardial infarction, sudden cardiac death and others [9]. An exemplary look at the emergencies myocardial infarction and stroke shows that related long-established quality improvement programs in the health care setting and awareness campaigns have often resulted in positive effects, in particular reduced fatality rates (cf. [10]). In 2017, to achieve similar goals for sepsis, the World Health assembly defined sepsis as a top priority, urging its member states to improve sepsis prevention, identification, documentation and treatments [11]. Yet, sepsis knowledge among health providers and the public is still lower than for myocardial infarction and stroke [12-14]. With *"(…) no gold standard diagnostic test"* ([1], p. 803) and sepsis being time-critical, there have been various attempts to improve its early recognition by better and earlier screening (cf. [1])

Given that the vast majority of sepsis cases start outside of the hospital [15-17], it is beneficial that Emergency Medical Services' (EMS) detect sepsis early: If EMS suspect sepsis,

- adequate treatment starts more frequently within the EMS [18],
- hospital admission rates are higher [19],
- time to sepsis assessment and treatment within the hospital is likely shorter [19-22],
- ICU admission rates are lower [19] and

- patients may benefit in terms of mortality [23-26].

Yet, a majority of sepsis cases remain unrecognized by EMS [27, 28]. One cause for non-recognition may be insufficient sepsis knowledge and low awareness in EMS (cf. [14]). To raise EMS' awareness of and interest in sepsis, it may be helpful to evaluate and communicate how frequent and deathly sepsis is among EMS patients compared to better-known emergencies like myocardial infarction and stroke. Therefore, the first two research questions addressed in this dissertation are:

1. **Among Emergency Medical Services patients, how does sepsis incidence compare to the incidence of myocardial infarction and stroke?**
2. **How does hospital and 30-day case fatality for sepsis compare to that of myocardial infarction and stroke?**

The international sepsis guidelines recommend screening tools with a strong emphasis on the assessment of vital signs and consciousness [29]. Thus, another reason for low sepsis suspicion rates may be deficiencies in the assessment and documentation of such parameters: Studies highlighted that EMS' non-documentation of vital signs was associated with lower sepsis suspicion rates, which in turn was connected to longer time-spans to respective treatments (e.g., antibiotics) in the hospital and higher mortality risks [20, 21, 23, 24]. Accordingly, this dissertation analyzes the documentation rates of vital signs and sepsis suspicion.

In Germany, about 59% of all EMS cases within the observation period were cared for by paramedics only, the rest in conjunction with emergency physicians [30]. Those two groups of staff usually differ in the education and training received as well as in the amount of exposure to severe cases (cf. [31]). Therefore, it was also tested whether the documentation rates differ between both groups of staff. Additionally, we hypothesized that EMS staff considers documentation of vital signs more dispensable in non-septic cases. These considerations led to the following questions:

3. **How often do EMS staff document screening-relevant parameters (e.g., body temperature)?**
4. **How do documentation rates for screening-relevant parameters differ between paramedics and prehospital emergency physicians?**

5. **How do documentation rates differ between patients who receive an inpatient sepsis diagnosis following their EMS use versus those without such a diagnosis?**
6. **How often do paramedics versus emergency physicians document sepsis suspicions?**

To aid sepsis recognition and care, the international Surviving Sepsis Campaign (SSC), regularly updates its sepsis guidelines. Due to their hitherto influence on national guidelines (e.g. in Germany and Japan [32, 33]), this dissertation takes an in-depth look at their update: Since 2021, they mention four screening tools for sepsis [29]:

- the quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA [34]),
- the Systemic Inflammatory Response Syndrome criteria (SIRS [35]),
- the Modified Early Warning Score (MEWS [36]) and
- the National Early Warning Score-2 (NEWS2 [37]).

In 2021, for the first time, the guidelines recommended "*against using qSOFA, compared with SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock"* ([29], p.1182). This phrasing, not to use qSOFA as a "single tool", has led to diverging interpretations whether qSOFA should only be used in combination with one or more of the other tools, may still be used by certain subgroups of care-givers within the care chain or whether it should not be used at all (cf. [38, 39]). At the same time, the guidelines also state: *"Neither SIRS nor qSOFA are ideal screening tools for sepsis."* ([29], p.1182). Overall, the SSC guidelines do not state which screening instrument to prefer or how their screening results differ. At the same time, current national guidelines often recommend *only* one tool, e.g., the qSOFA in Germany and Japan or the NEWS2 in England [9, 32, 33, 40]. Additionally contributing to insecurity, all sepsis screening studies cited in the international SSC guidelines refer to hospital settings only (e.g., emergency departments and intensive care units) [29]. As screening tools are population and setting sensitive, this leaves questions about the tools' utility for EMS to suspect or predict an inpatient sepsis early. Furthermore, the guidelines only cited one study which compares MEWS, NEWS, SIRS and qSOFA within the same dataset using the same method, but it refers to the screening tools' ability for hospital patients to predict in-hospital mortality and intensive care unit transfer [41] – not sepsis. Yet, other diseases that mimic sepsis are life threatening as well [42-44]. Drawing conclusions

from the tools' ability to predict severe outcomes such as *mortality* to how well the tools will predict sepsis may be inadmissible. Additionally, the guidelines recommend two out of four tools that are not completely feasible for EMS, as EMS usually lack information such as the amount of urine output or on leukocytes [45, 46]. Thus, it is questionable how valuable MEWS and SIRS are despite reduced amounts of parameters. This ambiguity pertaining to the four screening tools resulted in the following questions:

7. **How often do EMS patients screen positive to which screening tool mentioned in the SSC guidelines?**
8. **How are the screening tools' predictive abilities for an inpatient sepsis diagnosis?**
9. **How often do the screening tools identify the same or different EMS cases as potentially septic (true and false positive) or truly septic (true positive)?**

In summary, the doctoral thesis sheds light on sepsis incidence and case fatality for EMS users, the quality of documentation of screening-relevant variables and sepsis suspicion rates, as well as the screening tools' ability to predict an inpatient sepsis diagnosis following EMS use.

2 Methods

The presented questions were answered as part of a retrospective cohort study by analyzing single and linked data sets based on health claims data and EMS documentations.

2.1 Data sources and linkage

The study used pseudonymized

a.) health claims data by ten German statutory health insurance companies plus
b.) EMS documentation by paramedics (PM) and emergency physicians (EP) from the German federal states of Bavaria and Baden-Württemberg

A total of 221,429 EMS cases were recorded in the health claims data (dataset #1). The respective health insurance companies are open to any insured, independent from the federal state the insured resides in.

The EMS documentation by paramedics and emergency physicians (dataset #2) relies on electronic medical records of 110,419 cases. Documentation from other federal states could not be included, mostly due to a lack of primary data digitalization and/or federal laws on data protection (cf. [47]). The documentation by paramedics and emergency physicians related to discrete EMS cases: In regions for which the study obtained *both* paramedics' and emergency physicians' data, it was local standard for paramedics not to forward any documentation to the EMS administration, if an emergency physician joined the EMS case. In all other regions where no emergency physician data could be acquired, paramedics were obliged to hand in their own documentation of the complete case – whether an emergency physician was involved in the EMS case or not.

For 5,465 EMS cases, linkage of datasets #1 and #2 was possible, resulting in dataset #3. Linkage was achieved for EMS cases documented by paramedics from the federal states Bavaria or Baden-Württemberg and billed by any of the ten participating health insurance companies. As some cases lacked pseudonymized personal identifiers (in German: "Krankenversichertennummer") to link cases deterministically, linkage relied on probabilistic linkage, described in depth in [48, 49]. Due to different variables, only

data filled out by paramedics – not by emergency physicians – was linkable with health claims data.

All cases in datasets #1 to #3 could result in in- or outpatient care, could be with or without conveyance (including EMS' on-site care only). Datasets are described in more depth in Supplement S1 and S2.

2.2 Operationalization of sociodemographic characteristics

Gender existed as a binary code. Age was operationalized as the year 2016 (= year of the EMS case) minus the year of birth.

2.3 Operationalization of incidence and case fatality

Incidence as well as hospital and 30-days case fatality rate for EMS cases with sepsis, myocardial infarction and stroke based on health claims data and patients of all ages. A case was considered to have the respective diagnosis, if the inpatient diagnosis was coded for a hospital stay starting on the day the EMS was used. The operationalization of an inpatient sepsis diagnosis relied on a method developed for German statutory health claims data to detect *severe sepsis* and *septic shock* ([50], refined by [51]; see [52], Online Resource 2 for list of ICD codes). During the observation period, 2016, the former sepsis definition had not required any organ dysfunction yet. The sepsis operationalization within this dissertation, however, took into account the *current* sepsis definition, which stipulates the requirement of one or more organ dysfunction [29]. Thus, it included two approaches

1) explicit codes for severe sepsis and septic shock (Code R65.1: "*Systemic Inflammatory Response Syndrome of infectious origin with organ failure, severe sepsis*" or R57.2: "*septic shock*", cf. ICD-10-GM [53]), and
2) sepsis codes (e.g., B37.7: *"Candidal sepsis"*) that had to be present in combination with an organ dysfunction code (e.g., J960: *"Acute respiratory failure"; ibid.*).

Inpatient diagnosis of myocardial infarction (ICD codes I21, I22) and stroke (ICD I63, I64) had to fulfill the requirement to follow an EMS use directly, too. All diagnoses of interest could be based on primary or secondary ICD codes.

Case fatality rates only drew on cases with death or with an ongoing insurance status during the respective observation period. Survival information also covered deaths occurring during or past an EMS case or after hospitalization. For case fatality rates and inpatient diagnoses, the latest possible, individual end of the observation period was December 31st, 2017.

2.4 Operationalization of sepsis-relevant documentation and sepsis suspicions

For the calculation of documentation rates in dataset #2, screening-relevant parameters (e.g., body temperature) ticked as “not measured”/”not measurable” were transformed to missing values. A parameter was considered as recorded if it was filled at least once (e.g., during EMS arrival or upon transfer to the next provider). Some regional EMS data sets did not allow to distinguish whether the parameter “supplemental oxygen” was unticked as a missing value or due to not applying in the individual case. Thus, documentation rates for supplemental oxygen remain unreported.

If vital signs were physiologically implausible, the data were transformed to missing values: This only applied to a temperature outside the range of 30-43° Celsius (which was implausible in 0.09% of all cases) and respiratory rates apart from 0-150 per minute (implausible: 0.01% of all cases). All other vital signs were judged as plausible by two experts (see [52], Online Resource 3 for minimum and maximum values before imputation).

EMS staff documented a sepsis suspicion according to the data standard “Minimale Notfalldatensatz” (abbreviated MIND; translated: “minimal emergency dataset”; [54]). EMS in Baden-Württemberg stated to have used the version MIND3BW (not publicly available anymore). This implies that the code 1803 only refers to “septic shock” – during that time there was no option to check “sepsis” or “severe sepsis” in this federal state. This resulted in emergency physicians’ data referring to the suspicion of “septic shock” only. For paramedics of Baden-Württemberg, free texts for preliminary diagnoses were available for analysis, in addition to the code “septic shock”. For Bavaria, where only paramedics’ data was provided for analysis and the version MIND3.1 was used, the code related to a suspicion of “high fever infection/sepsis/septic shock”.

2.5 Operationalization of screening tools

All screening results were calculated retrospectively. The screening tools qSOFA, MEWS, SIRS and NEWS2

- draw on the assessment of vital signs and consciousness during EMS use (=screening)
- and were tested on how well they predict an inpatient sepsis diagnosis within the hospital stay directly following EMS use (=reference standard).

In alignment with guidelines [29, 55], we report diagnostic accuracy measures for all adult patients (≥18 years). The Modified Early Warning Score (MEWS) or SIRS variables were used without urine output, $paCO_2$ and leukocytes (overview on screening tools in [52], Online resource 4). For consciousness, NEWS2 demands a so-called A*C*VPU scheme with the "C" as an abbreviation for new "confusion" [56] – while the available dataset contained the common AVPU scheme [57]. Additionally, some German EMS coded the value "analgesically-sedated/narcosis". Since any observation worse than "A" (Alert) in the ACVPU scheme has to be transferred into a point score of three, this was done accordingly for the AVPU (including those with "analgesically-sedated/narcosis" as a score of three).

As only a minority of cases had all screening-relevant variables filled and missing value analysis showed no monotone pattern for screening-relevant parameters, adult patients' missing values were imputed ([52], Online Resource 3 for details on the multiple imputation). During multiple imputation, parameters were entered as independent and dependent variables, respectively, and underwent five imputations. Metric variables (e.g., temperature) were imputed using linear regression, the categorical variable "consciousness" was imputed using logistic regression.

To ease comparability with external studies and to test whether the overall trend for the compared four screening tools is consistent independently from how missing values are treated, a sensitivity analysis with three additional methods to treat missing values was conducted (see Supplement). Cases for which *all* screening-relevant parameters were missing in the raw data were excluded from imputation and from the sensitivity analysis.

For qSOFA and SIRS, a score of ≥ 2, for MEWS ≥4 and for NEWS2 ≥ 5 was judged as positive screening result.

2.6 Analysis

For descriptive and interferential analysis and visualization, IBM® SPSS® Statistics Version 26, Microsoft Excel and PowerPoint (Office Professional Plus 2016) and for Venn diagrams RStudio (Version 4.0.2) were used. Pairwise deletion was used for all analyses, except the analysis of documentation rates for screening-relevant variables. For group comparisons, independent samples were analyzed with Pearson's Chi²-tests (cf. Supplement S3), dependent samples with McNemar's Chi²-tests (cf. S4). The significance level was set at $\alpha=0.05$, without correction for multiple testing. An additionally conducted sensitivity analysis revealed that conclusions for the comparability between screening tools were not affected by Bonferroni correction for multiple testing for which the corrected α was set at 0.0083 (as an α of 0.05 is divided by 6 comparisons of the four screening tools).

3 Results

The following results relate to all EMS patients independent from any conveyance or hospital use. Within the health claims data (data #1) and the linked data (dataset #3), 58.3 %, respectively, 64.4 % of all cases resulted in an inpatient hospital stay (Supplement, Table S2).

3.1 Sociodemographic characteristics

In all datasets, the gender distribution was about equal. For patients' age, the mean was ≥55.0 and the median ≥58 (ibid.).

Out of all 221,429 EMS cases, 3,470 cases result in an inpatient sepsis diagnosis (dataset #1; Figure 1). Cases with an inpatient sepsis tend to be older and are more frequently male than cases without sepsis (Supplement, Table S2).

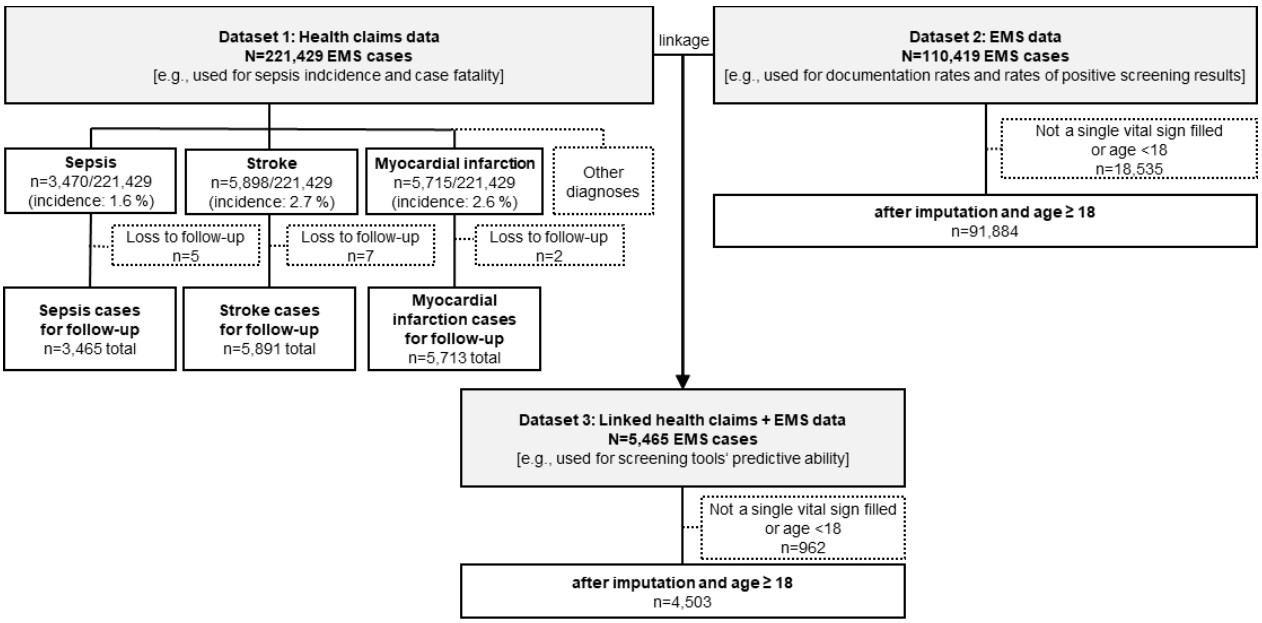

Figure 1: Study population (from Piedmont et al. [52] p.1327)

3.2 Incidence and case fatality

Among all EMS cases, 1.6 % [1.5; 1.6] resulted in an inpatient sepsis (dataset #1; n=3,470/221,429; Figure 1). The incidence of 2.7 % [2.6; 2.7] for an inpatient stroke and 2.6 % [2.5; 2.6] for an inpatient myocardial infarction was slightly higher than the sepsis incidence (ibid.).

The absolute number of deaths during the hospital stay or 30-days past EMS use was higher for sepsis (>1,094 cases) than for myocardial infarction or stroke (each <766; Figure 2).

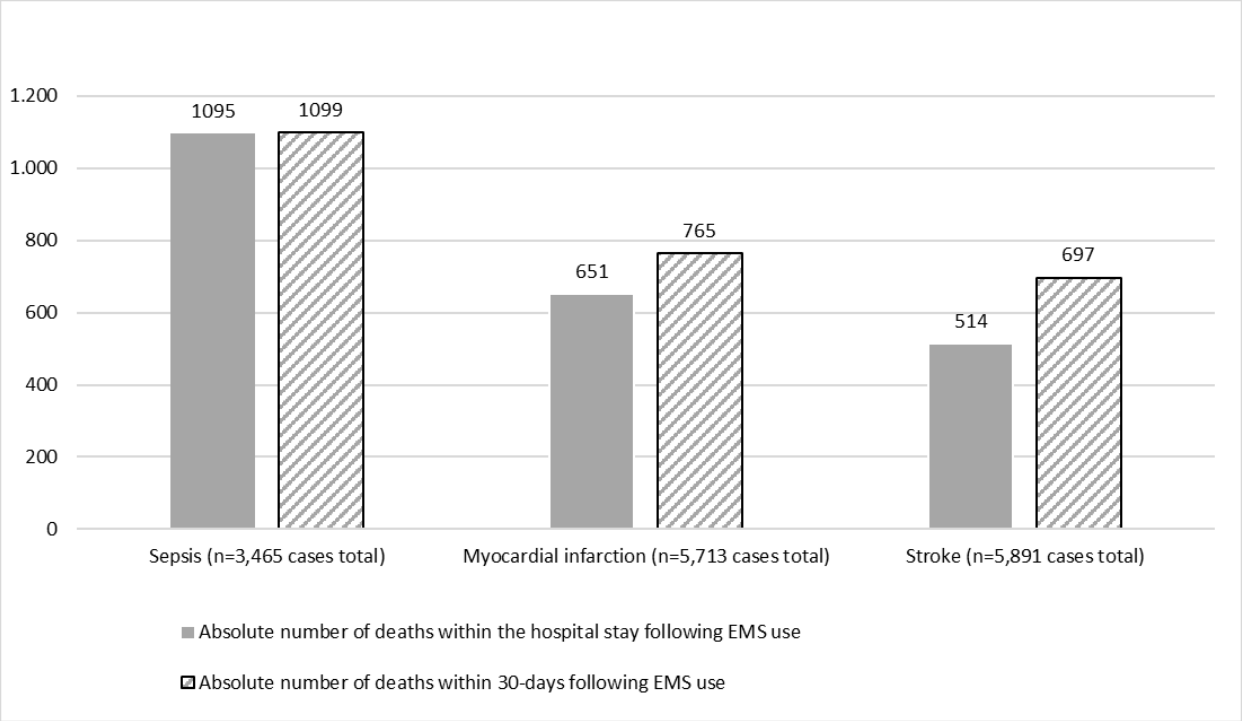

Figure 2: Comparison of the absolute numbers of deaths during the hospital stay or within 30-days following EMS use by inpatient diagnosis sepsis, myocardial infarction and stroke (Interpretation: Out of 3,465 cases with a diagnosis of an inpatient sepsis, 1,095 die within the hospital stay; dataset #1; own representation: Piedmont)

With an in-hospital and 30-days case fatality of 31.6 % [30.1; 33.2] and 31.7 % [30.2; 33.3], sepsis was more often deadly than stroke and myocardial infarction, which had a case fatality of 13 % or lower (Figure 3).

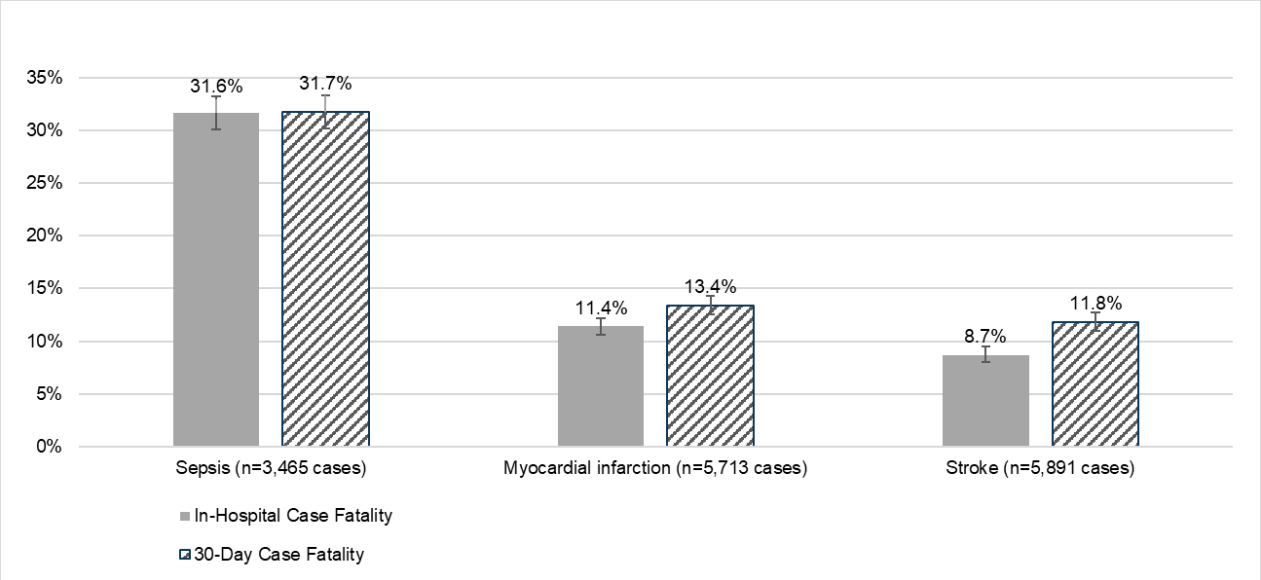

Figure 3: Comparison of case fatality (percent) for inpatient sepsis, myocardial infarction and stroke following EMS use (Dataset #1; incl. 95% confidence intervals; from Piedmont et al. [52], p. 1329)

3.3 Sepsis-relevant documentation and suspicion

Considering vital signs in dataset #2, 91.8 % of all cases documented by EMS staff (101,366 out of n=110,419) did not have a complete documentation of *all* parameters contained in qSOFA, NEWS2 or the reduced version of MEWS and SIRS. The least documented parameter was temperature (17.8 % [17.6; 18.0] filled; see Supplement Table S3).

Vital signs were more frequently coded by emergency physicians, except the Glasgow Coma Scale (an assessment for consciousness [58]) which was documented more frequently by paramedics. However, for all parameters, there was only a low association between documentation rates and the type of staff (indicating a weak effect of Cramer-V ≤0.1 for the comparison of paramedics versus emergency physicians). Especially temperature had low documentation rates by both paramedics and emergency physicians alike (<20 % of all cases, ibid.).

The linked dataset #3 (n=5,465), allowed analysis whether documentation rates differed between EMS cases that resulted in an inpatient sepsis versus those without: For most parameters, the documentation rates did not differ significantly between septic and non-

septic patients. The only exception is temperature which was recorded for 46.0 % of all cases with sepsis versus 21.5 % without; yet this association had a low effect size of V=0.07 (ibid.).

In dataset #2, there was not a single EMS case for which paramedics documented a sepsis suspicion (n=0 out of 106,935). None of their available free text entries contained a sepsis suspicion. Out of all cases documented by Emergency physicians (EP), the EP checked a suspicion of „septic shock“ in 0.1 % of all cases (5 out of n=3,483).

3.4 Screening results

The following screening results are based on the imputed screening-relevant parameters only. For results based on different methods to treat missing values, please see Supplement, Table S5.

For *adult* patients in the EMS data (dataset #2, n=91,884) and in the linked data (data set #3, n=4,504), qSOFA resulted in the lowest proportion of cases screening sepsis positive, while NEWS2 resulted in the highest proportion (Supplement, Table S4).

In dataset #3, sepsis incidence among adults is 1.7% [1.4; 2.1]. Of all cases in this dataset, 24.2 % [23.0; 25.5] were screening-positive in one or more of the screening tools (ibid.). Only 0.8 % [0.6; 1.1] screened sepsis-positive in all screening tools *simultaneously*. qSOFA achieved the highest specificity (Sp: 96.6 % [96.1; 97.1]) and positive predictive value (PPV: 10.7 % [9.8; 11.6%]), whereas NEWS2 achieved the highest sensitivity (Se: 73.1 % [71.8; 74.4]), AUROC (77.3 % [71.6; 83.1]) and negative predictive value (NPV: 99.4% [99.2; 99.6]). For MEWS and NEWS2, AUROC’s and NPV’s confidence intervals overlap slightly (ibid.). Out of all tools, qSOFA had the lowest sensitivity (Se: 23.1% [21.8; 24.3]).

Each tool *uniquely* identified a few cases as potentially septic which no other tool labeled as such (Figure 4A). NEWS2 was the tool with the highest percentage for uniquely screening sepsis positive: 8.2 % [7.4; 9.0%];] of all cases were only screening positive with NEWS2. Out of the total 78 inpatient sepsis cases, 16.7% [8.4; 24.9%] (n=13) were identified by NEWS2 only, but by no other screening tool (Figure 4B).

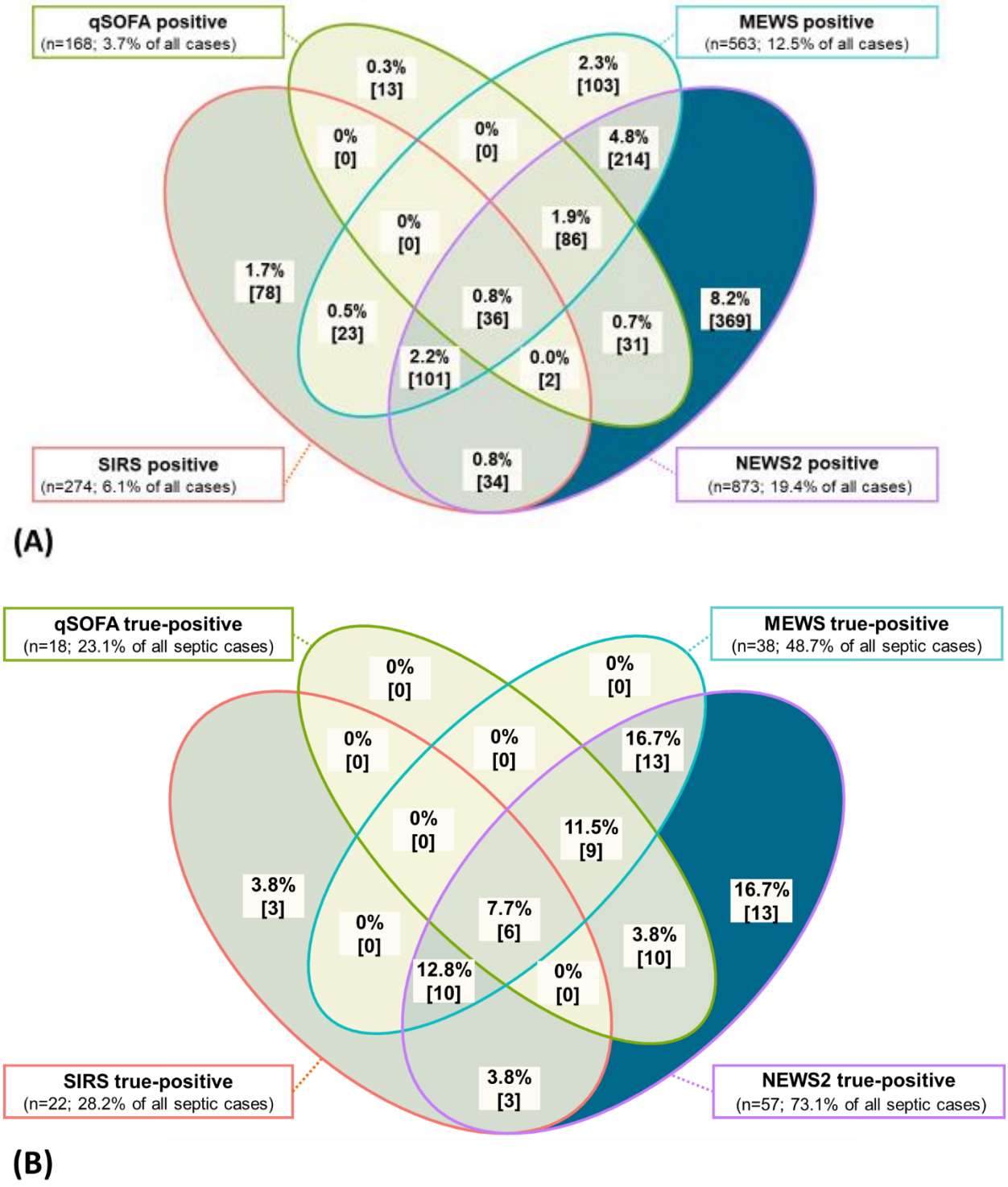

Figure 4: Schematic representation of intersections between screening tools (imputed, linked dataset #3; patient age ≥ 18 years; from Piedmont et al. [52], p. 1331)

(A) Percent and in square brackets absolute number of positive screenings (consisting of true-positives and false-positives) out of n=4,503 cases (of those, n=78 had a confirmed inpatient sepsis diagnosis)
(B) Percent and in square brackets absolute number of true-positive cases out of all patients with a confirmed inpatient sepsis diagnosis (n=78)

4 Discussion

Following a systematic literature search for sepsis screening in the prehospital setting (cf. [52], Online Resource 6), it may be concluded that this is the first study worldwide to allow comparisons of the screening tools' predictive ability for an inpatient sepsis of all EMS patients. To the best of our knowledge, it is also the first analysis of EMS cases' sepsis incidence and fatality with health claims data throughout Germany and the first multi-regional analysis of documentation rates for vital signs and sepsis suspicion with German EMS data.

4.1 Incidence and case fatality

Considering research question #1, the observed sepsis incidence of 1.6% was comparable to an incidence of 2.1-4 % for EMS patients in the emergency department [28, 59, 60] or EMS patients according to all hospital discharges [61]. Different to our results, in the U.S. study the incidence rate for sepsis was slightly higher than for myocardial infarction and stroke [61].

Those small variations in the sepsis incidence may derive from methodological or country-specific differences: For example,

1. the current incidence refers to *all* EMS patients which means the denominator includes
   a. patients not receiving any inpatient care (including those cared for on-site only) and
   b. patients independent of age;
2. different ICD coding schemes applied (e.g., ICD-10-GM in our study versus ICD-9-CM [61]);
3. cultural settings differed: In Germany, the barrier to use EMS is rather low. In general, patients only have to pay 10 Euro per EMS transport and – depending on the region and contracts – there can be financial incentives for dispatch centers and EMS to dispatch vehicles [62]. This may lead to an increased denominator and decreased incidence rate compared to other countries. At the same time, in Germany, EMS patients have comparably high proportions of transports to hospitals and inpatient admissions [63-66] which might increase the chance of being diagnosed as septic. Other potential influences – such as quality and extent

of prevention measures, comorbidities, out- and inpatient care – also likely differ from one country to another.

Confirming a sepsis diagnosis requires hospital resources (cf. [1]). For instance, septic patients refusing to be transported might have been missed. In alignment with other studies (e.g., [61]), the dissertation does not allow extracting sepsis incidence *during* EMS care, but it shows how many cases were septic within the hospital stay connected to their EMS use. To ease comparability with other studies and between diagnoses, we counted sepsis, myocardial infarction and stroke separately, albeit causal relationships are possible: Myocardial infarction and stroke may be a concomitant or sequel of sepsis and vice versa [4, 67-69].

Relating to research question #2, a U.S. study equally identified that the case fatality rate and absolute number of deaths was considerably higher for sepsis than for myocardial infarction and stroke [61]. In this dissertation, the sepsis hospital case fatality rate of 31.6% was higher than in two North American EMS studies (19.6% [61]; 28% [60]). Considering studies on all hospitalized patients – meaning EMS and non-EMS users –, there seems to be a tendency towards higher sepsis hospital case fatality rates in Germany compared to other industrialized countries, though cross-national comparability is limited [3, 70]. As other EMS studies lack 30-day follow-up including deaths *past* hospital discharge (e.g., [46]), external validity of this dissertation's 30-day case fatality is limited. Altogether, international comparisons on mortality and performance improvement programs for sepsis (cf. [71]) could be an indicator that the German EMS' case fatality rate is improvable.

In an own mixed-methods study, German health professionals also stated that one barrier hindering sepsis prevention and early detection is that sepsis is too seldom communicated and receives less public attention than other emergencies such as myocardial infarction [72]. To raise EMS staff's and public's awareness for sepsis, it may be worth communicating this dissertation's results on sepsis incidence and case fatality compared to myocardial infarction and stroke.

4.1.1 Strength and weaknesses of sepsis operationalization, incidence and case fatality

Since this is the first study for EMS patients' sepsis incidence and case fatality throughout Germany, the possibility of external validation is limited. A strength of the current study is that it analyzed the sepsis incidence based on a large data set of more than 200,000 EMS cases. Yet, health claims data encompasses the disadvantage that it contains billable EMS cases only. In Germany, health insurances cover EMS cases as so called "transportation costs" (German; "Fahrtkosten") and when they are due to compulsory *medical* reasons (cf. [73], § 60; in German: *"aus zwingenden medizinischen Gründen"*) connected to another – usually physician based –billable service by health insurance companies [74]. Care on site by paramedics only, without any transport or emergency physician joining, is usually not billable (ibid.). There have even been jurisdictions that health insurance companies did not have to bill a case with an emergency physicians on-site when a patient with critical health state refused to be transported [75]. Thus, health claims data has a slightly decreased denominator, e.g., due to EMS calls without any patient to be found on-site or patients refusing to be transported to hospitals. Cases that are neither payed for by insurance companies nor patients, count as "Fehleinsätze" (equaling "faulty emergency runs"). Nationwide statistics highlight that the amount of so called "Fehleinsätzen" is lower than 6% [30].

Considering the "reference standard" sepsis, diagnosing sepsis remains a challenging task (cf. [1, 76]) which may lead to sepsis being completely unrecognized and undocumented during a hospital stay [16, 77, 78] – even in cases of septic shock [51]. Manual, retrospective chart reviews by sepsis experts also indicate that a 100% interrater-agreement on which patient is truly septic can hardly be achieved [51, 79].

Additionally, ICD coding strategies for sepsis may be heterogeneous from one hospital to another and may be influenced by financial motives [51]. One strength of the current study is the use of data from various health insurance companies billing diverse hospitals and EMS providers nationwide, which may reduce the selection bias which would occur in single center studies. To further reduce the variability in sepsis documentation among hospitals, we used an ICD strategy that did not rely on sepsis codes only, as studies indicate sepsis undercoding in Germany [50, 51]. During the observation period, some of it could be *"due to regulations for the coding of sepsis to*

avoid overcoding: Patients without blood culture sampling cannot be coded as sepsis. In case of negative blood cultures, patients need to fulfill 4/4 SIRS criteria. Since in only about 2/3 of cases blood cultures are collected and only half deliver positive results [25], this may result in an underestimation of sepsis cases. Above that, 12% of severe sepsis patients have negative SIRS criteria [26] and thus are excluded from coding by the German coding regulations." ([50], p.8).

Out of a multiplicity of ICD coding strategies (cf. [80]), one commonly used approach is to combine infection codes with organ dysfunction codes. Among this approach, there are two frequently used methods, one developed by Martin et al. [81] and one by Angus et al. [82]. We used the Martin method [81] as operationalized for ICD-10 GM codes by Fleischmann-Struzek et al. [50] and refined by Schwarzkopf et al. [51] due to four reasons: It…

1. allows the identification of cases according to the current sepsis definition (with a mandatory organ dysfunction);
2. was validated with German health claims data and manual chart reviews as reference standard [50, 51];
3. has a higher positive predictive value than the Angus method [16, 50, 51, 83, 84];
4. was the most balanced in terms of over-/underestimation compared to the Angus method and another method tested which either overestimated sepsis incidence by 2.7-fold, respectively, underestimated by 2.2-fold in German claims data compared to the reference standard defined by manual chart reviews [50].

In the validation studies for EMS-users and EMS-non-users in Germany, the Martin method only achieved a sensitivity of 41.9% [30.9; 51.9] [50] or 40.5% [30.3; 51.5] [51]. Thus, this sepsis operationalization likely misses some septic cases in the current EMS study as well.

Considering the case-fatality, this dissertation's observation periods were chosen to allow comparison with other studies [60, 61] and to reduce non-causal attributions between a disease, respectively, syndrome and death that may be especially prone to occur in long-term follow-up periods. One strength is that this dissertation additionally provides case fatality rates for 30-day follow-up, making case fatality better comparable

between diagnoses by avoiding potential biases due to varying average lengths of hospital stays for sepsis, myocardial infarction or stroke.

4.2 Sepsis-relevant documentation and suspicion

Considering research question #3, the analyzed vital sign documentation was comparably sparse in other European studies [22], also in cases of infection [85] or sepsis [23]. Yet, some studies from other continents report much lower rates of missing values for screening-relevant vital signs (e.g., 0-4% missing values [45]). This indicates the high potential to improve documentation rates in Germany. Even during the study period, the German Medical Society for Intensive and Emergency care (Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin) defined the documentation of all screening-relevant parameters as *mandatory* part of the "Minimale Notfalldatensatz" (MIND) [54]. Obviously, both types of EMS staff – emergency physicians and paramedics – did not follow this recommendation, as identified as part of research question #4.

It remains questionable whether the mere obligation to fill those parameters leads to trustworthy results. Influences like time-consuming patients' or their affiliates' demands, emergent medical needs (cf. [23]), short driving times, technical problems or EMS staffs' attitude towards documentation might all result in mandatory fields being filled out with "nothing abnormal detected" values – independent from the real patient status. It may be beneficial to digitalize EMS documentation and program automatic, quickly visible reminders in case parameters are unfilled [86], but not to force EMS with mandatory fields to document all parameters. In addition, digital support to integrate vital sign measurements automatically into the EMS data set seems helpful (e.g., automatic integration of body temperature measured with electrical thermometer into the EMS data set). Currently, digitalization in German EMS is improvable [47, 87].

In reference to research question #5, documentation of vital signs such as temperature or respiratory rate is improvable for both septic and non-septic cases. A German survey pointed out that Emergency care providers strongly associated sepsis with increased body temperature [14] and EMS' measurement of temperature increased the odds of a sepsis suspicion [23]. This dissertation's results may seem hopeful insofar that cases resulting in an inpatient sepsis diagnosis had significantly higher documentation rates

for body temperature than cases without sepsis. At the same time, this potential consideration of an infection or sepsis is not represented in the documentation of sepsis suspicions and EMS still did not record any temperature for 54.0% of all inpatient sepsis cases. In other German and Dutch studies [22, 88], EMS patients with community-onset sepsis had low documentation rates for temperature, too. Notably, abnormal temperature is frequently not present in sepsis cases [89] and results on the predictive ability of elevated body temperature for an infection or sepsis are inconclusive [38, 60]. Thus, EMS ought to be sensitized that temperature is merely one valuable parameter and that only a *complete* patient assessment and combining parameters may improve the quality of sepsis suspicions.

Considering research question #6, other national and international studies have reported low sepsis recognition or suspicion rates by EMS staff, too [27, 28, 90]. In a German mono-site study, EMS missed 82% of all septic cases [28]. Yet, it is outstanding, that in the current dissertation, paramedics never recorded a sepsis suspicion. At the same time, the study elicited that sepsis suspicion rates are also low among emergency physicians. During the observation period, the sepsis definition according to the German guideline did not yet require any organ dysfunction (cf. [91]), while the international guidelines had just issued this new requirement in February 2016 [1]. Due to the German standard and since new guidelines take time to be implemented in regular care, one could have expected that this broader sepsis definition – not requiring an organ dysfunction –, would lower the threshold or barrier to document a sepsis suspicion. It is even more remarkable that also within regions with the pre-set option to code “high fever infection/sepsis/septic shock” no one checked this broad option including an unspecific high fever.

Altogether, EMS staff benefits from feedback and information on their patients’ hospital diagnoses to gain experience in prehospital sepsis detection (cf. [92]). This current study underpins that education and quality assurance measures for better documentation and sepsis suspicions should address both types of EMS staff – paramedics and emergency physicians – alike.

4.2.1 Strength and weaknesses of sepsis-relevant documentation and sepsis suspicion

The study contains the limitation that it remains unknown whether EMS *orally* forwarded any sepsis suspicion. It is also possible that EMS documented a sepsis suspicion in free texts that were unavailable for data analysis in one of the two federal states. At the same time, it is a strength of the study that it was able to show the lack of such free text entries in the other federal state. This leads to the conclusion that sepsis is likely too infrequently suspected in general.

Unfortunately, the emergency physician data set (as part of dataset #2) is small. There is a possibility that sepsis suspicion rates were higher, if physicians had been able to code “sepsis without shock” as well. Thus, transferability of the results for emergency physicians is limited. There are no German statistics which proportion of septic patients is cared for by paramedics only and which is also cared for by prehospital emergency physicians. Thus, we were only able to show that sepsis (or septic shock) suspicion rates are low in both groups of staff, yet the average sepsis suspicion rates for German EMS patients remains unknown.

The study also contains the weakness that the EMS data derives from two federal states only. Yet, as elaborated in the previous sections, external studies from other German federal states and countries support the validity by finding equally low documentation rates for sepsis-relevant parameters and sepsis suspicion rates.

4.3 Screening results

Comparing the rates of sepsis suspicions to the rates of positive sepsis screening results revealed that critical vital signs are not sufficiently converted into any sepsis suspicion. Some of it might be due to a lack of national recommendations for EMS’ sepsis screening tools during the first part of the observation period. The use of the qSOFA was only recommended by a German consensus statement for EMS since 2016 [9] and by the German sepsis guideline (for all health care providers) since 2018 [32]. At the same time, SIRS criteria were already a common recommendation to aid diagnosing sepsis [91], which – if the SIRS criteria had been applied – should have led to higher sepsis suspicion rates in the EMS data. Surveys show that a lack of knowledge considering qSOFA and general sepsis symptoms is still common in EMS staff [14] and

prehospital providers in general [93]. This makes it likely that EMS' sepsis screening remains too frequently unconducted nowadays.

In conclusion to research questions #7-9, the present study highlighted that the screening tools differ widely in terms of which patients they identify as potentially septic and how well they predict sepsis. They *"cannot be used interchangeably"* ([52], p.1333).

Recommendations on which screening tool to use should consider a bundle of aspects:

- Feasibility and suitability for the respective setting
- Accuracy in the prediction of an inpatient sepsis
- Desired trade-off between true and false positive rates (AUROC)
- Patient safety during screening (screenings have to be safe to administer)
- Costs

Screening tools should also demonstrate that they improve health outcomes and that their benefits overweigh the screenings' harms, including the harms caused by potential subsequent actions based on the screening results [94]. Other authors propose that screening tools should also be judged based on their *"immediate and long-term burdens on the healthcare system"* ([95], p.5). Currently, many of those aspects remain unknown, as sepsis studies on the screening tools' effect usually focus on potential benefits for septic or infected patients [18, 20-25, 96]. Thus, we compare the tools considering the remaining aspects in Table 1.

Table 1: Comparison of screening tools' advantages and disadvantages (own representation: Piedmont; image attribution: Thumbs-up icons by vectorspoint – Flaticon)

	qSOFA	MEWS	SIRS	NEWS2
Feasibility for EMS	• Completely feasible for EMS • Quick, easiest to remember (3 parameters, one threshold per parameter)	• Only a modified MEWS is feasible (without urine output); • Comparably complex tool if used manually without digital support (5 parameters remain, up to six thresholds per parameter)	• Only a modified SIRS is feasible (without information on white blood cells and PaCO2); • less complex compared to MEWS and NEWS2 (3 parameters remain, up to two thresholds per parameter)	• Completely feasible for EMS; • Comparably complex if used manually without digital support (most parameters of all compared tools, up to six thresholds per parameter)
Accuracy for prediction of an inpatient sepsis	Best in specificity, positive predictive value and positive likelihood ratio Worst in sensitivity	No additional benefit compared to qSOFA or NEWS2		Best in sensitivity and negative predictive values Worst in specificity
Balance of true and false positive rates (AUROC)	Inferior to NEWS2 in terms of AUROC			Best AUROC
Patient safety during screening (safe to administer)	All similar low patient safety risk if modified MEWS and SIRS are used (all non-invasive)			
Costs	All similar low costs if modified MEWS and SIRS are used (no laboratory values, no urine catheters)			

Legend: advantage disadvantage neutral

Image attribution: Thumbs up icons created by vectorspoint – Flaticon

Focusing on the tools' predictive abilities for an inpatient sepsis diagnosis, MEWS or SIRS provided little additional value: qSOFA or NEWS2 have better results in different accuracy measures. A meta-analysis from non-EMS settings also highlighted qSOFA's high specificity for a sepsis diagnosis, e.g., when compared to SIRS [97]. In the current study, qSOFA also had the highest specificity and positive predictive value, which makes it the comparably best tool *"to quickly identify patients at high risk of having or developing sepsis"* ([52], p.1331). qSOFA also has advantages in terms of feasibility which makes it comparably easy to remember by heart and to calculate, and all parameters are assessable during EMS care (Table 1). Unfortunately, qSOFA was the screening tool resulting in the highest number of septic patients overlooked. Additionally, other studies have shown that valuable intervention periods could remain unused as septic patients often turn qSOFA-positive late – on average later than they turn SIRS-positive – and frequently only when an organ dysfunction is clearly established [97, 98]. Considering sepsis' high lethality and risk of sequels [4],

we recommend against the use of the qSOFA *alone* as a single method to screen for sepsis early – in alignment with the SSC guidelines [29].

In contrast, NEWS2 is the best tool to predict as many septic patients as possible (highest sensitivity). It also has the best trade-off between sensitivity and specificity. Other prediction models using artificial intelligence (AI) in the hospital setting have resulted in similar AUROCs as for NEWS2 in our current prehospital study [99]. Considering the potential harm of an overlooked sepsis or delayed sepsis treatment [4] *"the use of the NEWS2 may be justified despite it having the lowest specificity of all tools."* ([52], p.1331)

Considering the usability of NEWS2 in real world settings, it ought to be kept in mind that it is a rather complex tool (cf. Table 1), needing an elaborate screening chart. Paramedics being questioned about the NEWS (a former version of the NEWS2; cf. former NEWS: [100]; current NEWS2: [37]) stated that the screening tool itself should be implemented in their electronic report form to encourage its use, but they showed some ambivalence towards *automatic* screening calculations [101]. As a study from the hospital setting concluded that 19% of all nurses mis-calculated the NEWS2 [102], it may still be worth to increase the feasibility of the NEWS2 by better digitalization and automatic calculation options. Naturally, the option for automatic score calculations may be a chance to lower the barrier for sepsis screening altogether, independent of any specific screening tool used.

One disadvantage of the NEWS2 *might* be that the current as well as an English and a Finnish study showed that it labeled every fourth to fifth EMS patient as positive [103, 104]. Thus, it seems worth to examine the effects on true-negative patients who *might* be down-prioritized due to Emergency Departments' (ED) limited resources conflicting with the high proportion of NEWS2 positive patients. This high proportion of patients screening positive in combination with a positive predictive value of (only) 6.5% in our study *might* also result in harms for false-positive patients such as an increase in antibiotics, conflicting with Antibiotic Stewardship [105, 106]. Another issue could be alarm fatigue in subsequent caregivers: One study has identified hospitals' low interest in EMS' NEWS results as a potential barrier hindering its effects [101], although it remains unknown whether this non-interest is related to the specific screening tool or applies to any screening tool. Another qualitative study with staff outside of acute

hospital settings found that communicating a NEWS2 score – compared to communicating symptoms only – helps to prompt the adequate response by the subsequent provider and shorten processes [107]. In a study in which general practitioner calculated the NEWS2 for patients for which they considered hospital admission, also 19% of all patients had NEWS2 scores of ≥ 5 [108]. On average this high sepsis suspicion rate based on the NEWS2 did not result in alarm fatigue but in faster EMS conveyance and hospital-internal processes (ibid.). It was also observed that the wide-spread implementation of NEWS in the out-of-hospital setting coincided with a reduced mortality in patients suspected to have sepsis; a trend that was not found outside of the implementation region [26].

The external validity of our results is limited: Our systematic literature search in PubMed and Cochrane Library revealed that out of 21 publications found, none compared all four screening tools in the prehospital setting ([52], Online Resource 6). Hand search yielded one study which unfortunately did not report any accuracy measure for a NEWS2 score threshold of ≥5 and was limited to EMS cases with infections diagnosed in the Emergency department [45]. Another study from England compared all but SIRS, only contained patients transported to the ED and excluded some patients not receiving regular ED care [46]. Despite all those methodological differences, both studies showed – for the three out of four tools tested in the respective study – the same tendencies as identified in the current dissertation: qSOFA was the most specific and NEWS2 the most sensitive tool (Supplement, Table S6).

4.3.1 Strength and weaknesses of screening results

One major strength of the current study is that it is the first to

- compare *all* screening tools
- regarding their ability to predict *sepsis* – not other severe outcomes –,
- *independent of any preliminary diagnosis* by EMS,
- referring to *established score thresholds* and
- giving distinct recommendations for prehospital *Emergency Medical Services*.

This strength becomes especially apparent as a single screening tool's accuracy measures extracted from one study compared to a single screening tool's results from another study likely leads to false conclusion, e.g., due to different patient selections, pretest-probability, sepsis operationalization, or – as Supplement S5 indicates – different ways to treat missing values per individual study.

We cannot rule out that some patients acquired an infection or manifested a sepsis during hospitalization, but past EMS use. At the same time, such cases would influence equally the predictive ability of *all* screening tools. It seems plausible that the screening tools' predictive ability were better if the reference standard of an inpatient sepsis was limited to those with an early sepsis diagnosis within hospitals. However, several studies concluded even for all hospital cases – including non-EMS user – that the vast *"majority of sepsis starts in the community setting and is present on admission"* ([52], p. 1332) (community onset: 90.3% [15]; present on admission: 86.8% [16]; hospital-acquired: 23.6% [17]). It is also known that septic ED patients arriving by EMS have more organ failures and higher sepsis acuity than septic patients arriving by other means [20, 109, 110]. Thus, it is likely that, among EMS users, the percentage of community-onset sepsis is even higher than the proportion reported in studies for *all* inpatient sepsis cases.

Another limitation is that the current data set of 4.503 adult EMS cases only contained 78 cases with an inpatient sepsis (cf. [111]). Yet, in total, after adding the Canadian [45] and English study [46], the superior rankings for NEWS2 and qSOFA were based on 30,113 EMS cases with 3,166 diagnosed as septic. External validation with more septic patients and using the same patient selection criteria would still be useful.

The current dissertation is limited to testing the SSC screening recommendations, though more than twenty different prehospital screening tools have been identified [45, 90]. This focus was chosen as the selected tools underwent a review and consensus process by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine and as the SSC screening recommendations have been adopted by many national guidelines (e.g., [32, 33]). Thus, this dissertation's close reference to the international guidelines may support future guideline developers and EMS providers.

A number of observations support the conclusion that imputation was the best method available in light of the documentation deficiency for screening-relevant parameters and that the screening results are plausible: With the imputed method,

1.) the screening results are in line with tendencies in other studies [45, 46].
2.) the proportion of NEWS2-positive patients is very similar to an English study [103]. Since NEWS2 uses many parameters that are also part of qSOFA, MEWS, and SIRS, there is a high chance that the imputation quality was accomplished for all screening tools.
3.) own sensitivity analysis for different methods to handle missing values showed a persistent ranking for the compared four screening tools, e.g., with NEWS2 being the most sensitive tool (see Supplement, Table S5).
4.) the comparison between observed and imputed vital signs depicted in [52], Online Resource 3, revealed little variance between imputed and original data.

As a limitation, all presented methods to handle documentation deficiencies are inferior compared to complete, trustworthy documentation by EMS staff. Better documentation rates in Germany are urgently needed, but – as previously discussed – there will probably always remain some cases for which EMS studies need imputations.

4.4 Implications for practice

As practical implications to achieve better documentation rates have already been discussed in section 4.2, this section focus on the practical use of screening tools. For EMS looking for a rule of thumb, it may be summarized:

- If a patient is qSOFA-positive, the probability of a subsequent clinical sepsis diagnosis is higher than for cases positive in other screening tools: Sepsis can be "ruled in" for qSOFA positive patients.
- If a patient is NEWS2 negative, sepsis is unlikely: Sepsis can be excluded, respectively "ruled-out", with a higher probability than in cases negative in other screening instruments.
- If a patient is NEWS2 positive, sepsis should be considered as differential diagnoses.

Since qSOFA has the highest specificity, positive likelihood ratio, and positive predictive value of all tools, EMS may use it to guide qSOFA-positive patients into sepsis-adequate hospitals and pathway (following the acronym "spin": Specific test – when positive –, rules in the disease).

In case of NEWS2 positive patients, EMS ought to communicate this result along with the reminder that sepsis could be a pertinent differential diagnosis. EMS staff as well as staff in the Emergency department should be educated that NEWS2 positive patients have an increased probability of sepsis and mortality [104, 108, 112, 113]. Given the current evidence and EMS' experiences with NEWS2 in England [114], we currently consider it valuable to prefer screening tools with a high sensitivity at this – often – first stage of assessment within the care chain in order to reduce the high case fatality [23-25].

If a patient screens positive in any screening tool, EMS should also be aware of the crucial role they may play in collecting information that subsequent providers might not have access to otherwise, e.g., by focusing on surrounding factors on-site such as present immunosuppressant or infection medication, questioning patients or bystanders about recent infections or searching for the site of infection and additional clues for higher severity than the screening tool may reveal, such as "*mottled or ashen appearance, non-blanching petechial or purpuric rash, cyanosis of skin, lips or tongue.*"

([115], p.97; cf. [116]). All of this may influence their choice which specific hospital to pre-alert and convey to. Independent from which screening tool is used, regular re-evaluation is mandatory to decide whether a sepsis pathway is (still) appropriate. Since the highest PPV of all tools was only 10.7% [9.8; 11.6], achieved by qSOFA, it needs to be clear that neither a positive qSOFA, nor a positive NEWS2 should *automatically* result in antibiotic treatment (cf. [114]). Naturally, EMS staff may refrain from labeling a patient with "sepsis suspicion", if – after a detailed assessment – other diagnoses are very likely to be the *sole* cause of a positive screening result (cf. sepsis mimics in [42]).

Concerning the question who to screen the international guidelines state: *"For hospitals and health systems, we recommend (…) sepsis screening for acutely ill, high-risk patients (…)."* ([29], p. e1065) It does not clarify how to identify those patients. In contrast, the Royal College of physicians recommends for the National Health System in the United Kingdom to implement the NEWS2 as a standardized "routine recording" for *all* patients of at least age 16 and without pregnancy ([37], p. xvii). For the decision who to screen, it needs to be considered:

- EMS seldom recognize sepsis or infection [27, 28, 90]; for example, EMS only documented the suspicion of an infection in 12% of all patients diagnosed as infectious in the ED [60]
- A qualitative study from Sweden identified: *"Another problem with these screening tools could be (…) that they are only used when AC [ambulance clinicians; author's note] already suspects sepsis based on other information."* ([92], p. 2)
- Our and another study [23] showed that even cases with an inpatient sepsis diagnosis often lack a complete EMS' vital sign assessment – which would help to identify high risk patients – and that alarming vital signs are often not converted into a sepsis suspicion.

Thus, the recommendation to only screen patients which EMS consider infectious, severely sick or septic might simply result in too many septic patients being overlooked and intervention periods unused.

4.5 Implication for medical guidelines and research

Considering that screening tools' accuracy and feasibility are strongly influenced, among others, by the availability of health status information (like laboratory results) and setting-specific pre-test probability, future guidelines and research on screening likely benefit from being more setting-specific.

Own qualitative interviews revealed the prehospital providers' impression that it lacks one explicit, scientifically soundly tested method for early prehospital sepsis screening; in German: *"Jeder macht das anders, (…) aber es gibt keine wissenschaftlich fundierte Lösung."* ([72], p.8); translated: *"Everyone does it differently, (…) but there is no scientifically sound solution"*. Too many different tools recommended at a time or frequent changes in recommendations may lead to insecurity and disinterest, hindering implementation in regular care. This phenomenon, that too many choices *can* lead to not choosing any option, has been observed in other scientific fields, such as customer research [117]. A review of 20 qualitative studies also concluded that contradictory guidelines are a major barrier for health professional's adherence to infection-related guidelines [118]. Our study in conjunction with the one from Canada [45] and England [46] indicate that it may be worth for EMS guidelines to omit recommendations for MEWS and SIRS.

It would be a shortcoming to believe that, once screening recommendations are established, they will remain stable over time. Recommendations are always influenced by preference weights or values clinicians, patients and other decision makers place on *"the probabilities of the respective health states"* ([119], p. 88), the screenings' consequences and surrounding factors. One example connected to the surrounding factors: In many countries, a shift towards patients using EMS more frequently in non-severe cases has been observed (cf. [63, 120]). This change in self-selection to use EMS influences sepsis prevalence in EMS, which in turn impacts the screening tools' predictive abilities (for the theoretical background on the prevalence's impact see: [121]). As an example for the changes in values, the more Emergency departments suffer from overcrowding, the more highly specific but less sensitive tools might be preferred to reduce waiting-times and harms for patients screening negative and health professionals' workload. In consequence, there may be a need for ongoing research to

quantify the impact of society's or health professional's decision for or against a certain screening tool or for a pre-selection of patients to screen [122].

To achieve the desired guidelines' effects on real care, there seems to be an ongoing need for research on how to lower the barrier for using any sepsis screening tool at all – to reduce the amount of health professionals basing their sepsis suspicions solely on previous experiences [92] or *"gut feeling"* ([93], p. 617). In a Korean study, only 60% of the EMS staff confirmed that they are *"willing to actively engage in the management of sepsis in the prehospital setting"* and they were not completely convinced that they *"will positively influence the behavior of the medical team in the emergency department"* ([123], p. 51). If there were more high-quality studies like randomized controlled trials showing screening's benefits (cf. [90]), this might motivate EMS. Additionally, research focusing on more patient-relevant outcomes could be helpful, such as quality of life, reduction of physical, cognitive and social impairments (cf. [4]).

Further studies should urgently also cover the screening tools' effects on *all* – septic and non-septic – patients and on potential adverse events, e.g., due to side-effects of antibiotics (cf. [29, 124, 125]), antibiotic resistance (cf. [29, 126]), administration of fluids despite being contraindicated (cf. [42]) or risks for non-septic patients being down-prioritized. At the same time, many potential adverse effects may be minimized if all providers are well trained that a positive screening result always calls for further assessment to rule out sepsis mimics.

Additional options to enrichen or even replace screening tools ought to be studied: There may be benefits from integrating additional data documented *prior* to EMS use (e.g., immunosuppressive diagnoses, medications, co-morbidities, gender according to Electronic Health Records or data from wearables) or *during* EMS use (e.g., point of care tests) into the screening tools. Research on new point-of-care tests, biomarkers or gene expressions might also change the way we predict or detect sepsis in the future. So far, AI models in hospitals showed predictive abilities similar to those of regular screening tools, even comparable to NEWS2 in our prehospital study [99, 127]. There are also indicators that they are rarely integrated in regular care [128]. Nonetheless, it seems plausible that AI improves early sepsis recognition in the future, leading to more personalized screenings.

5 Conclusions

To raise EMS' and public's sepsis awareness, it may be worth communicating the study result that sepsis is almost as frequent as myocardial infarction or stroke, but more frequently deadly. As shown, both paramedics and emergency physicians need to increase the proportion of patients with complete health status documentations as a prerequisite to improve their sepsis suspicion rates. The presumptions that EMS staff document vital signs more frequently for cases receiving an inpatient sepsis diagnosis, was falsified. As currently the majority of EMS patients lack complete vital sign assessments, EMS need to be better trained and motivated, why they should conduct *complete* vital sign documentations for all of their patients. Surrounding factors such as better digitalization, quality assurance programs and feedback loops may support improvements in documentation and sepsis suspicion rates.

The study elaborated that even for those vital signs already recorded, EMS often missed to translate critical signs into a sepsis suspicion. In conjunction with other studies [23, 27, 28, 60, 90, 92] and guidelines [37], this leads to the conclusion that EMS should *routinely* use sepsis screening tools for *all* adults. Though this unrestricted patient selection has already been implemented in England [37, 114], there remains a need for studies to assure that routine screening – especially with highly sensitive screening tools – does not result in harms.

This is the first study comparing all four screening tools currently mentioned in the SSC guidelines [29], using consistent methods and recommended screening thresholds for all adult EMS patients. Intersection analysis and accuracy calculation for the four screening tools revealed that EMS staff should be aware that the screening tools differ widely in terms of their abilities to predict sepsis. Due to its feasibility and highest specificity and positive predictive value in our and other studies [45, 46], qSOFA may be valuable to *quickly* identify patients with an increased sepsis risk. At the same time, EMS needs to be well trained that qSOFA missed 77% of all septic patients and should not be used as a stand-alone tool. NEWS2 qualified as the best tool to predict most septic patients and has shown to improve septic patients' mortality [26]. Due its comparably high sensitivity and negative predictive value, NEWS2 may also be a good tool to "rule out" patients, meaning, to detect those that are NEWS2-negative and likely non-septic. Altogether, we see an urgent need to train EMS and hospital staff on the

interpretation of a positive NEWS2 and to offer digitalized, automatized screening score calculations. For future guidelines, the current study and others [45, 46] indicate that EMS may omit SIRS and MEWS, as they were inferior to NEWS2's or qSOFA's accuracy measures.

All study results apply to the EMS setting and cannot be transferred to other settings automatically. In contrast to the current international and national guidelines [29, 32], health professionals could benefit from more setting-specific screening recommendations.

To date, there seems to be an unused potential of EMS to contribute to better, faster sepsis care and survival [18, 20-25]. At the same time, similar potentials for early sepsis screening and care are unused in settings prior and past EMS care as well [72, 93, 129]. Additionally, patients may benefit if the public had better knowledge about sepsis prevention, symptoms and about calling an EMS early when sepsis starts to manifest [130]. In summary, EMS are not the only ones able to contribute to a reduction of sepsis-related deaths, but EMS may make an impact by awareness and screening.

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Supplement

List of Supplements

Table S1: Characteristics of included data sets (own representation: Piedmont)

	Content	Sample and sub-sample	Observation periods
Dataset #1: health claims data	Billed EMS cases with ground and aerial vehicles indicating emergencies, excluding cases conducted with non-urgent vehicles only (in German: "Krankentransporte") and intra-/inter-hospital transfers; data also include follow-up information such as inpatient diagnoses and mortality during/past EMS care	Total: N=221,429 (all ages); • resulting in inpatient sepsis: n= 3,470; • not resulting in inpatient sepsis: n= 217,959	• year 2016: EMS cases • 2016 - 2017: EMS cases' individual follow-up (for inpatient diagnoses and case fatality) until 31st of December 2017
Dataset #2: EMS data	EMS cases documented by EMS providers (Emergency physicians and paramedics); data include, e.g., vital signs and sepsis suspicion/preliminary diagnosis during EMS care	Total: N=110,419 (all ages); • recorded by paramedics: n=106,936; • by emergency physicians: n=3,483; number of patients with/without inpatient sepsis only known for subsample (= dataset #3)	• year 2016
Dataset #3: health claims linked with EMS data	EMS cases with linkable EMS and health claims data; only data filled out by paramedics was linkable with health claims data	Total: N=5,465 (all ages); • resulting in an inpatient sepsis according to their health claims data: n=87; • not resulting in an inpatient sepsis: n=5,378	• year 2016: EMS cases • 2016 - 2017: EMS cases' individual follow-up

Table S2: Sociodemographic characteristics (analysis on case level, thus, multiple counts per patient possible; modified from Piedmont et al. [52], Online Resource 1)

	All cases				**With inpatient sepsis**			**Without inpatient sepsis**		
	Age		Female	% of cases with inpatient care following EMS use	Age		Female	Age		Female
	Five-number summary[1]	Mean[2]	%		Five-number summary[1]	Mean[2]	%	Five-number summary[1]	Mean[2]	%
Dataset #1: Health claims data	0; 38.0; 62.0; 79.0; 109.0	57.6; [57.5; 57.7]	47.5%; [47.3%; 47.7%]	58.3%; [58.1%; 58.5%]	0; 64.0; 75.0; 82.0; 98.0	71.8 [71.3; 72.3]	37.9% [36.3; 39.5]	0; 38.0; 62.0; 79.0;109.0	57.4; [57.3; 57.5]	47.6% [47.4; 47.8]
Valid n (out of n=221,429 cases total)	n=221,368 (excluding missings: n=61)			n=221,429 (all valid)	n=3,470 (all valid)			Cases without inpatient sepsis (n=217,898, excl. missings: n=61)		
Dataset #2: EMS data	0; 40; 66; 80; 116	59.4; [59.3; 59.6]	50.0%; [49.7%; 50.3%]	Cannot be calculated						
Valid n (out of n=110,419 cases total)	n=110,263 (excluding missings: n=156)		n=96,413 (excluding missings: n=14.006)							

Dataset #3: Linked health claims data + EMS data[3]	0; 35; 58; 77; 102	55.0; [54.4; 55.7]	46.5%; [45.2%; 47.8%]	64.4%; [63.2%; 65.7%]	26.0; 62.0; 73.0; 79.0; 94.0	70.5 [67.5; 73.4]	32.2% [23.1; 42.5]	0; 34.0; 57.0; 77.0; 102	54.8 [54.1; 55.4]	46.7% [45.4; 48.1]
Valid n (out of n=5,465 cases total)	n=5,465 (all valid)				n=87 (all valid)			n=5,378 (all valid)		

Legend:

[1] Five-number summary (in order): minimum, first quartile (P25), median (P50), third quartile (P75), maximum

[2] Lower and upper bounds of 95% confidence intervals in square brackets

[3] As filling rates for gender and age were better within the health claims data than in the EMS data, those calculations for the linked dataset #3 relied on claims data.

Table S3: Completeness rates (%) for screening relevant variables (modified from Piedmont et al. [52], p. 1328)

	EMS Dataset #2 (n=110,419); differentiated by EMS staff					linked Dataset #3 (n=5,465); differentiated by resulting inpatient sepsis diagnosis				
	All	EP (n=3,483)	Paramedics (n=106,936)	p-value	Cramer-V	All	With inpatient sepsis (n=87)	Without inpatient sepsis (n=5,378)	p-value	Cramer-V
Temperature[2,3,4]	17.8% [17.6; 18.0]	19.8% [18.5; 21.2]	17.7% [17.5; 18.0]		0.01	21.8% [20.8; 23.0]	46.0% 35.8; 56.4]	21.5% [20.4; 22.6]	<0.01	0.07
Respiratory rate[1,2,3,4]	27.9% [27.6; 28.1]	53.3% [51.6; 54.9]	27.0% [26.8; 27.3]		0.10	32.5% [31.2; 33.7]	40.2% [30.4; 59.7]	32.4% [31.1; 33.6]	0.12	0.21
Glasgow Coma Scale[1]	77.7% [77.5; 78.0]	67.8% [66.2; 69.3]	78.1% [77.8; 78.3]		0.04	80.3% [79.2; 81.3]	80.5% [71.2; 87.7]	80.3% [79.2; 81.4]	0.97	<0.01
Oxygen saturation[4]	79.2% [79.0; 79.5]	85.4% [84.2; 86.5]	79.0% [78.8; 79.3]	<0.01	0.03	80.5% [79.4; 81.5]	86.2% [77.8; 92.2]	80.4% [79.3; 81.4]	0.18	0.02
Systolic blood pressure[1,2, 4]	79.0% [78.8; 79.3]	86.9% [85.7; 88.0]	78.8% [78.5; 79.0]		0.04	78.9% [77.8; 80.0]	85.1% [76.5; 91.4]	78.8% [77.7; 79.9]	0.16	0.02
Heart rate[2,3,4]	81.7% [81.5; 82.0]	88.7% [87.6; 89.7]	81.5% [81.3; 81.7]		0.03	82.5% [81.5; 83.5]	86.2% [77.8; 92.2]	82.5% [81.5; 83.5]	0.36	0.01
Consciousness [AVPU scheme][2, 4]	86.3% [86.1; 86.5]	68.6% [67.0; 70.1]	86.9% [86.7; 87.1]		0.09	88.0% [87.1; 88.8]	89.7% [82.0; 94.8]	88.0% [87.1; 88.8]	0.63	0.01

Legend:

[1] part of qSOFA,

[2] part of MEWS,

[3] part of SIRS,

[4] part of NEWS2

EP=Emergency physicians

Table S4: Screening results with qSOFA, MEWS, SIRS and NEWS2 for all cases with patients ≥ 18 years (from Piedmont et al. [52], p. 1330)

Imputed EMS dataset #2; n=91,884; unknown number of cases with inpatient sepsis [1]				
	qSOFA	MEWS	SIRS	NEWS2
% of positive screening results per respective tool	4.3% [4.2; 4.4]	13.9% [13.7;14.2]	6.0% [5.9; 6.2]	22.6% [22.3; 22.9]
Imputed linked dataset #3; n=4,503 of which 78 cases had an inpatient sepsis				
	qSOFA	MEWS	SIRS	NEWS2
% of positive screening results per respective tool [95% CI]	3.7% [3.2; 4.3]	12.5% [11.6; 13.5]	6.1% [5.4; 6.8]	19.4% [18.3; 20.6]
Sensitivity (Se; percent, [95% CI])	23.1% [21.8; 24.3]	48.7% [47.3; 50.2]	28.2% [26.9; 29.5]	73.1% [71.8; 74.4]
Specificity (Sp; percent, [95% CI])	96.6% [96.1; 97.1]	88.1% [87.2; 89.1]	94.3% [93.6; 95.0]	81.6% [80.4; 82.7]
Area under the ROC curve (AUROC, Scores dichotomous, [95% CI])	0.598 [0.526; 0.670]	0.684 [0.615; 0.753]	0.613 [0.541; 0.684]	0.773 [0.716; 0.831]
Positive predictive value [95% CI]	10.7% [9.8; 11.6]	6.7% [6.0; 7.5]	8.0% [7.2; 8.8]	6.5% [5.8; 7.3]
Negative predictive value [95% CI]	98.6% [98.3; 99.0]	99.0% [98.7; 99.3]	98.7% [98.3; 99.0]	99.4% [99.2; 99.6]
Positive Likelihood Ratio (LR+)	6.8	4.1	5.0	4.0
Negative Likelihood Ratio (LR-)	0.8	0.6	0.8	0.3

[1] As the EMS records (dataset #2) lack information on the reference standard of an inpatient sepsis, this section only lists the percentages for positive screening results but cannot provide information on the tools' accuracy.

Table S5: Screening results with qSOFA, MEWS, SIRS and NEWS2 (percentages and [95%-CI]) differentiated by method of treating missing values (varying sample sizes, based on linked dataset #3; patient age ≥ 18 years; from Piedmont et al. [52], Online Resource 5)

	Method #1 Cases with missing values treated as "healthy" values (n=4,979)				**Method #2** Cases with at least two screening-relevant variables per tool filled in *all* screening tools (n=2,061)				**Method #3** Cases with at least two screening-relevant variables filled for the *respective* screening tool				**Method #4** Cases with imputed data (n=4,503)			
	qSOFA	MEWS	SIRS	NEWS2	qSOFA	MEWS	SIRS	NEWS2	qSOFA (n=3,873)	MEWS (n=4,235)	SIRS (n=2,101)	NEWS2 (n=4,258)	qSOFA	MEWS	SIRS	NEWS2
% of positive screening results	2.3%	6.6%	3.7%	15.5%	4.0%	11.6%	8.6%	22.0%	3.0%	7.8%	8.7%	18.1%	3.7%	12.5%	6.1%	19.4%
	[1.9; 2.7]	[5.9; 7.3]	[3.1; 4.2]	[14.5; 16.5]	[3.1; 4.8]	[10.2; 13.0]	[7.4; 9.8]	[20.2; 23.8]	[2.4; 3.5]	[7.0; 8.6]	[7.5; 9.9]	[17.0; 19.3]	[3.2; 4.3]	[11.6; 13.5]	[5.4; 6.8]	[18.3; 20.6]
Se	18.4%	37.9%	21.8%	63.2%	26.0%	56.0%	38.0%	84.0%	23.2%	44.0%	36.5%	73.3%	23.1%	48.7%	28.2%	73.1%
	[17.3; 19.5]	[36.6; 39.3]	[20.7; 23.0]	[61.9; 64.6]	[24.1; 27.9]	[53.9; 58.1]	[35.9; 40.1]	[82.4; 85.6]	[21.9; 24.5]	[42.5; 45.5]	[34.5; 38.6]	[72.0; 74.7]	[21.8; 24.3]	[47.3; 50.2]	[26.9; 29.5]	[71.8; 74.4]
Sp	98.0%	93.9%	96.7%	85.4%	96.6%	89.5%	92.1%	79.6%	97.4%	92.9%	92.0%	82.9%	96.6%	88.1%	94.3%	81.6%
	[97.6; 98.4]	[93.3; 94.6]	[96.2; 97.2]	[84.4; 86.3]	[95.8; 97.4]	[88.2; 90.8]	[90.9; 93.3]	[77.8; 81.3]	[96.9; 97.9]	[92.1; 93.7]	[90.9; 93.2]	[81.8; 84.0]	[96.1; 97.1]	[87.2; 89.1]	[93.6; 95.0]	[80.4; 82.7]
PPV	13.9%	10.0%	10.4%	7.1%	15.9%	11.7%	10.7%	9.3%	13.9%	10.0%	10.4%	7.1%	10.7%	6.7%	8.0%	6.5%
NPV	98.5%	98.8%	98.6%	99.2%	98.1%	98.8%	98.4%	99.5%	98.6%	98.9%	98.3%	99.4%	98.6%	99.0%	98.7%	99.4%
AUROC	0.582	0.659	0.593	0.743	0.613	0.728	0.650	0.818	0.603	0.684	0.643	0.781	0.598	0.684	0.613	0.773
	[0.514; 0.650]	[0.591; 0.728]	[0.525; 0.660]	[0.683; 0.803]	[0.522; 0.704]	[0.643; 0.812]	[0.561; 0.740]	[0.758; 0.877]	[0.526; 0.680]	[0.612; 0.757]	[0.555; 0.731]	[0.723; 0.840]	[0.526; 0.670]	[0.615; 0.753]	[0.541; 0.684]	[0.716; 0.831]
LR+	9.1	6.3	6.6	4.3	7.6	5.3	4.8	4.1	8.9	6.2	4.6	4.3	6.8	4.1	5.0	4.0
LR-	0.8	0.7	0.8	0.4	0.8	0.5	0.7	0.2	0.8	0.6	0.7	0.3	0.8	0.6	0.8	0.3

	positive in *all* four screening tools	positive in *all* four screening tools	positive in *all* four screening tools	positive in *all* four screening tools
	0.5%	1.2%	Not applicable due to different sample sizes per tool	0.8%
	(Se: 5.7%; Sp: 99.6%; PPV: 20.8%; NPV: 98.3%, AUROC: 0.527)	(Se: 10.0%; Sp: 99.1%; PPV: 20.8%; NPV: 97.8%; AUROC: 0.545)		(Se: 7.7%; Sp: 99.3%; PPV: 16.7%; NPV: 98.4%, AUROC: 0.535)
	positive in *any* of the screening tools	positive in *any* of the screening tools	positive in *any* of the screening tools	positive in *any* of the screening tools
	17.4%	26.2%	Not applicable due to different sample sizes per tool	24.2%
	(Se: 65.5%; Sp: 83.5%; PPV: 6.6%; NPV: 99.3%, AUROC: 0.745)	[Se: 88.0%; Sp: 75.4%, PPV: 8.2%; NPV: 99.6%; AUROC: 0.817)		(Se: 76.9%; Sp: 76.7%; PPV: 5.5%; NPV: 99.5%, AUROC: 0.768)

Legend:

Se: Sensitivity;
Sp: Specificity;
PPV: Positive predictive value;
NPV: Negative predictive value;
AUROC: Area under the ROC curve;
LR+: Positive Likelihood Ratio;
LR-: Negative Likelihood Ratio

Goodacre et al. [46] and Lane et al. [45] treat missing values for screening-relevant parameters as healthy values. Therefore, Table S6 includes this dissertation's missing value method #1 (="missings as healthy values") and #4 ("imputation"). Lane et al. only had small proportions of missing values (0-4% per parameter) [91], while Goodacre et al. do not report them [70].

Table S6: Test results comparing study by Lane et al. from Canada [45], Goodacre et al. from England [46] and own current study (based on method #1, treating missing values as "healthy values", and on method #4 with imputed values; own representation)

Screening tool	Study	Sensitivity	Specificity	PPV	NPV	C-statistics
qSOFA	Lane et al.	0.40 [0.38; 0.42]	0.94 [0.94; 0.95]	0.66*	0.85*	0.60 [0.56; 0.64]
	Goodacre et al.	0.10 [0.07; 0.13]	0.995 [0.993; 0.996]	0.34 [0.25; 0.44]	0.98 [0.97; 0.98]	Not reported for the same score threshold
	own current study, method #4	0.23 [0.22; 0.24]	0.97; [0.96; 0.97]	0.11 [0.10; 0.12]	0.99 [0.98; 0.99]	0.60 [0.53; 0.67]
	own current study, method #1	0.18 [0.17; 0.20]	0.98 [0.976; 0.984]	0.14*	0.99*	0.58 [0.51; 0.65]
MEWS	Lane et al.	0.53 [0.51; 0.55]	0.77 [0.77; 0.78)	0.39*	0.86*	Not reported for the same score threshold
	Goodacre et al.	0.55 [0.50; 0.60]	0.90 [0.896; 0.907];	0.13 [0.12; 0.15]	0.99 [0.98;0.99]	Not reported for the same score threshold
	own current study, method #4	0.49 [0.47; 0.50]	0.88 [0.87; 0.89]	0.07 [0.06; 0.08]	0.99 [0.987; 0.993]	0.68 [0.62; 0.75]
	own current study, method #1	0.38 [0.37; 0.39]	0.94 [0.93; 0.95]	0.10*	0.99*	0.66 [0.59; 0.73]
SIRS	Lane et al.	0.45 [0.43; 0.47]	0.72 [0.71; 0.73]	0.31*	0.83*	0.24 [0.21; 0.27]
	Goodacre et al.	Not reported				

	own current study, method #4	0.28 [0.27; 0.30]	0.94 [0.94; 0.95]	0.08 [0.07; 0.09]	0.99 [0.98; 0.99]	0.61 [0.54; 0.68]
	own current study, method #1	0.22 [0.21; 0.23]	0.97 [0.96; 0.97]	0.10*	0.99*	0.59 [0.53; 0.66]
NEWS2	Lane et al.	Not reported at all				Not reported for the same score threshold
	Goodacre et al.	0.78 [0.74; 0.82]	0.83 [0.83; 0.84]	0.12 [0.10; 0.13]	0.993 [0.991; 0.994]	Not reported for the same score threshold
	own current study, method #4	0.73 [0.72; 0.74]	0.82 [0.80; 0.83]	0.07 [0.06; 0.07]	0.99 [0.992; 0.996]	0.77 [0.72; 0.83]
	own current study, method #1	0.63 [0.62; 0.65]	0.85 [0.84; 0.86]	0.07*	0.99*	0.74 [0.68; 0.80]

Legend:

* Confidence intervals unreported in original publication

Statutory Declaration

“I, Silke Piedmont, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic “Sepsis Screening according to International Sepsis Guidelines – Relevance and Challenges for Emergency Medical Services in Germany” // “Sepsis-Screening gemäß internationaler Sepsis-Leitlinie – Relevanz und Herausforderungen für den Rettungsdienst in Deutschland”, independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; http://www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

October 24, 2024 Signature Silke Piedmont

Declaration of own contribution to the publication

This doctoral thesis was completely written by Silke Piedmont. All tables and figures in this dissertation and in the corresponding paper were conducted by Silke Piedmont, except the table on sociodemographic characteristics (Table S2 in this dissertation and Online Resource 1 of the paper) and figures on the screening tools intersections (Figure 4 in this dissertation and 3 in the paper) which were created based on a statistical evaluation by Silke Piedmont in cooperation with Ludwig Goldhahn.

The corresponding paper ([52]) is based on the following author contributions:

- Conceptualization: Piedmont, Silke; Bauer, Wolfgang;
- Methodology: Piedmont, Silke; Bauer, Wolfgang; Robra, Bernt-Peter; Goldhahn, Ludwig;
- Formal analysis and investigation: Piedmont, Silke; Goldhahn, Ludwig;
- Writing - original draft preparation: Piedmont, Silke;
- Writing - review and editing: all authors;
- Funding acquisition: Piedmont, Silke; Robra, Bernt-Peter

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Signature of doctoral candidate Silke Piedmont

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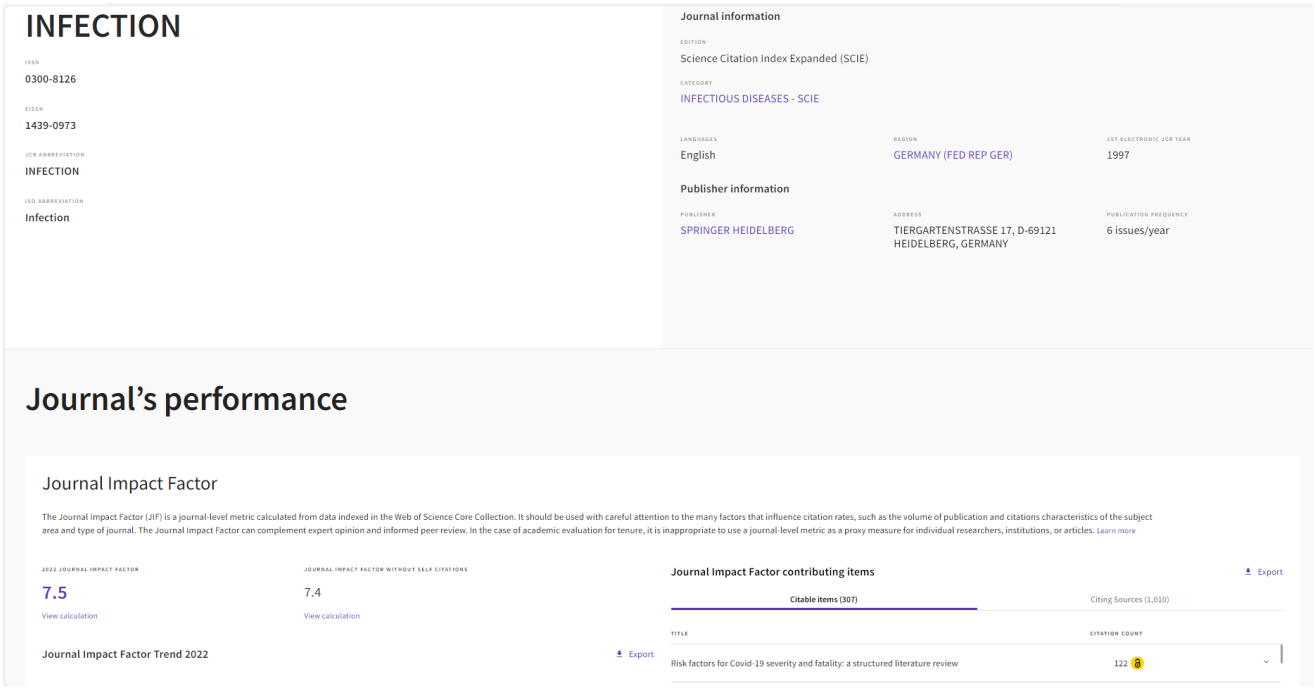

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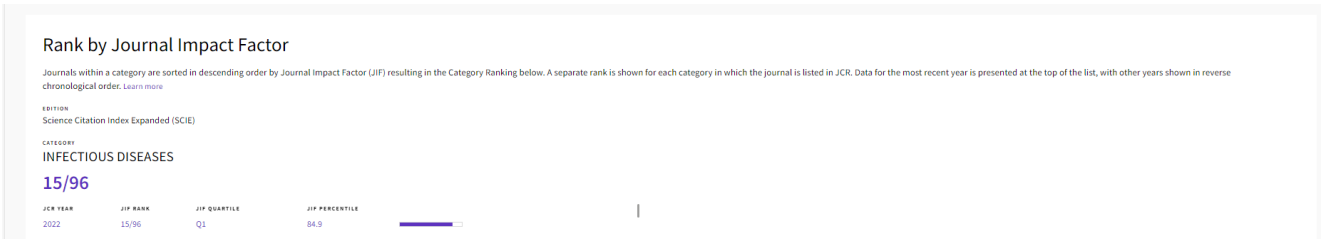

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RESEARCH

Sepsis incidence, suspicion, prediction and mortality in emergency medical services: a cohort study related to the current international sepsis guideline

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Abstract

Purpose Sepsis suspicion by Emergency Medical Services (EMS) is associated with improved patient outcomes. This study assessed sepsis incidence and recognition by EMS and analyzed which of the screening tools recommended by the Surviving Sepsis Campaign best facilitates sepsis prediction.

Methods Retrospective cohort study of claims data from health insurances ($n = 221{,}429$ EMS cases), and paramedics' and emergency physicians' EMS documentation ($n = 110{,}419$); analyzed outcomes were: sepsis incidence and case fatality compared to stroke and myocardial infarction, the extent of documentation for screening-relevant variables and sepsis suspicion, tools' intersections for screening positive in identical EMS cases and their predictive ability for an inpatient sepsis diagnosis.

Results Incidence of sepsis (1.6%) was similar to myocardial infarction (2.6%) and stroke (2.7%); however, 30-day case fatality rate was almost threefold higher (31.7% vs. 13.4%; 11.8%). Complete vital sign documentation was achieved in 8.2% of all cases. Paramedics never, emergency physicians rarely (0.1%) documented a sepsis suspicion, respectively septic shock. NEWS2 had the highest sensitivity (73.1%; Specificity:81.6%) compared to qSOFA (23.1%; Sp:96.6%), SIRS (28.2%; Sp:94.3%) and MEWS (48.7%; Sp:88.1%). Depending on the tool, 3.7% to 19.4% of all cases screened positive; only 0.8% in all tools simultaneously.

Conclusion Incidence and mortality underline the need for better sepsis awareness, documentation of vital signs and use of screening tools. Guidelines may omit MEWS and SIRS as recommendations for *prehospital* providers since they were inferior in all accuracy measures. Though no tool performed ideally, NEWS2 qualifies as the best tool to predict the highest proportion of septic patients and to rule out cases that are likely non-septic.

Keywords Sepsis · Incidence · Mortality · Emergency medical services · Paramedic · Screening

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Abbreviations

AUROC	Area under the receiver operating characteristic curve
CI	Confidence interval
ED	Emergency department
EMS	Emergency medical service
EP	Emergency physicians
ICD	International Statistical Classification of Diseases and Related Health Problems
LR +	Positive likelihood ratio
LR−	Negative likelihood ratio
MEWS	Modified early warning score
NEWS2	National early warning score 2
PM	Paramedics
SIRS	Systemic inflammatory response syndrome
Se	Sensitivity
Sp	Specificity
qSOFA	Quick sequential [sepsis-related] organ failure assessment

Introduction

Sepsis causes an estimated 20% of all global deaths [1]. There is a great potential to save lives and maintain patients' quality of life by recognizing and treating sepsis earlier [2–4]. As most sepsis cases start outside of the hospital [5, 6], Emergency Medical Services' (EMS) sepsis knowledge and screening is crucial: EMS' sepsis suspicions are associated with shortened time to in-hospital treatment and reduced mortality risks [7–9]. Yet, EMS only recognize a minority of sepsis cases [10, 11].

To aid sepsis screening, the 2021 updated international guideline by the Surviving Sepsis Campaign [12] (SSC) mentions:

- Criteria for Systemic Inflammatory Response Syndrome (SIRS [13]),
- Modified Early Warning Score (MEWS [14]) and
- National Early Warning Score 2 (NEWS2 [15])
- quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA [16]).

However, its authors "*recommend against using qSOFA, compared with SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock*" ([12], p. e1064). This leaves questions which tool to prefer or how to combine them.

In the past, the SSC guidelines have strongly influenced national screening recommendations (e.g., in Germany and Japan [17, 18]). Yet, the current SSC guideline's evidence seems improvable as it does not cite a single study which compares all four screening tools' predictive ability for sepsis and mostly relates to studies on the prediction of mortality—not sepsis. Furthermore, its recommendations base on hospital studies only (cf. [12]). Since screening tools' predictive ability depend on the setting they are applied in and two out of four screening tools are not completely feasible for EMS (cf. [19]), this leaves questions on their usefulness in the prehospital setting. Furthermore, national sepsis or EMS guidelines often recommend only one specific tool, e.g., the qSOFA in Germany or NEWS2 in England [17, 20, 21], or tools differ by region or EMS providers (e.g., with some Swedish EMS using NEWS2) [22]. All of these create uncertainty which screening tool is best in the EMS setting.

Improvable assessment and documentation rates for vital signs as well as general sepsis knowledge are additional challenges hindering early sepsis recognition [8, 23–27]. To inform EMS about the relevance of sepsis screening, the current study also compares the sepsis incidence and sepsis-related case fatality to those of myocardial infarction or stroke.

Methods

Aim

The study answers the following questions:

- *Incidence and case fatality*: How do sepsis incidence and case fatality compare to those of myocardial infarction and stroke?
- *Documentation of screening-relevant parameters*: How complete is documentation of screening-relevant parameters (e.g., temperature)? How do documentation rates differ between paramedics versus prehospital emergency physicians or between patients with versus without sepsis?
- *Sepsis suspicion*: How often do EMS document a sepsis suspicion? How often would EMS cases screen sepsis-positive, respectively with sepsis suspicion, if EMS staff had applied screening tools?
- *Comparison of screening tools*: How is each screening tool's predictive ability for sepsis? How frequently do tools label different patients with sepsis suspicion?

Data sources

The retrospective cohort study based on claims data by ten health insurance companies, plus EMS documentation by paramedics (PM) and emergency physicians (EP) from Germany (Fig. 1). Linking the pseudonymized data allowed determination of the screening tools' predictive ability during EMS care for the outcome of an inpatient sepsis diagnosis following EMS care (linkage details: [28]).

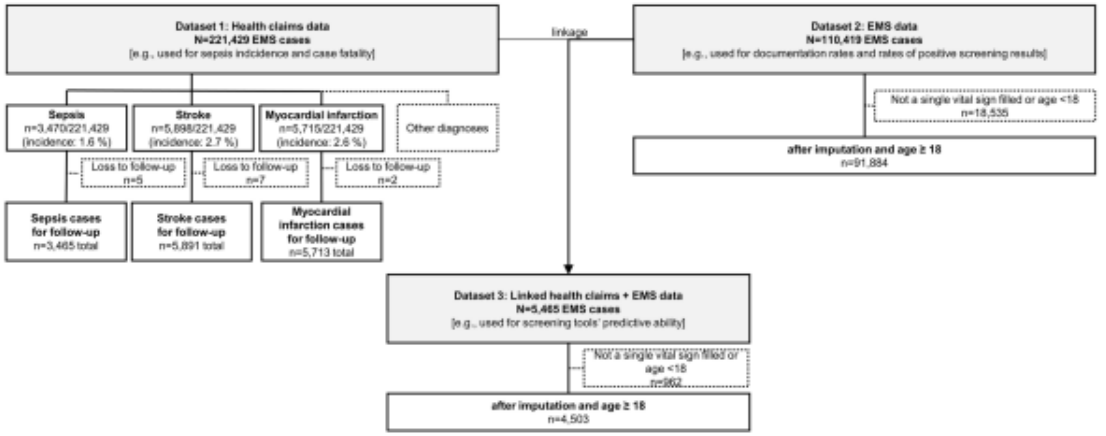

Fig. 1 Sample sizes for individual analyses on case level (Dataset #3: To be linkable, EMS cases had to be billed by respective health insurance company [dataset #1] and conducted by respective EMS provider [dataset #2])

- *Dataset #1 (health claims data)*: 221,429 German-wide EMS cases billed by 10 participating health insurance companies, with ground and aerial vehicles indicating emergencies in the year 2016 (including individual follow-up until December 31, 2017, for diagnosis and case fatality);
- *Dataset #2 (EMS data)*: 110,419 EMS cases documented by PM ($n = 106{,}936$) and EP ($n = 3483$) in the year 2016 in the federal states Bavaria and Baden-Württemberg, independent of any certain health insurance company (details in [28]); dataset includes EMS' vital signs documentation and sepsis suspicions
- *Dataset #3 (health claims #1 linked with EMS data #2)*: 5465 linkable EMS cases

Datasets #1 to #3 contained *all* EMS cases, e.g., cases resulting in in- or outpatient care, with or without conveyance and death on-site (see Online Resource 1 for rate of inpatient admissions).

Sepsis incidence and case fatality

Based on the health claims data (dataset #1), the study assessed sepsis incidence, hospital and 30-day case fatality rate for all EMS cases. A case was considered to result in an inpatient sepsis diagnosis if the diagnosis belonged to a hospital stay starting on the day of EMS use. A case without an inpatient sepsis diagnosis was considered to be non-septic. The diagnosis relied on an operationalization for German statutory health claims data to detect severe sepsis and septic shock ([29]; Online Resource 2). This strategy takes into account the current sepsis definition, which requires one or more organ dysfunctions [12]. Sepsis incidence and case fatality were compared to the inpatient diagnoses of myocardial infarction (ICD codes I21, I22) and stroke (ICD I63, I64).

Sepsis-relevant documentation, suspicion, and screening

In the EMS documentations (dataset #2), screening-relevant parameters (e.g., temperature) were deemed filled, if either the first or second assessment during EMS care was documented. Medically implausible data were transformed to missing values (Online Resource 3).

EMS' sepsis suspicions based on the standardized codes of the "Minimale Notfalldatensatz" (translated: "minimal emergency dataset"). Additionally, one region provided free text fields for preliminary diagnoses by paramedics (Online Resource 2).

Based on the recommended thresholds, retrospectively calculated qSOFA and SIRS scores ≥ 2, MEWS score ≥ 4 and NEWS2 scores ≥ 5 were judged as a positive screening result. We report the tools' predictive ability for an inpatient sepsis diagnosis (the "gold standard") of patients ≥ 18 years. As information on urine output, $paCO_2$, and leukocyte count is not routinely available to EMS staff, those Modified Early Warning Score (MEWS) or SIRS variables were omitted (Online Resource 4). In cases of missing values for screening-relevant variables, those values were imputed (Online Resource 3). To allow comparability with other studies, we also report screening results using other methods of handling missing values in Online Resource 5.

Analysis

Descriptive and interferential analyses were carried out using IBM® SPSS® Statistics Version 26 and Microsoft Excel. Venn diagrams were developed using RStudio (Version 4.0.2) and PowerPoint (Version 2309). All analyses used pairwise deletion except when reporting how frequent sepsis-relevant variables were (un)documented. Independent samples were compared with Pearson's (cf. Table 1), dependent samples with McNemar's chi^2 tests (for comparisons of screening results), accepting an $\alpha \leq 0.05$ without correction for multiple testing. In an additional sensitivity analysis, conclusions were not affected by Bonferroni correction for multiple testing.

Results

Out of 221,429 EMS cases, 3470 resulted in an inpatient sepsis diagnosis (dataset #1; Fig. 1). Those patients tended to be older and more frequently male compared to non-septic cases (Online Resource 1, incl. prevalence).

Sepsis incidence and case fatality

Sepsis incidence of 1.6% [1.5;1.6%] was slightly lower than the incidence of 2.7% [2.6; 2.7%] for stroke and 2.6% [2.5; 2.6%] for myocardial infarction (dataset #1; $n = 221,429$). The hospital and the 30-day case fatality for sepsis were significantly higher, with 31.6% and 31.7%, respectively, for sepsis and 13.4% or lower for myocardial infarction or stroke (Fig. 2; Online Resource 1). Within 30 days, 1095 sepsis, 697 stroke and 651 myocardial infarction cases died.

> Key result: Sepsis was about three times more likely to be fatal compared to myocardial infarction or stroke

Sepsis-relevant documentation and suspicion

Within dataset #2, paramedics (PM) never checked sepsis suspicion as "yes" (0 out of $n = 106,936$ PM cases). Analysis of free texts fields also revealed no documentation of any sepsis suspicions. Prehospital emergency physicians (EP) documented a suspicion of "septic shock" in 0.1% [0.02; 0.3%] of their cases (5 out of $n = 3,483$).

Only in 8.2% [8.0; 8.4%] of all cases (9053 out of $n = 110,419$), *all* parameters listed in Table 1 were documented. Temperature was the least often recorded. Completeness rates for screening-relevant variables are similar for both types of staff (PM versus EP; negligible to weak associations of Cramer-V $\leq 0,1$ for the relationship between

Table 1 Completeness rates for variables relevant for sepsis screening

	EMS Dataset #2 ($n = 110,419$); differentiated by EMS staff					linked Dataset #3 ($n = 5465$); differentiated by resulting inpatient sepsis diagnosis				
	All	Emergency physicians ($n = 3483$)	Paramedics ($n = 106,936$)	*p*-Value	Cramer-V	All	With sepsis ($n = 87$)	Without sepsis ($n = 5378$)	*p*-Value	Cramer-V
Temperature[b,c,d]	17.8% [17.6; 18.0]	19.8% [18.5; 21.2]	17.7% [17.5; 18.0]	< 0.01	0.01	21.8% [20.8; 23.0]	46.0% [35.8; 56.4]	21.5% [20.4; 22.6]	< 0.01	0.07
Respiratory rate[a,b,c,d]	27.9% [27.6; 28.1]	53.3% [51.6; 54.9]	27.0% [26.8; 27.3]	< 0.01	0.10	32.5% [31.2; 33.7]	40.2% [30.4; 59.7]	32.4% [31.1; 33.6]	0.12	0.21
Glasgow Coma Scale[a]	77.7% [77.5; 78.0]	67.8% [66.2; 69.3]	78.1% [77.8; 78.3]	< 0.01	0.04	80.3% [79.2; 81.3]	80.5% [71.2; 87.7]	80.3% [79.2; 81.4]	0.7	< 0.01
Oxygen saturation[d]	79.2% [79.0; 79.5]	85.4% [84.2; 86.5]	79.0% [78.8; 79.3]	< 0.01	0.03	80.5% [79.4; 81.5]	86.2% [77.8; 92.2]	80.4% [79.3; 81.4]	0.18	0.02
Systolic blood pressure[a,b,d]	79.0% [78.8; 79.3]	86.9% [85.7; 88.0]	78.8% [78.5; 79.0]	< 0.01	0.04	78.9% [77.8; 80.0]	85.1% [76.5; 91.4]	78.8% [77.7; 79.9]	0.16	0.02
Heart rate[b,c,d]	81.7% [81.5; 82.0]	88.7% [87.6; 89.7]	81.5% [81.3; 81.7]	< 0.01	0.03	82.5% [81.5; 83.5]	86.2% [77.8; 92.2]	82.5% [81.5; 83.5]	0.36	0.01
Consciousness[b,d]	86.3% [86.1; 86.5]	68.6% [67.0; 70.1]	86.9% [86.7; 87.1]	< 0.01	0.09	88.0% [87.1; 88.8]	89.7% [82.0; 94.8]	88.0% [87.1; 88.8]	0.63	0.01

95 % confidence intervals in square brackets

[a] Part of qSOFA

[b] Part of MEWS

[c] Part of SIRS

[d] Part of NEWS2

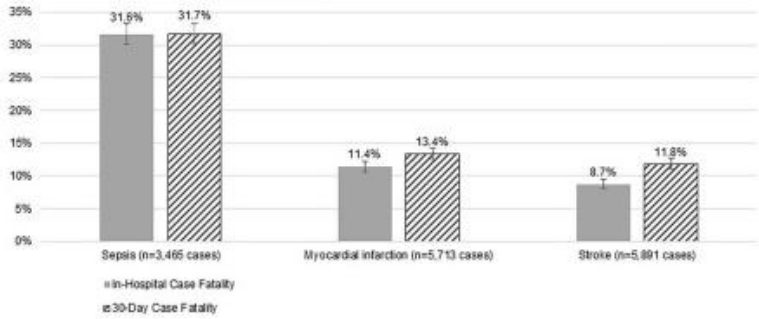

Fig. 2 In-hospital and 30-day case fatality for inpatient sepsis, myocardial infarction and stroke following EMS use (Dataset #1)

completeness rates and type of staff). In the linked dataset #3 ($n = 5465$), completeness rates were similar for most screening-relevant variables in cases of those with versus without sepsis (Table 1); only temperature was documented significantly more often for cases resulting in sepsis, but the effect size was low (46.0% vs. 21.5%; $V = 0.07$).

> Key results: Paramedics' and prehospital Emergency Physicians' documentations of vital signs and sepsis suspicions are improvable, also for patients diagnosed as septic in the hospital

Predictive ability of sepsis screening tools

Considering the "abnormal" vital signs in dataset #2 and #3, EMS could have labeled more patients with sepsis suspicions, if they had applied screening tools: The percentage of cases which would have screened positive (i.e., with sepsis suspicion) during EMS care was lowest for qSOFA and highest for NEWS2 (Table 2). qSOFA had the highest specificity and positive predictive value, while NEWS2 had the highest sensitivity and AUROC. SIRS and MEWS were inferior in all accuracy measures.

Screening tools differed greatly in terms of which EMS case they identified as potentially septic: Out of all EMS cases, 24.2% [23.0; 25.5%] were screening positive in *at least one* of the screening tools, but only 0.8% [0.6; 1.1] in *all* of the screening tools simultaneously (ibid.). Each tool labeled a few cases with sepsis suspicion, which no other tool did: NEWS2 was the tool with the highest percentage of *uniquely* labeling cases with sepsis suspicion (NEWS2 only: 8.2% [7.4; 9.0%]; Fig. 3A). Out of all patients with an inpatient sepsis, 16.7% [8.4; 24.9%] ($n = 13/78$) were only predicted by NEWS2 (Fig. 3B).

> Key results: EMS do not sufficiently convert critical vital signs into sepsis suspicions. Screening tools help predict more septic cases, but they differ widely in terms of which case they identify as potentially septic. NEWS2 is the best tool for predicting most septic cases and with the best trade-off between true-positive and false-positive rates

Discussion

This is the first study comparing the screening tools' predictive ability for an inpatient sepsis based on a large, linked data set for all EMS patients. It is also the first multi-regional analysis of EMS' sepsis incidence, case fatality, completeness of vital sign documentation and sepsis suspicion rates in Germany. The patients' in-hospital case fatality rate and absolute number of deaths with sepsis was much higher than those for myocardial infarction and stroke, which highlights the importance of identifying sepsis by EMS providers. These results are similar to those in a U.S. study for adult, hospitalized EMS users [31].

Our observed sepsis incidence of approximately 2% was similar to that in a Canadian EMS study (2.1% [32]) and slightly lower than in other studies (with incidences of 3–4%) [11, 31, 33]. Those differences may, among others, arise from methodological disparities, as our incidence refers to *all* EMS patients (in contrast to hospitalized patients only) and different ICD coding schemes applied (e.g., ICD-9-CM-coding strategies in [31] versus ICD-10-GM in our study). In contrast to our results, in the U.S. study, sepsis incidence was slightly higher than that of myocardial infarction and stroke (ibid.).

One reason for low sepsis suspicion rates might be that health providers' and the public's sepsis awareness is improvable: For example, knowledge about early warning signs is lower for sepsis than for myocardial infarction and stroke [25–27, 34, 35]. At the same time, this improvable sepsis knowledge gives hope that similar quality improvement and awareness programs which have been successful for myocardial infarction and stroke (cf. [36, 37]) may also reduce the high sepsis lethality.

Studies world-wide have shown similar low documentation rates for sepsis suspicions [10, 11, 38, 39] and vital

Table 2 Screening results with qSOFA, MEWS, SIRS and NEWS2 for all cases with age ≥ 18 years

Imputed EMS dataset #2; $n = 91{,}884$; unknown number of cases with inpatient sepsis				
	qSOFA	MEWS	SIRS	NEWS2
% of cases labeled with sepsis suspicion by respective tool [95% CI]	4.3% [4.2; 4.4]	13.9% [13.7;14.2]	6.0% [5.9; 6.2]	22.6% [22.3; 22.9]
Imputed linked dataset #3; $n = 4503$ of which 78 cases had an inpatient sepsis				
	qSOFA	MEWS	SIRS	NEWS2
% of cases labeled with sepsis suspicion by respective tool [95% CI]	3.7% [3.2; 4.3]	12.5% [11.6; 13.5]	6.1% [5.4; 6.8]	19.4% [18.3; 20.6]
Sensitivity (Se; percent, [95% CI])	23.1% [21.8; 24.3]	48.7% [47.3; 50.2]	28.2% [26.9; 29.5]	73.1% [71.8; 74.4]
Specificity (Sp; percent, [95% CI])	96.6% [96.1; 97.1]	88.1% [87.2; 89.1]	94.3% [93.6; 95.0]	81.6% [80.4; 82.7]
Area under the ROC curve (AUROC, Scores dichotomous, [CI])	0.598 [0.526; 0.670]	0.684 [0.615; 0.753]	0.613 [0.541; 0.684]	0.773 [0.716; 0.831]
Positive predictive value [95% CI]	10.7% [9.8; 11.6]	6.7% [6.0; 7.5]	8.0% [7.2; 8.8]	6.5% [5.8; 7.3]
Negative predictive value [95% CI]	98.6% [98.3; 99.0]	99.0% [98.7; 99.3]	98.7% [98.3; 99.0]	99.4% [99.2; 99.6]
Positive likelihood ratio (LR +)	6.8	4.1	5.0	4.0
Negative likelihood ratio (LR−)	0.8	0.6	0.8	0.3
	Cases labeled positive in *all* four screening tools			
% of cases labeled with sepsis suspicion by *all* four screening tools [95% CI]	0.8% [0.6; 1.1]			
Sensitivity (Se; percent, [95% CI])	7.7% [6.9; 8.5]			
Specificity (Sp; percent, [95% CI])	99.3% [99.1; 99.6]			
Area under the ROC curve (AUROC, Scores dichotomous, [CI])	0.535 [0.467; 0.603]			
Positive predictive value [95% CI]	16.7% [15.6; 17.8]			
Negative predictive value [95% CI]	98.4% [98.0; 98.8]			
	Cases labeled positive in *any* of the four screening tools			
% of cases labeled with sepsis suspicion by *any* of the four screening tools [95% CI]	24.2% [23.0; 25.5]			
Sensitivity (Se; percent, [95% CI])	76.9% [75.7; 78.2]			
Specificity (Sp; percent, [95% CI])	76.7% [75.5; 78.0]			
Area under the ROC curve (AUROC, Scores dichotomous, [CI])	0.768 [0.714; 0.823]			
Positive predictive value [95% CI]	5.5% [4.8; 6.2]			
Negative predictive value [95% CI]	99.5% [99.3; 99.7]			

CI confidence interval; *AUROC* area under the receiver operating characteristic curve

signs [23], even in samples limited to infections or sepsis [8, 24]. One study highlighted that better EMS' documentation rates of vital signs are associated with higher sepsis suspicion rates and that many septic cases were missed when EMS did not document vital signs completely [8]. It seems plausible that incomplete vital sign assessment results in overlooking patients who are in need for screening.

At the same time, our analyses highlight that even cases with incomplete vital sign assessment should have been documented with "sepsis suspicion" more frequently (Online Resource 5, method #1): For example, applying qSOFA to the raw, unimputed data would have led to at least 2.3% of all cases screening positive. As it was not until the middle of the observation period (July 2016) that a German consensus statement clearly recommended EMS to use the qSOFA [17], this may explain some parts of the low suspicion rates. Yet, studies show that qSOFA and general sepsis symptoms are still unknown to many EMS providers world-wide [25, 27]. Just like in our study, abnormal vital signs are often not "translated" into sepsis suspicion in other countries as well [40]. It remains possible that EMS orally forwarded a sepsis impression but did not document it. Yet, low documentation

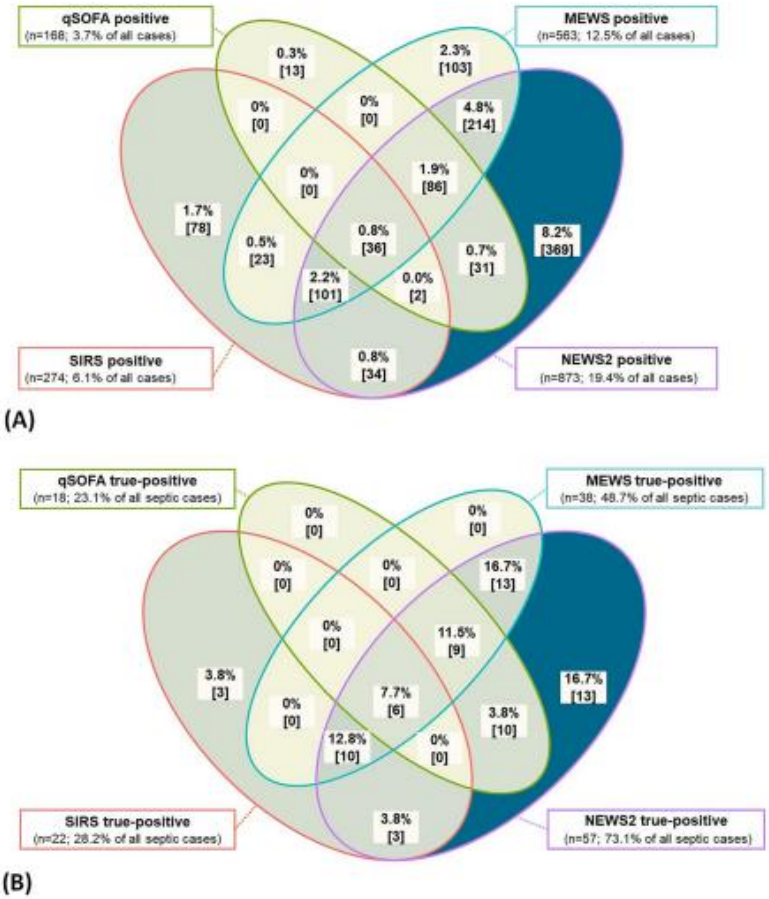

Fig. 3 Schematic representation of intersections between screening tools (imputed, linked dataset #3; patient age ≥ 18 years). **A** Percent and in square brackets absolute number of positive screenings (consisting of true-positives and false-positives) out of $n = 4503$ cases (of those, $n = 78$ had a confirmed inpatient sepsis). **B** Percent and in square brackets absolute number of true-positive cases out of all patients with a confirmed inpatient sepsis ($n = 78$)

rates for screening-relevant parameters, the lack of translation from alarming vital signs to a documented sepsis suspicion and surveys on EMS' improvable knowledge about sepsis symptoms make it unlikely that orally forwarded, yet undocumented sepsis suspicions occurred frequently.

The present study highlights that the screening tools' results differ greatly. As the qSOFA is easy to calculate and has the highest specificity and positive predictive values, it may be the best tool to quickly identify patients at high risk of having or developing sepsis. Yet, it may result in harm for septic patients, as it is the screening tool that misses the most septic cases. NEWS2 is best in recognizing as many septic patients as possible, and in keeping a good trade-off between true and false-positive rates. Its accuracy is within the range of models using artificial intelligence—though most of them are applied at later time-periods in the hospital setting, for which one could have expected increased predictive power due to more information and shorter prediction windows (cf. [41]). Given the high lethality of undetected sepsis or delayed treatment, the use of the NEWS2 may be justified despite it having the lowest specificity of all tools. Yet, in our study and in an EMS study from the U.K., NEWS2 identifies every fifth EMS patient as potentially septic [42]. This, in combination with a low positive predictive value, indicates a need for further evaluation, considering potential alarm fatigue in subsequent providers and harm for false-positive patients (cf. [43, 44]). Additionally, one ought to keep in mind that the NEWS2 is a comparably complex tool if not digitally supported [32].

In the current study and an EMS study by Lane et al. [19], MEWS or SIRS showed little practical advantage compared to qSOFA or NEWS2, as the latter had the better prediction results. MEWS' or SIRS' predictive ability may be better

in settings where both tools can be used with the complete number of parameters.

A practical rule of thumb for EMS staff could be:

(1) NEWS2 negative patients are the most *likely* to be non-septic ("rule out"),
(2) For NEWS2-positive patients, sepsis should be on the priority list of differential diagnoses,
(3) qSOFA-positive patients are the most *likely* to be septic, but a negative qSOFA is not suitable to dismiss a sepsis diagnosis.

The tools were tested for all adult EMS users, whereas the SSC guideline recommends sepsis screening for "acutely ill, high-risk patients" ([12], p. e1063), but does not state how to identify them. In contrast, the Royal College of Physicians' recommendations for the NEWS2 calls for a standardized "routine recording" for *all* patients ≥ 16 years without pregnancy ([45], p.8). Our study with its incomplete vital sign assessments, low sepsis suspicion rates despite alarming vital signs and other studies on the rare recognition of sepsis or infection [10, 11, 32, 38] lean toward the conclusion that too many patients and valuable intervention periods could be overlooked, if EMS were asked to only screen those patients they consider acutely ill or at high risk.

Altogether, screening tools are meant to prompt additional assessments, not as a diagnostic rule. False-negative and false-positive screening results reinforce the ongoing need for expert-based decision. Nonetheless, our retrospectively calculated screening results showed that screening tools are very valuable in identifying more septic patients compared to EMS staffs' currently documented sepsis suspicion rates.

Strengths and limitations

One strength of our study is the comparison of all screening tools using the same methods and dataset. This strength becomes especially apparent as the study showed that different methods to handle EMS documentation deficiencies influence screening results (see Online Resource 5). At the same time, imputation is always inferior to a trustworthy, complete patient documentation by EMS. Yet, as documentation deficiencies are common in other studies as well [8, 23, 24], imputation might currently be the best method available. Especially treating unrecorded parameters as "healthy" values likely leads to an underestimation of screening tools' predictive ability: This method resulted in the lowest sensitivities compared to all other methods for missing values. Another study also found more prominent documentation deficiencies in cases which were judged as "urgent journey" by the dispatch center [8]. There are indicators that the imputation achieved its aim and that the screening results are plausible:

(1) The screening results based on the imputed results equal the tendencies found in other studies, for example high specificity for qSOFA and high sensitivity for NEWS2 [19, 46].
(2) The rate of EMS cases labeled as septic by NEWS2 is very similar to an English study [42]. Since NEWS2 bases on many parameters that are also used for the three other screening tools, there is a high chance that the quality of imputation was similarly accomplished for all screening tools.
(3) Own sensitivity analysis using different methods for imputed versus non-imputed vital signs revealed that the overall ranking remains stable, with qSOFA being the most specific and NEWS2 being the most sensitive tool.

Apart from a systematic literature search which yielded no eligible study (Online Resource 6), our general research in the field identified only one other study which compared all screening tools, but it was limited to patients with infections diagnosed in the Emergency Department (ED) [19]. As EMS rarely recognize infections [32], it seems beneficial that our study is the first to include all patients independent from any presumptions or preliminary diagnoses by EMS.

For the emergency physicians' data, the former coding standard only allowed to extract how often they suspected a septic shock: Since their additional free text fields were unavailable for analysis, their suspicion rates for sepsis without shock remains unknown.

The study design has the limitation that it does not allow to extract how often sepsis was already present or fully manifested during EMS use: The screening tools were only tested for predicting an inpatient sepsis. At the same time, it is known that the majority of sepsis starts in the community setting and is present on admission [5, 47, 48]. We cannot rule out that some septic cases were missed, e.g., due to patients refusing to be conveyed to hospitals or deaths on-site resulting in not receiving an inpatient sepsis diagnosis.

As for this "gold standard", the inpatient sepsis diagnosis, one should take into consideration that diagnosing sepsis remains a challenging task altogether (cf. [49], p. 807). Even retrospective manual chart reviews by sepsis experts do not lead to 100% interrater-agreement for inpatient sepsis diagnoses ([30, 50] for sepsis-2-definition). Due to our large dataset, manual chart review to label (non)septic cases was not feasible. Health claims data have limitations, e.g., coding strategies are heterogeneous depending on the documenting provider [29, 51, 52]. A strength of our study is using data from several health insurance companies billing multiple hospitals, dampening the variability in sepsis labeling

among hospitals. Out of a variety of ICD coding strategies (cf. [53]), we favored the method by Fleischmann-Struzek et al. [30], refined by Schwarzkopf et al. [29], as it allowed the identification of cases according to the latest sepsis definition and reached the best balance between under- and overcoding compared to two different ICD strategies tested in two validation studies with German claims data [29, 30].

Overall, the results solely answer how valuable the tools are from a statistical point of view, but their usefulness in real-world settings is influenced by more factors (e.g., tools' feasibility, Emergency Department staff's reaction to screening results).

Conclusion

Sepsis incidence rates compared to documented sepsis suspicion and alarming vital signs reveal an urgent need for educational measures—for paramedics and emergency physicians alike—to increase the likelihood of *complete* patients' health status documentations and the translation of alarming vital signs into sepsis suspicion. Screening tools differ greatly and cannot be used interchangeably. Future guidelines should consider omitting recommendations for SIRS and MEWS for the *prehospital* setting. Though no tool provided ideal performance, we would currently recommend the NEWS2 due to its highest sensitivity and AUROC. However, as the NEWS2 leads to every fifth patient with sepsis suspicion, there is a need for real-world studies to determine its effect on all—septic and non-septic—patients. Clearly, tools with similar sensitivity but higher specificity would be helpful.

To raise awareness, it may be worth communicating that sepsis is more frequently deadly than stroke and myocardial infarction.

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Availability of data Due to German legislation on claims and EMS data, the data cannot be deposited publicly.

Declarations

Conflict of interest All authors have no conflict of interest to declare. The data were acquired as part of the project "Integrated emergency care: A focus on emergency medical services" (http://rettungsdienst-im-fokus.ovgu.de) which was funded by the German Innovation Fund of the Joint Federal Committee (G-BA) (funding identifier: 01VSF17032). The funder had no influence on the published results.

Ethical standards Data Protection Commissioners of the respective federal states and health insurance funds, as well as the Board of Medical Ethics of the University Magdeburg (65/18) approved of data protection and usage procedures. This study was performed in line with the principles of the Declaration of Helsinki and its later amendments.

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Curriculum Vitae

"Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht."

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