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Comparison of different scoring tools in early detection of sepsis

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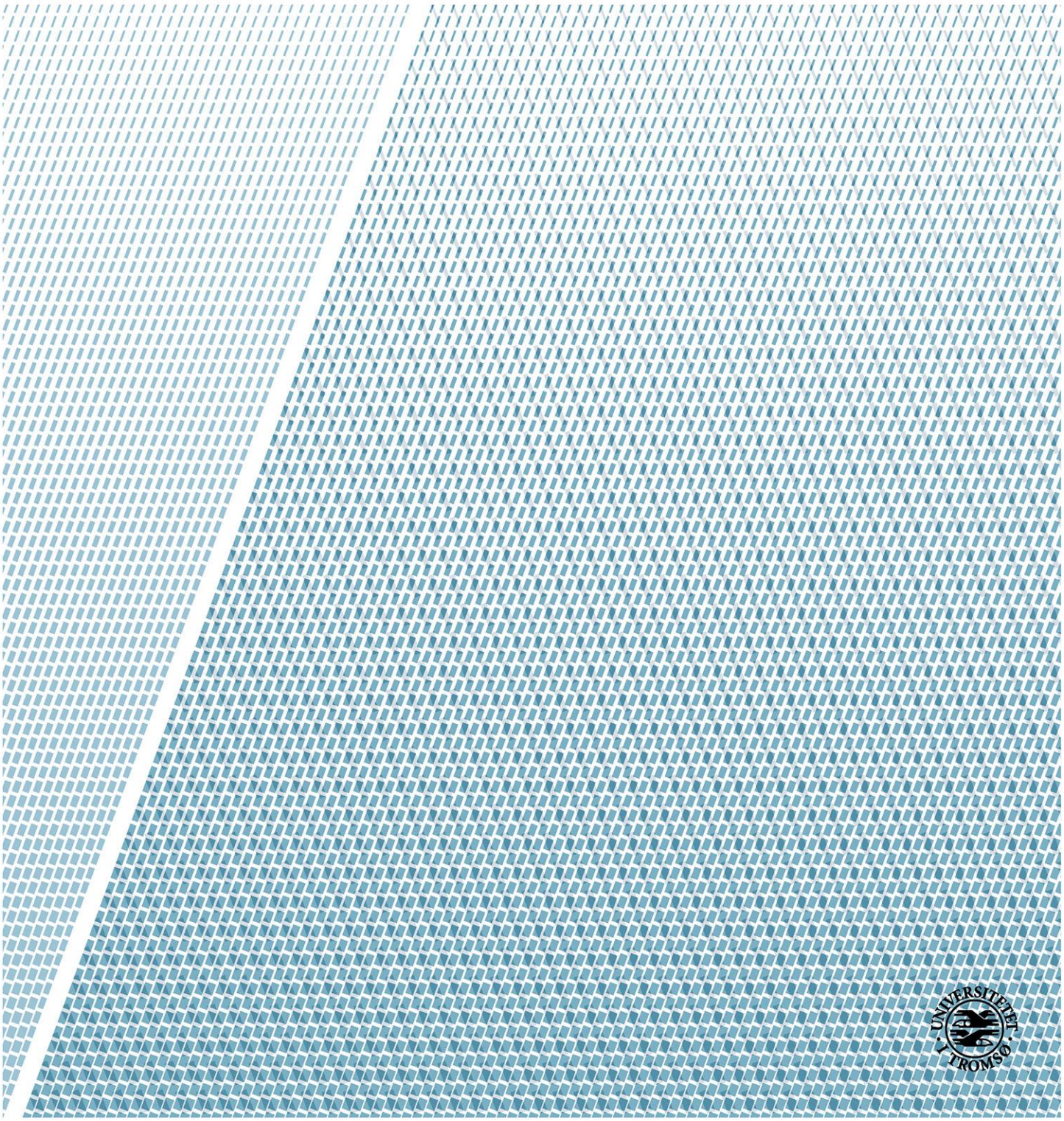

Preface

The idea behind this thesis started in 2017 when The Count Governor of Troms performed a supervision of sepsis in the Emergency Department (ED) at University Hospital of Northern Norway (UNN). The results identified serious deficiencies, resulting in patients being put at risk because they had to wait a long time before receiving antibiotic treatment. With this in mind, we contacted Dr. Trine Olsen in April 2017, who was assigned to the sepsis improvement project at UNN. We discussed possible aims for our thesis. Trine introduced us to the Surviving Sepsis Campaign as an inspiration (1). We agreed upon doing an internal quality assessment of early recognition of sepsis in the ED at UNN. We aimed to further investigate this life-threatening syndrome and hope that our thesis will bring more knowledge and focus to this important condition. Dr. Unni Ringberg, Associate Professor Department of Community Medicine and general practitioner is involved as co-supervisor.

First and foremost, we want to thank our main supervisor, Trine Olsen. You are encouraging and helpful, and your profound knowledge is impressive. Even though you have a busy schedule, you found time for us. Secondly, we would like to express a special gratitude to our co-supervisor, Unni Ringberg. Thank you for the constructive criticism and precise feedback. We are truly grateful for all the help and instructions we have received. Thomas Carlenhult also deserves a big thank you for reading through the material and correcting our language.

Lastly, we would like to acknowledge each other. We have done all of the work with this thesis together, and we started out the work process already during the fourth year. Despite some hectic semesters, we have always found time to meet to discuss the topic, problems regarding the work process and to work on the thesis. This thesis could not have been done without our excellent cooperation and good support. It has been an incredible journey, despite some downturns of the project. We have learned a lot about sepsis, and we are truly grateful that we had the opportunity to work on this important topic.

Tromsø, 30.05.2019

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Abstract

Background: Recently, the diagnosis of sepsis was redefined and of today there is no gold standard for diagnosing the syndrome. The increasing use of different screening tools for identifying sepsis in the Emergency Department (ED) calls for validation.

Objective: To evaluate the clinical usefulness of qSOFA, SIRS, TILT and NEWS as early warning scores for sepsis and in prediction of mortality in patients with suspected infection admitted to the ED. To assess if a modification by including risk factors to the different scoring tools could improve early recognition of sepsis.

Methods: The study was a retrospective study performed in the ED at a single center hospital in Norway in the period October 1. 2017 – January 14. 2018. The study sample consisted of patients (n=391) who were either received by The Emergency Medical Team (EMT) or were later admitted to the Department of Infection with either a yellow, orange or red triage according to the Rapid Emergency Triage and Treatment System (RETTS). Patients were selected using data from DIPS (the hospitals electronic health record). We measured sensitivity, specificity and area under the receiver characteristic curve (AUC) for detection of sepsis and mortality as end point.

Results: Of 391 patients screened, 270 patients were included and 139 had sepsis. NEWS ≥ 4 was of most clinical usefulness in detection of sepsis with a sensitivity of 0.78 (95% CI: 0.71-0.84) and a specificity of 0.59 (95% CI: 0.50-0.67). qSOFA ≥ 2 had lowest sensitivity with 0.48 (95% CI: 0.40-0.56), but highest specificity with 0.95 (95% CI: 0.90-0.98). Overall mortality was 27 %. NEWS identified most patients who experienced death within 7-days, 30-days and 1-year although the ROC curve of qSOFA was higher than of NEWS in predicting mortality. All modified screening tools demonstrated an increased ability to identify sepsis.

Conclusions: All scoring systems were able to recognize patients with sepsis. NEWS was found to be of more clinical usefulness compared to qSOFA, SIRS and TILT in early identification of sepsis. NEWS is at least equivalent or better than the other screening tools across most measures in predicting mortality. Our finding suggests that the implementation of risk factors in different screening tools could increase their clinical usefulness.

Abbreviations

ARDS	Adult Respiratory Distress Syndrome
AUC	Area under the curve
CI	Confidence Interval
CO	Cardiac Output
CVPU	(new) Confusion, Voice, Pain, Unresponsive
DIC	Disseminated Intravascular Coagulation
ED	Emergency Department
EMT	Emergency Medical Team
EPR	Electronic Patient Records
ESS	Emergency Signs and Symptoms
GCS	Glasgow Coma Scale
HIV	Human Immunodeficiency Virus
ICD-10	International Classification of Diseases 10th revision
ICU	Intensive Care Unit
MAP	Mean Arterial Pressure
MeSH	Medical Subject Headings
MEWS	Modified Early Warning Score
NEWS	National Early Warning Score
NPR	Norwegian Patient Registry
OR	Odds Ratio
qSOFA	Prehospital early sepsis detection (score), Quick SOFA
RETTS	Rapid Emergency Treatment and Triage System
ROC	Receiver Operating Characteristic
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential (sepsis induced) Organ Failure Assessment
TILT	“Tidlig Identifisering av Livstruende Tilstander”
UNN	University Hospital of Northern Norway
VIEWS	Vitalpac Early Warning Score

Nomenclature

DIPS	A system for electronic patient record (EPR).
Infection	Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.
NPR	NPR is a national database run by the Norwegian Directorate of Health, containing information about all hospital admissions in Norway (patient data, dates of hospitalization, type of hospital and Department, vital status at discharge and discharge codes).
Organ dysfunction	According to Task Force of the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) organ dysfunction should be defined according to the scoring system Sequential Organ Failure Assessment (SOFA) score (Table 5). An acute change in total SOFA score ≥ 2 points is to be understood as organ dysfunction.
Scoring systems	Scoring systems are tools that may heighten the clinical suspicion for a condition, for example sepsis, and encourage physicians to perform time-critical interventions.
Sepsis-1	Sepsis-1 was presented in 1991 and defined sepsis as the systemic inflammatory response syndrome (SIRS) to a confirmed infectious process. Criteria for SIRS are presence of 2 out of 4 of: heart rate >90/min, respiratory rate >20/min, temperature >38 or <36^{o}C or leukocyte count >12 000/cu mm or <4000/cu mm or >10% immature (band) forms. Severe sepsis was defined as sepsis + organ dysfunction, but criteria for organ dysfunction was not specified.

Sepsis-2

Sepsis-2 is often used for the definition according to the second sepsis consensus conference in 2001. The basic definition of sepsis was retained, and the list of sepsis criteria was expanded.

Sepsis-3

Sepsis-3 was launched in 2016. The new definition of sepsis now includes organ dysfunction. Sepsis is now defined as *life threatening organ dysfunction caused by a dysregulated immune response to an infection.* Criteria for sepsis-3 are an increase of 2 points or more from baseline in the SOFA-score (Table 5). The term *severe sepsis* is no longer in use.

Septic shock

Sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include:

- lactic acidosis
- oliguria
- an acute alteration in mental status.

Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

The local definition of organ dysfunction, UNN

The UNN´s definition of sepsis is the same as in Sepsis-3.
Organ dysfunction, however, was defined as listed on page 11.
The criteria for organ dysfunction are not as strict as criteria in Sepsis-3.

1 Introduction

1.1 Background

The definition of sepsis and the characterization of its different stages have changed three times in the past 28 years, most recently in March 2016 by the Sepsis-3 Task Force (2). They recognized the need to reexamine the current definitions of sepsis as a systemic inflammatory response syndrome (SIRS) due to infection (3). Sepsis is today defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (4).

Sepsis is a complex syndrome and is not completely understood (5). As of today, there is no gold standard for diagnosing sepsis. This has led to extensive research into diagnosis and treatment (1, 6). Sepsis remains a significant global health challenge and is one of the most common reasons for hospitalization and admissions to the intensive care unit (ICU) (7).

Clinically, sepsis is difficult to diagnose with symptoms often being non-specific. It is especially challenging within certain groups of people, like elderly, who are at greater risk of developing sepsis (8, 9). Early detection and management, including starting antibiotics within one hour after suspicion of sepsis, can improve and reduce morbidity and mortality (10).

Most patients admitted to a hospital with sepsis are initially assessed in the Emergency Department (ED). In the ED identification of sepsis is based on clinical judgment, experience and different clinical scoring systems (11, 12). A good scoring system may be useful in a clinical setting, helping doctors to identify patients at risk of sepsis and to give appropriate treatment as promptly as possible.

In 2016-2018 the Norwegian Board of Health Supervision performed a nationwide surveillance of the EDs in Norway. The aim was to investigate whether identification, diagnosis and treatment of patients with sepsis and suspected sepsis in the ED were adequate (13). Results from the first evaluation at UNN revealed that the majority of patients with sepsis received delayed examination by a doctor. Furthermore, the report confirmed that many patients with sepsis were not identified and the time from admission to establishing treatment was too long (13).

1.2 Definitions

1.2.1 Sepsis

Infections can affect all parts of the body, be localized or systemic. The severity ranges from mild infection to sepsis and septic shock. Multiple definitions and terminologies have been used to define both sepsis and septic shock, leading to inconsistency in diagnosing and reporting. The validity and clinical utility of the sepsis definitions have been questioned over the years. This led to redefinitions in 1991, 2001 and 2016 (2).

In 1991, an American consensus meeting (Sepsis-1) defined sepsis as the Systemic Inflammatory Response Syndrome (SIRS), with a score of two or higher in a response to a confirmed infection process (Table 1). The syndrome was divided into three subgroups; sepsis, severe sepsis and septic shock (12). However, the definition has been criticized for being overly sensitive and reporting many false negative cases (14, 15). This led to a second international consensus conference in 2001 (Sepsis-2). The basic definition of sepsis was retained, but the list of sepsis criteria was expanded (11). In 2016, based on new research findings, another new definition of sepsis was suggested by the Third International Sepsis Definitions Task force, designated Sepsis-3 (2).

In Sepsis-3, sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be represented by an increase in the Sequential, (sepsis-related), Organ Failure Assessment (SOFA) score of 2 points or more, in consequence of an infection (2) (Table 5). SOFA is commonly used inside the intensive care unit (ICU) and requires laboratory findings. In order to identify patients with sepsis outside the ICU, the Task Force introduced The Quick Sequential Organ Failure Assessment (qSOFA) score as a new screening tool (Table 2). A positive qSOFA score should stress the clinicians to further investigate for organ dysfunction and initiate appropriate measures (2, 16).

The Task Force further defined septic shock as a subset of sepsis, identified with persisting hypotension that requires vasopressors to maintain mean arterial pressure ≥ 65 mmHg and serum lactate level > 2mmol/l despite adequate volume resuscitation (2). They eliminated the terminology “severe sepsis” (2, 16).

Sepsis is a medical emergency, requiring early and effective treatment. A key strategy to improve management is to recognize and identify patients with sepsis at an early stage. This is important to prevent an adverse outcome (17). Different scoring systems such as qSOFA and SIRS are already commonly implemented in clinical practice outside the ICU. However, systems like "Tidlig identifisering av livstruende tilstander" (TILT) and the National Early Warning Score (NEWS) are track and trigger monitoring systems in use for detection of acute illness. These scoring tools are in use in several Norwegian hospitals. If these scoring tools can be shown to be of equivalent or higher prognostic accuracy in detecting sepsis, the rationale for using either qSOFA or SIRS may be called into question (18).

1.2.2 Triage

Triage is the first point of contact when a person arrives to the ED. At this point, the urgency of the patients´ conditions is decided and consequently how fast the patients will need medical evaluation and treatment. Emergency departments around the world use different triage systems to assess the severity of admitted patients´ conditions and to assign treatment priorities. Multiple patients may present with conditions that are time sensitive, like for example sepsis (19-21). A good triage screening and assessment tool may identify these patients as early as first triage.

1.2.3 Rapid Emergency Triage and Treatment System (RETTS)

RETTS is the most commonly used triage system in Norway and is currently in use at UNN. RETTS uses a combination of the patient´s presenting symptoms and signs in addition to vital values to categorize patients into different priority groups. Symptoms and signs are matched to one of the Emergency Signs and Symptoms (ESS) algorithms in accordance with RETTS-A and vital values are measured. The patient´s final triage priority is based on the most urgent findings. There are four priority categories: Red (immediate evaluation by a doctor), orange (can wait 10 minutes before evaluation), yellow (can wait 60 minutes before evaluation), green (can wait 120 minutes before evaluation), blue (can wait 240 minutes before evaluation) (20, 22).

1.2.4 Scoring systems

Early identification of sepsis requires attention to symptoms and signs (8). To the clinician, it is of prime interest to identify patients with both infection and suspicion of sepsis at an early stage. To heighten the clinical suspicion of sepsis and encourage physicians to perform time-

critical interventions, different scorings systems can be used. These have been introduced to help identify patients with sepsis and to determine the severity. Each scoring system uses different combination of parameters, and there is no consensus which scoring system is best in clinical practice (23). Screening tools are not adequate to make a diagnosis but may serve to identify patients at risk and to stratify the risk of an adverse outcome (24).

1.2.4.1 SIRS

Systemic inflammatory response syndrome (SIRS) can be used to identify sepsis. A positive SIRS requires a presence of an infection and two or more of the following four conditions: temperature >38°C or <36°C, heart rate >90/min, respiratory rate > 20 breaths/min or $PaCO_2$ < 4.3 kPa and leukocyte count >12 000/cu mm or <4000/cu mm or >10% immature (band) forms (12) (Table 1).

1.2.4.2 qSOFA

qSOFA is a new scoring tool that does not require laboratory tests and can be assessed quickly and repeatedly. It was developed to rapidly assess the patient clinically for risk of deterioration due to sepsis outside of the ICU (2). qSOFA requires the presence of an infection and two of the following three criteria: respiratory rate ≥22/min, systolic blood pressure ≤100 mmHg and any alteration in mental status (4) (Table 2).

1.2.4.3 TILT

TILT score is developed by a regional hospital in Agder, Norway. It is a paper-based evaluation tool for early identification of life-threatening conditions. It is based on the modified early warning score (MEWS) and includes the vital parameters; pulse, temperature, respiratory rate, blood pressure and mental status. Each parameter is assigned a value from 0-3 according to level of severity. With a score ≥ 4 the patient should be seen by a doctor (25) (Table 3).

1.2.4.4 NEWS

NEWS is based on the earlier VIEWS (VitalPAC Early Warning Score) and is implemented in hospitals across Europe. It has been developed to make a standardized system for early detection of patients with acute illness. NEWS was first produced in 2012. An updated version, NEWS2, was launched in 2017. NEWS2 is further referred to as NEWS (26).

NEWS contains of six physiological parameters (Table 4). Each of which is assigned a value between 0 and 3, along with an additional parameter for supplemental oxygen, which scores 0 or 2. Updated NEWS has a dedicated section (SpO_2 scale 2) for use in patients with hypercapnic respiratory failure. The parameters are summed to calculate the NEWS which may range between 0 and 20. Several studies have used different cutoff points for screening potential infectious patients for sepsis (18, 27, 28).

1.3 Epidemiology

In 2013, sepsis was ranked as the most expensive medical condition in a national study of inpatient hospital costs in the U.S.(29). An accurate estimate of the incidence and mortality of sepsis is difficult given the difficulty of diagnosing the syndrome. Multiple definitions and terminologies of sepsis have been used and this has led to major variations in reported incidence and mortality rates (2). The hospital mortality of sepsis has ranged from 25% to 80% over the last few decades (30). Studies have shown that the incidence of sepsis increases with age and men have a higher incidence than women in all age groups (31).

A Norwegian study from 1999 reported an overall sepsis incidence of 149 per 100 000 inhabitants per year, with a mean mortality of 13.5% (32). In a recent Norwegian national study from 2017, the overall incidence of hospitalized sepsis was 140 per 100 000 individuals per year. The incidence of sepsis in USA is estimated to be 300 cases per 100 000 population and is killing one in four (33-36). This indicates that sepsis is not uncommon.

1.4 Infection and pathophysiology in sepsis

An infection can affect all parts of the body. Both the microbe, the host properties and the time to diagnosis and treatment are crucial for the outcome. The pathophysiology of sepsis is still debated and not yet completely understood. Over the years it has become apparent that the key event in sepsis is a systemic inflammatory response to infectious agents (37).

If the microorganisms overcome the initial immune response, they spread to distant tissues and organs via the blood stream. The body triggers production of inflammatory mediators that are characterized by an inflammation and immune suppression (38, 39). If the immune system is healthy and the microorganisms involved are below a tolerance limit, the infection will be controlled and spontaneously cured (39).

The unbalanced immune response leads to a systemic release of pro-inflammatory cytokines, chemokines and vasoactive amines. The high amount of pathogens in the bloodstream during sepsis produce a severe acute reaction, which in turn can lead to microembolisms, bleeding and organ dysfunction (40).

Early in the course of sepsis, the body reacts by increasing the cardiac output (CO) to maintain blood pressure and organ perfusion as a response to reduced peripheral vascular resistance. As sepsis progresses, CO may frequently be reduced (41). Vasoactive mediators give vasodilation and together with increased endothelial permeability, the patient is in risk of edema and hypotension (42).

1.5 Clinical signs and symptoms

Patients with sepsis may present with different clinical symptoms depending on microorganisms, organ system involved and the patients´ predisposition for sepsis. The signs and symptoms of sepsis are often non-specific. Sepsis may initially look like flu, gastroenteritis or a chest infection with nausea, vomiting, diarrhea and ileus (43).

Early symptoms and signs may include fever or hypothermia. The absence of fever is more likely in the elderly, debilitated patients, patients with chronic alcohol abuse and in patients with uremia or hypothermia. Normal temperature may occur in immunosuppressed patients with sepsis (43-45). Furthermore, increased heart rate, hyperventilation and sometimes confusion or disorientation are often seen at an early stage (45).

As sepsis progresses it may result in anaerobic metabolism with high values of blood lactate leading to metabolic acidosis. Furthermore, vasoactive mediators and changes in permeability may lead to hypotension and result in a low urinary output. Sepsis is also associated with a number of peripheral manifestations involving the skin. The skin may be cold, clammy, pale, cyanotic or mottled and can develop rashes (43, 45).

At present, there is no single laboratory test that can accurately identify sepsis. However, drastic and acute change in biomarkers, should alert every doctor to include sepsis as a possible or contributing cause of these changes. Several biomarkers have been proposed and used to diagnose the syndrome. These laboratory findings include leukocytosis or leucopenia, thrombocytopenia and proteinuria. The acute phase response results in increased production

of C-reactive protein, ferritin, fibrinogen and complement components. Liver enzymes may also be abnormal, with elevated serum conjugated bilirubin and alkaline phosphate (45).

Sepsis has a number of serious complications. Acute respiratory distress syndrome (ARDS), acute renal injury (AKI) and disseminated intravascular coagulation (DIC) account for some of the most important organ dysfunctions (46). Complications may be fatal if left untreated or treated too late. If sepsis progresses to failure in multiple organs and shock, it may lead to death (38).

1.6 Risk factors associated with sepsis

Evidence suggests that some patients are at greater risk of developing sepsis because they are less able to fight infections due to changes in the immune system (47). In the presence of infection, risk factors should be considered and get the doctor to consider sepsis. Literature shows that age is an important risk factor, especially people over the age of 75 years who have comorbidities and reduced immune system or functional limitations (48). Elderly are especially vulnerable to community-acquired pneumonia and urinary tract infections which further predispose them for sepsis (49).

Another important risk factor is immunosuppression. Immunocompromised patients are often more vulnerable of community acquired infections as well as opportunistic infections. In this group of patients the symptoms may be masked or altered which makes it even harder to identify sepsis (50). Therefore, sepsis should be considered in every change in their condition (51). A complete list over possible risk factors are shown on page 13.

1.7 Sepsis, antibiotics and national guidelines

Sepsis is a time-sensitive illness since the disease develops rapidly and is potentially life threatening. Fast and proper diagnosis and appropriate treatment with antibiotic is essential for the outcome (52). Delayed antimicrobial therapy is associated with increased mortality and increases the risk of septic shock (53, 54). The mortality has been shown to increase by 7.6% for every hour of delay in starting antibiotic therapy (17, 55, 56).

Empirically antimicrobial therapy for sepsis should be broad from the start and the suspected site of infection should indicate the choice of antibiotics. A combined treatment with more

than one antimicrobial is frequently needed. Empirically antimicrobial therapy should cover both gram-positive and gram-negative bacteria and be capable of achieving therapeutic drug levels in the infected organ (57, 58).

International and national guidelines recommend initiating broad-spectrum antibiotics within one hour after suspected sepsis (1, 59). The national guidelines for treating sepsis in Norway are outlined in the national guideline for antimicrobial therapy issued by The Norwegian Directorate of Health and is currently under revision (60). Sepsis with unknown origin is treated with benzylpenicillin combined with an aminoglycoside (61). Aminoglycosides are rapid bactericides and are effective against a majority of microbes that are relevant in Norway. In cases of high risk for severe renal failure, aminoglycosides are contraindicated (60).

2 Objective

The overall aim of this thesis was to evaluate the clinical usefulness of four different scoring tools as early warning score for sepsis in patients with suspected or confirmed infection in the ED.

The specific objectives were:

- To evaluate the clinical usefulness of qSOFA, SIRS, TILT and NEWS for early identification of sepsis.
- To evaluate the usefulness of qSOFA, SIRS, TILT and NEWS in prediction of 7-days, 30-days and 1-year mortality.
- To assess if a modification of qSOFA, SIRS, TILT and NEWS by including risk factors to the different scoring tools could improve early recognition of sepsis.

3 Materials and Methods

3.1 Search strategy

Before initiating the study, we searched for relevant literature. Searches were performed 01.04.17, 01.09.18 and 01.02.19.

We used the following databases:

- Pubmed
- Google scholar

We used the following main search options:

I. "Sepsis" and "definition" and "organ failure"
II. "Sepsis" and "identification"
III. "Sepsis" and "screening tools" and "early warnings score"
IV. "Sepsis" and "SIRS" and "qSOFA" and "TILT" and "NEWS" and "MEWS" and "RETTS"
V. "Sepsis" and "pathophysiology"
VI. "Sepsis" and "outcome" and "treatment"
VII. "Sepsis" and "antibiotics"

We used MeSH terms to give the search high sensitivity:

- Etiology
- Sign and symptoms
- Hemodynamic
- Immune response
- Risk factors

The findings were put in a digital library of references, EndNote X8 and X9.

3.2 Study design

We performed a retrospective study at a single center hospital. The data was obtained from DIPS (the hospitals electronic health record) which contains data from the Norwegian Patient Registry (NPR).

3.3 Study sample

The study was performed in the ED at UNN, an urban teaching hospital in Tromsø, Norway in the period 01.10.17-14.01.18. Patients eligible for selection were either received by The Emergency Medical Team (EMT) or were later admitted to the Department of Infection.

3.3.1 Inclusion and exclusion criteria

Patients were selected using the following inclusion criteria: age ≥ 18, clinically suspicion of or confirmed infection according to the reason of admission, those who met the criteria for RETTS triage scale level yellow, orange, red and patients with no triage. We excluded patients younger than 18 years, those who had green and blue triage, patients treated with antibiotics in primary care and those who were admitted to all other Departments (Figure 1).

3.4 Data collection

3.4.1 Sources of data information

The authors reviewed the medical records of all eligible patients. We systematically searched through medical records (emergency-journal, admission note, discharge report) in DIPS using the patients´ NPR number. Data was registered into an excel spreadsheet. The spreadsheet was made together with our supervisor. Mortality data is reported in DIPS, with updated information from the Norwegian population registry.

3.4.2 Procedure of data collection

In this retrospective study, we discriminated between patients who had an infection with no suspicion of sepsis (sepsis = no), and those who had suspicion of sepsis (sepsis = yes). We defined patients with sepsis according to Sepsis-3. For identification of organ dysfunction, we screened to see if the patients fulfilled the consensus criteria of the local guideline at UNN which contains some minor modifications compared to the SOFA score, listed in Textbox 1. Organ dysfunction was defined as having one of the following parameters in an organ that was not directly affected by the infection. The parameters were retrospective registered by using data from the time of arrival at the ED.

Textbox 1	**Local sepsis guideline for organ dysfunction, UNN**
Parameters	
Alteration of mental status?	Signs of somnolence, confusion or impaired consciousness or GCS<15
Acute kidney failure?	Increase in s-creatinine > 26 µmol /L (last 48h) or increased ≥1.5x baseline or developed over the last seven days or signs of oliguria or anuria
Liver failure?	Bilirubin> 25 µmol/L
Coagulopathy?	30% reduction in platelets or <150 10^9/L in platelets or INR > 1.5
Affected / changed respiration?	< 90% SpO_2 without oxygen
Affected / changed circulation?	*Skin:* Cyanotic skin, lips or tongue, marbled, cold peripheral, clammy skin or reduced capillary filling *Signs of hypotension:* Systolic BT <100mmHg or decreased BT > 40mmHg from habitual BT or MAP <70mm Hg
Acidosis?	Lactate > 2 mmol/L or base excess ≤ -5

We gathered variables from the emergency journal. In order to standardize data collection, we recorded clinical and physiologic data registered at the time of arrival in the ED. These values were used to score patients according to the four tools for sepsis, qSOFA, SIRS, TILT and NEWS. If these arrival data were missing from the emergency-journal, we looked into the admission note.

The following variables were recorded:

- Gender: male/female
- Age
- Reason for admission
- Final diagnosis: ICD-10 diagnoses collected from the patients discharge note
- Organ dysfunction: yes/no, according to UNN´s criteria

- Scoring tools: Vital signs, symptoms and laboratory findings were used to calculate and score each patient (Table 1-4)
    - qSOFA, (0-3 points), *qSOFA positive = 2 or more*
    - SIRS, (0-4 points), *SIRS positive = 2 or more*
    - TILT, (0-15 points), *TILT positive = 4 or more*
    - NEWS, (0-20 points), *NEWS positive = 4 or more / 5 or more*
        - if otherwise not stated, NEWS is further referred to have a cutoff value of ≥ 4
- Mortality within 7-days, 30-days or 1-year: yes/no
- Antibiotic treatment: type of antibiotics
- Clinical judgement by the doctor in the ED: yes/no
    - Clinical judgement was based on the patient history with special reference to the vital parameters.
    - Judgement was also based on the following;
        - Treatment given (empiric antibiotic therapy and broad-spectrum antibiotics)
        - Use of scoring tools
        - Suspicion of sepsis commented by the doctor
- Risk factors: No risk factor was given 0-point, one risk factor was given 1-point and two or more risk factors were given 2-points. Risk factors are listed in Textbox 2.

In the present study, we defined risk factors as having one of the conditions listed in Textbox 2. This list is currently in use at UNN and is based on a publication from The National Institute for Health and Care Excellence (NICE) (62).

Textbox 2 Risk factors for sepsis. Local guideline, UNN

- Patients <1-year or >75 years old, or very frail people
- Patients who have impaired immune systems because of illness or drugs:
    - Chemotherapy for cancer treatment
    - Impaired immune function (such as those with HIV, diabetes or sickle cell disease, or people who have had a splenectomy)
    - Long term treatment with corticosteroids
    - Treatment with immunosuppressant drugs for non-malignant disorders, such as rheumatoid arthritis
- Patients who have had surgery, or other invasive procedures in the past six weeks
- Patients with any breach of skin integrity (such as cuts, burns, blisters, or skin infections)
- Patients who misuse drugs intravenously
- Patients with alcohol abuse
- Patients with indwelling lines or catheters
- Women who are pregnant or have given birth including cesarean section or had a termination of pregnancy or miscarriage in the past six weeks

3.4.3 Modified screening tools

In this study, we performed a modification of qSOFA, SIRS, TILT and NEWS by including "Risk factors" as an extra parameter. The modified versions are shown in Table 12. One point was added to each scoring system if the patient had one or more risk factors according to the criteria in Textbox 2. Eventually, we compared the performance of the modified tools against the classical in early recognition of sepsis in the ED.

3.4.4 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0. (Armonk, NY: IBM Corp).

Data regarding our study sample is presented using descriptive analyses with frequency tables, median and means. Clinical usefulness was quantified by calculating the sensitivity and specificity for each scoring tools. Results are reported with 95% Confidence Interval (CI). For association between qSOFA ≥ 2, SIRS ≥ 2, TILT ≥ 4 or NEWS ≥ 4 and having sepsis, we

used logistic regression to estimated odds ratio (OR). Chi-square test was used to compare the relationship between the different scoring tools and sepsis.

Receiver operating characteristic (ROC) curve is a statistical method that measures diagnostic accuracy of a test. A computer-generated ROC diagram plots the true positive rate (sensitivity) of a test on the *y*-axis against the false positive rate (100-specificity) on the *x*-axis, yielding the ROC area under the curve (AUC) (63, 64). In this study, the ROC curve and area under the ROC curve (AUC) were used to discriminate how well different scoring systems identified sepsis. We also used AUC values to determine the relationship between the different tools and mortality. AUC can range from 0.5 to 1.0. In this thesis, a value of 1.0 indicates a perfect discriminator ability. An AUC value > 0.8 is considered good, a range between 0.50-0.79 is considered as moderate, and an AUC value < 0.49 is considered as poor (65, 66).

3.5 Formal approval

This study is based on a quality improvement perspective, without additional intervention. Therefore, it was sufficient with approval from the Data Protection Officer at UNN, which authorizes the registration of data in a local quality register, as provided in the Health Care Act, §26. Approval of the Local Quality Register from the Security Representative at UNN Tromsø is available from 10.10.2017 and is valid three years from that date, attachment 8.2.

4 Results

4.1 Study sample characteristics

During the study period, 391 patients were selected and 270 (69%) fulfilled our inclusion criteria. The mean and median age of the study sample were 64 and 69 years (range, 18-99 years), with the majority 151 (56 %) being male. Sepsis was identified in 139 (52%) of the 270 patients who met the inclusion criteria, of whom 86 (62%) were men. Out of the 139 patients with sepsis 94 (68%) were over 65 years and 68 (49%) of the patients were over 75 years. Study sample characteristics are summarized in Table 6.

4.2 Comparison of the different scoring tools

The ability for the different scoring systems to identify sepsis are listed in Table 7.

Using the first vital parameter recorded at the time of arrival in the ED, qSOFA ≥ 2 identified 67 patients whereas SIRS ≥ 2 identified 106, TILT ≥ 4 identified 81, NEWS ≥ 4 identified 109 and NEWS ≥ 5 identified 99 patients.

NEWS ≥ 4 had the highest sensitivity with 0.78 (95% CI: 0.71-0.84) and a specificity of 0.59 (95% CI: 0.50-0.67). qSOFA had the lowest sensitivity, 0.48 (95% CI: 0.40-0.56), but the highest specificity with 0.95 (95% CI: 0.90-0.98).

The predictive performance of the different tools is shown in Figure 2, Table 7 and Table 8. The Area Under the receiver operating Characteristic curves (AUC) for identification of sepsis was poorest for SIRS, with an AUC of 0.61 (95% CI: 0.55-0.68), while qSOFA had an AUC of 0.72 (95% CI: 0.66-0.78). TILT and NEWS showed the similar value with no significant difference.

Table 9 outlines the odds ratio (OR) for sepsis. The OR was highest for positive qSOFA (0.19, 95% CI: 0.08-0.47), and lowest for positive SIRS (0.03, 95% CI: 0.02-0.05).

The Chi-Square test showed that there is a significant relationship between all the different scoring tools and sepsis.

4.3 Prediction of mortality

Three of 139 patients with sepsis died within 7-days and nine patients died within 30-days. Both SIRS and NEWS criteria were able to identify all these patients upon arrival at the ED. qSOFA did only identify one of three that died within 7-days.

26 patients died within 1-year after admission. NEWS identified 20 of these patients compared to TILT that only identified 12.

In total, 38 (27%) of the 139 patients died. Sensitivity for correctly identifying those experiencing mortality was 0.84 (95% CI: 0.70-0.93) for NEWS while qSOFA had highest specificity with 0.57 (95% CI: 0.48-0.67) (Table 10).

With regards to sepsis related mortality, the AUC value for the different stratification tools was significantly higher using qSOFA than NEWS ($p<0.001$ and $p<0.006$). The AUC value for qSOFA was 0.71 (95% CI: 0.62-0.81) and 0.64 (95% CI: 0.55-0.73) for NEWS. Performance characteristics are presented in Figure 3 and Table 11.

4.4 Modification of the different scoring systems

Figure 4 shows an overview over patients' risk factors. 23 of 139 patients with sepsis did not have any risk factors, 44 patients had one and 72 had two or more risk factors.

Table 13 demonstrates the ability for the modified scoring systems to identify sepsis. The results show an increase in sensitivity for all the tools. qSOFA alone would have identified 67 patients with sepsis, while the modified qSOFA identified 107 patients, given a new sensitivity of 0.77 (95% CI: 0.69-0.83). 118 patients would have fulfilled the new criteria of NEWS, with a new sensitivity of 0.85 (95% CI 0.78-0.90).

5 Discussion

5.1 Summary of findings

In this retrospective study, NEWS had the best sensitivity for detecting sepsis and was of more clinical usefulness compared to qSOFA, SIRS and TILT. NEWS was also superior in predicting overall mortality in patients with sepsis admitted to the ED. SIRS showed a problematically low specificity in identifying sepsis. qSOFA detected few of the sepsis cases and had a poorer sensitivity than the other screening tools, which is in agreement with previous literature (67).

When comparing the performance of the different risk stratification tools, qSOFA had the highest AUC value. Despite having a high AUC value, it should be stressed that the real characteristic of interest for clinical use are the sensitivity and specificity. Furthermore, we found that a modification of all four scoring systems by adding one point for *risk factors*, yielded a higher sensitivity. Our study is, to the best of our knowledge, the first to include risk factors as an additional parameter and the first to evaluate and compare these four scoring systems.

5.2 Characteristics of sepsis patients at UNN

In our retrospective study, 139 (52%) of the patients had sepsis according to sepsis-3 and UNN´s criteria for organ dysfunction. Despite a small study sample, the demographic characteristics are comparable with most sepsis studies (33, 68). We found that sepsis occurs more often in men than women. The higher occurrence of sepsis among men has been discussed in literature to be multifactorial. Studies have stated that factors like chronic health, behavioral factors and gender specific susceptibility to microbes, may be reasons why men are at higher risk (31, 69).

Furthermore, we found that 68 patients with sepsis were older than 75 years. If we adjusted the age cutoff to 65 years, 94 patients would have been included. This shows that sepsis is more common among the elderly (70). Results from a Spanish study reported that the mean age of affected patients has increased during the past decades (71). The Norwegian sepsis report from 1999, reports a mean age of 58 years, whereas in a recent retrospective study it was 73 years (31, 32). This is in line with our observations.

5.3 Sepsis definition

In the present study, we chose to refer to the Sepsis-3 definition of sepsis. To identify patients with organ dysfunction, we used the local sepsis guideline at UNN (page 11). This was done in order to be able to diagnose sepsis at an early stage in a non-ICU environment. Similar has been done in a recent study by Knoop (31). The use of the Sepsis-3 definition of organ dysfunction in an ED setting, where the definition of organ dysfunction is represented by an increase in the SOFA scoring system, is highly debated (72). In the Sepsis-3 definition, it is only recommended and not required that organ dysfunction is based on a SOFA score ≥ 2. At present time, there is no international consensus concerning an optimal clinical scoring system to identify early organ dysfunction in sepsis patients in an emergency or prehospital setting and there is no gold standard diagnostic test that identify sepsis.

In the revised Sepsis-3, qSOFA score is by several studies shown to be less sensitive in an emergency context when used as a screening tool (67, 72). The author of the Sepsis-3 study states that qSOFA should only be used as a quick bedside risk stratification tool to identify sepsis patients with high risk of poor outcome and should not rule out other screening tool for early sepsis identification. The author points out that qSOFA and SIRS criteria should be viewed as complementary and not competing (73).

Furthermore, the full SOFA score is often used in an intensive care context and requires laboratory findings like PaO_2, platelet count, creatinine level, and bilirubin level (2, 74). Some of these criteria are hard to obtain in an ED setting and therefore, we chose to use a less strict definition of organ dysfunction. Our modification may have given the possibility that our retrospective study is slightly biased towards a less severe patient group and makes it less comparable with other studies.

5.4 Scoring systems / Scoring tools

Many studies have analyzed and compared different scoring systems for identifying sepsis. Most studies have focused on SIRS and qSOFA (67, 75, 76) and few have compared these with NEWS (28). In the UK they use NICE guidelines to identify sepsis (62). To the best of our knowledge, nobody has done a comparison with TILT. Our findings suggest that no scoring systems had both high sensitivity and specificity in predicting those with sepsis in the ED. In an emergency setting, a sensitive tool is more important than a specific one. This is to avoid overlooking critically ill patients. Specificity might be more relevant in an ICU setting, to indicate whether a patient's treatment should be escalated (18, 77).

The SIRS criteria have been a part of the sepsis definition for more than two decades, and have been criticized in the literature for almost as long (12). One reason is that SIRS requires laboratory tests, and this may delay identification and treatment of sepsis (2). Furthermore, SIRS has been criticized for being oversensitive and may be present in many hospitalized patients, including those who never develop infection. Our results are consistent with other studies, also showing a problematically low specificity for SIRS (78-80). This indicates that having two or more elements of SIRS does not discriminate well enough for organ dysfunction.

Recent studies have raised questions to the use of qSOFA as a bedside screening tool. Mainly, because it is shown to identify patients late, after organ dysfunction has occurred. In the present study, qSOFA failed as a clinical screening tool with a sensitivity of only 48%. This is supported by a study from Norway by Askim et al. where qSOFA only had a sensitivity of 32% (67). Williams and colleagues reported a sensitivity of 29.9% (81). One reason qSOFA may fail to achieve high sensitivity may be due to not including important vital parameters like heart rate and temperature (82).

In our study, we have used ROC curves to show in a graphic way the diagnostic performance for the different screening tools. The area under the ROC, AUC, gives an idea about the benefit of using the different tests. The AUC value is a measure of the usefulness in general. A weakness by using the AUC value is that it emphasizes sensitivity and specificity equally. Therefore, the severity of the disease is not considered. For a severe condition like sepsis, it is most important to use a screening tool with high sensitivity. Another way to use the ROC curve is to compare the result based on utility approaches to reach a different conclusion than only based on AUC. Our findings may have changed if a utility-based endpoint was used instead of AUC (65, 83).

When comparing the performance of the different screening tools, the AUC value for qSOFA was higher than SIRS and NEWS. However, qSOFA had low sensitivity which highlights the limitations of using AUC alone when selecting a clinical screening tool. The consequent of using a screening tool with low sensitivity can be crucial when screening for sepsis, because of a high mortality rate. Despite a low sensitivity, qSOFA might be useful as a rapid and inexpensive tool to alert clinicians to further investigate the patients for organ dysfunction (2).

In our study, NEWS had the highest sensitivity. This result is consistent with one study from the UK that compared NEWS to qSOFA and SIRS (18). Usman et al. have also reported that NEWS was most accurate for triage detection of sepsis with a sensitivity of 84% (28). Unlike SIRS, NEWS does not require any laboratory findings and is fully calculable at triage. Furthermore, NEWS incorporates a higher number of physiological parameters and offers a greater scoring flexibility compared to the other scoring systems. Even though it consists of several clinical measurements, an application has now been developed for smart phones that makes NEWS a practical and easy bedside screening tool (84).

The NEWS review group has recommended a cutoff value of ≥ 5 when considering sepsis in patients with known or suspected infection (26). In the present study, we chose a cutoff value of ≥ 4, which is in line with guidelines from the Royal College of Physicians (85). The same cutoff value was also used in a study performed by Usman et al (28). The Royal College of Physicians recommend this threshold for separating low-risk patients from those who are at increased risk of developing sepsis (26). When testing with NEWS ≥ 5, the sensitivity decreased to 0.71 and the specificity increased to 0.69 (Table 7). Even though the cutoff value ≥ 5 resulted in a higher specificity, NEWS ≥ 4 still had the best sensitivity. As such, when

choosing a scoring tool, it is important to have in mind that a good sensitivity would identify more patient with potential sepsis, but at the same time lead to some overtreatment.

At UNN, they use TILT as a tool to assess and monitor the clinical condition of hospital patients in the wards. In this study, we wanted to investigate whether the already implemented tool in-hospital could be used as a model in predicting those with sepsis in an ED setting. Our results suggest that TILT is not sensitive enough as a replacement for already existing screening tools in the ED at UNN. Many institutions in Europe are now routinely using NEWS for early detection of patients at risk for deterioration. Some have also implemented it as a sepsis tool. Our results showed promising benefits of using NEWS in detection of sepsis. This is supported by two recent published studies (18, 28).

Results from the second evaluation in the ED at UNN from 2018, revealed that the majority of patients with sepsis were identified and received treatment within time (13). Our results add further to the debate about the clinical usefulness of different scoring systems. Currently, they use both qSOFA and SIRS when screening for sepsis. The present study shows that NEWS performed better than qSOFA and SIRS. UNN should consider whether there is any clinical benefit in adopting NEWS as both standardized clinical chart in-hospital and as a screening tool for sepsis (18). One can argue if a common scoring system like NEWS could support communication between healthcare professionals.

5.5 Risk factors

This thesis explores the concept of adding risk factors to the different scoring systems. Interestingly, we found that a modification of the scoring systems yield a higher sensitivity for all four scoring systems. It increased significantly for qSOFA, but did not add much to the performance of NEWS. qSOFA has been challenged as a screening tool in the ED despite its high specificity and low sensitivity. By adding risk factors, it performed better. One can therefore argue that the modified qSOFA score could offer an effective method for early detection of sepsis, since it can easily be assessed and quickly repeated. Our results prove that NEWS is already a good scoring system and that risk factors are of importance in a clinical setting.

There is evidence, that age is a risk factor for developing sepsis mainly because the elderly often have more comorbidities (70, 86). The current study does also support that age is an important risk factor. When considering cutoff, we used the age of 75 years as recommended in UNN´s criteria. Previous studies have recommended a cutoff at 65 years (86). In our study, we found that 68 patients with sepsis were over 75 years and 94 patients were over 65 years. By lowering the age limit to 65 years, 26 more patients would have been detected with sepsis. Results from our study highlights the importance of including risk factors and prompt the attention to the elderly when screening for sepsis.

A study by Martin and colleagues have found that age is an independent risk factor for determining the risk for sepsis (86). With this is mind, it would be interesting to conduct a similar study by adding two new parameters to the different scoring system where age is an independent risk factor.

5.6 Mortality

This study demonstrates that sepsis is associated with both short- and long-term mortality. We observed that one in 15 died within 30-days and that almost one in five died within 1-year. Our findings highlight the negative effects and consequences of sepsis. Studies have shown that patients suffering from sepsis have increased mortality and that those surviving sepsis might suffer from cognitive impairment and functional disability for years after hospitalization (87, 88). This is also illustrated in a systematic review by Winters et al. (88).

Regarding 1-year mortality, our findings are consistent with those from Wang et al. Results from their study demonstrated that individuals with sepsis had an increased rate of long-term death, even after accounting for comorbidities (89). They also found that sepsis is independently associated with increased mortality risk with a 1-year mortality of 23 %. It is important to have in mind that these results can be biased since the patient also can die from other causes.

In the present study, NEWS had the best sensitivity for predicting mortality. Even though our findings are based on a small number of participants, our results reflect the same outcome as in a larger study by Churpek et al. They presented and concluded that NEWS had the best test characteristics and was more accurate relative to both qSOFA and SIRS for predicting

mortality (80).

AUC values for the different scoring systems in prediction of mortality are higher in our study compared with those reported by Goulden et al. We found that qSOFA had a relatively high AUC value compared with the other tools. Recently, two studies also confirmed a high prognostic ability of qSOFA to predict mortality (76, 90). Even though, qSOFA preformed the best in our study, the AUC value for NEWS is in line with those reported by Goulden and colleagues (18).

Regarding the AUC results, it is important to stress that scoring tools are meant to be used in a clinical setting and therefor the sensitivity and specificity are of real interest instead of the overall accuracy. By using a high sensitivity tool, like NEWS, it is more likely to early identify patients at risk and provide early treatment and maybe improve outcome

5.7 Strengths and limitations

This study has a number of limitations. Firstly, it is a retrospective study which may increase the risk for misclassification, biases and confounding. Secondly, the study was performed at a single-center teaching hospital in Northern Norway. Larger multi-center prospective studies are needed to validate our results. Thirdly, our study sample was limited by the number of patients included and mainly consisting of Caucasians.

Furthermore, our inclusion criteria were strict and may present as a bias. We may have missed some patients by not screening all ED admissions. We only included patients who either were received by the medical team or those who later were admitted to the Department of Infection. However, we chose this approach because we aimed to determine the prognostic value of the different scoring tools. This patient group was thought to be more representative for our aim because they are more likely to have an infection and therefore at higher risk of developing sepsis.

Due to a lack of standardized documentation by the doctor, we found it challenging to determining the patients´ mental status when we retrospectively collected data. Further we found it difficult to evaluate the altered mental status in certain patients' group like those with dementia. This may have led to underreporting and is a certain bias in our study.

Since Sepsis-3 only recommends that organ dysfunction should be based on a SOFA score ≥2, we chose to use a minor modification because the use of SOFA score in a non-ICU is difficult. The use of a local definition of organ dysfunction makes it challenging for other studies to compare their findings with our results. Furthermore, we did not classify and categorize each individual organ dysfunction, neither how many organ systems that were affected. Therefore, we could not analyze the degree of the organ dysfunction or if the mortality was associated with certain organ systems.

A weakness in our study design is that we chose not to specify which type of risk factors the patient had. Because of this, we could not estimate which risk factor that had the strongest association with the development of sepsis. In the present study, we added one point to each scoring system if the patient had one or more of the defined risk factors. It would have been of interest to see if an increased cutoff limit (≥2 or more risk factors) would have affected the result.

The main strength in this study, is that the first vital parameter recorded at the time of arrival at the ED were used to screen patients for sepsis. A study by Seymour and others, included a 24 hours collection of vital parameters to calculate qSOFA. They also choose to record the worst value of qSOFA score during the same period. This could have biased their results to a higher qSOFA score. We chose a more realistic approach, which actually reflects the clinical practice at the ED. This is in our opinion a valid method to test predictive performance to the different scoring systems. However, one can argue that this might also be a limitation as we are aware that sepsis can develop rapidly and a sudden change in vital parameter occurs quickly. Another strength is that by excluding patients who received prehospital treatment with antibiotics, we limited the effect of confounding actions by clinicians.

6 Conclusion

This retrospective study from the ED at UNN, showed that all scoring systems included in the study were able to recognize patients with sepsis. In conclusion, NEWS was found to be of more clinical usefulness compared to qSOFA, SIRS and TILT in early identification of sepsis. NEWS is at least equivalent or better than the other screening tools across most measures in predicting mortality. Our finding suggests that the implementation of risk factors in different screening tools should be further studied. Even though, our study highlights the importance of

using a highly sensitive and easy calculable scoring system, it is important to remember that a scoring system should only be used in clinical context and should not replace clinical judgement.

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8 Attachments

8.1 Contract with supervisor and co-supervisor

Vedlegg 1: VEILEDNINGSKONTRAKT FOR MASTEROPPGAVE MEDISIN

VED DET HELSEVITENSKAPELIGE FAKULTET

Kontrakten leveres Seksjon for utdanningstjenester, Det helsevitenskapelige fakultet.

1 STUDENTENS PERSONALIA

Etternavn: Hagerup
Fornavn: Tina-Anita Dahl
Fødselsnummer (11 siffer) [redacted]
Studieadresse: [redacted]
Postnummer/-sted: 9105 Kvaløya
Telefon: [redacted]

Etternavn: Fremo
Fornavn: Kristin Kiplesund
Fødselsnummer (11 siffer) [redacted]
Studieadresse: [redacted]
Postnummer/-sted [redacted]
Telefon: [redacted]

2 AVTALEPERIODE

Avtalen gjelder fra:01.09.2017 til 01.06.2019

3 VEILEDNING

Angi hovedveileder og biveileder(e). En av veilederne må være fast vitenskapelig ansatt ved Det helsevitenskapelige fakultet. Hvis veileder planlegger å ha forskningstermin i kontraktsperioden, skal studenten informeres om dette når prosjektbeskrivelsen utarbeides. Veileder er i samarbeid med enheten ansvarlig for å sikre studenten veiledning i hele kontraktsperioden.

Veileders navn og kontoradresse: Trine Olsen, B1.882 UNN
Biveileders navn og kontoradresse: Unni Ringberg, MH L10.214
Biveileders navn og kontoradresse: Vegard Skogen, B1, UNN

1

Veileder skal ha forskningstermin i perioden:.....

Veilederen skal:

- gi råd om formulering og avgrensing av tema og problemstilling
- drøfte og vurdere hypoteser og metoder
- gi hjelp til orientering i faglitteratur og datagrunnlag (bibliotek, arkiv, etc.)
- drøfte opplegg og gjennomføring av fremstillingen (disposisjon, språklig form, dokumentasjon etc.)
- holde seg orientert om progresjonen i masterstudentens arbeid, og vurdere den i forhold til prosjektplanen, drøfte resultater og tolkningen av disse
- gi studenten veiledning i forskningsetiske spørsmål knyttet til forskningsprosjektet

Studenten forplikter seg til å legge fram rapporter eller utkast til deler av oppgaven for veileder, samt i sitt arbeid å etterleve forskningsetiske prinsipper som gjelder for fagområdet.

Begge parter har krav på jevnlig kontakt og orientering under arbeidets gang.

4 MASTEROPPGAVEN

Tittel:
Identification of sepsis by comparing clinical screening tools and clinical judgment A retrospective quality improvement study, University Hospital of Northern Norway, Tromsø.

5 RESSURSBRUK

Enhet prosjektet skal utføres ved: Medisinsk klinikk
Samarbeidspartnere av teknisk eller vitenskapelig art: Elin Teigen, Kvalitetsrådgiver MK .....
.....

6 ENDRINGER/BRUDD PÅ KONTRAKTEN

Alle endringer i veiledningskontrakten underveis i studiet (endring av prosjekt, veileder, forlengelse av kontraktsperiode og lignende) skal informeres om til Seksjon for forskningstjenester ved Det helsevitenskapelige fakultet.

Brudd på kontrakten skal behandles av Konfliktrådet ved det Helsevitenskapelige fakultet.

7 UNDERSKRIFTER

Undertegnede er kjent med ovenstående retningslinjer som legges til grunn for samarbeidet i den faglige veiledning. Det er både veileders og studentens ansvar at planen blir fulgt, både innholds- og framdriftsmessig.

Sted/dato: Underskrift:

Tromsø 26.09.17

Veileder: Trine Olsen .....

ID-nr.: 7120 400
Overlege Trine Olsen
Nyremedisinsk seksjon
Universitetssykehuset Nord-Norge HF
9038 Tromsø

Biveileder: ..... (UNNI RINGBERG)

Student: Kristin Kuplesund Fremo .....

Student: .....

8.2 PVO approval

UNIVERSITETSSYKEHUSET NORD-NORGE
DAVVI-NORGGA UNIVERSITEHTABUOHCCEVIESSU

PERSONVERNOMBUD

Til
Trine Olsen,
Medisinsk klinikk

Deres ref.:	Vår ref.:	Saksbehandler/dir.tlf.:	Dato:
	17/5451	Eva Henriksen / 95731836	10.10.2017

GODKJENNING AV BEHANDLING AV PERSONOPPLYSNINGER

Det vises til Meldeskjema for forskningsprosjekt, kvalitetsprosjekt og annen aktivitet som medfører behandling av personopplysninger som er melde- eller konsesjonspliktig i henhold til helseregisterloven og personopplysningsloven med forskrifter, mottatt 11.9.2017.

Meldingen gjelder prosjektet/registeret:

> ***Nr. 0752***
> ***Navn på prosjektet:*** *Kvalitetsregister for sepsisbehandling i UNN Tromsø - får vi det til?*

Prosjektet er et ***kvalitetsprosjekt*** hvor Universitetssykehuset Nord-Norge HF er behandlingsansvarlig.

> ***Formål:*** *«Formålet med dette er å opprette et kvalitetsregister for kontinuerlig oppfølging av behandling av pasienter med sepsis i UNN Tromsø. Det ses på om UNN oppfyller nasjonale krav i tillegg til interne UNN prosedyrer. Resultater her vil brukes til kontinuerlig forbedring i UNN, eksempelvis i forhold til opplæring av ansatte og for bruk i tavlemøter.»*

Personvernombudet (PVO) har vurdert prosjektet, og finner at behandlingen av person-opplysningene vil være regulert av § 7-12 i Personopplysningsforskriften og hjemlet etter Helsepersonelloven § 26.

PVO forutsetter at prosjektet gjennomføres i tråd med de opplysningene som er gitt, samt i henhold til Personopplysningsloven og Helseregisterloven med forskrifter. Videre forutsettes det at data anonymiseres etter prosjektavslutning ved at kodelista slettes.

PVO har på bakgrunn av og tilsendte meldeskjema med vedlegg registrert prosjektet og opprettet et eget område (mappe) på \\hn.helsenord.no\UNN-avdelinger\felles.avd\forskning (o:\) med navn **0752** hvor all data i forbindelse med prosjektet skal lagres.
I tillegg er det opprettet et område på \\hn.helsenord.no\UNN-avdelinger\felles.avd\forskning\key med navn **0752N** hvor nøkkelfil skal oppbevares. Tilgang til dette området er begrenset til kun å omfatte prosjektleder og dem som prosjektleder definerer. PVO vil ha tilgang til området.

Studentprosjektet med nummer 0747 benytter samme område på O:

Postadresse:	Avdeling:	Kvalitets- og utviklingssenteret	Telefon:	07766
UNN HF	Besøksadr.:		Internett:	www.unn.no
9038 TROMSØ	Fakturaadr:	UNN HF, c/o Fakturamottak, Postboks 3232, 7439 Trondheim	E-post:	personvernombudet@unn.no

PVO gjør oppmerksom på at dersom registeret skal brukes til annet formål enn det som er nevnt i meldingen, må dette meldes særskilt.

PVO skal ha melding når registeret er slettet. PVO skal også ha melding dersom registeret ikke er slettet eller ikke ferdig behandlet innen 3 år.

Med hjemmel i Forskrift om behandling av personopplysninger § 7-12 godkjenner PVO at behandlingen kan iverksettes.

Med vennlig hilsen

UNIVERSITETSSYKEHUSET NORD-NORGE HF

PVO-teamet
e.f.

Kopi: Klinikksjef Markus Rumpsfeld

Postadresse:	Avdeling:	Kvalitets- og utviklingssenteret	Telefon:	07766
UNN HF	Besøksadr.:		Internett:	www.unn.no
9038 TROMSØ	Fakturaadr:	UNN HF, c/o Fakturamottak, Postboks 3232, 7439 Trondheim	E-post:	personvernombudet@unn.no

9 Appendices

Appendix 1 - List of Tables

Appendix 2 - List of Figures

Appendix 3 - List of Gradings

Appendix 1 Tables

Table 1	**SIRS criteria (≥ 2)**
Body temperature	> 38.0 °C or < 36.0 °C
Heart rate	> 90/min
Respiratory rate	> 20 breaths/min or $PaCO_2$ 4.3 kPa in arterial blood gas analysis
White blood cell count	< 4000 /cu mm or > 12,000 cells/mm3

Table 2	**qSOFA score (≥ 2)**
Respiratory rate	≥ 22 breaths/min
Central nervous system	Alteration in mental status
Systolic blood pressure	≤ 100 mmHg

Table 3	**TILT (≥ 4)**						
	Score						
	3	**2**	**1**	**0**	**1**	**2**	**3**
Respiration rate (per minute)		< 9		9-14	15-20	21-29	>30
Pulse (per minute)		<40	41-50	51-100	101-110	111-129	>130
Systolic blood pressure (mmHg)	<70	71-80	81-100	101-199		≥220	
Temperature (°C)		<35.0	35.1-36.0	36.1-38.0	38.1-38.5	≥38.5	
Central nervous system			New onset confusion	Awake and alert	Response to voice	Response to pain	No response

Table 4	**NEWS^2 score (≥ 4)**						
				Score			
Organ system	3	2	1	0	1	2	3
Respiration Rate pr. min	≤ 8		9-11	12-20		21-24	≥ 25
Saturation SpO_2 (%) SCALE 1 (%) SCALE 2	≤ 91 ≤ 83	92-93 84-85	94-95 86-87	≥96 88-92/ ≤ 93 on air	93-94 on oxygen	95-96 on oxygen	≥97 on oxygen
Air or Oxygen?		Oxygen		Air			
Systolic blood pressure mmHg	≥ 90	91-100	101-110	111-219			≥220
Pulse per min	≤40		41-50	51-90	91-110	111-130	≥131
Consciousness				Alert			CVPU
Temperature	≤35.0		35.1-36.0	36.1-38.0	38.1-39.00	≥39.1	

Abbreviations: SpO_2; arterial oxygen saturation as measured by pulse oximetry, CVPU; (new) Confusion, Voice, Pain, Unresponsive

Table 5	**SOFA score**				
			Score		
Organ system	0	1	2	3	4
Respiration PaO2 /FiO2 (kPa)	≥ 53.3	< 53.3	< 40	< 26.7	< 13.3
Renal Creatinine (µmol/l) Urine output	< 110	110-170	171-299	300-440 < 500	> 440 < 200
Hepatic Bilirubin (µmol/l)	< 20	20-32	33-101	102-204	> 204
Coagulation Platelets x 103 /µl	≥ 150	< 150	< 100	< 50	< 20
Central nervous system Glasgow Coma Score	15	13-14	10-12	6-9	< 6
Cardiovascular Hypotension	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine < 5 or dobutamine	Dopamine 5.1-15, epinephrine ≤ 0.1 or norepinephrine ≤ 0.1[A]	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1[A]

Abbreviations: [A] Adrenergic agents (µg/kg/min) given for at least 1 hour, MAP; mean arterial pressure. FiO2; fraction of inspired oxygen, PaO_2; partial pressure of oxygen

Table 6	**Study sample characteristics**		
	All included ED patients	**Patients with sepsis**	**Non-survivors, total mortality**
Male, n (%)	151 (56)	86 (57)	24 (16)
Female, n (%)	119 (44)	53 (45)	14 (12)
Patients <75 years, n (%)	173 (64)	71 (41)	14 (8)
Patients ≥75 years, n (%)	97 (36)	68 (70)	24 (25)
Patients <65 years, n (%)	(64)	71 (41)	14 (8)
Patients ≥65 years, n (%)	(64)	71 (41)	14 (8)
All patients, n (%)	270 (100)	139 (51)	38 (27)
Age in years, mean (median)	64 (69)	67 (73)	74 (79)

Abbreviations: ED; Emergency Department

Table 7 The ability of the different screening tool to identify patients with sepsis in the Emergency Department, n

Scoring system	Ability to identify sepsis n = 139	Sensitivity (95% CI)	Specificity (95% CI)
qSOFA ≥ 2	67 (48.2%)	0.48 (0.40-0.56)	0.95 (0.90-0.98)
SIRS ≥ 2	106 (76.3%)	0.76 (0.69-0.83)	0.47 (0.38-0.55)
TILT ≥ 4	81 (58.3%)	0.58 (0.50-0.66)	0.77 (0.69-0.83)
NEWS ≥ 4	109 (78.4%)	0.78 (0.71-0.84)	0.59 (0.50-0.67)
NEWS ≥ 5	99 (71.2%)	0.71 (0.63-0.78)	0.69 (0.60-0.76)

Abbreviations: CI; Confidence Interval., n = 139 cases of sepsis among 270 patients

Table 8 The accuracy of diagnosing sepsis of the scoring systems, using ROC and AUC

Scoring system	Area	Std. Error [a]	Sig[b]	95% CI
qSOFA ≥ 2	0.72	0.03	0.00	0.66 – 0.78
SIRS ≥ 2	0.61	0.03	0.00	0.55 – 0.68
TILT ≥ 4	0.68	0.03	0.00	0.61 – 0.74
NEWS ≥ 4	0.69	0.03	0.00	0.62 – 0.75

[a] Under the nonparametric assumption, [b] Null hypothesis: true area = 0.5

Table 9 Association of scoring systems and sepsis, n=270

Scoring system	Diagnosed with sepsis, n	OR	95% CI
qSOFA ≥ 2	67	19.34	8.00 – 46.93
SIRS ≥ 2	106	2.80	1.66 – 4.71
TILT ≥ 4	81	4.70	2.77 – 7.99
NEWS ≥ 4	109	5.20	3.04 – 8.84

Abbreviations: n = Number of valid cases, OR = Odds Ratio

Table 10 Comparison of the different scoring systems when using mortality as endpoint

Outcome Measure	Scoring system	Ability to identify mortality	Sensitivity (95% CI)	Specificity (95% CI)	AUC
7-days mortality (n=3)	qSOFA ≥ 2	1 (33.3%)	0.33 (0.06-0.79)	0.51 (0.43-0.60)	
	SIRS ≥ 2	3 (100.0%)	1.00 (0.44-1.00)	0.24 (0.18-0.32)	
	TILT ≥ 4	3 (100.0%)	1.00 (0.44-1.00)	0.43 (0.35-0.51)	
	NEWS ≥ 4	3 (100.0%)	1.00 (0.44-1.00)	0.22 (0.16-0.30)	
30-days mortality (n=9)	qSOFA ≥ 2	6 (66.7%)	0.67 (0.35-0.88)	0.53 (0.45-0.61)	
	SIRS ≥ 2	9 (100.0%)	1.00 (0.70-1.00)	0.25 (0.19-0.33)	
	TILT ≥ 4	7 (77.8%)	0.78 (0.45-0.94)	0.43 (0.35-0.52)	
	NEWS ≥ 4	9 (100.0%)	1.00 (0.70-1.00)	0.23 (0.17-0.31)	
1-year mortality (n=26)	qSOFA ≥ 2	17 (65.4%)	0.65 (0.46-0.81)	0.56 (0.47-0.65)	
	SIRS ≥ 2	16 (61.5%)	0.62 (0.43-0.78)	0.20 (0.14-0.29)	
	TILT ≥ 4	12 (46.2%)	0.46 (0.29-0.65)	0.39 (0.30-0.48)	
	NEWS ≥ 4	20 (76.9%)	0.77 (0.58-0.89)	0.21 (0.15-0.30)	
Death in total (n=38)	qSOFA ≥ 2	24 (63.2%)	0.63 (0.47-0.77)	0.57 (0.48-0.67)	0.71 (0.62-0.81)
	SIRS ≥ 2	28 (73.7%)	0.73 (0.58-0.85)	0.22 (0.16-0.32)	0.55 (0.45-0.65)
	TILT ≥ 4	22 (57.9%)	0.58 (0.42-0.72)	0.42 (0.32-0.51)	0.60 (0.50-0.70)
	NEWS ≥ 4	32 (84.2%)	0.84 (0.70-0.93)	0.24 (0.17-0.33)	0.64 (0.55-0.73)

Sensitivity, Specificity, for sepsis by different modified screening tools in the ED
n = 139 cases of sepsis among 270 patients

Table 11 The diagnostic performance of the different scoring systems in prediction of in total mortality

Scoring system	AUC	Std. Error [a]	Sig[b]	95% CI
qSOFA ≥ 2	0.71	0.05	0.00	0.62 – 0.81
SIRS ≥ 2	0.55	0.05	0.33	0.45 – 0.65
TILT ≥ 4	0.60	0.05	0.05	0.50 – 0.70
NEWS ≥ 4	0.64	0.04	0.01	0.55 – 0.73

[a] Under the nonparametric assumption
[b] Null hypothesis: true area = 0.5

Table 12 Modified versions of the different scoring systems

modified-SIRS criteria (≥ 2)	
Body temperature	> 38.0 °C or < 36.0 °C
Heart rate	> 90/min
Respiratory rate	> 20 breaths/min or $PaCO_2$ 4.3 kPa in arterial blood gas analysis
White blood cell count	< 4000 /cu mm or > 12,000 cells/mm3
Risk factors[a]	≥ 1 Risk.F.

Risk.F. = Risk factors according to UNNs criteria

modified-qSOFA score (≥ 2)	
Respiratory rate	≥ 22 breaths/min
CNS	Alteration in mental status
Systolic blood pressure	≤ 100 mmHg
Risk factors[a]	≥ 1 Risk.F.

Risk.F. = Risk factors according to UNNs criteria

modified-NEWS² score							
	Score						
Organ system	3	2	1	0	1	2	3
Respiration Rate pr. min	≤ 8		9-11	12-20		21-24	≥ 25
Saturation SpO_2 (%) SCALE 1 (%) SCALE 2	≤ 91 ≤ 83	92-93 84-85	94-95 86-87	≥96 88-92/ ≤93 on air	93-94 on oxygen	95-96 on oxygen	≥97 on oxygen
Air or Oxygen?		Oxygen		Air			
Systolic blood pressure mmHg	≥ 90	91-100	101-110	111-219			≥220
Pulse Per min	≤40		41-50	51-90	91-110	111-130	≥131
Consciousness				Alert			CVPU
Temperature	≤35.0		35.1-36.0	36.1-38.0	38.1-39.00	≥39.1	
Risk factors [a]			1 or more Risk.F.		1 or more Risk.F.		

Risk.F. = Risk factors according to UNNs criteria

modified-TILT							
	Score						
	3	**2**	**1**	**0**	**1**	**2**	**3**
Respiration rate (per minute)		< 9		9-14	15-20	21-29	>30
Pulse (per minute)		<40	41-50	51-100	101-110	111-129	>130
Systolic blood pressure (mmHg)	<70	71-80	81-100	101-199		≥220	
Temperature (°C)		<35.0	35.1-36.0	36.1-38.0	38.1-38.5	≥38.5	
CNS			New onset confusion	Awake and alert	Response to voice	Response to pain	No response
Risk factors [a]			1 or more Risk.F.		1 or more Risk.F.		

Risk.F. = Risk factors according to UNNs criteria

Table 13 The ability for the different modified screening tool to identify patients with sepsis in the Emergency Department (n=139 cases of sepsis among 270 patients)

Scoring system	Ability to identify sepsis (n=139)	Sensitivity (95% CI)	Specificity (95% CI)
m-qSOFA ≥ 2	107 (77.0%)	0.77 (0.69-0.83)	0.69 (0.61-0.77)
m-SIRS ≥ 2	129 (92.8%)	0.93 (0.87-0.96)	0.29 (0.22-0.37)
m-TILT ≥ 4	97 (69.8%)	0.70 (0.62-0.77)	0.65 (0.56-0.73)
m-NEWS ≥ 4	118 (84.9%)	0.85 (0.78-0.90)	0.49 (0.40-0.57)

Abbreviations: CI; Confidence Interval, m; modified

Appendix 2 Figures

Figure 1 Flowchart of the inclusion process and separation into study sample

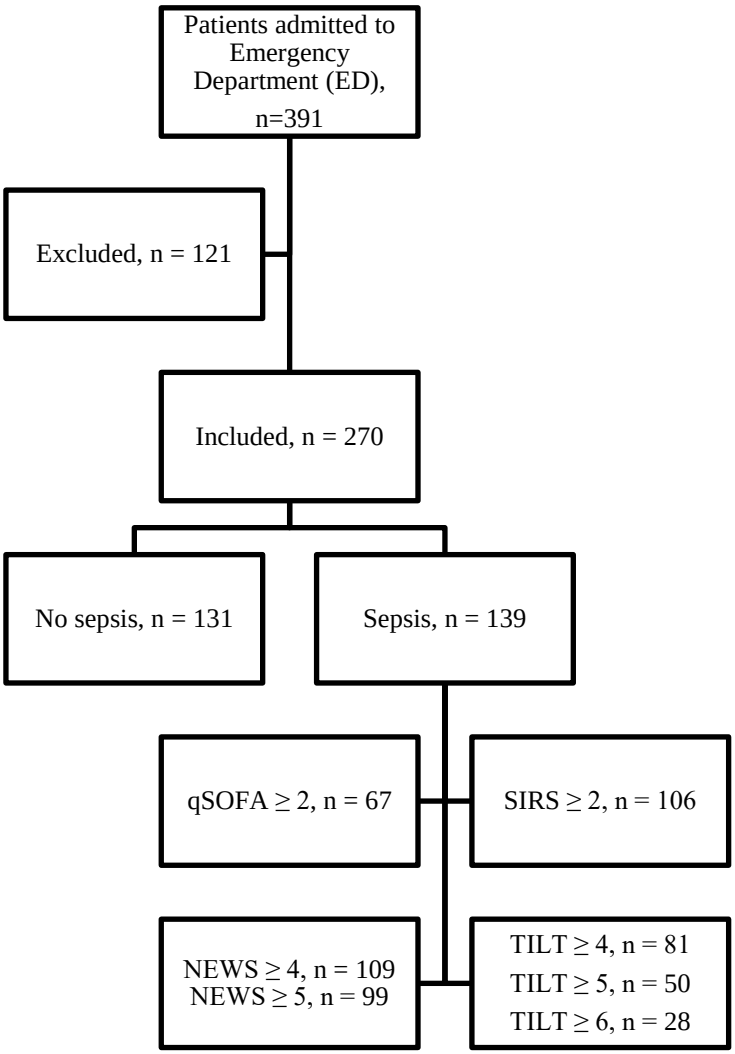
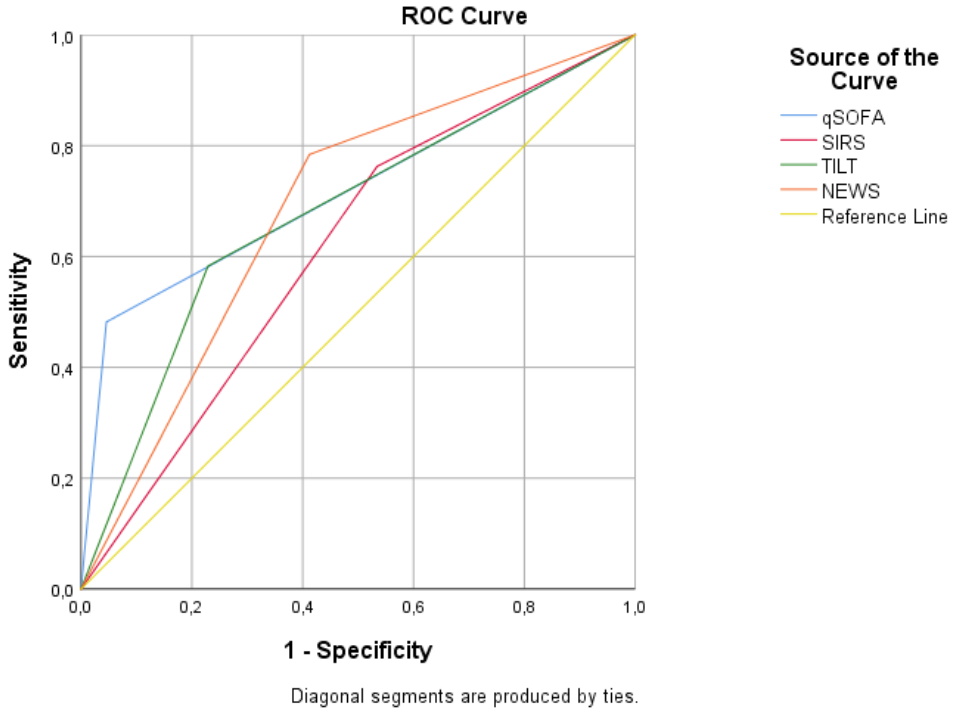
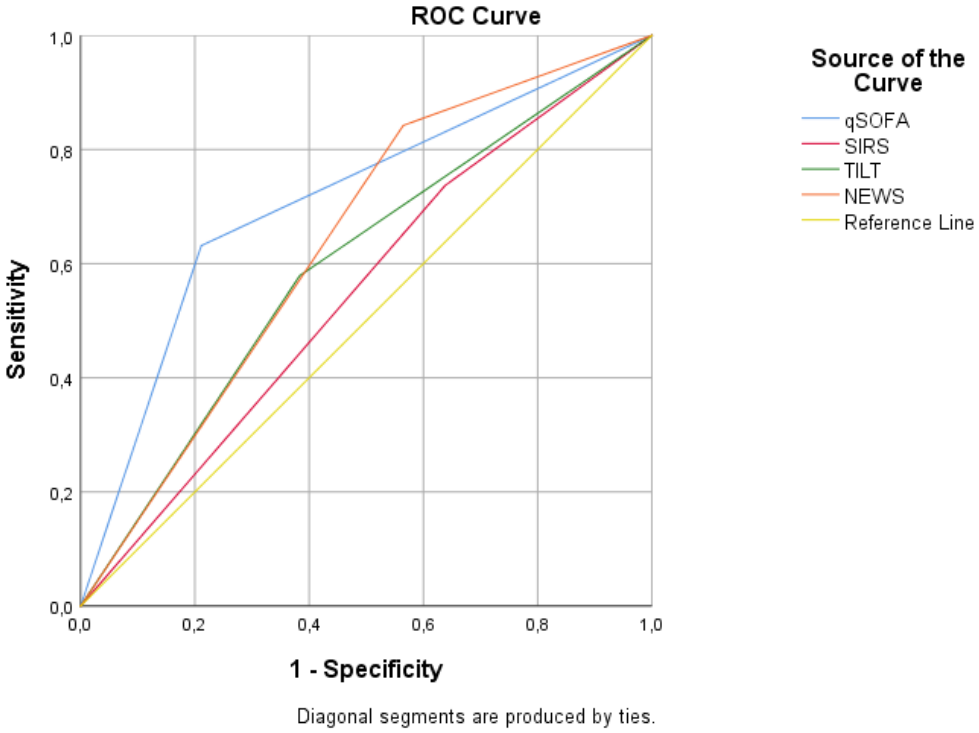


Figure 2 ROC curves for the different scoring systems in prediction of screening for sepsis, n



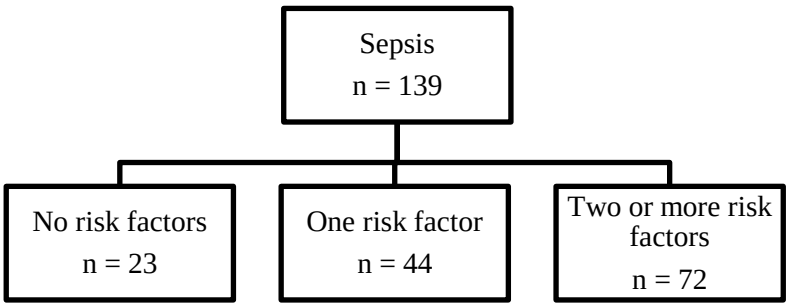
Abbreviations: AUC=Area under the reciver operating charateristic, ROC =Receiver operating characteristic
n = 139 cases of sepsis among 270 patients

Figure 3 ROC curves for the different scoring systems in prediction of total mortality, n



Abbreviations: AUC=Area under the reciver operating charateristic, ROC =Receiver operating characteristic
n = 38 cases of mortality among 139 patients with sepsis

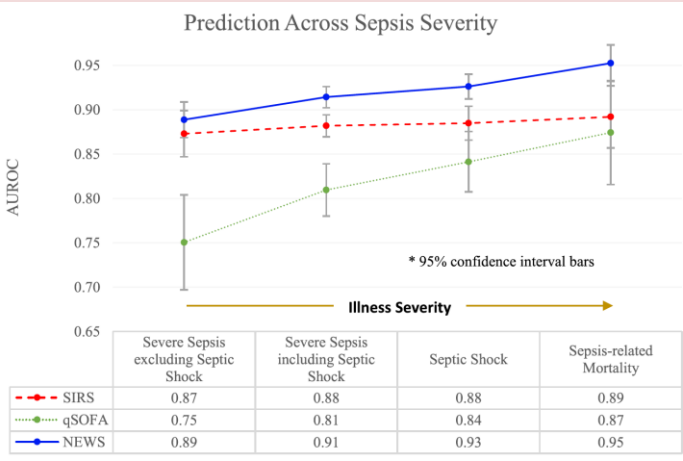
Figure 4 Flowchart illustrating sepsis patients with risk factors



Appendix 3 Gradings

Referance:
O.A. Usman, A.A. Usman and M.A. Ward, **Comparison of SIRS, qSOFA, and NEWS for the early identification of sepsis in the Emergency Department**, American Journal of Emergency Medicine, https://doi.org/10.1016/j.ajem.2018.10.058

GRADE	
Class of Evidence (CoE)	II
Recommendation	B

Objective	Material and method	Results	Discussion
This study reviewed the viability of NEWS as an early predictor of severe sepsis and septic shock (SS/SS) in an ED triage setting and evaluated its performance against SIRS and qSOFA. **Conclusion** NEWS is more accurate than both SIRS and qSOFA for the detection of all sepsis endpoints. NEWS was more specific with similar sensitivity relative to SIRS. qSOFA had the lowest sensitivity and is a poor tool for ED sepsis screening. **Country** USA **Year of data collection** 2014-2016	**Study design:** A retrospective analysis **Study population** The study consisted of 130.595 ED patients. 115.734 were included. 930 cases of SS/SS were identified. 14.861 were excluded. **Inclusion criteria:** • Adult (age ≥ 18 years) visiting the ED • The study population was based on the presence of SS/SS within 8 h of ED arrival • All ED patients with ICD-9 or ICD-10 codes related to sepsis and clinical concern or infection • Flagged patients with orders for blood cultures, urine cultures, or antibiotics within 12 h of ED arrival **Exclusion criteria:** • Patients lacking adequate clinical evaluation • Patients with a ventricular assist device (n=14,861, 11.4%) **Statistic methods:** Data analysis was conducted in R Foundation for Statistical Computing, 2017. Predictive ability was compared using AUROC. Sensitivities and specificities are reported with 95% Confidence Intervals (CI) using the Wilson Score interval.	NEWS was most accurate for triage detection of SS/SS (AUROC, 0.91, 0.88, 0.81), septic shock (AUROC, 0.93, 0.88, 0.84), and sepsis-related mortality (AUROC, 0.95, 0.89, 0.87) for NEWS, SIRS, and qSOFA, respectively  For the detection of SS/SS (95% CI), sensitivities were 84.2% (81.5–86.5%), 86.1% (83.6–88.2%), and 28.5% (25.6–31.7%) and specificities were 85.0% (84.8–85.3%), 79.1% (78.9–79.3%), and 98.9% (98.8–99.0%) for NEWS ≥ 4, SIRS ≥ 2, and qSOFA ≥ 2, respectively.	**Checklist:** - Are the groups comparable in relation to important background factors? **Only one group** - Are the groups recruited from the same section of the population? **Yes** - Were the exposed individuals representative for a defined section of the population? **Yes** - Was the study prospective? **No** - Were exposure and outcome measured equal and reliable? **Unknown** - Were sufficient number of persons in the study followed up? **Yes** - Is it performed drop out analyses? **No** - Was the follow up time lengthy enough to prove positive and/or negative outcomes? **Yes** - Are important confounding factors in design/implementation considered? **No** - Was the person who evaluated the results (end points) blinded group identification? **No** **Strength:** -Easy adaptable inclusion and exclusion criteria. -A large study population -The study was done based on values available at the time of triage **Limitations:** -The study was retrospective -Single-center study with a predominately African-American population -The study was unblended -The results was based on the Sepsis-2 guidelines, which may result in an incorporation bias favoring SIRS

	Severe Sepsis excluding Septic Shock	Severe Sepsis including Septic Shock	Septic Shock	Sepsis-related Mortality
SIRS	0.87	0.88	0.88	0.89
qSOFA	0.75	0.81	0.84	0.87
NEWS	0.89	0.91	0.93	0.95

Referance: Churpek, M.M.; Snyder, A.; Han, X.; Sokol, S.; Pettit, N.; Howell, M.D.; Edelson, D.P. **Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit**. Am. J. Respir. Crit.Care Med. 2017, 195, 906–911			**GRADE** Class of Evidence (CoE): IIb Recommendation: B
Objective	**Material and method**	**Results**	**Discussion**
To compare the accuracy of qSOFA as an early warning score with SIRS, MEWS, and NEWS in patients with suspected infection on the wards and in the ED for predicting adverse outcomes. **Conclusion** SIRS, MEWS, and NEWS are more accurate than the qSOFA score for predicting death and ICU transfer in non-ICU patients. These results suggest that qSOFA should not replace general early warning scores when risk-stratifying patients with suspected infection. **Country** Chicago, USA **Year of data collection** November 2008-January2016	**Study design:** Retrospective cohort **Study population:** 150,288 identified, 30,677 analyzed 47% male. Mean age: 58 years old (SD 18.0) **Inclusion criteria:** All patients admitted to the ED and ward with suspected infection **Exclusion criteria:** Patients without vital sign or laboratory data documented in the ED or wardsPatients who received mechanical ventilation or vasopressor medications before the first suspicion of infection **Statistic methods:** Patient characteristics were compared using: • t tests, Wilcoxon rank sum tests and $\chi 2$ tests Accuracy comparisons were performed using: • Sensitivity, specificity, (AUC) o A two-tailed $P < 0.05$ was considered statistically significant **Statistical analyses:** Stata (version 14.1; StataCorp, College Station, TX). **Founding:** University of Chicago	**The primary outcome**: in-hospital mortality. **Secondary outcome:** the composite of death or ICU stay after a patient met the suspicion of infection criteria. 30,677 patients were included. 1,649 (5.4%) died and 7,385 (24%) experienced the composite outcome (death or ICU transfer). Primary outcome: • 60% (n = 18,523) met the suspicion criteria in the ED • NEWS had the best AUC value for in-hospital mortality, (AUC, 0.77; 95% CI, 0.76–0.79), followed by MEWS (AUC, 0.73; 95% CI, 0.71–0.74), qSOFA (AUC, 0.69; 95% CI, 0.67–0.70), and SIRS (AUC, 0.65; 95% CI, 0.63–0.66) Secondary outcome: (Using the highest non-ICU score of patients): • SIRS ≥2: sensitivity of 91% and specificity of 13% • qSOFA ≥2: sensitivity 54% and specificity 67%, • MEWS ≥5: sensitivity 59% and specificity 70%, • NEWS ≥8: sensitivity 67% and specificity 66% Most patients met ≥2 SIRS criteria 17 hours before the combined outcome compared with 5 hours for ≥2 and 17 hours for ≥1 qSOFA criteria.	**Checklist:** - Are the groups comparable in relation to important background factors? **Only one group** - Are the groups recruited from the same section of the population? **Yes** - Were the exposed individuals representative for a defined section of the population? **Yes** - Was the study prospective? **No** - Were exposure and outcome measured equal and reliable? **Unknown** - Were sufficient number of persons in the study followed up? **Yes** - Is it performed drop out analyses? **Yes** - Was the follow up time lengthy enough to prove positive and/or negative outcomes? **Yes** - Are important confounding factors in design/implementation considered? **Not recorded** - Was the person who evaluated the results (end points) blinded group identification? **No** **Strength:** -Large study sample -Easy adaptable inclusion and exclusion criteria **Limitations:** -Single-center study in an academic U.S. hospital, so the results may not be generalizable -Handling of missing data: 66% of admissions were excluded due to missing data -No clear definition of sepsis (selection bias). May have excluded patients with sepsis and included others who were not.

Referance: Goulden R, Hoyle MC, Monis J, Railton D, Riley V, Martin P, et al. **qSOFA, SIRS and NEWS for predicting inhospital mortality and ICU admission in emergency admissions treated as sepsis.** Emergency medicine journal:EMJ. 2018;35(6):345-9.			**GRADE** Class of Evidence (CoE): IIb Recommendation: B
Objective	**Material and method**	**Results**	**Discussion**
To evaluate the prognostic accuracy of qSOFA, SIRS and NEWS for predicting inhospital mortality and ICU admission in the ED **Conclusion** NEWS has equivalent or superior value for most test characteristics relative to SIRS and qSOFA **Country** England, UK **Year of data collection** April 2016 and May 2017	**Study design:** Retrospective cohort **Study population:** n=1818 **Inclusion criteria:** • All adult patients presenting to the ED or medical admissions unit (MAU) with suspicion of or treated for sepsis • All those who had a sepsis form completed **Main clinical outcome:** • **The primary outcome**: inhospital mortality • **Secondary outcomes:** ICU admission and a composite of inhospital mortality **Statistic methods:** Predicting inhospital mortality and ICU admission: • Sensitivity, specificity • AUROC, positive • PPV • NPV • Negative likelihood ratio was calculated for each scoring system The sensitivity and spcificity for the primary outcome were compared using McNemar's test. The AUROC was compared using DeLong's method. **Missing data:** Missing information in the different scoring tool in the electronic form was recorded manually. For those still missing values of the scoring systems, missingness was predicted by other variables by using logistic regression **Statistical analyses:** Stata V.15.0 (Stata, College Station, Texas, USA)	Among 1818 patients, 53 were admitted to ICU (3%) and 265 died in hospital (15%). **AUC for inhospital mortality:** NEWS≥5 (65%, 95% CI 61% to 68%) qSOFA≥2 (62%, 95% CI 59% to 66%) **The sensitivity inhospital mortality:** NEWS≥5 (74%, 95% CI 68% to 79%) SIRS≥2 (80%, 95% CI 74% to 84%) qSOFA≥2 (37%, 95% CI 31% to 43%) **The specificity inhospital mortality:** NEWS≥5 (43%, 95% CI 41% to 46%) SIRS≥2 (21%, 95% CI 19% to 23%) qSOFA≥2 (79%, 95% CI 77% to 81%) **The negative predictive value inhospital mortality:** NEWS≥5 (91%, 95% CI 88% to 93%) SIRS≥2 (86%, 95% CI 82% to 89%) qSOFA≥2 (88%, 95% CI 86% to 90%)	**Checklist:** - Are the groups comparable in relation to important background factors? **Only one group** - Are the groups recruited from the same section of the population? **Yes** - Were the exposed individuals representative for a defined section of the population? **Yes** - Was the study prospective? **No** - Were exposure and outcome measured equal and reliable? **Unknown** - Were sufficient number of persons in the study followed up? **Yes** - Is it performed drop out analyses? **Yes** - Was the follow up time lengthy enough to prove positive and/or negative outcomes? **Yes** - Are important confounding factors in design/implementation considered? **Not recorded** - Was the person who evaluated the results (end points) blinded group identification? **No** **Strength:** -Their results are consistent with other studies -Preformed missing data analysis **Limitations:** - Lack of data on patient comorbidities and cause of death, limiting the ability to determine the specific role of sepsis -Retrospective study -Single center study

Reference:
Askim A, Moser F, Gustad LT, Stene H, Gundersen M, Asvold BO, et al. **Poor performance of quick-SOFA (qSOFA) score in predicting severe sepsis and mortality - a prospective study of patients admitted with infection to the emergency department.** Scandinavian journal of trauma, resuscitation and emergency medicine. 2017;25(1):56.

GRADE	
Class of Evidence (CoE)	IIb
Recommendation	B

Objective

To evaluate the clinical usefulness of qSOFA to predict severe sepsis and 7- and 30-day mortality and compare its performance to SIRS criteria and the Rapid Emergency Triage and Treatment System (RETTS).

Conclusion

qSOFA failed to identify two thirds of the patients admitted to the ED with severe sepsis. qSOFA failed to be a risk stratification tool as the sensitivity to predict 7-day and 30-day mortality was low. The sensitivity was poorer than RETTS-triage and the SIRS criteria.

Country

Norway

Year of data collection

2012

Material and methods

Study design
Observational cohort study

Study population:
The study consisted of 1568 ED patients

Inclusion criteria
All patients ≥16 years of age with a new onset of suspected or confirmed infection according to the (ESS47).
Patients with the 4 highest acuity levels according to the Rapid Emergency Triage and Treatment System (RETTS).

Exclusion criteria
Patients that left the ED before registration or had no identification.
Patients with blue triage.

Statistic methods
The data was analyzed using Stata version 13. The ROC and logistic regression analysis after MI were compared with the results from the complete-case analysis.

Results

Of the 1535 admitted patients, 108 (7.0%) fulfilled the Sepsis2 criteria for severe sepsis. The qSOFA score ≥2 identified only 33 (sensitivity 0.32, specificity 0.98) of the patients with severe sepsis, while the RETTS-alert ≥ orange identified 92 patients (sensitivity 0.85, specificity 0.55).

Sensitivity, Specificity, and Positive (PPV) and Negative Predictive Values (NPV) for severe sepsis by different identification tools in the Emergency department (*n* = 108 cases of severe sepsis among 1535 patients)

Identification tool	Severe sepsis	Sensitivity	Specificity	PPV	NPV
	n (% of 108 cases)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
SIRS ≥2 (-leukocytes)	80 (74.1%)	0.74 (0.65-0.82)	0.72 (0.70-0.75)	0.18 (0.16-0.19)	0.97 (0.96-0.98)
qSOFA ≥2[a]	33 (30.6%)	0.32 (0.23-0.42)	0.98 (0.97-0.99)	0.57 (0.45-0.68)	0.95 (0.94-0.96)
Red triage	37 (34.3%)	0.34 (0.25-0.44)	0.95 (0.94-0.96)	0.35 (0.27-0.43)	0.95 (0.94-0.95)
Orange triage	55 (50.9%)	0.51 (0.41-0.61)	0.60 (0.58-0.63)	0.09 (0.07-0.11)	0.94 (0.93-0.95)
≥ Orange triage	92 (85.2%)	0.85 (0.77-0.91)	0.55 (0.52-0.58)	0.13 (0.12-0.14)	0.98 (0.97-0.99)

Twenty-six patients died within 7 days of admission; four (15.4%) of them had a qSOFA ≥2, and 16 (61.5%) had RETTS ≥ orange alert.

Sensitivity, Specificity, and Positive (PPV) and Negative Predictive Values (NPV) for 7-day mortality by different stratification tools in the Emergency Department (*n* = 26 cases of deaths within 7 days among 1535 patients)

Stratification tool	Died within 7 days	Sensitivity	Specificity	PPV	NPV
	n (% of 26 cases)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Severe sepsis	8 (30.8%)	0.31 (0.14-0.52)	0.93 (0.92-0.94)	0.07 (0.04-0.12)	0.98 (0.98-0.98)
SIRS ≥2	17 (65.4%)	0.65 (0.44-0.82)	0.55 (0.52-0.57)	0.03 (0.02-0.03)	0.99 (0.98-0.99)
SIRS ≥2 (-leukocytes)	15 (57.7%)	0.58 (0.36-0.76)	0.70 (0.67-0.72)	0.03 (0.02-0.04)	0.99 (0.98-0.99)
qSOFA ≥2	4 (15.4%)	0.16 (0.05-0.36)	0.96 (0.95-0.97)	0.07 (0.03-0.15)	0.98 (0.98-0.99)
Red triage	8 (30.8%)	0.31 (0.14-0.51)	0.93 (0.91-0.95)	0.07 (0.04-0.12)	0.99 (0.98-0.99)
Orange triage	8 (30.8%)	0.31 (0.14-0.52)	0.60 (0.58-0.63)	0.01 (0.00-0.02)	0.98 (0.98-0.99)
≥ Orange triage	16 (61.5%)	0.62 (0.41-0.80)	0.53 (0.51-0.56)	0.02 (0.01-0.03)	0.99 (0.98-0.99)

Of the 68 patients that died within 30 days, 8 (11.9%) scored ≥2 on the qSOFA, and 45 (66.1%) had a RETTS ≥ orange alert.

Sensitivity, Specificity, and Positive (PPV) and Negative Predictive Values (NPV) for 30-day mortality by different stratification tools in the Emergency Department (*n* = 68 cases of deaths within 30 days among 1535 patients)

Stratification tool	Ability to identify those who died	Sensitivity	Specificity	PPV	NPV
	n (% of 68 cases)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Severe sepsis	19 (27.9%)	0.29 (0.18-0.41)	0.94 (0.92-0.95)	0.18 (0.12-0.24)	0.96 (0.95-0.97)
SIRS ≥ 2	42 (61.8%)	0.64 (0.51-0.75)	0.55 (0.53-0.58)	0.06 (0.05-0.07)	0.97 (0.96-0.98)
SIRS ≥ 2 (-leucocytes)	32 (45.6%)	0.48 (0.36-0.61)	0.70 (0.68-0.72)	0.07 (0.05-0.08)	0.97 (0.96-0.97)
qSOFA ≥2	8 (11.9%)	0.13 (0.05-0.25)	0.96 (0.95-0.97)	0.14 (0.07-0.23)	0.96 (0.96-0.96)
Red triage	14 (20.2%)	0.21 (0.12-0.32)	0.94 (0.92-0.95)	0.13 (0.08-0.19)	0.96 (0.96-0.96)
Orange triage	31 (45.6%)	0.46 (0.22-0.58)	0.61 (0.58-0.63)	0.05 (0.04-0.07)	0.96 (0.95-0.97)
≥ Orange triage	45 (66.1%)	0.66 (0.54-0.77)	0.54 (0.52-0.57)	0.06 (0.05-0.07)	0.97 (0.96-0.97)

The odds ratio (OR) for severe sepsis in the qSOFA ≥ 2 category (24.4, 95% CI 13.243.2) compared with the red triage group (9.7, 95% CI 6.115.5). Among the different identification tools, red triage and severe sepsis had the highest odds ratios for 7-day and 30-mortality.

Discussion

Checklist:
- Are the groups comparable in relation to important background factors? **Not two groups of cases**
- Are the groups recruited from the same section of the population? **Yes**
- Were the exposed individuals representative for a defined section of the population? **Yes**
- Was the study prospective? **Yes**
- Were exposure and outcome measured equal and reliable? **Unknown**
- Were sufficient number of persons in the cohort followed up? **Yes**
- Is it performed drop out analyses? **No**
- Was the follow up time lengthy enough to prove positive and/or negative outcomes? **Yes**
- Are important confounding factors in design/implementation considered? **No**
- Was the person who evaluated the results (end points) blinded group identification? **Not relevant**

Strengths:
-Easy adaptable inclusion and exultation criteria
-A large study population
-The study is the fourth study were qSOFA finds few of the sepsis cases in prehospital or at arrival to the ED

Limitations:
-The study was a single-center study
-The study was unblinded
-Lack of information on cormorbidities

Reference:	**GRADE**	
Williams JM, Greenslade JH, McKenzie JV, Chu K, Brown AFT, Lipman J. **Systemic Inflammatory Response Syndrome, Quick Sequential Organ Function Assessment, and Organ Dysfunction: Insights From a Prospective Database of ED Patients With Infection.** Chest. 2017;151(3):586-96.	Class of Evidence (CoE)	IIb
	Recommendation	B

Objective	Material and methods	Results	Discussion
1. Determine the prognostic impact of SIRS 2. Compare the diagnostic accuracy of SIRS and qSOFA for organ dysfunction 3. Compare standard (Sepsis-2) and revised (Sepsis-3) definitions for organ dysfunction in ED patients with infection **Conclusion** SIRS was associated with organ dysfunction and mortality. A qSOFA score ≥ 2 showed high specificity, but poor sensitivity. Mortality for organ dysfunction was comparable between Sepsis-2 and Sepsis-3. **Country** Australia **Year of data collection** 2007-2008 2009-2011	**Study design** Retrospective cohort **Study population** The study consisted of 8871 ED patients **Inclusion criteria** • Patients aged < 17 • Patients with infection or suspected infection in the ED **Exclusion criteria** • Patients transferred from other hospitals **Statistic methods** Analyses were performed using Stata, version 14 (StataCorp LC).	SIRS was associated with increased risk of organ dysfunction (relative risk (RR) 3.5) and mortality in patients without organ dysfunction (OR 3.2). SIRS and qSOFA showed similar discrimination for organ dysfunction (area under the receiver operating characteristic curve, 0.72 vs 0.73). qSOFA was specific but poorly sensitive for organ dysfunction (96.1% and 29.7%, respectively). Mortality for patients with organ dysfunction was similar for Sepsis-2 and Sepsis-3 (12.5% and 11.4%, respectively), although 29% of patients with Sepsis-3 organ dysfunction did not meet Sepsis-2 criteria. Increasing numbers of Sepsis-2 organ system dysfunctions were associated with greater mortality.	**Checklist:** - Are the groups comparable in relation to important background factors? **Not two groups of cases** - Are the groups recruited from the same section of the population? **Yes** - Were the exposed individuals representative for a defined section of the population? **Yes** - Was the study prospective? **No** - Were exposure and outcome measured equal and reliable? **Unknown** - Were sufficient number of persons in the cohort followed up? **Yes** - Is it performed drop out analyses? **No** - Was the follow up time lengthy enough to prove positive and/or negative outcomes? **Yes** - Are important confounding factors in design/implementation considered? **No** - Was the person who evaluated the results (endpoints) blinded group identification? **Not relevant** **Strengths:** • Easy adaptable inclusion and exclusion criteria. A large study population and reliable national database. • The study is the first assessment of the proposed Sepsis-3 criteria in the ED **Limitations:** • The methods used to identify patients may not have identified all ED patients with infection • Included patients may not have had an infection • Single-center study

Reference:
Jiang J, Yang J, Mei J, Jin Y, Lu Y. **Head-to-head comparison of qSOFA and SIRS criteria in predicting the mortality of infected patients in the emergency department: a meta-analysis.** Scandinavian journal of trauma, resuscitation and emergency medicine. 2018;26(1):56.

GRADE	
Class of Evidence (CoE)	Ia
Recommendation	A

Objective

To determine the diagnostic accuracy of the qSOFA criteria in predicting mortality in ED patients with infections and compared the performance with that of the SIRS criteria

Conclusion

qSOFA score ≥ 2 and SIRS score ≥ 2 are strongly associated with mortality in ED patients with infections.
qSOFA has a low sensitivity.
qSOFA and SIRS have limitations as risk stratification tools for ED patients with infections

Country

China

Year of data collection

2018

Material and methods

Study design
Meta-analysis

Study population:
Eight studies with a total of 52,849 patients were included

Search strategy
PubMed, EMBASE and Google Scholar (up to April 2018) were searched for related articles

Inclusion criteria
- ED patients with infections
- Clear diagnostic reference standard for infection was used
- The study purpose had to evaluate or compare the prognostic value of qSOFA and SIRS in predicting death within the same patient population
- Adequate information to perform true positives, false positive, false negatives and true negatives test

Exclusion criteria
- Review articles
- Letters
- Conference abstracts
- Expert opinions

Results

All studies indicated that a qSOFA score ≥ 2 was associated with a high risk of mortality in ED patients with infections, with a pooled risk ratio (RR) of 4.55 (95% CI, 3.38-6.14) using a random-effects model (I2 = 91.1%).

A SIRS score ≥ 2 was a prognostic marker of mortality in ED patients with infections, with a pooled RR of 2.75 (95% CI, 1.96-3.86) using a random-effects model (I2 = 89%).

When comparing the performance of qSOFA and SIRS in predicting mortality, a qSOFA score ≥ 2 was more specific; however a SIRS score ≥ 2 was more sensitive. The initial qSOFA values were of limited prognostic value in ED patients with infections.

Pooled performance characteristics of qSOFA and SIRS criteria for predicting mortality in ED patients with infections

	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (95% CI)
qSOFA	0.42 (0.31–0.54)	0.88 (0.83–0.92)	3.5 (2.8–4.4)	0.66 (0.56–0.78)	5 (4–7)	0.78 (0.74–0.81)
SIRS	0.81 (0.75–0.86)	0.41 (0.32–0.50)	1.4 (1.2–1.6)	0.47 (0.37–0.59)	3 (2–4)	0.70 (0.65–0.73)

Discussion

Checklist:
- Are the groups comparable in relation to important background factors? **Yes**
- Are the groups recruited from the same section of the population? **No**
- Were the exposed individuals representative for a defined section of the population? **Yes**
- Was the study prospective? **No**
- Were exposure and outcome measured equal and reliable? **Yes**
- Were sufficient number of persons in the study followed up? **Yes**
- Is it performed drop out analyses? **No**
- Was the follow up time lengthy enough to prove positive and/or negative outcomes? **Yes**
- Are important confounding factors in design/implementation considered? **Yes**
- Was the person who evaluated the results (endpoints) blinded group identification? **Not relevant**

Strengths:
-Easy adaptable inclusion and exclusion criteria.
-All the studies included are from 2017-2018
-Used data from PubMed, EMBASE and Google Scholar.
-Fairly equal consensus of variables across countries/continents.

Limitations:
-A small number of studies were included
-The studies included patients with different types of infection
-Different outcome measures were used:
  - In-hospital mortality
  - 7-days mortality
  - 30-day mortality
-Studies used various designs:
  - prospective and retrospective observational studies
-Different time points to calculate the scores was used

Reference:
Singer AJ, Ng J, Thode HC, Jr., Spiegel R, Weingart S**. Quick SOFA Scores Predict Mortality in Adult Emergency Department Patients With and Without Suspected Infection.** Annals of emergency medicine. 2017;69(4):475-9.

GRADE	
Class of Evidence (CoE)	IIb
Recommendation	B

Objective

To determine the association between qSOFA scores and outcomes in adult ED patients with and without suspected infection

Conclusion

Different qSOFA scores were associated with inhospital mortality, hospital admission, hospital length and ICU admission.
qSOFA is an easy tool that can be used in the ED to predict outcomes.

Country

USA

Year of data collection

2014-2015

Material and methods

Study design
Retrospective cohort
Study population
67475 ED adult visits meeting study criteria. Of whom 22.530 meet the inclusion/exlusion criteria and were admitted.
Inclusion criteria
Adult (>18 years)
Patients for whom a qSOFA score could be calculated within 2 minutes or less and reporting of vital signs

- systolic blood pressure,
- respiratory rate
- pulse rate,
- temperature
- oximetry
- MEWS

Exclusion criteria
Patients triaged to fast-track, dentistry, psychiatry, and labor and delivery were excluded
Statistic methods:
All analyses were performed with SPSS version 23.0; IBM, Armonk, NY.Univariate and multivariate analyses were performed to explore the association between qSOFA scores and inpatient mortality, admission, and length of stay. Receiver operating characteristics curve analysis and c statistics were also calculated for ICU admission and mortality.

Results

Of the 22.530 study patients, 16.507 (73%) had a qSOFA score of 0, 5290 (23%) had a score of 1649 (3%) had a score of 2, and 84 (0.4%) had a score of 3.
Primary results
The primary outcome was inhospital mortality.
The sensitivity and specificity of a qSOFA score greater than or equal to 2 for predicting mortality were 29% (95% CI 25% to 34%) and 97% (95% CI 97% to
97%), respectively, with a negative predictive value of 99% (95% CI 99% to 99%).

Table. Study outcomes.

qSOFA Score	Admission Rate, % (95% CI)	ICU Admission Rate, % (95% CI)	Mortality, % (95% CI)	Mean Hospital Length of Stay (95% CI), Hours*
Univariate associations (all patients)				
0	38 (37–39)	5.1 (4.8–5.5)	0.6 (0.5–0.8)	123 (119–127)
1	59 (58–61)	10.5 (9.7–11.4)	2.8 (2.4–3.3)	163 (155–171)
2	84 (81–87)	20.8 (17.8–24.2)	12.8 (10.4–15.7)	225 (192–358)
3	93 (85–97)	27.4 (18.5–38.4)	25.0 (16.5–35.9)	237 (185–288)
Univariate associations (suspected infection)				
0	72.7 (70.8–74.5)	4.8 (4.0–5.8)	1.4 (1.0–2.0)	
1	87.0 (85.1–88.6)	11.7 (10.1–13.5)	6.1 (4.9–7.5)	
2	96.1 (93.3–97.8)	25.0 (20.5–30.1)	15.8 (12.1–20.2)	
3	95.5 (86.4–98.8)	30.3 (19.9–43.0)	24.2 (14.9–36.6)	
Univariate associations (no suspected infection)				
0	32.4 (31.7–33.2)	5.2 (4.8–5.5)	0.5 (0.4–0.6)	
1	49.1 (47.5–50.7)	10.0 (9.1–11.0)	1.6 (1.2–2.1)	
2	70.9 (65.5–75.8)	16.3 (12.5–21.0)	9.6 (6.7–13.5)	
3	83.3 (57.7–95.6)	16.7 (4.4–42.3)	27.8 (10.7–53.6)	

Multivariate associations (all patients)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Coefficient (95% CI)
Age, per year	1.040 (1.038–1.042)	1.023 (1.020–1.026)	1.042 (1.035–1.049)	0.5 (0.3–0.7)
Female patient (reference is male patient)	0.68 (0.64–0.73)	0.62 (0.55–0.68)	0.78 (0.63–0.97)	−17 (−26 to −9)
qSOFA (per point)	2.21 (2.08–2.36)	1.96 (1.81–2.13)	3.05 (2.66–3.49)	35 (28–42)
Suspected infection	5.57 (5.10–6.09)	0.91 (0.79–1.03)	2.14 (1.69–2.71)	34 (25–44)

*Includes only admitted patients who survived to discharge.

Secondary results
Secondary outcomes were hospital admission, ICU admission and total hospital length of stay from ED triage to discharge from the hospital.
ICU admission (0 (5.1%), 1 (10.5%), 2 (20.8%), and 3 (27.4%)), and hospital length of stay (0 (123 hours), 1 (163 hours), 2 (225 hours), and 3 (237 hours)). Adjusted rates were also associated with qSOFA. The c statistics for mortality in patients with and without suspected infection were similarly high (0.75 (95% confidence interval 0.71 to 0.78) and 0.70 (95% confidence interval 0.65 to 0.74)), respectively.

Discussion

Checklist:
- Are the groups comparable in relation to important background factors? **Yes**
- Are the groups recruited from the same section of the population? **Yes**
- Were the exposed individuals representative for a defined section of the population? **Yes**
- Was the study prospective? **No**
- Were exposure and outcome measured equal and reliable? **Unknown**
- Were sufficient number of persons in the study followed up? **Yes**
- Is it performed drop out analyses? **No**
- Was the follow up time lengthy enough to prove positive and/or negative outcomes? **Yes**
- Are important confounding factors in design/implementation considered? **No**
- Was the person who evaluated the results (end points) blinded group identification? **No**

Strengths:
-Easy adaptable inclusion and exultation criteria
-A large study population
-The findings support the results from other studies

Limitations:
-The study was a single-center study
-The study was unblinded
-It was a retrospective study
-A large number of ED patients did not have simultaneous vital signs and MEWS documented and were thus excluded, (selection bias)
-No control for many potential confounders (laboratory tests, comorbidities)
-Patients were selected into 2 groups based on whether intravenous antibiotics were given in the ED. This may have led to an over- or underestimation of the number of patients with suspected infection