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Development and evaluation of a situation awareness model targeting Clinical Deterioration in the Emergency Department

PhD dissertation

Gitte Boier Tygesen

Health
Aarhus University
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ENGLISH SUMMARY

Prevention of clinical deterioration is important to ensure safety for patients attending an emergency department (ED). Early warning score systems have been widely implemented to increase patient safety and support clinicians' systematic observations and decisions. The systems are used for standard bedside monitoring to detect clinical deterioration, and consist of a trigger and response initiated by a decline or change in vital signs. The existing evidence on the effects on clinical outcomes in EDs is so far ambiguous. Several reasons for this have been suggested e.g. late decline in vital signs, staff being unaware of deterioration as well as the use of systems developed for other clinical settings. Studies have suggested that adding subjective parameters to the early warning score systems may enhance healthcare professionals' ability to detect clinical deterioration before the systems are triggered and, thus, prompt more proactive treatment and positively affect clinical outcomes. The overall aim of this PhD study was to develop and evaluate the effect of a "situation awareness model" targeting clinical deterioration and situation awareness.

In study I, we identified predictors of clinical deterioration in an adult population of hospitalised ED patients through a systematic literature search and review. We found 36 potential generic predictors of clinical deterioration; two presenting complaints, eight vital signs, twelve biochemical tests, ten comorbidities and four other predictors. In study II, the clinical relevance and applicability in ED settings of the identified predictors were determined by a panel of emergency medicine clinicians through a Delphi process. They considered the following 15 generic predictors to be relevant and applicable in clinical practice: 1) Biochemical tests: S-C-reactive protein, S-bicarbonate, S-lactate, S-pH, S-potassium, glucose, S-leucocyte counts and S-hemoglobin, 2) Vital signs: respiratory rate, saturation/ SpO_2, systolic blood pressure, altered mental state, pulse rate, dyspnoea, electrocardiogram and temperature, 3) Objective and subjective clinical observations: Skin conditions, pain and relatives' concern. In study III, we developed and tested a situation awareness model based on ten predictors identified in study II: vital signs, skin observations, pain, dyspnoea, relatives' concerns and additional patient concern, clinical intuition and clinical huddles regarding at-risk patients (meetings where staff discuss the patients at risk).

Use of the situation awareness model decreased the odds of clinical deterioration in the intervention EDs compared to the control EDs, implying effect on clinical deterioration. No effect on 7-day or 30-day mortality, ICU admission directly from the ED or 30-day readmission was found. Thus, the findings of the present thesis support the hypothesis that the new situation awareness model may enhance the effect of a conventional EWS system in detecting patients at risk of clinical deterioration in EDs and thereby potentially contribute to reducing clinical deterioration.

DANISH SUMMARY

Forebyggelse af klinisk forværring er vigtigt for at forbedre sikkerheden for patienter i akutafdelinger. Systemer til tidlig opsporing af klinisk forværring er implementeret bredt for at øge patientsikkerheden og understøtte klinikernes systematiske observationer og beslutningstagninger. Systemerne består af en trigger og et respons, der udløses af fald eller ændringer i vital parametrene og anvendes som standard observationspraksis for at identificere klinisk forværring. Den eksisterende evidens for effekten af systemerne på kliniske udfald i akutafdelinger er tvetydig. Flere årsager til den manglende evidens er påpeget, for eksempel sen påvirkning af vitale parametre, eller at personalet er uvidende om en forværring, men også implementering af systemer udviklet til andre rammer. Studier antyder, at en tilføjelse af subjektive parametre til systemet til tidlig opsporing af klinisk forværring kan understøtte sundhedspersonalet i at opspore klinisk forværring tidligere end nuværende systemer, og derved sikre en mere proaktiv behandling og positiv effekt på de kliniske udfald. Det overordnede formål med dette ph.d. studie var at udvikle og evaluere effekten af en "situation awareness model" rettet mod klinisk forværring og situationsbevidsthed, forståelsen af hele situation omkring patienten ("situation awareness").

Studie I, vi identificerede prædiktorer for klinisk forværring hos voksne indlagte patienter i akutafdelingen i et systematisk litteraturstudie. Vi fandt 36 potentielle prædiktorer for klinisk forværring: 2 symptomer ved ankomst, 8 vitale parametre, 12 biokemiske tests, 10 ko-morbiditeter og 4 andre prædiktorer. I studie II undersøgte vi den kliniske relevans og anvendelighed af prædiktorerne på baggrund af et panel, bestående af klinikere i det akutmedicinske område, i en Delphi proces. Klinikerne anså 15 generiske prædiktorer for at være relevante og anvendelige i klinisk praksis; 1) Biokemiske tests: serum C-Reaktivt Protein, serum laktat, serum pH, serum kalium, glukose, serum leukocytter og serum hæmoglobin, 2) vital parametre: respirations frekvens, saturation (SpO_2), systolisk blodtryk, ændret mental tilstand, puls, dyspnø, elektrokardiogram og temperatur, 3) objektive og subjektive kliniske observationer: hud, smerte og patient-pårørende bekymring. I studie III udviklede vi en "situation awareness model" og testede den i fire akutafdelinger (to interventionsafdelinger og to kontrolafdelinger) via et kontrolleret før- efter studie design. Modellen var baseret på 10 prædiktorer identificeret i studie II, vitale parametre, hud observationer, smerte, dyspnø og pårørende bekymring og i tillæg patient bekymring, klinisk intuition og "huddles" om risikopatienter (møder hvor personalet drøfter den enkelte patient).

"Situation awareness modellen" reducerede odds for klinisk forværring i interventionsafdelingerne sammenlignet med kontrolakutafdelingerne og derved antydes effekt på klinisk forværring. Der var ingen effekt på 7 og 30 dages mortalitet, indlæggelse i intensiv afdelinger direkte fra akutafdelingen eller 30 dages genindlæggelse.

Fundene i denne afhandling understøtter hypotesen om, at en ny "situation awareness model" muligvis kan øge effekten af det traditionelle system til tidlig opsporing af kritisk sygdom i forhold til identificering af klinisk forværring og derved potentielt reducere klinisk forværring.

DISSERTATION PAPERS

This dissertation is based on the following papers, and they will be referred to using their Roman numerals:

I. In review: Tygesen GB, Lisby M, Kirkegaard H, Raaber N, Rask MT.
Generic predictors of clinical deterioration in adult Emergency Department patients: a systematic review. Internal Journal of Emergency Medicine

II. In review: Tygesen GB, Kirkegaard H, Raaber N, Rask MT, Lisby M.
Consensus on predictors of clinical deterioration in emergency departments: a Delphi process study. Acta Anaesthesiologica Scandinavica

III. In review: Tygesen GB, Lisby M, Raaber N, Rask MT, Kirkegaard H.

Early warning score systems supplemented by huddles, simple clinical characteristics and subjective parameters decrease clinical deterioration in the emergency departments – a controlled intervention study. European Journal of Emergency Medicine

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The work presented in this dissertation is the result of my PhD studies carried out at the Department of Emergency Medicine, Horsens Regional Hospital and the Department of Clinical Medicine, Health, Aarhus University in close collaboration with the Research Centre for Emergency Medicine, Aarhus University.

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Gitte Boier Tygesen

ABBREVIATIONS

APVU	A: alert, V: verbal, P: pain, U: unresponsive score
BI-portal	Business Intelligence – portal
CA	Cardiac Arrest
CCL	Cetrea Clinical Logistics
CD	Clinical Deterioration
ECG	Electrocardiogram
ED	Emergency department
EMR	Electronic Medical Record
EWS	Early Warning Score
GBT	Gitte Boier Tygesen
GCS	Glasgow Coma Scale
GP	General Practitioner
HK	Hans Kirkegaard
HR	Hearth Rate
ICU	Intensive Care Unit
ISBAR	Identification, Situation, Background, Assessment, Recommendation
IQR	Inter Quartile Range
LOS	Length of stay
MDC4	Major Diagnostic Categories 04
MTR	Mette Trøllund Rask
ML	Marianne Lisby
NOS	Newcastle-Ottawa Scale
NR	Nikolaj Raaber
PACS	Singapore Patient Acuity Category Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
REDCAP	Research Electronic Data Capture
RR	Respiratory Rate
RRS	Rapid Response System
SpO_2	Peripheral Capillary Oxygen Saturation
SysBP	Systolic Blood Pressure
TP	Temperature

CONTENTS

STUDY OVERVIEW

Study I

Paper I: Generic predictors of clinical deterioration in adult emergency department patients: a systematic review.

A systematic review of the literature to identify generic predictors of clinical deterioration in adult ED patients.

Study II

Paper II: Consensus on predictors of clinical deterioration in emergency departments: a Delphi study

The second study uses a Delphi technique to select predictors of clinical deterioration considered to be relevant, applicable and generic in the ED context by a panel of emergency medicine clinicians.

Study III Intervention

Paper III: Early warning score systems supplemented by huddles, simple clinical characteristics and subjective parameters decrease clinical deterioration in the emergency departments – a controlled intervention study.

The third study is a controlled pre and post study that investigated the effect of a situation awareness model targeting clinical deterioration.

CHAPTER 1. INTRODUCTION

In the last few decades, there has been an increased focus on recognising and responding to clinical deterioration in hospitalised adult patients.[1] We now know that clinical deterioration is often preceded by abnormal vital signs, and that decline has been described to occur from 6 to 48 hours before an adverse event.[2, 3] Assuming that these adverse events are preventable, Morgan et al. proposed in 1997 the first early warning score (EWS) system to alert clinicians to deteriorating patients based on aggregated, weighted scores of vital signs.[1] Today, EWS systems are widely used in Danish emergency departments (ED) to ensure systematic observation and measurement of vital signs.[4] Some researchers have investigated the effect of EWS systems on patient outcomes, but with various results on mortality and intensive care admission.[5, 6] Different explanations for this variation in patient outcomes have been offered, e.g. unrecognised deterioration, communication and teamwork, and systems developed for other settings.[7-16] Finally, physiological parameters may decline late in the course of a disease, which makes it difficult to improve the patient's condition.[7-11]

New approaches, such as the inclusion of additional parameters in existing EWS systems, can be used to gather further knowledge on how to improve patient outcomes and, potentially, identify deteriorating patients even before their vital signs decline.[17, 18, 18-22] So far, studies have primarily examined in-hospital patients; thus, clinical deterioration of adult ED patients remains an important challenge for healthcare providers. In this dissertation, we address some of the knowledge gaps by identifying generic predictors of clinical deterioration in an adult ED population, introducing predictors that have not been examined in ED settings, and developing and testing a situation awareness model targeting clinical deterioration in ED settings in a controlled pre- and post study.

CHAPTER 2. BACKGROUND

This literature review aims to give an overall insight into the organisation of the ED in the Danish healthcare system and a summary of relevant literature supporting the issues and hypotheses in the dissertation (Appendix 1 – Description of search strategy)

2.1 The Danish emergency healthcare system

In 2007, an acute care reform changed the organisation of the Danish emergency healthcare system. The five regions of Denmark were given autonomy to organise their EDs, and 21 acute care hospitals were consolidated so that emergency care was provided at fewer, but larger, units.[23] Today, EDs are independent departments that serve as a single entrance into acute care hospitals. Exceptions to this are patients requiring obstetric attendance, stroke and acute myocardial infarction care which is provided in specialised in-patient units and in some regional hospitals paediatric patients are referred to other hospitals if admission is required.[4, 23, 24] The EDs consist of an emergency unit and a short-stay unit for patients (medical and surgical), that are expected to be discharged within 24 to 48 hours. Patients with expected length of stay exceeding 48 hours are transferred to inpatient units.

The acute care reform, resulted in an increased focus on the principle of 'the right patient in the right bed' and avoidance of unnecessary acute and preventable admissions to improve quality.[25] This approach requires healthcare professionals to distinguish between patients who can be safely sent home and those who need additional care. The reorganisation seems to reduce the average length of stay (LOS) at hospitals as well as the number of readmissions within 30 days after discharge, with no increase in 30 days mortality.[26, 27] Safety and quality of care are crucial given the current pressures on acute medical services, including an increasing number of patients and an ageing population with more comorbidities.[26-29]

2.2 Clinical deterioration

Clinical deterioration has been defined as a change or movement from one clinical state to a worse clinical state with an increased risk of morbidity (e.g. organ dysfunction), a protracted hospital stay, disability or death.[30, 31] In 2018, a concept analysis[32] suggested a more operational definition of clinical deterioration: '*a dynamic state experienced by a patient compromising hemodynamic stability, marked by physiological decompensation accompanied by subjective or objective findings*'.[32] A dynamic state refers to variation in physiological parameters, decompensation refers to loss of the ability to maintain homoeostatic function physiologically or psychologically, and subjective and objective determination refers to vital signs, intuition and a sense of 'concern'.[32]

Clinical deterioration often starts with subtle changes in vital signs or physiological parameters indicating a worsening in patient condition.[33] Clinical deterioration can occur at any time during hospitalisation; declines in patients' vital signs have been described from 6 to 48 hours before an adverse event.[2, 3] The nurses are often the first in the multidisciplinary team to recognise deterioration[32], which places them in a fundamental position for recognising and responding to deterioration.

It can be challenging to recognise and respond to clinical deterioration, and in 2015, Danish national guidelines for early recognition of deteriorating patients were published, including a recommendation of implementing early warning systems to support systematic monitoring.[34] A high number of ED patients (12–31%) deteriorate despite systems intended to identify patients at risk of clinical deterioration.[35-38] A decrease in these numbers is essential to ensure safety and quality of treatment. In 2017 and 2018, there were 890,160 and 873,958 adult acute hospital admissions in Denmark, persons over the age of 70 accounting for 44% and 45% of all acute admissions respectively.[39] The complexity of healthcare increases as the ageing population with multiple comorbidities grows. This makes identification of deteriorating patients increasingly essential.[40, 41]

2.3 Early warning score system

EWS systems using an aggregated, weighted score of vital signs were introduced in 1997 to alert clinicians to deteriorating patients.[1] The EWS system is based on the principle that clinical deterioration can be detected by changes in multiple vital sings as well as large changes within a single vital sign.[42, 43]
Generally, EWs have a track (abnormal vital signs compared to normal vital signs to generate a single composite score) and a trigger (predetermined calling or response criteria). The EWS is statistically linked to an increased risk of clinical deterioration such as death or admission to an intensive care unit.[8]
The predetermined calling or response criteria often consist of increased observation, alerts to senior nursing and medical staff and assessment by critical care outreach teams.[7] The included vital signs and thresholds can differ between the different early warning score systems depending on the targeted population.[44]

Studies in EDs have investigated EWS systems targeting undifferentiated and condition-specific ED populations (patient group with a certain suspected condition).[44] Studies of EWS systems (e.g. VIEWS, MEWS, MEWS with GCS, MEWS plus, MEWS max, REMS, APACHE II, RAPS, Vital Sign Score, Worthing Physiological Score) targeting the undifferentiated ED population have revealed acceptable to excellent discriminatory ability to predict mortality based on area under the receiver operating characteristic curves (AUROC, 0.70–0.79, 0.80–0.89, ≥90). Except for RAPS, which had a AUROC of <0.70.[45-54] However, variability between studies regarding, e.g. thresholds, oxygenation

and mental status, is present. It seems that the discriminatory ability is high regarding mortality, but the ability to predict adverse outcomes like ICU and hospital admission is more ambiguous. Nevertheless, REMS was found to be superior (AUROC > 0.75) in predicting hospital admission, length of hospital stay and in-hospital mortality compared to RAPS and MEWS in adult ED patients.[55] The ability of EWS systems to help predict clinical deterioration is widely accepted today,[56, 57] and they are now a standard bedside monitoring practice in many countries[35-37]

Common to the EWS systems is the overall of identifying patients that are at high risk of clinical deterioration so that healthcare professionals can prevent clinical deterioration resulting in death or unplanned admission to the intensive care unit (ICU).[58, 59]

Yet, the ability of EWS systems to predict adverse outcomes does not mean that they are effective in preventing deterioration through early detection.[5, 6] In a systematic review of 28 EWS systems applied in an ED, only one study addressed this question. This study revealed small or no difference in preventing deterioration or adverse events; however, was concluded that the evidence in the study was of very low quality.[44]

Recent studies have investigated the ability of additional predictors to detect clinical deterioration in ED patients, perhaps even before the triggering of the existing EWS systems. These studies have included biochemical tests such as lactate[60 22, 61], pH[62] , inflammatory blood markers like white cell count, procalcitonin and midregional-proadrenomedullin[63], albumin, creatinine, haemoglobin, potassium, sodium, urea and white cell count[64], blood glucose, bicarbonate, white cell count and a history of metastates[65], soluble urokinase plasminogen activator receptor[21, 66]. But also age[67-69], comorbidities[70], functional impairment and mobility[71, 72] and patients' subjective feelings of improvement have been studied.[73, 74] Serum lactate added to NEWS was found to increase the predictive ability to detect in-hospital mortality in critically ill geriatric patients. However it was not a sufficiently powerful predictor to support definitive clinical decisions.[22]

NEWS in combination with five additional predictors, namely higher NEWS at triage, equal or increase of NEWS after ED management, coronary artery disease comorbidity, use of a vasoactive agent and initial serum bicarbonate level lower than 23.5 mmol/L identified patients at risk of in-hospital cardiac arrest more effectively than NEWS alone (AUROC 0.78 vs 0.91).[75] It seems that the more information we have about patients, the better we can predict the outcome. This means that we need to identify the risk factors / predictors and apply them more systematically to ensure an effect on the clinical outcomes when possible.

Various reasons for EWS systems' failure to detect or escalate clinical care when the EWS system is triggered have been suggested, including implementation of systems developed for other settings, culture, high workload, poor communication, insufficient medical staff, insufficient monitoring and risk identification, inherent risk to overlook clinical signs and subtle changes in patients' conditions, requirements of technical and non-technical skills and confidence, all of which may

affect situational awareness.[7-16] On the other hand, it seems that improvements in recognition and triggering patient deterioration can be achieved if there is a sufficient skill mix among staff, possibility to use EWS protocols flexibly together with clinical decision and if staff have access to ongoing, multiprofessional, competency-based education.[15]

Research should investigate whether new predictors or combinations of predictors or increased awareness may help ED clinicians detect clinical deterioration earlier and thereby have an effect on patient outcomes.

2.4 Rapid response systems

Rapid response systems (RRSs) were introduced in the 1990s. Studies had revealed suboptimal care in EDs prior to ICU admission, implying the possibility to prevent the adverse outcomes[76, 77] and identification of clinical deterioration by changes in vital sings can be done prior to cardiac arrest.[78, 79] The need for earlier prevention of clinical deterioration was urged, leading to implementation of an early response throughout the hospital to at-risk patients by introducing a medical emergency team[80, 81] also known as an outreach team in the RRS.[76, 77]

RRSs and EWS systems are closely related and often used together in the acute care chain. Both were developed to prompt identification and treatment of acutely, critically ill patients based on physiological deviations.[58, 59, 80, 82]

Additionally, both have a track and trigger (afferent limb) to identify and respond to abnormal vital signs, clinical deterioration or crisis and trigger a response (efferent limb). RRSs typically consist of four components: 1) afferent limb 2) efferent limb 3) feedback loop and 4) administrative or governance component. The afferent limb is designed to recognise crises based on, e.g. abnormal vital signs (can be a EWS system), neurologic abnormalities, sudden-onset chest pain or clinicians concern,[83-85] and trigger a response. The efferent limb consists of a responding team often known as a medical emergency team (typically including a physician), rapid response team (often nurse led) or critical care outreach team tailored to the organisation's goals. The team helps to treat and prevent further deterioration or to transfer the patient to the right level of care by providing knowledge, skills, equipment and personnel. The feedback loop provides knowledge of how to prevent future occurrences. The administrative or governance component is used for coordination and facilitation of improved care through, for example, the acquisition of equipment and provision of education for hospital staff regarding the RRS process.[86, 87]

The outreach team in RRSs differs from the EWS systems as not all EWS system include an outreach team or else the outreach team is only activated in the higher EWS (e.g. ≥5).[85, 86] Thus, RRSs are activated when the patients have critical unmet needs that result in risk of imminent danger or risk of serious harm.[86, 87]

In addition to vital signs, many organisations include a 'staff concern' criterion to allow for activation of the rapid response team. In some institutions, relatives or patients can also activate this system.[86, 88, 89] The knowledge about the 'staff concern' or intuition criterion in EWS systems is limited, but in settings other than the ED, it has been shown to decrease ICU admissions and to identify deteriorating patients before the EWS system is triggered.[18, 90]

Further research should contribute to the understanding of whether adding a 'staff concern' or intuition criteria to the EWS system may assist in early identification of the deteriorating patient and the decision-making regarding when and how to respond to the deterioration and thereby impact clinical outcomes.

2.5 Clinical intuition

Intuition has been defined as the ability to understand or know something immediately based on feelings rather than facts; however, a more nuanced approach is that intuition is a part of the complex decision-making process.[91, 92] [91, 92] '*Instinct and intuition are described as the initial part of rational and systematic decision-making and as informed by clinical expertise'*[92(p 1587)].

Clinical intuition or concern has evolved over the last 30 years since Benner and Tanner described the nurse's ability to learn through patterns of recognition as the foundation of intuition and a significant part of the expert nurse's decision-making process.[93, 94] Gut feeling has also been used to describe the nurse's intuition as *'having the feeling something was not right and adjusting their care accordingly, but not being able to explain with hard data why they felt that way'*.[95] In emergency care, intuition has been studied in triage situations showing that ED nurses use intuition to institute higher levels of care which results in appropriate and prompt care that reduces morbidity and mortality.[95]

Nurses often identify deteriorating patients through intuition rather than through a change in vital signs[90, 96, 97] Over the past few years, clinical intuition has been described as an important factor in clinical decision making not only in nursing but also in experienced physicians'[98], general practitioners' [99] and emergency physicians'[100] diagnostic processes and in surgical practice.[101] Douw et al.[96] performed a systematic review of clinical intuition and defined ten factors that contribute to trigger one's intuition regarding deteriorating patients: change in breathing, change in circulation, temperature (TP), change in mentation, agitation, pain, unexpected trajectory, patient indicates that they feel unwell, subjective observation by nurses and knowing without a rationale.

Nurses develop competence over time, which can help them anticipate a patient's decline before any objective evidence of deterioration. [96, 102, 103] Clinical intuition is a nontechnical skill which contribute to clinical decision making. It evolves with clinical experience and helps healthcare

professionals understand patients' conditions and deepen their understanding of the situation (situation awareness).[104, 105]

In 2014, an algorithm assisting nurses to develop skills prompting early detection, intervention and communication in situations of patient deterioration was developed and examined in post-operative patients. The results indicated that the development of clinical intuition can be accelerated or supported by use of an algorithm. The algorithm supported nurses' critical thinking (including intuition) related to observations and vital signs monitoring with actions required based on the observations supported by strategies for communication.[20]

Clinical intuition seems to be an important part of recognising and responding to early clinical deteriorating involving understanding of the situation and not only the EWS.[94] The possibility to impact clinical outcomes by supporting clinicians' situation awareness and clinical decision-making related to observations and vital signs monitoring through algorithms is highly relevant and crucial to patient safety.

2.6 Situation awareness

Situation awareness is informally defined as '*knowing what's going on'* and formally defined as *'the perception of the elements of the environment within a volume of time and space, the comprehension of their meaning, and the projection of their status in the near future*'.[106] Situation awareness is adapted from principles in high-risk organisations. It is considered as a human factor approach exploring the impact of attention and cognitive functions; thus, situation awareness constitutes a critical component of clinical decision-making.[107, 108]

Endsley has described a theory of situation awareness in dynamic systems which is widely used in healthcare. It describes the importance of situation awareness and the complexity in perceiving and understanding the integrated meaning of the perceived to understand the situation forming the basis for decision-making.[106] Endsley introduces three levels of situation awareness: Perception of elements in the current situation, Comprehension of the current situation and Projection of future status. The selection of action and performance is described as separate stages that will proceed directly from the clinician's situation awareness. Endsley describes several factors that influence the process because clinicians differ in their ability to acquire situation awareness, even given the same data input. It is argued to be due to an individual's information-processing mechanisms, which are influenced by innate abilities, experience and training. Furthermore, the individual may have certain preconceptions and objectives that can influence and affect the interpretation and forming of situation awareness. In addition, the system design may affect situation awareness by providing the necessary information in an understandable way. However, workload, stress and complexity may also affect situation awareness.[106]

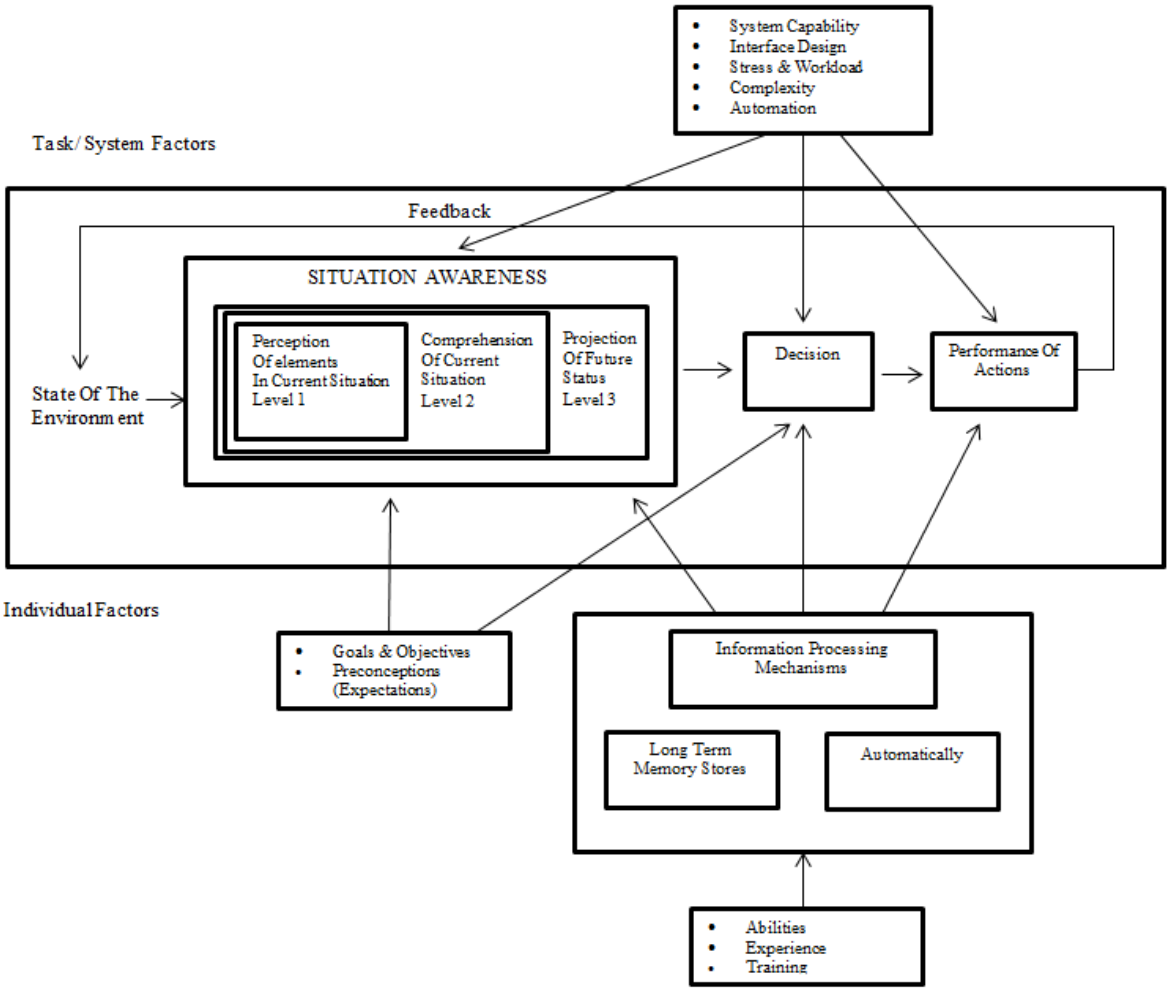


Figure 1. Model of situation awareness in dynamic decision-making.[106] Replica - Reproduced with permission from Human Factors. Toward a Theory of Situation Awareness in Dynamic Systems, Mica R. Endsley, Human Factors, SAGE Publications, 03/01/1995. *Copyright © 1995, © SAGE Publications*

Brady et al.[17] adapted and simplified the three levels of situation awareness in Endsley's model to illustrate how it can be applied to the care of hospitalised patients (Figure 2). Figure 2 illustrates how a structure may improve situation awareness and how links to clear actions may guide clinicians to rapid identification, mitigation and, when necessary, an escalation of the recognition of risk in deteriorating patients.[17] Each level of situation awareness is associated with a unique threat, and, hence, potential systems- and training-level interventions are required. At the first level, a systematic gathering of data regarding risk status is conducted (e.g. vital signs and relatives' concerns). At the second level, healthcare professionals determine what these observations mean (e.g. worsening dehydration may indicate compensated shock) and initiate appropriate interventions, which may involve diagnostic tools or bringing expert clinicians to the bedside. At the third level, healthcare professionals must project potential outcomes (e.g. hypovolemic shock may progress to arrest if no action is taken). Solutions could include time-

bound plans and escalation pathways. Together, the three levels serve as a paradigm for identifying risk, making decisions and acting upon initial observations, and this approach has inspired the intervention and introduction to the intervention in study III.

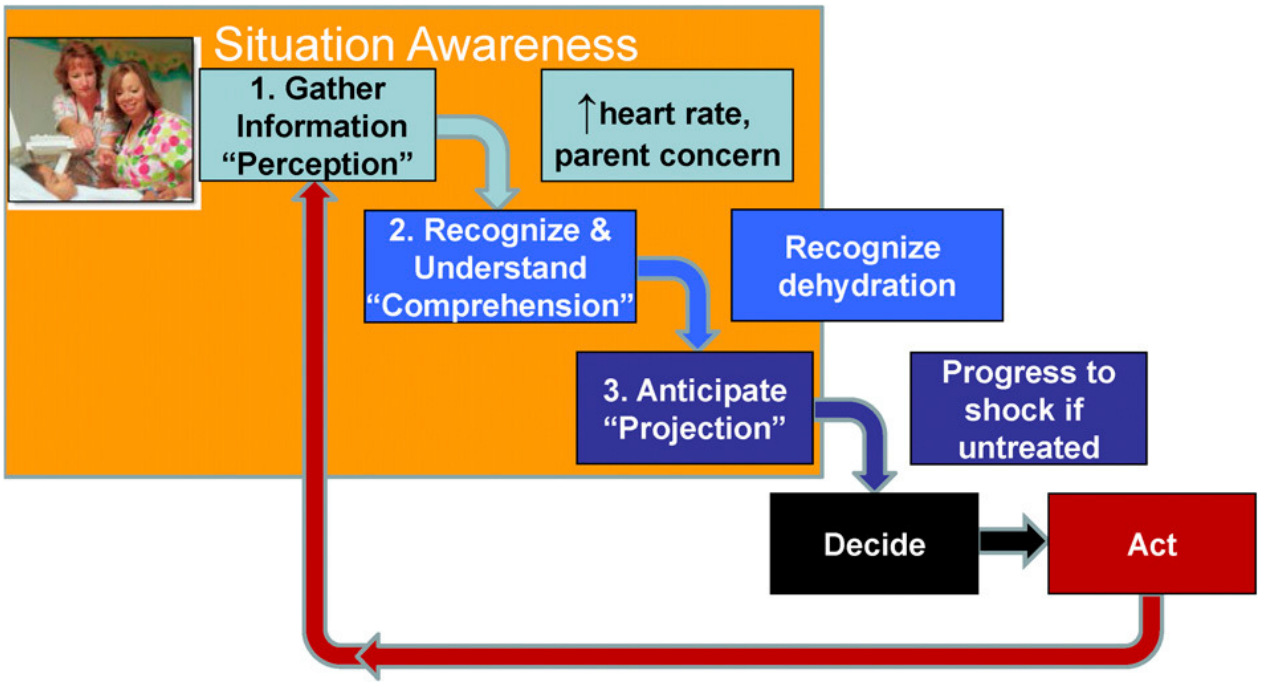


Figure 2. Model of the application of the three levels of situation awareness in healthcare, including the relationship between the three levels and clinical examples of how they fit together [17]. Reproduced with permission from Hospital Pediatrics 4 (3):143–6. Copyright © 2019 by the AAP.

This approach to situation awareness is used in the Cincinnati Situation Awareness algorithm to increase patient safety. The model origins from the Cincinnati Children's Hospital Medical Center in the United States and will further on be referred to as the Cincinnati Situation Awareness algorithm. The model supports the clinicians in identifying patients at risk, mitigating and escalating the care of patient's at risk by applying principles from high-risk organisations. The risk model is combined with a formalised process which requires that patients at risk of clinical deterioration be discussed with an experienced colleague and proactively treated. The model includes screening for five risk factors: family concerns, high risk therapy, presence of an elevated EWS, watcher/ clinician's gut feeling and communication concerns.

Furthermore, the model also includes systematically conducted unit and inpatient-based huddles. Huddles seem to origin from football back in 1894 and consisted of a circular formation where the players face each other to communicate plan and strategies.[109] An acronym for huddle has been suggested for preoperative settings; however, it is considered to be relevant across all healthcare settings. The acronym for HUDDLE stands for Healthcare, Utilising, Deliberate, Discussion,

Linking, Events. It should remind the clinicians of the importance of a deliberate discussion linking events to their occurrence and hereby increasing awareness, patient safety and communication in the team.[109] The unit-based huddle in the Cincinnati Situation Awareness algorithm is held between the charge and bedside nurse, regardless of the patient's condition every 4 hours. Huddles are also held whenever new risk factors are identified, aiming to trigger a bedside evaluation by experienced nurses and physicians. When a risk is identified, the huddles are led by a watch stander charge nurse (the person in charge of knowing which patients are at risk) and senior resident (in the UK, a registrar). An inpatient-based huddle is held three times daily with a charge nurse from each inpatient unit and the manager of patient services who oversees the flow and staffing of inpatients. The aim of these huddles is to discuss risk factors present but not fully addressed and whether any predicted Medical Response Team activations are expected. In addition, they evaluate transfers to an ICU. In an observational time-series study, the model was found to be associated with a near 50% reduction in unsafe ICU transfers and a decrease in severe safety events.[17, 18] So far, this promising model has not been evaluated in a controlled study design or in an adult population.

The few extant studies on this topic suggest that increasing nurses' situation awareness and adding subjective parameters, such as clinical concern, may improve EWS systems and improve their effect on clinical outcomes by prompting more proactive treatment.[20, 90]

2.7 Rationale for the study

The literature revealed the following:

- High prevalence of clinical deterioration among ED patients, even when EWS systems are implemented
- EWS systems lack impacts on patient outcomes
- EWS systems must be developed for the setting in which they are implemented to ensure that the predictors are relevant and applicable
- A deterioration in vital signs increases the patient's risk of death

- Increasing situation awareness and adding additional parameters to the existing EWS systems may, increase healthcare professionals' ability to detect clinical deterioration and earlier triggering of the EWS system and, thereby, prompt more proactive treatment and positively affect clinical outcomes

In a patient safety perspective, it is essential to examine additional predictors' ability to enhance EWS systems, decrease clinical deterioration and thereby improve patient outcomes. In particular, it is important to explore the predictors associated with clinical deterioration in adult ED patients to ensure relevance and applicability. In our situation awareness model we included predictors identified as targeting clinical deterioration in ED patients. Inspired by the Situation Awareness algorithm developed by Brady et al., we decided to include subjective parameters, such as clinical intuition and concern and patients' or relatives' concerns, and huddles in our situation awareness model in spite of the outcome of the literature review and the Delphi process.[17, 18]

CHAPTER 3. AIMS AND HYPOTHESES

3.1 Aim

The overall aim of this study was to develop and evaluate the effect of a situation awareness model targeting clinical deterioration in a Danish adult ED population.

The specific aims were as follows:

- To identify generic predictors of clinical deterioration in an adult population of hospitalised ED patients (Study I)
- To determine the relevance and applicability of generic predictors of clinical deterioration in EDs (Study II)
- To investigate the effect of a situation awareness model targeting clinical deterioration (Study III)

3.2 Hypothesis

Implementation of the new situation awareness model reduces the number of patients with clinical deterioration.

The three studies in this dissertation regard adults as children's clinical and vital signs differ from those of adults[110], prompting another setup for recognition of clinical deterioration.

CHAPTER 4. MATERIALS AND METHODS

4.1 Study I Systematic review

The first study in this dissertation is a systematic review intended to identify generic predictors of clinical deterioration in adult ED patients that should be considered for inclusion in the situation awareness model. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[111]

4.1.1 Selection of studies

A systematic search was performed in several databases: PubMed, EMBASE (Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL), EBSCOhost, PsychINFO and the Cochrane Library. The databases were searched from the time they were established to July 2016 (Appendix 2). The literature search was performed by two reviewers, GBT and MTR, in collaboration with a research librarian.

4.1.2 Inclusion criteria for studies

4.1.2.1 Study design

Observational studies (i.e. cohort, cross-sectional and case-control studies) were included, as were RCT studies that reported separate estimates for a passive (i.e. usual treatment) control condition.

4.1.2.2 Patients

ED patients with somatic symptoms aged 16 years and above were included.

4.1.2.3 Intervention

Generic non-compounded risk factors or predictors that were widely applicable to the ED population and to routine care practices were examined. Generic predictors were defined as predictors widely applicable to the ED population and to routine care practice. Non-compounded predictors were defined as independent predictors, rather than predictors that were part of an aggregated score, such as the Charlson Comorbidity Index. An exception was the Glasgow Coma Scale (GCS) due to its widespread clinical use in EDs.

4.1.2.4 Outcomes

Clinical deterioration was defined as cardiac arrest, death within 30 days of ED admittance or direct admission to the ICU from the ED. Only studies written in German, English or a Scandinavian language (i.e. Danish, Swedish or Norwegian) were included. The two reviewers, GBT and MTR, independently screened titles and abstracts and assessed studies' eligibility by

reading the full text of articles. Disagreements were resolved by consensus or a third reviewer, ML.

4.1.3 Exclusion criteria for studies

Studies focusing on out-of-hospital cardiac arrest, trauma patients, and patients primarily diagnosed with a psychiatric disorder or predictors for specific diseases, e.g. predictors not applicable on a broad ED population, were excluded.

4.1.3.1 Methodological quality assessment

The methodological quality of the studies was independently assessed by GBT and MTR using the Newcastle-Ottawa Scale (NOS)[112], which was developed for quality assessment of non-randomised studies. Points were given based on the following:

- Selection of the study groups (maximum score = 4)
- Comparability of the groups (maximum score = 2)
- Ascertainment of either the exposure or outcome of interest for case-control or cohort studies (maximum score = 3)

The maximum score is 9.[112] In the comparability category, we decided a priori that studies controlling for age would be assigned 1point and those controlling for age and the severity of patients' conditions would be assigned 2 points.

4.1.4 Data extraction

Data from the included studies were extracted by GBT and reviewed by MTR. Data extraction forms were developed a priori and comprised the following information: lead author's surname, year of publication and journal, country of origin, study design, study population (size and selection), exposure and outcome assessment, whether covariates were adjusted for, main results (measures of association with 95% confidence intervals (CIs) and p-values) and risk of bias assessment.

4.1.5 Statistical analyses

Data were narratively synthesised and described according to the study design, predictor categories (presenting complaints, independent vital signs, biochemical tests, comorbidities and other predictors) and outcomes. We rated predictors based on whether they were associated with an increased or decreased risk of clinical deterioration and whether the estimates in the original studies were statistically significant or statistical significance could not be determined. We developed forest plots to display the predictors estimates.

4.2 Study II Delphi study

The second study in this dissertation was a Delphi study. The aim of this study was to determine the clinical relevance and applicability of generic predictors of clinical deterioration in patients in EDs. It employed a modified two-stage Delphi technique [113] involving health care professionals (nurses and physicians) in emergency medicine.

4.2.1 Study design

From December 2016 to January 2017, we used a modified two-stage Delphi technique[113] to identify consensus-derived predictors of clinical deterioration. The consensus process was originally developed by Helmer and Dalkey[114] and is often used to address complex problems that exceed the analytic capabilities of one person and must be addressed by a group of experts.[115, 116] In this study, we asked the panel members to rate potential predictors of clinical deterioration in patients in EDs relative to the following two dimensions (with relevance being superior to applicability):

Dimension 1: Relevance

- Relevant marker of clinical deterioration in patients in EDs

Dimension 2: Applicability

a) Capable of indicating a change over a short time (hours) in patients while in the ED
b) Generic in nature
c) Possible to detect bedside (i.e., available while the clinician is present)

4.2.2 Delphi panel

The panel members in this study were physicians and nurses with at least 2years of experience in EDs or working with emergency medicine patients. It was a requirement that the health care professionals worked in the ED at the given time to ensure they had experience from the ED and thereby strengthen the selected predictors applicability in these setting. At the time of the study, Denmark had no specialty in emergency medicine; however, the Organisation of Danish Medical Societies had defined a supra-specialty in emergency medicine in which medical specialist could be certified if fulfilling a curriculum close to what was defined by the European Association of Emergency Medicine.[117]

The participants were recruited from three Danish healthcare organisations: 1) Danish Society of Anaesthesiology and Intensive Care Medicine, representing 1,437 anaesthesiologists and doctors in intensive care medicine; 2) Danish Emergency Nursing Association, representing 163 nurses in emergency medicine; and 3) The Organisation of Danish Medical Societies, representing 125 scientific societies in medicine with 25,000 members. Each organisation was asked to invite members according to the abovementioned criteria.

4.2.3 The Delphi process

4.2.3.1 Predictors presented in the Delphi process

The panel was asked to reach consensus on 33 predictors of clinical deterioration in patients in EDs identified from the literature.[38, 43, 50, 61, 62, 65, 118-138]

The predictors were classified into three categories: biochemical tests (Bicarbonate, Lactate, pH, Potassium, Glucose, Leucocytes, Haemoglobin, Sodium, Creatinine, Thrombocytes, Erythrocyte, Albumin, Bilirubin, Haematocrit, Blood culture, Urea); vital signs and parameters (Respiratory rate, Saturation, Systolic blood pressure, Altered mental state, Pulse rate, Dyspnoea, an ECG, TP, Diastolic blood pressure, Capillary refill) and clinical symptoms and signs; (Pain, Nausea, Diarrhoea, Jaundice, Suspicion of infection, Aspiration, Vomiting).

4.2.3.2 First round of the Delphi process

A questionnaire presenting the 33 predictors was distributed to the panel members individually by e-mail. Surveys were web-based using the survey platform Research Electronic Data Capture (REDCAP) hosted at Central Denmark Region. Two reminders were sent for each round. The panel members were requested to rate the predictors based on their professional knowledge and experience without considering the costs. If a panel member did not have sufficient knowledge to rate a predictor, they could answer 'don't know'. They were also encouraged to include written comments to support or qualify their scores. Finally, they were invited to suggest additional, relevant predictors based on their clinical experience. New predictors had to be suggested by more than one panel member from round 1 to be considered important for inclusion in round 2.

For each predictor, the panel members were asked to indicate their extent of agreement on a scale from 1 (completely disagree) to 9 (completely agree) on questions related to relevance and applicability.

4.2.3.3 Second round of the Delphi process

In the second round, the panel members were asked to reassess the clinical relevance (dimension 1) of non-consensus predictors from round 1, based on: the overall median score and interquartile range (IQR); a reminder of their own personal score; and anonymous comments made by the panel members, see Table 1 for example. In addition, they were asked to rate new predictors relative to both relevance and applicability.

Table 1: Example of predictor presentation in Round 2 with the panel's scores, reminder of personal score and additional comments (Tygesen et al. 2020, Paper II)

To what extent do you agree that sodium is a relevant predictor of clinical deterioration?									
1. Strongly disagree ○	2 ○	3 ○	4 ○	5 ○	6 ○	7○	8 ○	9. Strongly agree ○	Don't know ○
In the first round, you answered [x], and the panel's median score was 7 (IQR: 4–9).									
The comments from the panel in the first round: • Best to substantiate clinical suspicions and some poisoning conditions • Abnormal sodium is rarely treated urgently • Bedside assessment requires an arterial blood gas • Very low sodium does not necessarily have to be corrected quickly in the ED due to the risk of 'osmotic demyelination syndrome (ODS)' • Chronically low in patients with alcohol use disorder • Must be assessed in relation to the problem and the individual patient • May be relevant in hyponatraemia • Slow marker									

IQR Interquartile range

4.2.4 Analysis

Consensus on inclusion of a predictor was considered by a median score and interquartile range (IQR) of 7–9 and exclusion by a median and IQR of 1–3.[139] All other scores were considered non-consensual or equivocal, requiring panel reassessment in Round 2. That is, a predictor with non-consensus in relevance and not excluded based on applicability was sent to Round 2 for reassessment unless the panel members had indicated concerns regarding the predictor (e.g., overlapping with other predictors). The purpose of the three questions related to applicability was to support and refine the decision of whether to include or exclude a non-consensus predictor and thus determine whether it should proceed to the second round.

After the first round of the Delphi process, the research group (GB, HK, MTR, ML) met to ensure that each predictor was handled in accordance with the aforementioned criteria together with comments suggesting that a predictor was not exclusive (e.g. overlapping). After the second round, the final decision regarding non-consensus predictors was made by the research group and an invited impartial physician with considerable clinical experience in emergency medicine (NR), who had not participated as a panel member or in any of the previous work related to the Delphi study. Decisions regarding inclusion or exclusion of non-consensus predictors were based on the above-mentioned criteria and panel members' comments. In case of disagreement in the research group, the impartial expert's opinion was implemented. To capture any differentiated effect due to dropouts, we performed sub-analyses excluding the anaesthesiologists and physicians in intensive care medicine.

4.2.5 Ethics

When collecting research data from humans, the researcher should demonstrate great responsibility and consider ethical aspects. The study protocol should adhere to the Helsinki Declaration[140] and participation must be voluntary. Although this study was not an intervention study, we adopted the principles from the declaration. The invited panel members received an email before consenting with explanations of aim, method and anonymisation and that they could withdraw from the project at any given time without further explanation. The collected data and panel members were anonymised through-out the study. The study was approved by the Danish Data Protection Agency (J no. 1-16-02-34-16), and Danish legislation exempts this type of study from approval.

4.3 Study III Controlled intervention study

The third study in this dissertation was an intervention study with a controlled pre and post design that examined whether the situation awareness model for EDs could impact clinical deterioration.

4.3.1 Design

The study used a controlled pre and post design and included four regional EDs in Central Denmark Region. Two EDs were assigned to the intervention group and two to the control group. All EDs went through a baseline period, referred to in the rest of this study as the pre-intervention period (July–December 2016) and a post-intervention period (November 2017–April 2018).

4.3.2 Setting

Each of the four hospitals serves a population of 200,000–300,000 people in Central Denmark Region, with around 16,000 ED visits annually due to minor injuries and 15,000–18,000 admissions to short stay units or in-hospital units; The involved EDs consist of an emergency room, and an integrated short stay unit with approximately 30–38 beds, including triage beds for receiving injured and acutely ill patients (medical and surgical). Patients with an expected LOS of more than 48 hours are transferred to inpatient units. Patients with a shorter admission time are discharged directly from the EDs. Patients attending the ED can be: 1) referred by a general practitioner (GP) or a GP's on out-of-hours service; 2) conveyed by ambulance after an emergency call or 3) by self-referral.

The number of employed health professionals differs in relation to professions: physicians (approx. 30–40) and nurses and social and healthcare assistants[1] (approx. 75–120) depending on the ED's size. One- to two-thirds of the physicians were specialists. The nurses were all registered nurses with ED experience; however, some had less than 1 year of experience.

[1] *A social and healthcare assistant performs practical and personal assistance, care and nursing tasks, health promotion and prevention activities, coordination guidance and training and rehabilitation*

If you wish to work as a social and healthcare assistant in Denmark, you must have an authorisation issued by the Danish Patient Safety Authority.[177]

4.3.3 Patients

Inclusion criteria: All patients aged ≥ 18 years with medical or surgical complaints attending one of the four EDs during the inclusion periods.

Exclusion criteria: minor medical or surgical injuries defined as patients with 1) LOS in the ED of less than 4 hours, 2) cardiac arrest, 3) major trauma or 4) medical or surgical resuscitations. Patients could only enter once in the pre and the post periods; the first admission in each period was included.

4.3.4 Procedures

All participating departments had been using an aggregated EWS system based on National Early Warning Score (NEWS) as a standard observation system for approximately 9 years.[34] In the control group, usual routine was applied using a standard EWS system and corresponding algorithms. In the intervention group, a modified EWS system was used.

4.3.5 Standard EWS

The standard EWS system included respiratory rate, saturation (SpO_2), systolic blood pressure, pulse rate, TP and level of consciousness according to an 'A: alert, V: verbal, P: pain, U: unresponsive' score with corresponding action algorithms (Table 2). Each vital sign could be assigned 0–3 points, where a higher score indicates more severe deterioration. The scores were aggregated to a score between 0 and ≥ 5. A score of 0–1 was considered low risk and meant a reassessment in 8 hours. Patients with a score of 2 were reassessed in 1 hour, and if the score was 3–4 or the patient had a single parameter with a score of 2, a physician was asked to assess the patient. A consultant was asked to assess patients with a score of ≥ 5.

Table 2 Standard early warning score (EWS) with physiological parameters, corresponding weighted score and normal range

Vital sign	Score						
	3	2	1	0	1	2	3
Respiratory rate per min	≤8		9–11	12–20		21–24	≥25
Oxygen saturation	≤84	85–89	90–92	≥93			
Systolic blood pressure	≤69	70–79	80–99	100–199		≥200	
Heart rate		≤39	40–49	50–89	90–109	110–129	≥130
Temperature	<33.9	34–35.9		36–37.9	38–38.9	39–39.9	≥40
Level of consciousness				A	V	P	U

A; alert, V: verbal, P: pain, U: unresponsive

4.3.6 Intervention - EWS

The intervention consisted of the standard EWS system and five additional parameters comprising clinical characteristics: 1) skin observations (cold, clammy, pale, and cyanotic), 2) dyspnoea

reported by the patient, 3) pain (new or increasing) reported by the patient, 4) clinical intuition (clinical concern) and 5) patients' or relatives' concerns.

Vital signs, skin observations, dyspnea, pain and patient and relatives concerns were applied in accordance with the results from study II. We decided not to include biochemical tests and co morbidities in this version of our model even though they reached consensus in study II. Different approaches to the final model were considered and the research group decided to test parameters supporting clinical observations and monitoring without biochemical tests in the first model. It was crucial that the model only included parameters that clinicians could provide within a short timeframe in the ED setting. Furthermore, economy and ethics was considered in this priority. The reasons are further explained and discussed in the discussion section. Introduction of clinical intuition and patients' or relatives' concerns was inspired by the Cincinnati Situation Awareness model as described in the background section '2.6 Situation awareness'.[18]

We designed the model over the situational awareness structure again inspired by the Cincinnati Situation Awareness model[18] to help the clinicians gather information and to recognise and understand, anticipate, decide and act supported by huddles, escalation plans and communication as described in the following.

In the modified EWS system, the nurse considered new or escalating deterioration if 1) the vital signs triggered the EWS (as outlined in Table 2, with corresponding actions described in 4.3.5 Standard EWS) and/or if 2) one of the additional five parameters was present (e.g. present or absent). If deterioration was suspected, a physician was called. In uncertain cases, the nurse would review the patient with an experienced nurse and subsequently call the physician if deterioration was suspected. In these situations, the patient's clinical condition was reassessed, and the physician outlined a plan including actions to be taken, expected outcome of actions, deadline for reassessment and precautions that should be taken if the expected outcome failed to happen. At-risk patients were highlighted at the electronic dashboards and discussed amongst the care team in huddles twice a day (morning and afternoon) as described below. The discussion incorporated the patient's symptoms and a plan including treatment response (Figure 3; Process overview). For further details please see Appendixes 3 and 4 for Pocket card (in Danish 'lommekort') and the corresponding guideline (in Danish 'retningslinje').

4.3.7 Huddles

The huddles were held twice a day (morning and afternoon) and consisted of a short team gathering at ward level lasting approximately 15 minutes. The participants stood up during the process.

The participants were the nurse coordinator, consultant and the nurse responsible for the patient discussed. They met and discussed patients in the ward. The discussion primarily focused on risk of clinical deterioration; however, patients waiting for transfer or discharge were also discussed regarding the prioritisation of resources.
The patient's history, risk and escalation plan were reviewed to allow for professional sparring. The responsible physician gave an overview of the patient's progress with a brief description of:

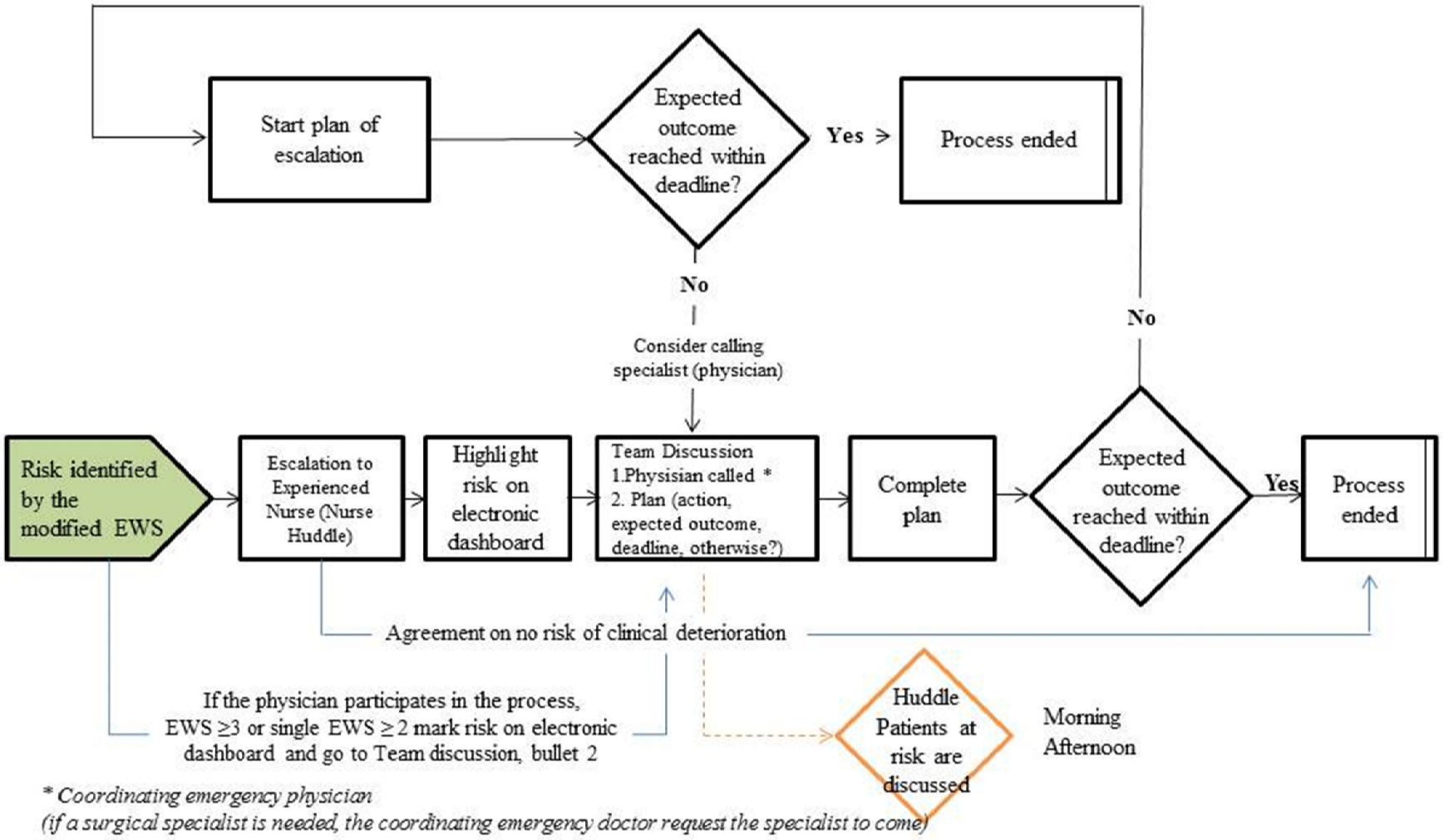
- The patient's medical history
- Identified risk of clinical deterioration
- Treatment and escalation plan

The researcher observed the huddles frequently, though no audit for content and frequency was made.

4.3.8 Communication

We used a structured communication tool called ISBAR (Identification, Situation, Background, Assessment, Recommendation)[141] to support the clinicians' communications regarding patients at risk of deteriorating. This communication tool was already implemented in the hospitals of Central Denmark Region. As the healthcare professionals were already familiar with this tool, we introduced it only in the training in the model in the case scenarios; the training is further described below.

Figure 3 Process overview of the patient safety model targeting clinical deterioration in admitted adult emergency department patients



Note: When risk of clinical deterioration was identified by a abnormal early warning score and/or one of the additional parameters (skin, dyspnoea, pain, clinical concern, patient or relatives concern) the process was activated.

Prior to the study's start, the nurses and social and healthcare assistants in the intervention departments had one and a half hours of mandatory training in the new modified EWS system and the huddles that focused on the the underlying process of deterioration. (Appendix 4; Education programme). The physicians were given a half an hour's training. The differences in the training programmes were due to different tasks and roles in the modified EWS system and situational awareness model. The nurses received an in-depth introduction to situation awareness and were trained in the modified EWS by use of scenarios as it was their role to screen the patients. After the initial introduction, the local champions supported the primary investigator in helping staffs adhere to the protocol by answering questions related to the intervention. Face-to-face discussions in the clinical setting on how to find and fill out the template or which physician to call when deterioration was expected were also performed. Adherence to the model was audited weekly by checking how many patients had an EWS with the new parameters registered in their electronic medical record (EMR) by the researcher (data were obtained from an electronic system; Business Intelligence – portal).

4.3.9 Outcome measures

The primary outcomes were clinical deterioration defined as an increase in vital sign scores[38] measured by EWS,[142] i.e. increase in EWS from either 0 or 1 to score ≥ 2, or an increase from score ≥ 2 and above.[142] That is, a patient with an initial EWS of 4 and a follow-up EWS of 4 had no deterioration, whereas a patient with an initial EWS of 0 and a follow-up EWS of 2 had deteriorated. An increase in EWS from 0 to 1 was not considered deterioration.

In addition, a composite clinical deterioration was defined as clinical deterioration in combination with death or ICU admission directly from an ED.

The primary outcomes were measured as the difference in the proportion of clinical deterioration between the pre and post intervention period adjusted with the control groups to account for variation over time.
Secondary outcomes: 1) proportion of 30-day readmission, 2) proportion of 7-day mortality, 3) proportion of 30-day mortality and 4) proportion ICU admission directly from ED.

4.3.10 Data collection

Data on vital sign measurements, EWS, death, LOS and ICU admissions were retrieved from the four hospitals' EMR in both the pre- and post periods. All data on mortality were obtained from the Danish Civil Registration System.[143] To assist staff in all steps of the intervention, a specific template was constructed for data entry into the EMR (Appendix 6, Template in EMR).

4.3.11 Statistical analysis

Sample size calculations were based on the following assumptions: clinical deterioration occurs in 12% of ED patients[35, 142, 144], and a clinically relevant reduction of 15% in the proportions of patients with clinical deterioration, 80% power and a significance level of 5%. Accordingly, the sample size comprised 19,564 participants, with 4,891 in each of the four (pre- and post periods in the intervention and control groups).[145] Around 1,000 patients a month were admitted to each of the four participating EDs; thus, according to the number of admitted patients the post period was set to 6 months, accounting for patients with missing data (approx.. 20%). A similar pre period of 6 months was used.[145]

The primary outcome was analysed using difference-in-difference regression[145, 146] (i.e. the mean difference within groups [post – pre] compared between the groups [intervention and control]). Both the primary and secondary end-points analyses were adjusted for EWS at admission and according to gender and age using logistic regression analysis.

Patients with no EWS or only one EWS registered were included in the primary analysis as 'no deterioration' instead of missing values.

Data are presented as median (interquartile range) or proportions wherever appropriate. Analyses are performed with a significance level of 5% and results are presented with a 95% CI.

To capture any differentiated effect on outcome due to the entry condition of the patients, we performed sub-analyses on the patients' EWS at admission.

4.3.12 Missing data or data entry failures

If patients did not have a registered EWS but all vital signs except TP were registered, a score was generated by setting the TP to normal.[147] This was done for 285 observations.

To ensure catching data entry errors, we limited the analysis to patients with a respiratory rate ≥ 4 bpm and ≤ 60 bpm, TP ≥ 20˚C and ≤ 42˚C, systolic blood pressure ≥ 30 mmHg and ≤ 300 mmHg, pulse ≥ 20 bpm and ≤ 300 bpm, Glasgow coma scale ≥ 3 (0–2 not in scale), and oxygen saturation ≥ 45%.

Statistical analyses were performed with STATA software version 15.1 (Stata Corp, College Station, TX, United States).

CHAPTER 5. ETHICS AND APPROVALS

There are several ethical aspects that must be considered in intervention studies involving patients. At the time the present study was planned, there was a lack of evidence regarding how to improve the clinical outcomes of EWS systems for adult ED patients. Studies have suggested that adding subjective predictors to EWS systems could be beneficial. [18, 90] However, these studies were carried out with populations other than ED patients and therefore are not necessarily directly transferable. Hence, it was ethically appropriate to involve ED patients in our study of the effects of clinical deterioration.

Permission to complete the study was obtained from the management at each hospital, the Data Protection Agency in Denmark (J no. 1-16-02-34-16) and the Danish Patient Safety Authority (J no. 3-3013-1539). According to Danish law, the study did not require approval from the National Committee on Health Research Ethics. Study III was registered on ClinicalTrials.gov with the identifier NCT03457272. All data were anonymised and kept according to regulations.

As previous mentioned, approval for the Delphi study (study II) was obtained from the above-mentioned authorities. Those invited to complete the surveys were informed that participation was voluntary and all answers would be treated confidentially. It was emphasised that no individual answers would be available to other participants and that the participant were able to withdraw at any time during the study.

CHAPTER 6. OVERVIEW OF RESULTS

This chapter provides an overview of the main results in the three studies.

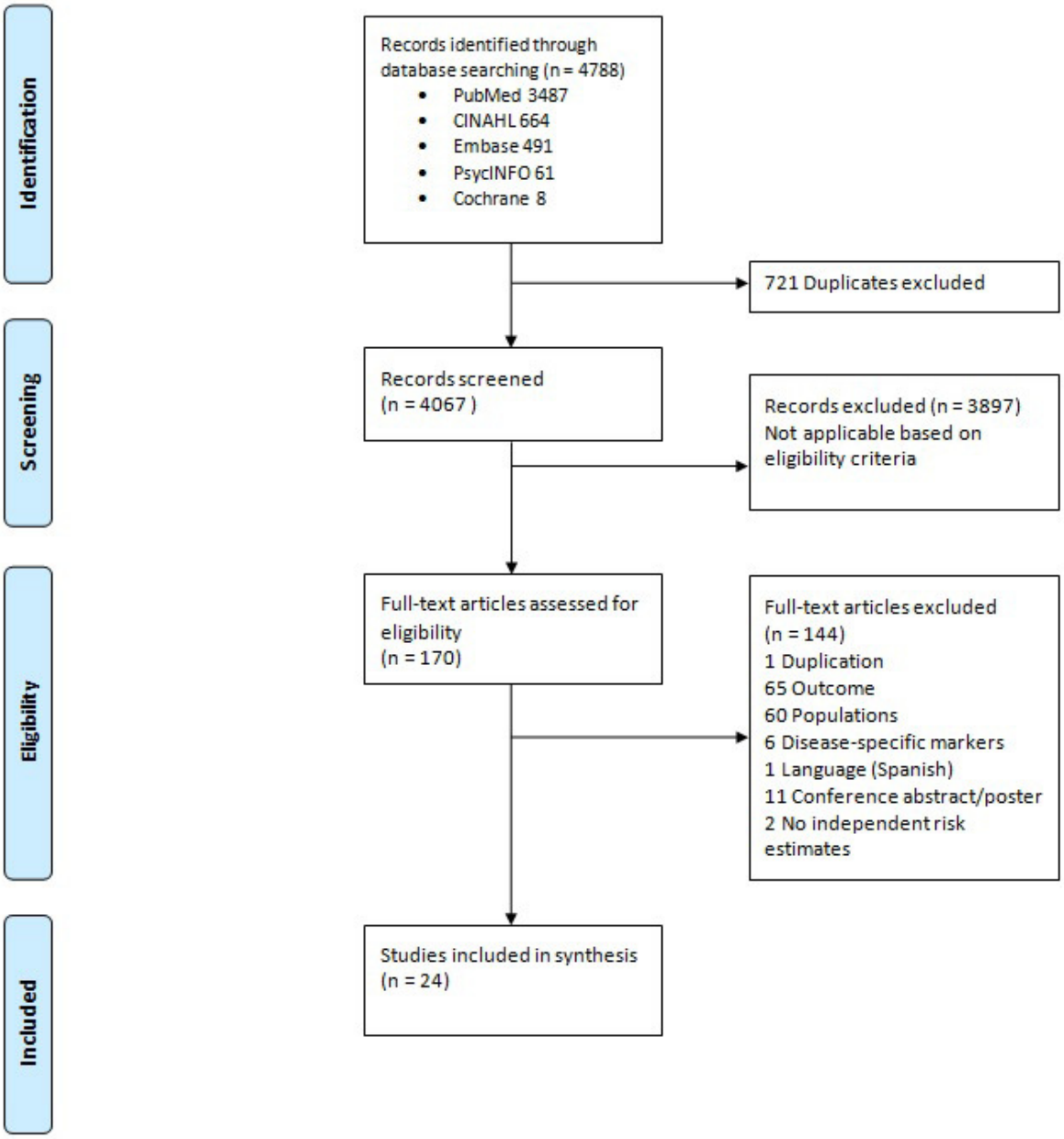
6.1 Study I

In study I, we systematically reviewed the literature to identify generic predictors of clinical deterioration in adult ED patients.

6.1.1 Results

In all, 4788 records were identified, leaving 4067 records to be screened after search for duplicates. A total of 170 records underwent full text review, and 24 studies[38, 43, 50, 61, 62, 65, 118-135] fulfilled the inclusion criteria (Figure 4).

Figure 4 PRISMA flowchart of selection of eligible studies



6.1.1.2 Characteristics of included studies

The included studies were distributed as 22 cohort studies, one cross-sectional study and one case-control study. The quality assessments of the studies showed 16 studies with NOS score 9, which was the highest possible score; three with score 8; four with score 7 and one with score 6, indicating that there were few studies with methodological considerations.

6.1.1.3 Predictors identified

A total of 36 potential generic predictors of clinical deterioration in adult ED patients were identified. The predictors were associated with ICU admission, mortality (death within 30 days of ED attendance) and, to a lesser extent, cardiac arrest (CA) and the composite outcome of ICU admission and mortality. Measures of associations with clinical deterioration are presented in

Figures 6–9. All identified predictors are displayed in the forest plots (Figures 6–8), whereas predictors that were statistically significantly associated with clinical deterioration are described below.

Presenting complaints

The predictors included two presenting complaints (*jaundice and gastrointestinal symptoms* like nausea, vomiting and diarrhoea) that increased the risk of ICU admission in patients presenting to the ED with low urgency on the Australian Triage Scale.[120]

Vital signs

Eight independent vital signs were found to increase the risk of clinical deterioration across subgroups. *High respiratory rate (RR)* predicted ICU admissions and mortality across subgroups comprising admitted ED patients, patients with differentiated infections and those with low and high urgencies. The risk of death increased with increases in RR.[43, 65, 120, 126, 130, 132, 135] One study found that a high RR (>20) predicted cardiac arrest in patients with Singapore Patient Acuity Category Scale 1–2(PACS).[126]

Across the subgroups a *high heart rate (HR)* (>100) was found to predict ICU admission and mortality, and similar to RR, the risk of death was found to increase with increases in the HR.[43, 65, 126, 132, 135] Risk of ICU admission was found to increase gradually in patients with tympanic TP ≥38˚C with increase in the HR.[130] In patients with high urgency, a *low HR* (<60) predicted increased risk of ICU admission[126], and the absence of tachycardia (HR ≤100) was found to predict increased mortality in patients with hyperglycaemia.[127] One study found that HR abnormalities (<60,>100) at triage increased the risk of ICU admission in patients with lower urgency.[120]

Across studies of admitted ED patients, a low *GCS* was a predictor of mortality and ICU admissions in patients with low and high urgency and in hyperglycaemic patients[43, 65, 126, 127] In addition, GCS <15 was found to predict cardiac arrest in patients with high urgency.[126]

Low systolic blood pressure (BP) (80–89 mmHg and <90 mmHg) predicted ICU admissions, mortality and a composite outcome of the two while a systolic BP of <80mmHg predicted only ICU admissions in admitted ED patients and in patients with suspicion of infection.[43, 62, 127] *High systolic blood pressure* (>140mmHg) was negatively associated (protective) with ICU admission, CA and mortality in patients with high urgency on PACS (1-2).[126] Systolic BP as a continuous variable confirmed the negative association with mortality in patients with similar urgencies.[135]

Temperature (TP) abnormalities at triage (TP<35, ≥37.9) increased the risk of ICU admission in patients with low urgency.[120] In addition, absence of fever was found to be a negative predictor of ICU admission and death in patients in whom a blood culture drawn.[62]

Oxygenation/ SpO_2 levels of <80% and levels between 80 and 89% were found to predict ICU admission and mortality whereas levels of 90–94% increased the risk of mortality in admitted ED patients.[43] Low *SpO_2* as a continuous variable confirmed the findings of increased risk of mortality in patients with triage levels 1–3.[135]

Finally, the *number of affected vital signs* increased the risk of mortality in admitted ED patients.[38, 43]

Biochemical tests

Twelve different biochemical tests were found to be predictor's of clinical deterioration. *Partial pressure of oxygen* (PaO_2) <9kPa (68mmHg) and <60mmHg (8kPa) predicted ICU admission and the composite outcome of ICU admission and mortality in patients with suspected infection[62, 132] *Sodium* levels of >145mmol/L (high) and <130mmol/L(low) were found to predict ICU admission and the composite outcome of ICU admission and mortality in patients with infection and in patients with high urgency.[65, 132]

Potassium: In admitted medical ED patients, hypokalaemia (<2.9mmol/L) increased the risk of mortality.[129] *High and low leukocytes* were found to predict ICU admissions in patients with pneumonia and high urgency.[65, 132]

Low *arterial pH and blood urea nitrogen* (≥11mmol/L) was found to predict ICU admissions in patients with pneumonia.[132] Higher levels of serum *lactate* (2–3.9mmol/l and ≥ 4mmol/L) increased mortality in patients who had a blood culture or arterial blood gas drawn.[61, 62]

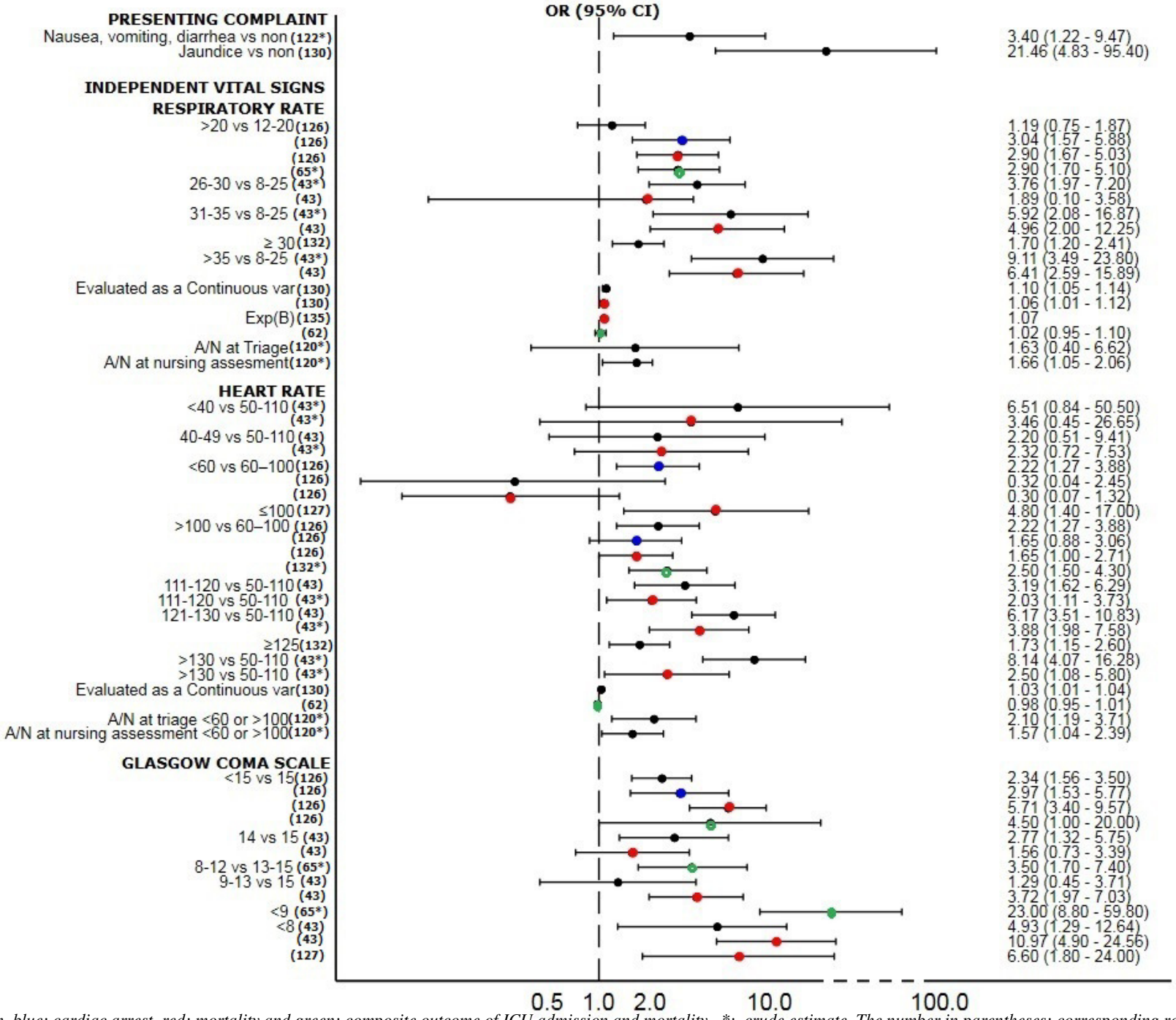
Level of *Haemoglobin* <10g/dL (6.1mmol/L) or an haematocrit of <30% were associated with increased mortality in hyperglycaemic patients. [127] G*lucose* levels of >7.0mmol/L (=126 mg/dl) predicted the composite outcome of ICU admission and mortality in patients with high urgency.[65] Patients with high urgency and both high and low levels of *bicarbonate* (>26mmol/L, <22mmol/L) had an increased risk of the composite outcome of ICU admission and mortality.[65] This association was not significant in patients having a blood culture drawn at arrival.[31] Both positive and negative *blood cultures* compared to none were to be associated with an increased risk of mortality in admitted patients with medical conditions.[121, 122] A study of patients admitted to the medical admission unit assessed *albumin* and found hypoalbuminemia (<35g/L [=5.1ụmol/L]) as a predictor of 30-day mortality.[128]

Comorbidities

Twelve different comorbidities predicted clinical deterioration. The high disability group (system to score the burden of 'disability' and assess its relevance to outcomes of acute hospital admissions) and MDC4 (American diagnosis system corresponding to a single organ system or cause) were associated with increased mortality in ED patients.[121, 122, 130] The MDC4 categories Respiratory, Cardiac and Neurological had the strongest associations with in-hospital mortality in

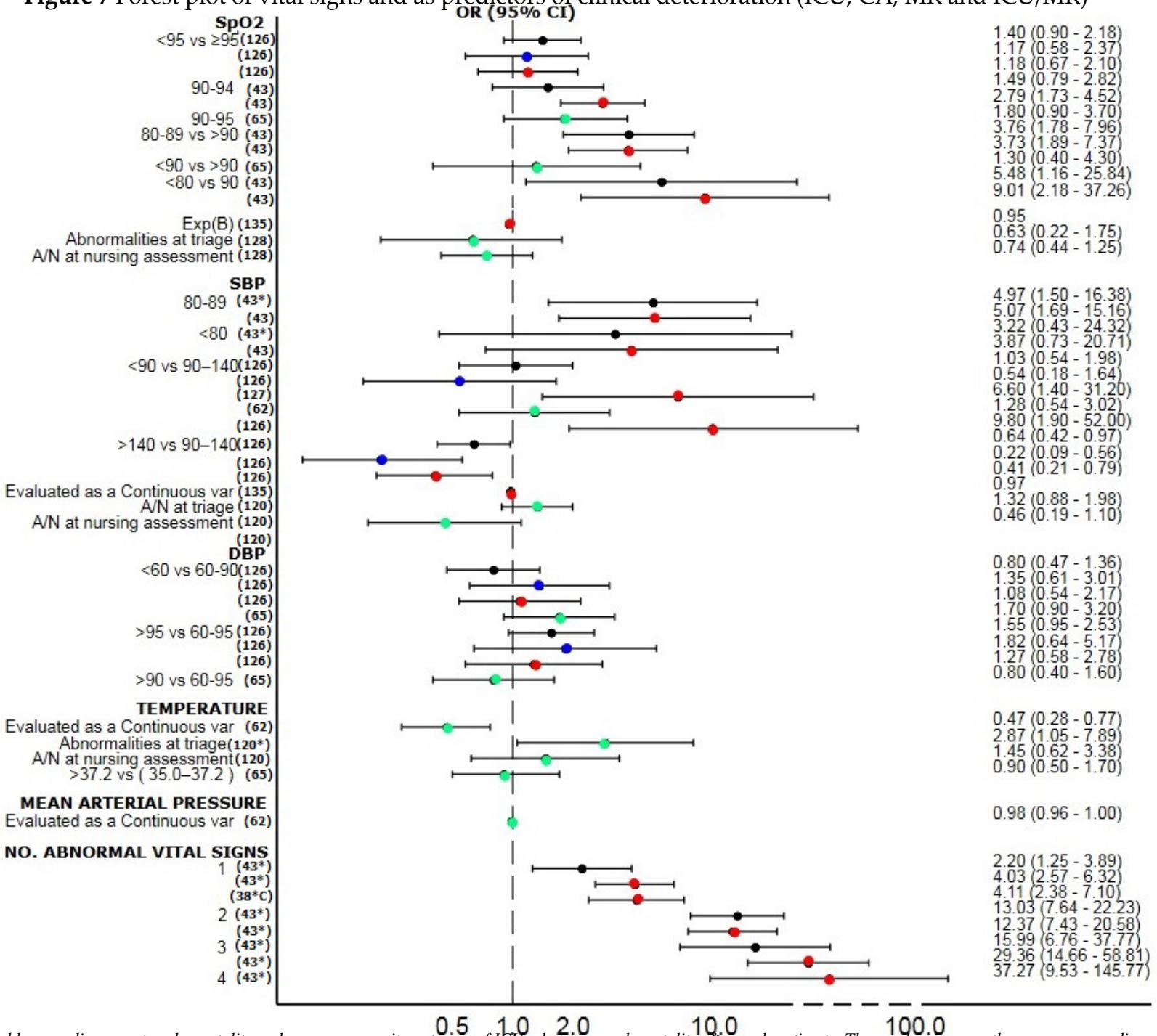
the admitted patients with medical conditions.[121] Similar associations between cardiac disease and increased risk of mortality were found in febrile patients.[130] Presence of malignancy[61, 135], history of cancer[127] and metastatic neoplasm[65], diabetes, seizure, dementia[124] increased the risk of mortality in the differentiated subgroups of patients presenting with syncope, high and low urgency, arterial blood gas drawn and hyperglycaemic patients. The number of comorbidities increased the risk of mortality in admitted patients with medical conditions and patients discharged from the ED.[121, 122, 125] *Other predictors* increasing the risk of clinical deterioration were a recent visit for syncope within 30 days of the index ED visit in patients with syncope[124], in hyperglycaemic patients with infection as the precipitating factor increased the risk[127] and in patients with pneumonia and multilobar infiltrates or pleural effusion detected by an X-ray increased the risk.[132]

Figure 6 Forest plot of presenting complaints and vital signs as predictors of clinical deterioration (ICU, CA, MR and ICU/MR)



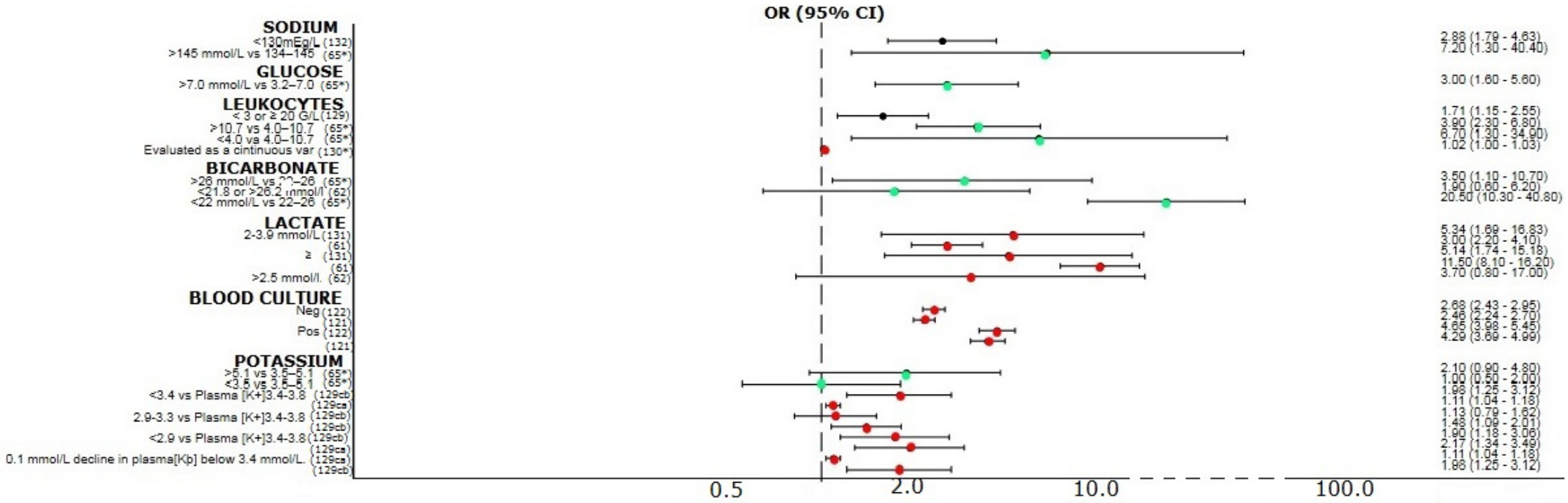
*Dots; black: ICU admission, blue: cardiac arrest, red: mortality and green: composite outcome of ICU admission and mortality. *: crude estimate. The number in parentheses: corresponding reference in the text and reference list e.g. (126) reference number 126. ICU- Intensive Care Unit admission, CA- cardiac arrest, MR-mortality rate, ICU/MR- composite outcome of ICU and MR, OR (95%CI)- odds ratio with corresponding 95% confidence interval, vs- versus, Exp(B)- exponentiation of the B coefficient in logistic regression, A/N- abnormal.*

Figure 7 Forest plot of vital signs and as predictors of clinical deterioration (ICU, CA, MR and ICU/MR)



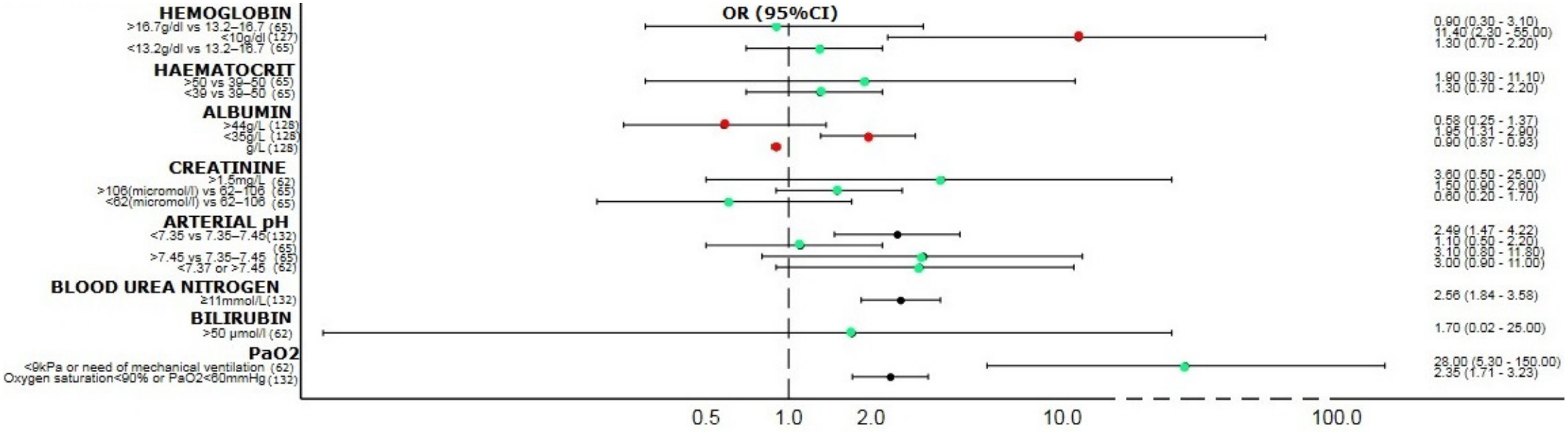
*Dots; black: ICU admission, blue: cardiac arrest, red: mortality and green: composite outcome of ICU admission and mortality. *: crude estimate. The number in parentheses: corresponding reference in the text and reference list e.g. (126) reference number 126. ICU- Intensive Care Unit admission, CA- cardiac arrest, MR-mortality rate, ICU/MR- composite outcome of ICU and MR, OR (95%CI)- odds ratio with corresponding 95% confidence interval, vs- versus, Exp(B)- exponentiation of the B coefficient in logistic regression, A/N- abnormal, SpO_2 – oxygen saturation, SBP- systolic blood pressure, DBP- diastolic blood pressure, NO- number.*

Figure 8.1 Forest plot of biochemical tests as predictors of clinical deterioration (ICU, CA, MR and ICU/MR)



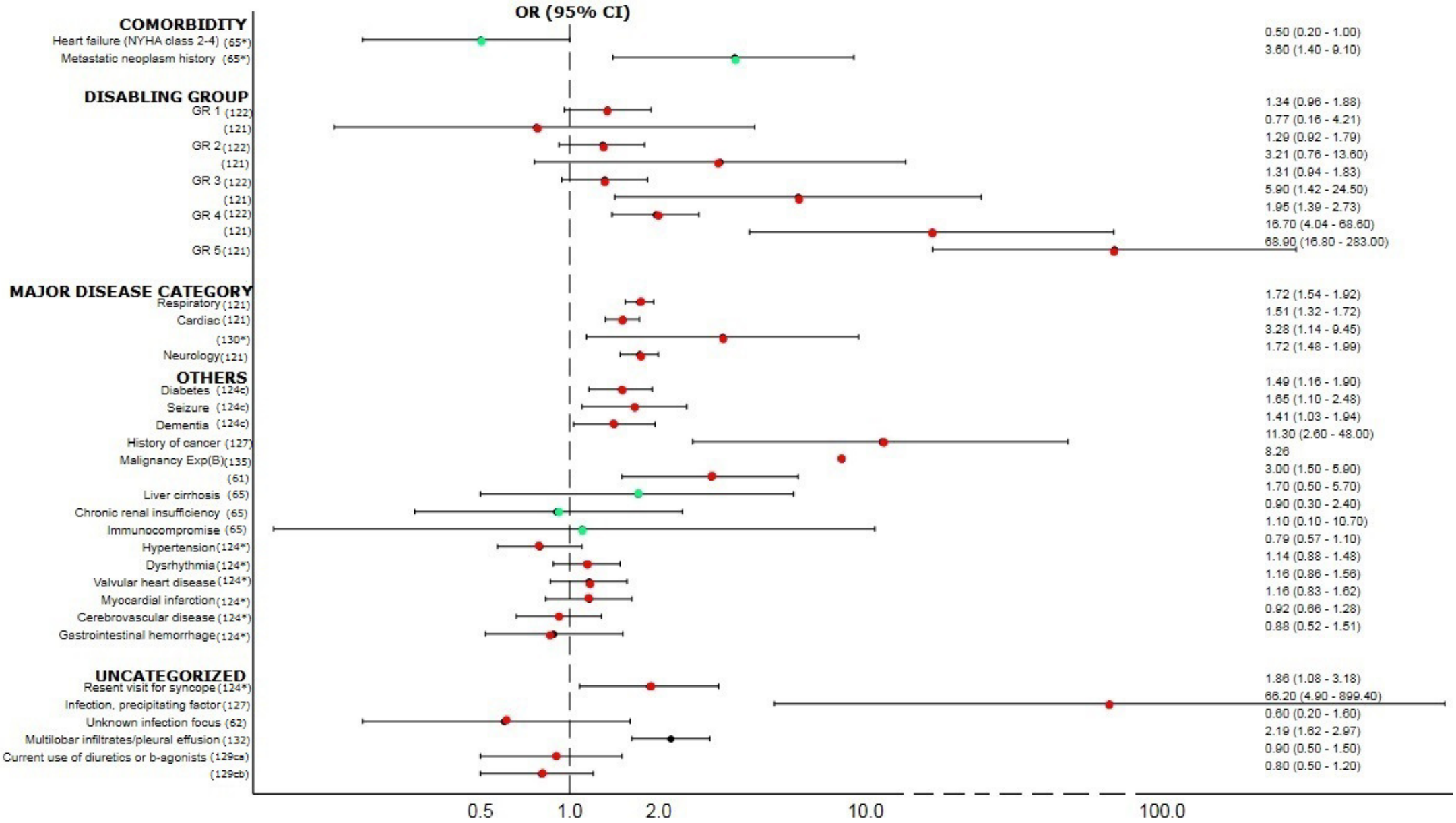
*Dots; black: ICU admission, blue: cardiac arrest, red: mortality and green: composite outcome of ICU admission and mortality. *: crude estimate. The number in parentheses: corresponding reference in the text and reference list e.g. (126) reference number 126. ICU- Intensive Care Unit admission, CA- cardiac arrest, MR-mortality rate, ICU/MR- composite outcome of ICU and MR, OR (95%CI)- odds ratio with corresponding 95% confidence interval, vs- versus.*

Figure 8.2 Forest plot of biochemical tests as predictors of clinical deterioration (ICU, CA, MR and ICU/MR)



*Dots; black: ICU admission, blue: cardiac arrest, red: mortality and green: composite outcome of ICU admission and mortality. *: crude estimate. The number in parentheses: corresponding reference in the text and reference list e.g. (126) reference number 126. ICU- Intensive Care Unit admission, CA- cardiac arrest, MR-mortality rate, ICU/MR- composite outcome of ICU and MR, OR (95%CI)- odds ratio with corresponding 95% confidence interval, vs- versus.*

Figure 9 Forest plot of biochemical tests as predictors of clinical deterioration (ICU, CA, MR and ICU/MR)



*Dots; black: ICU admission, blue: cardiac arrest, red: mortality and green: composite outcome of ICU admission and mortality. *: crude estimate. The number in parentheses: corresponding reference in the text and reference list e.g. (126) reference number 126. ICU- Intensive Care Unit admission, CA- cardiac arrest, MR-mortality rate, ICU/MR- composite outcome of ICU and MR, OR (95%CI)- odds ratio with corresponding 95% confidence interval, vs- versus. vs- versus, Exp(B)- exponentiation of the B coefficient in logistic regression, Neg- Negative, Pos- Positive*

6.2 Study II

In study II we used a Delphi technique to select the predictors of clinical deterioration that were considered to be clinically relevant, applicable and generic in the ED context by a panel of emergency medicine clinicians.

Even though the 36 predictors identified in the systematic review, feeding the Delphi process, were predictors of clinical deterioration, obviously not all were applicable in the ED setting or could be monitored over time as the criteria's in this study required. Therefore the research group eliminated 13 predictors before conducting the Delphi study e.g. partial pressure of oxygen and the comorbidities.

Conversely, the biochemical tests creatinine, thrombocytes, erythrocyte, bilirubin and pain, aspiration, dyspnoea, abnormal electrocardiogram (ECG), diastolic blood pressure and capillary refill time was included in the Delphi process despite not being presented in the systematic review. This is due to the Delphi study being performed prior to a reassessment of all the included studies in the systematic review, which led to exclusion of these predictors. This bias is elaborated in the discussion section (7.3.2).

6.2.1 Results

6.2.1.1 Dropout rate

We recruited 68 clinicians, 29 anaesthesiologists and physicians working in intensive care medicine (43%), 23 emergency medicine nurses (34%) and 16 physicians with a supra-specialty in emergency medicine (23%) to our panel in the first round of the Delphi study. In the second round, there was a dropout rate of 29%, resulting in a response rate of 71% of panellist from the first round. Of the 48 panellists in the second round, 25 were anaesthesiologists and physicians working in intensive care medicine (52%), 14 were emergency medicine nurses (29%) and 9 were emergency medicine physicians (19%).

6.2.1.2 First round

The panellist reached consensus on clinical relevance for 13 of the 33 predictors in the first round (Figure 9): serum bicarbonate, serum lactate, serum pH, serum potassium, glucose, serum leukocyte count, respiratory rate , saturation, systolic blood pressure, altered mental state, pulse rate, dyspnoea and ECG changes (Table 3). None of the predictors were rated as clinically irrelevant in this round (median or IQR = 1–3).

Twenty predictors reached no consensus for clinical relevance. Nine predictors were excluded, and 11 were sent to round 2. The research group excluded blood culture,

albumin, urea, suspicion of infection, aspiration and vomiting based on written comments from the panellists indicating that the predictors were not relevant in the clinical setting due to e.g., analysis time, response time and disagreement on the ability to function as a predictor in the Danish ED setting. Furthermore, erythrocyte, bilirubin and haematocrit were excluded based on comments regarding overlap with other predictors. The panellists suggested five additional predictors: serum C-reactive protein, reduced urine production, anxiety, relatives' concerns and skin condition (i.e., cold, clammy, pale and cyanotic; Table 3). Anxiety, relatives' concerns and skin condition were primarily suggested by nurses. The five predictors were added to the survey, resulting in a total of 16 predictors assessed in Round 2 (Figure 10).

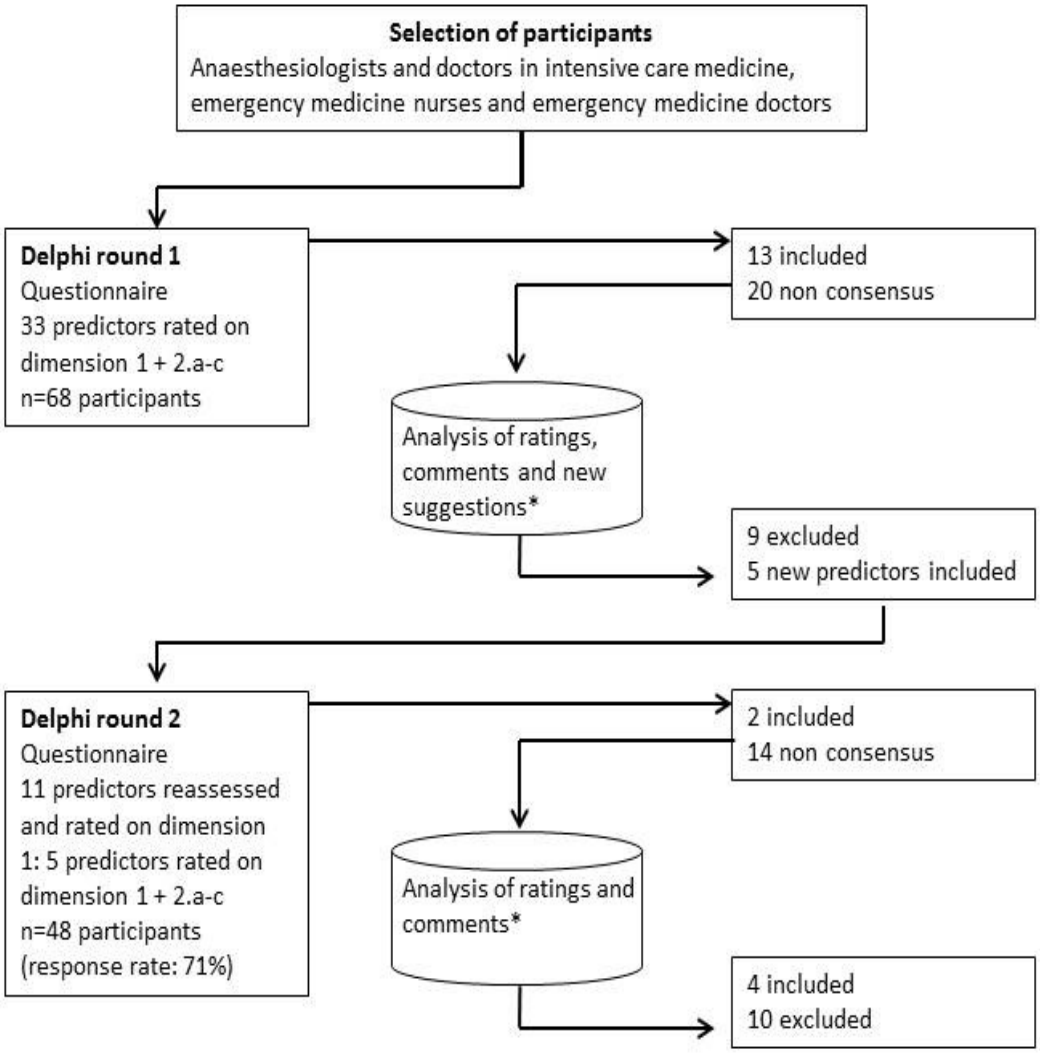
An analysis of clinical relevance only including nurses and physicians with a sub-specialty in emergency medicine showed similar results with a very small deviation regarding TP and ECG changes (median = 8, IQR = 7–9 & median = 9, IQR = 6–9). The deviation did not lead to changes in the overall results as TP would have been included in Round 1 instead of 2 and non-consensus regarding ECG changes in Round 1.

6.2.1.3 Second round

In Round 2, the panellists reached consensus on the clinical relevance of TP and skin condition, leaving 14 non-consensus predictors. The research group including the clinical specialist excluded 10 predictors and included the following four predictors: C-reactive protein, serum haemoglobin, pain and relatives' concerns (Figure 10, Table 3). The research group decided to include these predictors as they are easily accessible and easy to apply to a broad ED population. The exclusion of sodium, creatinine, thrombocytes, diastolic blood pressure, capillary refill, nausea, diarrhoea, jaundice, reduced urine production and anxiety was based on the panellists' written comments. The predictors were described to overlap with other predictors or required repeated measurements (e.g. reduced urine production requires continuous hourly measurement of urine volume).

The option to skip a question was seldom used by the panellists apart from urea. Urea was only rated by 13 of 68 panellists. A sub-analysis of the predictor's clinical relevance only including nurses and physicians with a sub-specialty in emergency medicine revealed a minor deviance on jaundice (median = 5.0, IQR = 3.5–6.0). This deviation would have led to exclusion of jaundice by the panellists rather than the research group.

Figure 10. A General overview of the two-round Delphi process. (Paper II, Tygesen et al. 2020, in review)



Note: Dimension 1 refers to the predictor's relevance (relevant marker of clinical deterioration in EDs). Dimension 2a–c refers to applicability: a) capable of indicating changes over a short time, b) generic in nature and c) possible to detect bedside.

* The research group evaluated non-consensus predictors and excluded those that were considered as overlapping with other predictors according to the panel's comments. The final decisions on non-consensus predictors after the second round were made by the research group and an invited impartial expert in emergency medicine; decisions of inclusion or exclusion of non-consensus predictors were based on the ratings and the panel's comments.

Table 3. Included and excluded predictors in the Delphi process (Paper II, Tygesen et al. 2020, in review)

Predictor	Round 1 (n = 68)				Round 2 (n = 48)				Decision
	Relevance	Applicability			Relevance	Applicability			
	1	2a	2b	2c	1	2a	2b	2c	
	Median Score (IQR)				Median Score (IQR)				
Biochemical tests									
Bicarbonate	9.0 (7–9)	9.0 (7–9)	7.0 (5–9)	7.0 (4–9)					In
Lactate	9.0 (8–9)	9.0 (8–9)	8.0 (5–9)	8.0 (2–9)					In
pH	9.0 (9–9)	9.0 (8.8–9)	9.0 (5–9)	9.0 (7–9)					In
Potassium	8.0 (7–9)	8.0 (7–9)	7.0 (5–9)	7.0 (3–9)					In
Glucose	8.0 (7–9)	8.0 (6–9)	7.0 (5–9)	8.0 (5.5–8)					In
Leucocytes	8.0 (7–9)	7.5 (6–9)	7.0 (4–9)	3.0 (1–6)					In
Haemoglobin	6.0 (4–9)	8.0 (7–9)	7.0 (5–9)	7.0 (4–8)	6.0 (4.5–7)[5]				In
Sodium	7.0 (4–9)	7.0 (6–9)	7.0 (5–8)	6.5 (2–8)	6.0 (4–7)[4]				Ex
Creatinine	8.0 (6–9)	8.0 (6–9)	7.0 (4–8)	4.5 (2–7)	7.0 (5.5–9)[4]				Ex
Thrombocytes	6.0 (5–8)	7.0 (5–9)	6.0 (3–8)	2.0 (1–5)	6.0 (5–7)[4]				Ex
Erythrocyte	4.5 (2–7)[4]	6.0 (5–7)	6.0 (3–7)	3.0 (1–6)					Ex
Albumin	5.0 (3–6)[2]	5.5 (4–8)	5.0 (3.5–7)	3.0 (1–5)					Ex
Bilirubin	6 .0 (5–7)[4]	7.0 (5–8)	5.0 (4–7)	5.0 (2–7)					Ex
Haematocrit	6.0 (4–7)[4]	7.0 (5–8)	6.0 (4–8)	5.0 (2–7)					Ex
Blood culture	7.0 (4–9)[1]	6.0 (3.5–8)	5.0 (2–9)	1.0 (1–4)					Ex
Urea	2.0 (1–5)[1,3]	5.0 (2–6.6)	4.0 (2–6)	1.0 (1–3)					Ex
Vital signs/parameters									
Respiratory rate	9.0 (9–9)	9.0 (8.5–9)	8.0 (6–9)	9.0 (9–9)					In
Saturation	9.0 (8–9)	9.0 (8–9)	8.0 (5–9)	9.0 (9–9)					In
Systolic blood pressure	9.0 (8–9)	9.0 (8–9)	8.0 (6–9)	9.0 (9–9)					In
Altered mental state	9.0 (8–9)	9.0 (8–9)	7.0 (4–9)	9.0 (9–9)					In

Pulse rate	9.0 (8–9)	9.0 (8–9)	8.0 (6–9)	9.0 (9–9)					In
Dyspnoea	9.0 (7.5–9)	9.0 (8–9)	7.0 (4–9)	9.0 (8–9)					In
Electrocardiogram	9.0 (7–9)	9.0 (8–9)	7.0 (4–8)	8.0 (8–9)					In
Temperature	8.0 (6.5–9)	9.0 (7–9)	7.0 (4–9)	9.0 (8–9)	8.0 (7–8.5)				In
Diastolic blood pressure	8.0 (6–9)	8.0 (6–9)	6.0 (5–9)	9.0 (8–9)	7.0 (5.5–9)[4]				Ex
Capillary refill	8.0 (6–9)	8.0 (6–9)	7.0 (4–9)	9.0 (9–9)	7.0 (5–8.5)[4]				Ex
Clinical symptoms and signs									
Pain	7.0 (6–9)	8.0 (7–9)	5.0 (3–8)	9.0 (7.5–9)	7.0 (5–7.5)[5]				In
Nausea	5.0 (4–7)	6.0 (5–7)	5.0 (2–6)	8.0 (6–9)	5.0 (3–6)[4]				Ex
Diarrhoea	6.0 (3–7)	6.0 (4–7)	4.0 (3–7)	8.0 (7–9)	5.0 (3–6)[4]				Ex
Jaundice	7.0 (5–8)	6.0 (5–8)	5.0 (4–7)	8.0 (7–9)	5.0 (4–7)[4]				Ex
Suspicion of infection	8.0 (5.5–9)[1]	7.0 (4–8.5)	5.0 (3–7)	7.0 (5–8)					Ex
Aspiration	8.0 (5–9)[1]	6.0 (3–8)	5.0 (2–7)	7.0 (5–9)					Ex
Vomiting	6.0 (5–7)[1]	6.0 (5–7)	5.0 (2–7)	8.0 (7–9)					Ex
Suggested in Round 1									
Skin (cold, clammy, pale and cyanotic)					8.0 (7–9)	8.0 (7–9)	8.0 (6–9)	9.0 (8–9)	In
C-reactive protein					7.0 (6–8)[5]	7 (6.5–8.5)	7.0 (5–8)	2.0 (1–5)	In
Relatives' concerns					6.0 (4–7)[5]	6.0 (3–7)	5.0 (2–6)	6 (5–8)	In
Reduced urine production					8.0 (6–9)[4]	8.0 (7–9)	7.0 (5–8)	8.0 (7–9)	Ex
Anxiety					4.0 (2–6)[4]	3.0 (2–6)	4.0 (2–6)	7.0 (5–9)	Ex

Note: 1–4 indicates whether a predictor was excluded based on the rating of the predetermined dimensions: 1) written comments that it is not a relevant predictor (Dimension 1); 2) inability to indicate change over time (Dimension 2a); 3) no bedside determination (Dimension 2c); and 4) written comments that it overlaps with another predictor, that it demands repeated measurements or other comments. 5 indicate non-consensus predictors included by the research group based on ratings and comments. Abbreviations: IQR: Interquartile range, CP: Clinical practice, LS: Literature search, In: Included, Ex: Excluded.

6.3 Study III

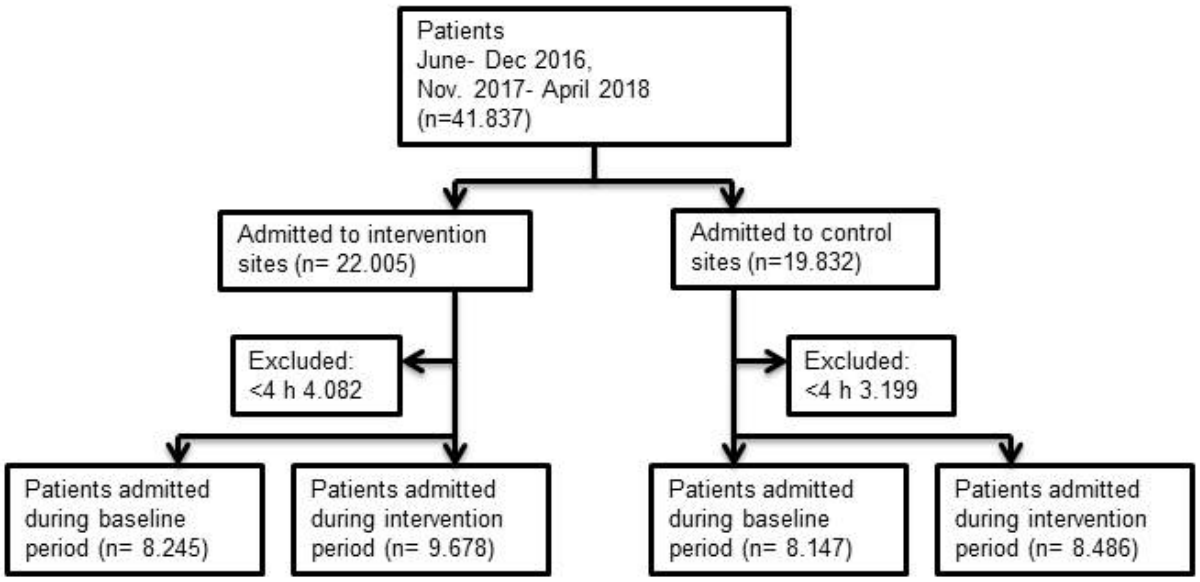
In study III, we investigated whether a situation awareness model consisting of the conventional EWS system and additional parameters of skin appearance, dyspnoea, pain, clinical intuition, patients' and relatives' concerns (present or absent) and huddles could reduce the proportion of patients with clinical deterioration.

6.3.1 Study III – Results of the intervention

6.3.1.1 Patient characteristics

All eligible patients admitted to one of the four EDs during the pre and post periods were included (N = 41,837) Figure 11. Patients hospitalised for less than 4 hours (N = 7,281) were excluded (17.4%). In total, 34,556 patients met the inclusion criteria distributed and were distributed as follows: 21,839 with two or more registered EWSs, 1,723 with no registered EWS and 10,994 with one registered EWS (Table 4). Patients with none or one EWS registered were included in the analyses as 'no clinical deterioration'. These patients had a shorter LOS in the ED and were younger, supporting the assumption of no clinical deterioration (Table 4).

Figure 11. Flow diagram illustrating in- and exclusion of patients in the study



n: number, h: hour

Table 4 Characteristics of the entire study population (Paper III, Tygesen et al. 2020, in review)

Characteristics	Intervention A	Intervention B	Control C	Control D	Only 1 EWS measured	No EWS measured
Pre intervention, n	**3,605**	**4,640**	**2,344**	**5,803**	**5,267**	**994**
Post intervention, n	**4,357**	**5,321**	**2,369**	**6,117**	**5,727**	**729**
Age, years, median [IQR]						
Pre	63 [44-76]	63 [44-77]	66 [49-79]	64 [45-77]	59 [40-74]	57 [41-73]
Post	66 [48-78]	64 [45-78]	70 [53-81]	66 [48-77]	60 [42-74]	58 [41-74]
Gender, female, n (%)						
Pre	1,897 (52.62)	2,377 (51.23)	1,188 (50.68)	3,034 (52.28)	2,759 (52.38)	479 (48.19)
Post	2,266 (52.01)	2,736 (51.42)	1,182 (49.89)	3,064 (50.09)	2,920 (50.99)	350 (48.01)
LOS ED, hours [IQR]						
Pre	14 [8-23]	15 [8-23]	14 [9-19]	12 [7-21]	7 [6-10]	7 [5-9]
Post	12 [7-22]	15 [8-23]	15 [10-20]	13 [7-22]	7 [5-10]	6 [5-9]
LOS in-hospital, days [IQR]						
Pre	2 [1-4]	1 [1-4]	2 [1-4]	1 [1-4]	1 [1-3]	1 [1-2]
Post	2 [1-4]	1 [1-4]	2 [1-4]	1 [1-4]	1 [1-2]	1 [1-1]
No of EWS measurements pr. patient stratified by EWS at admissions, median [IQR]						
EWS 0-1						
Pre	2[1-3]	2[1-3]	2[1-3]	1[1-2]		
Post	2[1-3]	2[1-3]	2[1-3]	1[1-2]		
EWS 2						
Pre	3 [2-5]	3 [2-4]	2[2-3]	2[1-2]		
Post	3 [2-4]	3 [2-4]	2[2-3]	2[1-3]		
EWS 2-4						
Pre	3 [2-5]	3 [2-4]	3 [2-3]	2 [1-3]		
Post	3 [2-4]	3 [2-4]	3 [2-4]	2 [1-3]		
EWS ≥5						
Pre	4[3-6]	3 [2-5]	3 [2-4]	2 [1-3]		
Post	4[3-6]	3 [2-5]	3 [2-4]	2 [2-3]		

Note: Characteristics of population with two or more EWS measured and one EWS measured. Intervention A and B refers to the two intervention sites and Control C and D refers to the two control sites in the study. IQR = Inter quartile range, LOS = Length of stay, ED = Emergency Department, n= number, EWS = Early Warning Score

6.3.1. 2 Clinical deterioration – primary outcome

Clinical deterioration increased from the pre period to the post period in both intervention and control groups (Table 5). The difference-in-difference regression analysis showed a significantly reduced odds of clinical deterioration (22%, OR 0.78, 95%CI [0.68; 0.9]) and significantly reduced composite clinical deterioration (21%, OR 0.79 95%CI [0.69; 0.90]) in the intervention groups compared to the control groups adjusted by EWS at admission, and by gender and age (Table 5). The risk of clinical deterioration increased mostly in patients with admission EWS 2 and admission EWS ≥ 5 when compared to admission EWS 0–1. The analysis is considered to be robust because similar results were obtained when patients with no EWS measured and one EWS measured were included in the analysis as 'no deterioration' instead of 'missing values'

Table 5. Crude and adjusted difference-in-difference analyses of clinical deterioration in patients with TOKS of ≥2 (Paper III).

	Pre	Post	Post vs Pre	Intervention vs Control
	% (n)	% (n)	OR(95% CI)	Ratio of ORs
Intervention				**Crude**
	A 20.6% (2,861)	21.7% (3,377)	1.07 (0.95; 1.21)	0.79 (0.69; 0.89)
	B 25.6% (3,321)	26.3% (3,815)	1.03 (0.93; 1.15)	p<0.001
Control				**Adjusted***
	C 16.7% (1,737)	21.1% (1,830)	1.34 (1.13; 1.58)	0.79 (0.69; 0.90)
	D 14.6% (3,254)	18.5% (3,458)	1.33 (1.17; 1.52)	p<0.001

In unadjusted analysis, N=23,653. In adjusted analysis, N=21,930 (1,723 missing data regarding their admission EWSs). OR: odds ratio; Pre: period before intervention; Post: period after intervention

* Adjusted based on EWSs for admission, gender and age.

6.3.1.2 Secondary outcomes

6.3.1.2.1 7- and 30-day mortality

Of the 34,556 patients in the study, 572 (1.6%) died within 7 days and 1,432 (4.1%) died within 30 days. Difference-in-difference regression showed no statistically significant change in 7-day mortality or 30-day mortality between the intervention and control groups (adjusted OR 0.99, 95% CI [0.7; 1.41] & adjusted OR 0.86, 95% CI [0.68; 1.08]).

6.3.1.2.2 ICU admission directly from ED

The odds of ICU admission decreased by 46% in the difference-in-difference regression (OR 0.54, 95% CI [0.29; 0.99]) in the intervention EDs compared to the control EDs. This decrease was not statistically significant when adjusted by EWS at admission and by gender and age (OR 0.59, 95%CI [0.32; 1.1]) (Table 6).

Table 6 Crude and adjusted difference-in-difference analysis of ICU admission directly from ED and 30-day readmission (Paper III)

		Pre	Post	Post vs Pre	Intervention vs Control
ICU admission directly from ED					
		% (n)	**% (n)**	**OR(95% CI)**	**Ratio of ORs**
Intervention					**Crude**
	A	0.67% (3,605)	0.37% (4,357)	0.55 (0.29; 1.04)	0.54 (0.29; 0.99)
	B	0.52% (4,640)	0.51% (5,321)	0.98 (0.56; 1.7)	p = 0.049
Control					**Adjusted***
	C	0.13% (2,344)	0.30% (2,369)	2.30 (0.6; 9)	0.59 (0.32; 1.1)
	D	0.50% (5,803)	0.65% (6,117)	1.31 (0.82; 2.1)	p = 0.098
30-day readmission					
Intervention					**Crude**
	A	5.90% (3605)	7.00% (4,357)	1.19 (0.99; 1.42)	1.11 (0.94; 1.32)
	B	7.10% (4,640)	7.40% (5,321)	1.04 (0.89; 1.21)	P = 0.202
Control					**Adjusted***
	C	6.40% (2,344)	5.70% (2,369)	0.90 (0.71; 1.14)	1.11 (0.93; 1.32)
	D	7.10% (5.803)	7.20% (6,117)	1.02 (0.88; 1.17)	p = 0.220

Note: Persons at risk are indicated by n. In the unadjusted analysis, N=34,556. In the adjusted analysis, N=32,833 (1,723 missing data regarding their admission EWSs). OR: odds ratio; Pre: period before intervention; Post: period after intervention.

* Adjusted based on EWS at admission, gender and age.

6.3.1.2.3 30-day readmission

Within 30 days, 2,378 (6.9%) patients were readmitted. No statistically significant change in 30-day readmission was found between the intervention and control groups (adjusted OR 1.11, 95% CI [0.93; 1.332]). Overall, a slight increase in readmission was observed from the pre- to post- period apart from one study site in the control group, however all changes were statistically insignificant (Table 6).

CHAPTER 7 DISCUSSION

7.1 Key findings

The overall aim of this PhD was to develop and evaluate the effect of a situation awareness model targeting clinical deterioration in a Danish adult ED population. We hypothesised that implementation of the situation awareness model could increase patient safety by reducing the number of patients with clinical deterioration.

In **study I**, we identified 36 possible generic predictors of clinical deterioration in adult ED patients based on the 24 studies included in the systematic review.

In **study II**, a panel of emergency medicine clinicians (nurses and physicians) and a research group found 19 predictors to be clinically relevant and applicable to detection of clinical deterioration in ED patients.
In **study III**, we developed and tested a situation awareness model based on ten predictors (including relatives' concerns) identified in study II, clinical intuition, patient's concerns and clinical huddles , that identified at-risk patients. We found an association between the situation awareness model and clinical deterioration suggesting that the odds of clinical deterioration were increased significantly less in the intervention EDs compared to the control EDs. No effect on the secondary outcomes of 7- and 30-day mortality and ICU admission directly from the ED and 30-day readmission was observed in the intervention group compared to the control group.

7.2 Discussion of main findings in the light of other studies

7.2.1 Predictors of clinical deterioration and the situation awareness model

Effective monitoring of patients is crucial for surveillance and early detection of impending clinical deterioration and care management. EWS systems are used as a system to support effective monitoring; however, the effects on clinical outcomes are ambiguous, and many different reasons for this have been highlighted.[7-16]

We explored possible generic predictors of clinical deterioration in adult ED patients (study I) and asked emergency medicine clinicians to rate which were clinically relevant and applicable in the ED setting (study II). This approach was used to identify possible new predictors not already included in EWS systems and to ensure the predictors ability to measure effect on clinical outcomes as suggested in previous studies.[7-10] Additionally, to ensure followership by future users of the model (clinicians) and most importantly, to develop a model for the emergency area as this has been highlighted as reasons for the ambiguous results of EWS on clinical outcomes.

We were inspired by the Cincinnati Situation Awareness algorithm[18] and had prior to both study I and study II decided to include the parameters of clinical intuition and patients' and relatives' concerns in the model. The involvement of relatives' or family's concerns is supported in another study showing that they often provide vital information.[148]

The informative value of patients expressing that they feel unwell is supported in a descriptive study of 32 experienced nurses describing characteristics in patients and the process of recognition the nurses use to recognise patients about whom the nurses are seriously worried about.[149] This study furthermore identified four patient characteristics similar to our parameters that the nurses relied on when calling a medical emergency team: feeling 'not right', skin colour, agitation and observations marginally changed or did not change at all.[149] A similar descriptive study in the emergency care setting revealed similar characteristics, but also respiratory characteristics and new or increasing pain[102]; however, these findings were based on interview of 17 nurses.

After study I and study II, the associations between clinical deterioration and the included vital signs were evident and deemed both clinically relevant and applicable by the emergency medicine clinicians. We included the following vital signs in our model (RR, oxygen saturation (SpO_2), sys BT, HR, TP and level of consciousness by APVU). Since Central Denmark Region already used a conventional EWS consisting of these parameters, we adapted this system in our model. It is a modified version of NEWS I, and the modification consists of changes in the thresholds. In addition, the information regarding supplemental oxygen is not included.[150] These changes in thresholds makes it difficult to perform direct comparisons with other EWS systems; thus, highlighting the need for a national or even an international EWS system.

The last parameters included in the model were dyspnoea, pain and skin observations, the last being suggested by the Delphi panel. Breathing problems may be detected by different approaches e.g. vital parameters and observations of the patients respiration but was included in the model as a patient reported parameter (dyspnoea) when the healthcare professionals asked if they experienced or felt breathing problems. Studies of patients presenting to the EDs indicates that patient with dyspnoea as the presenting complaint have a higher risk of mortality compared to other ED patients[151, 152]; thus, implying that it can be an early predictor of clinical deterioration.

On the other hand, dyspnoea may be correlated with the respiratory vital signs; therefore its unique contribution to clinical deterioration should be investigated further to rule out a false high score and hereby a possible unnecessary alarm. Nevertheless, it seems that patients can contribute with information's of their condition.[149] A study investigating the association between patients' subjective feeling of improvement at the first re-assessment after admission to hospital and in-

hospital mortality found it to be an independent predictor of reduced in-hospital mortality in acutely ill medical patients; the study included 403 patients and was performed in Uganda.[74] The model included the pain parameter by asking the patients if they had experienced new or escalating pain. Similar approaches have been used in other studies[153] and seems to contribute with valuable information on clinical deterioration.[102, 149]
The association of skin observations and clinical deterioration was not reported in study I. Nevertheless, skin observations are used in other EWS systems[90] and seem to be an observation that often contributes to the nurses' observations when recognising the deteriorating patient.[102, 149, 154]

We included huddles in the model to discuss patients identified to be at-risk inspired by the Cincinnati Situation Awareness algorithm.[18] Furthermore, the huddles was included to support clinician's situation awareness when the clinicians used them as short structured case management discussions with focus on essential information.[109] In our model, huddles were held twice a day, and the clinicians discussed the patients at risk, plans etc. This also provided a training opportunity where more experienced clinicians could coach less experienced clinicians. Nevertheless, only the researcher observed the huddles to support the processes and no audit for content and frequency was made. It is also important to notice that some patients suspected to be at risk of clinical deterioration were discussed with more experienced colleges before the huddles, unfortunately we are not able to report this number even though we introduced a template to collect the data. We suspect this may be explained by workload. However, this approach may assist the lees experienced staff in their clinical decision making.

To support the clinicians' communications concerning deteriorating patients, we used the communication tool ISBAR (Identification, Situation, Background, Assessment, Recommendation) as it was already implemented in the hospitals in Central Denmark Region. This tool was also suggested in a comparable study that developed a situation awareness algorithm for post-surgical patients.[20]

An important part of implementing the model was training regarding 1) the underlying process of deterioration; 2) the new parameters in the model and huddles regarding at-risk patients; 3) proactive plans, including the period of time in which one can expect the parameter to be improved; and 4) what to do if normality is not achieved. The training was supported by face-to-face discussions in the clinical setting led by the local champions and primary investigator to ensure adherence to the protocol throughout the intervention period. A mixed methods study evaluating a model for detection and management of deteriorating patients showed an increase in knowledge and confidence regarding recognition and management of deteriorating patients and a

decrease in number of concerns.[155] In addition, other studies have found that educational interventions to support staff members' clinical decision-making and judgment are beneficial.[156] We did not investigate staff members' clinical decision-making, although it is likely that not only the afferent and efferent limbs in the model but also training, and the subsequent clinical decision-making, may affect clinical outcomes. Also, we did not examine the effect of the single sub-components in the model; thus, we cannot provide information about them.

When comparing our situation awareness model to other EWS systems or models targeting clinical deterioration, it appears that such a model in combination with clinical huddles and a structured communication tool has not previously been tested. The most comparable model is the Cincinnati Situation Awareness algorithm.[18] In this study a high reduction of almost 50% (4.4 to 2.4 transfers per 10,000 non-ICU inpatient days) in unsafe transfers to an ICU was found in children.[18]

Unsafe transfers was defined as '*transfer from an acute care floor to an ICU where the patient received intubation, inotropes, or ≥ 3 fluid boluses in first hour after arrival or before transfer*'.[18] They also found an increase in days between serious safety events defined as severe harm or death after variation from expected practice.[18] It is not possible to draw direct parallels to the result in our study because we only looked at adults.

Other comparable models are the Dutch Early-Nurse-Worry-Indicator-Score (DENWIS)[19] which was tested in in-hospital settings.

The study of the DENWIS model revealed a high AUROC (0.81) when studying Worry as a predictor of the composite outcome of unplanned ICU admission/High Dependency Unit admissions or unexpected mortality. The DENWIS model (0.85) had a lower AUROC than the EWS (0.86). Adding Worry and the EWS to the DENWIS model resulted in higher AUROCs (0.87 and 0.91, respectively) compared with the EWS solely based on vital signs.[19] We have not yet studied the AUROC in our model; however this should be done in future studies to determine the value of the entire model as well as the contribution of each of the included parameters in the model.

Finally, the Surveillance Algorithm for Post-Surgical Patients despite developed for surgical patients.[20] Unfortunately, it is not possible to compare the findings of this study with our findings as it has so far only been reported by interviews based on few data. However, when quantitative results from the Surveillance Algorithm for Post-surgical Patients study are published, it will be interesting to compare them with ours as they used a model very similar to our situation awareness model.

Nevertheless, we hypothesised that implementing our situation awareness model would increase patient safety by reducing the number of patients with severe clinical deterioration. The proportion of clinical deterioration observed in patients in the EDs in both periods is similar to the proportions observed in other studies. [35-38] We found that the odds for clinical deterioration of patients were reduced in the intervention EDs compared to the control EDs.

7.2.2 Biochemical tests

We chose not to include biochemical tests and comorbidities in our first version of the situation awareness model due to the following reasons. First, it was crucial that information related to the parameters would be available within a short timeframe. Second, due to economic and organisational reasons such as costs associated with and/or access to relevant point-of-care equipment available for bed-side use.

Also, ethics was discussed regarding whether we should implement biochemical tests like arterial blood gas in all patients attending the ED. As mentioned in **study I**, new studies on biochemical tests have been published since we conducted our literature review in 2016, the results of which must be taken into account when testing a model that includes biochemical tests. However, adding biochemical tests to EWS systems has been the subject of much debate and investigation and has not always shown to improve outcomes.[157, 158]

We did not find any effect on mortality, readmissions or ICU admission, although we did observe a decrease in ICU admissions in the intervention groups. It is possible that adding biochemical tests would have affected these outcomes as they were found to be strong predictors in **study I,** and biochemical tests involving S-C-reactive protein, S-bicarbonate, S-lactate, S-pH, S-potassium, glucose, S-leucocyte counts and S-haemoglobin were rated as relevant and applicable by the clinicians in **study II**. In addition, studies published after the performance of the systematic literature review in **study I** may have contributed with valuable knowledge in this regard.

We found that bicarbonate and lactate were the strongest biochemical predictors of clinical deterioration in **study I**. However, more recent biomarkers may have lead to even better predictions. Hence, it is necessary to further examine how biochemical predictors may contribute to even earlier identification of deteriorating patients. As an example pro-adrenomedullin, a biomarker of inflammation, has shown to be a strong predictor, particularly with regard to all-cause 30-day mortality.[159] Moreover, the ability of copeptin (a biomarker of stress) and procalcitonin (a biomarker of infection) levels to identify patients at risk of high treatment urgency has been studied and may contribute with further information.[159]

Non-specific prognostic biomarkers, such as soluble urokinase plasminogen activator receptor (suPAR), have been investigated in the context of emergency medicine in combination with the

National Early Warning Score (NEWS), age and sex and were shown to improve predictions of in-hospital, 30-day and 90-day mortality compared to NEWS, age and sex.[66] The findings suggest that suPAR is superior to age, albumin, C-reactive protein and haemoglobin in the prediction of 30-day and 10-month mortality,[21, 160] hence, may also be a relevant predictor.

7.3 Methodological considerations

The following sections discuss internal validity in relation to the three studies' and the final model regarding designs, data collection, bias, confounding and missing data. External validity is also discussed, with focus on generalisability.

7.3.1 Study I

Study I was a systematic review aiming to identify generic predictors of clinical deterioration in adult ED patients.

The review was performed and reported in accordance with the PRISMA guidelines.[111, 161]

First, we sought to minimise publication bias by including studies in languages other than English. Although unique results are often published in English-language journals, we may have overlooked important knowledge published in languages not included in this study.[162]

Second, in contrast to the PRISMA recommendations, one person initially assessed titles and abstracts to screen papers for legibility, and one person initially extracted the data, which, however, was assessed by a second reviewer. The screening was based on a predetermined guide, and if any questions arose, the study was assessed by the second reviewer. This may have led to some studies being overlooked (i.e. selection bias)[111, 161], although the guidelines ensured that the reviewer adopted a systematic approach with regard to simple issues such as population (e.g. age) and setting (e.g. out-of-hospital cardiac arrest). Even though the data were assessed by the second reviewer, the fact that only one reviewer extracted data may have introduced a small, but unlikely, risk that data were not extracted.[111, 161]

Third, as we only searched the published literature, we may have overlooked predictors in the unpublished literature.[111, 161] Importantly, only observational studies were included in the review because the risk factors or predictors we searched for were primarily reported in cohort studies. In observational studies, the risk of confounding and causal conclusions is especially important to

consider.[163] Thus, this was taken into account during quality assessment by increased attention to questions related to this area. We investigated only the association between predictors and clinical deterioration, not causality.

Fourth, in the review, we identified predictors often studied in subgroups of the ED population, which introduced a risk of potential selection bias (e.g. patients may be healthier or more ill than typical patients from the population). Furthermore, this may hamper the clinical applicability in a general ED setting

Fifth, we only included studies that discussed ICU admissions directly from the ED, and we made a pragmatic choice to impose a maximum of 30-day mortality (excluding studies only reporting, e.g. 1-year mortality) to increase the likelihood that death was related to events in the ED. Moreover, multiple studies reporting other outcomes or conducted on in-patient units were excluded.

Sixth, the large number of studies not fulfilling the inclusion criteria in the review demonstrates the degree of difficulty in constructing a concise search strategy in this area. This is mainly considered to be due to a huge variability in the terms used for clinical deterioration and the substitute terms used instead. The inconsistency in the terms applied may have increased the risk of missing relevant studies in our search. We sought to minimise this risk by applying an initial search for terms applied in the databases, followed by a search in the databases based on all the identified terms, and lastly, by systematically searching cross-references in already included studies.

Seventh, we were not able to strengthen the evidence by combining data due to the heterogeneity of studies primarily because of the use of different subgroups (population) and study designs (i.e. selection bias).

The focus was to identify generic predictors of clinical deterioration that could be applied across an unselected adult ED patient population. However, it is important to notice that risk stratification tools for specific subgroups may provide more accurate risk estimation in symptom-specific patient groups. Accordingly, our study implies the difficulties in identifying predictors applicable in the ED population as a whole.

Except for the inclusion of studies in which the Glasgow Coma Score was applied, we only included studies investigating non-compounded predictors to ensure that the isolated association related to a single predictor was estimated. This was to form the basis for assessment of whether

adding a predictor to existing EWS systems could potentially advance the system's ability to detect clinical deterioration.

Finally, it is important to note that our literature search was performed at the beginning of the PhD study and served as the background for subsequent studies. Thus, recent studies are not included.

In the manuscript drafting process, we re-assessed all the included studies, which led to exclusion of studies based on population criteria such as, e.g. age, and this could have led to exclusion of studies that had at first been rated as relevant and thereby also exclusion of predictors.

7.3.2 Study II

In the Delphi study, we used a panel of clinicians in emergency medicine to select predictors of clinical deterioration that are considered relevant and applicable in the clinical ED settings. The Delphi method has contributed to a systematic and anonymous consensus process that strengthened the reliability of the knowledge accumulated from the participating clinicians and, consequently, the predictors selected. The Delphi process has limited the bias often occurring in face-to-face processes favouring the leading expert's opinion or preferences.[114, 164, 165]

The level of expertise and the number of participants in the panel are considered important for a reliable outcome.[164] The use of experts or clinicians in Delphi processes is much debated, although it has been recommended that participants to some extent should be experts who reflect current knowledge and views.[165] However, a study of Delphi methodology in health research suggested a minimum of 3 years of experience within the studied area.[164] We used panellists with a minimum of 2 years of experience in the ED that were to be working in the ED at the time of the survey. This was to ensure that the clinicians had a minimum of knowledge and were aware of the newest guidelines and organisation. Yet, this is less experience than recommended and may potentially have hampered the ability to reach consensus regarding the predictors. In our study, we wanted a geographic representation from different parts of Denmark and from the emergency medicine field. Hence, we invited nurses and physicians working with patients in the ED through professional organisations. Still considerations of homogeneity or heterogeneity must be considered, and we determined that a diverse panel would lead to better performance by allowing for wider ranges of alternatives and perspectives.[165] Additionally, the anaesthesiologists were asked to focus their assessment on patients with deterioration in the ED. We found it crucial that they were involved in the selection of predictors as they are often involved in assessments of the most critically ill patients in the EDs, thus contributing knowledge of the patients and risk factors.

A wide variation in numbers of panel members is found in Delphi studies, and there seems to be no clear recommendations hereof. [164, 165] However, their willingness to contribute is considered crucial for the process and outcomes, which was the approach we undertook when inviting participants rather than the numbers of invited.

The predictors included in the Delphi study were identified in the systematic review (**study I**). To account for predictors that we may have overlooked e.g. from the unpublished literature, or that have not yet been studied, the panelists were asked to suggest clinically relevant and applicable predictors.

As previously mentioned in section 7.3.1, some predictors were excluded from the systematic review (paper 1) due to a re-assessment of all the studies during the manuscript drafting process. Unfortunately, this meant that the predictors capillary refill, pain, jaundice, diastolic blood pressure, an ECG, dyspnoea, bilirubin, creatinine, thrombocytes and erythrocytes were incorrectly included in the Delphi process and may have introduced a potential risk of selection bias. Apart from pain, dyspnoea and an ECG, all the others were excluded by the panellist in the Delphi process. Thus, they did not bias the results. The three included predictors were found to have a significant association with clinical deterioration in subgroups of adult ED patients and, moreover, were rated as relevant and applicable by the panellists. Hence, we find this shortcoming to be of minor importance for the overall findings of clinical relevance and generic and applicable predictors of clinical deterioration in EDs.

The association between the predictors and clinical deterioration was established in the systematic review (paper I), but we chose not to let the panel assess the scientific strength (effect size) to ensure that the ratings were based on the panels' clinical experience and knowledge and the predictors' applicability to standard care in ED setting.

Another method could have been to use statistical selection of predictors or variables by repeated testing between models yielding the forward selection or backward elimination of variable selection algorithms[166], but that approach might have compromised the clinical perspective, transferability and applicability of the results. The last mentioned was considered to be of particular importance as we wanted to ensure high adherence to the predictors when applied to the model in study III. Thus, the panellists were asked to rate the clinical relevance and applicability of the proposed predictors for detecting deteriorating patients in ED settings.

A methodical weakness of the Delphi study is uncertainty of the appropriate number of voting rounds. Even though many studies have used two rounds[113], it has been argued that this may not be sufficient to achieve stability and that at least three rounds are preferable.[164] We purposely

chose to perform two rounds as more rounds may decrease participation between voting rounds, increase random error and reduce accuracy.[167] Moreover, it has been shown that the highest increases in consensus and feedback concerning accuracy occur between the first and second round.[167]

In line with other Delphi studies[139, 168, 169], we decided to use medians and IQRs to establish consensus as they are considered more robust regarding the effect of outliers and stronger than standard deviations.[170]

The research group excluded 16 predictors and included five predictors for which consensus was not reached. The method of selection was primarily based on the Delphi panel's comments; however, this approach may have influenced the final selection of predictors. Considerations must be directed toward the questions asked in round two as round one can generate comprehensive information when applying the group comments, scores and new predictors to be rated in round two. The extra material needing assessment in round two may lead to dropouts.[164] We used the research group to ensure that questions not considered to be relevant were not skipped until the second round based on the written comments, and to ensure that a final decision on predictors not reaching consensus was made.

Analysis of missing responses among panelists revealed an unequal drop out among the emergency nurses and physicians compared to the anaesthesiologists. To account for a possible association between the panel's voting and professional background, we performed a sub-analysis, which indicated minimal influence on inclusion/exclusion of predictors because of profession.

Despite the abovementioned limitations in this study, we believe that the selected predictors are relevant and applicable in regard to clinical deterioration in patients in the Danish ED setting and may have the potential to increase patient safety.

7.3.3 Study III

The aim of study III was to investigate the effect of a situation awareness model on clinical deterioration.

7.3.3.1 Intervention

Several studies have investigated the effect of EWS systems in EDs, revealing evidence on the ability to predict clinical deterioration although with ambiguous results regarding clinical outcome.[45-54] Different explanations have been suggested to explain the effect on the clinical outcomes such as, e.g., lack of protocol adherence due to workload, lack of situation awareness, insufficient monitoring, poor communication and requirements of technical and non-technical skills.[7-16]

7.3.3.1.1 The intervention

Few studies of the EWS systems included additional predictors to enhance the effect on the EWS systems. Other approaches were, therefore, needed to enhance the effect on EWS systems regarding clinical outcomes.

Study I and study II investigated possible generic predictors of clinical deterioration in EDs narrowed down to 19 predictors rated as clinically relevant and applicable in the ED setting. Even though narrowed down to 19 predictors, it was considered to be unrealistic to assess these in an everyday clinical ED setting. Hence, the research group in this PhD project decided to include only ten predictors and clinical intuition as decided a priory. Clinical intuition and patients' and relatives' concerns were inspired by the Cincinnati Situation Awareness algorithm[18]; however, the latter was also suggested and included in the Delphi study. Thus, they were not investigated in ED settings and the predictive ability was not determined.

It maybe that including some of the other identified predictors from the Delphi study would have enhanced the EWS system even more; however, compared to other studies regarding EWS systems in EDs, the strength of this present design was inclusion of predictors rated relevant by clinicians in the field. In addition, the use of a situation awareness focus, communication of the patients' conditions (huddles and ISBAR) and a more proactive approach to what to do next (escalation plan) was a strength.

7.3.3.1.2 Design

The study was designed as a controlled pre and post study, also defined as quasi-experimental studies measuring performance before and after an intervention to investigate valid causal inferences. These studies are often easier to conduct and more feasible for complex settings than randomised controlled trials, but with lower internal validity and generalisability.[171] To strengthen the study and account for the risk of bias, we included two control EDs and two intervention EDs so we could visualise all influences during the period, allowing a more precise estimation of period effects.[171]

7.3.3.1.3 Main finding

We observed an increased proportion of patients with clinical deterioration in the post period compared with the pre period in all four EDs, with the largest increase in the control group. No changes in registration practice or in the organisation of the EDs were reported that could explain the results. Furthermore, there was no increase in the number of EWS measurements, which could have explained why more patients with clinical deterioration were observed. However, a general increase in age between the pre and post periods was observed, and there has been great focus on visitation and prevention of acute admissions in the last few years. This may have led to a more complex study population in the post period. The increase in the proportion of patients who clinically deteriorated in both groups in the post period may also in part be explained by a period effect or seasonal variation due to more winter months in the post period than in the pre period.[172] This maybe also explain why we observed a numerical increase in mortality.[25] In the primary analyses, we did not include information on how the patients presented to the ED or whether the patient belonged to a medical or surgical specialty, which may have provided further information on case mix between groups as a possible explanation in line with a previous study.[173] Nevertheless, the increase in the proportion of clinical deterioration was even higher in the control groups than in the intervention groups, supporting the contribution of the situation awareness model.

We only found a significant effect on clinical deterioration but not on the secondary outcomes of ICU admission, mortality or readmissions. We defined a clinical deterioration as an increase in the EWS score and did not consider an equally high EWS score at the next measurement as deterioration even though this is found to increase the risk of in-hospital cardiac arrest.[75] Additionally, we only considered ICU admissions directly from the ED and not ICU admission occurring shortly after transport from the ED to an inpatient unit which also might have increased the number of ICU admissions.

Despite the use of an electronic template to register the modified EWS and corresponding actions, it was not possible to track adherence to the protocol nor whether all parts of the intervention were applied. Additionally, no systematic investigation regarding resource utilisation was performed; thus, we are not able to report how many times physicians were called to assess a patient in the post period compared to the pre period.

The results must be interpreted with caution. Internal validity was increased by including EDs from the same region; thus, all EDs were subject to the same regional policies. Due to the risk of bias regarding referral patterns, the mix of cases and structural changes, we controlled for

severity, age and gender and tracked changes that could affect outcomes in the EDs during the study periods. External validity was strengthened by the long control and intervention periods.

We believe that the unselected cohort of admitted medical and surgical patients from the four EDs supports the generalisability of the results. No patients were lost during follow-up due to the Civil Personal Registration numbers available in Denmark. We excluded 7,281 patients with LOS of less than 4 hours to avoid contamination with less severe patients and thus reduced the comparability between EDs. This decision limits the generalisability to EDs in which patients are observed and treated for more than 4 hours.

To account for vital signs entered without a TP, which was not associated with a registered EWS, we generated a surrogate EWS by substituting the missing value with 0 (normal)based on the assumption that it was unrecorded due to a lack of fever. This was only done for 285 observations, thus not considered to greatly influence the EWS level.

We observed 1,723 patients for whom no EWS was registered and 10,994 patients for whom one EWS registered. These patients were younger and had a shorter admission time, indicating lower severity. When patients with one or no EWS were included in the analysis as 'no deterioration', the effect was not changed, indicating that the analysis is robust and there is no contamination of patients with less severe injury or illness between or within groups. Differences in LOS were observed between the EDs, but each group contained one ED with longer in-hospital LOS, and thus not expected to substantially influence the results.

Overall, our findings suggest that additional parameters and huddles offer more information than that provided by the standard EWS system and usual clinical assessments.

7.4 Model

The strength of the design of this situational awareness model was the establishment of the predictors' ability to detect clinical deterioration. Furthermore, the involvement of the clinicians in pointing out the most relevant predictors is believed to strengthen the applicability in the clinical setting. Identifying predictors in the literature, by chart reviews or interviews, is another way to develop a model[18, 168, 174] and provides good understanding of the way it functions in a clinical setting; however, it does not provide information on the predictors' correlations or effect size. We could have identified possible predictors in a dataset, but secondary or administrative data sources must often be utilised because datasets with study endpoints and all key predictors are not available. Depending on the purpose of a prediction model, cross-sectional, longitudinal or

prospective cohort data can be utilised for predictor identification. The predictor selection would then be established by its ability to predict sensibility; however, the numbers of predictors may decrease the efficiency, feasibility and convenience of the model and therefore also requiring an experts' judgement of clinical relevance. Subsequently, a model generation must be provided by a statistical method, e.g. a step-wise selection to remove non-significant predictors. To establish the model's final power, it should be tested in different datasets and eventually tested in different populations.[175] Further exploration is needed to understand possible correlations between the parameters included in our model; moreover, to be able to weight the additional parameters besides the vital signs. This may also add to identifying predictors not contributing with unique information to the model and thereby reduce the numbers of alarms.[175]

We believe it is crucial to involve clinicians in selection of predictors to ensure causality and adherence to the protocol; otherwise there is an inherent risk that clinicians simply do not use the final model.

7.5 Generalisability

As described, the different studies have several strengths and weaknesses. In **study I**, external validity is strengthened by the fact that the predictors are identified in ED settings and represent different subgroups of the ED population. In **study II**, external validity was strengthened by the large number of clinicians participating in the panel who came from different professions and thus had different opinions regarding the clinical relevance of the predictors of deteriorating ED patients. Anaesthesiologists were overrepresented in the panel, but their ratings were similar to those of the other clinicians and therefore did not compromise validity. In **study III**, the results regarding the effect of the situation awareness model on clinical deterioration must be generalised with some caution, as all the included hospitals are located in the same region and hence may not be representative of hospitals in other Regions of Denmark or ED settings abroad. Regional contexts must be considered further when discussing the applicability of the results to all Danish EDs; however, these are considered to be minor.

CHAPTER 8 CONCLUSION

The conclusions of the three studies reported in this dissertation are summarised below. They must be interpreted in the context of the considerations discussed in the previous section.

The overall aim of this dissertation was to develop and investigate the effect of a situation awareness model targeting clinical deterioration. It contributes to the existing knowledge on EWS systems and the effect of additional parameters and huddles on patient outcomes.

- In the systematic literature review we identified 36 predictors significantly associated with clinical deterioration in adult ED patients. The predictors comprised presenting complaints, vital signs, biochemical tests, comorbidities and other predictors, all reflecting the complexity of the nature of the deteriorating patient. Data were narratively synthesised due to clinical heterogeneity caused by differences in study design, subgroups and outcome measures, thereby affecting the ability to compare and combine data from the different studies. Our findings imply that further attention should be paid to the use of vital signs, biochemical tests and comorbidities as predictors of clinical deterioration. However, the potential of the predictors to assist in managing the deteriorating patients and thereby improve clinical outcomes needs further investigation.

- In a Delphi study, clinicians rated clinical relevance and applicability of predictors identified in the literature and newly suggested predictors' for use in the ED settings. Nineteen potential predictors of clinical deterioration widely regarded as clinically relevant and applicable were selected. The predictors was classified into three categories: biochemical tests (serum C-reactive protein, serum bicarbonate, serum lactate, pH, serum potassium, glucose, leucocyte counts and serum haemoglobin); vital signs and parameters (respiratory rate, saturation, systolic blood pressure, altered mental state, pulse rate, dyspnoea, an ECG and TP); and clinical observations and parameters (skin conditions, pain and relatives' concerns).

- In a controlled pre and post study designed to investigate whether adding additional parameters, skin observations, dyspnoea, pain, clinical intuition, patients' or relatives' concerns and huddles to the conventional EWS, could reduce the proportion of clinical deterioration through earlier identification of the deteriorating patient. We found a reduction of the odds of clinical deterioration compared to the standard EWS system, suggesting association of reduced risk of clinical deterioration when applying the modified EWS comprising a situation awareness model. No impacts on the secondary outcomes of 7-

or 30-day mortality, ICU admissions directly from the ED or readmission within the unselected ED population could be established.

In conclusion, our findings imply that a situation awareness model consisting of a conventional EWS system and the addition of simple clinical characteristic, patients and relatives concern, clinical intuition and clinical huddles, provide more information on the clinical deterioration than the conventional EWS system and traditional clinical assessments of clinical deterioration.

CHAPTER 9 PERSPECTIVES AND FUTURE RESEARCH

This dissertation provides knowledge about simple clinical and subjective parameters and huddles that may enhance the effect of conventional EWS system to detect patients at risk of clinical deterioration in EDs.

Furthermore, the findings also raise several issues that may need further considerations.

Our results indicate that the situation awareness model had a positive impact on clinical deterioration, although not on the secondary outcomes of ICU admission, mortality and readmission. Future investigations should include analysis of patients with the same high EWS during admission as a 'worsening' in clinical deterioration as it seems that a high EWS at admission without an observed decline may introduce a high risk of adverse outcomes such as ICU admission and death. It can be discussed whether a positive effect on ICU admission should be a decrease or an increase depending on the patient's needs, it may be positive if a patient needing intensive care is transferred earlier, and it may be positive if more patients are transferred to ICU if they need this step up in treatment, safe transfers in contrast to unsafe. We did not find any effects on the proportion of ICU admission; however, it would be interesting to examine whether there was a change in the time spent in the ICU. Additionally, it would be interesting to include data in the analysis regarding admission to an ICU shortly after arrival to the in-patient unit.

Our study also highlights the importance of considering period influences when planning new studies in situations where an RCT is not possible. Hence, we recommend inclusion of control departments if planning a pre and post study.

Furthermore, weighting of the predictors should be established to ensure that all predictors provide unique information and no unnecessary alarms.

Our situation awareness model was setup to support different processes in identifying and escalating the patients at risk of clinical deterioration. It was meant to serve as a guide in observations supporting perception, comprehension, and projection to decide and act upon the patient's condition. All to support the clinician's non technical skills and situation awareness. We did not investigate the effect on situation awareness hence the model's impact on the staffs' situation awareness should be elaborated to understand how data are gathered, how staffs reflect on observations, initiation of appropriate interventions and projecting potential outcomes (the three steps in situation awareness) and if these steps are supported by the model. This information may contribute to understand the issues related to identifying clinical deterioration and escalation and further understanding of the models effect, need for improvement and how to further support the clinician's situation awareness. Further investigations should also examine how the clinical decision-making effects the model to understand how to encourage staff members to adhere to the algorithms, rely on their clinical intuition and provide proactive treatment. We plan to further explore how nurses' clinical intuition and patients' and relatives' concerns contribute to identifying and responding to patients at risk of clinical deterioration, building on the findings in this thesis and a study of the healthcare professionals' situational awareness. The impact of increased situation awareness and the use of intuition and concern to reduce clinical deterioration will be compared to conventional early warning systems and tested in a clinical controlled study design.

The results of the systematic review imply that attention should be paid to vital signs, biochemical tests and comorbidities when assessing the patients at risk of clinical deterioration. This information is highly relevant in the light of today's ageing population, which is associated with more comorbidity and thus increased complexity of treatment in EDs and the increasing access to point of care tests. It seems that both comorbidities and biochemical tests highly increase the risk of clinical deterioration, and these parameters may enhance the detection of deteriorating patients even further when combined with the EWS system or even the present situation awareness model.

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APPENDICES 1 - 6

1. Search strategy

2. Search strategy Systematic Review

3. Pocket card – 'lommekort' (Danish version and English version)

4. Guideline – 'retningslinje'

5. Education programme

6. Template in EMR

1. Search strategy for Background section

Search	PubMed	Hits
Search 1. **Clinical deterioration**	(((((((("Emergency Service, Hospital"[Mesh]) OR (((ED) OR "short stay unit") OR Emergency department))) OR "Subacute Care"[Mesh]))))) AND (("Intuition"[Mesh]) OR "Clinical intuition"))) NOT ((((((((((("Emergency Service, Hospital"[Mesh]) OR (((ED) OR "short stay unit") OR Emergency department))) OR "Subacute Care"[Mesh]))))) AND (("Intuition"[Mesh]) OR "Clinical intuition")) AND ((infant[MeSH] OR child[MeSH] OR adolescent[MeSH])))) OR pediatric)	
Search 2. **Early warning score system**	((((((EWS) OR early warning score) OR (("track and trigger")))) AND (((ED) OR "short stay unit") OR Emergency department))) NOT ((((((((EWS) OR early warning score) OR (("track and trigger")))) AND (((ED) OR "short stay unit") OR Emergency department)) AND ((infant[MeSH] OR child[MeSH] OR adolescent[MeSH])))) OR pediatric)	
Search 3. **Rapid response systems**	((("Rapid response systems") AND (ED OR "short stay unit" OR Emergency department))) NOT (((((("Rapid response systems") AND (ED OR "short stay unit" OR Emergency department)) AND ((infant[MeSH] OR child[MeSH] OR adolescent[MeSH])))) OR pediatric)	
Search 4. **Clinical intuition**	(((((((("Emergency Service, Hospital"[Mesh]) OR (((ED) OR "short stay unit") OR Emergency department))) OR "Subacute Care"[Mesh]))))) AND (("Intuition"[Mesh]) OR "Clinical intuition"))) NOT ((((((((((("Emergency Service, Hospital"[Mesh]) OR (((ED) OR "short stay unit") OR Emergency department))) OR "Subacute Care"[Mesh]))))) AND (("Intuition"[Mesh]) OR "Clinical intuition")) AND ((infant[MeSH] OR child[MeSH] OR adolescent[MeSH])))) OR pediatric)	
Search 5. **Situation awareness**	((("Situation awareness") AND ((("Emergency Service, Hospital"[Mesh]) OR (((ED) OR "short stay unit") OR Emergency department))) OR "Subacute Care"[Mesh]))) NOT (((((("Situation awareness") AND ((("Emergency Service, Hospital"[Mesh]) OR (((ED) OR "short stay unit") OR Emergency department))) OR "Subacute Care"[Mesh])) AND ((infant[MeSH] OR child[MeSH] OR adolescent[MeSH])))) OR pediatric)	
Search 5. Safety attitude questionnaire	((((((((ED) OR "short stay unit") OR Emergency department)) OR "Emergency Service, Hospital"[Mesh])) AND "safety attitude questionnaire")) NOT pediatric	

PubMed was searched using medical subject headings (MeSH) and/ or free-text when appropriate using "AND/OR" combinations. Titles and abstracts were reviewed and relevant papers for full-text reading were selected. Meta-analysis, systematic reviews, case-control, original experimental and

observational studies were included. Case reports, comments and overviews were excluded.

In search 1, the focus was to define clinical deterioration.

In search 2, the focus was to describe the content of the early warning score systems in EDs, the effect and reasons for lack of effect.

In search 3, the focus was to describe rapid response systems to capture differences between the early warning score system.

In search 4, the focus was to describe and define clinical intuition and in search 5, the focus was to describe and define situation awareness.

In search 6, the focus was to describe the safety attitude questionnaire.

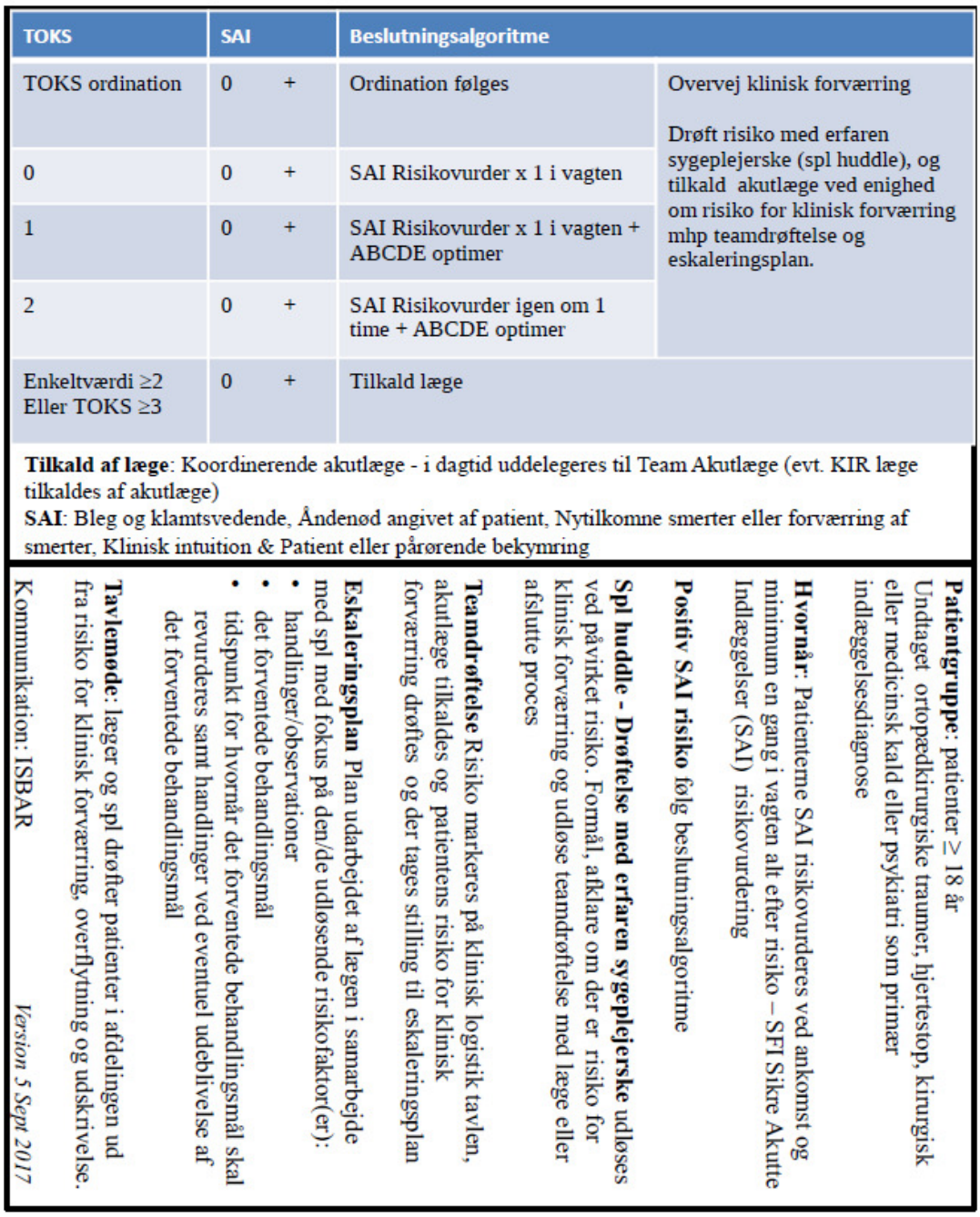
The reference lists in the selected papers were reviewed to identify additional relevant papers.

2. Search strategy Systematic Review
Example of search strategy used in PUBMED

((((((("Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh]) OR "Clinical Trial"[Publication Type]) OR ("Observational Studies as Topic"[Mesh] OR "Observational Study"[Publication Type])) OR "Random Allocation"[Mesh]) OR "Double-Blind Method"[Mesh]) OR "Single-Blind Method"[Mesh]) AND ((((((((((("Clinical deterioration"[All Fields] OR deteriorated[All Fields]) OR deterioration[All Fields]) OR deteriorations[All Fields]) OR "deteriorating patients"[All Fields]) OR "deteriorating patient"[All Fields]) OR worsening[All Fields]) OR "critical condition"[All Fields]) OR "critical conditions"[All Fields]) OR deteriorate[All Fields]) OR ((((((((((((((("Adverse outcome"[All Fields] OR "Adverse outcomes"[All Fields]) OR "Adverse medical events"[All Fields]) OR "Adverse medical event"[All Fields]) OR "adverse event"[All Fields]) OR "adverse events"[All Fields]) OR "safety event"[All Fields]) OR "safety events"[All Fields]) OR "Heart Arrest"[Mesh]) OR "Respiratory suppression"[All Fields]) OR "Respiratory depression"[All Fields]) OR "respiratory arrest"[All Fields]) OR "Death, Sudden"[Mesh]) OR "Death, Sudden"[All Fields]) OR "Death"[Mesh]) OR "Death"[All Fields]) OR ((((("admissions"[All Fields] OR "admission"[All Fields]) OR "transfers"[All Fields]) OR "transfer"[All Fields]) AND (((((("Critical Care Nursing"[Mesh] OR "Critical Care Nursing"[All Fields]) OR "Intensive Care Units"[Mesh]) OR "Intensive Care Units"[All Fields]) OR "Critical Care"[Mesh]) OR "Critical Care"[All Fields])))) AND (("acute admission unit"[All Fields] OR "acute medical unit"[All Fields]) OR ((((("emergency service, hospital"[MeSH Terms] OR ("emergency"[All Fields] AND "service"[All Fields] AND "hospital"[All Fields]) OR "hospital emergency service"[All Fields] OR ("emergency"[All Fields] AND "department"[All Fields]) OR "emergency department"[All Fields]) OR (("accidents"[MeSH Terms] OR "accidents"[All Fields] OR "accident"[All Fields]) AND ("emergency medicine"[MeSH Terms] OR ("emergency"[All Fields] AND "medicine"[All Fields]) OR "emergency medicine"[All Fields]))) OR ("emergency service, hospital"[MeSH Terms] OR ("emergency"[All Fields] AND "service"[All Fields] AND "hospital"[All Fields]) OR "hospital emergency service"[All Fields] OR ("accident"[All Fields] AND "emergency"[All Fields] AND "department"[All Fields]) OR "accident and emergency department"[All Fields])) OR ("emergency medical services"[MeSH Terms] OR ("emergency"[All Fields] AND "medical"[All Fields] AND "services"[All Fields]) OR "emergency medical services"[All Fields]))))) AND ((((((("risk assessment"[MeSH Terms] OR "risk assessment"[All Fields]) OR ("precipitating factors"[MeSH Terms] OR ("precipitating"[All Fields] AND "factors"[All Fields]) OR "precipitating factors"[All Fields] OR "triggers"[All Fields])) OR ("risk factors"[MeSH Terms] OR "risk factors"[All Fields])) OR predictor[All Fields]) OR predictors[All Fields]) OR prediction[All Fields])) AND (Danish[lang] OR English[lang] OR Norwegian[lang] OR Swedish[lang])

3.1 Pocket card (in Danish "lommekort")

Danish version used in the study, see English version on the next page



TOKS	SAI		Beslutningsalgoritme	
TOKS ordination	0	+	Ordination følges	Overvej klinisk forværring Drøft risiko med erfaren sygeplejerske (spl huddle), og tilkald akutlæge ved enighed om risiko for klinisk forværring mhp teamdrøftelse og eskaleringsplan.
0	0	+	SAI Risikovurder x 1 i vagten	
1	0	+	SAI Risikovurder x 1 i vagten + ABCDE optimer	
2	0	+	SAI Risikovurder igen om 1 time + ABCDE optimer	
Enkeltværdi ≥2 Eller TOKS ≥3	0	+	Tilkald læge	

Tilkald af læge: Koordinerende akutlæge - i dagtid uddelegeres til Team Akutlæge (evt. KIR læge tilkaldes af akutlæge)
SAI: Bleg og klamtsvedende, Åndenød angivet af patient, Nytilkomne smerter eller forværring af smerter, Klinisk intuition & Patient eller pårørende bekymring

Patientgruppe: patienter ≥ 18 år
Undtaget ortopædkirurgiske traumer, hjertestop, kirurgisk eller medicinsk kald eller psykiatri som primær indlæggelsesdiagnose

Hvornår: Patienterne SAI risikovurderes ved ankomst og minimum en gang i vagten alt efter risiko – SFI Sikre Akutte Indlæggelser (SAI) risikovurdering

Positiv SAI risiko følg beslutningsalgoritme

Spl huddle - Drøftelse med erfaren sygeplejerske udløses ved påvirket risiko. Formål, afklare om der er risiko for klinisk forværring og udløse teamdrøftelse med læge eller afslutte proces

Teamdrøftelse Risiko markeres på klinisk logistik tavlen, akutlæge tilkaldes og patientens risiko for klinisk forværring drøftes og der tages stilling til eskaleringsplan

Eskaleringsplan Plan udarbejdet af lægen i samarbejde med spl med fokus på den/de udløsende risikofaktor(er):
- handlinger/observationer
- det forventede behandlingsmål
- tidspunkt for hvornår det forventede behandlingsmål skal revurderes samt handlinger ved eventuel udeblivelse af det forventede behandlingsmål

Tavlemøde: læger og spl drøfter patienter i afdelingen ud fra risiko for klinisk forværring, overflytning og udskrivelse.

Kommunikation: ISBAR

Version 5 Sept 2017

3.2 English version, only translated for display in this dissertation

<table>
<tr><th>TOKS</th><th>SEA</th><th colspan="2">Decision algorithm</th></tr>
<tr><td>TOKS prescription</td><td>0 +</td><td>Prescription is followed</td><td rowspan="5">Consider clinical deterioration

Discuss risk with experienced nurse (nurse huddle) and call emergency physician if you agree on risk of clinical deterioration for the purpose of initiating team discussion and escalation plan.</td></tr>
<tr><td>0</td><td>0 +</td><td>SEA Risk assessment x 1 during shift</td></tr>
<tr><td>1</td><td>0 +</td><td>SEA Risk assessment x 1 during shift + ABCDE optimisation</td></tr>
<tr><td>2</td><td>0 +</td><td>SEA Risk assessment again after 1 hour + ABCDE optimisation</td></tr>
<tr><td>Single value ≥2

Or TOKS ≥3</td><td>0 +</td><td>Call physician</td></tr>
<tr><td colspan="4">Call for physician: SIF (during admission)/Physician on call (after admission) 8.30 AM-9.30 PM, Physician on call 9.30 PM -8.30 AM,

Surgical physician on call for surgical patient. SEA: Pale, clammy/sweaty. Shortness of breath reported by patient.

New pain or worsening of pain, Clinical intuition & Concern of patient or significant other</td></tr>
</table>

TOKS "Tidlig opsporing af kritisk sygdom" in Danish (in English; early identification of critical illness). SEA Safe emergency admissions (Sikre akutte Indlæggelser in Danish)

Patient group: patients ≥ 18 years

Exclusion: orthopedic trauma, cardiac arrest, surgical or medical call (unless admitted in the Emergency Department) or in case of psychiatric illness being the primary diagnosis for admission.

When: Patients are risk assessed according to SEA at arrival and at least once during each shift depending on risk – SFI Safe Emergency Admissions (SEA) risk assessment

Positive SEA risk - follow decision algorithm

Nurse huddle – Discussion with an experienced nurse is initiated if risk is present. Purpose, determine if there is a risk of clinical deterioration and initiate team discussion with physician or terminate process.

Team discussion Risk is highlighted on the clinical logistics board, emergency physician is called and the patient's risk of clinical deterioration is discussed and a decision regarding escalation plan is made.

Escalation plan – Plan, which is made by the physician in cooperation with the nurse, focusing on the triggering risk factor(s):

- Actions/observations
- The expected result of treatment

- Timeline for when the expected result of treatment should be reevaluated as well as actions if the expected result of treatment is absent

Board meeting: physicians/nurses discuss the patient regarding risk of clinical deterioration, transfer and discharge. 7.30 AM + 5.30 PM

Communication: ISBAR

4. Clinical guideline
This guideline is translated from Danish to English only for the purpose of this dissertation

Title

Guideline for use of the patient safety model ”Safe Emergency Admission (SEA)”

Purpose

Patient group/course of treatment/other target group

Definition of terms

Procedure

Documentation

Responsibility

References

Purpose

The algorithm in this guideline comes from the project ”Safe Emergency Admissions” which aims at developing and testing a new patient safety model.

The aim of the algorithm is to lower the number of patients that develop severe clinical deterioration during their stay in the emergency department.

Specific purpose of the algorithm:

- Early identification of patients at risk of clinical deterioration
- Support of timely response and escalation of observation, care and treatment
- And to prevent the development of severe clinical deterioration

This guideline is linked to the PhD project “Safe Emergency Admissions” and is therefore only valid during the project period 1.10.2017 - 30.4.2018.

Patient group/Course of treatment/Other target group

Target group patients

Adult patients ≥18 years, admitted to the emergency departments at Horsens Regional Hospital and Regional Hospital Central Jutland (section A2).

Exceptions

Patients received as trauma, cardiac arrest, surgical or medical call or patients admitted with a psychiatric illness as their primary diagnosis.

If the patient is subsequently admitted to the emergency department, the SEA algorithm is initiated, when a plan for the patient is made.

Target group Staff

Physicians, nurses, social- and healthcare assistants.

Area of application

See target group.

Some patients may also need another form of monitoring e.g. telemetry.

Definition of terms

The Algorithm Safe Emergency Admissions (SEA) consists of a risk assessment formed by a collection of systematic, routine observations of the admitted emergency patient. SEA consists of vital parameters within TOKS as well as subjective assessments as described under Risk Factors. Actions and processes are connected to the algorithm to ensure a systematic approach, see figure 1 and 2.

Clinical intuition An intuitive feeling that ”something is wrong” with the patient despite lacking or unclear clinical indication for this e.g. that the condition is not yet present in the vital values. [1-3]

Patient’s/significant others’ concern The concern of the patient or their significant others that the patient's clinical condition has deteriorated or deteriorates within a short period of time.

This can be e.g. a change in behavior or a feeling of "not feeling well", "that something is different, is not as it usually is" or that "the end is near" .3-5

Shortness of breath The patient's experience of shortness of breath i.e. not being able to breathe or being short of breath.

Team discussion A process where a physician and a nurse meet to discuss the patient's risk factors and decide on an escalation plan.

Escalation Plan Plan for the patient prepared by the physician in collaboration with the nurse focusing on the triggering risk factors. The plan contains actions, the expected result of treatment, timeline for when the expected result of treatment should be reassessed and actions in case the expected result of treatment is absent.

ISBAR Identification, Situation, Background, Analysis, Advice.

ISBAR is a systematic communication tool to ensure the exchange of information between professionals in a secure and unambiguous manner.6

Huddle A ward/ward level meeting where the ward's physicians and nurses meet and discuss patients in the ward based on risk, transfer and discharge. Is held during day and night shifts.

Course of action

All admitted patients who belong to the target group are risk assessed according to the SEA algorithm. This is done in conjunction with receiving the patients in the emergency department immediately after triaging the patient.

If the patient is received by a doctor and nurse, the assessment and team discussion are performed immediately. Afterwards, the algorithm below is followed.

> No risk factors - the process ends with a SEA/TOKS prescription with observation frequency. At a minimum, the SEA algorithm is repeated once during each shift together with TOKS
>
> Affected risk factor - the process ends with a team discussion and an escalation plan

If the patient is received by a nurse, the assessment is carried out and the algorithm below is followed:

No risk factors - the process is completed and the next assessment is performed according to the SEA algorithm's TOKS part - at least once during each shift

Affected risk factor - the patient is discussed with an experienced nurse and if there is agreement that the risk factor compromises the patient's condition, i.e. agreement regarding the risk of clinical deterioration, a physician is consulted. The process ends with a team discussion and an escalation plan.

Figure 1 Pocket card

TOKS	SEA	Decision algorithm	
TOKS prescription	0 +	Prescription is followed	Consider clinical deterioration Discuss risk with experienced nurse (nurse huddle) and call emergency physician if you agree on risk of clinical deterioration for the purpose of initiating team discussion and escalation plan.
0	0 +	SEA Risk assessment x 1 during shift	
1	0 +	SEA Risk assessment x 1 during shift + ABCDE optimisation	
2	0 +	SEA Risk assessment again after 1 hour + ABCDE optimisation	
Single value ≥2 Or TOKS ≥3	0 +	Call physician	
Call for physician: SIF (during admission)/Physician on call (after admission) 8.30 AM-9.30 PM, Physician on call 9.30 PM -8.30 AM, Surgical physician on call for surgical patient. SEA: Pale, clammy/sweaty. Shortness of breath reported by patient. New pain or worsening of pain, Clinical intuition & Concern of patient or significant other			

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Patient group: patients ≥ 18 years

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Positive SEA risk - follow decision algorithm

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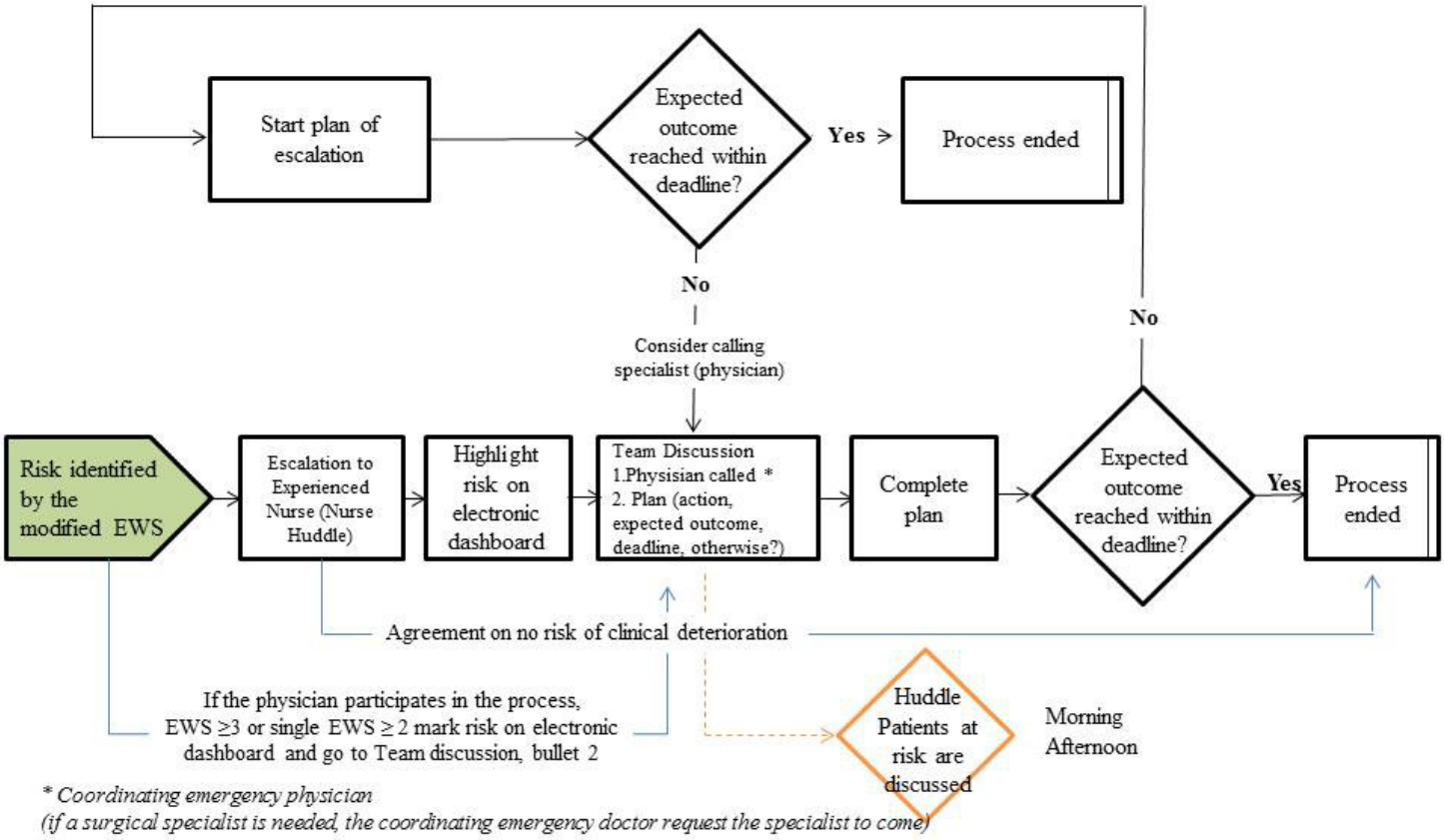
Team discussion Risk is highlighted on the clinical logistics board, emergency physician is called and the patient's risk of clinical deterioration is discussed and a decision regarding escalation plan is made.

Escalation plan – Plan, which is made by the physician in cooperation with the nurse, focusing on the triggering risk factor(s):

- Actions/observations
- The expected result of treatment
- Timeline for when the expected result of treatment should be reevaluated as well as actions if the expected result of treatment is absent

Figure 2 Process overview



Huddle: physicians/nurses discuss the patient regarding risk of clinical deterioration, transfer and discharge. 7.30 AM + 5.30 PM

Communication: ISBAR

Huddle (Board Meeting)

Huddles are held during day and night shifts and focuses on professional discussion regarding the patient's history, risk and escalation plan.

The huddle meetings are held in each department at. 7.30 AM and 5.30 PM

Duration: approx. 10 minutes

Location: Office aisle 2

The board meeting is led by the physician on call.

The review of patients is prioritised on the basis of the clinical logistics board (CLL) based on:

• Identified risk of clinical deterioration

• Discharge

• Transfer

• Incoming

The patient responsible physician or physician on call presents (with regard to professional discussion) the patient's course of treatment with a brief description of:

• The patient's history

• Identified risk of clinical deterioration

• Treatment and escalation plan

7.30 AM

Purpose: Professional handover from physician to physician including review of at-risk patients, allocation of rounds for early discharge. Thereafter, Emergency BV and flow distribute the remaining patients for rounds.

Participants: Outgoing and incoming Emergency on call physician, SLF, other physicians starting their shift at 7.30 AM, Flow and Emergency Coordinator as well as the nurses with at-risk patients/unresolved patients.

Location: Office aisle 2

5.30 PM

Purpose: Professional handover from physician to physician including review of at-risk patients, allocation of resources according to current capacity.

Participants: Outgoing and incoming Emergency physician on call, SLF, Flow and Emergency Coordinator as well as the nurses with at-risk/unresolved patients.

Location: Office aisle 2

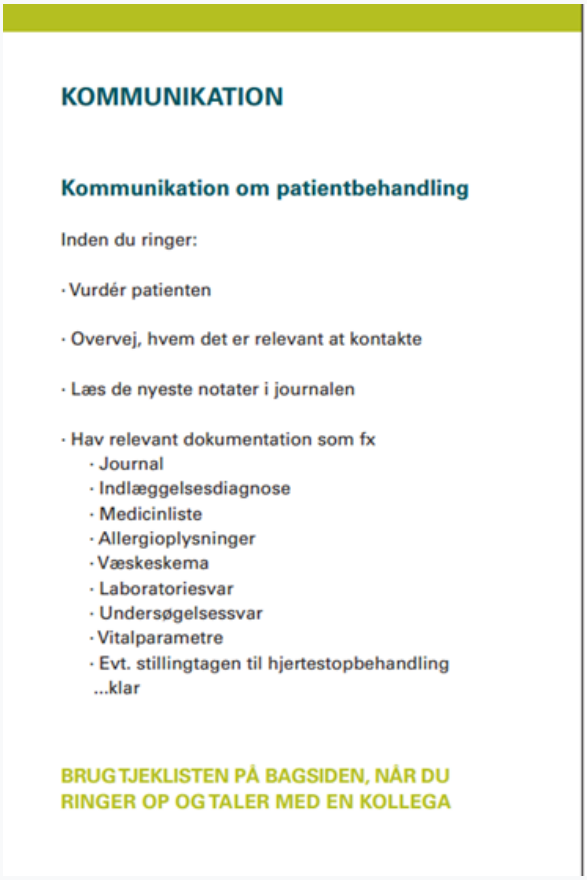
Documentation

The nursing staff documents the measured vital values and risk factors in the SAI SFI, and notes any potential at-risk patients on the clinical logistics board (CCL).

The physician documents in the Emergency Note and the SFI "TOKS, prescription" at a single score of ≥2 as well as at TOKS ≥3 or other affected risk factor. Observation frequency, escalation plan and acceptable score are documented.

Communication

Communication about the patients' risk factors in connection with discussions with an experienced nurse, team discussions and huddles are conducted in accordance with ISBAR to ensure a systematic exchange of information between professionals in a safe and unambiguous manner.



KOMMUNIKATION

Kommunikation om patientbehandling

Inden du ringer:

· Vurdér patienten

· Overvej, hvem det er relevant at kontakte

· Læs de nyeste notater i journalen

· Hav relevant dokumentation som fx
  · Journal
  · Indlæggelsesdiagnose
  · Medicinliste
  · Allergioplysninger
  · Væskeskema
  · Laboratoriesvar
  · Undersøgelsessvar
  · Vitalparametre
  · Evt. stillingtagen til hjertestopbehandling
  ...klar

BRUG TJEKLISTEN PÅ BAGSIDEN, NÅR DU RINGER OP OG TALER MED EN KOLLEGA

I
IDENTIFIKATION
· Sig dit navn, din funktion og afdeling eller afsnit
· Sig patientens navn, CPR-nr. og afdeling

S
SITUATION
· "Jeg ringer fordi... (beskriv)"
· "Jeg har målt følgende værdier:
BT__/__ Puls__ RF__ SAT__Temp__" *eller*
· "Jeg har observeret væsentlige ændringer i BT/Puls/RF/bevidsthedsniveau/Sat/hudfarve/EKG/Sår/GI/Gyn"

B
BAGGRUND
· Indlæggelsesdiagnose og -dato
· Kort referat af sygehistorie indtil nu

A
ANALYSE
· "Jeg mener, at problemet er... (beskriv)"
· "Problemet er nok kardielt/respiratorisk/neurologisk/.."
· "Jeg kender ikke problemet, men pt. har fået det værre"
· "Patienten er ustabil. Vi må gøre noget"
· "Jeg er bekymret"

R
RÅD
· "Skal vi ikke...(beskriv)"
· "Hvad synes du, at jeg skal gøre?"
· "Hvilke undersøgelser vil du foreslå"
· "Hvad mener du, at jeg skal observere og hvor ofte"
· "Hvornår skal vi tales ved igen?"

Responsibility

The Department Management is responsible for making sure that the guideline is known and used in the department.

References

1. Ingeman ML, Christensen MB, Bro F, Knudsen ST, Vedsted P. The danish cancer pathway for patients with serious non-specific symptoms and signs of cancer-a cross-sectional study of patient characteristics and cancer probability. BMC Cancer. 2015;15:421-015-1424-5.

2. Stolper E, Van Royen P, Van de Wiel M, et al. Consensus on gut feelings in general practice. BMC Fam Pract. 2009;10:66-2296-10-66.

3. Douw G, Schoonhoven L, Holwerda T, et al. Nurses' worry or concern and early recognition of deteriorating patients on general wards in acute care hospitals: A systematic review. Crit Care. 2015;19:230-015-0950-5.

4. Cioffi J, Conway R, Everist L, Scott J, Senior J. 'Changes of concern' for detecting potential early clinical deterioration: A validation study. Aust Crit Care. 2010;23(4):188-196.

5. Cioffi J, Conwayt R, Everist L, Scott J, Senior J. 'Patients of concern' to nurses in acute care settings: A descriptive study. Aust Crit Care. 2009;22(4):178-186.

6. Dansk Selskab for Patientsikkerhed. Håndbog i sikker mundtlig kommunikation.(Danish Society for patient Safety, Handbook in safe oral communication)

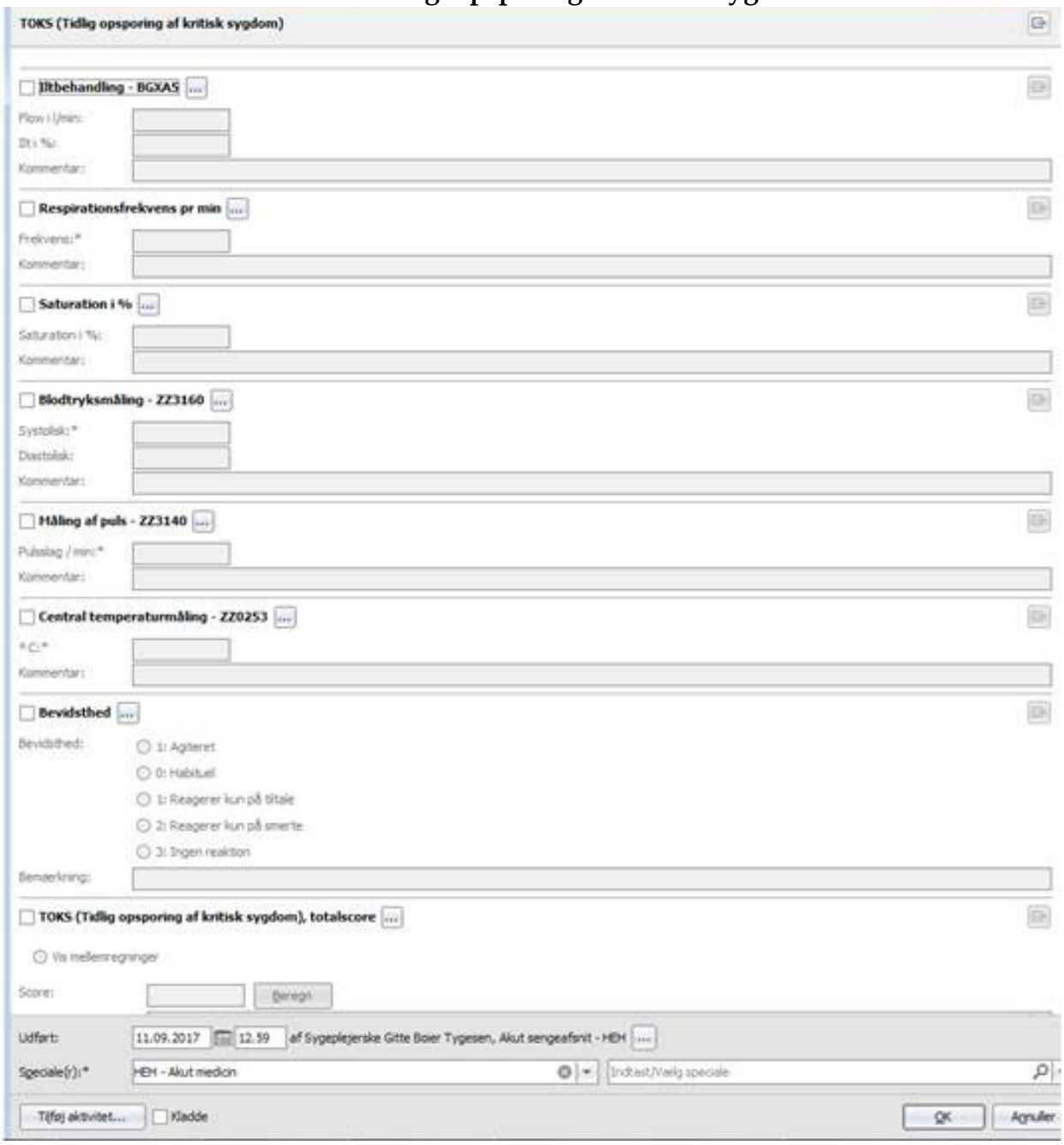
5. Education program

Title: Projekt Sikre akutte indlæggelser (eng. Project, Safe acute admissions)

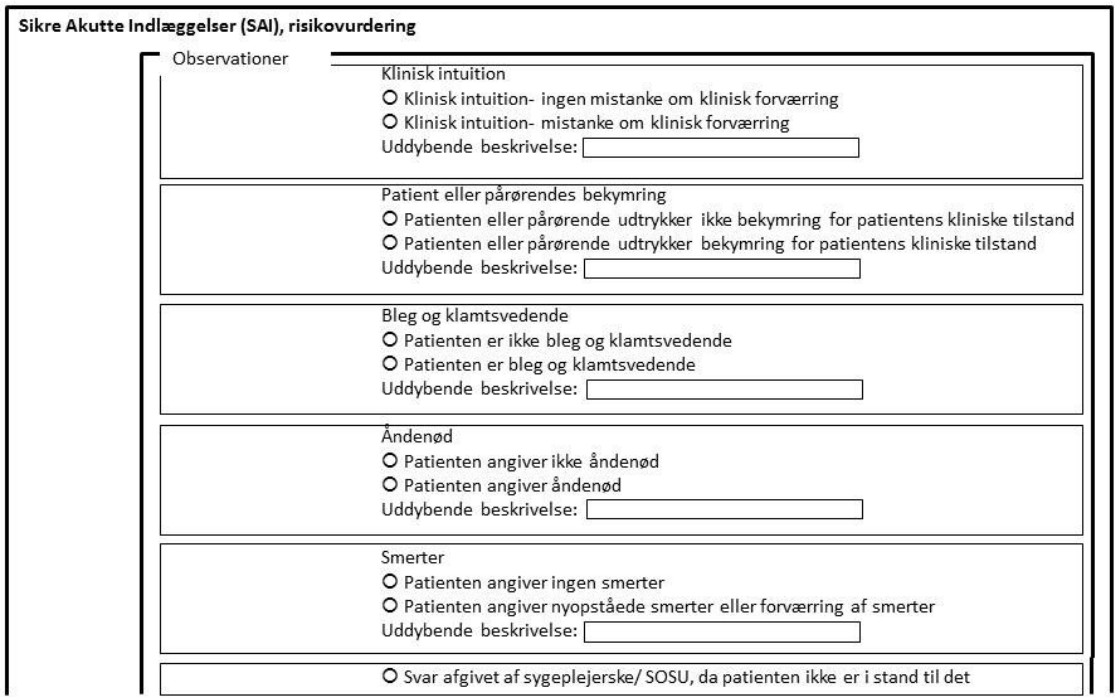
Content	Learning outcome
1. Introduction to the PhD project Safe Acute Admissions (short title)	Insight to organisation, aim and hypothesis, and method
2. Introduction to the modified EWS system	Insight to situation awareness and recognition of clinical deterioration. Understanding the modified EWS system, plans and huddles • Target group • Vital signs and new parameters • Actions and respond • Who to call • Clinical decision support – what to do • Huddles • Process overview, pocket card and template
3. Case training	Scenario training
4. How to communicate (ISBAR)	Understanding ISBAR*

Note: *ISBAR is a standard communication protocol in Danish hospitals (Danish. Identifikation, situation, baggrund, analyse, råd) (eng. – Identification, situation, background, analysis, recommendation)[176]

6. Template in EMR
SFI/ Dokumentation TOKS – Tidlig Opsporing af kritisk Sygdom



SFI/ Dokumentation



Sikre Akutte Indlæggelser (SAI), risikovurdering

Observationer

Klinisk intuition
- ○ Klinisk intuition- ingen mistanke om klinisk forværring
- ○ Klinisk intuition- mistanke om klinisk forværring

Uddybende beskrivelse:

Patient eller pårørendes bekymring
- ○ Patienten eller pårørende udtrykker ikke bekymring for patientens kliniske tilstand
- ○ Patienten eller pårørende udtrykker bekymring for patientens kliniske tilstand

Uddybende beskrivelse:

Bleg og klamtsvedende
- ○ Patienten er ikke bleg og klamtsvedende
- ○ Patienten er bleg og klamtsvedende

Uddybende beskrivelse:

Åndenød
- ○ Patienten angiver ikke åndenød
- ○ Patienten angiver åndenød

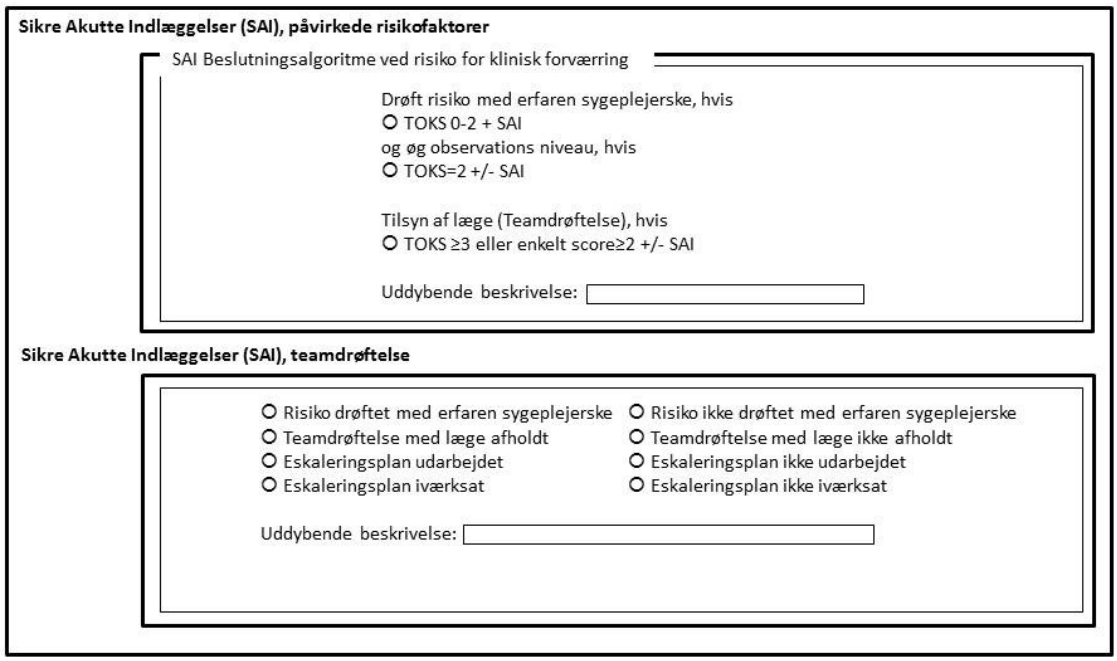
Uddybende beskrivelse:

Smerter
- ○ Patienten angiver ingen smerter
- ○ Patienten angiver nyopståede smerter eller forværring af smerter

Uddybende beskrivelse:

○ Svar afgivet af sygeplejerske/ SOSU, da patienten ikke er i stand til det

SFI/ Dokumentation



Sikre Akutte Indlæggelser (SAI), påvirkede risikofaktorer

SAI Beslutningsalgoritme ved risiko for klinisk forværring

Drøft risiko med erfaren sygeplejerske, hvis
- ○ TOKS 0-2 + SAI

og øg observations niveau, hvis
- ○ TOKS=2 +/- SAI

Tilsyn af læge (Teamdrøftelse), hvis
- ○ TOKS ≥3 eller enkelt score≥2 +/- SAI

Uddybende beskrivelse:

Sikre Akutte Indlæggelser (SAI), teamdrøftelse

- ○ Risiko drøftet med erfaren sygeplejerske
- ○ Teamdrøftelse med læge afholdt
- ○ Eskaleringsplan udarbejdet
- ○ Eskaleringsplan iværksat
- ○ Risiko ikke drøftet med erfaren sygeplejerske
- ○ Teamdrøftelse med læge ikke afholdt
- ○ Eskaleringsplan ikke udarbejdet
- ○ Eskaleringsplan ikke iværksat

Uddybende beskrivelse:

PAPERS I-III AND DECLARATION OF CO-AUTHORSHIP

Tygesen GB, Lisby M, Kirkegaard H, Raaber N, Rask MT.
Generic predictors of clinical deterioration in adult Emergency Department patients: a systematic review.

Internal Journal of Emergency Medicine

PAPER I

Title page

Generic predictors of clinical deterioration in adult Emergency Department patients: a systematic review

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ABSTRACT

Aim To examine generic predictors associated with clinical deterioration in adult patients in emergency departments.

Design Systematic review

Data sources PubMed, EMBASE (Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost), PsycINFO and Cochrane electronic databases.

Eligibility criteria for selecting studies Randomized controlled trials and observational studies in German, English or Scandinavian languages that report generic predictors associated with clinical deterioration, defined as admission to the intensive care unit, cardiac arrest in the emergency department and 30-day mortality in a population of adult patients in emergency departments.

Results We identified 36 potential generic predictors of clinical deterioration. The predictors represented various clinical parameters and were categorized as follows: 1) Presenting complaints (n=2), i.e. the main symptom presented at admission; 2) Independent vital signs (n=8), e.g. respiratory rate and heart rate; 3) Biochemical tests (n=12); 4) Comorbidities (n=10); and 5) Other predictors (n=4).

Conclusions In this systematic review, we identified several predictors of clinical deterioration possible to apply broad in emergency departments and relevant to clinicians. Based on our findings, further attention should be paid to the use of vital signs, biochemical tests and comorbidities as predictors of clinical deterioration. Future research in this area should investigate the strength and validity of these predictors in a general emergency department population as well as the ability to impact patient outcome.

What is already known about this subject?

Several studies in settings other than the emergency department have investigated the effect of adding additional parameters, such as clinical concern, breathing difficulties, increase in supplemental O_2 and biomarkers, to the parameter of basic vital signs in order to detect the patients at risk of clinical deterioration.[1-3] Although much attention has been paid to patient safety, we need further knowledge about risk factors that may assist in detecting clinical deterioration in adult patients in emergency departments.

What this study adds?

This study identifies thirty-six predictors of clinical deterioration relevant to clinicians in emergency departments. The predictors included presenting complaints, vital signs, biochemical tests, comorbidities and other predictors all reflecting the complexity of the nature of the deteriorating patient. Based on our findings, further attention should be paid to the effect on clinical outcomes when combining EWS systems with vital signs, biochemical tests and comorbidities.

BACKGROUND

Prevention of clinical deterioration is essential to ensure the safety of adult patients in emergency departments (EDs).[4, 5] In previous decades, triage systems and early warning score (EWS) systems have been implemented to increase patient safety.[4, 5] Triage systems are used to determine patients' clinical urgency and the order in which patients should receive care[6, 7]and EWS systems are designed to identify patients at high risk of clinical deterioration in order to take precautions to decrease cardiac arrest, death and unplanned admission to the intensive care unit (ICU). EWS systems are primarily based on basic vital signs and use an afferent and efferent limb to detect events and trigger a systematic response. The EWS systems are often used in addition to triage to support clinical decisions as to the level of observation or when to step up treatment.

A variety of EWS systems have been implemented in hospitals worldwide, with variable success.[8, 9] Despite the use of EWS systems, 12-17% of ED patients still deteriorate.[10-12]A systematic review of EWS systems' ability to predict mortality or ICU transfer in medical patients in the ED and in the Acute Medical Unit (AMU) revealed that two EWS systems were favourable to predict the endpoints of clinical deterioration.[13] The majority of the studies were performed on ED and AMU populations using heterogeneous prognostic scores. In conclusion, impending studies should concentrate on a simple and easy to use prognostic score aiming a system usable throughout the acute care chain.[13]

Variation in the effectiveness of EWS systems in terms of patient outcomes may be caused by the implementation of systems intended for other clinical settings, insufficient monitoring and risk identification, which may lead to poor awareness of the patient's condition, insufficient treatment and care.[14, 15] Furthermore, the effect of EWS systems may be impaired as physiological parameters such as vital signs often deteriorate late in the course of a disease, making improvement of the patient's condition even more demanding.[16]

The poor performance of EWS systems points to a need for further clinical risk stratification to identify and manage patients at potential risk of clinical deterioration at an early stage of a disease.[10, 11, 17]A few studies have investigated the effect of adding additional parameters, such as clinical concern, breathing difficulties, increase in supplemental oxygen and biomarkers, to the parameter of basic vital signs in order to detect the patients at risk of clinical deterioration.[1-3] Based on these studies it seems that adding such parameters to existing EWS systems may improve their ability to predict clinical deterioration even earlier.

Though the effect of EWS systems have been widely explored little is known about risk factors that may improve the existing EWS systems in detecting clinical deterioration in adult patients in EDs. For better developing and planning of future EWS trials it is the aim of this systematic review to identify generic predictors associated with clinical deterioration e.g. ICU admission, cardiac arrest (CA) or death, in a population of adult ED patients.

METHODS

The study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]

Selection criteria

Inclusion criteria are presented in Table 1. We included studies on adult somatic patients that investigated generic, non-compounded risk factors or predictors. We defined generic predictors as predictors widely applicable to the ED population and to routine care practices. Non-compounded predictors were defined as independent predictors, rather than predictors that were part of an aggregated score, such as the Charlson Comorbidity Index. An exception was the Glasgow Coma Scale (GCS) due to its widespread clinical use. The outcome of interest was clinical deterioration. In this systematic review we operationalized clinical deterioration by ICU admission, CA, death within 30 days or a composite outcome of the aforementioned in line with a previous study.[19] Studies on predictors focusing on children (<16 years), trauma patients, out-of-hospital CA patients, patients with a psychiatric disorder as a primary diagnosis or disease-specific predictors, e.g. predictors not applicable on a broad ED population, were excluded.

Search strategy

We searched PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature, PsycINFO and Cochrane electronic databases for studies from 1990 until June 2016.

A three-step search strategy was developed and conducted in collaboration with a research librarian. First, to ensure comprehensive key words and index terms for the final search strategy, we conducted an initial limited search on synonyms of the ED predictors: clinical deterioration, CA, ICU admission and death in PubMed, EMBASE and Cochrane followed by an analysis of the text words contained in the titles and abstracts of the articles' index terms. Second, we performed a systematic search across all the databases using all identified keywords and index terms (Supplementary files I). Third, the reference lists of records included in the review were searched for additional studies.

Study selection

The first author initially screened titles and abstracts of the identified records and excluded those that clearly didn't meet the eligibility criteria related to study design, population (age, setting) and relevant predictors studied (predictors present at ED presentation e.g. exclusion of out of hospital CA). Subsequently, the first and last author independently screened the titles and abstracts of the remaining records in relation to criteria's in Table 1. Full text articles of records passing this screening procedure were retrieved and independently assessed for final inclusion by the two reviewers. Any disagreements between reviewers throughout the review process were resolved by consensus or by involvement of a third reviewer.

Table 1 Inclusion criteria

Study design	Observational studies, i.e. cohort, cross-sectional and case-control studies. Randomized controlled trials (RCT) in which separate outcome estimates for a control group (i.e. treatment as usual) were reported.
Population	Emergency Department patients with somatic symptoms ≥ 16 years.
Predictors	Generic, non-compounded risk factors or predictors applicable across the broad ED population and routine care practices.
Outcome	Clinical deterioration defined as transfer or admission to ICU directly from the ED, CA in the ED and death within 30 days of ED attendance.
Language	German, English or Scandinavian languages (Danish, Swedish and Norwegian).
Publication date	Until June 2016.

Risk of bias

Two reviewers independently assessed the methodological quality of the included studies using the Newcastle-Ottawa Scale (NOS).[20] Discrepancies in the NOS ratings were managed by consensus or by the involvement of a third reviewer.

The NOS is developed for quality assessment of nonrandomized studies and consists of a system in which points are given based on 1) the selection of the study groups (max score =4); 2) the comparability of the groups (max score =2); and 3) the ascertainment of either the exposure or outcome of interest for case-control or cohort-studies, respectively (max score =3).

The maximum total NOS-score is nine, and a value below nine indicates methodological problems.[20] In the category "comparability", we decided a priori that studies controlling for age would be assigned one point and an additional point if a factor of severity reflecting the patient's condition was controlled for (e.g. comorbidity, triage category).

Data extraction

Data from the included studies were extracted by the first author and registered in a data extraction sheet. Afterwards, all data extracted were checked and compared with the original studies by the last author. Data extraction forms were developed a priori and comprised the following information: first author surname, year of publication and journal, country of origin, study design, study population, risk factors/predictors investigated, and outcome assessed, covariates adjusted for and results (measures of association with 95% CI and p-values). A few studies lacked report of age, in these cases; the authors were contacted by email.

Data synthesis and analysis

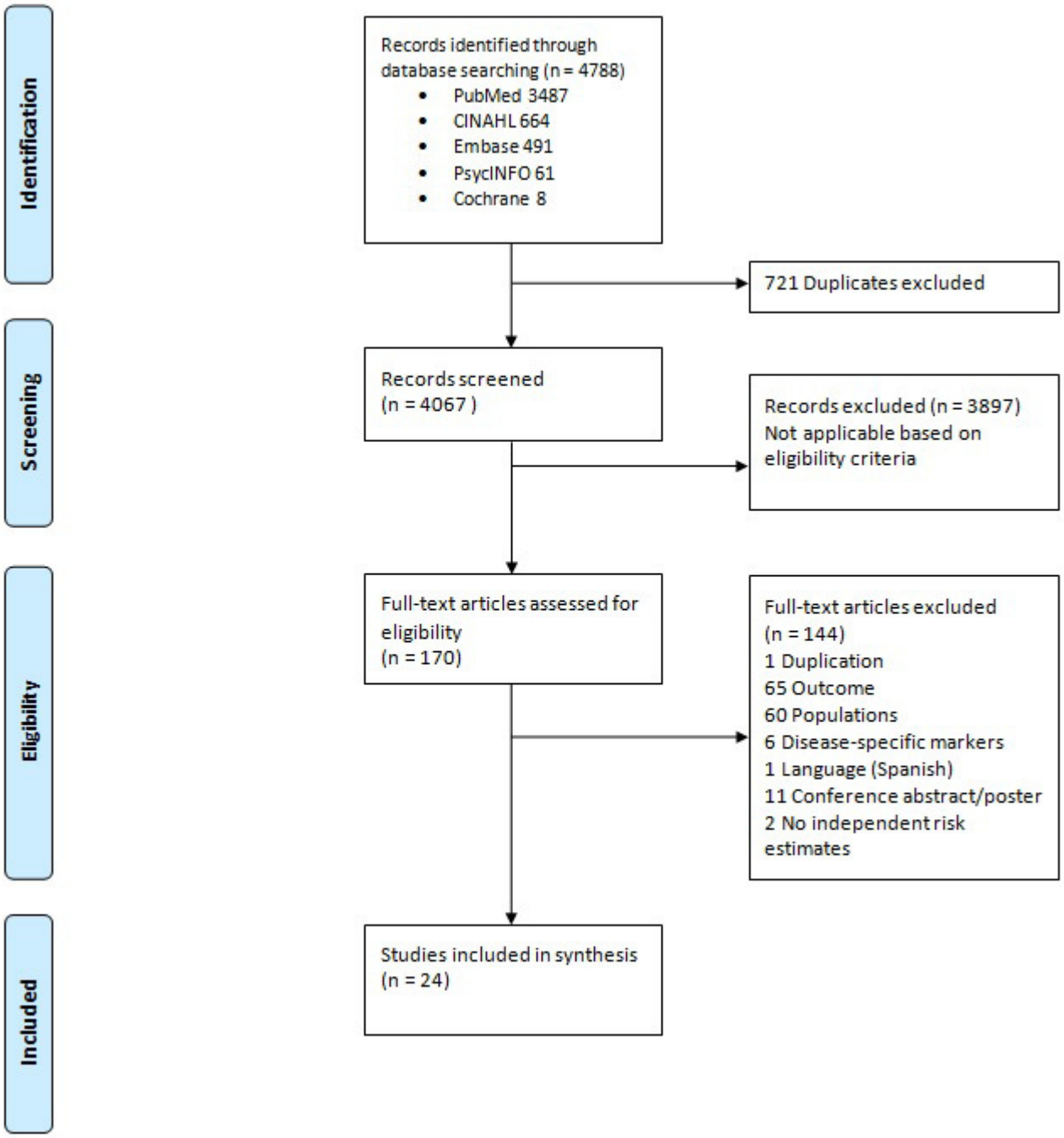
Data were narratively synthesized due to clinical heterogeneity caused by differences in study design, subgroups and outcome measures affecting the ability to compare and combine data from the different

studies. We rated predictors as associated with an increased risk or decreased risk of clinical deterioration if the estimates in the original studies were statistically significant or as undetermined if no statistical significance could be detected (Supplementary files III). The estimated associations between the investigated predictors and clinical deterioration are displayed in a forest plot.

RESULTS

A total of 4788 records were identified in the databases. Of these, 721 were duplicates, leaving 4067 records to be screened for inclusion. A total of 170 records underwent full-text review for eligibility, cross-reference search prompted no additional studies for inclusion and 24 studies met the inclusion criteria (Figure 1).

Figure 1 PRISMA flowchart of selection of eligible studies

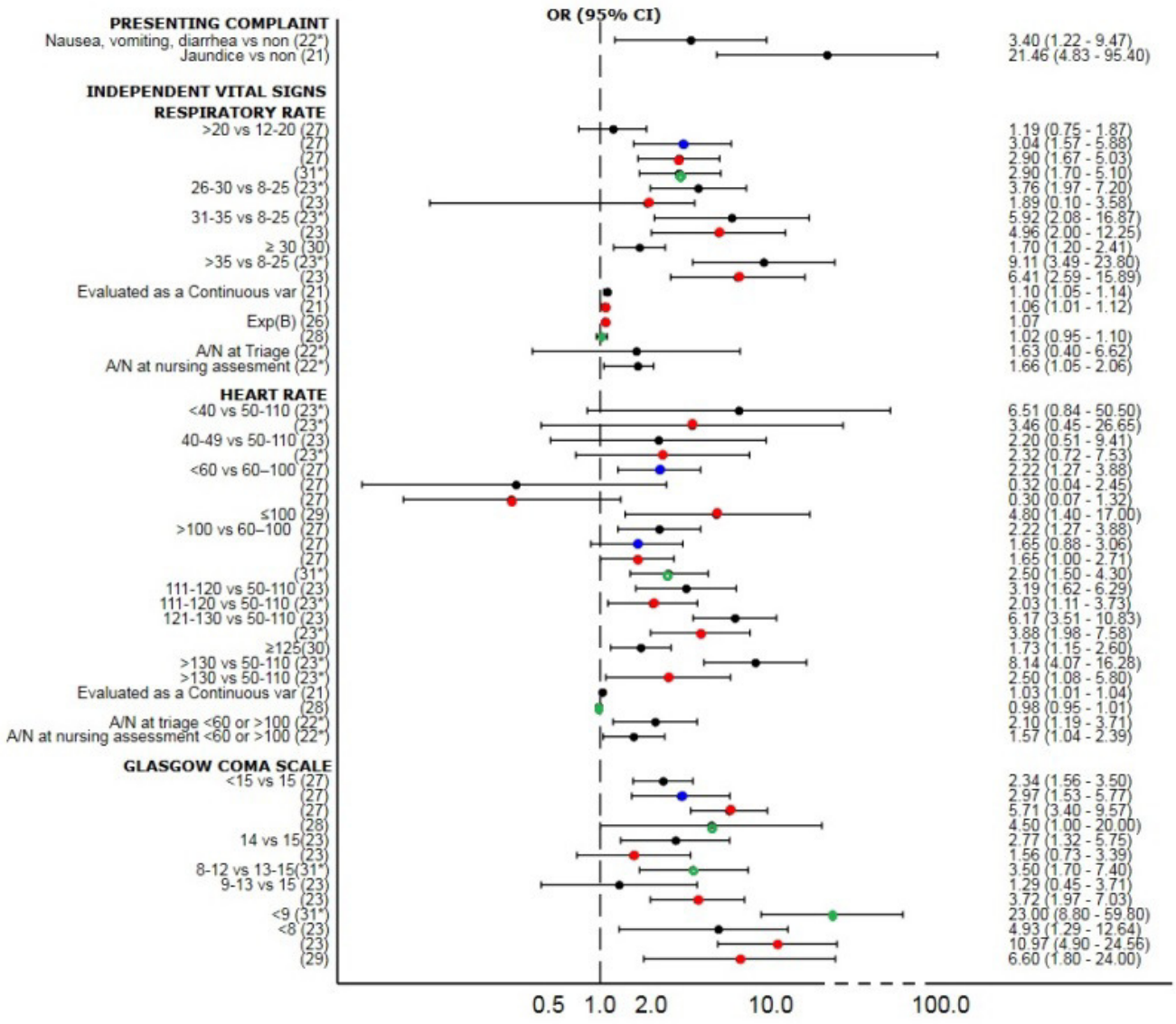


Characteristics of included studies

We included 22 cohort studies, one cross-sectional study and one case-control study. No RCT studies fulfilled the inclusion criteria. In Table 2, the study characteristics and quality assessment scores (NOS) are presented (Supplementary file II). Thirty-six potential predictors of clinical deterioration were identified. These were labelled and categorized as 1) Presenting complaints (n=2), i.e. the patient's main symptoms at admission, 2) Independent vital signs (n=8), 3) Biochemical tests (n=12), 4) Comorbidity (n=10), and 5) Other predictors (n=4). Measures of associations with clinical deterioration are presented in Figure 2a-2d

(Supplementary file III). Predictors that were found to be statistically significantly associated with clinical deterioration are further described below; all identified predictors are displayed in the forest plots.

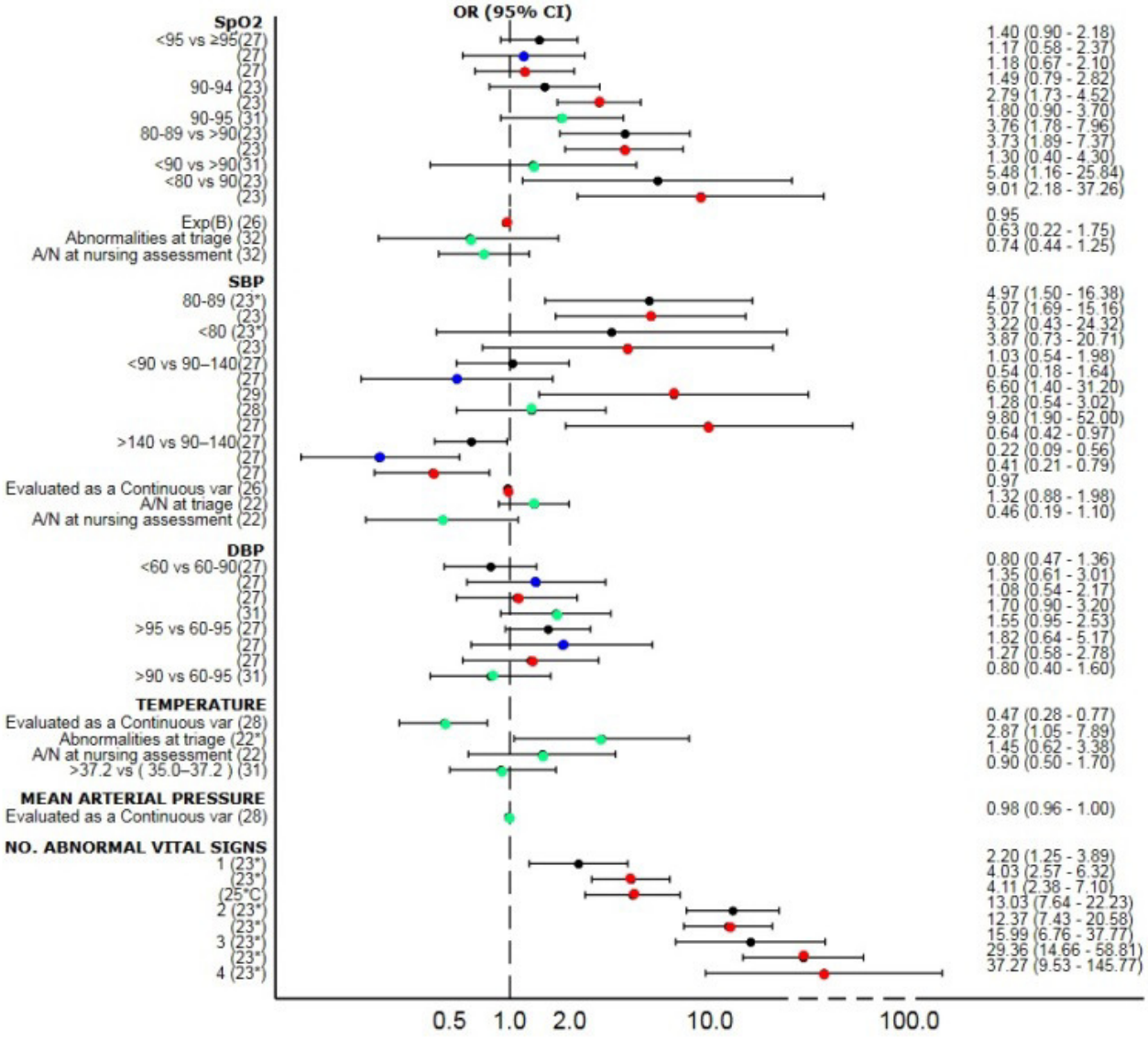
Figure 2.a Forest plot of effect sizes (odds ratio and 95% confidence interval) of: Presenting complaints and vital signs as predictors of clinical deterioration and outcome (ICU, CA, MR and ICU/MR)



*Dot colors; black: ICU admission, blue: cardiac arrest, red: mortality and green: composite outcome of ICU admission and mortality. * - crude estimate and the number refers to the corresponding reference in the text e.g. (21) reference number 21.*

Abbreviations: ICU- Intensive Care Unit admission, CA- cardiac arrest, MR-mortality rate, ICU/MR- composite outcome of ICU and MR, OR (95%CI)- odds ratio with corresponding 95% confidence interval, vs- versus, Exp(B)- exponentiation of the B coefficient in logistic regression, A/N- abnormal, SpO_2 – oxygen saturation, SBP- systolic blood pressure, DBP- diastolic blood pressure, NO- number.

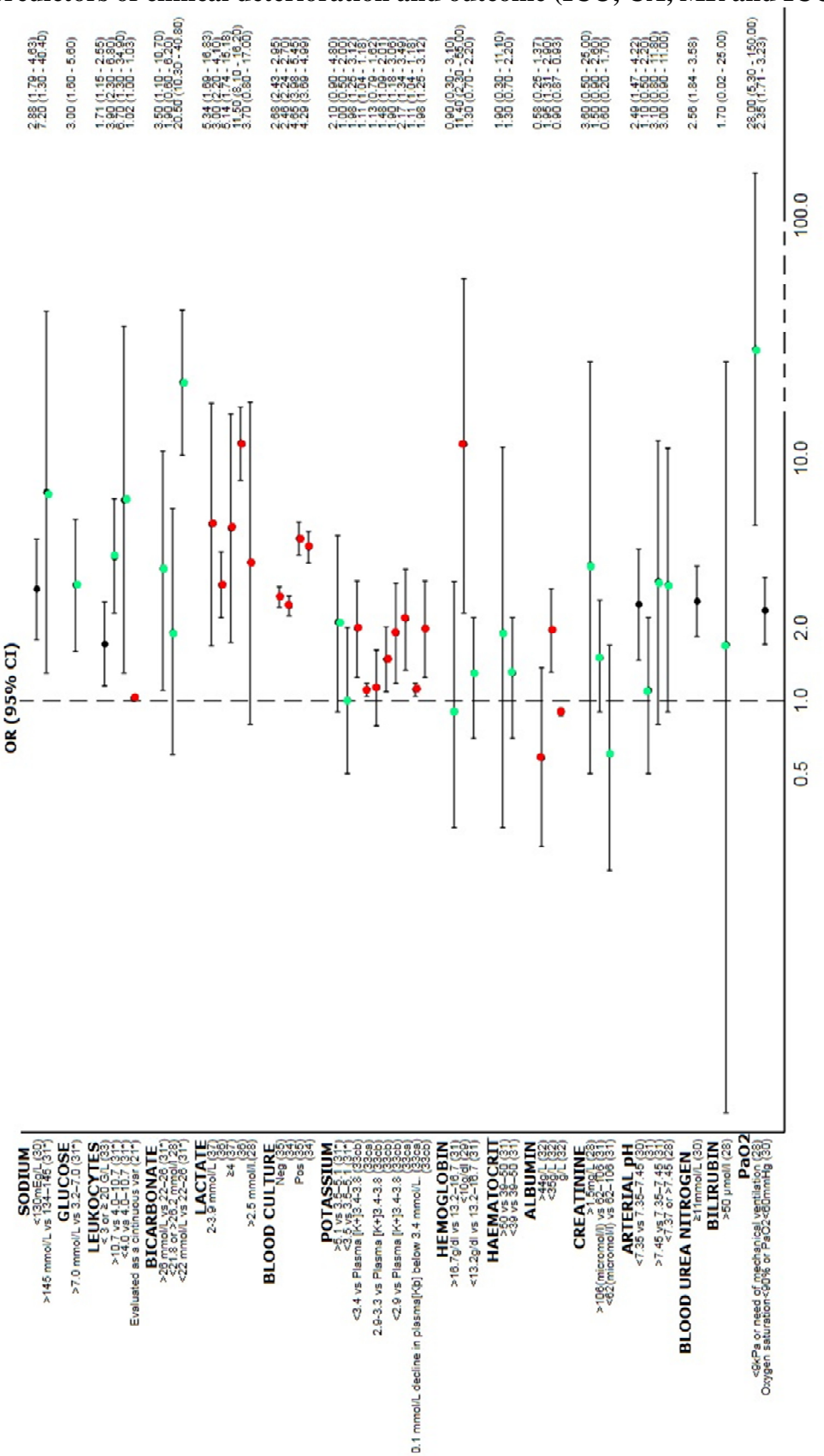
Figure 2.b Forest plot of effect sizes (odds ratio and 95% confidence interval) of: Vital signs as predictors of clinical deterioration and outcome (ICU, CA, MR and ICU/MR)



*Dot colors; black: ICU admission, blue: cardiac arrest, red: mortality and green: composite outcome of ICU admission and mortality. * - crude estimate and the number refers to the corresponding reference in the text e.g. (21) reference number 21t.*

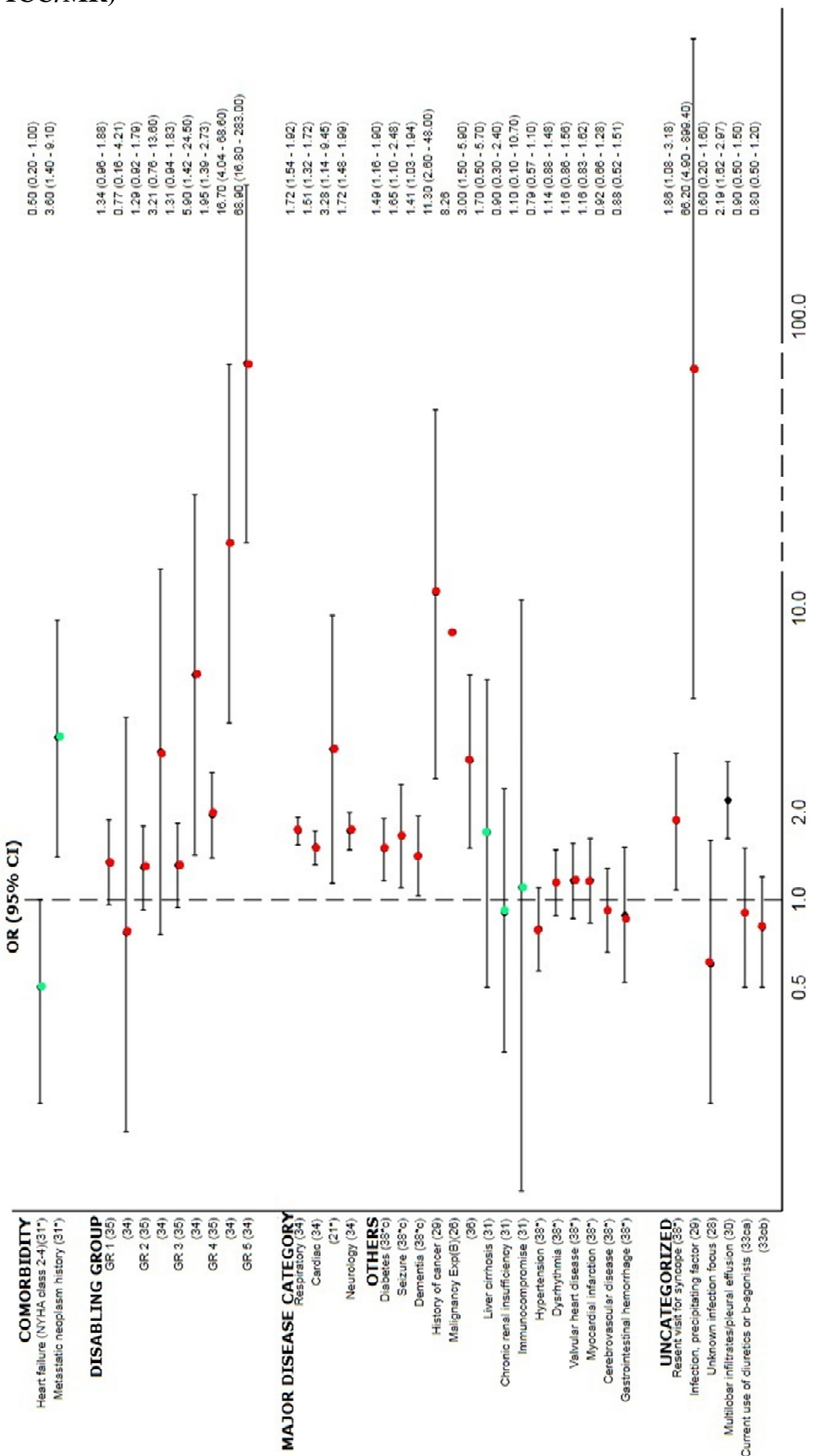
Abbreviations: ICU- Intensive Care Unit admission, CA- cardiac arrest, MR-mortality rate, ICU/MR- composite outcome of ICU and MR, OR (95%CI)- odds ratio with corresponding 95% confidence interval, vs- versus, Exp(B)- exponentiation of the B coefficient in logistic regression, A/N- abnormal, SpO_2 – oxygen saturation, SBP- systolic blood pressure, DBP- diastolic blood pressure, NO- number.

Figure 2.c Forest plot of effect sizes (odds ratio and 95% confidence interval) of: Biochemical test as predictors of clinical deterioration and outcome (ICU, CA, MR and ICU/MR)



Dot color; black: ICU admission, red: mortality and green: composite outcome of ICU admission and mortality.: crude estimate and the number refers to the corresponding reference in the text e.g. (21) reference number 21. Abbreviations: ICU- Intensive Care Unit admission, CA- cardiac arrest, MR-mortality rate, ICU/MR- composite outcome of ICU and MR, OR (95%CI)- odds ratio with corresponding 95% confidence interval, vs- versus, Neg- Negative, Pos- Positive*

Figure 2.d Forest plot of effect sizes (odds ratio and 95% confidence interval) of: Comorbidity and other or uncategorized predictors as predictors of clinical deterioration and outcome (ICU, CA, MR and ICU/MR)



Dot color; black: ICU admission, red: mortality and green: composite outcome of ICU admission and mortality.: crude estimate and the number refers to the corresponding reference in the text e.g. (21) reference number 21. Abbreviations: ICU- Intensive Care Unit admission, CA- cardiac arrest, MR-mortality rate, ICU/MR- composite outcome of ICU and MR, OR (95%CI)- odds ratio with corresponding 95% confidence interval, vs – versus, GR - group*

Presenting complaints

Presenting complaints were examined as predictors of clinical deterioration in patients presenting to the ED with category 3, 4 or 5 on the Australian Triage Scale and in patients with a tympanic temperature of ≥38˚C. In the febrile patients jaundice was found to be a predictor of increased mortality. [21] In another study gastrointestinal symptoms (nausea, vomiting and diarrhoea) were found to increase the risk of ICU admission in the patients with low urgency.[22]

Independent vital signs

Eleven studies examined vital signs as independent predictors of clinical deterioration and reported eight predictors.[21-31]

Eight of the studies assessed *respiratory rate* (RR).[21-23, 26-28, 30, 31]High RR was found to predict ICU admissions and mortality across subgroups comprising admitted ED patients and patients with differentiated infections and urgencies as triage category 1-3, Singapore Patient Acuity Category Scale (PACS) 1-2 and patients triaged to the resuscitation room. The risk of death increased with increases in RR.[21-23, 26, 27, 30, 31] One study found that a high RR (>20) predicted CA in patients with (PACS) 1-2.[27]
Eight of the studies assessed *heart rate* (HR) as a predictor of clinical deterioration.[21-23, 27-31]Across subgroups comprising admitted ED patients, patients with ED triage 1-3, PACS 1-2, patients with pneumonia and patients triaged to the resuscitation room, a high HR (>100) was found to predict ICU admission and mortality, and the risk of death was found to increase with increases in the HR.[23, 26, 27, 30, 31] In patients with tympanic temperature ≥38˚C, the risk of ICU admission was found to increase incrementally with each unit increase in the HR.[21] In patients with PACS 1-2 a low HR (<60) was a predictor of increased ICU admission [27]and the absence of tachycardia (HR ≤100) was found to be a predictor of increased mortality in patients with hyperglycaemic.[29] Finally, one study found that HR abnormalities (<60,>100) at triage increased the risk of ICU admission in patients with lower acuity on the Australian triage scale (3,4 or5).[22]

Five studies assessed *Glasgow coma score* (GCS).[23, 27-29, 31] Across studies of admitted ED patients with PACS 1-2, hyperglycaemic patients and patients triaged to the resuscitation room , a low GCS was a predictor of mortality and ICU admissions.[23, 27, 29, 31] Furthermore, an abnormal GCS (<15) was found to predict CA in patients with high triage on the PACS when adjusted for age.[27]

Across differentiated subgroups six studies assessed *blood pressure* (BP) as a predictor of clinical deterioration.[22, 23, 26-29] High *systolic BP* (>140mmHg) was negatively associated with ICU admission, CA and mortality in patients with PACS 1-2.[27] An analysis of low systolic BP as a continuous variable confirmed the negative association with mortality in patients with a similar triage in the categories

1-3, the higher the blood pressure the lower the mortality.[26] Low systolic BP, categorized as 80–89mmHg and <90mmHG, was found to predict ICU admissions, mortality and a composite outcome of the aforementioned, whereas a systolic BP of <80mmHg predicted only ICU admissions in admitted ED patients and in patients with suspicion of infection.[23, 28, 29]

Temperature was investigated in three studies across subgroups. In the first study, temperature was examined as a continuous variable, where the absence of fever was a negative predictor of ICU admission or death in patients with a blood culture drawn.[28]In the second study, temperature abnormalities at triage (TP<35, ≥37.9) were a positive predictor of increased risk of ICU admission in patients triaged 3-5 on the Australian triage scale.[22]

Five studies investigated levels of *oxygenation* (pulse-oximetry) across subgroups as a predictor of clinical deterioration.[22, 23, 26-28] They found that saturation levels of <80% and levels between 80–89% were positively associated with both ICU admission and mortality and that levels of 90–94% were only positively associated with mortality in admitted ED patients.[23] An analysis of low saturation as a continuous variable confirmed the association the lower the oxygenation the higher the mortality in patients triaged to the categories 1-3.[26]
The association between the *number of affected vital signs* and mortality was investigated in two studies, which showed that mortality increased as the number of abnormal vital signs increased in admitted ED patients.[23, 25]

Biochemical tests
Biochemical tests were assessed as predictors of clinical deterioration in 12 studies, and 12 different predictors were uncovered.[21, 27-37]

Partial pressure of oxygen (PaO_2): Two studies of patients with infection suspicion found levels of PaO_2 <9kPa(68mmHg) and <60mmHg (8kPa) to predict ICU admission and the composite outcome of ICU admission and mortality (ICU/MR).[28, 30]
High (>145mmol/L) and low (<130mmol/L) levels of *sodium* were found to predict clinical deterioration in terms of ICU admission and the composite outcome of ICU/MR in two studies investigating patients with infection or triaged to the resuscitation room.[30, 31]

The association between *potassium* levels and 7-day and 8- to 30-day mortality was examined in two studies of patients triaged to the resuscitation room and patients admitted to an acute medical department.[31, 33] In

the admitted medical patients hypokalaemia (<2.9mmol/L) was found to be associated with increased mortality.[33]
Three studies assessed *leucocytes*, and two studies found high and low leukocytes to predict ICU admissions in patients with pneumonia or triaged to the resuscitation room.[30, 31]

Across the subgroups of patients with infection and triaged to the resuscitation room three studies assessed *arterial pH*.[28, 30, 31] In the study of patients with pneumonia low arterial pH was found to predict ICU admissions.[30]
Blood urea nitrogen (≥11mmol/L) was found to predict ICU admissions in one study of patients with pneumonia.[30]
Lactate was assessed as a clinical predictor of mortality in three studies.[28, 36, 37] Two of the studies found high levels of serum lactate (2–3.9mmol/l and ≥ 4mmol/L) to be associated with increased mortality in patients having a blood culture or arterial blood gas drawn.[28, 36]
Haemoglobin was assessed in two studies of patients with hyperglycaemic and patients triaged to the resuscitation room[29, 31], and haemoglobin levels of <10g/dL (6.1mmol/L) or an Hct of <30% were associated with increased mortality in the hyperglycaemic patients.[29]
One study found *glucose* levels of >7.0mmol/L (=126 mg/dl) to predict the composite outcome of ICU/MR in patients triaged to the resuscitation room.[31]
Two studies assessed *bicarbonate*.[28, 31] In patients triaged to the resuscitation room high and low levels of bicarbonate (>26mmol/L, <22mmol/L) were found to predict the composite outcome of ICU/MR.[31] The association was not present in patients having a blood culture drawn at arrival.[31]

Both positive and negative *blood cultures* versus none were found to be associated with increased mortality in admitted general medical ED patients.[34, 35]

One study of patients admitted to the medical admission unit assessed *albumin* and found hypoalbuminemia (<35g/L [=5.1μmol/L]) as a predictor of 30-day mortality.[32]

Comorbidity
In nine studies, comorbidity was assessed as a predictor of clinical deterioration, resulting in 12 different predictors.[21, 26, 29, 31, 33-36, 38]
Major Disease Category 4 (MDC4, American diagnosis system corresponding to a single organ system or cause) and *disabling diagnosis* (system to score the burden of 'disability' and assess its relevance to outcomes of acute hospital admissions) were assessed in three studies of febrile patients and admitted general medical ED patients.[21, 34, 35] The high disability group and MDC4 were associated with increased mortality in ED patients.[21, 34, 35] The strongest associations of the MDC4 category for in-

hospital mortality were found to be Respiratory, Cardiac and Neurological in the admitted general medical ED patients.[34] The positive association between cardiac disease and increased risk of mortality was also demonstrated in the study of febrile patients.[21]Diabetes, seizure, dementia[38], presence of malignancy[26, 36], history of cancer[29] and metastatic neoplasm[31]were predictors of increased mortality present in the differentiated subgroups of patients presenting with syncope, triage category 1-3, arterial blood gas drawn, hyperglycaemic or triaged to the resuscitation room. In addition, an increase in the number of comorbidities was associated with increased mortality rates in admitted general emergency medical patients and patients discharged from the ED.[34, 35, 39] *Other predictors:* Additional predictors of clinical deterioration in patients with syncope were a recent visit for syncope (visits within 30 days of the index ED visit) [38], infection as the precipitating factor in hyperglycaemic patients[29]and multilobar infiltrates or pleural effusion detected by an X-ray in patients with pneumonia.[30]

Table 2 Study characteristics

Author	Year	Country	Population	Sample size (n)	Predictor assessed	Outcome	NOS
Cohort							
Barfod[23]	2012	Denmark	Patients >16 years admitted through the ED, to the ED observatory unit or to a general ward	6279	Triage Vital signs	MR ICU	9
Cattermole[40]	2014	Hong Kong	ED patients ≥18 years managed in the resuscitation room	234	Vital signs Biochemistry EWS	MR/ICU	9
Cattermole[31]	2009	Hong Kong	ED patients triaged to the resuscitation room	330	Vital signs Biochemistry Demography Comorbidity Clinical interventions	MR/ICU	9
Chen[41]	2014	China	ED patients with sepsis	680	EWS	MR ICU	9
Considine[22]	2009	Australia	ED patients triaged to low urgency	386 pairs	Vital signs Presenting complaints	MR	7
Conway[34]	2015	Ireland	Admitted ED medical patients	36.271	Triage EWS Biochemistry Demography Comorbidity Disabling diagnosis	MR	9
Conway[35]	2015	Ireland	Admitted ED medical patients	36.271	Triage EWS Biochemistry Comorbidity Disabling diagnosis Doctors experience	MR	9
Corfield[42]	2014	Scotland	ED patients with suspicion or confirmation of infection	2003	EWS	MR ICU MR/ICU	8

Derose[38]	2012	USA	ED patients with syncope or near syncope	22.189	Demography Comorbidity	MR	9
Gabayan[39]	2011	USA	Patients discharged from an ED to home or a non–acute care facility	475.829	Demography Comorbidity Discharge diagnosis	MR	9
Henriksen[25]	2014	Denmark	Admitted ED medical patients	1440	Vital signs	MR	9
Hong[27]	2013	Singapore	ED patients triaged to high urgency	1025	Vital signs Demography	ICU MR CA within 72 h	9
Huang[29]	2013	Taiwan	ED patients with hyperglycaemic crises	368	Vital signs Comorbidity Biochemistry	MR	9
Jellinge[32]	2014	Denmark	Admitted ED medical patients	5894	Biochemistry	MR	9
Jensen[33]	2015	Denmark	Consecutively admitted medical patients to the Acute Medical Department	11.998	Demography Comorbidity Biochemistry Current use of medicine	MR	9
Knott[21]	2004	Australia	Patients with a temperature of 38°C or greater	803	Vital signs Demography Comorbidity Biochemistry	ICU MR	9
Mikkelsen[37]	2009	USA	Patients with serum lactate level measured or a indicator of sepsis	830	Biochemistry	MR	9
Pedersen[36]	2015	Denmark	Patient having an arterial blood gas (ABG) sample drawn within 4 h of arrival to the ED	5360	Demography Comorbidity Biochemistry Discharge category	MR	9
Renaud[30]	2009	North America Europe	ED patients with pneumonia.	6560	Vital signs Demography Comorbidity Biochemistry	ICU	7
Ruwald[43]	2013	Denmark	All Danish residents with a first-time discharge for syncope from the ED	37705	EWS	MR CA within 1 week	8
Subbe[44]	2001	United Kingdom	Admitted ED medical patients	673	EWS	ICU	6
Yeh[45]	2014	Taiwan	Patients with two sets of blood culture	1063	EWS	MR	8
Cross-sectional study							
Oskay[26]	2015	Turkey	ED patients with a low to high triage urgency	770	Vital signs Comorbidity	MR	7
Case control							
Jessen[28]	2015	Denmark	Patients admitted to the ED who had a blood culture	224	Vital signs Biochemical tests Infection	ICU/MR	7

			drawn upon admission				

ICU: Intensive care unit. MR: Mortality. CA: cardiac arrest. EWS: Early warning score systems. Demography: e.g. age, sex. ABG: arterial blood gas

PACS: Singapore Patient Acuity Category Scale. TP≥38C: Patients with temperature ≥ 38 degrees Celsius

DISCUSSION

A total of 24 studies were included in this systematic review of generic predictors of clinical deterioration in adult ED patients. Statistically significant associations were found in 36 generic predictors. These were distributed as two 'presenting complaints', eight 'independent vital signs', twelve 'biochemistry tests', ten 'comorbidities' and four 'other predictors'. The predictors were primarily associated with ICU admission, mortality and, to a lesser extent, CA, as well as the composite outcome of ICU/MR.

Discussion of results

Consistent with previous studies, our results support the use of vital signs to identify patients at risk of clinical deterioration across subgroups in the ED setting. Across studies, RR, HR, GCS, SpO_2, SBP and, to a lesser extent, TP were independently associated with clinical deterioration. One study found a clear positive relationship between the number of abnormal vital signs and the risk of deterioration.[23] Compared to normal references, patients with a high RR and patients with a high HR were nine times and eight times more likely to experience clinical deterioration, respectively. Furthermore, patients with an abnormal GCS were found to be five times more likely to experience clinical deterioration. The findings of a high RR and a high HR being the most severe or strongest predictors of clinical deterioration among the vital signs are supported by a recent study of vital signs and EWS systems.[12]

Though abnormal vital signs clearly are predictors of clinical deterioration and vital signs are the main components of EWS systems, the effect of EWS systems on clinical outcomes remains ambigious.[10-12]As previously argued a possible explanation may be that the patient's condition has already deteriorated to a state difficult to reverse when the vital parameters triggered the EWS system.[16] Therefore, adding biochemical tests to EWS systems in order to increase their effects on outcomes has been a cause for much debate and investigation. We found bicarbonate and lactate to be the strongest biochemical predictors of clinical deterioration. Abnormally high bicarbonate tripled the risk of clinical deterioration, and patients with low bicarbonate were 20 times more likely to experience clinical deterioration. Patients with abnormally high lactate levels were 11 times more likely to experience clinical deterioration. Though certain biochemical tests may be strong predictors of clinical deterioration, findings of their ability to improve outcomes of clinical deterioration have been inconsistent.[46, 47] Therefore, adding, for example, lactate to an existing EWS system does not necessarily contribute to increased performance compared to an EWS based on vital signs only.[46]

Investigations of new biochemical tests not included in this review have originally been used for only small and very specific subsets of ED patients, or are not yet applied in routine ED care, may add to the understanding of how biochemical predictors can contribute to earlier identification of deteriorating patients. For example pro-adrenomedullin (a biomarker of inflammation), copeptin (a biomarker of stress) and procalcitonin (a biomarker of infection) have been studied for their ability to identify patients at risk of high treatment urgency. Pro-adrenomedullin proved to be the strongest predictor, particularly with regard to all-cause 30-day mortality.[48] The effects of introducing a nonspecific prognostic biomarker, such as soluble urokinase plasminogen activator receptor (suPAR), in emergency medicine have also been investigated. The combination of suPAR, The National Early Warning Score (NEWS), age and sex improved prediction of in-hospital-, 30-day and 90-day mortality compared to NEWS, age and sex alone.[49] Findings have also suggested that suPAR is superior to age, albumin, C-reactive protein and haemoglobin in the prediction of 30-day and 10-month mortality.[50]

While measurements of vital signs are readily available, the applicability of biochemical predictors in the ED depends on quick test results to ensure timely decision making and proactive treatment. We found positive and negative blood cultures to predict mortality. The results of these tests appear days after the ED situation, and their use for early identification of clinical deterioration is thus worthless. [35]Additionally, the findings of both positive and negative blood cultures versus none predict mortality and may be related to the underlying illness in the subgroup indicating a severity of the patients' symptoms when blood cultures are drawn. Consequently if biomarkers are going, to improve the performance of EWS systems, they should be analysed upon arrival at the ED, and test results should be readily available. New point of care testing equipment yielding fast and accurate test results are under development and may improve the use of biochemical tests in the early detection of clinical deterioration in ED patients.

We found that comorbidities predict clinical deterioration, though not all comorbidities were independent predictors of negative clinical outcomes. Studies have shown that comorbidities not only affect the prognosis of a disease directly and that the aggregation of comorbidities increases the risk of a negative clinical outcome, but also that comorbidities may indirectly affect a prognosis because they affect the choice of treatment.[51, 52] Therefore, it may be challenging to add comorbidities to existing EWS systems. Yet, it is important that clinicians take comorbidities into account when evaluating a patient's risk of clinical deterioration.

Corresponding with the predictors identified in our study, EWS systems rely to a great extent on objectively measurable parameters. We did not find any studies on subjective variables that fulfilled our inclusion criteria. However, studies from other specialized settings indicate that subjective assessments should also be considered in relation to clinical deterioration. In the surgical setting, nurses have been able to identify the

patient's deterioration before the EWS systems are triggered and have thereby been able to respond earlier when adding clinical concern.[1] Furthermore, adding clinical concern to EWS has shown a decrease in ICU transfers among children in the pediatric setting.[2] Thus, there seems to be a rather un-investigated field regarding the improvement of existing EWS systems.

It is important to note that we only investigated the association between predictors and clinical deterioration and not causality. Future investigations in this area should address the predictive validity and clinical impact of the identified predictors when added to existing EWS systems. Furthermore, future investigations should focus on clinical outcomes in a general ED population in order to support an adequate response to abnormalities and a more proactive treatment of patients at risk of clinical deterioration.

Strenghs and limitations

The review was based on rigorous methods. The comprehensive search strategy led to the identification of studies that in general were of high quality; however eight of the twenty four included studies had a NOS score below maximum score. Furthermore various predictors represent broad aspects and indicators of the clinical condition in the ED patients.

As to potential limitations, five areas needs to be further addressed. First, the risk of publication bias is a well-recognized limitation of systematic reviews.[53] We sought to minimize this by including studies in languages other than English in order to avoid bias introduced by the tendency to publish unique results in English journals and otherwise in a journal of native language. The large number of studies not fulfilling our inclusion criteria demonstrates the degree of difficulty in constructing a concise search in this area. This is mainly considered to be caused by a huge variability in the terms used for clinical deterioration and our choice of surrogates hereof. The inconsistency in the terms applied within the field may have increased the risk of missing relevant studies in the search applied. However, we sought to minimize this risk by an initial search for terms applied in the databases followed by a systematic search of the database based on all terms identified and finally, by systematically searching cross-references in articles from already included studies.

Second, clinical deterioration was previously defined by a change or movement from one clinical state to a worse clinical state with an increased risk of morbidity (e.g. organ dysfunction), a protracted hospital stay, disability or death.[19, 54] In 2018, after our search, a more operational definition was suggested defining clinical deterioration as 'a dynamic state experienced by a patient compromising hemodynamic stability, marked by physiological decompensating accompanied by subjective or objective findings'.[55] We chose to operationalize clinical deterioration as transfer to ICU or ICU admissions, CA and 30-day mortality. We

only included studies that discussed ICU admissions directly from the ED. Thus, multiple studies reporting other outcomes or were conducted on the clinical wards were excluded. The latter were excluded in order to increase the likelihood that the cause of the transfer or admission was related to the patient's condition, treatment and care during the stay in the ED. Furthermore, a shorter observation period than 30-day mortality would probably have increased the likelihood that death was related to circumstances in the ED.

Third, the identified predictors were often studied in subgroups of the ED population, e.g. in medical ED patients, which hampers the clinical applicability of the results in a general ED setting.

Fourth, heterogeneity between the studies was present due to different subgroups and we found that the data was too inhomogeneous to be pooled, eg. difference in study design, population etc. Therefore, we were not able to strengthen the evidence by combining data and perform a Meta analysis. The focus of this review was to identify generic predictors that could be applied across the whole ED patient population. However, risk stratification tools like Wells score or HEART score for specific subgroups (eg. pulmonary embolism, acute coronary syndrome) may provide more accurate risk estimation. Accordingly, our study illustrates the difficulties in finding predictors applicable in the ED population as a whole.

Finally, besides from GCS, we only included studies that discussed non-compounded predictors and thus excluded those that discussed composite predictors. The reason for this was that we wanted to ensure that the isolated association related to a single predictor was estimated. This would form the basis for assessment of whether adding a specific predictor to existing EWS systems could potentially improve the system's ability to detect clinical deterioration.

CONCLUSIONS

Thirty-six predictors significantly associated with clinical deterioration in adult ED patients were identified. The predictors included presenting complaints, vital signs, biochemical tests, comorbidities and other predictors all reflect the complexity of the nature of the deteriorating patient. Based on our findings, further attention should be paid to the use of vital signs, biochemical tests and comorbidities as predictors of clinical deterioration. However, the potential of these predictors to assist in the treatment of deteriorating patients and thereby improve clinical outcomes needs further investigation.

List of abbreviations

ABG Arterial blood gas
AMU Acute medical unit
BP Blood pressure
CA Cardiac arrest

ED Emergency Department
EWS Early warning score
GCS Glasgow coma score
HR Heart rate
ICU Intensive Care Unit
MDC4 Major Disease Category 4
MR Mortality rate
NEWS National Early Warning Score
NOS Newcastle-Ottawa Scale
PACS Singapore Patient Acuity Category
PaO_2 Partial pressure of oxygen
PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT Randomised controlled trial
RR Respiratory rate
SBP Systolic blood pressure
SpO_2 oxygen saturation
suPAR soluble urokinase plasminogen activator receptor
TP Temperature

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

All authors contributed to the study design, acquisition, analysis and interpretation of the data and revision of the manuscript. All authors read and approved the final manuscript.

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None.

SUPPLEMENTARY FILES I-III

I SEARCH STRATEGY PUBMED

((((((("Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh]) OR "Clinical Trial"[Publication Type]) OR ("Observational Studies as Topic"[Mesh] OR "Observational Study"[Publication Type])) OR "Random Allocation"[Mesh]) OR "Double-Blind Method"[Mesh]) OR "Single-Blind Method"[Mesh]) AND ((((((((((("Clinical deterioration"[All Fields] OR deteriorated[All Fields]) OR deterioration[All Fields]) OR deteriorations[All Fields]) OR "deteriorating patients"[All Fields]) OR "deteriorating patient"[All Fields]) OR worsening[All Fields]) OR "critical condition"[All Fields]) OR "critical conditions"[All Fields]) OR deteriorate[All Fields]) OR ((((((((((((((("Adverse outcome"[All Fields] OR "Adverse outcomes"[All Fields]) OR "Adverse medical events"[All Fields]) OR "Adverse medical event"[All Fields]) OR "adverse event"[All Fields]) OR "adverse events"[All Fields]) OR "safety event"[All Fields]) OR "safety events"[All Fields]) OR "Heart Arrest"[Mesh]) OR "Respiratory suppression"[All Fields]) OR "Respiratory depression"[All Fields]) OR "respiratory arrest"[All Fields]) OR "Death, Sudden"[Mesh]) OR "Death, Sudden"[All Fields]) OR "Death"[Mesh]) OR "Death"[All Fields]) OR ((((("admissions"[All Fields] OR "admission"[All Fields]) OR "transfers"[All Fields]) OR "transfer"[All Fields]) AND ((((("Critical Care Nursing"[Mesh] OR "Critical Care Nursing"[All Fields]) OR "Intensive Care Units"[Mesh]) OR "Intensive Care Units"[All Fields]) OR "Critical Care"[Mesh]) OR "Critical Care"[All Fields])))) AND (("acute admission unit"[All Fields] OR "acute medical unit"[All Fields]) OR ((((("emergency service, hospital"[MeSH Terms] OR ("emergency"[All Fields] AND "service"[All Fields] AND "hospital"[All Fields]) OR "hospital emergency service"[All Fields] OR ("emergency"[All Fields] AND "department"[All Fields]) OR "emergency department"[All Fields]) OR (("accidents"[MeSH Terms] OR "accidents"[All Fields] OR "accident"[All Fields]) AND ("emergency medicine"[MeSH Terms] OR ("emergency"[All Fields] AND "medicine"[All Fields]) OR "emergency medicine"[All Fields]))) OR ("emergency service, hospital"[MeSH Terms] OR ("emergency"[All Fields] AND "service"[All Fields] AND "hospital"[All Fields]) OR "hospital emergency service"[All Fields] OR ("accident"[All Fields] AND "emergency"[All Fields] AND "department"[All Fields]) OR "accident and emergency department"[All Fields])) OR ("emergency medical services"[MeSH Terms] OR ("emergency"[All Fields] AND "medical"[All Fields] AND "services"[All Fields]) OR "emergency medical services"[All Fields])))) AND ((((((("risk assessment"[MeSH Terms] OR "risk assessment"[All Fields]) OR ("precipitating factors"[MeSH Terms] OR ("precipitating"[All Fields] AND "factors"[All Fields]) OR "precipitating factors"[All Fields] OR "triggers"[All Fields])) OR ("risk factors"[MeSH Terms] OR "risk factors"[All Fields])) OR predictor[All Fields]) OR predictors[All Fields]) OR prediction[All Fields])) AND (Danish[lang] OR English[lang] OR Norwegian[lang] OR Swedish[lang])

II Risk of bias table for publications on risk factors

Author and year	Country	Risk of bias			
		Selection	Comparability	Exposure/ outcome	NOS-score
Cohort					
Barfod et al. 2012[23]	DK	****	**	***	9
Cattermole et al. 2014[40]	HK	****	**	***	9
Cattermole et al. 2009[31]	HK	****	**	***	9
Chen et al. 2014[41]	CHN	****	**	***	9
Considine et al. 2009[22]	AUS	**	**	***	7
Conway et al. 2015[34]	IRL	****	**	***	9
Conway et al. 2015[35]	IRL	****	**	***	9
Corfield et al. 2014[42]	SCT	****	*	***	8
Derose et al. 2012[38]	USA	****	**	***	9
Gabayan et al. 2011[39]	USA	****	**	***	9
Henriksen et al. 2014[25]	DK	****	**	***	9
Hong et al. 2013[27]	SGP	****	*	***	9
Huang et al 2013[29]	TW	****	**	***	9
Jellinge et al. 2014[32]	DK	****	**	***	9
Jensen et al. 2015[33]	DK	****	**	***	9
Knott et al 2004[21]	AUS	****	**	***	9
Mikkelsen et al. 2009[37]	USA	****	**	***	9
Pedersen et al. 2015[36]	DK	****	**	***	9
Renaud et al. 2009[30]	NA/ EUR	***	**	**	7
Ruwald et al. 2013[43]	DK	***	**	***	8
Subbe et al. 2001[44]	UK	****		**	6
Yeh et al. 2014[45]	TW	****	*	***	8
Cross-sectional study					

Oskay et al. 2015[26]	TUR	****		***	7
Case control					
Jessen et al. 2015[28]	DK	**	**	***	7

III Table of identified predictors and their association with clinical deterioration (ICU admission, cardiac arrest and mortality)

Predictor	Classification	Level	ICU admission	Cardiac arrest	Mortality	Composite
Presenting complaint						
Presenting complaint	Nausea, vomiting and diarrhea		↑[22]*			
	Jaundice				↑[21]	
Independent vital signs						
RR	High	>20	→[27]	↑[27]	↑ [27]	↑[31]*
		26-30	↑[23]*		→[23]	
		31-35	↑[23]*		↑[23]	
		≥30	↑ [30]			
		>35	↑[23]*		↑[23]	
	When evaluated as a continuous variable		↑[21]		↑ [21] [26]	→[28]
	Abnormalities at Triage		↑[22]*			
	Abnormal at first nursing assessment		↑[22]*			
HR	Low	<40	→[23]*		→[23]*	
		40-49	→ [23]		→[23]*	
		<60	↑ [27]	→ [27]	→ [27]	
		≤100			↑[29]	
	High	>100	↑ [27]	→ [27]	→ [27]	↑[31]*
		111-120	↑[23]		↑[23]*	
		121-130	↑[23]		↑[23]*	
		≥125	↑[30]			
		>130	↑[23]*		↑[23]*	
	When evaluated as a continuous variable – OR increases incrementally with each unit increase		↑[21]			→[28]
	Abnormalities at Triage	<60 or >100	↑[22]*			
	Abnormalities at first nursing assessment	<60 or >100	→ [22]*			
GCS	Abnormal	<15	↑[27]	↑[27]	↑[27]	→[28]
		14	↑[23]		→[23]	
		8-12				↑[31]*
		9-13	→[23]		↑[23]	
		<9				↑[31]*
		<8	↑[23]		↑[23] [29]	
SpO_2/ SaO_2		<95	→[27]	→[27]	→[27]	
		90-94	→[23]		↑[23]	
		90-95				→[31]
		80-89	↑[23]		↑[23]	
		<90				→[31]
		< 80	↑ [23]		↑[23]	
	When evaluated as a continuous variable				↑[26]	
	Abnormalities at Triage					→[22]
	Abnormal at first nursing assessment					→[22]
SBP	Low	80-89	↑[23]*		↑[23]	
		<80	↑[23]*		→[23]	
		<90	→[27]	→[27]	↑ [29] → [27]	↑[28]
	High	>140	↓[27]	↓[27]	↓[27]	

	When evaluated as a continuous variable				↓ [26]	
	Abnormalities at Triage					→[22]
	Abnormal at first nursing assessment					→[22]
DBP	Low	<60	→[27]	→[27]	→[27]	→[31]
	High	>95	→[27]	→[27]	→[27]	
		>90				→[31]
Temperature	When evaluated as a continuous variable					↓[28]
	Abnormalities at Triage					↑[22]*
	Abnormal at first nursing assessment					→[22]
	>37.2					→[31]
Mean arterial pressure	When evaluated as a continuous variable					→[28]
No. abnormal vital signs	1		↑[23]*		↑[23]* [25]*c	
	2		↑[23]*		↑[23]*	
	3		↑[23]*		↑[23]*	
	4				↑[23]*	
Biochemical tests						
Sodium		<130mEg/L	↑[30]			
	High	>145 mmol/L				↑[31]*
Glucose	High	>7.0 mmol/L				↑[31]*
Leukocytes	< 3 or ≥ 20 G/L		↑[30]			
	High	>10.7				↑[31]*
	Low	<4.0				↑[31]*
	When evaluated as a continuous variable				→[21]*	
Bicarbonate	High	>26 mmol/L				↑[31]*
		<21.8 or >26.2				→[28]
	Low	<22 mmol/L				↑[31]*
Lactate		2-3.9 mmol/L			↑[37] [36]	
		≥4			↑[37] [36]	
		>2.5 mmol/l.			→[28]	
Blood culture		Neg			↑[35] [34]	
		Pos			↑[35] [34]	
Potassium	Hyperkalaemia	>5.1				→[31]*
	Hypokalaemia	<3.5				→[31]*
		<3.4			↑ [33]Cb →[33]Ca	
		2.9-3.3			↑[33]Cb →[33]Ca	
		<2.9			↑[33]Ca [33]Cb	
	When evaluated as a continuous variable	0.1 mmol/L decline in plasma [Kþ] below 3.4 mmol/L.			↑[33]Ca [33]Cb	
Hemoglobin		>16.7g/dl				→[31]
		<10g/dl			↑[29]	
		<13.2g/dl				→[31]
Haematocrit	High	>50				→[31]
	Low	(<39				→[31]
Albumin	High albumin	>44g/L			→[32]	
	Hypoalbuminemia	<35g/L			↑[32]	

	Albumin as a continius variable (g/L)				↓[32]	
Creatinine		>1.5mg/L				→[28]
		>106 μmol/L				→[31]
		<62 μmol/L				→[31]
Arterial pH		<7.35	↑[30]			→ [31]
		>7.45				→[31]
		Abnormal pH (pH<7.37 or pH>7.45.)				→[28]
Blood urea nitrogen		≥11mmol/L	↑[30]			
Bilirubin		>50 μmol/L				→[28]
PaO_2	<9kPa or need of mechanical ventilation					↑[28]
	Oxygen saturation<90% orPaO_2<60mmHg		↑[30]			
Comorbidity						
Heart failure (NYHA class 2-4)						→[31]*
Metastatic neoplasm history						↑[31]*
Disabling	Groups	1			→[35] [34]	
		2			→[35] [34]	
		3			→[35] [34]	
		4			↑[35] [34]	
		5			↑ [34]	
Major disease category	Respiratory				↑[34]	
	Cardiac				↑[34] [21]*	
	Neurology				↑[34]	
Diabetes					↑[38]*[c]	
Seizure					↑[38]*[c]	
Dementia					↑[38]*[c]	
Cancer history					↑[29]	
Malignancy					↑ [26] [36]	
Liver cirrhosis						→[31]
Chronic renal insufficiency						→[31]
Immunocompromise						→[31]
Hypertension					→[38]*	
Dysrhythmia					→[38]*	
Valvular heart disease					→[38]*	
Myocardial infarction					→[38]*	
Cerebrovascular disease					→[38]*	
Gastrointestinal hemorrhage					→[38]*	
Uncategorized						
Resent visit for syncope					↑[38]*[c]	
Clinical interventions	CPR					↑[31]*
Infection as the precipitating factor					↑[29]	
Unknown infection focus						→[28]
Multilobar infiltrates or pleural effusion			↑[30]			
Current use of diuretics or b-agonists					→[33]	

*↑: increased risk. →: non significant. ↓: decreased risk. SBP: systolic blood pressure. DBP: diastolic blood pressure. *: unadjusted. a: 0-7 days mortality. b: 8-30 days mortality. c: hazard ratio. CPR: Cardiopulmonary resuscitation*

Abbreviations: ICU- Intensive Care Unit admission, CA- cardiac arrest, MR- mortality rate, ICU/MR- composite outcome of ICU and MR, OR (95%CI)- odds ratio with corresponding 95% confidence interval, PaO_2- partial pressure of oxygen.

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Tygesen GB, Kirkegaard H, Raaber N, Rask MT, Lisby M.
Consensus on predictors of clinical deterioration in emergency departments: a Delphi process study.

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PAPER II

Title page

Consensus on predictors of clinical deterioration in emergency departments: a Delphi process study

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ABSTRACT

Background: To increase patient safety and reduce patient deterioration in emergency departments, additional methods are needed to discover clinical deterioration at an earlier stage. The aim of this study was to determine the relevance and applicability of generic predictors of clinical deterioration in emergency departments.

Methods: Thirty-three predictors of clinical deterioration identified in the literature were assessed in a modified two-stage Delphi process. Sixty-eight emergency medicine clinicians (physicians and nurses) participated in the first round and 48 in the second round. The panel members were asked to rate the proposed predictors for relevance (relevant marker of clinical deterioration) and applicability (indicates change in clinical presentation over time, generic in nature and possible to detect bedside).

The panel was asked to rate their level of agreement on a 9-point Likert scale. They were also invited to propose additional generic predictors between the two rounds. New predictors suggested by more than two clinicians were included in the second round along with non-consensus predictors from the first round. Final decisions of non-consensus predictors after the second round were made by a research group and an invited impartial physician with considerable clinical experience in emergency medicine.

Results: The Delphi process resulted in 19 relevant and applicable predictors based on vital signs (n = 8), biochemical tests (n = 8), objective clinical observations (n = 1) and subjective clinical observations (n = 2).

Conclusion: The Delphi process guided the selection of 19 potential predictors of clinical deterioration widely accepted as relevant and applicable in emergency departments.

1 INTRODUCTION

Clinical deterioration in hospitalised patients is often preceded by deterioration in physiological parameters.[1] In 1997, Morgan et al. [2] proposed the first early warning score (EWS) system to alert clinicians to deteriorating patients using an aggregated, weighted score of vital signs. Early warning scores generally have a track (abnormal vital signs) and a trigger (predetermined calling or response criteria).[3] The predetermined calling or responses of the EWS often consist of increased observation, alerts to senior nursing and medical staff and review by critical care outreach teams.[4] A systematic review identified 28 early warning systems used in emergency departments (EDs) and found that they predicted adverse outcomes, such as mortality and intensive care unit/hospital admissions, in adult patients.[5] However, a lack of high-quality studies examining the effects on patient outcomes was also noted.[5]

Today, track-and-trigger systems are implemented in many EDs, but these systems designed for inpatients cannot be expected to perform as well when applied to patients in EDs because differences in the case mix create different probabilities of deterioration.[4, 6] Despite implementation of EWSs and track-and-trigger systems, 12–31% of ED patients still deteriorate and have increased risk of adverse outcomes.[7-10]

New approaches, such as adding biomarkers and more subjective parameters (e.g., clinical concerns), have been suggested to identify patients at risk of clinical deterioration at even earlier stages, thus enhancing proactive treatment and thereby decreasing adverse outcomes. Biomarkers in EWS systems increase the ability to predict clinical deterioration in some populations and settings.[5, 11] In addition, structured use of nurses' clinical intuitions or concerns have been shown to identify clinical deterioration earlier than a trigger threshold to call a rapid response team.[12] However, it is yet unknown whether adding such new predictors may help ED clinicians detect clinical deterioration earlier. To improve patient safety in EDs, the aim of this Delphi study was to determine the relevance and applicability of potential predictors of clinical deterioration in EDs identified in the literature.

2 METHODS

2.1 Study design

From December 2016 to January 2017, we used a modified two-stage Delphi technique[13] to identify consensus-derived predictors of clinical deterioration. The consensus process was originally developed by Helmer and Dalkey[14] and is often used to address complex problems that exceed the analytic capabilities of one person and must be addressed by a group of experts.[15, 16] In this study, we asked the panel members to rate potential predictors of clinical deterioration in EDs relative to the following two dimensions (with relevance being superior to applicability):

Dimension 1: Relevance

- Relevant marker of clinical deterioration in EDs

Dimension 2: Applicability

a) Capable of indicating a change over a short time (hours) while in the ED
b) Generic in nature
c) Possible to detect bedside (i.e., evident while the clinician is present)

2.2 Delphi panel

The panel members in this study were doctors and nurses with at least two years of experience in EDs or working with emergency medicine patients. At the time of the study, Denmark had no specialty in emergency medicine; however, the Organization of Danish Medical Societies had defined a supra-specialty in emergency medicine in which medical specialist could be certified if fulfilling a curriculum close to what was defined by the European Association of Emergency Medicine.[17]

The participants were recruited from three Danish healthcare organisations: 1) Danish Society of Anaesthesiology and Intensive Care Medicine, representing 1,437 anaesthesiologists and doctors in intensive care medicine; 2) Danish Emergency Nursing Association, representing 163 nurses in emergency medicine; and 3) The Organization of Danish Medical Societies, representing 125 scientific

societies in medicine with 25,000 members. Each organisation was asked to invite members according to the abovementioned criteria.

2.3 The Delphi process

2.3.1 Predictors

The panel was asked to reach consensus on 33 predictors of clinical deterioration in EDs identified from the literature (Appendix).[10,11,18-39]

The predictors were classified into three categories: biochemical tests (n = 16), vital signs and parameters (n = 10) and clinical symptoms and signs (n = 7).

2.3.2 First round

A questionnaire presenting the 33 predictors was distributed to the panel members individually by e-mail, and the web-based surveys were completed using the Research Electronic Data Capture hosted at Central Denmark Region. Two reminders were sent for each round. Panel members were requested to rate the predictors based on their professional knowledge and experience without considering costs. If a panel member did not have sufficient knowledge to rate a predictor, they were given an option to tick a box labelled 'don't know'. They were also encouraged to include written comments to support or qualify their scores. Finally, they were invited to suggest additional relevant predictors based on their clinical experience. For each predictor, the panel members were asked to indicate their extent of agreement on a scale from 1 (completely disagree) to 9 (completely agree) to statements regarding relevance and applicability.

2.3.3 Second round

In the second round, panel members were asked to reassess the clinical relevance of non-consensus predictors from Round 1 based on the overall median score and interquartile range (IQR), a reminder of their own personal score and anonymous comments made by the panel members (see Table 1 for example).

In addition, they were asked to rate new predictors, which had to be suggested by more than one panel member from round 1 to be included in Round 2.

Table 1: Example of predictor presentation in Round 2 with the panel's scores, reminder of personal score and additional comments

To what extent do you agree that sodium is a relevant predictor of clinical deterioration?									
1. Strongly disagree ○	2 ○	3 ○	4 ○	5 ○	6 ○	7○	8 ○	9. Strongly agree ○	Don't know ○
In the first round, you answered [x], and the panel's median score was 7 (IQR: 4–9).									
The comments from the panel in the first round: • Best to substantiate clinical suspicions and some poisoning conditions • Abnormal sodium is rarely treated urgently • Bedside assessment requires an arterial blood gas • Very low sodium does not necessarily have to be corrected quickly in the ED due to the risk of "osmotic demyelination syndrome (ODS)" • Chronically low in patients with alcohol use disorder • Must be assessed in relation to the problem and the individual patient • May be relevant in hyponatremia • Slow marker									

IQR Interquartile range

2.4 Analysis

Consensus on inclusion of a predictor was considered by a median score and interquartile range (IQR) of 7–9 and exclusion by a median and IQR of 1–3.[40] All other scores were considered non-consensus or equivocal, requiring panel reassessment in Round 2. That is, a predictor with non-consensus in relevance and not excluded based on applicability was sent to Round 2 for reassessment unless the panel members had indicated concerns regarding the predictor (e.g., overlapping with other predictors). The purpose of the three questions related to applicability was to support and refine the decision of whether to include or exclude a non-consensus predictor and thus determine whether it should proceed to the second round.

After the first round of the Delphi process, the research group (GB, HK, MTR, ML) met to ensure that each predictor was handled in accordance with the aforementioned criteria together with comments suggesting that a predictor was not exclusive. After the second round, the final decision regarding non-consensus predictors was made by the research group and an invited impartial doctor with considerable clinical experience in emergency medicine (NR), who had not participated as a panel member or in any

of the previous work related to the Delphi study. Decisions of inclusion or exclusion of non-consensus predictors were based on the above-mentioned criteria and panel members' comments. In case of disagreement, the impartial expert's opinion was implemented. To capture any differentiated effect due to tiered dropouts, we performed sub-analyses excluding the anaesthesiologists and doctors in intensive care medicine.

2.5 Ethics

The collected data were anonymised. The study was approved by the Danish Data Protection Agency (J no. 1-16-02-34-16). Danish legislation exempts this type of study from approval.

3 RESULTS

3.1 Response rate

The 68 panel members participating in the first round of the Delphi process included 29 anaesthesiologists and doctors working in intensive care medicine (43%), 23 emergency medicine nurses (34%) and 16 doctors with a supra-specialty in emergency medicine (23%). In the second round, the 48 panel members who participated included 25 anaesthesiologists working in intensive care medicine (52%), 14 emergency medicine nurses (29%) and nine emergency medicine doctors (19%). There was a dropout rate of 29%.

3.2 First round

Consensus on clinical relevance was reached for 13 of the 33 predictors (Figure 1): serum bicarbonate, serum lactate, serum pH, serum potassium, glucose, serum leukocyte count, respiratory rate, saturation, systolic blood pressure, altered mental state, pulse rate, dyspnoea and electrocardiogram (Table 2). None of the predictors in this round were rated as clinically irrelevant (median or IQR = 1–3).

No consensus for clinical relevance was reached for 20 predictors. Nine of these predictors were excluded, and 11 were sent to the second round. The research group decided to exclude blood culture, albumin, urea, suspicion of infection, aspiration and vomiting based on several written comments from the panel on the predictors not being relevant in the clinical ED setting due to e.g., analysis time, response time and disagreement on the its ability to function as a predictor in the ED. In addition, erythrocyte, bilirubin and haematocrit were excluded due to comments of overlap with other predictors. The panel suggested five additional predictors: serum C-reactive protein, reduced urine production, anxiety, relatives' concerns and skin condition (i.e., cold, clammy, pale and cyanotic; Table 2). The latter three were primarily suggested by nurses. The predictors were added to the survey, and a total of 16 predictors were assessed in Round 2 (Figure 1).

The sub analysis of clinical relevance without anaesthesiologists and doctors in intensive care medicine showed similar results with a very small deviance on temperature (median = 8, IQR = 7–9) and electrocardiogram (median = 9, IQR = 6–9). The deviance would have led to inclusion of temperature

in Round 1 instead of 2 and non-consensus regarding electrocardiogram in Round 1; however, this would not have changed the overall results.

3.3 Second round

In Round 2, the panel reached consensus on the clinical relevance of two of 16 predictors: temperature and skin condition, leaving 14 non-consensus predictors. The research group excluded 10 predictors and included the following four predictors: C-reactive protein, serum haemoglobin, pain and relatives' concerns (Figure 1, Table 2). Haemoglobin, C-reactive protein and relatives' concerns reached equivocal ratings by the panel. The research group determined that because these indicators are easily accessible and apply to a broad ED population, they were included. The exclusion of sodium, creatinine, thrombocytes, diastolic blood pressure, capillary refill, nausea, diarrhoea, jaundice, reduced urine production and anxiety was based on the panel's written comments. These predictors overlapped with others or required repeated measurements (e.g. reduced urine production requires continuous hourly measurement of diuresis).

The panel rarely used the option to skip a question, apart from urea, which was only rated by 13 of 68 panel members. A sub analysis of the predictor's clinical relevance when excluding anaesthesiologists and doctors in intensive care medicine showed a minor deviance on jaundice (median = 5.0, IQR = 3.5–6.0). This deviance would have led to the exclusion of jaundice by the panel and not the research group.

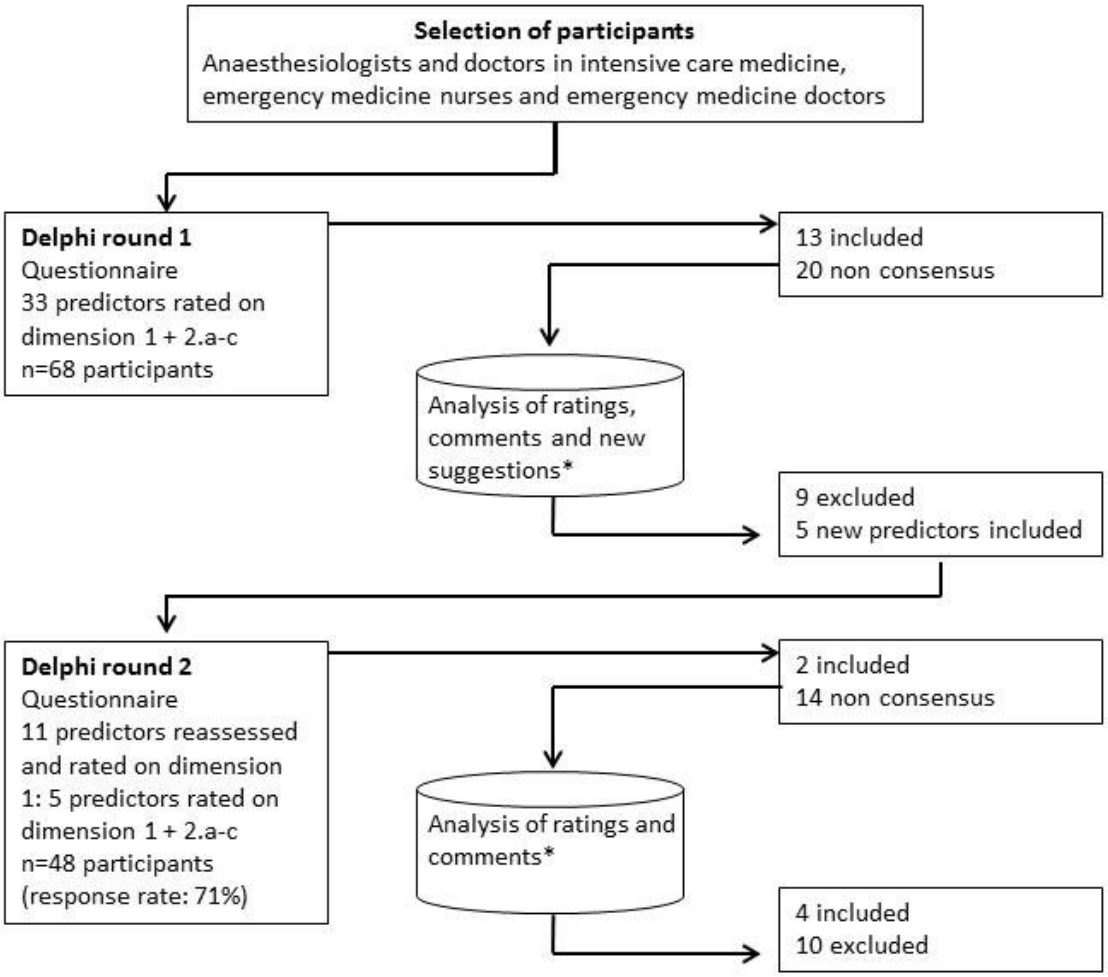

Figure 1. A Ggeneral overview of the two-round Delphi process.

Note: Dimension 1 refers to the predictor's relevance (relevant marker of clinical deterioration in EDs). Dimension 2a–c refers to applicability: a) capable of indicating changes over a short time, b) generic in nature and c) possible to detect bedside.

* The research group evaluated non-consensus predictors and excluded those that were considered as overlapping with other predictors according to the panel's comments. The final decisions on non-consensus predictors after the second round were made by the research group and an invited impartial expert in emergency medicine; decisions of inclusion or exclusion of non-consensus predictors were based on the ratings and the panel's comments.

Table 2. Included and excluded predictors in the Delphi process

Predictor	Round 1 (n = 68)				Round 2 (n = 48)				Decision
	Relevance	Applicability			Relevance	Applicability			
	1	2a	2b	2c	1	2a	2b	2c	
	Median Score (IQR)				Median Score (IQR)				
Biochemical tests									
Bicarbonate	9 (7–9)	9 (7–9)	7 (5–9)	7 (4–9)					In
Lactate	9 (8–9)	9 (8–9)	8 (5–9)	8 (2–9)					In
pH	9 (9–9)	9 (8.8–9)	9 (5–9)	9 (7–9)					In
Potassium	8 (7–9)	8 (7–9)	7 (5–9)	7 (3–9)					In
Glucose	8 (7–9)	8 (6–9)	7 (5–9)	8 (5.5–8)					In
Leucocytes	8 (7–9)	7.5 (6–9)	7 (4–9)	3 (1–6)					In
Haemoglobin	6 (4–9)	8 (7–9)	7 (5–9)	7 (4–8)	6 (4.5–7)[5]				In
Sodium	7 (4–9)	7 (6–9)	7 (5–8)	6.5 (2–8)	6 (4–7)[4]				Ex
Creatinine	8 (6–9)	8 (6–9)	7 (4–8)	4.5 (2–7)	7 (5.5–9)[4]				Ex
Thrombocytes	6 (5–8)	7 (5–9)	6 (3–8)	2 (1–5)	6 (5–7)[4]				Ex
Erythrocyte	4.5 (2–7)[4]	6 (5–7)	6 (3–7)	3 (1–6)					Ex
Albumin	5 (3–6)[2]	5.5 (4–8)	5 (3.5–7)	3 (1–5)					Ex
Bilirubin	6 (5–7)[4]	7 (5–8)	5 (4–7)	5 (2–7)					Ex
Haematocrit	6 (4–7)[4]	7 (5–8)	6 (4–8)	5 (2–7)					Ex
Blood culture	7 (4–9)[1]	6 (3.5–8)	5 (2–9)	1 (1–4)					Ex
Urea	2 (1–5)[1,3]	5 (2–6.6)	4 (2–6)	1 (1–3)					Ex
Vital signs/parameters									
Respiratory rate	9 (9–9)	9 (8.5–9)	8 (6–9)	9 (9–9)					In
Saturation	9 (8–9)	9 (8–9)	8 (5–9)	9 (9–9)					In
Systolic blood pressure	9 (8–9)	9 (8–9)	8 (6–9)	9 (9–9)					In
Altered mental state	9 (8–9)	9 (8–9)	7 (4–9)	9 (9–9)					In
Pulse rate	9 (8–9)	9 (8–9)	8 (6–9)	9 (9–9)					In
Dyspnoea	9 (7.5–9)	9 (8–9)	7 (4–9)	9 (8–9)					In
Electrocardiogram	9 (7–9)	9 (8–9)	7 (4–8)	8 (8–9)					In
Temperature	8 (6.5–9)	9 (7–9)	7 (4–9)	9 (8–9)	8 (7–8.5)				In
Diastolic blood pressure	8 (6–9)	8 (6–9)	6 (5–9)	9 (8–9)	7 (5.5–9)[4]				Ex
Capillary refill	8 (6–9)	8 (6–9)	7 (4–9)	9 (9–9)	7 (5–8.5)[4]				Ex
Clinical symptoms and signs									
Pain	7 (6–9)	8 (7–9)	5 (3–8)	9 (7.5–9)	7 (5–7.5)[5]				In
Nausea	5 (4–7)	6 (5–7)	5 (2–6)	8 (6–9)	5 (3–6)[4]				Ex
Diarrhoea	6 (3–7)	6 (4–7)	4 (3–7)	8 (7–9)	5 (3–6)[4]				Ex
Jaundice	7 (5–8)	6 (5–8)	5 (4–7)	8 (7–9)	5 (4–7)[4]				Ex
Suspicion of infection	8 (5.5–9)[1]	7 (4–8.5)	5 (3–7)	7 (5–8)					Ex
Aspiration	8 (5–9)[1]	6 (3–8)	5 (2–7)	7 (5–9)					Ex

Vomiting	6 (5–7)[1]	6 (5–7)	5 (2–7)	8 (7–9)					Ex
Suggested in Round 1									
Skin (cold, clammy, pale and cyanotic)					8 (7–9)	8 (7–9)	8 (6–9)	9 (8–9)	In
C-reactive protein					7 (6–8)[5]	7 (6.5–8.5)	7 (5–8)	2 (1–5)	In
Relatives' concerns					6 (4–7)[5]	6 (3–7)	5 (2–6)	6 (5–8)	In
Reduced urine production					8 (6–9)[4]	8 (7–9)	7 (5–8)	8 (7–9)	Ex
Anxiety					4 (2–6)[4]	3 (2–6)	4 (2–6)	7 (5–9)	Ex

Note: 1–4 indicates whether a predictor was excluded based on the rating of the predetermined dimensions: 1) written comments that it is not a relevant predictor (Dimension 1); 2) inability to indicate change over time (Dimension 2a); 3) no bedside determination (Dimension 2c); and 4) written comments that it overlaps with another predictor, that it demands repeated measurements or other comments. 5 indicates non-consensus predictors included by the research group based on ratings and comments.

Abbreviations: IQR: Interquartile range, CP: Clinical practice, LS: Literature search, In: Included, Ex: Excluded.

4 DISCUSSION

A panel consisting of emergency medicine clinicians assessed 33 predictors of clinical deterioration in EDs identified from a literature search and five additional predictors suggested by the panel. During a two-stage Delphi process, 15 predictors were considered to be relevant and applicable for determining clinical deterioration. Four of the remaining non-consensus predictors were also included based on the panels' ratings and comments. The 19 predictors were classified into three categories: biochemical tests (serum c-reactive protein, serum bicarbonate, serum lactate, serum pH, serum potassium, glucose, leucocyte counts and serum haemoglobin); vital signs and parameters (respiratory rate, saturation, systolic blood pressure, altered mental state, pulse rate, dyspnoea, electrocardiogram and temperature); and clinical observations and parameters (skin conditions, pain and relatives' concerns).

4.1 Comparability with other findings

The 19 selected predictors reflect what clinicians in emergency medicine found clinically relevant and applicable for early detection of patient deterioration. The Delphi method is widely accepted as a systematic approach to reach consensus in emergency medicine.[41-44] It is often used to select indicators, particularly when parameter selection is complex and several experts' opinions are needed to answer questions in an iterative process.[16,41]

Unsurprisingly, several vital signs and biochemical tests are among the highest-ranked predictors (Dimension 1). Vital signs and EWS systems are used widely in EDs, and the selection of vital signs may therefore reflect clinicians' theoretical knowledge of predictors combined with clinical practice experience.[5,11,45] The vital signs in this study are similar to those included in two well-studied systems, the National Early Warning Score (NEWS) and the Modified Early Warning Score.[46]

In line with the present findings, biochemical tests are often used to predict risk of intensive care admission, cardiac arrest and mortality. Several studies have supported that clinicians perceive these tests as relevant markers of clinical deterioration.[19,28,31,32] Along with EWS systems, biochemical tests have been examined in various contexts but often in more select populations.[28,31] Thus, routinely available biochemical test (albumin, creatinine, haemoglobin, potassium, sodium, urea and leucocytes) tested together with NEWS have indicated better performance than NEWS alone in ED patients.[47,48] In our study, the panel found potassium, leucocytes and haemoglobin to be the most relevant predictors of

clinical deterioration in ED patients. Despite many studies investigating the addition of biochemical tests for vital signs in EWS systems, the results of clinical outcomes are still ambiguous.

Previous studies have shown that nurses in acute care settings tend to use subjective signs to recognise patient deterioration.[49,50] Subjective signs are described as 'subtle cues that arouse the suspicion of nurses but are difficult to quantify' and are among the most used criteria to recognise deterioration, even before the manifestation of objective signs.[49,51] In our study, only anxiety, pain (new or worsening/escalating pain) and relatives' concerns were suggested as subjective predictors of clinical deterioration, perhaps due to difficulties in describing and quantifying these signs.

Nonetheless, our findings are in line with a study examining criteria for when to call a physician regarding a patient of concern. The worrying symptoms was identified as respiratory, neurological and circulatory combined with signs such as new or escalating pain, unexpected recovery trajectory and new observations and symptoms, including patient's feeling of impending doom.[49]

Predictors suggested by the panel may also reflect specific professional practices. In the present study, nurses proposed objective and subjective predictors (skin condition, anxiety and relatives' concerns) that may be rooted in their clinical practice because nurses heavily use both subjective and objective observations to determine clinical deterioration.[52] In the present study, only skin observations were viewed as relevant by the entire panel. Other EWS systems, such as the single-parameter early warning criteria system used to activate a rapid response system team, use predictors such as concern and changes in skin colour.[45,53]

The predictors that the panel rated as relevant may aid in early detection of clinical deterioration and support the use of EWS systems, leading to positive impacts on clinical outcomes.

4.2 Strengths and limitations of this study

The initial predictors in the present study were based on published studies; thus, we may have overlooked predictors in the non-published literature. The predictors were identified in the literature search (Appendix), and their association with clinical deterioration was already established. We chose not to share the predictors' scientific strength with the panel to ensure that they based their ratings on clinical experience, knowledge and the predictors' applicability to standard care in EDs. Alternatively,

the selection of predictors could have been based on predictive values or associated risk, compromising the clinical perspective, transferability and applicability.

All panel members had clinical experience in different specialities of emergency medicine, strengthening the reliability of the findings. Most of the members participated in both Delphi rounds (68 in Round 1 and 48 in Round 2). Between the two voting rounds, the research group evaluated non-consensus predictors and excluded those that were considered as overlapping with other predictors according to the panel's comments. This process was done to avoid dropout caused by annoyance and workload. The dropout involved more nurses (13%) and doctors (10%) in emergency medicine than anaesthesiologists and doctors working in intensive care medicine. The distribution of the members could have favoured the choice of predictors related to the anaesthesiology speciality. However, based on the sub analysis, this did not seem to be the case, perhaps due to the four dimensions specifically related to EDs and the requirement of the clinicians to have clinical tasks in EDs.

The panel's scores and comments were included to increase the number of reasoned responses and decrease the number of rounds necessary to achieve consensus.[54] Additionally, to reduce the risk of random assessment, the clinicians had the option to respond 'don't know' if they had limited or no experience with a suggested predictor. Serum urea was the only predictor where this option was used by several panel members, indicating low bias related to random assessments. Consensus on predictors could have been increased by conducting more rounds in the Delphi process. However, more rounds may have also led to decreased participation, thus increasing random errors and reducing accuracy.[55] Furthermore, several studies have shown that the highest increase in consensus and feedback occurs between the first and second rounds.[55] Decisions on inclusion or exclusion of predictors by the research group were based on the panel's ratings and comments on relevance and applicability, leading to exclusion of nine predictors in Round 1 and 10 in Round 2 and inclusion of four in Round 2. Therefore, it could be argued that these decisions may have affected the final selection of predictors; however, we believe this risk to be of minor importance, as the decisions were based on thorough assessments of the panel's ratings and comments. While acknowledging these limitations, we believe that our study identifies generic predictors of clinical deterioration throughout the patient pathway in the ED, which has the potential to increase patient safety and inform further research.

4.3 Clinical implications and future studies

The study results suggest that clinicians perceive a broad range of predictors of clinical deterioration as important in the observation of ED patients. Awareness of predictors of clinical deterioration is essential to ensure patient safety in emergency care, predict adverse outcomes, allocate resources to deteriorating patients and escalate care and treatment. Future studies should investigate whether implementation and systematic monitoring of these 19 predictors can prevent adverse outcomes in a general ED population, preferably in controlled trials.

4.4 Conclusion

The Delphi process identified 19 potential predictors of clinical deterioration widely regarded as relevant and applicable. These indicators are considered to indicate change over time, be generic in nature and can be determined at the bedside in EDs.

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Patient consent for publication

Not required.

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Competing Interest

None declared.

Appendix: Applied Search Strategy Using PubMed

((((((("Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh]) OR "Clinical Trial"[Publication Type]) OR ("Observational Studies as Topic"[Mesh] OR "Observational Study"[Publication Type])) OR "Random Allocation"[Mesh]) OR "Double-Blind Method"[Mesh]) OR "Single-Blind Method"[Mesh]) AND ((((((((((("Clinical deterioration"[All Fields] OR deteriorated[All Fields]) OR deterioration[All Fields]) OR deteriorations[All Fields]) OR "deteriorating patients"[All Fields]) OR "deteriorating patient"[All Fields]) OR worsening[All Fields]) OR "critical condition"[All Fields]) OR "critical conditions"[All Fields]) OR deteriorate[All Fields]) OR ((((((((((((((("Adverse outcome"[All Fields] OR "Adverse outcomes"[All Fields]) OR "Adverse medical events"[All Fields]) OR "Adverse medical event"[All Fields]) OR "adverse event"[All Fields]) OR "adverse events"[All Fields]) OR "safety event"[All Fields]) OR "safety events"[All Fields]) OR "Heart Arrest"[Mesh]) OR "Respiratory suppression"[All Fields]) OR "Respiratory depression"[All Fields]) OR "respiratory arrest"[All Fields]) OR "Death, Sudden"[Mesh]) OR "Death, Sudden"[All Fields]) OR "Death"[Mesh]) OR "Death"[All Fields]) OR ((((("admissions"[All Fields] OR "admission"[All Fields]) OR "transfers"[All Fields]) OR "transfer"[All Fields]) AND (((((("Critical Care Nursing"[Mesh] OR "Critical Care Nursing"[All Fields]) OR "Intensive Care Units"[Mesh]) OR "Intensive Care Units"[All Fields]) OR "Critical Care"[Mesh]) OR "Critical Care"[All Fields])))) AND (("acute admission unit"[All Fields] OR "acute medical unit"[All Fields]) OR ((((("emergency service, hospital"[MeSH Terms] OR ("emergency"[All Fields] AND "service"[All Fields] AND "hospital"[All Fields]) OR "hospital emergency service"[All Fields] OR ("emergency"[All Fields] AND "department"[All Fields]) OR "emergency department"[All Fields]) OR (("accidents"[MeSH Terms] OR "accidents"[All Fields] OR "accident"[All Fields]) AND ("emergency medicine"[MeSH Terms] OR ("emergency"[All Fields] AND "medicine"[All Fields]) OR "emergency medicine"[All Fields]))) OR ("emergency service, hospital"[MeSH Terms] OR ("emergency"[All Fields] AND "service"[All Fields] AND "hospital"[All Fields]) OR "hospital emergency service"[All Fields] OR ("accident"[All Fields] AND "emergency"[All Fields] AND "department"[All Fields]) OR "accident and emergency department"[All Fields])) OR ("emergency medical services"[MeSH Terms] OR ("emergency"[All Fields] AND "medical"[All Fields] AND "services"[All Fields]) OR "emergency medical services"[All Fields])))) AND ((((((("risk assessment"[MeSH Terms] OR "risk assessment"[All Fields]) OR ("precipitating factors"[MeSH Terms] OR ("precipitating"[All Fields] AND "factors"[All Fields]) OR "precipitating factors"[All Fields] OR "triggers"[All Fields])) OR ("risk factors"[MeSH Terms] OR "risk factors"[All Fields])) OR predictor[All Fields]) OR predictors[All Fields]) OR prediction[All Fields])) AND (Danish[lang] OR English[lang] OR Norwegian[lang] OR Swedish[lang])

Similar searches based on the database's index words was applied to EMBASE, Cumulative Index to Nursing and Allied Health Literature, PsycINFO and Cochrane electronic databases for studies from 1990 to June 2016.

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Early warning score systems supplemented by huddles, simple clinical characteristics and subjective parameters decrease clinical deterioration in the emergency departments – a controlled intervention study. European Journal of Emergency Medicine
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PAPER III

Title

Early warning score systems supplemented by huddles, simple clinical characteristics and subjective parameters decrease clinical deterioration in the emergency departments – a controlled intervention study

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Abstract

Background: Early warning score (EWS) systems can predict adverse outcomes; however, the effect on clinical outcomes in emergency departments (ED) is ambiguous. Studies have suggested that adding subjective parameters to EWS systems might prompt more proactive treatment and positively affect clinical outcomes. The objective of the study was to investigate the effect of a modified EWS system consisting of vital parameters and objective and subjective clinical parameters in adult ED patients.

Methods: This is a controlled pre and post interventional study. In adult ED patients we examined if a conventional (EWS) system supplemented with clinical parameters and huddles of at-risk patients could reduce clinical deterioration. Supplemental parameters were: skin observation, clinical intuition and patients' and relatives' concerns, and pain and dyspnea reported by the patient. We also examined whether the aforementioned affected mortality, intensive care unit admissions or readmission compared to a conventional EWS system alone.

Results: We included 34,556 patients. Patients with two or more registered early warning scores were included in the primary analysis (N=21,839). Using difference-in-difference regression, we found a reduced odds of clinical deterioration of 21% (OR 0.79 95%CI [0.69; 0.90]) in the intervention groups compared with the controls. No impact on mortality, intensive care unit admissions, or readmissions was found.

Conclusion: The modified EWS system including vital signs, objective and subjective parameters aid to reduce the odds of clinical deterioration among an unselected adult population of ED patients.

INTRODUCTION

Clinical deterioration (CD) in emergency departments (EDs) is an important issue in patient safety; 12–31% of patients deteriorate during their time in the ED, with a subsequent increased risk of mortality[1-4]. CD can occur at any time during hospitalization[5] and is often preceded by abnormal vital signs 6–24 hours, or even up to 48 hours, before an adverse event[5-7].

Early warning score (EWS) systems are based on the measurement of vital signs and are used to identify patients at risk of CD[8]. The ability to predict CD based on vital signs and EWS systems is widely accepted[9,10] and EWS systems are now standard bedside monitoring practice[1-3]. Despite the widespread use of EWS systems, evidence of the effects on clinical outcomes is still lacking, specifically in EDs. In general, the lacking effect may be caused by insufficient monitoring and risk identification, leading to poor situational awareness[11,12]. Another reason may simply be that physiological monitoring via vital signs deviate late in the course of a disease, making improvement of the patient's condition more difficult[13].

Rapid response systems, implemented in general wards, use parameters such as intuition and concern in addition to vital signs[14]. Moreover, studies conducted in surgical departments and among children suggest that increasing nurses' situational awareness and adding subjective parameters, such as clinical concern and patients' and relatives' concerns, to the existing EWS systems may enhance their effect on clinical outcomes by prompting earlier, more proactive treatment[16,17].

The aim of the present study was to investigate the effect on CD when combining additional clinical parameters and huddles with an existing EWS.

METHODS

Study design

The study used a controlled pre-and-post design and included four regional EDs. Two EDs were appointed to the intervention group and two to the control. All EDs underwent a 6 month baseline period further on mentioned as the pre-intervention period (July-December 2016) and a 6 month post-intervention period (November 2017-April 2018).

Setting

Each hospital serves a population of 200.000-300.000 people in the Central Denmark Region. The involved EDs consist of an emergency room for minor medical and surgical patients and an integrated short stay unit (medical and surgical). Patients whose admission is expected to exceed 48 hours are transferred to inpatient units. Each ED has around 16,000 patients attending the emergency room only and 15,000-18,000 admitted to short stay units. Patients are referred by a general practitioner (GP) or a GP on out-of-hours service, conveyed by ambulance after an emergency call or by self-referral (minor part).

Patients

Inclusion criteria: Patients ≥ 18 years with medical or surgical complaints.

Exclusion criteria: minor medical or surgical injuries defined as patients with length of stay (LOS) less than four hours, and patients with cardiac arrest, trauma or medical or surgical resuscitations. Only the first admission in a study period was included.

Standard EWS

The standard EWS system based on National Early Warning Score was used for several years prior to study start. It included respiratory rate, saturation, systolic blood pressure, pulse rate, temperature and level of consciousness according to an "A-alert, V-verbal, P-pain, U-unresponsive" score with corresponding action algorithms (Supplementary files I). Each vital sign can be assigned 0-3 points where a higher score indicates more severe deterioration. They were aggregated to a score between 0 and ≥ 5. A score of 0-1 was considered low risk and reassessment within 8 hours. The score of 2 meant reassessment in 1 hour, and if the score was 3-4 or the patient had a single parameter with a score of 2, a physician assessed the patient. A senior physician assessed the patients with scores of ≥ 5.

Intervention - EWS

The intervention consisted of the standard EWS system and five additional parameters comprising clinical characteristics; 1) skin observations (cold, clammy, pale, and cyanotic), 2) dyspnea reported by the patient, 3) pain (new or increasing), 4) clinical concern and 5) patients' or relatives' concern.

In the modified EWS system, the nurse considered new or escalating deterioration if 1) the vital signs triggered the standard EWS (Supplementary file I) and/or if 2) one of the additional five

parameters were present. If deterioration was observed, a physician was called. In uncertain cases, the nurse reviewed the patient with an experienced nurse and called the physician if deterioration was suspected. Reassessment of the patient's condition and subsequent plan was then made including; actions to be taken and expected outcome, deadline for reassessment and precautions the nurse should take if the expected outcome was absent. At risk patients were highlighted at electronic dashboards and discussed amongst the care team in huddles (i.e. short team gathering including the nurse coordinator, senior consultant and nurse) twice a day in relation to symptoms, plan, and treatment response (Supplementary file II).

Prior to study start, the nurses had one and a half hours of introduction to the modified EWS system and huddles underpinning the underlying process in deteriorating. The physicians had a half hour introduction. The differences in the training program were due to different tasks. Local champions assisted the primary investigator in adherence (staff) to the protocol. In addition, the number of patients registered with the modified EWS in their electronic medical record was weekly assessed.

Outcome measures

The primary outcomes were CD defined as an increase in standard EWS from either 0 or1 to score ≥ 2, or an increase from score ≥ 2 and above[18]. That is a patient with an initial EWS of 4 and a follow-up EWS of 4 had no deterioration, whereas a patient with an initial EWS of 0 and a follow-up EWS of 2 had deteriorated. An increase in EWS from 0 to 1 was not considered deterioration.

In addition, a composite CD defined as CD in combination with death or ICU admission directly from ED.

The primary outcomes was measured as the difference in the proportion of CD between the pre and post intervention period adjusted with the control groups to account for variation over time.

Secondary outcomes: 1) proportion of 30-day readmission, 2) proportion of 7-day mortality, 3) proportion of 30-day mortality and 4) proportion of ICU admission.

Data on vital sign measurements, EWS, death, LOS and ICU admissions were retrieved from the hospitals' electronic medical record. To assist staff in all steps of the intervention, a template was constructed for data entry into the electronic medical record. Mortality data was obtained from the Danish Civil Registration System [19].

Statistical analysis

Sample size calculations were based on the assumptions: CD occurs in 12% of ED patients[1,18,20], and a clinically relevant reduction of 15% in the proportions of patients with CD, an 80% power and a significance level of 5%. Accordingly, the sample size comprised of 19,564 participants, with 4,891 in each of the four EDs (pre- and post periods in the intervention and control groups)[21]. Around 1,000 patients a month were admitted to each of the EDs; thus, corresponding to a 6 months pre and post period when accounting for patients with missing data (approx. 20%)[21].

The primary outcome was analyzed using difference-in-difference regression[21,22] (i.e. the mean difference within groups [post – pre] compared between the groups [intervention and control]). Both the primary and secondary end-point analyses were adjusted for EWS at admission, gender, and age using logistic regression analysis.

Patients with no EWS or one EWS registered were included in the primary analysis as "no deterioration" instead of missing values.

Data are presented as median (interquartile range) or proportions wherever appropriate. Analyses are performed with a significance level of 5% and results are presented with a 95% confidence interval.

To capture any differentiated effect on outcome due to the entry condition of the patients, we performed sub-analyses on patients' EWS at admission.

Missing data

If patients did not have a registered EWS but all vital signs were registered except temperature, a score was generated by setting the temperature to normal. This was done for 285 observations. Statistical analyses were performed with STATA software version 15.1 (Stata Corp, College Station, TX, United States).

Ethical considerations

The study was approved by the Danish Data Protection Agency (1-16-02-34-16) and the Danish Patient Safety Authority (3-3013-1539). According to Danish law, the study did not require approval from the National Committee on Health Research Ethics.

ClinicalTrials.gov (NCT03457272).

RESULTS

Patients

In total, 41,837 patients were included in the four EDs; 7,281 (17.4%) were excluded due to LOS in the ED of less than 4 hours leaving 16,392 patients in the pre period and 18,164 in the post period (Supplementary file III). 21,839 patients (63.2%) had two or more EWS registered, enabling detection of deterioration. 1,723 patients had no EWS registered while 10,994 had one EWS registered; these observations were included in the analyses as “no clinical deterioration” (Table 1). Patients with one or no EWS registered were younger and had a shorter LOS in the ED (Table 1).

Table 1 Characteristics of the entire study population

Characteristics	Intervention A	Intervention B	Control C	Control D	Only 1 EWS measured	No EWS measured
Pre intervention, n	**3,605**	**4,640**	**2,344**	**5,803**	**5,267**	**994**
Post intervention, n	**4,357**	**5,321**	**2,369**	**6,117**	**5,727**	**729**
Age, years, median [IQR]						
Pre	63 [44-76]	63 [44-77]	66 [49-79]	64 [45-77]	59 [40-74]	57 [41-73]
Post	66 [48-78]	64 [45-78]	70 [53-81]	66 [48-77]	60 [42-74]	58 [41-74]
Gender, female, n (%)						
Pre	1,897 (52.62)	2,377 (51.23)	1,188 (50.68)	3,034 (52.28)	2,759 (52.38)	479 (48.19)
Post	2,266 (52.01)	2,736 (51.42)	1,182 (49.89)	3,064 (50.09)	2,920 (50.99)	350 (48.01)
LOS ED, hours [IQR]						
Pre	14 [8-23]	15 [8-23]	14 [9-19]	12 [7-21]	7 [6-10]	7 [5-9]
Post	12 [7-22]	15 [8-23]	15 [10-20]	13 [7-22]	7 [5-10]	6 [5-9]
LOS in-hospital, days [IQR]						
Pre	2 [1-4]	1 [1-4]	2 [1-4]	1 [1-4]	1 [1-3]	1 [1-2]
Post	2 [1-4]	1 [1-4]	2 [1-4]	1 [1-4]	1 [1-2]	1 [1-1]
No of EWS measurements pr. patient stratified by EWS at admissions, median [IQR]						
EWS 0-1						
Pre	2[1-3]	2[1-3]	2[1-3]	1[1-2]		
Post	2[1-3]	2[1-3]	2[1-3]	1[1-2]		
EWS 2						
Pre	3 [2-5]	3 [2-4]	2[2-3]	2[1-2]		
Post	3 [2-4]	3 [2-4]	2[2-3]	2[1-3]		
EWS 2-4						
Pre	3 [2-5]	3 [2-4]	3 [2-3]	2 [1-3]		
Post	3 [2-4]	3 [2-4]	3 [2-4]	2 [1-3]		
EWS ≥5						
Pre	4[3-6]	3 [2-5]	3 [2-4]	2 [1-3]		
Post	4[3-6]	3 [2-5]	3 [2-4]	2 [2-3]		

Note: Characteristics of population with two or more EWS measured and one or no EWS measured. Intervention A and B refers to the two intervention sites and Control C and D refers to the two control sites in the study. IQR = Inter quartile range, LOS = Length of stay, ED = Emergency Department, n= number, EWS = Early Warning Score

Primary outcome - clinical deterioration

Occurrence of CD increased from pre to post in both groups (table 2). However using difference-in-difference regression, we found significantly reduced odds of CD (22%, OR 0.78 95%CI [0.68; 0.9]) and significantly reduced odds of composite CD (21%, OR 0.79 95%CI [0.69; 0.90]) in the intervention groups compared with the control groups adjusted by EWS at admission, gender, and age (Table 2). Similar results were obtained when patients with no EWS and one EWS measured were included in the analysis as “no deterioration” instead of "missing values" indicating robust analysis.

Table 2 Crude and adjusted difference-in-difference analysis of clinical deterioration in patients with EWS measured twice or more, 7-day mortality and ICU admission directly from ED

		Pre	Post	Post vs Pre	Intervention vs Control
		% (n)	% (n)	OR(95% CI)	Ratio of ORs
Single outcome (EWS)*					
Intervention					**Crude**
	A	19.9% (2,855)	21.3% (3,370)	1.07 [0.95; 1.21]	0.785 [0.69; 0.9]
	B	25% (3,308)	25.6% (3,803)	1.03 [0.93; 1.15]	p<0.001
Control					**Adjusted*****
	C	16.2% (1,734)	20.6% (1,826)	1.34 [1.13; 1.58]	0.78 [0.68; 0.9]
	D	13.4% (3,228)	17.2% (3,438)	1.33 [1.17; 1.52]	p<0.001
Composite outcome (EWS, ICU, Mortality)*					
Intervention					**Crude**
	A	20.6% (2,861)	21.7% (3,377)	1.07 [0.95; 1.21]	0.79 [0.69; 0.89]
	B	25.6% (3,321)	26.3% (3,815)	1.03 [0.93; 1.15]	p<0.001
Control					**Adjusted*****
	C	16.7% (1,737)	21.1% (1,830)	1.34 [1.13; 1.58]	0.79 [0.69; 0.90]
	D	14.6% (3,254)	18.5% (3,458)	1.33 [1.17; 1.52]	p<0.001
7-day mortality**					
Intervention					**Crude**
	A	1.6% (3,605)	1.8% (4,357)	1.11 [0.79; 1.57]	0.99 [0.71; 1.38]
	B	1.3% (4,640)	1.5% (5,321)	1.13 [0.81; 1.59]	p = 0.967
Control					**Adjusted*****
	C	1.9% (2,344)	2.3% (2,369)	1.19 [0.8; 1.8]	0.99 [0.7; 1.41]
	D	1.6% (5,803)	1.7% (6,117)	1.1 [0.83; 1.46]	p = 0.969
ICU admission directly from ED**					
Intervention					**Crude**
	A	0.67% (3,605)	0.37% (4,357)	0.55 [0.29; 1.04]	0.54 [0.29; 0.99]
	B	0.52% (4,640)	0.51% (5,321)	0.98[0.56; 1.7]	p = 0.049
Control					**Adjusted*****
	C	0.13% (2,344)	0.3% (2,369)	2.3 [0.6; 9]	0.59 [0.32; 1.1]
	D	0.5% (5,803)	0.65% (6,117)	1.31 [0.82; 2.1]	p = 0.098

*In unadjusted analysis, N = 23,653. In adjusted analysis, N = 21,930 (1,723 missing data regarding their admission EWSs). ** N in unadjusted analysis = 34,556, N in adjusted analysis = 32,833 (1,723 missing admission EWS statuses) *** Adjusted based on EWSs at admission, gender, and age.

Intervention A and B refers to the two intervention sites and Control C and D refers to the two control sites in the study. n: persons at risk, OR: Odds Ratio, Pre: period before intervention, Post: period after intervention, ED: Emergency Department, ICU: Intensive Care Unit

Secondary outcomes

Seven-day mortality

Of the 34,556 patients in the study, 572 (1.6%) died within seven days. Difference-in-difference regression showed no statistically significant change in 7-day mortality between the intervention and control groups (adjusted OR 0.99, 95% CI [0.7; 1.41]) (Table 2).

30-day mortality

Of the 34,556 patients in the study, 1,432 (4.1%) died within 30-days in the total cohort. One study site had a significant increase in 30-day mortality between the pre and post period. There was no statistically significant change in 30-day mortality between the intervention and control group (adjusted OR 0.86, 95% CI [0.68; 1.08]) (Supplementary file II).

ICU admission directly from the ED

Difference-in-difference regression demonstrated that odds of ICU admission decreased by 46% (OR 0.54, 95% CI [0.29; 0.99]) in the intervention group compared to the control group. However, the decrease was not statistically significant when adjusted by EWS at admission, gender, and age (Table 2).

Readmission within 30 days

A total of 2,378 (6.9%) were readmitted within 30 days. There was no statistically significant change in 30-day readmission between the intervention and control group (adjusted OR 1.11, 95% CI [0.93; 1.332]) (Supplementary file IV).

DISCUSSION

In this controlled pre-and-post study, we found that a modified EWS system reduce the odds of CD compared to a standard EWS system.

The study was designed to investigate whether adding additional parameters and huddles to the conventional EWS could reduce the proportion of CD through earlier identification of the deteriorating patient. Vital signs, skin observations, dyspnea, pain and relatives concerns were based on the results of a modified Delphi technique identifying potentially relevant and applicable predictors of CD in an adult ED population (*article in review*); whereas, clinical intuition and

patients' concern were inspired by the Cincinnati Situation Awareness model[17]. Studies in other settings have found that adding subjective parameters to EWS may lead to improved patient outcomes (e.g. decrease in ICU admissions and identifying the deteriorating patient before triggering the EWS system)[17,23-25]. The findings in our study support the possibility to influence patient outcomes positively when using a wider approach to increase situational awareness and thereby identify early signs of deterioration[15,26,27].

We found no statistically significant change in 7- or 30-day mortality between the intervention and control groups which is in line with previous studies investigating associations of mortality and EWS systems[18,28]. We noted a trend towards reduced ICU admission in the intervention group compared to the control group. However the difference seemed to be influenced by case mix as the difference was no longer present in the adjusted analysis.

In addition, no statistical significant differences were found in 30-days readmissions between the intervention and control group; though, a small, insignificant risk of readmission between intervention and control groups was noted. These findings were generally in line with comparable studies. We found that EWS at entry to the ED was associated with an increased risk of CD in accordance with other studies[3,4].

The strengths of this study include the unselected cohort of admitted medical and surgical patients from four EDs, supporting generalizability. We conducted a controlled pre-and-post study though quasi-experimental studies introduce the risk of compromising the internal and external validity. Therefore, we employed two controls and two intervention emergency departments to strengthen associations within and between groups. The controlled pre-and-post design ensured that period influence was incorporated. Due to the Danish Civil Personal Registration number, no persons were lost to follow up. If all vital signs except for temperature were present to generate a EWS, we substituted the missing value with 0 and assumed that it was unrecorded due to no temperature increase. This was only done in 285 observations; thus not assumed to have substantially influenced the EWS level.

The study has some limitations to consider. Overall, there was an increased proportion of patients with CD in the post-period compared with the pre-period in all four EDs; however with the largest increase in the control group. There is no obvious explanation for the overall increased proportion of patients at risk. We are not aware of any changes in registration practice or in the organization of the EDs that could affect and explain the results. In addition, there was no increase in number of

EWS measurements (Table 1), which could have explained why more patients with CD were observed. However, the results showed a general increase in age between the pre and post period. Since 2015, there has been great focus on visitation and prevention of acute admissions, which may have led to a more complex study population in the post period. Also, a seasonal variation has been suggested to influence case mix in the ED and may be present due to data collection periods (July-December and November-April)[29]. Furthermore, this may, in part, explain why we observed a numerical increase in mortality[30].

The EDs assigned to the intervention group had a numerically higher proportion of CD in the pre-intervention period compared to the control EDs, which may have influenced the outcomes. However, as the proportion of CD was observed to be even higher in other EDs (31%), we do not expect a greater influence on the results[4].

The resolution to exclude patients admitted less than four hours to avoid contamination in the cohort of patients with lower severity limits the generalizability to departments where patients are treated and observed for more than four hours.

We found an initial numerical different LOS in the four EDs (Table 1). The two EDs with longer LOS are distributed in both the control and intervention group thus expected only to influence results minimally.

Despite use of an electronic template to register the use of the modified EWS, it was not possible to track whether all parts of the intervention were applied according to the protocol and no systematical investigation regarding resource utilization was performed.

While acknowledging these limitations, we believe that our study supports the use of additional parameters and huddles providing further clinical relevant information beyond the conventional EWS system and clinical assessment. Further research should investigate resource utilization and which additional parameters are most commonly used and have the highest impact on outcome. Additionally, the model's impact in other settings and potential improvements by use of biochemical tests should be investigated.

CONCLUSION

In the present study, the introduction of a modified EWS system reduced the odds of CD among an unselected adult ED population. There was no impact on 7- or 30-day mortality, ICU admissions or 30-day readmission associated with this modified situation awareness model.

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Conflict of interest statement

None.

Supplementary file I

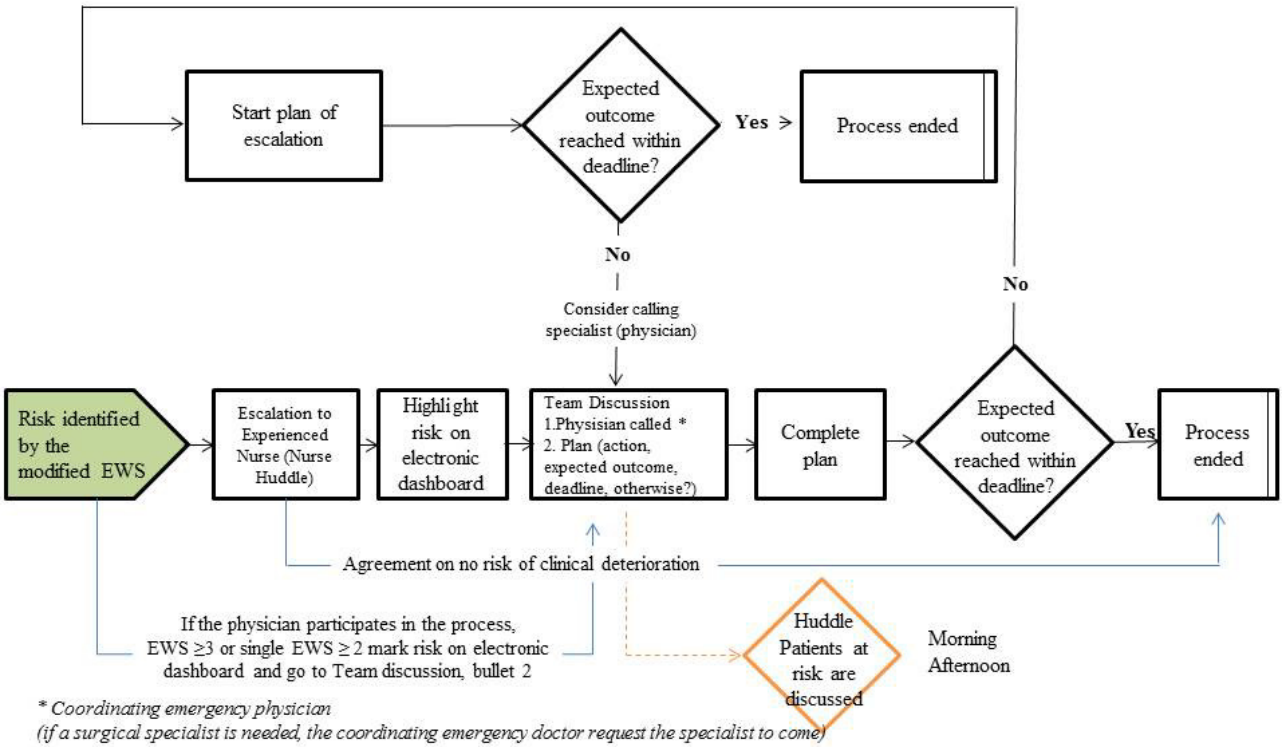
Table Standard early warning score (EWS) with physiological parameters, corresponding weighted score and normal range

Vital sign	**Score**						
	3	**2**	**1**	**0**	**1**	**2**	**3**
Respiratory rate per min	≤8		9-11	12-20		21-24	≥25
Oxygen saturation	≤84	85-89	90-92	≥93			
Systolic blood pressure	≤69	70-79	80-99	100-199		≥200	
Heart rate		≤39	40-49	50-89	90-109	110-129	≥130
Temperature	<33.9	34-35.9		36-37.9	38-38.9	39-39.9	≥40
Level of consciousness				A	V	P	U

A alert, V verbal, P pain, U unresponsive

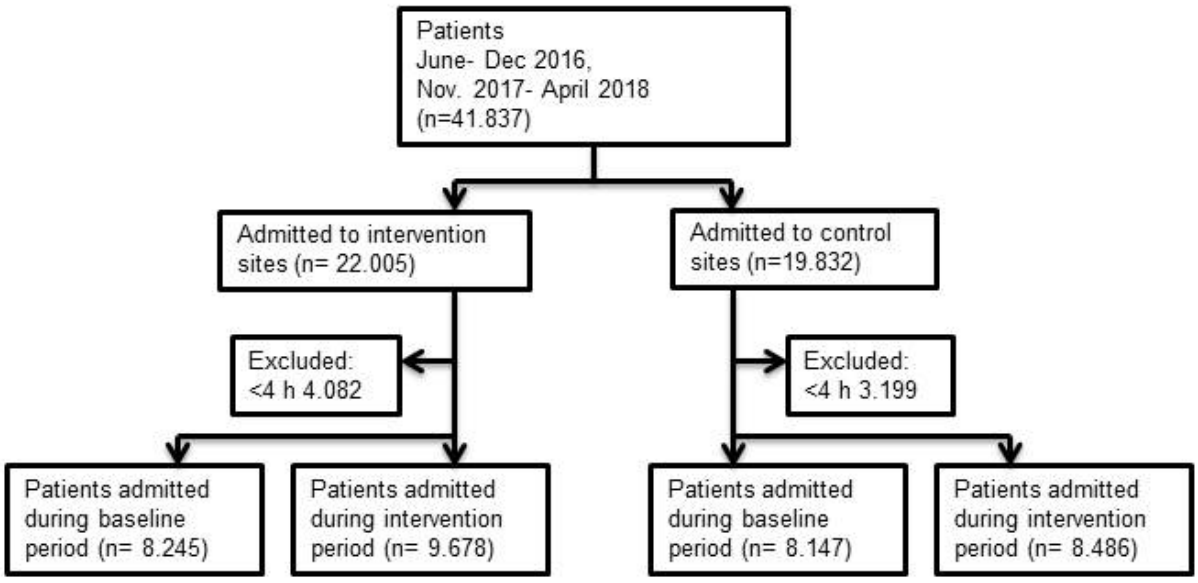
Supplementary file II

Figure Process overview of the situation awareness model targeting clinical deterioration in admitted adult emergency department patients



Note: When risk of clinical deterioration was identified by a abnormal early warning score and/or one of the additional parameters (skin, dyspnoea, pain, clinical concern, patient or relatives concern) the process was activated.

Supplementary file III Flow diagram illustrating in- and exclusion of patients in the study



Supplementary file IV

Table Crude and adjusted difference-in-difference analysis of 30-day mortality and 30-day readmission

30-day mortality					
Intervention					**Crude**
	A	4.3% (3,605)	4.5% (4,357)	1.06 [0.85; 1.32]	0.86 [0.69; 1.06]
	B	3.6% (4,640)	3.9% (5,321)	1.09 0.88; 1.34]	p = 0.170
Control					**Adjusted***
	C	4,2% (2,344)	5.6% (2,369)	1.36 [1.04; 1.77]	0.86 [0.68; 1.08]
	D	3.6% (5,803)	4.3% (6,117)	1.2 [0.99; 1.44]	p = 0.191
30-day readmission					
Intervention					**Crude**
	A	5.9% (3605)	7% (4,357)	1.19 [0.99; 1.42]	1.11 [0.94; 1.32]
	B	7.1% (4,640)	7.4% (5,321)	1.04 [0.89; 1.21]	P = 0.202
Control					**Adjusted***
	C	6.4% (2,344)	5.7% (2,369)	0.9 [0.71; 1.14]	1.11 [0.93; 1.32]
	D	7.1% (5.803)	7.2% (6,117)	1.02 [0.88; 1.17]	p = 0.220

Note: n refers to persons at risk, N in unadjusted analysis = 34,556, N in adjusted analysis = 32,833 (1,723 missing admission EWS statuses) OR = Odds Ratio, Pre = period before intervention, Post = period after intervention* adjusted by EWS at admission, gender, and age, ED= Emergency Department, ICU=Intensive Care Unit

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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Gitte Boier Tygesen

This declaration concerns the following article/manuscript:

Title:	Generic predictors of clinical deterioration in adult Emergency Department patients: a systematic review
Authors:	Gitte Boier Tygesen, Marianne Lisby, Hans Kirkegaard, Nikolaj Raaber, Mette Trøllund Rask

The article/manuscript is: Published ☐ Accepted ☐ Submitted X In preparation ☐
If published, state full reference:
If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?
No x Yes ☐ If yes, give details:
The PhD student has contributed to the elements of this article/manuscript as follows:
Has essentially done all the work

A. Has essentially done all the work
B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution
F. N/A

Element	Extent (A-F)
1. Formulation/identification of the scientific problem	B
2. Development of the method	B
3. Planning of the experiments and methodology design and development	B
4. Involvement in the experimental work/clinical studies/data collection/obtaining access to data	B
5. Development of analysis plan and preparation of data for analysis	A
6. Planning and conducting the analysis of data	A
7. Interpretation of the results	B
8. Writing of the first draft of the manuscript	A
9. Finalization of the manuscript and submission	A

Signatures of first- and last author, and main supervisor

Date	Name	Signature
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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Gitte Boier Tygesen

This declaration concerns the following article/manuscript:

Title:	Consensus on predictors of clinical deterioration in emergency departments: a Delphi process study
Authors:	Gitte Boier Tygesen, Hans Kirkegaard, Nikolaj Raaber, Mette Trøllund Rask, Marianne Lisby

The article/manuscript is: Published ☐ Accepted ☐ Submitted X In preparation ☐
If published, state full reference:
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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Gitte Boier Tygesen
This declaration concerns the following article/manuscript:

Title:	Early warning score systems supplemented by huddles, simple clinical characteristics and subjective parameters decrease clinical deterioration in the emergency departments – a controlled intervention study
Authors:	Gitte Boier Tygesen, Marianne Lisby, Nikolaj Raaber, Mette Trøllund Rask, Hans Kirkegaard

The article/manuscript is: Published ☐ Accepted ☐ Submitted X In preparation ☐

If published, state full reference:
If accepted or submitted, state journal: European Journal of Emergency Medicine

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D. Has contributed (10-33 %)
E. No or little contribution
F. N/A

Element	Extent (A-F)
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