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The I-EWS Study: Individual Early Warning Score (I-EWS) - Does clinical assessment improve detection of acute deterioration in hospitalized patients – a cluster-randomized trial

Revised title:

Adjusting Early Warning Score by clinical assessment: a study protocol for a cluster-randomized, multicentre study of an Individual Early Warning Score (I-EWS).

Short version of the final protocol

(Ver 6, Aug 31, 2018)

Introduction

Every year more than 250,000 patients are admitted in the Capital Region of Denmark. During admissions, the clinical track and trigger system "Early Warning Score (EWS)" is used to systematically observe and detect acutely deteriorating patients. The system is designed to prevent serious adverse events like unanticipated transfer to the intensive care unit, cardiac arrest and unexpected death. EWS consists of standardized measurements of the patient's vital signs and an escalation protocol that determines further actions based on the aggregated EWS score. At admission, and as a minimum twice a day, nurses measure vital signs on all hospitalized patients. Depending on the predetermined cut-off values (i.e. heart rate above 150 bpm = 3 points) an aggregated score is calculated. Based on the total score, the escalation protocol determines the time interval for the next measurement as well as a clinical action (i.e. call for attending doctor). EWS is developed to detect and to treat potentially deterioration of disease that might lead to critical illness and death. In its current form, there is only limited room for individual clinical assessment. A standardized track and trigger system like EWS does not differentiate between different types of disease or the patient's individual physiological response. Therefore, there is a potential risk that the system fails to detect a patient with an abnormal stress response. Additionally; patients suffering from chronic illness might have different normal values than healthy patients, leading to unnecessarily excess observation, measurement, and suboptimal usage of limited staff resources.

Further improvement and optimizing of the EWS track and trigger system is necessary, as there is potential to improve patient care and use staff resources more appropriate. The current study will examine the effect of a new Individual EWS (I-EWS) with incorporated clinical assessment using the staff's professional experience and providing even more personalized observation and treatment.

Aim of the study

The aim of the study is to investigate the impact of the I-EWS that has a systematic involvement of clinical assessment and the possibility to adjust the score, whilst keeping the same escalation protocol. I-EWS will be compared to the existing EWS with a focus on mortality, critical illness, and the use of staff resources.

Hypothesis

The main hypothesis is that I-EWS will be non-inferior to the existing NEWS algorithm regarding 30-day mortality, but the introduction of clinical assessment results in fewer I-EWS scores per patient per day than with NEWS.

Method

The study is a prospective, cluster randomized, cross-over, non-inferiority study. The participating eight hospitals are randomly assigned to six and a half months with either I-EWS or the existing EWS track and trigger system. Computer generated numbers are used to randomize the hospitals to either the intervention or control arm of the study. A single cross-over will take place resulting in a total study period of 13 months. I-EWS is only available at hospitals assigned to I-EWS (Grey areas in the figure below). All EWS scores and subsequent actions are documented in real time. Each period will start with 14 days of implementation, and before cross-over patients will be followed by an observation period of 30 days (indicated by shaded areas below).

Hospital	1 period: 6 ½ months	2. period: 6 ½ months
Herlev & Gentofte Hospital (2 units)	Cluster 1	Cluster 1
Amager og Hvidovre Hospital (2 unit)	Cluster 2	Cluster 2
Nordsjællands Hospital (2 units)	Cluster 3	Cluster 3
Bispebjerg Hospital (1 unit)	Cluster 4	Cluster 4
Glostrup Hospital (1 unit)	Cluster 5	Cluster 5
Sjællands Universitetshospital (2 units)	Cluster 6	Cluster 6
Slagelse Hospital (1 unit)	Cluster 7	Cluster 7
Holbæk Hospital (1 unit)	Cluster 8	Cluster 8

Intervention: Prior to project start ambassadors from all the participating wards will receive 2 hours of education depending on which EWS their hospital is randomized to use. Hospitals randomized to use I-EWS will receive an introduction course and hospitals using EWS will receive a brush-up course. Subsequently, they will be responsible for teaching at their respective wards. I-EWS, like the current EWS, will apply systematic observation, where patients continue to be evaluated according to vital signs and assigned a score of 0-20. The innovation in I-EWS is that SP systematically calls for staff to reassess the assigned score after they have entered the patient's vital signs. Afterwards it is possible to adjust the score by a maximum of +6 or -4. Nursing staff reevaluate when vital signs and clinical assessment are compared, whether the patient is in the correct observation range, and if the clinical actions defined for this range is relevant.

Ethics

The trial was presented to the Regional Ethics Committee, who decided that no formal approval was needed in accordance with Danish law (J.nr. 1701733). The Danish Data protection agency has approved the project. The trial will be registered at clinicaltrials.gov.

Existing workflows are utilized as well as I-EWS is built into SP, so we do not expect the personal to experience a higher workload. When the possibility to individually adjust the observational frequency is given, there is a risk of overlooking critical illness. Therefore, the study only allows a reduction of maximum four points. When carried out, this means that a high EWS score will still trigger more frequent observation. The overall ethical assessment is that the study is safe. As

observed in previous research (publication under review) the introduction of clinical assessment when using triage have improved the risk evaluation in emergency patients, therefore we do not expect that the study will bring along a higher risk for the hospitalized patient.

Statistical analysis plan

Sep 18, 2018, (revised July 11, 2019)

This document contains the statistical analysis plan for the I-EWS study. The statistical analysis plan has been completed prior to the availability of the outcome data and aims to clarify the analyses.

Time line

The study will start at October 1, 2018. Due to implementation patients will be enrolled at October 15, 2018 with planned end of inclusion after one year, October 1, 2019. Follow-up will be concluded on November 1, 2019. The primary analysis will be conducted when the last patient has been followed for 30 days and data is available, which is expected to be Jan 2020.

Background

The primary research question is: A New EWS algorithm (I-EWS) that systematically incorporate clinical assessment, allowing nurses to adjust the I-EWS score will be non-inferior to the existing EWS algorithm and lead to fewer unnecessary EWS measurements, allowing a better utilisation of limited resources.

The study is a cluster-randomized cross-over multi-centre controlled interventional trial conducted at eight large hospitals.

Inclusion/Exclusion criteria

Eligible hospitals

1. Located in the Capital Region or Region Zealand I Denmark
2. Arrival of acutely admitted patients in on-site Emergency department
3. Systemised use of Early Earning Score (EWS) on patients admitted
4. Access to Medical Emergency Team
5. Access to Intensive Care Units (ICU)

Patient inclusion criteria

1. ≥18 years at admittance at participating hospital
2. Admittance in a department/Ward using systematised EWS
3. Admittance for more than 24 hours

Patients will be included at the first admission in the study period (index admission) and will remain in this group (intervention/control) for a follow-up period of 30 days. All subsequent admissions (readmissions) will be ignored.

Exclusion

1. Patients arriving at the gynaecological-, obstetric-, and paediatric department
2. If a "do not resuscitate"-order or "no NEWS/I-EWS registration" are identified, patients will be excluded for further analysis at the time of registration.

Definition of clusters

Eligible hospitals can consist of one or two units. A hospital is defined based on its administrative organisation and catchment area. Each hospital will generate one cluster and two (time) periods (control and intervention). See schematic figure 1 below

Randomisation

Prior to the study start participating clusters will be randomised to start as either intervention or control. Eight cluster will be available, and we will be using stratified randomisation based on size of hospitals (number of unique admissions, more than 25,000 admissions is defined as large hospitals, less than 25,000 is small hospitals), to balance a potential size difference between the intervention and control group. The randomization will be performed using computer-generated numbers. The randomisation will allocate participating hospitals to periods of intervention or control in a 1:1 ration. A cross-over will occur after 6.5 months and is expected to be at April 15, 2019.

Ethics

The study was presented to the Regional Ethics Committee, who decided that no formal approval was needed in accordance with Danish law (J.nr. 1701733). Data management has been approved by the Danish Data Protection Agency (ID: HGH-2017-116, I-suite:06030).

Study variables:

The following data are collected as a minimum for the included patients:

- Age and gender
- Personal Identification number (Danish Civil Registration number (CPR)

- Presence of Do Not Resuscitate (DNR) order

- Presence of "No EWS registration"

- EWS/I-EWS Scores

- Registered actions to the EWS/I-EWS escalation protocol

    - Responsible nurse contacted

    - Treatment plan already made

    - Doctor contacted

    - MET contacted

    - Other

    - Charlson Comorbidity Index

At follow-up (30 days after inclusion of last patient) the following data is collected from the National Patient Registry (NPR) and the electronic patient journal system Sundhedsplatformen:

- Contacts with the hospital system (including all historical contacts).

- Information regarding admissions (date, time and place of admission and discharge).

- Diagnoses (follow-up during study period, historical and in relation to index admission).

- Date of death or emigration (only very few cases of emigration are expected).

Sundhedsplatformen, hospital based local databases, and clinical databases (such as DANARREST) will provide data on:

- Registered Cardiac arrest

- MET activation

Endpoints
The primary endpoint;

- All-cause mortality at 30 days

Co-primary endpoint;

- The number of NEWS/I-EWS scores per patient per day

The secondary endpoints;

- Length of hospital stay

- All-cause mortality at 2 days

- All-cause mortality at 7 days

Additionally, the following will be reported;

Use of EWS / I-EWS;

- Frequency of changes in I-EWS scores that lead to an escalation or de-escalation in the escalation protocol

- Comparison of changes in EWS score due to I-EWS modification (intervention group) and due to temporary or chronic acceptable values (control group)

- The number of Cardiac arrests* during hospital stay, reported in numbers (%) and per 10,000 ward days

- Scores generating a call for Mobile Emergency team (MET) reported in absolute number (%) and per 10,000 ward days

- Scores generating calls for the attending doctor, reported in absolute number (%) and per 10,000 ward days

*Definition – Presence of a clinical cardiac arrest (as defined in the resuscitation guidelines) in patients without a DNAR (Do Not Attempt Resuscitation) order. Registered in DANARREST.

Sample size calculation

The study is designed as a non-inferiority study to show that I-EWS is not inferior to the existing EWS algorithm with a non-inferiority margin (Δ) of 0.5% regarding 30-day all-cause mortality. The participating hospitals will admit 189,000 individual patients within one-year, individual sizes (admissions) are described on p.12, The sample size is based on the following assumptions: I) within a the inclusion period of ten months, the participating hospitals are expected to admit 150,000 individual patients II) mean all-cause mortality is 2.9% with variations as described on p. 11, III) a variation in mortality of 25% over the course of the year. The non-inferiority margin is set at 0.5%, and if the intervention has an effect of 0, the study has above 90% power to confirm noninferiority. In a previous cohort of 103,733 patients the mean (SD) number of scores per patient per day was 2.3 (2.0) and 15.4% of patients had one NEWS score of ≥ 6. With the expected

inclusion, we will be able to detect a difference of 0.04 in mean number of scores and a difference of 0.6% in the number of patients with one NEWS $\geq$6 with a power > 90%.

Study end

The follow-up for all patients ends after at total study period of 13 Months and is expected to end at the October 31, 2019.

Statistical plan for main outcome paper

Statistical analyses will be performed using SAS and R. Reporting of results will be in accordance with the CONSORT criteria with extension to cluster randomised trials.

Analyses will be done using R. P < 0.05 will be considered statistically significant.

Consort diagram

A modified CONSORT trial profile will be used to describe patient flow and total number patients in each group and at each cluster. All patients not included in analysis will be explained.

Baseline description of groups:

Table of summary statistics for patients and at hospital or cluster level for each group (intervention or control) will be presented with baseline variables (Number of patients, number of admissions, age, sex, Charlson Comorbidity index, hospital characteristics)

Continuous variables will be summarized with: n (based on non-missing sample size), mean, standard deviation, median, interquartile range, number of missing values. Categorical variables will be reported as frequency and percentages (based on non-missing sample size) and number of missing values. Continuous and ordinal variables will be tested by Wilcoxon analysis or t-tests as appropriate for differences between groups. Categorical variables will be tested with chi-square.

Primary outcome analysis

The primary outcomes will be an **analysis of all-cause mortality and NEWS/I-EWS scores per patient per day between the intervention and control group**. Patients will be followed as one cohort and data will be analysed as randomized and in accordance with the intention-to-treat principle.

Inclusion: Patients will be included at the first admission at the participating hospitals in the study period (index admission) and will remain in this group (intervention/control) for follow-up of 30 days. Admission is defined as a contact to a hospital with a duration of more than 24 hours. All subsequent admissions (readmission) will be ignored. Any patient lost to follow-up will be censored at the last time known to be alive.

The main analysis of the primary outcome for motality will be done using logistic regression that accounts for clustering with adjustment for hospital ID, age, and sex. Intraclass correlation

coefficient with 95% confidence intervals will be reported. Results will be presented at the individual patient level. Assessment of cluster-level differences will be performed. NEWS/I-EWS scores per patient per day will be compared using linear regressions.

Each period will start with 14 days of implementation, and before cross-over patients will be followed by an observation period of 30 days Periods of implementation and observation will be censored in the analyses (patients admitted in these periods will not be included in the analyses). Cumulative incidence plots (1-survival) will be calculated using the Kaplan-Meier method and presented.

Sensitivity analyses of the primary endpoint

In addition to the ITT analysis, a per-protocol analysis will be performed. In this analysis, interventional patients with missing or incomplete (missing a I-EWS modification in more than 1/3 of the total number of measurements) I-EWS measurement will be excluded. Finally, a sensitivity analysis will be performed, where patients that are transferred between hospitals will be excluded. Sensitivity analyses will be performed for the last three months of each intervention period and excluding departments where I-EWS protocol was not followed.

Subgroup analyses of primary endpoint

The primary outcomes will be calculated for the following subgroups, including a test for interactions: Age ($\leq$39 years, 40 to 69 years, $\geq$ 70 years), admissions at defined cluster, and according to the primary discharge diagnosis; cardiovascular disease, infections, pulmonary disease neurological disease, cancer and surgery done during admission. Results will be presented graphically using a forest plot.

Secondary endpoints

Secondary endpoints regarding mortality will be analysed using the same analysis as the primary endpoint. Length of hospital stay between groups will be compared by linear regression following the same adjustment principles as for the primary outcome.

Additional measurements

The frequency of changes in I-EWS that led to an escalation or de-escalation in the escalation protocol will be reported. Changes in NEWS due to CROS values and changes in I-EWS due to clinical assessment will be compared using Poisson regression models.

Handling of missing data

The primary outcome analysis should be subject to no or little missing data as it is based on Danish register data. Patients lost to follow-up (tourists) will be censored at the last registration.

Handling of diagnoses for outcome and subgroups

Diagnoses obtained from the National Patient Registry are coded with the ICD-10 system. The original chapters will be used to group patients according to diagnoses. The primary diagnosis will be used when constructing. The following will define the subgroups:

Cancer: Chapter II: Neoplasms (C00-C97 + D37-D48).

Cardiovascular disease: Chapter IX: Diseases of the circulatory system (I09-I52 + I70-I89)

Pulmonary disease: Chapter X: **(**DJ00-DJ99)

Infections: Chapter I: (A00-B99 + J00-J22 + N10-N11+ N30-N31 + G00-G09)

Neurological disease: Chapter VI: Diseases of the nervous system (G09-G47 + I60-I69)

Surgical conditions: Presence of surgical procedure codes divided into different specialties (general, orthopedic, other)

Hospital	Unique admission in 2016	Death within 30 days
Herlev & Gentofte Hospital (2 units)	41.420	1122 (2.64 %)
Amager & Hvidovre Hospital (2 unit)	26.466	833 (3.05 %)
Nordsjællands Hospital (2 units)	34.159	872 (2.49 %)
Bispebjerg Hospital (1 unit)	13.013	480 (3.55 %)
Glostrup Hospital (1 unit)	6.598	181 (2.67 %)
Sjællands Universitetshospital (2 units)	34.125	845 (2.42 %)
Holbæk Hospital (1 unit)	16.125	531 (3.19 %)
Slagelse Hospital (1 unit)	17.999	705 (3.77 %)
I alt	189.922	5.569 (2,9 %)

Number of unique admissions is based on the wards that are expected to participate in the study.