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Novel risk factors for poor outcome in frail cardiac surgery patients

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Chapter 4

Continuous monitoring of vital signs and clinical deterioration in frail elderly cardiac surgery patients, AGE AWARE study:

A prospective observational cohort study.

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ABSTRACT

Introduction

Frail patients are at increased risk for postoperative complications. Continuous monitoring of vital signs can detect clinical deterioration early. This study analyses continuous vital signs before clinical deterioration in frail cardiac surgery patients at the general ward.

Methods

A prospective, single center study in frail patients undergoing cardiac surgery. Primary endpoint was clinical deterioration, defined as modified Early Warning Score (MEWS) ≥ 5 . Heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO₂) were continuously monitored for 72 hours at the general ward. Predefined thresholds were used to define abnormal HR, RR and SpO₂ during 4 hours before clinical deterioration and compared with controls. Duration in minutes and time weighted average (TWA) of abnormal vital signs were calculated to examine the association with clinical deterioration using logistic regression analysis.

Results

Clinical deterioration occurred in 22/70 (31%) patients. RR was abnormal during 70% of the time, but not different between groups (71% vs. 68%, $P=0.60$). TWA of abnormal RR was associated with clinical deterioration (OR 2.54, 95% CI 1.05 – 6.47). Among patients with clinical deterioration, oxygen use $>5\text{L O}_2/\text{min}$ and arrhythmia were more common (77% vs. 54% among controls, $P<0.001$ and 31% vs. 11% of controls, $P<0.01$, respectively). However, abnormal continuous SpO₂ and HR measurements were not associated with clinical deterioration.

Conclusion

Frail patients often experience postoperative clinical deterioration at the general ward. Clinical deterioration was preceded by more severe abnormal RR compared to controls, but not by differences in abnormal HR or SpO₂.

INTRODUCTION

Population aging and healthcare innovations have increased the number of elderly undergoing cardiac surgery. Cardiac surgery aims to improve functional capacity and overall survival in elderly patients, but may also precipitate major morbidity and mortality.¹⁻³ Perioperative management of older patients is complex due to multiple comorbidities and frailty. As a result, a significant number of elderly experience a complication after surgery.^{4,5} Especially frail patients are at increased risk for complications, leading to longer length of stay, in-hospital mortality and poor functional recovery.^{4,6-9} The majority of complications occur on the general ward during the early postoperative period, with limited monitoring of vital signs.^{1-3,8,10,11}

Complications are often preceded by minutes to hours of vital sign deterioration.^{2,3,12} Modified early warning scores (MEWS) are used by nurses to quickly assess clinical status using vital signs, including heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO₂).¹³ MEWS are used to activate rapid response teams if clinical deterioration is detected.¹⁴⁻¹⁸ Timely intervention of complications is crucial, as delayed treatment is associated with increased morbidity and mortality.^{14,19} As MEWS are typically recorded once every 8 hours, early signs of deterioration could easily be missed.

Continuous monitoring of vital signs in surgical patients at the general ward may have the potential to early detect clinical deterioration and improve outcomes.²⁰⁻²⁵ In recent years, wireless devices capable of continuously monitoring of vital signs have become available.^{26,27} This study analyses vital signs, according to predefined thresholds for HR, RR and SpO₂, using continuous monitoring in frail elderly prior to clinical deterioration following cardiac surgery. The central hypothesis is that clinical deterioration is preceded by significant changes in vital signs.

METHODS

Ethics

Ethical approval for this study (Medical Ethics Research Committee United, number R19.018) was provided by the local ethics committee of St. Antonius Hospital, Nieuwegein, the Netherlands (Chairperson Dr. R.J.E. Grouls) on 12 September 2019.

Design

The Anaesthesia Geriatric Evaluation (AGE) AWARE study was a single centre prospective observational cohort study in the Netherlands (St. Antonius Hospital, Nieuwegein). Inclusion took place from March 2020 until December 2021. The study was registered at clinicaltrials.gov (identifier: NCT03944967) and performed in accordance with the Declaration of Helsinki. All patients provided written informed consent. This manuscript adheres to the applicable STROBE guidelines.²⁸

Population and setting

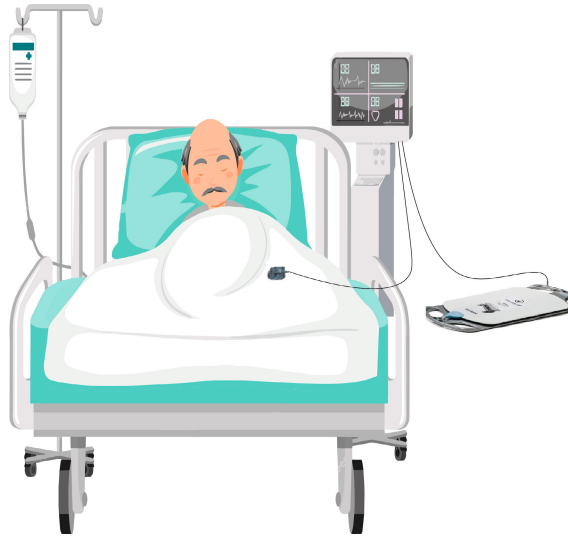
This study included patients aged ≥ 70 years with clinical frailty scale (CFS)²⁹ ≥ 4 , undergoing elective open cardiac surgery. All patients visited the outpatient anaesthesia clinic for routine preoperative screening. According to local procedures patients were postoperatively admitted to the intensive care unit (ICU) for at least one day, depending on surgical risk. A patient was transferred to the general ward for further recovery after meeting protocolled ICU discharge criteria. These criteria included; complete recovery from anaesthesia, hemodynamically stability with no evidence of significant bleeding, core body temperature $>36^\circ\text{C}$ and normal blood gas values. At arrival on the general ward, patients were connected to the continuous monitoring device.

Vital sign monitoring

Postoperative vital signs were monitored using the EarlySense system (EarlySense Ltd, Ramat Gan, Israel). The EarlySense is indicated for the remote continuous non-invasive monitoring of HR, RR and SpO₂ in hospitalised patients and consists of a contactless piezoelectric sensor that is placed under the mattress, a bedside monitor and re-usable oximeter. An overview of the measurement setup is demonstrated in **Figure 1**. The sensor and oximeter measures HR, RR and SpO₂ six times a minute. Both sensors are connected to the monitor that averages and displays the measurements every 60 seconds, as long as the patient remains in bed for HR and RR, and as long as the patient is connected to the oximeter for SpO₂. In cases of signal instability for HR and RR, characterised by excessive talking, eating, prolonged patient movement, or irregular HR or RR patterns such as periodic breathing or arrhythmia, the system defaults and the signal freezes. When a proper signal is being detected, the measurement resumes.

Patients were continuously monitored for three consecutive postoperative days (i.e. 72 hours) or until hospital discharge, death or readmission to the ICU. For this study, continuously measured data were blinded for patients and healthcare professionals.

Figure 1. Overview of measurement setup with the EarlySense remote monitoring system.



Routine spot check MEWS measurements were conducted by nurses at least every 8 hours at the general ward or more frequently on clinical indication. **Table 1** shows the predefined EWS thresholds for the MEWS scoring system. According to local protocols, appropriate measures were taken when MEWS increased, varying from increasing the spot check frequency to activating the rapid response team.

Missings and artefacts

Artefacts of continuous monitoring data were labelled as missing in case vital signs were outside physiological ranges; HR: 20 – 200 bpm, RR: 3 – 50 breaths/min and SpO₂: 60 – 100%. If patients had missing values <5 minutes, we applied the last measured value carried forward. If a period of missing values lasted ≥ 5 minutes and <10 minutes, we used the calculated average of the last measured values at the beginning and end of this period and altered the missing values into this average. If a period of missing values exceeded 10 minutes, all values were coded as missing. Finally, the data were classified according to the predefined EWS thresholds following the MEWS scoring system (**Table 1**). For example, a HR of 120 bpm was assigned an EWS HR 2, and a RR of 25 breaths/min an EWS RR 2. Henceforth, we will refer to the predefined EWS thresholds for each vital sign as EWS HR, EWS RR and EWS SpO₂.

Table 1. (M)EWS scoring system.

(M)EWS	3	2	1	0	1	2	3
RR/min		<9		9 - 14	15 - 20	21 - 30	>30
HR/min		<40	40 - 50	51 - 100	101 - 110	111 - 130	>130
SBP (mmHg)	<70	70 - 80	81 - 100	101 - 180	181 - 200	201 - 220	>220
Oxygen administration					<5L O ₂ /min	≥5L O ₂ /min	
SpO ₂ (%)	<85	85 - 89	90 - 95	>95			
Temperature (°C)		<35	35.0 - 36.0	36.1 - 37.3	37.4 - 38.5	>38.5	
AVPU			Agitated	Alert	Verbal	Pain	Unresponsive
Urine production	Decreased last 6 hours: 1 point		Normal		Excessive last 6 hours: 1 point		
‘Sense of unease’ nurse: 1 point							

(M)EWS: (modified) early warning score system; RR: respiratory rate; HR: heart rate; SBP: systolic blood pressure; SpO₂: oxygen saturation; AVPU: alert, verbal, pain unresponsive.

For spot check MEWS measurements conducted by nurses, the following assumptions were made: in case of a missing value for oxygen administration, we assumed no additional oxygen administration; In case urine production was missing, we assumed urine production was 'Normal'; If 'sense of unease' nurse was missing, we assumed there was 'None'; and, if Alert, Verbal, Pain, Unresponsive (AVPU) was missing, we assumed the patient was 'Alert'. These assumptions were made based on our expectation that a deviating value would have been clearly documented by nurses.

Primary outcome

The primary endpoint was clinical deterioration within 72 hours after ICU discharge. Clinical deterioration was defined as MEWS ≥ 5 using spot check EWS monitoring by nurses.^{17,18} The analysis was performed based on the first occurrence of clinical deterioration in each patient.

Selection of continuously measured vital sign data

Continuous vital sign data were analysed during the 4 hours before clinical deterioration. For each patient with clinical deterioration a control group was established, including multiple patients without clinical deterioration with data recorded over the same 4 hour time period. For example, in a patient experiencing clinical deterioration at 12 hours after arrival at the general ward, the data from 8 – 12 hours was analysed and compared with continuous data in the same period of controls. By conducting comparisons at corresponding time points, a fair assessment was achieved between patients with clinical deterioration and controls, accounting for their stages in the postoperative recovery process.

Sample size analysis

Few data is available on vital sign deteriorating after ICU discharge in cardiac surgery patients. Patients may experience frequent, short episodes of severe deteriorated vital signs; or vital signs may linger slightly below potentially harmful thresholds for hours. For this reason we choose predefined threshold values to define a deterioration of HR, RR and SpO₂. This makes it difficult to perform a formal sample size calculation. Our pilot study enrolled 70 patients, based on practical feasibility and in accordance with other studies on postoperative remote monitoring of vital signs.^{21,32,33} With 70 patients and an incidence of deterioration >30%, we are confident to be able to test the hypotheses. It should be noted that the sample size deviates from the originally registered in the protocol at clinicaltrials.gov, as a result of prolonged slow patient enrolment due to a declining operating room program.

Statistical analysis

Baseline characteristics of patients with clinical deterioration were compared to controls. Descriptives were presented as frequencies and percentages (%) for dichotomous and categorical data and for continuous data as mean \pm SD. Although data was not normally distributed, mean values were reported for clinically implications. Differences were tested using the independent T-test for continuous variables or a chi-square or Fisher's exact test for categorical variables, as appropriate.

For the spot check EWS monitoring performed by nurses over the complete 72 hour period, the proportion of measurements within each EWS threshold was calculated and compared between patients with clinical deterioration and controls. For each of the continuously measured vital signs, the duration and severity of abnormal vital signs was calculated for patients with clinical deterioration and controls during the selected 4 hour period. Duration was computed as the mean number of minutes spent within each EWS threshold. Severity of vital sign abnormality was expressed as the time weighted average (TWA). The TWA was constructed by calculating the area under the threshold (AUT) divided by the total measured monitoring time. An example of the TWA calculation is presented in **Supplementary figure 1**.

For each vital sign, the association between the duration of abnormal vital signs and TWA with clinical deterioration was analysed using logistic regression models. Effect estimates are expressed as ORs with corresponding 95% CI. P-values of ≤ 0.05 were considered statistically significant. Data analysis was performed using R statistics (version 1.4.1717, 2009-2021 Rstudio).

RESULTS

The AGE AWARE study included 95 patients. In 4 patients (4%) surgical treatment was changed and no longer met the inclusion criteria; 4 patients (4%) died before ICU discharge and 2 patients (2%) had a postoperative complication before continuous monitoring. Furthermore, 15 patients (16%) were not monitored due to a limited number of monitoring systems. In total, 70 patients were included in the analysis, with a median monitoring time of 72 hours [IQR 52 – 72]. Reasons for early discontinuation of monitoring included: transfer to another hospital for further recovery (12/24 patients, 50%), technical problems with the monitoring system (9/24 patients, 38%), readmission to the ICU (2/24 patients, 8%) or full recovery and discharge to home (1/24 patients, 4%). Baseline characteristics were not different between patients with clinical deterioration and controls (**Table 2**). A median of 11 spot check MEWS measurements were conducted per patient during the first 72 hours [IQR 9 – 13] (**Supplementary table 1**). Clinical deterioration was observed in 22 (31%) patients. The median time until the occurrence of clinical deterioration was 31 hours [IQR 14 – 42 hours] after arrival at the general ward. A total of 18 patients with clinical deterioration were included in the analysis, as 4 patients did not have 4 hours of continuous monitoring data prior to the occurrence of clinical deterioration. Overall 16% of continuous HR, 17% of continuous RR and 54% of continuous SpO₂ data, in the 4 hours prior to clinical deterioration was missing.

Table 2. Baseline characteristics.

Patient characteristics	Clinical deterioration	Control	P-value
Sex, male/female sex	14/4 (78%/22%)	35/17 (67%/33%)	0.59
Age, yrs	76 (74 – 77)	75 (74 – 78)	0.84
EuroSCORE II	1.9 (1.5 – 2.9)	1.8 (1.3 – 3.0)	0.46
Clinical Frailty Scale			0.23
4	9 (50%)	30 (58%)	
5	9 (50%)	17 (33%)	
6 or more	0	5 (9%)	
Total <i>n</i> of medication	7 (5 – 8)	7 (6 – 8)	0.42
Type of surgery			
Single CABG	5 (28%)	21 (40%)	0.50
Single valve	8 (44%)	13 (25%)	0.21
Aortic surgery	0	3 (6%)	0.71
Combined surgery	5 (28%)	15 (29%)	1

Table 2. Baseline characteristics. (continued)

Patient characteristics	Clinical deterioration	Control	P-value
Length of stay ICU, days	1 (1 - 1)	1 (1 - 1)	0.27
Readmission ICU	4 (22%)	1 (2%)	0.02
Length of hospital stay, days	9 (7 - 16)	7 (6 - 9)	0.02

Continuous variables reported as median (IQR), categorical variables as frequency (%).

N/no.: number; yrs: years; CABG: coronary artery bypass grafting; ICU: intensive care unit.

Continuous vital sign monitoring

Table 3 demonstrates the mean duration in minutes spent within each EWS thresholds for HR, RR and SpO₂ during the 4 hour period. Continuous HR monitoring revealed that EWS HR 0, indicative of a normal HR, was observed during 73% of the time in patients with clinical deterioration, compared to 80% of the time in the control group (P=0.377). Nevertheless, MEWS spot checks revealed an irregular HR in 31% of patients with clinical deterioration, compared to 11% in controls (P<0.01). This can be explained by the inability of the EarlySense system to capture irregular HR. Duration of abnormal HR was not associated with increased risks of clinical deterioration (**Supplementary table 2**). Additionally, TWA for HR was not significantly different between groups and not associated with clinical deterioration (OR 5.19, 95% CI 0.82 - 21.42, **Table 4**).

An abnormal RR (EWS RR >0) was very common in frail patients after cardiac surgery. In the 4 hours before clinical deterioration, EWS RR >0 occurred during 70% of the time, which was not different for patients with clinical deterioration and controls (P=0.60). No association was found between duration of abnormal RR and clinical deterioration (**Table 3 and Supplementary table 2**). TWA for RR was 1.43 for patients with clinical deterioration and 1.17 in controls (P=0.09). Severity of abnormal RR was associated with an increased odds for clinical deterioration (OR 2.54, 95% CI 1.05 - 6.47). This implies, for example, that patients with a mean EWS RR 2 over the complete measuring period exhibit a 2.54-fold increased odds of developing clinical deterioration compared to patients with a mean EWS RR 1 (P=0.04).

Hypoxemia requiring O₂ therapy after cardiac surgery was common (**Supplementary table 1**). Specifically, 77% of the MEWS spot check measurements indicated oxygen use >5L O₂, in patients with clinical deterioration compared to 54% among controls (P<0.001). Duration of EWS SpO₂ ≥ 2 was longer in the control group (27 minutes vs. 13 minutes in patients with clinical deterioration, P=0.02). The association between the duration of EWS SpO₂ 2 and clinical deterioration was negative (OR 0.92, 95% CI

0.85 – 0.98, **Supplementary table 2**). This may be explained by higher amounts of O₂ therapy after cardiac surgery among patients experiencing deterioration, masking desaturation (**Supplementary table 1**). TWA of hypoxemia was not different between groups and not associated with clinical deterioration (OR 0.67, 95% CI 0.31 – 1.32), **Table 4**).

Table 3. Duration spent within each EWS threshold during the 4-hour period.

	Clinical deterioration	Control	P-value
Heartrate EWS 0	175 ± 76	195 ± 58	0.377
Heartrate EWS 1	18 ± 47	10 ± 35	0.49
Heartrate EWS 2	2 ± 4	1 ± 6	0.361
Heartrate EWS 3	1 ± 3	0 ± 0	0.347
<i>Heartrate missing</i>	<i>43 ± 50</i>	<i>32 ± 47</i>	<i>0.545</i>
Respiratory rate EWS 0	25 ± 53	36 ± 59	0.472
Respiratory rate EWS 1	77 ± 74	101 ± 68	0.228
Respiratory rate EWS 2	82 ± 69	60 ± 67	0.187
Respiratory rate EWS 3	13 ± 24	3 ± 10	0.126
<i>Respiratory rate missing</i>	<i>42 ± 49</i>	<i>38 ± 48</i>	<i>0.922</i>
Oxygen saturation EWS 0	22 ± 45	25 ± 52	0.807
Oxygen saturation EWS 1	52 ± 66	79 ± 86	0.15
Oxygen saturation EWS 2	10 ± 15	20 ± 41	0.022
Oxygen saturation EWS 3	3 ± 12	7 ± 25	0.243
<i>Oxygen saturation missing</i>	<i>151 ± 88</i>	<i>108 ± 102</i>	<i>0.079</i>

Mean number of minutes per EWS threshold during 4 hour period with standard deviation. Data is not normally distributed, so an independent t-test is performed. We reported the mean for clinically implications.

Table 4. Severity of abnormal vital signs during the selected 4-hour period.

	Clinical deterioration	Control	P-value
TWA HR	0.15	0.06	0.19
TWA RR	1.43	1.17	0.09
TWA SpO ₂	0.64	0.83	0.24

TWA: time weighted average; HR: heart rate; RR: respiratory rate; SpO₂: oxygen saturation.

DISCUSSION

This study demonstrates that clinical deterioration is common after cardiac surgery, with an incidence of 31% in frail elderly patients at the general ward. In the 4 hours prior to clinical deterioration, there were no differences in vital signs between patients with clinical deterioration and controls. However, continuous monitoring of RR might be able to early detect deteriorating patients, as TWA of abnormal RR was significant associated with higher odds of clinical deterioration.

Patients admitted to hospitals nowadays often present with increasingly complex health problems and a higher chance of experiencing severe illness during hospital stay.³⁴ It is known that a delayed or absent response to deterioration has been labelled as 'failure to rescue', leading to escalation of care.^{12,15-17,25} In addition, calculating trends over time and vital sign variability have been proved to be independent predictors of critical illness in ward patients.^{12,23-25} Henceforth, it is more important than ever that health care personnel on the general ward can identify early signs of clinical deterioration. As nurses measure vital signs once every 8 hours, early identification of deterioration might easily be missed.¹⁴⁻¹⁷ Today, a lot of effort is going into developing continuous monitoring systems capable of identifying changes in patients' medical condition that could result in deterioration.^{12,14,15,17,25} Few studies on combined surgical and medical wards found early identification of deterioration, increased rapid response activation and a decreased need for patient rescue as benefits of continuous monitoring.^{10,12,35} In the nonsurgical population, implementation of continuous monitoring was associated with a significant decrease in mortality.³⁶ Nevertheless, research in the surgical population is limited. As far as we know, no research has been conducted in the frail elderly population undergoing cardiac surgery, which presents a compounded level of risk. In frail elderly following cardiac surgery in our study, RR was abnormal for the majority of time. Additionally, we found an association between severity of abnormal RR and higher odds of clinical deterioration. This association did not demonstrate clinical differences in our population because the variance in TWA between the groups was small. Yet, this might be attributable due to early identification and treatment of patients with abnormal RR by nurses using MEWS measurements, potentially masking the differences observed with continuous monitoring, resulting in a small TWA difference between both groups. Efforts to implement continuous monitoring assume it will provide clinically valuable trends superior than measuring vital signs with fixed thresholds by intermittent monitoring. Different studies found RR to be the most accurate predictor in detecting clinical deterioration.²³⁻²⁵ They specifically referred to the analysis of trends in vital signs, such as variability in RR and minimum SpO₂.²³⁻²⁵ As RR was abnormal 70% of the time of MEWS measurements

in all frail elderly patients and TWA for abnormal RR was significantly associated with clinical deterioration, this might provide treatment options to improve patient outcome after cardiac surgery.

Our study has limitations. Most importantly, due to the nature of the monitoring system, HR and RR were recorded exclusively when the patient was in bed, while SpO₂ was measured only when the device was attached to the patients' finger. Instances when patients were out of bed due to required transportation for examinations or when patients were ambulatory due to recovery, contributed to a significant amount of missing data and might have led to attrition bias. The potential attrition bias is likely because of patients who were doing well discontinued continuous monitoring. Furthermore, the monitoring device was unable to capture irregular heart rhythms, which are frequently observed among post cardiac surgery patients. As a result, continuous HR monitoring in our study proved inadequate for early detection of clinical deterioration. Lastly, as our sample size was relatively small and the analysis was performed in a high risk population, the generalizability is limited.

Conclusions

In conclusion, frail elderly patients often experience clinical deterioration at the general ward following cardiac surgery. Clinical deterioration was preceded by more severe abnormal RR compared to controls, but not by differences in abnormal HR or SpO₂. Before implementation of continuous noninvasive ward monitoring, we need to await the results of adequately powered randomised controlled trials demonstrating its effectiveness in preventing clinical deterioration to improve surgical patient outcome.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. Proportion of scored EWS thresholds by MEWS spot check measurements over the complete 72 hour measurement period.

MEWS	Clinical deterioration	Control	P-value
Heartrate EWS 0	82%	96%	0.096
Heartrate EWS 1	3%	3%	0.56
Heartrate EWS 2	5%	1%	<0.01
Heartrate EWS 3	10%	0	0.05
Respiratory rate EWS 0	6%	32%	<0.001
Respiratory rate EWS 1	69%	65%	<0.001
Respiratory rate EWS 2	21%	3%	<0.001
Respiratory rate EWS 3	3%	0	<0.001
SpO ₂ EWS 0	82%	83%	0.052
SpO ₂ EWS 1	17%	17%	0.294
SpO ₂ EWS 2	<1%	<1%	0.257
SpO ₂ EWS 3	<1%	0	0.331
Oxygen administration EWS 0	23%	46%	0.166
Oxygen administration EWS 1	67%	51%	0.009
Oxygen administration EWS 2	10%	3%	0.124
Systolic bloodpressure EWS 0	85%	91%	0.102
Systolic bloodpressure EWS 1	13%	9%	0.178
Systolic bloodpressure EWS 2	1%	0	0.331
Systolic bloodpressure EWS 3	<1%	0	0.331
Temperature EWS 0	55%	46%	0.042
Temperature EWS 1	44%	53%	0.50
Temperature EWS 2	1%	1%	0.596
Urine production EWS 0	99%	100%	0.017
Urine production EWS 1	<1%	0	0.331
Urine production EWS 2	<1%	0	0.331
“Sense of unease” nurse	2%	0	0.163
Abnormal AVPU	0	0	-

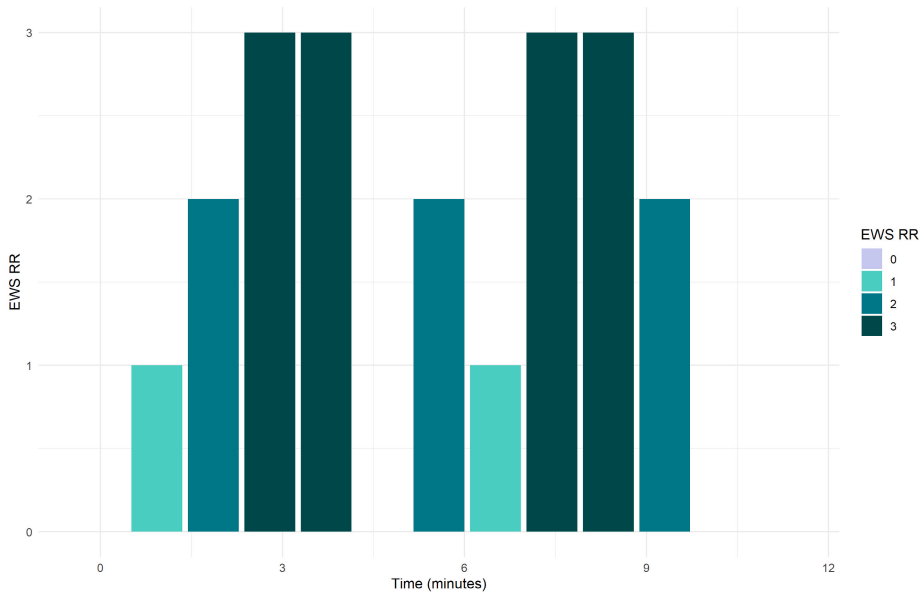
Categorical variables as frequency (%); % of spot check measurements in each category; (M) EWS: (modified) early warning score system; SpO₂: oxygen saturation; AVPU: alert, verbal, pain unresponsive.

Supplementary table 2. Association between duration in minutes within each EWS threshold and clinical deterioration.

	Odds Ratio	95% CI	P-value
Heartrate EWS 0	0.99	0.98 - 1.01	0.37
Heartrate EWS 1	1.01	0.99 - 1.05	0.50
Heartrate EWS 2	1.14	0.88 - 1.69	0.37
Heartrate EWS 3	1.41	0.84 - NA*	0.60
Respiratory rate EWS 0	0.99	0.97 - 1.01	0.47
Respiratory rate EWS 1	0.99	0.98 - 1.00	0.22
Respiratory rate EWS 2	1.01	1.00 - 1.02	0.18
Respiratory rate EWS 3	1.07	1.00 - 1.22	0.18
Oxygen saturation EWS 0	1.00	0.97 - 1.02	0.80
Oxygen saturation EWS 1	0.99	0.97 - 1.00	0.15
Oxygen saturation EWS 2	0.92	0.85 - 0.98	0.03
Oxygen saturation EWS 3	0.94	0.80 - 1.03	0.29

**Due to limited variation in the HR data, the upper limit of the CI could not be calculated. CI: confidence interval.*

Supplementary figure 1. Example plot of TWA RR in the 4-hour period before clinical deterioration.



Example of time weighted average (TWA) for RR. The TWA combines the duration and severity, i.e. EWS score 0 – 3, divided by total measured monitoring time. First, the area under/above the threshold (AUT) is calculated for this 12 minute period.

The AUT in the example above is: (EWS 0 x 4 min) + (EWS 1 x 2 min) + (EWS 2 x 3 min) + (EWS 3 x 4 min) = 20 EWS*min

Then, the AUT is divided by the total measured monitoring time, which in this example was 12 minutes.

$TWA = 20 \div 12 \text{ min} = 1.67 \text{ EWS}$. This means that over this 12 minute period, the average EWS was 1.67. In case of any missing vital sign values, the number of missing measurements were subtracted from the total number of measurements in that time period. Thus, for example, in case the patient was out of bed for 30 minutes over the 240 minute period of interest, the AUT was divided by 210 minutes (e.g. 240-30).

