Risk stratification in emergency medicine: towards improved age and sex adjusted risk assessment

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AGE AND SEX ADJUSTED INTERPRETATION OF PHYSIOLOGICAL VARIABLES IN EMERGENCY DEPARTMENT PATIENTS.


EMERGENCY

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THE ASSOCIATION BETWEEN VITAL SIGNS AND CLINICAL OUTCOMES IN EMERGENCY DEPARTMENT PATIENTS OF DIFFERENT AGE CATEGORIES.

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ABSTRACT

Background Appropriate interpretation of vital signs is essential for risk stratification in the Emergency Department (ED) but may change with advancing age. In several guidelines, risk scores such as SIRS and qSOFA, commonly used in emergency medicine practice (as well as critical care) specify a single cut-off or threshold for each of the commonly measured vital signs. Although a single cut-off may be convenient, it is unknown whether a single cut-off for vital signs truly exists and if the association between vital signs and in-hospital mortality differs per age-category.

Aims To assess the association between initial vital signs and case-mix adjusted in-hospital mortality in different age categories.

Methods Observational multi-centre cohort study using the Netherlands Emergency department Evaluation Database (NEED) in which consecutive ED patients ≥18 years were included between 1 January 2017 and 12 January 2020. The association between vital signs and case-mix adjusted mortality were assessed in three age categories (18-65; 66-80; >80 years) using multivariable logistic regression. Vital signs were each divided in five to six categories, e.g., systolic blood pressure (SBP) categories (≤80, 81–100, 101–120, 121-140, >140mmHg).

Results We included 101,416 patients of whom 2374 (2.3%) died. Adjusted Odds Ratios for mortality increased gradually with decreasing SBP and decreasing peripheral oxygen saturation (SpO_2). Diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) had quasi-U-shaped associations with mortality. Mortality did not increase for temperatures anywhere in the range between 35.5-42.0°C, with a single cut-off around 35.5 °C below which mortality increased. Single cut-offs were also found for MAP <70mmHg and respiratory rate >22/min.. For all vital signs, older patients had larger increases in absolute mortality compared to younger patients.

Conclusion For SBP, DBP, SpO_2, and HR no single cut-off existed. The impact of changing vital sign categories on prognosis was larger in older patients. Our results have implications for the interpretation of vital signs in existing risk stratification tools and acute care guidelines.

INTRODUCTION

Vital signs are used for risk stratification in nearly all acute care guidelines.[21, 39-41] Many risk stratification tools, such as SIRS, qSOFA, CURB-65,[21-25] specify a single cut-off (or threshold) for each of the commonly measured vital signs, suggesting that one cut-off may discriminate between good and bad prognosis. However, recent studies in patients with traumatic brain injury and sepsis showed that prognosis linearly worsened with decreasing systolic blood pressure (SBP), without an identifiable single threshold.[28, 29] Similarly, linear, or U-shaped instead of dichotomous associations may exist for other vital signs used in ED risk stratification.

In addition, most risk stratification models are applied in all ED patients irrespective of age. However, a recent study showed that risk stratification tools are inappropriate for older ED patients.[27, 42] The association between vital signs and outcomes may change with advancing age due to physiological changes. Arterial walls become stiffer in older patients, heart rate response to stress is blunted and fever is absent in many older patients with sepsis.[12]

Although a single cut-off for vital signs may be convenient in risk stratification tools, numerical scores based on predicted mortality will possibly better inform physicians and prevent impaired recognition of early deterioration in ED patients. Physiological changes with increasing age may implicate that currently used risk stratification tools should be age-adjusted. This is particularly important given the ageing of the population with an increasing number of older ED patients.

Therefore, the aims of the present study are two-fold: First, to assess the associations of vital signs and relevant clinical outcomes (e.g., mortality and Intensive Care Unit (ICU)/Medium Care Unit (MCU) admission) and whether a single cut-off or threshold exists for each vital sign, and second, to study whether associations of vital signs and relevant clinical outcomes change with advancing age.

METHODS

Study design and setting

This observational multi-centre study was conducted in three EDs in the Netherlands, each with approximately 25,000-30,000 ED visits per year. Data from the three sites spanned slightly different times: data for the tertiary centre included visits between 1 January 2017 – 8 June 2019, and data from the two urban teaching hospitals were from 1 January 2019 – 12 January

2020 1 January 2017 – 31 December 2019, respectively. The tertiary care centre uses the Manchester Triage System (MTS) and both urban hospitals use the Dutch Triage Standard (NTS). The study was approved by the medical ethics committee of the LUMC. The study was registered in the Netherlands Trials Register: NL8422.

Selection of participants
All consecutive ED patients ≥18 years were included if one or more of the following vital signs were measured: respiratory rate (RR), peripheral oxygen saturation (SpO_2), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), heart rate (HR) and temperature.

Data collection
Data were collected from the Netherlands Emergency department Evaluation Database (NEED), the Dutch quality registry for EDs (www.stichting-need.nl), a record containing clinical data from all ED visits from the participating hospitals. Supplementary file 1 provides a detailed description of the data collected in the NEED. Twice a year all clinical data from the participating hospitals is downloaded into the record. Onset of participation in the NEED differs per hospital. For the current study, data were available from three of the nine participating hospitals. The NEED stores data using the web-based application Project Manager Internet Server (ProMISe, Leiden, the Netherlands, https://www.msbi.nl/promise/promise.aspx). Privacy sensitive data are encrypted by a trusted third party (ZorgTTP, Houten, the Netherlands, www.zorgttp.nl) with Trusted Reversible Encryption Service.

The vital signs measured at the beginning of ED presentation, before ED treatment, were recorded in the NEED. Only one set of vital signs was recorded per patient. If patients arrived by own transport, HR, SpO_2 and temperature were measured in a triage room by a nurse mostly in seated, sometimes supine, position. These vital signs were entered manually in the hospital information system. Once moved to a patient room, the other vital signs were measured by a nurse with the MP52 IntelliVue, Intellivue MP30, Intellivue MX400 or MX500 monitor (Philips, Eindhoven, the Netherlands). Multi-patient reusable latex-free NIBP Comfort Care Cuff from Philips were used with cuff a small cuff (27-35cm), medium cuff (35-45cm), large cuff (42-54cm) and extra-large cuff (44-56cm), depending on the size of the patient. Vital signs registered in the patient room were automatically transferred in the hospital information system, except for temperature, which was entered manually. Temperature was measured with a Genius™ 3 Tympanic Thermometer. If patients arrived by ambulance, vital signs were measured in supine position in the patient room as described. In the tertiary care centre,

vital signs were automatically measured every 2.5 to 15 min and transferred to the electronic patient file with PDMS software (Chipsoft, the Netherlands), depending on the personalized setting for a specific patient. Median values of vital signs were registered for the first 10 minutes of measuring.

Measurements
Before we could perform statistical analysis, several variables had to be synchronized among hospitals. Beforehand we could not assume that the association between vital signs and outcomes were linear. Therefore, vital signs were categorized into ranges based on expected distribution, and commonly used reference intervals: RR (Not measured, 0-9, 10-19, 20-29, ≥30/min), SpO_2 (0-80, 81-85, 86-90, 91- 95, 96-100%), SBP (0-80, 81-100, 101-120, 121-140, >140mmHg), DBP (0-60, 61-80, 81-100, 101-120, >120mmHg), MAP (0-60, 61-80, 81-100, 101-120, >120mmHg), HR (0-50, 51-75, 76-100, 101-125, >125beats/min.), temperature (Not measured, 0-30, 31-34, 35-37, 38-39, ≥40°C).

Correspondent to literature,[43] RR and temperature were often not registered. To limit the number of missings in the analyses, we included a category "not registered". In EDs in the Netherlands, vital signs are not registered for all patients. For example, vital signs are often not registered in patients with an ankle distortion or a single fracture, because they are at low risk of adverse events and often discharged, and RR is often only registered if patients are considered critically ill by the nurse. Therefore, the fact that vital signs are registered may provide relevant information for risk stratification. Supplementary file 2 describes how the variables triage levels, chief complaints (the top ten chief complaints was used) and treating specialties were modified before they could be used as potential confounders in the statistical analyses.

Patients were stratified into three age categories: 18-65, 66-80 and >80 years. These age categories were chosen based on the mean SBP in the general population in the Netherlands according to the National Institute for Public Health and the Environment (RIVM, www.rivm.nl). The mean SBP increases substantially above 65 years.

Outcome
The primary outcome was whether there was a vital sign category that could be used as a cut-off to predict the outcomes of in-hospital mortality and ICU or MCU admission, which also included the Coronary Care Unit.

Sample size estimation
Approximately five to ten events per variable are needed to prevent overfitting in association studies.[44] The NEED contained 148,828 ED visits of patients ≥18 years. We estimated that in ~60% of the ED visits vital signs were registered resulting in ~90,000 ED visits which could be used for the analyses. In-hospital mortality was estimated to be ~3%. Included patients were stratified in three age categories, yielding ~90,000 / 3 = 30,000 patients per age category. Thus, we expected to have ~0.03 x 30,000 = 900 events per group to be able to adjust for the 37 potential confounders (see main statistical analysis) in the analyses with in-hospital mortality as outcome, which is appropriate to prevent overfitting.

Statistical analyses
Patient characteristics were described as mean (standard deviation (SD)) for normally distributed data, and median (interquartile range (IQR)) for skewed data. Categorical data were presented as number (N, (%)).

For all analyses, one category per vital sign was used as reference category (i.e. reference category for HR was 50-75 beats/min.). The number of measured vital signs outside the reference range were calculated.

We used multivariable logistic regression analyses for the association between vital sign categories and the primary and secondary outcomes. The following potential confounders were entered in the models for which then backward stepwise elimination was performed: age, sex, triage level, top ten chief complaints, hospital, treating specialty, disposition (ward, ICU/MCU), SpO_2, temperature (including category 'not registered'), GCS (not assessed, assessed and 15 points, assessed and <15 points), lab tests (0=no lab tests performed, 1= any lab test performed), blood gas analyses (0= not tested, 1= tested), number of consultations in the ED (0, 1, 2 or ≥3 consultations), and performed radiological test (0= none, 1= any test). Other vital signs were not entered in the models because of potential multicollinearity among vital signs. The number of consultations, lab tests and radiological tests were used as measures of comorbidities/complexity, as has been suggested previously.[45, 46] Triage level, GCS, blood gas analyses and ICU/MCU admission were used as disease severity measures.[27] ICU/MCU admission is not only an outcome, but also a proxy of disease severity not captured in the initial vital signs. For example, a patient with an initial SBP of 90 mmHg who responds to fluid resuscitation can be admitted to a normal ward and has a different risk for in-hospital mortality compared to a patient who also has an initial SBP of 90 mmHg does not respond to fluid resuscitation and consequently needs ICU admission. In other words, the variable ICU/

MCU admission also reflects the response to treatment. For the secondary outcome, the potential confounder disposition was replaced by the amount of fluid administration as a proxy of disease severity. Multicollinearity was assumed not to be a problem if variation inflation factors (VIF) were below three. The associations between vital sign categories and case-mix adjusted outcomes were assessed in two ways to give better insight in differences between age categories, as the relative risk for the outcome may be similar among age categories, while the absolute risk may be different due to different baseline risk at the reference values. We used adjusted odds ratios (AORs) with 95%-confidence intervals (95%-CI) as relative risk measure and predicted (case mix-adjusted) mortality as absolute risk measure.

In the figures, the AORs of in-hospital mortality were plotted as a function of vital sign categories for the pooled data and for all age categories. If we observed a sudden rise or decline in AORs by changing vital sign categories, we performed minimal p-value analyses to assess a more precise value for the possible threshold. In these analyses, we changed the vital sign into a binary value (below or above a cut-off value) in the multivariable logistic regression as described above. We repeated the analyses with all possible cut-off values in steps of 0.5°C (temperature), 1/min. (RR), 5.0mmHg (SBP, DBP, MAP), 5.0 beats/min. (HR) or 5.0% (SpO_2). The cut-off value with the lowest p-value for the AOR was considered as threshold. In this way, a threshold was determined in approximately continuous data of the vital sign. Thresholds with minimal p-value analyses were not determined if vital signs had no clear single cut-off.

A P-value<0.05 was considered as statistically significant. Data were analysed using SPSS (version 25.0, IBM, New York, USA).

Subgroup and sensitivity analyses

We performed subgroup analyses for suspected infection and trauma patients to assess whether aetiology affected the primary associations of interest. See supplementary files 3 and 4 for case definitions. A sensitivity analyses was performed to assess whether hospital transfers may have influenced our results, as we did not follow-up on these patients. The main analyses were repeated in which patients transferred to other hospitals were considered as deceased.

RESULTS

Patient inclusion and characteristics

Figure 1 shows that of the 147,728 ED visits of patients ≥18 years, 101,416 patients were included in whom vital signs were measured.

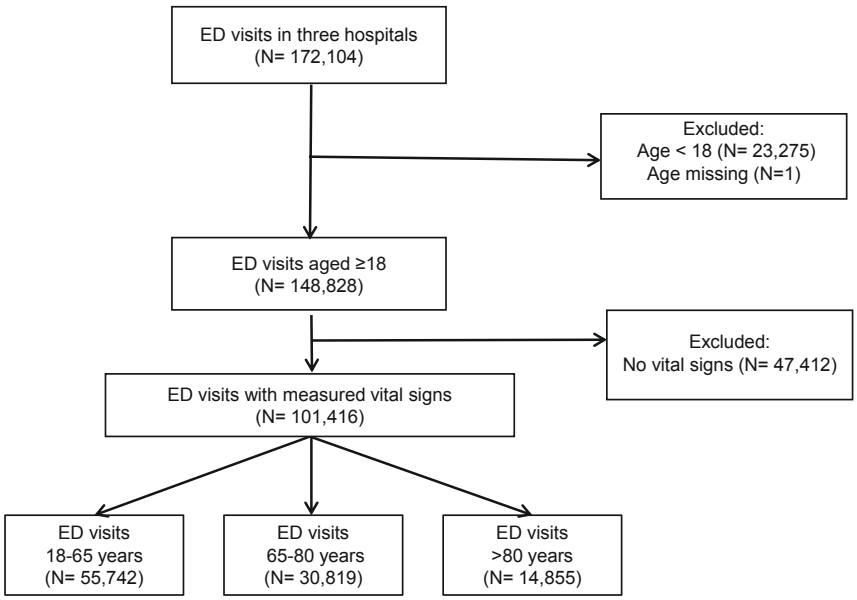


Figure 1. Patient inclusion and flow through the study. Observational multi-centre cohort study using the Netherlands Emergency department Evaluation Database (NEED). Three different age categories were included in which vital signs were measured.

Table 1 shows patient characteristics of the total cohort and per age-category. The mean age of included patients was 59.6 years (19.6). Table 1 also shows the percentage of patients in whom vital signs fell outside the reference ranges which are normally used in adults. For most values, the rate of abnormal vital signs increased with advancing age.

Table 1. Patient characteristics for the total cohort and different age categories.

	Total cohort N= 101,416 (100%)	18-65 N=55,742 (55%)	66-80 N=30,819 (30%)	>80 N=14,855 (15%)
Demographics N, (%)				
Sex, female	50,333 (49.6)	28,226 (50.7)	13,752 (44.6)	8315 (56.0)
Age, mean (SD)	59.6 (19.6)	45.3 (14.1)	72.9 (4.2)	85.8 (3.9)
Hospital setting N, (%)				
LUMC	28,361 (28.0)	17,980 (32.3)	7536 (24.5)	2845 (19.2)
MCL	53,378 (52.6)	27,048 (48.5)	17,698 (57.4)	8632 (58.1)
CZE	19,677 (19.4)	10,714 (19.2)	5585 (18.1)	3378 (22.7)
Treating specialty N, (%)				
Emergency medicine	17,656 (17.4)	11,062 (19.8)	4274 (13.9)	2320 (15.6)
Surgical	19,434 (19.2)	11,902 (21.4)	5076 (16.5)	2456 (16.5)
Medical	62,262 (61.4)	31,096 (55.8)	21,157 (68.6)	10,009 (67.4)
Top-10 chief complaints N, (%)				
Feeling unwell	20,414 (20.1)	9192 (16.5)	7392 (24.4)	3830 (26.3)
Abdominal pain	14,185 (14.0)	10,136 (18.2)	3035 (10.0)	1014 (7.0)
Dyspnoea	11,937 (11.8)	4975 (8.9)	4673 (15.4)	2289 (15.7)
Chest pain	11,067 (10.9)	6327 (11.4)	3523 (11.6)	1217 (8.4)
Extremity problems	8106 (8.0)	3736 (6.7)	2422 (8.0)	1948 (13.4)
Collapse	3868 (3.8)	1722 (3.1)	1433 (4.7)	713 (4.9)
Trauma	3778 (3.7)	2263 (4.1)	876 (2.9)	639 (4.4)

Table 1. Patient characteristics for the total cohort and different age categories. (continued)

	Total cohort N= 101,416 (100%)	**18-65 N=55,742 (55%)**	**66-80 N=30,819 (30%)**	**>80 N=14,855 (15%)**
Palpitations	3376 (3.3)	1665 (3.0)	1370 (4.5)	341 (2.3)
Wounds	2256 (2.2)	1442 (2.6)	601 (2.0)	213 (1.5)
Headache	2144 (2.1)	1465 (2.6)	475 (1.6)	204 (1.4)
Miscellaneous	18,311 (18.2)	11,437 (22.9)	4465 (14.9)	2147 (14.7)
Vital signs Mean (SD) [N] {% outside of reference category*}				
RR (/min.)	18 (6) [68,662] {23.4}	17 (6) [34,923] {18.3}	19 (6) [22,545] {27.1}	19 (6) [11,194] {32.1}
SPO2 (%)	97 (6) [91,785] {14.2}	99 (3) [49,628] {8.5}	96 (9) [28.374] {18.1}	96 (4) [13,783] {23.6}
SBP (mmHg)	133 (34) [89,531] {79.1}	128 (28) [47,444] {76.3}	137(40) [28,189] {81.7}	141 (34) [13,898] {83.3}
DBP (mmHg)	83 (17) [89,475] {60.7}	84(16) [47,424] {62.5}	81(18) [28.169] {58.7}	80 (19) [13,882] {58.3}
MAP (mmHg)	99(19) [89,512] {50.9}	98(18) [47,438] {47.9}	100 (21) [28.181] {53.8}	100 (21) [12,407] {54.7}
HR (beats/min.)	86 (52) [84,776] {23.4}	87(69) [44,611] {18.3}	86 (22) [26978] {27.1}	83 (21) [13,187] {32.1}
Temperature (°C)	37.0 (2.0) [82,364] {42.1}	37.0 (0.8) [45,073] {39.7}	37.0 (3.3) [25.349] {44.6}	36.9 (0.9) [11,942] {45.8}

Table 1. Patient characteristics for the total cohort and different age categories. (continued)

	Total cohort N= 101,416 (100%)	**18-65 N=55,742 (55%)**	**66-80 N=30,819 (30%)**	**>80 N=14,855 (15%)**
Proxies of disease severity N, (%)				
Triage level				
Blue and Green	22,414 (22.1)	12,952 (23.2)	6222 (20.2)	3240 (21.8)
Yellow	43,804 (43.2)	24,511 (44)	13,021 (42.2)	6272 (42.2)
Orange	28,176 (27.8)	14,750 (26.5)	9198 (29.8)	4228 (28.5)
Red	5339 (5.3)	2590 (4.6)	1896 (6.2)	853 (5.7)
GCS				
Not assessed	91,143 (89.9)	51,021 (91.5)	27,288 (88.5)	12,834 (86.4)
15	9041 (8.9)	4154 (7.5)	3170 (10.3)	1717 (11.6)
<15	1232 (1.2)	567 (1.0)	361 (1.2)	304 (2)
Fluid administration				
None	82,182 (81)	45,626 (81.9)	24,623 (79.9)	11,933 (80.3)
0-500ml	9164 (9.0)	4734 (8.5)	2909 (9.4)	1521 (10.2)
>500ml	10,070 (9.9)	5382 (9.7)	3287 (10.7)	1401 (9.4)
Blood gas analyses	21,750 (21.4)	9874 (17.7)	7924 (25.7)	3952 (26.6)

Table 1. Patient characteristics for the total cohort and different age categories. (continued)

	Total cohort N= 101,416 (100%)	**18-65 N=55,742 (55%)**	**66-80 N=30,819 (30%)**	**>80 N=14,855 (15%)**
Proxies of comorbidities/complexity N, (%)				
Number of consultations				
None	34,657 (34.2)	20,575 (36.9)	9671 (31.4)	4411 (29.7)
1	57,810 (57.0)	30,107 (54)	18,633 (60.5)	9070 (61.1)
2	6369 (6.3)	3193 (5.7)	2012 (6.5)	1164 (7.8)
>2	829 (0.8)	417 (0.7)	257 (0.8)	155 (1.0)
≥1 lab test	84,434 (83.3)	44,232 (79.4)	27,144 (88.1)	13,058 (87.9)
Radiological test**	60,739 (59.9)	29,741 (53.4)	19,908 (64.6)	11,090 (74.7)

Abbreviations: N= number, SD = standard deviation, LUMC= Leiden University Medical Centre, MCL= Medical Centre Leeuwarden, CZE= Catharina Hospital Eindhoven, RR = respiratory rate, SPO2 = peripheral oxygen saturation, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, HR = heartrate, GCS = Glasgow Coma Scale, mmHg = millimetre of mercury, °C= degrees Centigrade, ml = millilitres.

*Used reference categories were: SBP 100-140mmHg, DBP 60-90mmHg, MAP 70-100mmHg, HR 60-80beats/min., RR 12-20/min. SpO_2 ≥95%, temperature 36.5-37.5°C.

** If one or more of the following radiological tests were performed: Ultrasound, radiography, and computer-tomography.

Table 2. Adjusted Odds Ratios (AORs) for the association between vital signs and in-hospital mortality by different age groups.

	Total cohort	18-65 years	66-80 years	>80 years
Systolic blood pressure (mmHg)				
>140*	1.00			
121-140	1.35 (1.18-1.54)	1.68 (1.22-2.33)	1.28 (1.04-1.57)	1.39 (1.12-1.72)
101-120	1.91 (1.67-2.19)	2.50 (1.81-3.45)	1.75 (1.42-2.16)	1.97 (1.57-2.46)
81-100	2.62 (2.22-3.09)	2.82 (1.92-4.13)	2.83 (2.21-3.61)	2.44 (1.84-3.25)
0-80	4.07 (3.31-5.01)	6.38 (4.20-9.70)	3.33 (2.41-4.60)	4.17 (2.87-6.05)
Diastolic blood pressure (mmHg)				
>120	1.73 (1.37-2.19)	1,82 (1.08-3.07)	2.25 (1.57-3.20)	1.26 (0.84-1.88)
101-120	1.15 (0.96-1.37)	1.48 (1.04-2.10)	1,24 (0.95-1.63)	0.88 (0.65-1.20)
81-100*	1.00			
61-80	1.23 (1.09-1.39)	1.62 (1.24-2.11)	1,30 (1.08-1.56)	0.99 (0.82-1.21)
0-60	2.12 (1.84-2.44)	3.42 (2.47-4.73)	2,32 (1.87-2.88)	1.59 (1.27-2.00)
Mean Arterial blood pressure (mmHg)				
>120*				
101-120	0.88 (0.75-1.03)	1.01 (0.68-1.50)	0.81 (0.64-1.02)	0.95 (0.74-1.23)
81-100	1.06 (0.90-1.23)	1.56 (1.07-2.27)	0.88 (0.70-1.12)	1.11 (0.86-1.42)
61-80	1.73 (1.47-2.05)	2.02 (1.33-3.07)	1.72 (1.33-2.21)	1.75 (1.32-2.30)
0-60	3.27 (2.60-4.10)	5.72 (3.48-9.42)	2.86 (2.01-4.09)	3.17 (2.17-4.64)

Table 2. Adjusted Odds Ratios (AORs) for the association between vital signs and in-hospital mortality by different age groups. (continued)

	Total cohort	18-65 years	66-80 years	>80 years
Peripheral oxygen saturation (%)				
96-100*	1.00			
91-95	1.46 (1.31-1.62)	1.68 (1.30-2.18)	1.30 (1.10-1.53)	1.48 (1.25-1.77)
86-90	2.18 (1.83-2.61)	3.28 (2.17-4.94)	1.84 (1.41-2.39)	2.22 (1.66-2.97)
81-85	3.58 (2.80-4.58)	3.70 (2.08-6.57)	2.66 (1.81-3.92)	4.92 (3.32-7.29)
0-80	6.28 (5.05-7.82)	11.1 (7.40-16.6)	4.50 (3.19-6.34)	4.99 (3.30-7.56)
Respiratory rate (/min)				
Not registered*	1.00			
0-9	0.99 (0.49-2.01)	0.79 (0.24-2.69)	1.54 (0.58-4.07)	0.58 (0.08-4.46)
10-19	1.10 (0.92-1.30)	0.82 (0.60-1.13)	1.15 (0.87-1.51)	1.41 (1.02-1.94)
20-29	1.83 (1.53-2.18)	1.47 (1.04-2.06)	1.89 (1.43-2.50)	2.28 (1.64-3.15)
>30	2.89 (2.32-3.60)	2.57 (1.62-4.06)	3.23 (2.31-4.53)	3.17 (2.15-4.68)
Heart rate (beats/min)				
>125	2.98 (2.44-3.64)	4.17 (2.77-6.29)	2.47 (1.79-3.41)	2.76 (1.95-3.90)
101-125	2.50 (2.16-2.91)	2.61 (1.85-3.69)	2.71 (2.16-3.40)	2.22 (1.72-2.86)
76-100	1.43 (1.25-1.63)	1.34 (0.97-1.85)	1.48 (1.21-1.82)	1.48 (1.21-1.81)
51-75*				
0-50	1.61 (1.19-2.17)	2.04 (1.02-4.08)	1.67(1.04-2.69)	1.54 (0.96-2.45)

Table 2. Adjusted Odds Ratios (AORs) for the association between vital signs and in-hospital mortality by different age groups. (continued)

	Total cohort	18-65 years	66-80 years	>80 years
Temperature (°C)				
Not registered*				
≥40	0.49 (0.28-0.86)	0.40 (0.12-1.33)	0.43 (0.17-1.10)	0.65 (0.26-1.60)
38-39	0.68 (0.57-0.80)	0.69 (0.47-1.00)	0.74 (0.57-0.95)	0.57 (0.42-0.78)
35-37	0.89 (0.78-1.00)	0.91 (0.69-1.18)	0.81 (0.67-0.98)	0.97 (0.78-1.20)
31-34	2.74 (1.96-3.82)	4.11 (2.25-7.50)	2.10 (1.23-3.58)	2.77 (1.52-5.04)
0-30	1.54 (0.52-4.54)	1.17 (0.15-9.34)	0.60 (0.06-5.74)	4.04 (0.64-25.6)

*= reference category in the regression analyses
The following potential confounders were entered in the model for through backward stepwise regression: age, gender, top ten chief complaints, hospital, treating specialty, SpO_2, temperature, proxies of disease severity (triage level, Glasgow Coma Scale, blood gas analyses, Intensive Care Unit admission) and proxies of disease comorbidities/complexity (number of consultations, lab tests, performed radiological tests).

The association between vital signs and clinical outcomes

The AORs for predicted mortality (table 2) increased gradually with worsening values of SBP and SpO_2, while DBP, MAP and HR had a quasi-U-shaped association with mortality (Figures 2 and 3). There was no clear cut-off point between categories of SBP, DBP, SpO_2 and HR and AORs for mortality. The AOR for RR gradually increased between 10-19mm (Figure 3), with a substantial increase for mortality at 22/min. The AOR of mortality showed a substantial increase for temperature below a threshold of 35.5°C; however, temperatures above this were not associated with mortality. For MAP, a threshold at <70mmHg was found for mortality. Although single cut-offs for MAP, RR and temperature exist, using these cut-offs would ignore further increase of risk with more extreme values of these vital signs.

Older patients had larger increases in case-mix adjusted predicted mortality compared to younger people with changing vital sign categories (right panels in figure 2 and 3). In contrast, AORs for mortality decreased or increased to a similar extent with changing vital sign categories. Only patients aged 18-65 years with an SpO_2 <80% had higher odds for mortality (AOR 11.09; 7.40-16.62) compared to patients aged 66-80 years (AOR 4.50; 3.19-6.34) and >80 years (AOR 4.99; 3.30-7.56).

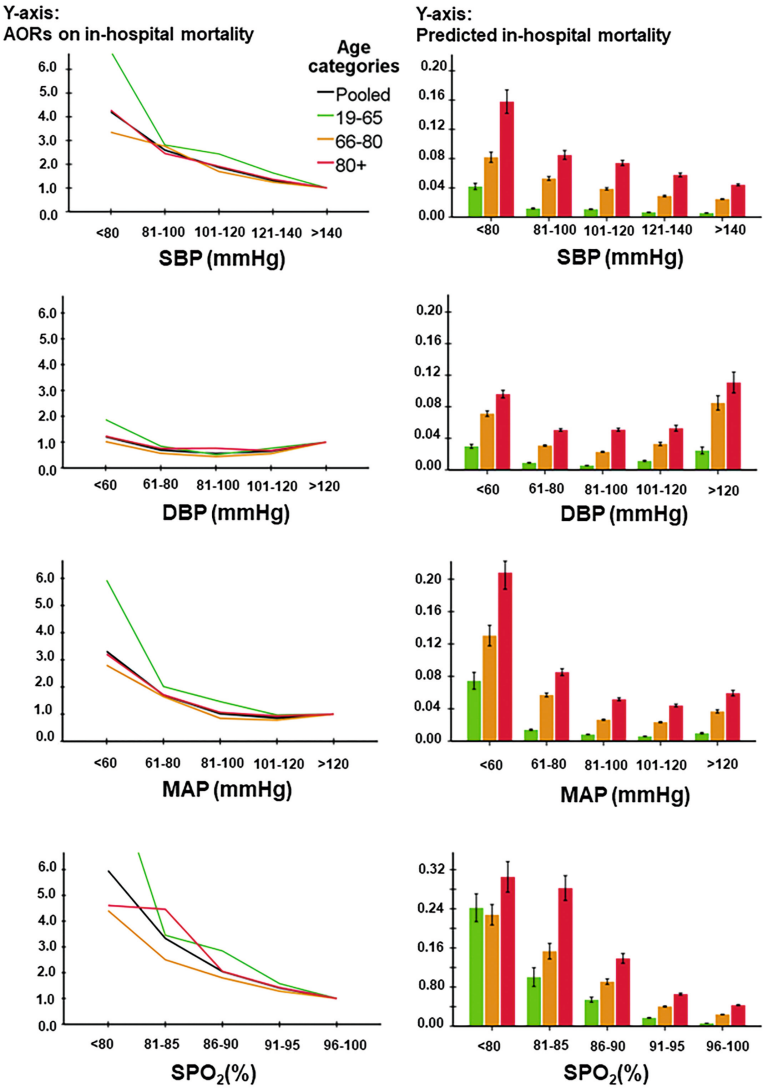


Figure 2. Adjusted odds ratios (AORs) for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and peripheral oxygen saturation (SpO_2) for in-hospital mortality (left side) and predicted in-hospital mortality (right side) as a function of vital signs in different age categories. Note that the black line is the pooled data of all three age categories together. The following potential confounders were entered in the model for in-hospital mortality through backward stepwise regression: age, gender, triage level, top ten chief complaints, hospital, treating specialty, disposition, SpO_2 (except for association of SpO_2), temperature (except for association of temperature), Glasgow coma scale, lab tests, number of consultations in the emergency department and performed radiological test.

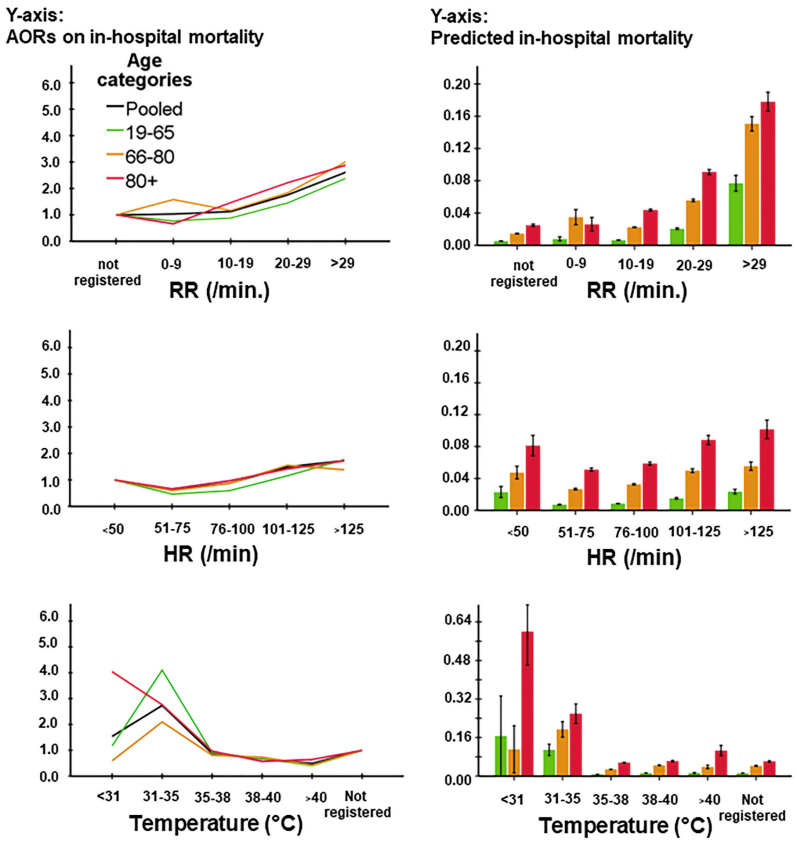


Figure 3. Adjusted odds ratios (AORs) for respiratory rate (RR), heart rate (HR) and temperature for in-hospital mortality (left side) and predicted in-hospital mortality (right side) as a function of vital signs in different age categories. Note that the black line is the pooled data of all three age categories together. The following potential confounders were entered in the model for in-hospital mortality through backward stepwise regression: age, gender, triage level, top ten chief complaints, hospital, treating specialty, disposition, SpO_2, temperature, Glasgow coma scale, lab tests, number of consultations in the emergency department and performed radiological test.

For ICU/MCU admission (table 3, supplementary files 5 and 6), SBP had a relevant cut-off in the category of <80mmHg and was calculated at 70mmHg with minimal p-value analysis. For MAP, a threshold of <60mmHg existed for admission to the ICU/MCU. When RR was registered, AOR for ICU admission was at least doubled compared to when it was not recorded, but no other cut-off was seen. Temperature < 31 °C had a substantially higher likelihood for ICU admission.

Table 3. Adjusted Odds Ratios (AORs) for the association between vital signs and ICU/MCU admission by different age groups.

	Total cohort	18-65 years	66-80 years	>80 years
Systolic blood pressure (mmHg)				
>140*	1.00			
121-140	0.89 (0.82-0.97)	0.90 (0.79-1.03)	0.95 (0.83-1.09)	0.94 (0.75-1.17)
101-120	0.98 (0.89-1.08)	1.01 (0.88-1.17)	0.95 (0.81-1.12)	1.14 (0.88-1.46)
81-100	0.97 (0.84-1.11)	0.97 (0.79-1.18)	0.93 (0.74-1.16)	1.21 (0.86-1.72)
0-80	1.94 (1.64-2.30)	2.11 (1.63-2.72)	1.98 (1.50-2.60)	1.88 (1.21-2.94)
Diastolic blood pressure (mmHg)				
>120	2.18 (1.85-2.58)	2.34 (1.83-3.00)	2.31 (1.76-3.03)	1.54 (0.98-2.40)
101-120	1.34 (1.21-1.48)	1.30 (1.12-1.51)	1.36 (1.15-1.61)	1.34 (1.01-1.77)
81-100*	1.00			
61-80	0.93 (0.86-1.00)	0.99 (0.88-1.12)	0.82 (0.72-0.93)	1.00 (0.81-1.22)
0-60	1.32 (1.18-1.49)	1.71 (1.41-2.07)	1.32 (1.10-1.58)	1.04 (0.78-1.37)
Mean Arterial blood pressure (mmHg)				
>120*	1.00			
101-120	0.74 (0.67-0.82)	0.69(0.60-0.81)	0.81 (0.70-0.95)	0.73 (0.56-0.93)
81-100	0.64 (0.57-0.70)	0.65(0.56-0.76)	0.62 (0.52-0.73)	0.72 (0.56-0.93)
61-80	0.76 (0.67-0.86)	0.78(0.64-0.95)	0.80 (0.66-0.98)	0.73 (0.53-1.00)
0-60	1.70 (1.40-2.06)	2.18(1.61-2.96)	1.89 (1.38-2.58)	1.28 (0.81-2.02)

Table 3. Adjusted Odds Ratios (AORs) for the association between vital signs and ICU/MCU admission by different age groups. (continued)

	Total cohort	18-65 years	66-80 years	>80 years
Peripheral oxygen saturation (%)				
96-100*	1.00			
91-95	1.16 (1.06-1.26)	1.15 (1.00-1.32)	1.16 (1.02-1.32)	1.04 (0.85-1.26)
86-90	1.39 (1.18-1.65)	1.35 (1.00-1.84)	1.41 (1.10-1.82)	1.44 (1.01-2.05)
81-85	2.43 (1.90-3.10)	3.72 (2.48-5.60)	2.18 (1.49-3.19)	1.67 (0.97-2.90)
0-80	3.00 (2.41-3.74)	3.34 (2.33-4.81)	3.55 (2.55-4.95)	1.92 (1.11-3.32)
Respiratory rate (/min)				
Not registered*	1.00			
0-9	4.15 (2.96-5.82)	3.71 (2.37-5.81)	4.29 (2.38-7.74)	6.59 (2.02-21.50)
10-19	2.37 (2.01-2.79)	2.28 (1.82-2.87)	2.27 (1.73-2.97)	2.58 (1.58-4.19)
20-29	3.15 (2.66-3.73)	3.11 (2.45-3.96)	2.96 (2.25-3.90)	3.53 (2.16-5.76)
>30	5.16 (4.19-6.35)	5.59 (4.07-7.69)	5.61 (4.03-7.81)	5.20 (3.00-9.03)
Heart rate (beats/min)				
>125	2.53 (2.23-2.87)	2.69(2.23-3.24)	2.10 (1.71-2.59)	2.92 (2.11-4.02)
101-125	1.52 (1.36-1.68)	1.45(1.24-1.69)	1.55 (1.31-1.83)	1.37 (1.03-1.81)
76-100	1.10 (1.01-1.19)	1.00(0.88-1.13)	1.20 (1.05-1.37)	1.18 (0.96-1.46)
51-75*	1.00			
0-50	1.34 (1.08-1.65)	1.10(0.74-1.62)	1.25 (0.90-1.74)	2.11 (1.38-3.23)

Table 3. Adjusted Odds Ratios (AORs) for the association between vital signs and ICU/MCU admission by different age groups. (continued)

	Total cohort	18-65 years	66-80 years	>80 years
Temperature (°C)				
Not registered*	1.00			
≥40	0.50 (0.32-0.78)	0.53(0.29-0.97)	0.53 (0.25-1.14)	0.30 (0.07-1.28)
38-39	0.35 (0.30-0.41)	0.38(0.30-0.49)	0.37 (0.28-0.47)	0.28 (0.18-0.43)
35-37	0.64 (0.59-0.70)	0.63(0.56-0.71)	0.66 (0.58-0.76)	0.64 (0.51-0.79)
31-34	1.36 (1.00-1.84)	1.58(1.02-2.43)	1.14 (0.67-1.92)	1.41 (0.62-3.17)
0-30	3.95 (1.59-9.82)	5.90(1.36-25.66)	1.89 (0.36-9.95)	11.6 (1.64-81.7)

Abbreviations: ICU = intensive care unit, MCU= medium care unit
*= reference category in the regression analyses
The following potential confounders were entered in the model for through backward stepwise regression: age, gender, top ten chief complaints, hospital, treating specialty, $SpO_{2,}$ temperature, proxies of disease severity (triage level, fluid administration, Glasgow Coma Scale, blood gas analyses) and proxies of disease comorbidities/complexity (number of consultations, lab tests, performed radiological tests).

Younger patients had larger increases in predicted ICU/MCU admission compared to older patients with increasing DBP, RR, HR, and decreasing SpO_2 categories (supplementary file 5 and 6). In contrast, AORs changed to a similar extent among all age categories for changing vital signs.

Subgroup and sensitivity analyses
The AORs for mortality increased or decreased to the same extent in the subgroups with suspected infection and trauma patients, and in the sensitivity analyses, regardless of the patient's age category (supplementary file 3, 4 and 7).

DISCUSSION

The present study has two main findings. First, in-hospital mortality increased gradually with decreasing SBP and SpO_2, without the existence of a single threshold for these vital signs. For DBP, MAP and HR, we found quasi-U-shaped associations with in-hospital mortality. A single cut-off existed for MAP, RR, and temperature, however, using these single cut-offs would ignore further increase of risk with more extreme values of these vital signs. Secondly, absolute mortality increased substantially more in older compared to younger patients with changing vital sign categories.

The use of a single threshold for SBP in many acute care guidelines and risk stratification tools deserves scrutiny.[23-25, 47, 48] The linear association between SBP and mortality in an unselected ED population corresponds with previous studies in traumatic brain injury, sepsis, hypertension and unselected ED patients.[28, 49, 50] Our study suggests that a single cut-off is also absent for SpO_2 correspondent to earlier findings in a study by Ljunggren et al. in 96,512 unselected ED patients.[11] Interestingly, temperatures above 35.5°C, i.e. normal temperature and fever, were not significantly associated with mortality in our and Ljunggren's study. This finding is in contrast to what has been suggested in several risk stratification tools, like the national and modified EWS, in which points are assigned for high temperature.[51] It should be noted, however, that the original EWS was not intended to be a predictor of outcome, but rather to be a simple tool to assist inexperienced nursing or medical staff in recognizing patients at risk for deterioration and in securing immediate, more experienced help.[52]

In addition to a threshold for temperature, we also found a single cut-off for MAP and RR. RR was the least registered vital sign, but our findings confirm the importance of RR given the strong association with mortality and the higher odds for ICU/MCU admission if RR was registered, compared to if it

was not registered. The threshold we found for MAP <70mmHg was similar to the thresholds used in several guidelines.[39, 40] Interestingly, the odds for ICU admission only started to increase with MAP below 60mmHg. Probably, physicians are less triggered to admit patients to an ICU or MCU with a MAP between 60-80mmHg. This discrepancy between the associations of MAP and in-hospital mortality versus ICU admission warrants further research as it may reflect unrecognized hypotension, and patients with higher MAPs may need ICU admission.

Different from other studies, we have studied the effect of age on associations between vital signs and outcome. Older patients had larger increases in the absolute risk for mortality with changing vital sign categories compared to younger patients, while the relative risk for mortality had similar increases. Previously, the use of different single cut-off values for SBP in trauma patients has been suggested for advanced age.[53] Although prognosis has been found to deteriorate at higher SBP threshold, our data suggest not to use a single cut-off at all.

The findings of the present study have several implications for clinical practice. Although a single cut-off may be convenient and easy to use, our first finding suggests that the use of a cut-off for several vital signs in risk stratification tools and acute care guidelines are inappropriate.[21-23, 39-41] The use of a single cut-off suggests that above or below this specific threshold prognosis changes substantially. Using only a single threshold, like for SBP or RR in qSOFA, does not mean that the chosen threshold for SBP of 100mmHg discriminates better between low and high-risk patients than a threshold of 90, 110, 120, 130, 140 mmHg and so on, as has been demonstrated previously for SBP in traumatic brain injury.[28] Even if a single cut-off exists, i.e. if an association between outcome and a vital sign is only apparent from a certain value, dichotomous risk stratification would ignore further increase of the risk with more extreme values of the vital sign. This implicates that several risk stratification tools and acute care guidelines could be improved by using numerical scores based on AORs or predicted mortality rather than using dichotomous variables.[21-23, 39-41] Currently, these grading scores are already used in EWS, although the scores in the EWS are not supported by AORs derived from prediction models.[51]
APACHE II is a good example of a numerical score for ICU patients.[54] Similar risk stratification scores may be developed for the ED to improve recognition, initial resuscitation and disposition.

Our second main finding implicates that risks scores need to be age-adjusted. The effect of vital signs on mortality did change with advancing

age, because baseline risk for older age was higher. For example, if SBP decreased and the risk on in-hospital mortality increased fourfold, the effect on younger patients with a baseline mortality risk of i.e. 0.5% would be much smaller than the effect on older patients with a baseline mortality risk of i.e. 4.0%. More points may be assigned in a numerical score for older age for similar vital signs.
Interestingly, the subgroup analyses in sepsis and trauma patients suggests that the etiology of changes in vital signs does not affect the impact of vital signs on relevant outcomes. Future studies should incorporate our findings in development of risk stratification tools and acute care guidelines for ED patients using numerical scores based on absolute risks.

Our study has several strengths like a large sample size with unselected patients and the multicentre design. Several limitations merit emphasis. First, this observational study used the NEED, which lacks information about the medical history and comorbidities of patients. However, to overcome this, we used variables that are associated with comorbidities and complexity.[45] Second, information bias cannot be completely ruled out although data collection was largely automatized and only reliably registered variables are collected in the NEED. Finally, we missed outcomes of patients who were hospitalized elsewhere. However, the sensitivity analyses in which we considered these patients as deceased, yielded similar results.

CONCLUSION

The use of a single cut-off for each vital sign in acute care guidelines and risk stratification tools deserves scrutiny, as our results show that clinical outcomes increase gradually or in a U-shaped fashion with changing vital signs. A threshold for MAP, RR and temperature exists, however, using these single cut-offs would ignore further increase of risk with more extreme values of these vital signs. Age-adjusted numerical scores will improve risk stratification, as older patients have larger absolute increases in mortality with changing vital signs, even after adjusting for confounders.

SUPPLEMENTARY FILE 1

Data collected in the Netherlands Emergency department Evaluation Database (NEED) and their definitions are described in detail.

GENERAL DATA OF PARTICIPATING EMERGENCY DEPARTMENTS

In the NEED, several hospitals and the emergency department characteristics are registered once a year.

1. Which hospital. Coding: <Hospital Code>.

2. Type of hospital. Urban = 0. Urban (STZ = Foundation of top clinical hospitals) teaching hospital = 1. Academic Medical Centre = 2.

3. Number of patients in the region of the relevant hospital. This information can be obtained for each participating hospital by the NZa (was once used to calculate the hospital budgets).

4. Emergency physicians. a. Number of emergency physicians working at the emergency room in the hospital on the first of January of the year in question. b. Emergency physicians in fulltime equivalent. c. Number of residents in emergency medicine on the first of January of the year in question. d. Number of residents not in training on the first of January of that year.

5. Presence of emergency physicians. a. Non-24/7 presence by emergency physicians = 0. Minimum of 1 emergency physician 24 hours a day, 7 days a week = 1. b. How many emergency physicians, residents in emergency medicine and residents not in training are working average at the emergency department daily for patient care. Number per shift. The number of shifts for emergency physicians also must be defined.

6. Number of trauma surgeons employed by the hospital (so NO general surgeons). Trauma surgeons in FTE.

7. Number of internists in acute medicine employed by the hospital. (So NOT general internists).

8a. Trauma centre No = 0. Level 2 = 1. Level 1 = 2.

8b. Intensive care in hospital. Not present = 0. Present = 1.

9. Medium Care (or high care) present in hospital. Not present = 0. Present = 1.

10. Number of visits per year on the emergency department (so NOT the number of emergency patients per year). This only accounts for the number of patients at the emergency department. If a separate emergency cardiac care is present or GP clinic is integrated, these patient visits are counted separately.

11. Number of emergency department visits per year. N.

12. General Practitioner clinic integrated within the emergency department. No = 0. Yes = 1.

13. Emergency cardiac care present AT or NEXT to the emergency department. Not present = 0. Present = 1

14. Quality indicators by the Dutch Society of Emergency Physicians (DSEP (NVSHA). See also the NVSHA website. www.nvsha.nl.

Quality indicators for Acute Coronary Syndrome (ACS).

1.Are patients with (suspected) ACS treated at your emergency department? Indicate whether any patients are suspected for acute coronary syndrome at your emergency department. Answer: No = 0. Yes = 1.

2. For patients with (suspected) ACS, do you have a protocol about administration of aspirin?

Indicate whether a protocol is used at the emergency department for the administration of aspirin in cases of suspected acute coronary syndrome. Mention which protocol. Answer: No = 0. Yes = 1.

3. Time for administration of aspirin to patients with (suspected) ACS registered at the emergency room?

Specify whether the exact time of administration of aspirin given to patients with suspicion of acute coronary syndrome is registered at the emergency department. This can be a written or electronic registration. Answer: No = 0. Yes = 1.

Quality indicator Complication registration.

A complication is an unintended and undesired event or condition during or following medical treatment which is harmful to the health of the patient needing change in medical treatment, or if irreversible health damage exists.

1. Complication registrations

Is a complication registration used at the emergency department? Only one answer is possible. If this question is answered with "no", the other questions with indicator "Triage on Emergency Department" do not apply. You can continue to answer the questions with the next indicator. Answer: No = 0. Yes = 1.

2. Complication meeting

A complication meeting at least four times a year at the emergency room? Answer only yes or no. Answer: No = 0 Yes = 1.

3. Complication Registration

Here we would like you to briefly specify which CR you are using. If possible, you can attach a copy of the list of complications registered. Please note: This does not concern completed lists with numbers of complications.

Free text: ...

Quality indicator child abuse / domestic violence.

1.Presence of child abuse protocols

A written child abuse protocol used at the emergency department which meets the following minimum competencies? A. A multidisciplinary child abuse team is active in the hospital. B. Employees at the emergency department are trained in identifying child abuse. Answer: Yes, to both: 3 A yes, B no: 2 A no, B yes: 1 No = 0.

2. Screening instrument

Does the ED use a screening instrument to signal child abuse, such as the SPUTOVAMO form or a derivative? Answer: No = 0. Yes = 1.

Which screening instrument is used at the emergency room?

(multiple answers possible): SPUTOVAMO form. No = 0. Yes = 1 Top - toe examination. No = 0. Yes = 1. Otherwise, describe: <Free text ...>

3. Number of completed screening documents.

What is the number of completed screening documents at the emergency department, in relation to the total number of children up to and including 18 years old at the emergency department? **n** Number of completed screening documents at the ED in January 2011

N Total number of children up to and including 18 years at the emergency room in January 2011

n / N * 100% Screening document percentage

4. Protocol "parent notifications" Is a protocol used at the emergency department for the reporting of children as victims of domestic violence / suicidal attempt / auto mutilation / excessive alcohol and / or drug use? Answer: No = 0. Yes = 1. Notifications:

Quality indicator pain relief.

1.Pain scoring systems Is a pain scoring system used at the emergency department? Answer: No = 0. Yes = 1. If yes, which scoring system: <Free text>

2. Time registration of pain relief. Is the exact time recorded when pain relief is given in the emergency room? Answer: No = 0. Yes = 1.

3. Pain protocols

Is a pain protocol used at the emergency room? Answer: No = 0. Yes = 1. Comments <Free text>

Quality indicator Sepsis.

1.Sepsis protocol Is a sepsis protocol used at the emergency department? Answer: No=0. Yes=1. If yes, which protocol <free text>

2. Screening document Is a screening document used for sepsis in the emergency room? Answer: No=0. Yes=1. If yes, which document: <free text>

3. Time registration for administering of antibiotics to patients with sepsis Is time of administering of antibiotics to patients with sepsis registered at the emergency department? Answer No=0. Yes=1. Comments <free text>

Quality indicator Procedural sedation and analgesia (PSA)

PATIENT RECORDS.

The following basic principles are used: 1) Facts are recorded, e.g. times. Derived variables are generated afterwards, such as duration of stay. 2) Continuous variables are not categorized because this will lead to data loss. 3) Only create categories for coding, considering a remaining category "other" and the possibility to indicate "unknown" The following data is collected from all patients:

Demographic information. In general, the social service number (BSN) and date of birth are registered for each patient. In addition, a unique code is registered for each emergency room visit.

1.Age Age in years at the time of registration at the emergency registration desk.

2. Sex. Male or female. Code: Female = 0. Male = 1

3. Date and time Registration of ED presentation. DD-MM-YEAR-HOUR-MIN.

Transport to the hospital.

4. Type of arrival at the hospital. Arrival at the emergency room by ambulance or by own transport (i.e. walking, bicycle / moped or public transport). Encoding: Own transport = 0. Arrival with ambulance = 1. 9 = Unknown

5. Referral status. Self-referrer or referred by GP or another specialist. Encoding: Self-referrer = 0. Referred by physician = 1. Referred by specialist = 2. 9 = Unknown. For variable 4 and 5, more variables are possible. This still has to be discussed and agreed with the participating hospitals. Example: Anyone who enters by ambulance after a 112-call, would that be a self-referrer?

General information in the ED.

6. Triage category. Triage category according to Manchester triage system upon arrival of patient. Coding: Blue = 1, green = 2, yellow = 3, orange = 4, red = 5. If the Boston triage system is used, the corresponding categories 1 to 5 will be used. If a Dutch triage system is used, it will be entered.

7. Main specialism or supervisor. In case this is not known, the specialty will be recorded which admits the patient.

Coding: emergency physician = 0. Surgery = 1. Internal medicine (or super specialism of internal medicine for example gastroenterologist or vascular medicine) = 2. Cardiology = 3. Neurology = 4. Urology, ENT or ophthalmology = 5. Pediatrics = 6. Other = 7.

8. Presenting complaint according to MTS, NTS, etc triage system. So not the entry complaint according to the registration desk employee. Coding: Complaint 1 = 1, complaint 2 = 2, ... Complaint 52 = complaint 52.

9. Resuscitation in shock (trauma) room. Coding: Treatment in standard treatment room = 0. Shock room / trauma room = 1.

The definition of a shock room still needs to be determined by the participating emergency departments. They need to agree whether, for example, thrombolysis is part of this or not. The exact conditions of this room must be specified?

10. Initial vital signs at the time of triage or in the ED treatment room. So NOT mentioned on arrival at the treatment room. This variable only needs to be registered if it has been measured. If not measured, the space is left empty.

Oxygen saturation as measured with a pulse oximeter used in the hospital (percentages without oxygen). If measured when oxygen is given, note the number of liters / min of oxygen. Systolic and diastolic blood pressure (mmHg).Heart rate measured with pulse oximeter (beats / min.).Temperature measured with an ear thermometer (degrees Celsius). Glascow coma scale (EMV score). A separate variable is made of each vital parameter, with limit values and units. The Early Warning Score can then be calculated.

11a. Additional blood tests on the emergency room. If blood has not been obtained and sent for analyses, a 0 will be entered. If blood has been sent for analyses, a 1 will be entered.

11b. If blood has been obtained, the following values are entered. Carefully check whether the units at all EDs are the same! Blood gas obtained. 0 = No. 1 = Yes. If yes: Venous = 0. Arterial = 1. pH ...PO2 (KPa), PCO2 (KPa), Bicarbonate (mmol / L), B.E. ... *Biochemistry:* Sodium

(mmol / L), K (mmol / L), Creatinine (µmol / L) Urea (mmol / L), ASAT (U / L), ALAT (U / L), yGT (U / L), AF (U / L), LDH (U / L), CK (U / L), High sensitive Troponin (ng / L), CRP (mg / L), Pro-BNP (mg / L), Procalcitonin (mg / L), Lactate (mmol / L) *Hematology:* Hb (mmol / L), Leucocytes ($x10^9$ / L), Platelets ($x10^{12}$ / L), D-dimer (mg / L), INR *Toxicology:* Ethanol (mg / L), Paracetamol (mg / L) *Blood cultures collected at the emergency room and sent for cultures:*
0 = No. 1 = Yes. Blood cultures should be at least one set (i.e. an aerobic and an anaerobic). *Urine collected at the emergency room and send for cultures:* 0 = No. 1 = Yes. *Urinary sediment collected at the emergency room:* 0 = No. 1 = Yes. *Urine toxicological analysis performed at the emergency department:* 0 = No. 1 = Yes.

12a. Additional X-ray diagnostics at the emergency room.
If no X-ray diagnostics has been performed at the emergency room, a 0 is entered. If a type of X-ray diagnostics has been performed at the emergency room, a 1 is entered. Definition: 0 should also be entered, if the patient is sent for an X-ray by the GP, and afterwards sent to the Emergency Department.

12b. If X-ray diagnostics have been performed, the type of examination must be recorded. Conventional X-ray, extremity. 0 = No. 1 = Yes. Conventional X-ray, divers (including chest X-ray). 0 = No, 1 = Yes. Abdominal ultrasound (including FAST). 0 = No, 1 = Yes. Ultrasound for deep vein thrombosis (DVT). 0 = No, 1 = Yes. Ultrasound, divers. 0 = No, 1 = Yes. Head CT. 0 = No, 1 = Yes. CT-Cervical spine. 0 = No, 1 = Yes. CT pulmonary embolism. 0 = No, 1 = Yes. CT aorta. 0 = No, 1 = Yes. CT chest-abdomen (trauma). 0 = No, 1 = Yes. Patients can receive multiple examinations at the emergency room.
13. Number of consultations at the emergency room. Coding: No consultations = 0. A consultation = 1. Two consultations = 2. Three consultations = 3, etc.

Outcomes
14. Emergency department lengths of stay. Duration in minutes. Discharge time of the emergency room minus the registration time at the emergency room. (So NOT the announcement or triage time).
15. Discharge destination (disposition) Home, to general ward, medium care (MC) or Coronary Care Unit (CCU) or intensive care (ICU). Died in ED. Transfer to another hospital. Scheduled outpatient clinic after ED visit and related to ED visit.
16. Hospital length of stay. In days. Discharge date minus recording date. If a patient at the emergency room is discharged home, the hospital duration is 0 days. If people are registered before midnight and leave the ED after midnight, this should be accounted as 0 days!
17. Hospital mortality. Coding: Leaving the hospital alive = 0. Died in ED or brought in dead (for example during CPR) = 1. Died in hospital before discharge = 2.
18. Return to ED with medical problem / complaints. Coding: No return with medical problems within 7 days after registration time on ED = 0. Return to the ED within a week after discharge with a medical problem which may or may not be related to the previous ED visit = 1. Return to the ED within a week after discharge with a medical problem which is clearly related to the previous ED visit = 2.

Otherwise = 3

19. ICD-10 code and diagnosis after discharge from the emergency room and hospital.

20. Diagnosis Treatment Code (DBC or DOT).

SUPPLEMENTARY FILE 2

The following variables were calculated or modified:

- Triage levels were considered equal among hospitals. Non-urgent triage levels (blue and green) were merged into one triage level, because of the low number of ED patients and events in the triage level blue.
- The Manchester Triage System (MTS) was used in the tertiary care centre, and consisted of 51 possible chief complaints. The Dutch Triage Standard (NTS) consisted of 50 possible triage chief complaints and was used in the two urban hospitals. The MTS and NTS were merged into one chief complaints list. The MTS, NTS and the merged chief complaints list are shown below. If chief complaints did not match, a new chief complaint was made. In total the merged list contained 51 different chief complaints. The top ten chief complaints were used in the present study to adjust the primary associations of interest (feeling unwell; abdominal pain; dyspnea; chest pain; extremity problems; collapse; trauma; palpitations; wounds; headache, and a miscellaneous category containing all the other chief complaints.
- Treating specialty was categorised to minimalize the number of categories and use as potential confounder: surgical (i.e. surgery, orthopaedics, ophthalmology, urology, ear-nose-throat), medical (internal medicine, cardiology, neurology, gastroenterologist, psychiatry, and remaining specialties) and emergency medicine if no other specialty had been involved. Specialities were assigned before ED treatment during patient registration. Self-referred patients and critically ill patients are generally assigned to the Emergency Medicine. If a patient is referred by a general practitioner, he/she is often referred to a specific specialty.

Merged chief complaints (N=51)	MTS chief complaints (N=51)	NTS chief complaints (N=50)
Abdominal pain	Abdominal pain in adults Abdominal pain in children	Abdominal pain in adults Abdominal pain in children
Abscesses & local infections	Abscesses and local infections	
Allergy, bites & stings	Allergy Bites and stings	Allergic reaction and stings
Apparently drunk	Apparently drunk	
Assault	Assault	
Asthma	Asthma	
Back pain	Back pain	Back pain
Behaving strangely & suicidal	Behaving strangely	Behaving strangely or suicidal
Breast infection		Breast infection
Burns & scalds	Burns and scalds	Burns and scalds
Chest pain	Chest pain	Chest pain
Collapse	Collapsed adult	Collapse Dizziness
Constipation		Constipation
Coughing		Coughing
Crying baby	Crying baby	
Dental problems	Dental problems	Dental problems
Diabetes	Diabetes	Diabetes
Diarrhea & vomiting	Diarrhea and vomiting	Diarrhea Vomiting

Merged chief complaints (N=51)	MTS chief complaints (N=51)	NTS chief complaints (N=50)
Dyspnea	Shortness of breath in adults Shortness of breath in children	Shortness of breath
Ear problems	Ear problems	Ear problems
Exposure to chemicals	Exposure to chemicals	
Extremity problems	Limb problems	Arm problems General/limb trauma Leg problems
Eye problems	Eye problems	Eye problems
Facial problems	Facial problems	Facial trauma Nosebleed
Falls	Falls	
Feeling unwell	Unwell adult Unwell child	Fever in adults Fever in children Neurological failure Unwell adult Unwell child
Fits	Fits	Fits
Foreign body	Foreign body	Foreign body
Gastro-intestinal (GI) bleeding	Gastro-intestinal (GI) bleeding	
Genital problems	Testicular pain	Genital problems
Headache	Headache	Headache
Implantable Cardioverter Defibrillator (ICD)		Implantable Cardioverter Defibrillator (ICD)

Merged chief complaints (N=51)	MTS chief complaints (N=51)	NTS chief complaints (N=50)
Irritable child	Irritable child	
Limping child	Limping child	
Major incidents – primary	Major incidents – primary	
Mental illness	Mental illness	
Near-drowning		Near-drowning
Neck pain	Neck pain	Neck problems Neck trauma
Overdose & poisoning	Overdose and poisoning	Poisoning
Palpitations	Palpitations	Palpitations
Per vaginum (VP) bleeding	Per vaginum (VP) bleeding	Per vaginum (VP) bleeding
Pregnancy	Pregnancy	Childbirth
Rashes	Rashes	Rashes
Rectal problems		Rectal problems
Self-harm	Self-harm	
Sexually acquired infection	Sexual acquired infection	
Throat problems	Sore throat	Throat problems

Merged chief complaints (N=51)	MTS chief complaints (N=51)	NTS chief complaints (N=50)
Trauma	Head injury Torso injury Major trauma	Head trauma Thorax trauma Abdominal trauma Back trauma
Urinary problems	Urinary problems	Urinary problems
Worried parent	Worried parent	
Wounds	Wounds	Wounds

Abbreviations: MTS=Manchester Triage System, NTS= Dutch Triage Standard, N= number

SUPPLEMENTARY FILE 3

Adjusted Odds Ratios (AORs) for the association between In-hospital mortality and vital signs by different age groups in a subgroup analysis: suspected infection.

	Total cohort	18-65	66-80	>80
Systolic blood pressure (mmHg)				
>140*	1.00			
121-140	1.01 (0.79-1.28)	.97 (0.53-1.77)	1.08 (0.75-1.54)	0.96 (0.65-1.41)
101-120	1.56 (1.24-1.96)	1.74 (1.02-2.98)	1.63 (1.15-2.33)	1.41 (0.96-2.06)
81-100	1.85 (1.42-2.40)	1.39 (0.74-2.63)	2.49 (1.68-3.68)	1.64 (1.05-2.57)
0-80	2.58 (1.88-3.56)	3.55 (1.82-6.93)	2.62 (1.55-4.42)	2.08 (1.17-3.69)
Diastolic blood pressure (mmHg)				
>120*	1.00			
101-120	0.60 (0.36-1.03)	1.21 (0.40-3.60)	0.50 (0.23-1.10)	0.40 (0.15-1.09)
81-100	0.68 (0.43-1.08)	0.68 (0.25-1.91)	0.54 (0.28-1.04)	0.89 (0.39-2.00)
61-80	0.64 (0.41-1.01)	0.91 (0.33-2.49)	0.50 (0.26-0.96)	0.71 (0.32-1.59)
0-60	1.00 (0.64-1.58)	1.59 (0.57-4.44)	0.91 (0.47-1.76)	0.89 (0.40-2.00)
Mean Arterial blood pressure (mmHg)				
>120*	1.00			
101-120	0.86 (0.63-1.18)	1.02 (0.48-2.16)	0.79 (0.49-1.26)	0.85 (0.50-1.45)
81-100	0.89 (0.66-1.19)	1.12 (0.56-2.27)	0.71 (0.45-1.11)	0.98 (0.60-1.62)
61-80	1.22 (0.90-1.67)	1.33 (0.64-2.77)	1.35 (0.86-2.14)	1.07 (0.63-1.83)
0-60	2.22 (1.52-3.23)	3.23(1.38-7.58)	2.34 (1.31-4.17)	1.75 (0.92-3.33)

	Total cohort	18-65	66-80	>80
Peripheral oxygen saturation (%)				
96-100*	1.00			
91-95	1.09 (0.91-1.31)	1.15 (0.76-1.75)	1.08 (0.82-1.42)	1.01 (0.74-1.36)
86-90	1.37 (1.04-1.81)	1.55 (0.79-3.05)	1.43 (0.96-2.12)	1.18 (0.72-1.94)
81-85	2.01 (1.32-3.07)	1.10 (0.38-3.22)	2.40 (1.26-4.59)	2.09 (1.03-4.24)
0-80	3.24 (2.13-4.86)	2.80 (1.21-6.45)	3.78 (2.02-7.09)	2.58 (1.25-5.35)
Respiratory rate (/min)				
Not measured*	1.00			
0-9	#	#	#	#
10-19	1.08 (0.78-1.49)	1.19 (0.61-2.33)	0.95 (0.59-1.54)	1.11 (0.60-2.05)
20-29	1.66 (1.20-2.27)	2.20 (1.13-4.31)	1.48 (0.93-2.34)	1.52 (0.84-2.76)
>30	2.45 (1.70-3.51)	3.86 (1.73-8.60)	2.61 (1.54-4.43)	1.88 (0.98-3.62)
Heart rate (beats/min)				
>125	2.63 (1.88-3.68)	4.03 (1.88-8.66)	1.70 (0.99-2.93)	2.99 (1.70-5.26)
101-125	1.78 (1.34-2.37)	1.59 (0.76-3.33)	1.68 (1.09-2.60)	2.05 (1.29-3.28)
76-100	1.33 (1.01-1.74)	1.55 (0.76-3.14)	1.13 (0.75-1.72)	1.57 (1.02-2.43)
51-75*	1.00			
0-50	1.64 (0.89-2.99)	3.52 (0.83-15.0)	1.12 (0.40-3.17)	2.12 (0.84-5.31)

	Total cohort	18-65	66-80	>80
Temperature (°C)				
Not measured*	1.00			
≥40	0.41 (0.23-0.75)	0.35 (0.10-1.25)	0.35 (0.13-0.95)	0.53 (0.20-1.38)
38-39	0.52 (0.39-0.68)	0.59 (0.31-1.11)	0.54 (0.36-0.80)	0.41 (0.26-0.65)
35-37	1.14 (0.88-1.48)	1.50 (0.82-2.72)	1.01 (0.69-1.49)	1.09 (0.70-1.71)
31-34	2.59 (1.50-4.46)	5.97 (2.18-16.4)	1.28 (0.47-3.51)	2.41 (0.95-6.15)
0-30	0.70 (0.08-6.26)	#	#	#

*= reference category, # No outcome events for this category
Case definition: Patients with suspected infection were selected if blood cultures were obtained in the ED, and if patients were hospitalized.

SUPPLEMENTARY FILE 4

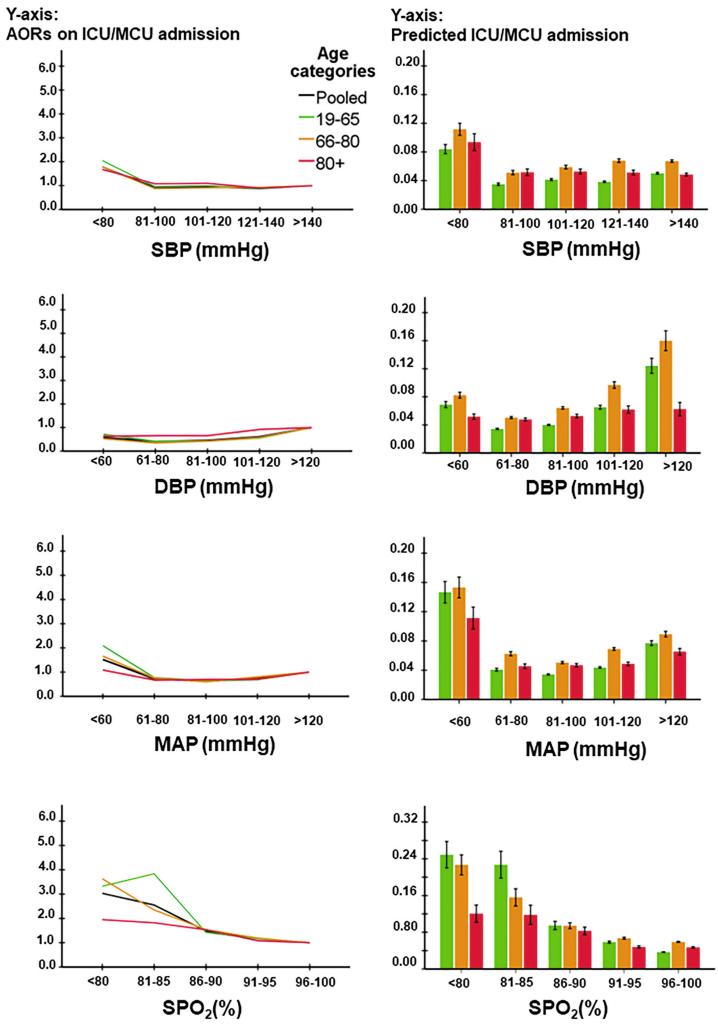
Adjusted Odds Ratios (AORs) for the association between In-hospital mortality and vital signs in a subgroup analysis: Trauma.

	Total cohort
Systolic blood pressure (mmHg)	
>140*	1.00
121-140	1.18 (0.73-1.94)
101-120	1.31 (0.75-2.30)
81-100	1.64 (0.79-3.41)
0-80	1.72 (0.67-4.40)
Diastolic blood pressure (mmHg)	
>120*	1.00
101-120	0.80 (0.29-2.23)
81-100	0.35 (0.13-0.91)
61-80	0.46 (0.18-1.20)
0-60	0.72 (0.26-2.01)
Mean Arterial blood pressure (mmHg)	
>120*	1.00
101-120	0.50 (0.30-0.85)
81-100	0.56 (0.33-0.95)
61-80	1.13 (0.63-2.04)
0-60	1.70 (0.64-4.50)
Peripheral oxygen saturation (%)	
96-100*	1.00
91-95	1.87 (1.24-2.82)
86-90	5.75 (3.14-10.52)
81-85	6.88 (2.61-18.12)
0-80	4.59 (1.55-13.57)
Respiratory rate (/min)	
Not measured*	1.00
0-9	#
10-19	1.95 (1.04-3.65)
20-29	2.28 (1.16-4.48)
>30	4.55 (1.35-15.31)

	Total cohort
Heart rate (beats/min)	
>125	4.22 (1.76-10.1)
101-125	2.49 (1.43-4.33)
76-100	1.03 (0.66-1.59)
51-75*	1.00
0-50	2.05 (0.74-5.68)
Temperature (°C)	
Not measured*	1.00
≥40	#
38-39	1.16 (0.42-3.19)
35-37	1.20 (0.78-1.85)
31-34	4.84 (1.13-20.75)
0-30	0.74 (0.04-15.27)

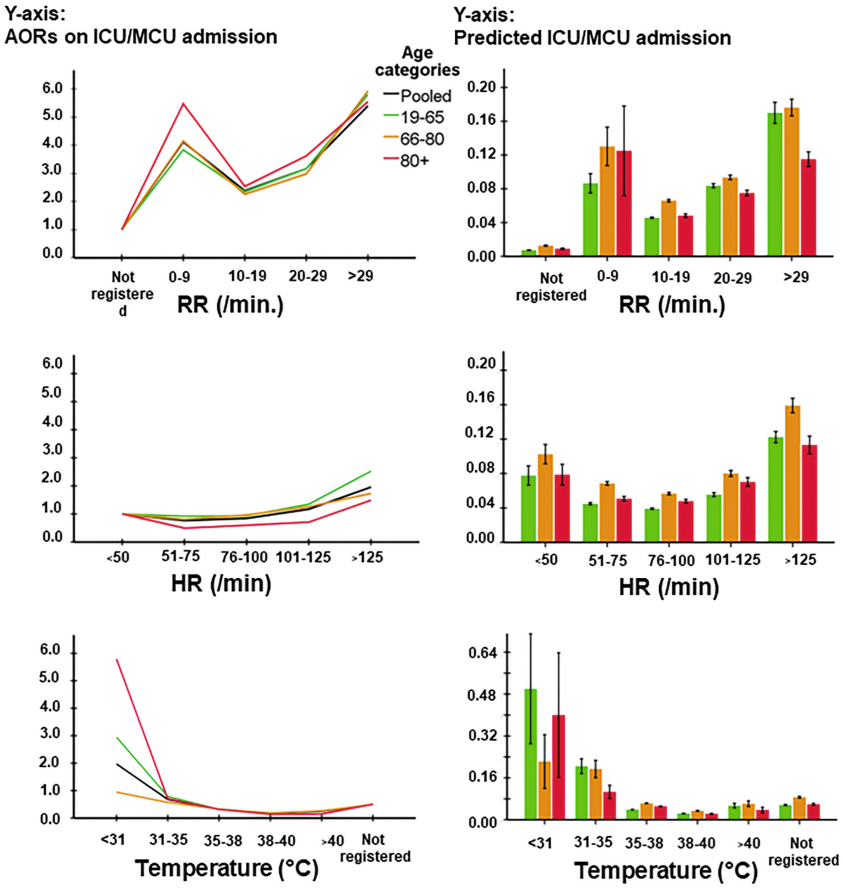
*= reference category
No outcome events for this category
Case definition: Trauma patients were selected by hospitalized patients, triaged orange or red and by the following triage presenting complaints: Severe trauma; facial complaints; fall; extremity complaints; large scale incidents; neck pain; thorax injury; head injury; wounds. Additionally, a radiological test had to be performed.

SUPPLEMENTARY FILE 5



Adjusted odds ratios (AORs) for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and peripheral oxygen saturation (SpO_2) and intensive care unit (ICU) / medium care unit (MCU) admission (left side) and predicted ICU/MCU admission (right side) as a function of vital signs in different age categories. Note that the black line is the pooled data of all three age categories together. The following potential confounders were entered in the model for in-hospital mortality through backward stepwise regression: age, gender, triage level, top ten chief complaints, hospital, treating specialty, fluid administration, SpO_2, temperature, Glasgow Coma Scale, lab tests, number of consultations in the ED and performed radiological test.

SUPPLEMENTARY FILE 6



Adjusted odds ratios (AORs) for respiratory rate (RR), heart rate (HR) and temperature for intensive care unit (ICU) / medium care unit (MCU) admission (left side) and predicted ICU/MCU admission (right side) as a function of vital signs in different age categories. Note that the black line is the pooled data of all three age categories together. The following potential confounders were entered in the model for in-hospital mortality through backward stepwise regression: age, gender, triage level, top ten chief complaints, hospital, treating specialty, fluid administration, SPO_2, temperature, GCS, lab tests, number of consultations in the ED and performed radiological test.

SUPPLEMENTARY FILE 7

Sensitivity analysis in which the associations between vital signs and in-hospital mortality were investigated. Patients transferred to other hospitals from the ED were considered as deceased.

	Total cohort
Systolic blood pressure (mmHg)	
>140*	1.00
121-140	1.14 (1.03-1.26)
101-120	1.63 (1.47-1.80)
81-100	1.72 (1.52-1.95)
0-80	1.98 (1.69-2.32)
Diastolic blood pressure (mmHg)	
>120*	1.00
101-120	0.73 (0.60-0.90)
81-100	0.67 (0.56-0.81)
61-80	0.71 (0.59-0.85)
0-60	0.97 (0.80-1.17)
Mean Arterial blood pressure (mmHg)	
>120*	1.00
101-120	0.86 (0.77-0.97)
81-100	0.98 (0.87-1.10)
61-80	1.22 (1.08-1.39)
0-60	1.76 (1.46-2.12)
Peripheral oxygen saturation (%)	
96-100*	1.00
91-95	1.31 (1.21-1.43)
86-90	1.92 (1.66-2.23)
81-85	2.58 (2.06-3.23)
0-80	3.97 (3.26-4.84)
Respiratory rate (/min)	
Not measured*	1.00
0-9	0.84 (0.50-1.41)
10-19	1.15 (1.03-1.29)
20-29	1.60 (1.42-1.81)
>30	2.56 (2.16-3.03)

	Total cohort
Heart rate (beats/min)	
>125	1.89 (1.61-2.22)
101-125	1.59 (1.43-1.78)
76-100	1.12 (1.03-1.22)
51-75*	1.00
0-50	1.27 (1.01-1.60)
Temperature (°C)	
Not measured*	1.00
≥40	0.38 (0.23-0.60)
38-39	0.60 (0.52-0.68)
35-37	0.86 (0.79-0.94)
31-34	2.05 (1.53-2.75)
0-30	1.00 (0.36-2.81)

*= reference category
No events for this category