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Resolving the observe zone: validation of the ESC 0/3-hour and the APACE criteria for NSTEMI triage

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ABSTRACT

Background High-sensitivity cardiac troponin tests have enhanced early myocardial infarction diagnosis, yet many patients still land in the observe zone (OZ). Guidelines suggest a 3-hour troponin measurement for those in the European Society of Cardiology (ESC) 0/1 hour-algorithm's OZ, but evidence on extended troponin testing times and their impact on diagnostic accuracy and outcomes remains sparse.

Methods Patients with suspected acute coronary syndrome were consecutively enrolled in a single-centre observational study. The triage protocol allowed an optional third troponin measurement at 3 hours or later to evaluate the performance and safety of two validated triage algorithms used to resolve the OZ.

Results Of the 4605 patients, 948 were triaged to the OZ (20.6%). The prevalence of non-ST-segment elevation myocardial infarction (NSTEMI) within the OZ was 7.2%. 212 patients (22.3% of OZ patients) had a third troponin measurement and were included in the comparative analysis. For diagnosing NSTEMI, the ESC 0/3-hour criteria showed lower sensitivity (69.4%) than the criteria defined in the Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) study (86.1%, p=0.053), with both having high negative predictive value (93.5% vs 87.5%, p=0.339). By definition, the ESC 0/3-hour algorithm categorises all patients into rule-in or rule-out, eliminating the need for an OZ, whereas 55.6% of patients remained in the OZ with the APACE criteria. Mortality rates in the OZ were similar across different timing protocols, with 30-day rates of 0.78% for third blood draws within 210 min (n=128) and 1.19% for those over 210 min (n=84); 3-year rates were 5.51% and 4.82%, confirming the safety of extended sampling.

Conclusions Although the ESC 0/3-hour criteria have a lower sensitivity than the APACE criteria, it is by definition more effective because it does not leave patients in the OZ. Extending the timing for the third troponin measurement beyond 3 hours proves to be effective and safe, supporting its implementation in clinical practice.

Trial registration number NCT03111862.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ High-sensitivity cardiac troponin testing has enhanced early myocardial infarction diagnosis. However, a significant proportion of patients end up in an observe zone (OZ), which complicates rapid and accurate patient triage.

WHAT THIS STUDY ADDS

⇒ This study contributes real-world data comparing two proposed algorithms—the European Society of Cardiology 0/3-hour and the Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) criteria—to resolve the observe zone (OZ) in rapid triaging of acute coronary syndrome. It highlights the complexity of managing OZ patients, who, despite their high comorbidity burden often requiring hospital admission, may also be safely discharged with a plan for early follow-up, thus underscoring the need for tailored patient management strategies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may inform future guidelines by advocating for extended troponin measurement intervals when earlier assessments are unfeasible, such as due to emergency department crowding, staffing shortages or logistical delays. These findings support the safe use of prolonged sampling times to aid in patient stratification and decision-making in clinical practice, enhancing the flexibility and effectiveness of acute care protocols in varied healthcare settings.

INTRODUCTION

The use of high-sensitivity cardiac troponin (hs-cTn) assays has enabled earlier and more accurate diagnosis of myocardial infarction (MI). The current 2023 European Society of Cardiology (ESC) Guidelines[1] recommend the preferential use of the ESC hs-cTn 0/1-hour or 0/2-hour triage protocols which provide optimised cut-offs for rule-out and rule-in of MI, whereas the ESC 0/3-hour protocols are regarded as an option only if the faster algorithms are not available. However, a relevant proportion of patients cannot be triaged into a diagnostic category in 20–40% of cases[2–4] in the observe zone (OZ), an indeterminate category which

is associated with adverse long-term outcomes[5 6] and requires further diagnostic work-up.[7 8] For this purpose, the 2020 ESC Guidelines[7] recommend a broader use of echocardiography and a third troponin measurement 3 hours after the initial troponin. The criteria for the cut-off and concentration change from 0 hour to 3 hours were proposed by the Association for Acute Cardiovascular Care (ACVC) consensus group on biomarkers[9] and were validated for patients in the OZ in the Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) study,[2] along with a derivation and validation study of novel criteria. The ESC 0/3-hour criteria allow a higher troponin change threshold (7 ng/L) at 3 hours and include a relative change rule (20%) for values >14 ng/L, while the APACE criteria are more stringent, requiring a lower absolute change (4 ng/L) and a stricter 3-hour threshold (<15 ng/L). For rule-in, the ESC 0/3-hour criteria use a multistep approach with absolute (≥52 ng/L) and combined absolute/relative changes, whereas the APACE criteria rely on a single threshold (≥6 ng/L change over 3 hours). In addition, the performance of a few other algorithm modifications,[10] including criteria based on troponin alone as well as a combination of troponin and clinical scores, was compared in a small Asian cohort.[11]

However, at present, there is no consensus on the criteria that are needed to optimally discriminate between an acute and a chronic troponin elevation within the OZ. In addition, no evidence exists on the performance, effectiveness and safety of a modification of the 0/3-hour algorithm in the not uncommon setting in real-world practice where the third blood sample had been collected more than 3 hours after the baseline sample. A measurement of high-sensitivity cardiac troponin T (hs-cTnT) at 6 hours instead of 3 hours had already been proposed in the past in an opinion paper from the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care[9] to permit a diagnosis if hs-cTn is not available at 3 hours.

Therefore, the present substudy of the RAPID-CPU (High Sensitivity Cardiac Troponin T assay for rapid Rule-out - Chest Pain Unit) registry had two objectives: First, to compare the performance, effectiveness and safety of the two different validated algorithms for the triage of patients in the OZ, and second, to test whether an extension of the time interval to the third troponin measurement beyond 3 hours is effective and safe.

METHODS

Study population

The RAPID-CPU study is a prospective single-centre observational study conducted in the Chest Pain Unit (CPU) of the Department of Cardiology of the University Hospital of Heidelberg, Germany. The CPU in Heidelberg is one of approximately 360 CPUs that have received certification from the German Society of Cardiology after formal audits for quality of care.[12 13] For this analysis, patients with suspected acute coronary syndrome (ACS) based on a broad range of symptoms, including chest pain, dyspnoea, epigastric discomfort, back pain or pain in shoulder or arm, were included over a 24-month period from June 2016 to July 2018. Patients who presented with dyspnoea that was attributed to acute heart failure were excluded. Patients with ST-segment elevation myocardial infarction (STEMI), referrals from other hospitals for revascularisation therapies and a few other presentations were excluded. Details on inclusion and exclusion criteria have been reported earlier.[14] Physicians and medical staff receive regular training on the preferred ESC 0/1-hour algorithm, but also on the ESC 0/2-hour and ESC 0/3-hour protocols. Timing of repeated blood collection and adherence to the protocol is not supervised. Until the launch of the 2020 ESC Guidelines on Non ST-elevation acute coronary syndrome (NSTE-ACS),[7] the routine measurement of a third troponin at 3 hours in patients triaged into the OZ was not recommended.[15]

Triage and diagnosis

The ESC 0/1-hour protocol was used in the emergency department (ED) as the default protocol after June 2016. The time for the second and eventually third troponin measurements was not supervised. In addition, a third blood draw among patients triaged into the OZ was not mandatory per 2015 ESC Guidelines on NSTE-ACS,[15] and the number and timing of serial measurements were executed at the discretion of the treating physician. In clinical routine, hs-cTnT was measured using the Roche fifth-generation Elecsys hs-cTnT (Roche Diagnostics, Penzberg, Germany) on a COBAS 411 or a COBAS E601 analyser. *The limit of blank and the limit of detection (LoD) were established at 3 and 5 ng/L (COBAS 411) or 2 and 3 ng/L (COBAS E601), respectively. In clinical routine, an LoD of 5 ng/L was applied. The coefficient of variation was determined to be 10% at a concentration of 13 ng/L based on 100 measurements. In accordance with manufacturer guidelines, a 99th percentile upper reference limit of 14 ng/L was applied. Sex-specific cut-offs were not used in this analysis.* Troponin values were reported to one decimal place in our retrospective analysis. An MI was ruled out if the initial hs-cTnT was below the LoD (5 ng/L) in patients presenting more than 3 hours after the onset of symptoms, or in the presence of an initial hs-cTnT <12 ng/L and a concentration change <3 ng/L. Patients were classified as 'rule-in' if the initial hs-cTnT was greater than or equal to 52 ng/L, or in the presence of a concentration change of 5 ng/L or more. As classification algorithms were used with respect to sampling time, the ESC 0/2-hour protocol was applied if the second hs-cTnT measurement was taken after 2 hours. All applied rules are shown in online supplemental table S1. Patients who could not be assigned to either the rule-out or rule-in category were classified into the OZ. The final diagnosis was made by the treating physician based on the third universal definition of myocardial infarction (UDMI) and all available clinical information.[16] For research purposes, all diagnoses were

readjudicated by two cardiologists who were not involved in the initial management. In case of uncertainty, a third cardiologist was consulted.

Unstable angina was diagnosed in patients with clinically suspected ACS if hs-cTnT remained persistently below the 99th percentile (upper limit of normal;ULN), or if hs-cTnT exceeded the 99th percentile (but <52 ng/L) without a relevant rise and/or fall.[17] Among patients triaged as 'rule-in', a non-STEMI (NSTEMI) including type 1 or type 2 MI was diagnosed according to the criteria of the third UDMI. Otherwise, differential diagnosis included myocarditis, takotsubo stress cardiomyopathy, pulmonary embolism or atrial tachyarrhythmias.

Protocols for interpretation of the third hs-cTnT within the observe zone

The local standard protocol used the criteria of the 0/3-hour algorithm to interpret the third hs-cTnT. Per 0/3-hour protocol,[9] MI was ruled out if an initially normal hs-cTnT did not rise by 7 ng/L, a 50% increase of the 99th percentile ULN, or in the absence of a concentration change of 20% or less if initial hs-cTnT exceeded the 99th percentile ULN. This protocol included a retesting of troponin within 6 hours as an option, if the 3-hour troponin was not available. Accordingly, in the present study, the protocol was applied for patients who received the third troponin within 180±30 min and as a modification for patients with a third troponin ≥210 min. For comparison, we tested the performance, effectiveness and safety of the APACE criteria.[2] The APACE criteria apply stricter thresholds for rule-out (<15 ng/L, Δ<4 ng/L) and rule-in (Δ≥6 ng/L).

Follow-up and clinical endpoints

Patients were contacted at least 6 months after discharge by telephone or in written form. In addition, information about death during follow-up (FU) was obtained from the patient's hospital notes, the family physician's records and from death certificates. The endpoints were assessment of triage performance defined as the proportion that could be triaged as rule-out or rule-in, effectiveness defined as the percentage of patients in whom the protocol could be applied and safety defined as rates of all-cause mortality during FU.

Statistical analysis

Continuous variables were tested for normal distribution and were presented either as means with 95% CIs or as medians with minimum and maximum. The normality of data distribution was assessed by the Kolmogorov-Smirnov test. Groups were compared using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Kaplan-Meier curves and the log-rank test were used. Performance, effectiveness and safety were assessed by comparing timing strategies (<210 min, >210 min and overall) within the ESC 0/3-hour algorithm and the APACE algorithm, applied to patients remaining in the OZ after initial triage. We calculated sensitivities and negative predictive values (NPVs) for ruling out index NSTEMI, specificities and positive predictive values (PPVs) for ruling-in index NSTEMI, and effectiveness, that is, the proportion of patients triaged toward rule-out or rule-in of NSTEMI. All hypothesis testing was two tailed and p values <0.05 were considered statistically significant. All statistical analyses were performed using R (V.4.2.0, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among 4605 patients, 3657 were diagnosed as either rule-in (n=920, 20.0%) or rule-out (n=2737, 59.4%) and 948 remained in the OZ (20.6%). *We have included all OZ patients in further analysis from 0/1-hour and 0/2-hour algorithms, since both allow an OZ classification. In our study population, 64% (n=2931) were initially categorised using the ESC 0/1-hour algorithm, while 22% (n=1022) were assessed with the 0/2-hour protocol, and 14% (n=652 patients) were assessed with the 0/3-hour protocol.* 212 patients (22.3% of OZ patients) had a third troponin measurement and were included in the comparative analysis (figure 1). The timing of the third blood draw is illustrated in online supplemental figure S1A. The third hs-cTnT was collected at 180±30 min in 128 (60.4 %) patients and >210 min (median 235 min (220, 259), range 211–426 min) in 84 (39.6%) patients.

The prevalence of NSTEMI within the OZ was 7.2% (n=68), while the overall prevalence of NSTEMI in the total study population was 14.6% (n=672). Baseline characteristics of patients classified into the OZ are given in table 1. After rule-out, 83 patients corresponding to 48.8% of the entire 'rule-out' category with the ESC 0/3-hour algorithm were discharged from the ED after a median length of ED stay of 5.0 (4.7, 6.2) hours. Patient flow and diagnostic performance for the initial decision based on the first two blood samples, along with the suggested resolution with the 0/3-hour hs-cTnT change criteria as well as with the novel APACE criteria, are shown in figure 2. This figure accounts for extended sampling times (third hs-cTnT collected at 180±30 min in 128 (60.4%) patients and >210 min in 84 (39.6%) patients, median 235 min (220, 259)). A strict 3-hour protocol is shown separately in online supplemental figure S2.

Diagnostic performance and effectiveness of ESC 0/3-hour and APACE criteria

We calculated the performance measures and assessed the effectiveness of the 0/3-hour, the modified 0/3-hour and the APACE criteria; details are displayed in table 2. In our retrospective study, the effectiveness of the 0/3-hour algorithm increased by 39.6% (additional 84 cases) when longer time intervals than 3 hours were permitted. The extension of time interval from 3 hours to a median of 4 hours (range 211–426 min) did not change sensitivities (0.706 (95% CI 0.469 to 0.867) vs 0.684 (95% CI 0.460 to 0.846), p=0.876) or NPV (0.955 (95% CI 0.898 to 0.980) vs 0.900 (95% CI 0.799 to 0.953), p=0.353) compared

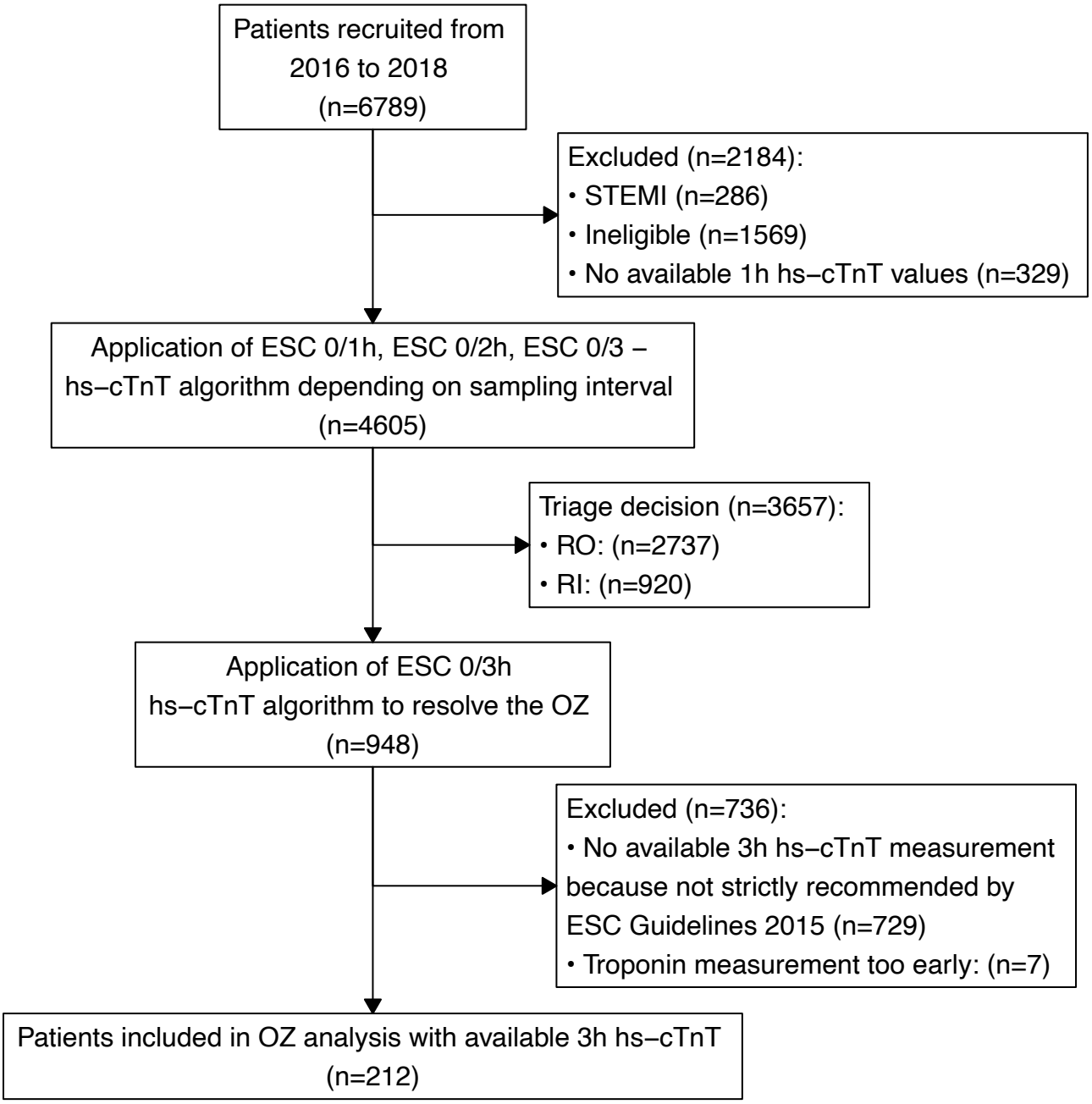

Figure 1 Flow chart of study recruitment and triage decision process. This flow chart outlines the recruitment, exclusion and triage decision processes for patients from 2016 to 2018 using European Society of Cardiology (ESC) high-sensitivity cardiac troponin T (hs-cTnT) algorithms. OZ, observe zone; RI, rule-in; RO, rule-out; STEMI, ST-segment elevation myocardial infarction.

with a strict 3-hour retesting interval. The extension of retesting interval allowed the identification of 13 additional cases of NSTEMI. On the other hand, specificity (0.831 (95% CI 0.722 to 0.903) vs 0.946 (95% CI 0.887 to 0.975), p=0.025) and PPV (0.542 (95% CI 0.351 to 0.721) vs 0.667 (95% CI 0.437 to 0.837), p=0.369) decreased slightly, while the rates of detected NSTEMI did not differ significantly between the two groups (9.4% vs 15.5%, p=0.178). There were differences regarding the performances of the ESC 0/3-hour and APACE algorithms. The sensitivity of the ESC 0/3-hour algorithm was lower (0.694 (95% CI 0.531 to 0.820)) compared with the APACE algorithm (0.861 (95% CI 0.713 to 0.939), McNemar p=0.014), and NPVs remained similarly high at 0.935 (95% CI 0.888 to 0.963) for the ESC 0/3-hour algorithm versus 0.875 (95% CI 0.739 to 0.945, McNemar p=0.174) for the APACE algorithm. Specificities of the ESC 0/3-hour algorithm were slightly higher (0.903 (95% CI 0.851 to 0.939) vs 0.835 (95% CI 0.773 to 0.883), McNemar p=0.011); similarly, PPV was higher for the ESC 0/3-hour algorithm (0.595 (95% CI 0.445 to 0.730) vs 0.463 (95% CI 0.337 to 0.594), McNemar p=0.014). The most important difference was found, by design, in the proportion of patients who remained in the OZ after applying each

Table 1 Characteristics of patients triaged to the observe zone

	Overall n=212	Rule-in n=42	Rule-out n=170
Age (mean (SD))	71.43 (13.79)	70.36 (14.01)	71.70 (13.76)
Sex, female (%)	88 (41.5)	17 (40.5)	71 (41.8)
Mortality (%)	11 (5.2)	2 (4.9)	9 (5.3)
Hypertension (%)	179 (86.5)	37 (90.2)	142 (85.5)
Diabetes (%)	73 (35.3)	12 (30.0)	61 (36.5)
Cholesterol (%)	111 (61.0)	21 (56.8)	90 (62.1)
Smoking (%)	26 (13.8)	9 (23.7)	17 (11.3)
History of coronary artery disease (%)	105 (49.8)	17 (41.5)	88 (51.8)
First high-sensitivity troponin T (median (IQR))	16.00 (11.00, 23.00)	17.50 (14.00, 22.75)	16.00 (10.00, 23.00)
Last high-sensitivity troponin T (median (IQR))	18.00 (11.75, 26.00)	26.50 (22.00, 37.00)	15.00 (11.00, 23.00)
Absolute change in high-sensitivity troponin T (median (IQR))	3.00 (2.00, 4.00)	4.00 (2.25, 6.00)	3.00 (2.00, 4.00)
GRACE score (mean (SD))	120.83 (34.88)	130.41 (35.83)	118.49 (34.35)
Diagnosis (%)			
NSTEMI	36 (17.0)	25 (59.5)	11 (6.5)
UA	49 (23.1)	2 (4.8)	47 (27.6)
NCCP	127 (59.9)	15 (35.7)	112 (65.9)
OZ resolution=rule-out (%)	179 (84.4)	9 (21.4)	170 (100.0)

Detailed characteristics of all patients placed in the observe zone are given, including those subsequently triaged as rule-in and rule-out based on the extended European Society of Cardiology (ESC) 0/3-hour algorithm.
GRACE, Global Registry of Acute Coronary Events; NCCP, non-cardiac chest pain; NSTEMI, non-ST-segment elevation myocardial infarction; OZ, observe zone; UA, unstable angina.

algorithm. Using the ESC 0/3-hour algorithm, all cases categorised into the OZ were retriaged into the rule-out or rule-in category, whereas the OZ could not be resolved in 55.6% (n=109) of cases using the APACE algorithm (online supplemental figure S1C).

Safety of triage

Overall mortality rates at 30 days and after 3 years of FU were 0.9% and 5.2%, respectively (table 3). Patients in whom the OZ category could not be resolved after applying the APACE algorithm retained a mortality of 1.7% at 30 days and 6.8% at the end of FU. Figure 3A,B show Kaplan-Meier curves for all-cause mortality stratified by either ESC 0/3-hour criteria or the novel APACE criteria including admission status if ruled out. The number of fatalities was similar with the strict and longer sampling time protocol supporting the safety of a time interval extension (rule-out and discharge: 3.4% vs 0.0%, p=0.399; rule-out and admit: 5.9% vs 11.4%, p=0.341; rule-in: 11.1% vs 0.0%, p=0.132). Nine of the 11 fatalities occurred in the retriaged rule-out category using the ESC 0/3-hour algorithm. Noteworthy, seven of the nine cases had been hospitalised for further in-house diagnostic work-up and treatment, whereas two cases were discharged home directly from the ED, one against medical advice (table 4). Six of the 11 deaths occurring beyond the initial 30 days after index presentation were related to advanced decompensated heart failure (n=3), cancer (n=2) and sepsis (n=1); two cases could not be followed up. Among the two cases with suspected NSTE-ACS, death occurred 79 days after successful percutaneous coronary intervention (PCI) in one case, whereas diffuse coronary artery disease precluded any revascularisation in another case who died 108 days after index admission. One case with presumed non-cardiac chest pain declined hospital admission for additional in-hospital work-up.

DISCUSSION

Patients categorised into the OZ are at higher risk for adverse outcomes, pose diagnostic uncertainty and require further evaluation.[5–8] The 2022 American College of Cardiology Expert Consensus on Chest Pain in the Emergency Department[8] suggests using risk scores to further stratify these patients. However, a recent secondary analysis of the High-Sensitivity Cardiac Troponin I Assays in the United States (HIGH-US) study[18] revealed that risk scores are unlikely to improve triage without additional troponin measures and imaging. Therefore, our validation study, conducted in a large registry providing real-world evidence, is important because it validates two different troponin-based algorithms that have been proposed to resolve the OZ. In addition, we assessed the

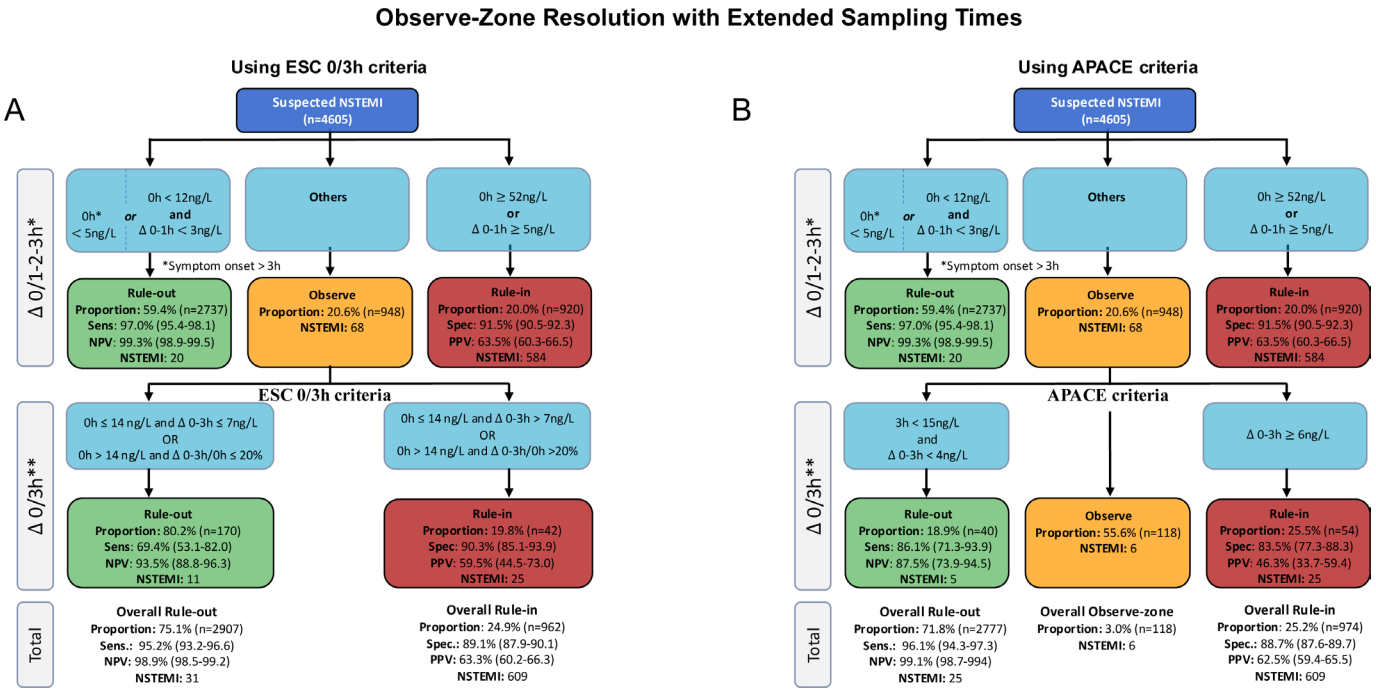

Figure 2 Patient flow using the proposed monitoring zone resolution algorithms and allowing for extended sampling times. The flow chart illustrates the patient flow and diagnostic results using the European Society of Cardiology (ESC) 0/1-hour high-sensitivity cardiac troponin T algorithm and the investigated algorithms to resolve the observe zone. Notably, sampling times were not strictly adhered to as per the 3-hour algorithm, allowing for extended sampling times. (A) Resolution of the observe zone with the ESC 0/3-hour algorithm. (B) Resolution of the observe zone with the proposed novel Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) algorithm. *The cut-offs for the Δ 0/1-hour algorithm are shown as this was the most commonly used algorithm. For Δ 0/2-hour and Δ 0/3-hour algorithm cut-offs, see online supplemental figure S2. **Missing measurement: proportion in observe zone 77.6% (n=736), NSTEMI: 32. NPV, negative predictive value; NSTEMI, non-ST-segment elevation myocardial infarction; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

performance, effectiveness and safety of a time interval extension of the ESC 0/3-hour algorithm beyond 3 hours that could enable a triage in the not uncommon setting that a third hs-cTnT value has been collected more than 3 hours (180±30 min) after the baseline measurement.

Based on findings from a single-centre observational study over 24 months, we report *four key findings*:

First, some results on the performance of the ESC 0/3-hour algorithm are discordant with the findings from the APACE study.[2] In the latter, sensitivity (33.3% vs 69.4%, p<0.001) and NPV (84.5% vs 93.5%, p<0.001) of the modified ESC 0/3-hour algorithm[10] were considerably lower, whereas specificity (98.4% vs 90.3%, p<0.001) and PPV (85.1% vs 59.5%, p<0.001) were significantly higher than in our evaluation. Furthermore, the number of missed NSTEMIs was significantly higher in the APACE study using the ESC algorithm than in the present study (80 of 564 (14.2%) vs 11 of 212 (5.2%), p<0.001). In contrast, the APACE criteria applied in the APACE substudy[2] yielded sensitivities and NPVs of 99.2% and 99.3%, and only one NSTEMI (0.2%, 1 of 564) was missed. The proportions of patients ruled out and ruled in were 91.7% and 8.3% with the 0/3-hour algorithm and 24.5% and 11.2% with the APACE criteria. This strong discrepancy that favours the use of the APACE criteria over the 0/3-hour criteria is controversial. An Asian validation study[11] on 350 adults with suspected ACS triaged 128 (36.6%) into the OZ. Among these, the ESC 0/3-hour algorithm criteria[9] that contained the absolute concentration change of 7 ng/L or a relative concentration change of 20% or more if baseline troponin concentrations exceeded the 99th percentile ULN—without the addition of a clinical score—provided similar NPVs for 'rule-out' (96.5% vs 94.5%) and higher PPV (66.3% vs 37.1%) compared with the APACE criteria. In addition, the criteria of the new 0/1-hour algorithm proposed by Vigen *et al*[10] did not contain the 20% concentration change rule that was used in the Asian study,[11] and which should apply if the hs-cTn baseline concentration exceeds the 99th percentile ULN.[9] The incorporation of the relative change criterion of 20% or more appears particularly important because stable elevations of hs-cTn exceeding the 99th percentile ULN are highly prevalent in most OZs. Thus, the observed differences in algorithm performance likely reflect variations in population characteristics and healthcare settings, indicating the need for additional prospective validation studies.[2 10 11] Differences in baseline cardiovascular risk, pretest probability of NSTEMI and institutional troponin measurement practices may contribute to these findings. Additionally, variations in ED workflow and adherence to algorithmic timing constraints can influence real-world outcomes. Differences in clinical decision-making, including the use of additional risk stratification tools, may further impact

Table 2 Performance and effectiveness of diagnostic algorithms at different time intervals

Measure	ESC within 210 min	ESC >210 min	ESC overall	APACE within 210 min	APACE >210 min	APACE overall
NSTEMI, n	17 (0.133)	19 (0.226)	36 (0.17)	17 (0.133)	19 (0.226)	36 (0.17)
Eligible patients, n	128 (0.604)	84 (0.396)	212 (1)	128 (0.604)	84 (0.396)	212 (1)
Residual OZ, n	Not applicable			74 (0.578)	44 (0.524)	118 (0.557)
Rule-out criteria	Absolute Δ 0–3 hours ≥7 ng/L (if initial hs-cTnT≤14 ng/L; relative Δ 0–3 hours ≥20% (if hs-cTnT>14 ng/L)			hs-cTnT 3 hours <15 ng/L and 0/3-hour absolute change <4 ng/L		
Sensitivity (95% CI)	0.706 (0.469 to 0.867)	0.684 (0.460 to 0.846)	0.694 (0.531 to 0.820)	0.824 (0.590 to 0.938)	0.895 (0.686 to 0.971)	0.861 (0.713 to 0.939)
NPV (95% CI)	0.955 (0.898 to 0.980)	0.900 (0.799 to 0.953)	0.935 (0.888 to 0.963)	0.880 (0.700 to 0.958)	0.867 (0.621 to 0.963)	0.875 (0.739 to 0.945)
Number of rule-outs, n	110 (0.859)	60 (0.714)	170 (0.802)	25 (0.195)	15 (0.179)	40 (0.189)
Missed NSTEMI, n	5 (0.039)	6 (0.071)	11 (0.052)	3 (0.023)	2 (0.024)	5 (0.024)
Rule-in criteria	Absolute Δ 0–3 hours ≥7 ng/L (if initial hs-cTnT≤14 ng/L; relative Δ 0–3 hours ≥20% (if hs-cTnT>14 ng/L)			0/3-hour absolute change ≥6 ng/L		
Specificity (95% CI)	0.946 (0.887 to 0.975)	0.831 (0.722 to 0.903)	0.903 (0.851 to 0.939)	0.838 (0.758 to 0.895)	0.831 (0.722 to 0.903)	0.835 (0.773 to 0.883)
PPV (95% CI)	0.667 (0.437 to 0.837)	0.542 (0.351 to 0.721)	0.595 (0.445 to 0.730)	0.379 (0.227 to 0.560)	0.560 (0.371 to 0.733)	0.463 (0.337 to 0.594)
Number of rule-ins, n	18 (0.141)	24 (0.286)	42 (0.198)	29 (0.227)	25 (0.298)	54 (0.255)
Detected NSTEMI, n	12 (0.094)	13 (0.155)	25 (0.118)	11 (0.086)	14 (0.167)	25 (0.118)

The ESC 0/3-hour and APACE algorithms are evaluated in the diagnosis of NSTEMI at different troponin sampling intervals.
APACE, Advantageous Predictors of Acute Coronary Syndromes Evaluation; ESC, European Society of Cardiology; hs-cTnT, high-sensitivity cardiac troponin T; NPV, negative predictive value; NSTEMI, non-ST-segment elevation myocardial infarction; OZ, observe zone; PPV, positive predictive value.

Table 3 Mortality outcomes at 30 days and end of follow-up

	ESC within 210 min n=128	ESC >210 min n=84	ESC overall n=212	APACE within 210 min n=128	APACE >210 min n=84	APACE overall n=212
All-cause mortality						
30 days, n	1 (0.008)	1 (0.012)	2 (0.009)	1 (0.008)	1 (0.012)	2 (0.009)
End of follow-up*, n	7 (0.055)	4 (0.048)	11 (0.052)	7 (0.055)	4 (0.048)	11 (0.052)
Mortality at end of follow-up*						
Rule-out and discharge, n	2/58 (0.034)	0/25 (0.000)	2/83 (0.024)	0/20 (0.000)	0/9 (0.000)	0/29 (0.000)
Rule-out and admit, n	3/52 (0.059)	4/35 (0.114)	7/87 (0.081)	0/5 (0.000)	1/6 (0.167)	1/11 (0.091)
Rule-in, n	2/18 (0.111)	0/24 (0.000)	2/42 (0.048)	4/29 (0.138)	0/25 (0.000)	4/54 (0.076)
Unresolved observe zone, n	Not applicable			3/74 (0.041)	3/44 (0.068)	6/118 (0.051)

The table shows the overall mortality rates comparing outcomes based on the timing of ESC (within and beyond 210 min) and APACE decisions, with data for each category and overall totals.
*End of follow-up at 3 years.
APACE, Advantageous Predictors of Acute Coronary Syndromes Evaluation; ESC, European Society of Cardiology.

observed algorithm performance in real-world scenarios. Second, the 0/3-hour algorithm enables a resolution of the OZ in all 212 patients by design. The third hs-cTnT triaged 80.2% (170 cases) into the rule-out and 19.8% (42 cases) into the rule-in category. In contrast, the APACE algorithm retriaged 18.9% from the OZ rule-out and 25.5% to the rule-in category. However, still 55.6% (118 cases) remained unresolved. Our findings are in agreement with the APACE substudy,[2] showing that a relevant proportion of patients will be unresolved after application of the APACE algorithm.

Third, our findings confirm observations that the OZ is associated with poor intermediate and long-term prognosis. In contrast and consistent with previous trials,[5 6 14 18] mortality risk was only 0.9% within the initial 30 days after index presentation but then gradually increased to 4.2% within 1 year. Several reasons, including older age, higher prevalence of structural heart disease, coronary heart disease, diabetes and more comorbidities including chronic kidney disease, have been claimed to account for this higher long-term mortality in the OZ.[6] In the present study, after resolution of the OZ using the ESC criteria,

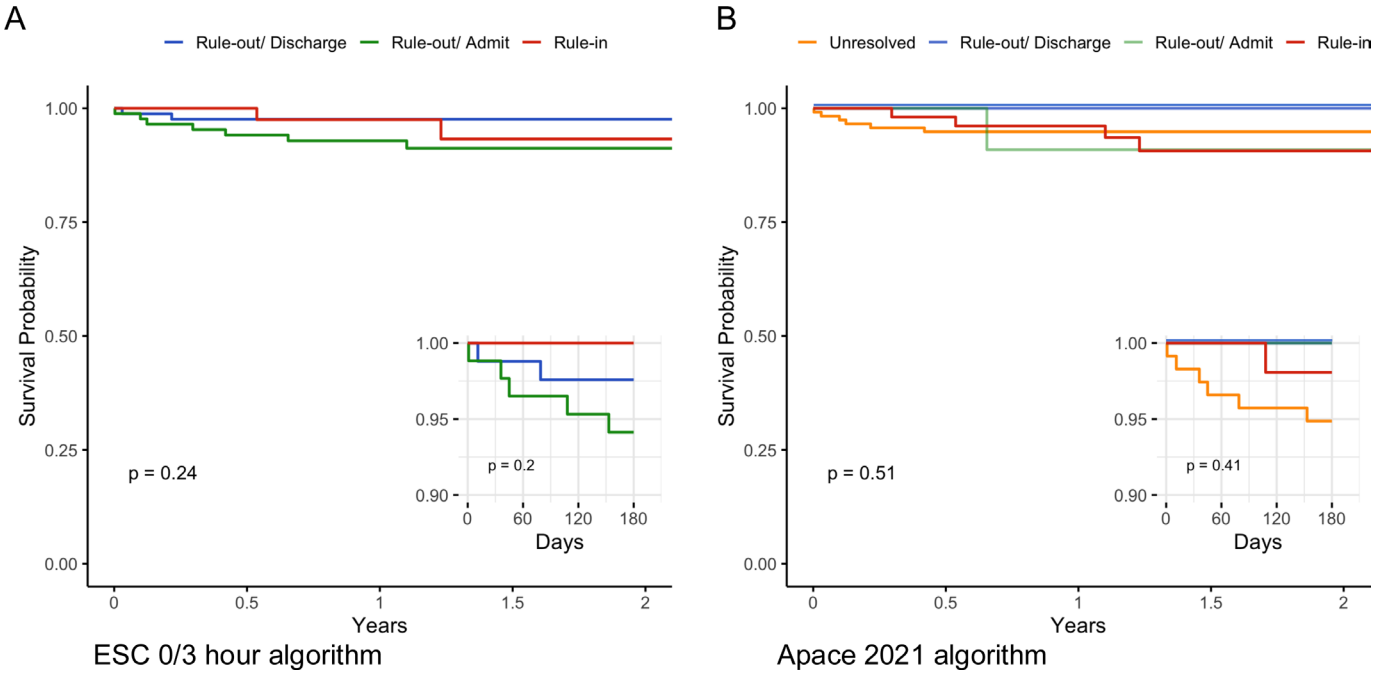

Figure 3 Kaplan-Meier curves for all-cause mortality during follow-up for different triage categories. Long-term survival outcomes are being studied in relation to each triage decision. (A) Triage decisions are shown for patients triaged into categories using the European Society of Cardiology (ESC) 0/3-hour algorithm. (B) The Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) decisions are shown with the additional unresolved group.

Table 4 Clinical and demographic characteristics of patients who died during follow-up

Age range (decades)	CPU adjudication	Time to death (days)	hs-cTnT profile (ng/L)	GRACE score	ESC 3-hour/APACE decision	Hospital admission	Individual history
80s	NSTEMI	1	47; 50; 50	212	RO/OZ	Admitted	Admission with cardiac decompensation (NT-proBNP 18 787 ng/L) followed by cardiogenic shock the next day, significant hs-cTnT kinetics >1000 ng/L, therapy escalation withheld on patient consent.
90s	NCCP	11	17; 17; 18	140	RO/OZ	Discharged	Patient presented again 2 days later and was discharged against medical advice.
70s	NCCP	36	17; 20; 19	106	RO/OZ	Admitted	Fall, hyponatraemia (126 mmol/L), cardiac decompensation.
70s	NCCP	45	24; 21; 24	123	RO/OZ	Admitted	Negative stress MRI, suspected pulmonary focus on PET-CT.
60s	NCCP	79	15; 14; 15	125	RO/OZ	Discharged	During follow-up, successful LAD PCI and 2× DES, then negative stress MRI.
80s	UA	108	40; 38; 32	187	RO/RI	Admitted	No intervention options 5 months prior, status post-CABG, severely reduced LVEF, cardiac decompensation, dementia.
90s	UA	153	45; 45; 42	162	RO/OZ	Admitted	Follow-up transapical TAVI; stage IV CKD, pulmonary hypertension.
80s	NCCP	196	23; 27; 37	140	RI/RI	Admitted	Severe aortic stenosis, then sepsis due to left forearm thrombophlebitis with *Staphylococcus aureus*, prostate cancer.
80s	NCCP	402	43; 43; 37	123	RO/RI	Admitted	Obstructive adenocarcinoma of the oesophagus, palliative care.

APACE, Advantageous Predictors of Acute Coronary Syndromes Evaluation; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CPU, chest pain unit; DES, drug-eluting stent; ESC, European Society of Cardiology; GRACE, Global Registry of Acute Coronary Events; hs-cTnT, high-sensitivity cardiac troponin T; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; NCCP, non-cardiac chest pain; NSTEMI, non-ST-segment elevation myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OZ, observe zone; PCI, percutaneous coronary intervention; PET, positron emission tomography; RI, rule-in; RO, rule-out; TAVI, transcatheter aortic valve implantation; UA, unstable angina.

no differences regarding demographics or other clinical baseline characteristics were observed, except differences in peak levels and absolute concentration changes of hs-cTnT between those triaged into rule-out or rule-in. Our findings highlight previous reports that risk stratification within the OZ is challenging using clinical scores alone.[8 18] Using the APACE algorithm, only one death occurred in the rule-out category, but four of nine fatalities were seen in the rule-in category. The remaining six deaths occurred in the OZ that had not been resolved by the algorithm. Thus, although the APACE algorithm seems to be superior to the ESC algorithm in terms of identification of patients at very low risk, this algorithm is hampered by a large proportion of patients at risk left over in the unresolved OZ. The residual mortality risk within the 'rule-out' category using the ESC algorithm and within the unresolved OZ using the APACE algorithm points to the still unmet need to refine risk stratification in the OZ. Overall, the majority of deaths in the OZ occurred beyond the initial 30 days after index presentation and were not related to NSTE-ACS. Our findings support the hypothesis that patients triaged into the OZ may be considered for early discharge due to a very low event rate of only 0.9% within the initial 30 days. However, high mortality risk beyond 30 days after index presentation requires additional diagnostic work-up or treatment that should be pursued either during index hospitalisation or early postdischarge. Of the two cases who died after early hospital discharge, one case had received successful PCI after readmission, while the other case left the hospital against medical advice.

Fourth, in 2012, an opinion paper from the Study Group on Biomarkers in Cardiology of the ESC Working Group had proposed an extension of the time interval from 3 hours to 6 hours for retesting of hs-cTn as an option if hs-cTn concentrations were not available at 3 hours.[9] However, there is no clinical evidence on the performance, effectiveness and safety of the modified 0/3-hour algorithm. Our findings support that the 0/3-hour algorithm may be applied safely even if time intervals are longer and may be of particular help in real-world settings where timing of serial measurements is not supervised and clinical circumstances may cause time delays. Extending the time interval for a third troponin

measurement is expected to improve sensitivity and NPV, as longer intervals allow for greater troponin changes to accumulate, enhancing differentiation between acute and chronic troponin elevations. This concept is well supported by troponin kinetics, as myocardial injury typically leads to a progressive rise in troponin over several hours, with peak sensitivity occurring between 6 and 12 hours after symptom onset.[19 20] However, despite its high clinical plausibility, the impact of extending sampling times beyond 3 hours had not been systematically validated prior to this study. Our findings confirm the safety of extended sampling intervals, demonstrating that a delay beyond 3 hours does not negatively impact patient outcomes. This finding is very important for the vast majority of EDs that are not using a supervised timing of serial troponin measurements, and FU blood draws are usually considerably longer than the proposed intervals, including a tolerance time of 10 min.[21] In real-world ED settings, strict adherence to fixed troponin sampling times is often impractical due to logistical constraints, patient-specific factors and workflow priorities.[22] These results support a more flexible, pragmatic approach to troponin-based triage in clinical practice. Furthermore, our findings highlight the need to develop clinical decision support tools that help guide the selection of the most appropriate diagnostic algorithm based on the actual sampling time used. Fears for overdiagnosis or underdiagnosis of MI are unsubstantiated as longer time intervals would rather increase sensitivity and specificity of serial troponin testing, as late increases of hs-cTn have been reported in a considerable proportion of patients.[23] The issue of late occurrence of relevant concentration changes was also pointed out by Hammarsten *et al*, showing that 14% of patients with confirmed NSTEMI presenting with already elevated troponin at admission will show a relative change of <20% within 6 hours.[24] Thus, the extension of the sampling interval will rather improve the diagnosis.

CONCLUSIONS

Our findings suggest that the resolution of the OZ improves triage, enabling better discrimination of low and high-risk patients. The 0/3-hour algorithm appears more attractive for initial triage as it enables a complete resolution of the OZ by design, whereas 55.6% of patients remain in the OZ using the novel APACE algorithm. Another important finding is that extending the time interval between the initial blood draw and the third measurement beyond the first 3 hours is similarly effective, does not lead to more reclassifications and is similarly safe (0.8% vs 1.2% within 30 days and 3.9% vs 4.7% at 1 year).

Limitations

Given that a third troponin measurement was not routinely recommended until the 2020 ESC Guidelines on NSTE-ACS,[7] only 22.4% of patients (212 of 948) who were categorised into the OZ received a third blood draw at 3 hours after the initial blood draw. At that time, the OZ was not well characterised and little information existed on the higher long-term mortality associated with a classification into the OZ. The decision to admit or discharge a patient was made at the discretion of the attending physician after individual risk stratification including but not limited to the clinical picture with and without calculation of the Global Registry of Acute Coronary Events (GRACE) 1.0 score. Information on the ability of algorithms to resolve the OZ remains sparse because few studies have routinely measured a third troponin at 3 hours if the result of the ESC 0/1-hour protocol was inconclusive. In the OZ, all-cause death occurred late and was related to severe underlying acute or chronic diseases that require specialist care. In our setting, the majority of cases were admitted to hospital regardless of the final triage categorisation and received additional evaluations or treatments. Accordingly, our findings on relatively low mortality rates beyond 30 days cannot be generalised and may likely underestimate mortality rates in other hospitals, geographical regions or healthcare systems.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee of the Medical Faculty of Heidelberg (S-313/2017) and was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Informed consent of the individual patient was waived by the Ethics Committee of the Medical Faculty of Heidelberg. Participants gave informed consent to participate in the study before taking part.

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Data availability statement No data are available. This study analysed retrospectively the collected data from routine care of consecutive patients admitted to the emergency department. Sharing patient-level data requires individual patient consent, which is not feasible in this case. Therefore, we are unable to share patient-level data.

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