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High-sensitivity troponin T is an important independent predictor in addition to the Simplified Acute Physiology Score for short-term ICU mortality, particularly in patients with sepsis

Peder Andersson [a,b,*], Attila Frigyesi [a,b]

[a] Department of Clinical Sciences, Section for Anaesthesiology and Intensive Care, Lund University, SE-22185 Lund, Sweden
[b] Department of Intensive and Perioperative Care, Skåne University Hospital, SE-22185 Lund, Sweden

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ABSTRACT

Purpose: Elevated cardiac troponin levels have been shown to be associated with a poor prognosis under some intensive care conditions. This study investigated whether inclusion of high-sensitivity troponin T (hsTnT) increased the prognostic accuracy of the Simplified Acute Physiology Score (SAPS 3) for general intensive care unit (ICU) patients, cardiac arrest patients, or patients with a non-cardiac arrest diagnosis.
Materials and methods: We performed a single-center cohort study of ICU patients with an hsTnT measurement on ICU admission at a tertiary university hospital between February 2010 and June 2017.
Results: Of 4185 first-time admissions, 856 patients (20.5%) had hsTnT evaluated at ICU admission. Factoring in ICU admission hsTnT values increased the ability of SAPS 3 to accurately predict 30-day mortality (odds ratio 1.27, 95% confidence interval: 1.15–1.41, $p < 0.001$). Elevated hsTnT levels were not independently associated with 30-day mortality in cardiac arrest patients. In sepsis patients, hsTnT evaluation in addition to SAPS 3 evaluation improved the area under the receiver operating characteristic curve by >10%.
Conclusion: Addition of hsTnT evaluation to SAPS 3 enhances the predictive capability of this model in relation to mortality. In sepsis, the hsTnT level may be an important prognostic marker.

1. Introduction

Calculating the prognosis for patients admitted to intensive care units (ICU) is complicated, due to the large spectrum of comorbidities and a wide range of underlying causes of admission. A number of scoring systems, such as the Acute Physiology and Chronic Health Evaluation (APACHE) and the Simplified Acute Physiology Score (SAPS), have been developed to predict the risk of mortality for ICU patients. APACHE differs from SAPS in that it involves the collection of prognostic information during the first 24 h of ICU admission, whereas SAPS 3 (the 3rd version of SAPS) gathers prognostic information within the first hour of ICU admission [1]. Neither of these models include cardiac troponin in their algorithms, even though troponin levels are linked to an increased mortality risk and it is the biomarker of choice for the diagnosis of myocardial necrosis [2-5]. Cardiac troponin has also been shown to be a predictor of prolonged length of stay and mortality in the ICU [6,7]. However, it remains uncertain whether cardiac troponin is a useful predictor of mortality when compared with, or included in, the prediction models used in the ICU today [8-12]. The prognostic value of cardiac troponin in the ICU seems to vary depending on the reason of admission; for respiratory distress, pneumonia and sepsis, cardiac troponin seems to be a strong predictor of mortality [13-21], however in cardiac arrest survivors cardiac troponin seems unable to predict mortality [22-24].

The cardiac troponin complex consists of three subtypes which are C (TnC), I (TnI), and T (TnT); both TnI and TnT are suitable for the detection of myocardial injury. During the last decade, the high-sensitivity cardiac troponin T (hsTnT) assay has been developed. This assay is a modification of the fourth-generation TnT assay and has a variety of modifications, which allow the detection of lower concentrations of TnT compared to earlier methods [25]. hsTnT assays have been shown to be a better predictor of all-cause mortality than other types of cardiac troponin [26]. To our knowledge, the prognostic role of hsTnT in relation to SAPS 3 has not yet been investigated.

The objective of this study was to investigate whether hsTnT values obtained on ICU admission improve the prognostic accuracy of SAPS 3 for 1) ICU patients in general, 2) cardiac arrest patients, and 3) non-cardiac arrest patients along with the top 3 diagnoses in this group. We further sought to quantify any potential prognostic improvement using the odds ratio (OR) and the area under the receiver operating characteristic curve (AUC). Finally, we aimed to quantify the prognostic importance of hsTnT alone. It was hypothesized that hsTnT improves

* Corresponding author at: Department of Intensive and Perioperative Care, Skåne University Hospital, SE-22185 Lund, Sweden.
E-mail address: peder.andersson@med.lu.se (P. Andersson).

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the ability of SAPS 3 to predict 30-day mortality following ICU admission.

2. Materials and methods

2.1. Patients and study parameters

In this retrospective study, we identified all adult admissions to the general ICU at Skåne University Hospital in Lund, Sweden, between 25th February 2010 and 30th June 2017. This tertiary university hospital ICU manages both medical and surgical cases, whereas cardiothoracic, neurosurgical, and vascular cases are managed elsewhere. Those admitted to the ICU for either 'basic and observational care' or re-admission were excluded from the analysis. The term 'basic and observational care' was defined as reason of admission when no other reason for admission was present in the original SAPS 3 study. We gathered information from patient records including the primary cause of ICU admission, the SAPS 3 score, survival data, and the highest hsTnT value obtained within 1.5 h of ICU admission. Initially, we proposed a time frame of 60 min; however, we extended this time frame to 90 min to ensure a sufficient study population. The primary cause of ICU admission (confirmed on discharge) was chosen from a small subset of the 10th revision of the International Classification of Diseases (ICD-10). Patients with valid hsTnT recordings on admission were examined to identify if inclusion of hsTnT enhanced the predictive ability of SAPS 3 for 30-day mortality. Second, patients with hsTnT measurements were divided into two groups based on their diagnoses; either 'cardiac arrest' or 'non-cardiac arrest'. 'Non-cardiac arrest' patients were further divided into the three most frequent diagnoses: 'sepsis', 'heart failure', and 'respiratory failure'. Sepsis, severe sepsis, and septic shock diagnoses were combined as 'sepsis'. Left ventricular failure diagnosis and unspecified heart failure diagnosis were combined as 'heart failure'.

2.2. SAPS calculation

SAPS 3 uses information based on known comorbidities (e.g. age, chronic heart failure, cancer etc.) prior to ICU admission, the reason for ICU admission, physiological parameters, and laboratory findings (e.g. creatinine, platelets, leukocytes etc.) on ICU admission to calculate the estimated mortality risk (EMR) for each patient admitted to the ICU [1]. Physiological parameters and laboratory findings are recorded within 1 h of ICU admission. EMR is then calculated as follows:

$$\mathrm{EMR} = e^{\mathrm{Logit}} / \left(1 + e^{\mathrm{Logit}}\right)$$

where

$$\mathrm{Logit} = 7.199704 \times \ln\left(\mathrm{SAPS\ 3\ score} + 10.34171\right) - 32.06302.$$

The formula above is the Swedish calibration from 2016 which estimates 30-day mortality, in contrast to the original SAPS 3 model which estimates in-hospital mortality [27].

After calculating EMR, the standardized mortality ratio (SMR) can be calculated by dividing the 30-day mortality by the EMR. An actual 30-day mortality rate close to the EMR gives an SMR near 1. If more than expected survive, then the SMR is <1. Equally, an SMR >1 means excess mortality versus the EMR rate.

2.3. hsTnT analysis

A Cobas® 8000 analyzer (Roche, Germany) was used to analyze hsTnT. The lower detection limit was 5 ng/L and the upper detection limit was 9999 ng/L. Unless otherwise stated, calculations on hsTnT were performed using the natural logarithm of hsTnT in order to give more weight to the lower hsTnT values. Group characteristics for patients with and without hsTnT on ICU admission were compared based on age, sex, EMR, 30-day mortality, SMR, and length of stay.

2.4. Statistical analyses

For all statistical analyses, a p-value < 0.05 was considered statistically significant. The Mann-Whitney U test was used to assess for differences between two independent variables. To assess for differences in proportions, Pearson's chi-square test was used. Using hsTnT levels and EMR as independent variables, we used multivariate logistic regression analysis of 30-day mortality to determine if hsTnT improved the predictive power of SAPS 3. To quantify changes in discrimination when adding hsTnT to SAPS 3, the area under the receiver operating characteristic curve (AUC) was calculated for all diagnoses. Bootstrap hypothesis testing using the percentile method was employed to test for differences in SMR.

2.5. Ethics

This study was conducted with the approval of the regional ethical committee in Lund, Sweden with registration number 2016/464. This ethical approval permitted the researchers to study short and long-term mortality retrospectively in relation to laboratory findings and clinical parameters obtained in the ICU. We started to investigate the effect of hsTnT in relation to SAPS 3 in June 2017 and we used all the retrospective data available at that time. hsTnT values were analyzed on clinical indications only.

3. Results

We identified 5664 admissions to the ICU during the study period. Of these admissions, 4769 were actual ICU admissions (i.e. after exclusion of patients admitted for 'basic and observational care') and 4185 were first-time admissions. Of the 4185 first-time admissions, 856 patients (20.5%) had hsTnT measured within 90 min of ICU admission. The group with hsTnT measured on admission were significantly older (mean 66.6 vs 58.2 years, $p < 0.001$), had a significantly higher severity of illness, as measured by EMR (mean 36.5% vs 24.0%, $p < 0.001$), and a significantly higher 30-day mortality compared to the group without hsTnT on ICU admission (mean 33.8% vs 24.0%, $p < 0.001$). However,

Table 1
Characteristics of the study population for patients with and without measured hsTnT on admission to the intensive care unit.

	hsTnT group	non-measured hsTnT group	p-Value
No. of patients	856	3329	<0.001
Age, mean, years (SD)	66.6 (14.7)	58.2 (18.8)	<0.001
Male, %	39.3	41.9	0.40
EMR, median, % (SD)	31.9 (24.7)	16.1 (23.2)	<0.001
EMR, mean, % (SD)	36.5 (24.7)	24.0 (24.7)	<0.001
30-day mortality, %	33.8	24.0	<0.001
SMR	0.93	1.00	<0.001
Length of stay, median, days (SD)	1.63 (4.05)	1.40 (4.47)	0.019
Distribution of admission diagnoses, %:			
Cardiac arrest	28.9	7.3	<0.001
Non-Cardiac arrest	71.1	92.7	<0.001
Sepsis	10.0	11.5	0.24
Heart failure	5.5	1.2	<0.001
Respiratory failure	4.7	4.6	1.00

EMR: Estimated mortality rate based on the 3rd version of the Simplified Acute Physiology Score (SAPS 3); SD: standard deviation; SMR: standardized mortality ratio; hsTnT: high-sensitivity troponin T.

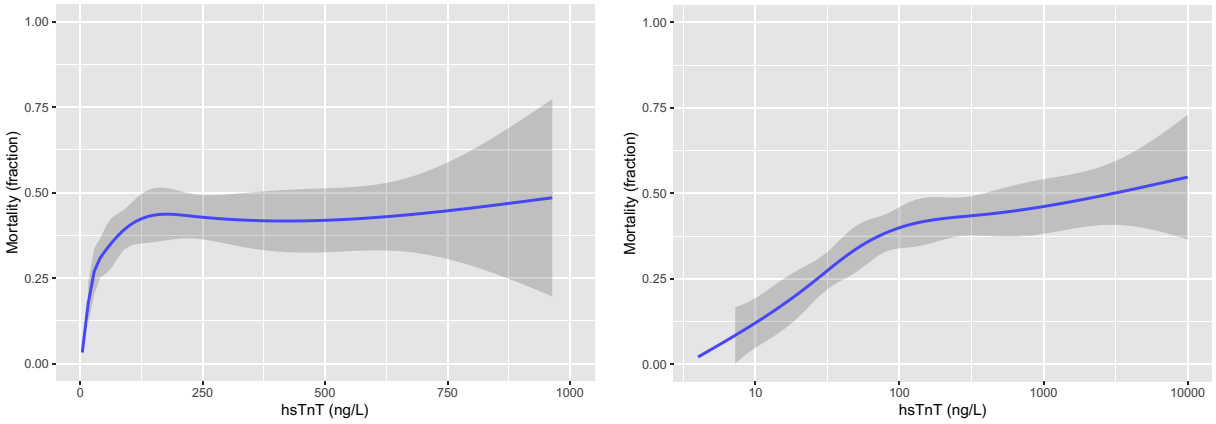

Fig. 1. *The association between hsTnT measurements and 30-day mortality.* hsTnT values of 0–1000 ng/L are shown on the left panel to illustrate the rapidly increasing mortality rate with an increasing hsTnT value from <5 ng/L to hsTnT of 125 ng/L. On the right panel, hsTnT values of 1–10,000 ng/L are shown on a logarithmic scale.

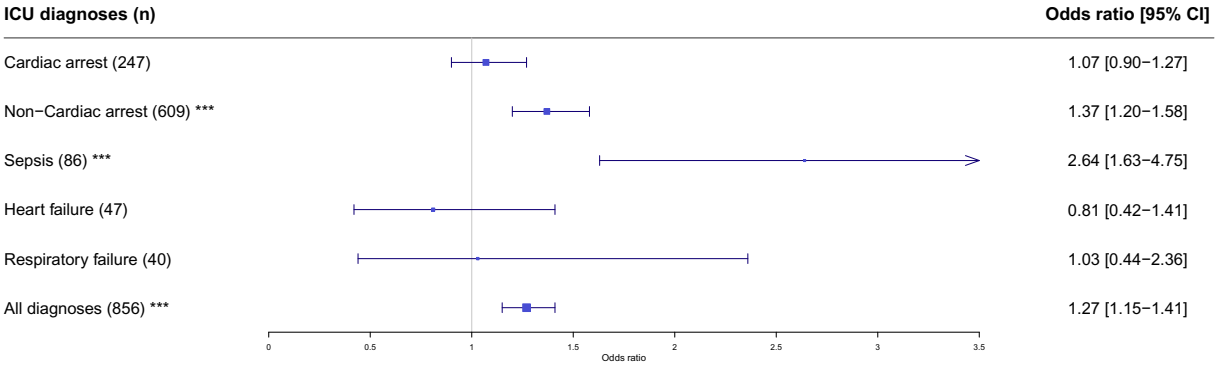

Fig. 2. *Forest plot of odds ratios for hsTnT added to SAPS 3 for different ICU diagnoses.* ***$p < 0.001$. All hsTnT calculations were performed using the natural logarithm.

Table 2
Odds ratio and AUC for the hsTnT group and hsTnT group combined with SAPS 3.

	hsTnT alone			SAPS 3 & hsTnT				
	Odds ratio (95% CI)	p-value	AUC hsTnT alone, %	Odds ratio (95% CI)	p-value	AUC SAPS 3 alone, %	AUC SAPS 3 + hsTnT, %	*p*-value
All	1.36 (1.25–1.49)	<0.001	65.3	1.27 (1.15–1.41)	<0.001	78.3	79.3	0.15
Cardiac arrest	0.97 (0.83–1.12)	0.64	52.1	1.07 (0.90–1.27)	0.46	78.9	78.8	0.59
Non-Cardiac arrest	1.51 (1.34–1.72)	<0.001	68.3	1.37 (1.20–1.58)	<0.001	76.1	77.6	0.16
- Sepsis	2.72 (1.70–4.82)	<0.001	79.3	2.64 (1.63–4.75)	<0.001	71.2	83.1	<0.01
- Heart failure	0.94 (0.55–1.53)	0.8	53.2	0.81 (0.42–1.41)	0.48	75.3	76.8	0.57
- Respiratory failure	1.13 (0.54–2.43)	0.74	51.9	1.03 (0.44–2.36)	0.95	64.1	64.3	0.34

hsTnT: high-sensitivity troponin T; AUC: area under the receiver operating characteristic curve; SAPS 3: the 3rd version of Simplified Acute Physiology Score; CI: confidence interval. All hsTnT calculations were performed using the natural logarithm.

SMR was lower for the hsTnT group than for the non-hsTnT group (0.93 vs 1.00, $p < 0.001$). No differences were identified in the male-to-female ratio between the two groups ($p = 0.40$). The demographic characteristics of the study population are shown in Table 1. The mean hsTnT was 488 ng/L, while the median hsTnT was 75 ng/L. As shown in Fig. 1, an elevation in hsTnT was strongly associated with 30-day mortality for hsTnT values up to 125 ng/L. For hsTnT values above 125 ng/L, the 30-day mortality remained stable at around 45 to 50%. A more linear relationship was found between the logarithm of hsTnT and 30-day mortality.

Using multivariate binomial logistic regression on 30-day mortality, the addition of hsTnT measurements were found to enhance the prognostic capability of SAPS 3 to predict 30-day mortality for all diagnoses (OR 1.27, 95% confidence interval [CI]: 1.15–1.41, $p < 0.001$), 'non-cardiac arrest' (OR 1.37, 95% CI: 1.20–1.58, $p < .001$), and 'sepsis' (OR 2.64, 95% CI: 1.63–4.75, $p < .001$). No significant improvement in predictive ability was identified for 'cardiac arrest', 'heart failure', and 'respiratory failure' patients when hsTnT was added to SAPS 3 (Fig. 2).

Using hsTnT in a univariate logistic regression showed a good prognostic value for predicting 30-day mortality in 'sepsis' patients (AUC 79.3%) and intermediate prognostic value for the overall ICU population (AUC 65.3%) and 'non-cardiac arrest' patients (AUC 68.3%). Interestingly, hsTnT did not show any useful prognostic value in 'cardiac arrest', 'heart failure', and 'respiratory failure' patients, all of which had AUCs around 50%. Adding hsTnT to SAPS 3 increased the AUC by >10% in 'sepsis' patients (83.1% vs 71.2%, $p < 0.01$), but did not improve discrimination in the other categories. The results of the regression analyses and AUC calculations are shown in Table 2. The prognostic value of hsTnT, when added to SAPS 3 for patients admitted with 'sepsis', is shown in Fig. 3.

Table 3 shows that SMR increased with increasing hsTnT values for 'non-cardiac arrest' patients. For lower hsTnT values (<500 ng/L), the

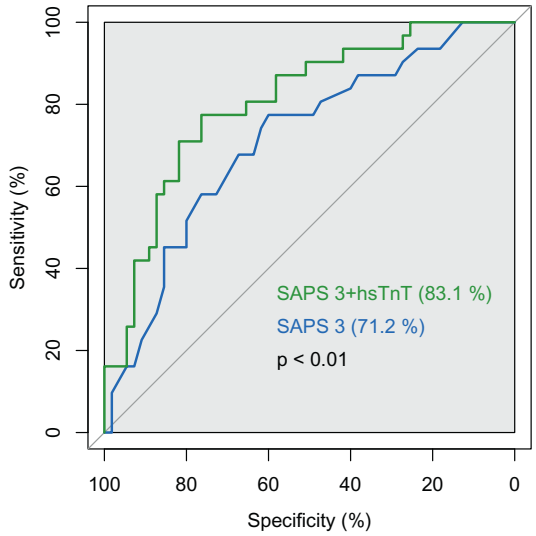

Fig. 3. *Comparing the AUC and Odds Ratios for SAPS 3 with and without hsTnT for patients admitted with 'sepsis' to the ICU.* All hsTnT calculations were performed using the natural logarithm.

Table 3
SMR for 'non-cardiac arrest' patients for different hsTnT strata.

Measured hsTnT (ng/L)	30-day mortality (%)	EMR (%)	SMR	Number of patients
<5	0.0	9.6	0.00	24
5–29	12.9	23.7	0.54	171
30–99	28.8	35.0	0.82	219
100–499	34.7	40.4	0.86	144
500–10,000	51.0	37.8	1.35	51
hsTnT analyzed within 1.5 h	26.4	32.3	0.82	609
hsTnT not analyzed within 1.5 h	21.7	22.4	0.97	3087

hsTnT: high-sensitivity troponin T; EMR: Estimated mortality rate based on the 3rd version of the Simplified Acute Physiology Score (SAPS 3); SMR: standardized mortality ratio. All hsTnT calculations were performed using the natural logarithm.

SMR was <1, while for higher hsTnT values (≥500 ng/L), the SMR was >1. The EMR for patients in the 5–29 ng/L hsTnT group was similar to the EMR in the non-hsTnT group, although the 30-day mortality was significantly lower ($p < 0.001$) in the 5–29 ng/L hsTnT group than in the non-hsTnT group.

4. Discussion

To our knowledge, no study has investigated and subsequently identified whether the newer version of the troponin T assays, hsTnT, can add value to the SAPS 3 prediction model either overall, or for patients with specific diagnoses. In this study, we found that hsTnT, was able to improve the ability of the SAPS 3 model to predict short-term mortality with an OR of 1.27 (95% CI 1.15–1.41, $p < 0.001$). However, the OR was not high enough to influence the overall prognostic value of SAPS 3 when measured by AUC.

Many cardiac arrests are due to acute myocardial infarction, and it is well known that increased levels of hsTnT are associated with a worse prognosis in these patients. Interestingly, our study did not find any association between 30-day mortality and elevated hsTnT levels on ICU admission for patients who had suffered cardiac arrest. This correlates well with previous findings wherein cardiac troponin T has been shown to be poorly associated with short-term outcomes [22-24]. Perhaps the most striking finding in our study was to what degree the addition of hsTnT to SAPS 3 improved prognostic accuracy for patients in the 'sepsis' group (AUC improved by over 10%). Using hsTnT alone as a predictor resulted in a better AUC than SAPS 3 for the 'sepsis' group (AUC 79.3% vs 71.2%); furthermore, combining hsTnT and SAPS 3 resulted in an AUC of 83.1%. These diagnosis-specific findings correspond well with previous findings; previous studies suggest that troponin-T is associated with increased short- and long-term mortality [17,19,24]. However, the positive effect on prognostic predictive ability we identified after addition of hsTnT to SAPS 3, for septic patients, was greater than anticipated. This is an important finding which could improve ICU decision making for patients with sepsis; this point warrants further investigation.

As hsTnT alone showed poor discrimination in cardiac arrest patients, we next examined the non-cardiac arrest group in relation to SMR. Surprisingly, we found that the SMR for the hsTnT group was lower than the SMR for the patient group in which hsTnT was not measured, indicating a better overall survival in the hsTnT group than predicted. A possible explanation for this observation could be that higher hsTnT levels may have directed the clinicians to a more aggressive approach in lowering the mortality rate, and thus lowering the SMR. Another possible explanation is that a calibration error of EMR, due to possible discrepancies between EMR and 30-day mortality at different EMR levels affected SMR [28]. EMR for the 5–29 ng/L hsTnT patient group was approximately the same as that for the group of patients in which hsTnT was not measured. If hsTnT did not influence the mortality risk for our patients, these two patient groups would have the same observed 30-day mortality. When comparing these two groups, the 30-day mortality differed significantly (Table 3). By having two groups with similar EMR levels, 30-day mortality for these groups can be compared without risk of interference from a calibration error, as mentioned above [28]. The overall hsTnT threshold for a beneficial SMR was approximately 500 ng/L, i.e. far higher than the diagnostic threshold for myocardial infarction. Patients with hsTnT lower than 500 ng/L had a lower mortality than expected, whereas patients with hsTNT values between 500 ng/L and 9999 ng/L had a higher mortality than expected. It is also worth considering that the hsTnT group had a higher EMR than the group in which hsTnT was not measured.

The non-prospective sampling of hsTnT and the higher severity of illness in the hsTnT group were the most notable limitations of our study. The fact that the group with the hsTnT group was older entails a higher EMR which is accounted for in SAPS 3. In fact, age is the single most important predictive factor of SAPS 3. Approximately 21% of our study cohort had hsTnT measured upon ICU admission. To ensure a sufficient large study population, we increased the window in which we accepted hsTnT values post ICU admission to 90 min instead of 60 min. Assessment for hsTnT was done on clinical advice, which we, due to the nature of our database, do not have any pertinent information about. Naturally, this leads to a high risk of selection bias. The possibility of selection bias could be explained by the difference in morbidity adjusted outcome in the hsTnT sample group. However, it is important to note that it does not explain how the increasing levels of hsTnT is related to the increasing risk of death, as found by the logistic regression analysis.

It should also be noted that the primary diagnoses used in our study could have been over- or under-reported, which may have affected the prognostic strength for certain subgroups.

Despite these shortcomings, we recommend that the measurement of hsTnT on ICU admission should be considered for future ICU scoring systems, especially in patients with sepsis. Future studies need to validate the findings of this study. This is because of the potential for selection bias in the study design, as we were unable to elucidate why, in most cases, hsTnT analysis was performed. We plan to analyze admission hsTnT for 900 consecutive sepsis patients, fulfilling the SEPSIS 3 criteria, in a multicenter study in southern Swedish ICUs.

5. Conclusion

We found the hsTnT value to be an independent predictor of mortality when added to SAPS 3, especially in sepsis, where hsTnT seems play

an important prognostic role. Adding hsTnT to SAPS 3 improved the AUC by >10% for patients with sepsis. Further studies are needed to validate these findings.

Declaration of Competing Interests

The authors have no conflicts of interest.

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