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Rapid rule out of acute myocardial infarction in the observe zone using a combination of presentation N-terminal pro-B-type natriuretic peptide and high-sensitivity cardiac troponin I

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ABSTRACT

Background and aims: The release of N-terminal pro-B-type natriuretic peptide (NT-proBNP) is strongly triggered by myocardial ischemia. We aimed to investigate whether the addition of NT-proBNP to high-sensitivity cardiac troponin (hs-cTnI) at presentation could provide better performance in risk stratification and thus early rule-out of acute myocardial infarction (AMI) in patients of the "observe zone".

Methods: Emergency department (ED) patients presenting with symptoms suspicious for AMI were consecutively enrolled. Blood samples were obtained at presentation and tested for hs-cTnI and NT-proBNP. All available medical records pertaining to the patient from ED presentation to 30-day follow-up were used for adjudication of the primary outcome. The incremental diagnostic value added by NT-proBNP to hs-cTnI was evaluated by receiver operating characteristic (ROC) analysis, continuous net reclassification improvement (cNRI), and integrated discrimination improvement (IDI). Sensitivity, specificity, positive and negative predictive values were used to assess the diagnostic accuracy of different approaches for early rule out.

Results: Of the 165 patients we analyzed, 55 (33.3%) had index AMI. For hs-cTnI alone, area under the curve for index AMI was not significantly increased after adding NT-proBNP (0.773 vs 0.809; p = .076). Adjustment of hs-cTnI by NT-proBNP improved the predictive value of hs-cTnI, showed by cNRI (0.418, 95%CI 0.102–0.735, p = .009) and IDI (0.055, 95%CI 0.017–0.092, p = .004). Compared to hs-cTnI, the combined test identified 14% more patients as low-risk and safe for early discharge.

Conclusions: Combination of presentation hs-cTnI and NT-proBNP provided better predictive performance for AMI in patients of the observe zone presenting with symptoms of chest pain as compared to hs-cTnI alone. The combined test outperformed hs-cTnI by correctly identifying nearly 14% more patients as low-risk and safe for early discharge. Future multi-center studies are needed to verify the results and to determine the best clinical use of the combination of NT-proBNP and hs-cTnI in the early diagnosis of AMI.

1. Introduction

Chest pain is one of the most common reasons for presentation to the Emergency department (ED), which accounts for approximately 9–10% of annual visits [1]. The potential causes of chest symptoms vary from benign to life threatening, while only a small proportion of patients will ultimately have a diagnosis of acute myocardial infarction (AMI) [2]. Due to resource constraints, many of these patients might be suitable for direct discharge from the ED [3]. Rapid identification and rule-out of patients without AMI are of vital clinical importance, which would reduce overcrowding in the ED, patients' uncertainty and anxiety, and enormous costs for the health care system [4–6].

Major improvements in the diagnosis of AMI occurred with the introduction of high-sensitivity cardiac troponin (hs-cTn) assays and the development of data-driven optimized diagnostic algorithms, which has enabled the application of recently developed rapid "rule-in" and "rule-out" strategies [7–13]. Among these, Lindahl et al. [14] suggested a novel 0/2-hour algorithm for early rule-out and rule-in of AMI. In the first triage step, this algorithm interprets initial high-sensitivity cardiac troponin I (hs-cTnI) levels as quantitative variables and assigns patients

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being evaluated for AMI into three groups: patients with initial hs-cTnI levels < 2 ng/L to "rule-out", patients with initial hs-cTnI levels > 100 ng/L to "rule-in" and the remaining patients with diagnostic uncertainty to the "observe zone". Patients assigned to the observe zone would require repeat testing and subsequent second rounds of triage after 2 h. While management is largely accelerated and simplified in patients assigned to "rule-out" and "rule-in" groups, diagnostic uncertainty remains in patients assigned to the "observe zone". Thus, further risk stratification and early rule-out of AMI would be best suited for patients assigned to the observe zone.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels are strongly related to myocardial ischemia [15,16]. Sakai et al. [17] suggested that NT-proBNP was significantly increased with the aggravation of coronary artery stenosis. Measurement of NT-proBNP at presentation was shown to help improve early diagnostic accuracy and risk stratification in patients suspected of AMI [18]. As a supplement to this novel 0/2-hour algorithm [14], we hypothesize that combining presentation NT-proBNP and hs-cTnI could further risk stratify patients in the observe zone and consequently increase the discharge rate by early rule-out of those deemed low risk.

We aimed to investigate whether the addition of presentation NT-proBNP to hs-cTnI could provide better performance in risk stratification compared to hs-cTnI alone, and help early rule-out of AMI in patients assigned to the observe zone in the novel 0/2-hour algorithm [14].

2. Methods

This study was a prospective observational study that consecutively enrolled patients with acute chest pain presenting to the ED of Xinhua Hospital, affiliated with Shanghai Jiaotong University School of Medicine, from August 2017 to October 2018.

2.1. Participants

Patients were eligible for inclusion if age ≥ 18 years, with chest pain suspicious for AMI with duration of ≥10 min and onset of last episode within 12 h. Exclusion criteria included patients with terminal kidney failure requiring regular dialysis, traumatic injuries or pregnancy. The study was carried out according to the principles outlined in the Declaration of Helsinki and approved by Shanghai Jiaotong University Xinhua Hospital Ethics Committee. Written informed consent was obtained from patients or their relatives.

Subjects underwent routine clinical assessment by an ED physician that included medical history, physical examination, 12-lead electrocardiograph (ECG), standard blood tests including serial measurement of hs-cTn and chest X-rays. Treatment and disposition of patients were at the discretion of the treating physician.

2.2. Data collection

Baseline blood samples for the determination of NT-proBNP and hs-cTnI were collected at presentation (0 h) in ethylenediamine tetraacetic acid (EDTA) tubes; blood draws were serially obtained after 3 (± 30 min) and 6–24 h. After centrifugation, the plasma was stored at −80 °C within 1 h of draw. These samples were later analyzed in a blinded and independent manner in a dedicated core laboratory for both NT-proBNP and hs-cTnI at each time interval.

The plasma levels of NT-proBNP were measured on Elecsys proBNP (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's recommendations for all NT-proBNP measurements. The lower limit of detection (LoD) of the assay was 5 ng/L. The intra-assay coefficient of variation was 5% and the inter-assay coefficient of variation was 7% at a value of 250 ng/L. Hs-cTnI levels were measured on the VIDAS high-sensitivity troponin I assay (bioMérieux), a quantitative sandwich immunoassay. The hs-cTnI has a 99th percentile concentration of 19 ng/L and was estimated at 7% coefficient of variation (CV) at this value. The LoD was between 1.3 and 3.2 ng/L.

2.3. Outcome measures

The primary outcome was index AMI, which is a composite endpoint of cardiac arrest, cardiovascular death, cardiogenic shock or AMI during the index presentation. Adjudication of the final diagnosis was performed by two independent cardiologists using all available medical records pertaining to the patient from the time of ED presentation to 30-day follow-up. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist. The diagnosis of AMI was according to the Fourth Universal Definition of Myocardial Infarction [19].

2.4. Data analysis

Baseline characteristics of the samples were reported by index AMI using standard descriptive statistics. Data were expressed as median ± interquartile range (IQR) for continuous variables and as numbers (n) and percentages (%) for categorical variables. Comparison between independent groups were made using the Student *t*-test for continuous variables and the Pearson chi-squared test for categorical variables. To limit the influence of extreme observations, biomarker levels were $\log_{10}$-transformed, and their distributions were standardized to a mean of zero and standard deviation (SD) of 1 to facilitate comparison of effect sizes between biomarkers. The Pearson correlation coefficient was calculated to assess the correlation between NT-proBNP and hs-cTnI. A binary logistic regression model was used to calculate predicted probabilities for assessment of the combined test and hs-cTnI alone. We determined the area under the receiver operating characteristic (ROC) curve (AUC) to assess discriminatory performance; comparison of AUCs was performed by the method of DeLong et al. [20]. Continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI) were performed to analyze the degree to which the addition of NT-proBNP improved the discriminatory performance of hs-cTnI alone. Calibration was analyzed with the Hosmer-Lemeshow (HL) goodness-of-fit test. To derive and test the optimal cutoff value of predicted probability for safe early rule-out, the cutoff was that which maximized the percentage ruled-out at a sensitivity of ≥99%. Diagnostic accuracy for rule-out was assessed using sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), and McNemar's chi-square test was used to assess the difference of sensitivity and specificity between different models. Binomial exact confidence intervals were reported for each proportion. Two-sided P value < 0.05 indicated statistical significance. All statistical analyses were performed by SPSS for Windows 23.0 (SPSS lnc), MedCalc 9.6.4.0 (MedCalc software), and R-programming language (version 3.5.2).

3. Results

We enrolled 409 patients and 165 of them had suitable available data for inclusion in the analysis (240 patients had a troponin concentration not within the observe zone, 2 subjects had no available blood sample measurements and 2 subjects lost contact after early-discharge). Baseline characteristics of 165 patients for analysis are shown in Table 1. The median age was 64 years, 64.8% were male, and 33.3% had index AMI during the presentation. Compared to patients without index AMI, patients with index AMI were more likely to be male, have medical history such as hypertension and smoking, and have increased ECG changes such as ST depression or elevation and left bundle branch block.

Hs-cTnI levels were significantly higher in patients with index AMI compared to patients without index AMI (median 30.0 ng/L vs 8.0 ng/L, $p < 0.001$). Conversely, NT-proBNP levels were significantly lower in

Table 1
Baseline characteristics of patients in the observe zone.

Baseline characteristics	Observe zone (N = 165)	Index AMI (n = 55, 33.3%)	No index AMI (n = 110, 66.7%)	P value
Median age (IQR), years	64 (59–71)	65 (59–72)	62 (55–69)	0.140
Male gender, No. (%)	107 (64.8)	42 (76.4)	65 (59.1)	0.022
Medical history, No. (%)				
Diabetes	38 (23.0)	17 (30.9)	21 (19.1)	0.089
Hypertension	84 (50.9)	38 (69.1)	46 (41.8)	0.001
Previous AMI	27 (16.4)	10 (18.2)	17 (15.4)	0.655
Previous revascularization	30 (18.2)	8 (14.5)	22 (20.0)	0.392
Stable angina/known CAD	53 (32.1)	21 (38.2)	32 (29.1)	0.238
Current or past smoker	68 (41.2)	30 (54.5)	38 (34.5)	0.015
Vital stats				
Heart rate, beats/min (IQR)	76 (70–84)	76 (70–88)	76 (70–84)	0.843
Systolic BP, mmHg (IQR)	132 (124–142)	130 (114–144)	132.5 (128–142)	0.356
Diastolic BP, mmHg (IQR)	77 (70–82)	77 (68–85)	77 (70–81)	0.955
ECG changes, No. (%)				
ST depression or elevation	44 (26.7)	29 (52.7)	15 (13.6)	< 0.001
T-wave inversion	25 (13.9)	10 (18.2)	13 (11.8)	0.266
Left bundle branch block	7 (4.2)	5 (9.0)	2 (1.8)	0.029
Atrial fibrillation	4 (2.4)	2 (3.6)	2 (1.8)	0.474
Presentation blood samples, ng/L				
hs-cTnI, median (IQR)	13.0 (5.0–37.5)	30.0 (17.0–61.0)	8.0 (5.0–17.2)	< 0.001
NT-proBNP, median (IQR)	85.8 (38.4–210.0)	59.8 (35.9–175.1)	98.4 (40.6–219.7)	0.039

AMI = acute myocardial infarction, IQR = Interquartile range, CAD = coronary artery disease, BP = blood pressure, ECG = Electrocardiograph.

patients with index AMI compared to patients without index AMI (median 59.8 ng/L vs 98.4 ng/L, p = .039). Correlation analysis between NT-proBNP and hs-cTnI showed that NT-proBNP was positively correlated with hs-cTnI ($R = 0.227$, p = .003).

Table 2 summarized the results of the univariate and multivariate logistic regression analyses of $\log_{10}$-transformed biomarkers. After adjustment for two potentially confounding variables ($p < 0.25$) [21], hs-cTnI (odds ratio [OR] = 3.68, 95%CI 2.33–5.80, $p < .001$) showed strong association to index AMI, and a low level of NT-proBNP (OR = 0.53, 95%CI 0.36–0.79, p = .002) was an independent predictor of index AMI in the multivariate logistic regression analysis.

The AUC increased from 0.773 (95%CI 0.702–0.835) for hs-cTnI alone to 0.809 (95%CI 0.740–0.866) for combination of hs-cTnI and NT-proBNP, although the difference in the AUCs (0.036, p = .076) indicated no statistical significance (Fig. 1,Table 3). Incremental discriminative value of adding NT-proBNP to hs-cTnI was confirmed by the cNRI and the IDI (Table 3). The IDI for NT-proBNP was 0.055 (95%CI 0.017–0.092, p = .004), suggesting further average separation of index AMI from non-index AMI by NT-proBNP; the cNRI for NT-proBNP was 0.418 (95%CI 0.102–0.735, p = .009), with $cNRI_{Index\ AMI}$ contributing 0.200 and $cNRI_{non\text{-}Index\ AMI}$ 0.218, showing that NT-proBNP led to a significant net reclassification of patients' risk in the appropriate directions. Calibration plots (Fig. 2) graphically showed the observed probability plotted against the predicted probability, both prediction models showed good calibration with no deviation of the "logistic calibration" line from the diagonal. Moreover, the Hosmer-Lemeshow test indicated better calibration (HL test, Chi-square = 5.943, p = .746) of the combined test for prediction of index AMI than hs-cTnI alone (Chi-square = 11.348, p = .253).

The optimal cutoff values of predicted probability for rule-out were 0.058 for the hs-cTnI prediction model and 0.092 for the combined test model, respectively (Table 4). The prediction models both yielded 100% sensitivity (95%CI: 93.5%–100%) and 100% NPV (95%CI: 59.0%–100% for hs-cTnI, 88.1%–100% for the combined test) for index AMI. The integrated diagnostic accuracy of sensitivity and specificity differed significantly between the two models ($p < 0.0001$). Specificity of the combined test was significantly higher than hs-cTnI alone ($p < .001$). In addition, hs-cTnI identified 7/165 patients (4.2%) as low-risk for early rule-out, while the combined test identified 29/165 patients (17.6%) as low-risk, an absolute difference of 13.4% ($p < .001$), and none of these deemed low-risk had index AMI (miss rate = 0).

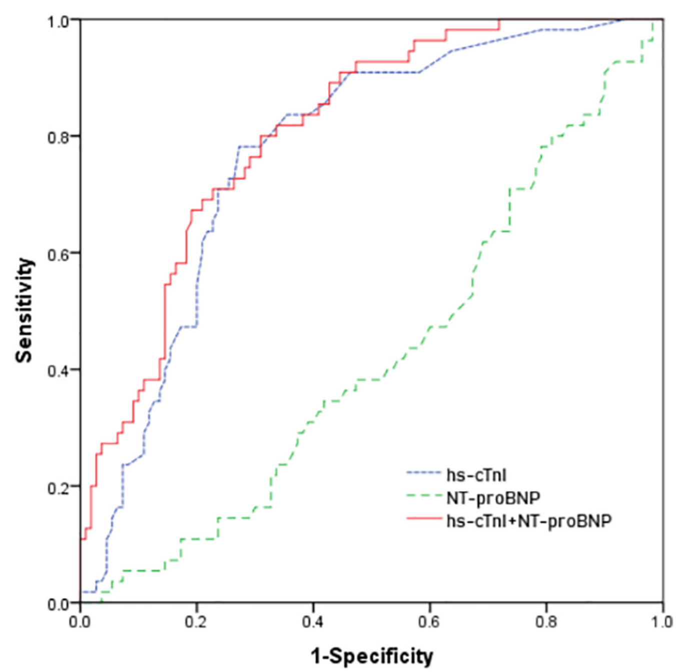

Fig. 1. Diagnostic performance of high-sensitivity cardiac troponin I (hs-cTnI) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in receiver operating characteristic curve analysis.

Table 2
Univariate and Multivariate Logistic regression analysis of biomarkers for index AMI.

Variables	Unadjusted OR (95%CI)	P value	Adjusted OR (95%CI)	P value
hs-cTnI	2.97 (1.98–4.46)	< 0.001	3.68 (2.33–5.80)	< 0.001
NT-proBNP	0.77 (0.55–1.07)	0.110	0.53 (0.36–0.79)	0.002

OR = odds ratio, 95%CI = 95% confidence interval.

Table 3
Improvements in discriminatory performance upon addition of NT-proBNP to hs-cTnI for Index AMI in the observe zone.

		P value
Index AMI, n (%)	55 (33.3)	
Non-Index AMI, n (%)	110 (66.7)	
Continuous NRI		
$cNRI_{Index\ AMI}$	0.200	
$cNRI_{non\text{-}Index\ AMI}$	0.218	
cNRI	0.418 (95%CI 0.102–0.735)	0.009
IDI statistics		
IDI	0.055 (95%CI 0.017–0.092)	0.004
AUC		
hs-cTnI	0.773 (95%CI 0.702–0.835)	
NT-proBNP	0.578 (95%CI 0.499–0.654)	
hs-cTnI + NT-proBNP	0.809 (95%CI 0.740–0.866)	
Difference	0.036	0.076
Hosmer-Lemeshow test		
hs-cTnI	Chi-square = 11.348	0.253
hs-cTnI + NT-proBNP	Chi-square = 5.943	0.746

NRI = net reclassification improvement, cNRI = continuous net reclassification improvement, IDI = integrated discrimination improvement, 95%CI = 95% confidence interval, AUC = area under the receiver operating characteristic curve.

4. Discussion

With the introduction of hs-cTn assays, algorithms based on a single blood test [8,9] or on repeated tests after 1 [10,11] or 2 [12,13] hours have been proposed, some of which have been recommended for clinical use in the recent 2015 European Society of Cardiology Guidelines [22], but the number of directly ruled-out patients at presentation is limited and assay-dependent. The novel 0/2-hour algorithm suggested by Lindahl et al. [14] largely simplified the allocation and management of patients suspected of AMI, whereas nearly half of patients remained in the “observe zone” with diagnostic uncertainty requiring repeated cTn measurement and further investigation. Further risk stratification of patients suspected of AMI in the observe zone at presentation remains challenging for us; a means to do that would provide a tool to increase early discharge rate by identifying some of the patients in the observe zone as low-risk and potentially eligible for safe early discharge. We found that the combined test of hs-cTnI and NT-proBNP levels at presentation could identified nearly 18% patients in the observe zone for safe early discharge.

Measurement of NT-proBNP at presentation was shown to help improve early diagnostic accuracy and risk stratification in patients

Table 4
Diagnostic accuracy of the combined test model and hs-cTnI for safe early rule-out.

Index AMI	hs-cTnI	hs-cTnI + NT-proBNP
Cutoff of predicted probability	0.058	0.092
Patients deemed low risk, n (%)	7 (4.2)	29 (17.6)
Sensitivity (95%CI)	100 (93.5–100)	100 (93.5–100)
Specificity (95%CI)	6.4 (2.6–12.7)	26.4 (18.4–35.6)
PPV (95%CI)	34.8 (27.4–42.8)	40.4 (32.1–49.2)
NPV (95%CI)	100 (59.0–100)	100 (88.1–100)
Miss rate (%)	0	0

suspected of AMI [18]. We found lower median NT-proBNP levels in patients with index AMI than those without, which disagrees with the previous study by Haaf et al. [18]. Several reasons may account for this discrepancy, predominantly that the major group that we assessed was patients within the observe zone; in addition, differences in races, previous treatments and pathogeneses of AMI may also account for the discrepancy.

A low level of NT-proBNP after adjustment by hs-cTnI was an independent predictor of index AMI for patients in the observe zone, NT-proBNP and hs-cTnI were positively correlated, and hs-cTnI showed a strong association to index AMI (OR = 3.68). Moreover, an AUC of 0.773 confirmed the hs-cTnI as a valuable tool in risk stratification. The change of AUC when NT-proBNP was added to hs-cTnI was not statistically significant, however, the incremental diagnostic discrimination of the combined test was validated by new statistical metrics (cNRI and IDI). A net 21.8% of the patients without AMI were reclassified into lower risk, and the cNRI reached an impressive 41.8%, which suggested that NT-proBNP led to a significant net reclassification of patients' risk in the appropriate directions. IDI for NT-proBNP showed further average separation of index AMI from non-index AMI. As indicated by Pencina et al. [23], biomarker performance differed across these metrics. The change of AUC depends heavily on the strength of the baseline model (hs-cTnI), which is true to a lesser degree for the IDI [23]. cNRI depends mainly on the effect size of the candidate marker (NT-proBNP) and its correlation with the baseline model (hs-cTnI), thus employing the cNRI provided a metric of discrimination not as easily influenced by the strength of the baseline model [23]. The performance of risk prediction models is assessed by both their discrimination and calibration [24]. Both the combined test and hs-cTnI showed good calibration according to the calibration plots (Fig. 2). In addition, the HL test indicated that the combined test showed better calibration, which supported that the combined test predicts more accurately than hs-cTnI

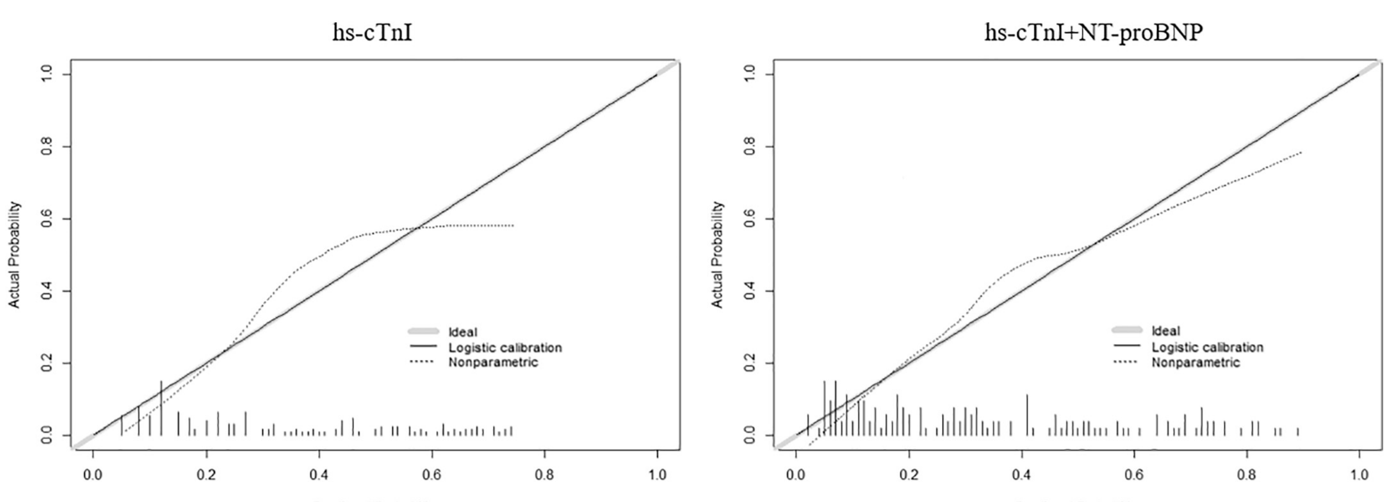

Fig. 2. Calibration plots for hs-cTnI and combined test (hs-cTnI + NT-proBNP) in the prediction of index AMI.

alone.

As different metrics of diagnostic performance, safety was assessed as the sensitivity and NPV for rule-out of AMI, and efficacy was quantified by the proportion of patients triaged for rule-out or rule-in for AMI within a specific duration of time; however, a tradeoff between safety and efficacy exists [25,26]. It is suggested to maintain a high sensitivity (≥99%) while increasing the percentage of low-risk patients identified for early discharge, ensuring a most frequently cited acceptable miss rate of < 1% [27,28]. The high sensitivity required often comes at the expense of identifying fewer patients for early discharge. The cutoff values of the combined test and hs-cTnI both yielded 100% sensitivity and 100% NPV for rule-out with no index AMI missed. Moreover, the combined test could identify nearly 14% more patients for safe early discharge than hs-cTnI alone.

5. Limitations

First, as we excluded those with terminal kidney failure requiring for regular dialysis, we cannot analyze on the diagnostic accuracy among these patients. Second, all patients we enrolled were Asian, so these results could be different when studied in other races. Third, reference cutoff values for hs-cTnI and NT-proBNP may be assay-specific, absolute cutoff values do not exist and they may vary from hospital to hospital. Fourth, the cutoff value of the predicted probability should not be implemented in isolation, and correlation with appropriate clinical assessment is needed.

6. Conclusion

Within ED patients assigned to the observe zone presenting with symptoms of chest pain, combination of hs-cTnI and NT-proBNP at presentation resulted in higher diagnostic value for AMI than hs-cTnI alone. The combined test outperformed hs-cTnI by correctly identifying nearly 14% more patients as low-risk and safe for early discharge. Future multi-center studies are needed to verify the results and to determine the best clinical use of combination of NT-proBNP and hs-cTnI in the early diagnosis of AMI.

Conflict of interests

The authors report no relationships that could be constructed as a conflict of interest.

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