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ORIGINAL ARTICLE

Diagnostic accuracy of high-sensitivity troponin I in an accelerated protocol to assess 30-day outcomes among chest pain patients in the emergency department

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Abstract

Introduction: In Malaysia, acute coronary syndrome is the leading cause of hospitalisation. Identification of patients with low 30-day risk of major adverse cardiac event (MACE) may facilitate an early and safe discharge from overcrowding emergency departments (ED). This study aimed to determine the diagnostic accuracy of high-sensitivity-cardiac-troponin-I (hs-cTnI) for ruling out 30-day MACE among chest pain patients in ED. *Materials and Methods*: A prospective observational study using an Accelerated Diagnostic Protocol (ADP) which included Thrombolysis-in-Myocardial-Infarction (TIMI) score, electrocardiogram, and 0- and 3-hour hs-cTnI. TIMI = 0 and ≤1 was used in ADP-1 and ADP-2, respectively. *Results:* 20 (10%) and 64 (32%) of 201 patients were low-risk, whereby none of whom developed MACE in ADP-1 and ADP-2, respectively. Using the overall hs-cTnI cut-off, ADP-1 had a Sensitivity (Sn) of 100% [95% Confidence Interval (CI)] (51.7 to 100), Specificity (Sp) of 10.2% (6.5 to 15.6), Negative Predictive Value (NPV) of 100% (80.0 to 100) and Positive Predictive Value (PPV) 3.3% (1.4 to 7.4). ADP-2 yielded a Sn of 100% (51.7 to 100), Sp of 32.8% (26.4 to 40.0), NPV of 100% (92.9 to 100) and PPV of 4.4% (1.8 to 9.7). Using gender-specific hs-cTnI cut-off, either that of Abbott or a Malaysian population, yielded similar diagnostic accuracy; except the former produced slightly higher Sp of 75.4% (68.7-81.1). *Conclusion:* Using either the overall or gender-specific cut-offs, both protocols yielded 100% diagnostic accuracy for ruling out MACE which may enable a safe early discharge of up to 32% of chest pain patients in ED.

Keywords: High-sensitivity-troponin I (hsTnI), Accelerated Diagnostic Protocol (ADP), diagnostic accuracy, major adverse cardiac effect (MACE), emergency department.

INTRODUCTION

In Malaysia, acute coronary syndrome (ACS) represents a large number of hospitalisations.[1] Occurring in 141 per 100,000 populations per year, ST-elevation myocardial infarction (STEMI) accounts for the majority (46.1%) of acute coronary syndrome (ACS); followed by unstable angina (UA) (28.7%) and non-ST-elevation myocardial infarction (NSTEMI) (25.2%).[2] Although STEMI patients are known to have the highest mortality rate,[3] NSTEMI patients still carry a poorer long-term prognosis, whereby they are at risk of developing major adverse cardiac events (MACE), with a 30-day mortality of 9.2%.[3,4] It was reported that at 1-year post-ACS, NSTEMI patients had a higher mortality rate of 23% compared to STEMI patients of 17.9%.[5] As such, early assessment should incorporate risk stratification using one of the risk scoring systems, such as Thrombolysis in

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Myocardial Infarction (TIMI) Risk Score.[6] Such stratification conveys prognostic information and dictates patient management.[7]

Also in Malaysia, emergency department (ED) overcrowding is a well-known and ongoing challenge[1], particularly in public hospitals.[8] It has been reported that 23.6% (104 out of 440) of critically ill patients in ED presented with ACS, with the leading symptom of chest pain, majority [20% (87 out of 104)] of which, was attributed to NSTEMI and UA .[9] In such an acute setting, early identification of both chest pain patients with an ACS and those at very minimal short-term (30-days) risk of cardiac adverse effect is of paramount importance, allowing an earlier but safe discharge, with proper follow-up in an outpatient setting for any objective further evaluation.[10] Thus, this would potentially avoid unnecessary inpatient admissions and can therefore reduce ED overcrowding.

Oftentimes, clinical presentation of patients with a life-threatening ACS overlap that of patients subsequently found to be non-ACS, hence the importance of cardiac biomarkers in assisting the diagnosis.[11] Serial testing of cardiac biomarkers is essential in differentiating NSTEMI from UA, whilst detection of a rise and/or fall pattern further differentiates an acute myocardial injury from a chronic event such as congestive heart failure.[12]

Troponin, a myofibril protein physiologically involved in myocardial muscle contraction, is now the preferred cardiac biomarker mainly due to its superior cardio-specificity and analytical sensitivity.[12] Since its first generation, troponin assays have evolved substantially.[11] With a 100-fold increase in the analytical sensitivity, the high-sensitivity cardiac troponin (hs-cTn) assay is now able to quantify myocardial necrosis as small as 1 gram.[11] With the advent of a high-sensitivity cardiac troponin I (hs-cTnI) assay, an earlier detection of myocardial injury is now possible compared to that of conventional troponin assay.[11,13] The latter requires a serial testing of at least 6 hours apart to detect the rise or fall of troponin for diagnosis of NSTEMI/UA, which may compound the issue of overcrowding as well as delays in commencing treatment and the need for admissions for ruling out acute myocardial infarction (AMI).[14] Incorporating a hs-cTn assay, serial testing can be done much earlier and therefore protocols using hs-cTn assays can thus accelerate the ruling of AMI patients with low risk of serious short-term cardiac adverse effects, who are safe for earlier discharge.[14]

The objective of this study was to determine the diagnostic performance of an hs-cTnI assay in combination with a TIMI score of 1 or less in a 3-h Accelerated Diagnostic Protocol (ADP) for assessing chest pain patients with probable NSTEMI/UA in the ED, Serdang Hospital. Identification of patients at low-risk, often defined as having a <1-2% risk of developing MACE at 30 days who are safe for early discharge may help reduce unnecessary admission and ED overcrowding.[15] Globally, similar protocols have been previously evaluated and reviewed.[10,16-18]

MATERIALS AND METHODS

Study design and subjects

This was a prospective observational study. A calculated sample size of 130 was generated using a formula based on specificity. Consecutive Malaysian patients of 18 years and older presenting to the ED with a complaint of chest pain with onset within 12 hours of presentation and electrocardiogram (ECG) changes of NSTEMI were recruited, following written informed consent. Patients were excluded if they were non-Malaysian, had a STEMI, or other non-atheroma cardiac ischaemic causes such as sepsis, hypertensive emergency or anaemia. Overall recruitment occurred between November 2016 and June 2017.

Ethics approval

This study was in accordance with the principles of the Declaration of Helsinki and approved by the Medical Research Ethics Committee, Ministry of Health Malaysia [NMMR-14-191223214 (IIR)].

Procedures

Patients were treated with normal care in accordance with the practice at the local hospital, including measurement of high-sensitivity-cardiac-troponin T (hs-cTnT) at presentation and serially as clinically indicated. The results of the index tests were not revealed to the attending clinicians and hs-cTnT results were used in patient management. Follow up on patients within 30 days (including initial hospital attendance) was done using telephone and hospital records. A MACE is considered as any of the following conditions, namely AMI, cardiac arrest, death (cardiac), emergency revascularisation, cardiogenic shock, ventricular arrhythmia or high atrioventricular block needing intervention.[19] Adjudication of MACE was performed by a cardiologist, who was unaware

of the outcome of the index test but was aware of ECG and the serial hs-cTnT results from the normal care. AMI was diagnosed in the presence of myocardial necrosis associated with a clinical setting consistent with myocardial ischaemia and in the presence of at least one hs-cTnI value exceeding the 99th percentile with rise/fall pattern.[12] Blood samples for hs-cTnI were collected at presentation and 3 hours later, centrifuged and serum was frozen in aliquots at -80°C until analysis. The hs-cTnI analysis was done on the Architect i2000sr analyser in the Pathology Department, Serdang Hospital, with a limit of detection (LOD) of 5 ng/L and an overall 99th percentile cut-off points of 26.2 ng/L with a corresponding coefficient of variation (CV) of 4%. Analysis was also done using gender-specific hs-cTnI cut-offs, of female > 15.6 ng/L or >18.6 ng/L and male > 34.2 ng/L or > 29.9 ng/L, as recommended by the manufacturer or based on a Malaysian population, respectively.[20] The diagnostic protocols in this study included a combination of 1) TIMI score, 2) ECG and 3) hs-cTnI values at 0 and 3 h. The ADP is considered negative when all parameters were negative and patient is categorised as low risk of developing 30-day MACE. In ADP-1, low-risk patients were those with a TIMI score of 0, no new ischaemic ECG changes and 0- and 3-h hs-cTnI ≤ the cut-offs. In ADP-2, low risk patients had a TIMI≤1 (0 or 1) with no ischaemic ECG changes and 0- and 3-h hs-cTnI ≤ the chosen cut-offs.

Statistical analysis

Statistical analyses were done using the IBM SPSS Statistics for Windows, Version 22.0, SPSS Inc., Armonk, NY: IBM Corp). Baseline characteristics of the subjects were determined. The mean ± standard deviation (SD) and median ± interquartile range (IQR) were reported for continuous variables. For categorical data, the proportions in each of the ADP-positive and –negative groups were determined. Chi-square analyses were used to determine the sensitivity (Sn), specificity (Sp), positive and negative predictive values (PPV and NPV, respectively) for the primary event (30-day MACE) for each ADP and its members individually or in combination.

RESULTS

Two hundred and five patients were recruited, with 4 excluded patients (unavailable during follow-up) (FIG 1). Study subjects were mostly older than 50 years Malay men with TIMI>1 and dyslipidaemia being the most common cardiovascular disease (CVD) risk factor (TABLE 1). A total of 6 (3.0%) patients had MACE within 30 days, four were NSTEMI (TABLE 2).

Incorporating hsTnI with a TIMI≤1 (ADP 2) classified 32% (64 out of 201) of patients as low risk of developing a 30-day MACE (TABLE 3). Fewer patients, 10% (20 out of 201), were

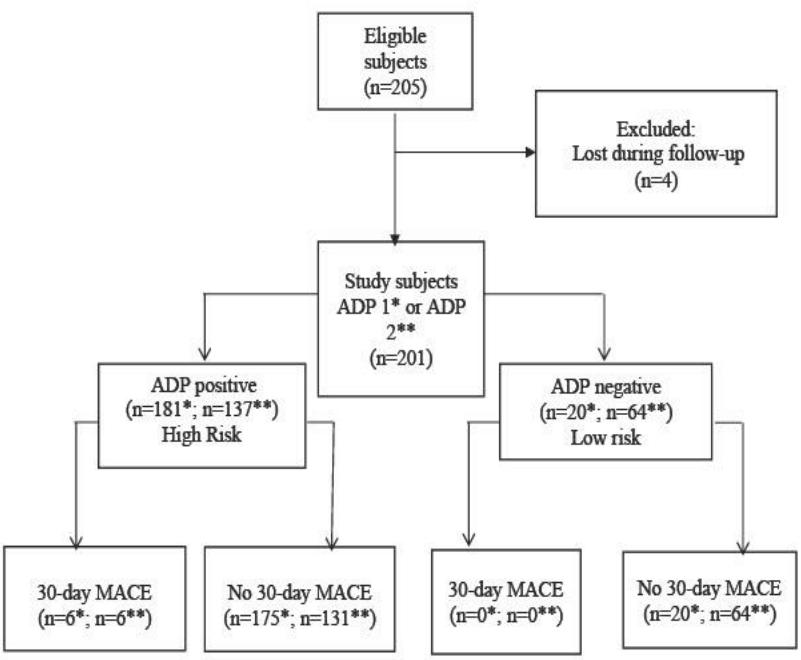

Figure 1: Flow chart of the study activities

TABLE 1: Baseline characteristics of the study population

Variable	(N=201) N (%)
Age	
<50 years	61 (30)
≥50 years	140 (70)
Gender	
Male	144 (72)
Female	57 (28)
Ethnicity	
Malay	108 (54)
Chinese	49 (24)
Indian	44 (22)
Risk factor*	
Hypertension	99 (49)
Diabetes Mellitus	85 (42)
Dyslipidaemia	108 (54)
Family history	43 (21)
Smoking (Current)	50 (25)
TIMI score	
≤1	76 (38)
>1	125 (62)

TIMI: Thrombolysis-in-Myocardial-Infarction; *total number of patients in all categories exceeds the study population (n=201) due to multiple factors reported by individual patients

classified as low risk when using TIMI=0 (ADP 1) (TABLE 3). TABLE 4 shows the diagnostic accuracy [95% Confidence Interval (CI)] of the parameters of ADP 1 and 2, either alone or in different combinations. In this study, utilisation of hs-cTnI based on either the overall or gender-specific (TABLE 4) cut-off in ADP 1 and ADP 2 yielded the same Sn of 100% (95% CI: 51.7-100) and NPV of 100% (95% CI: 80.0-100 and 92.9 to 100 for ADP-1 and ADP-2, respectively). Using TIMI=0 alone gave the same sensitivity of 100% (95% CI: 51.7-100) NPV of 100% (95% CI: 82.2 to 100); whilst TIMI≤1 alone yielded a lower sensitivity of 66.7 (95% CI: 24.1-94.0) and NPV of 97.4% (95% CI: 90.0-99.5) (TABLE 4). Utilisation of hs-cTnI alone gave the second highest NPV of 99.3% (95% CI: 95.6 to 100) (TABLE 4).

TABLE 2: Frequency of major adverse cardiac events during initial hospital attendance or 30-day follow-up

Major Adverse Cardiac Event	No of Event (n=6)
NSTEMI	4
STEMI	0
Cardiac Arrest	0
Cardiovascular Death	0
Cardiogenic Shock	1
Emergency Revascularisation	1

NSTEMI non-ST elevation myocardial infarction; STEMI ST-elevation myocardial infarction

DISCUSSION

In this study, the average age of the study participants was 55.3 years, of whom were predominantly older (≥50 years old) Malay men (TABLE 1). Similarly, the study population reflected the national data of predominantly Malay male NSTEMI and UA patients.[21] The mean age of the study participants was, however, lower compared to those of NSTEMI and UA patients reported by the registry, of 61.1 and 60.2 years, respectively.[21] Also, a higher proportion (30%) of patients 50 years and younger was seen in this study, in contrast to the national data of about 18% and 19% of NSTEMI and UA patients, respectively (which in combination made up to roughly 19%).[21]

Among ACS patients (including STEMI) reported in the national registry, the commonest CVD risk factor was hypertension (65%), followed by diabetes mellitus (DM) (46%) and dyslipidaemia (39%).[21] In contrast, hypertension was the second most common risk factor among the current study participants (49%), followed by DM (42%), whilst the commonest risk factor was dyslipidaemia (54%). Similar studies among STEMI/UA patients in other populations showed that the commonest CVD risk factor was a family history of coronary artery disease followed by hypertension and dyslipidaemia.[17,18]

In this study, most patients (62%) were high-risk of CVD (TIMI >1), with only 38% of patients defined as low risk (TIMI ≤ 1) (TABLE 1), which might be partly explained by Serdang Hospital being a tertiary cardiac referral centre. Using a common hs-cTnI cut-off point of 26.2 ng/L, ADP 1 (TIMI = 0, 0 and 3 hours hsTnI <26.2ng/L and negative ECG) identified 20 patients (10%) as low risk (TABLE 3). None of them developed MACE, although 2 patients presented with recurrent chest pain to ED within 30 days, they were adjudicated as unstable angina, which was not a MACE. ADP 2 using TIMI score ≤ 1 (as opposed to TIMI 0) classified 64 (32%) patients as low risk (TABLE 3). Interestingly, their 0-h

TABLE 3: Occurrence of major adverse cardiac events during initial hospital attendance or 30-day follow-up according to individual and combinations of the ADP test parameters (overall and gender-specific hsTnI cut-off)

		MACE (n=6) n (%)			No MACE (n=195) n (%)			Total (n=201) n (%)		
		Overall	Gender-specific		Overall	Gender-specific		Overall	Gender-specific	
		Abbott^	Abbott~	Malaysian~~	Abbott^	Abbott~	Malaysian~~	Abbott^	Abbott~	Malaysian~~
ECG ∞	Positive	1 (17)	1 (17)	1 (17)	13 (7)	13 (7)	13 (7)	14 (7)	14 (7)	14 (7)
	Negative	5 (83)	5 (83)	5 (83)	182 (93)	182 (93)	182 (93)	187 (93)	187 (93)	187 (93)
TIMI = 0	Positive*	6 (100)	6 (100)	6 (100)	172 (88)	172 (88)	172 (88)	178 (89)	178 (89)	178 (89)
	Negative	0(0)	0(0)	0(0)	23 (12)	23 (12)	23 (12)	23 (11)	23 (11)	23 (11)
TIMI ≤ 1	Positive**	4 (67)	4 (67)	4 (67)	121 (62)	121 (62)	121 (62)	125 (62)	125 (62)	125 (62)
	Negative	2 (33)	2 (33)	2 (33)	74 (38)	74 (38)	74 (38)	76 (38)	76 (38)	76 (38)
hs-TnI	Positive^^	5 (83)	5 (83)	5 (83)	54 (28)	48 (25)	54 (28)	59 (29)	53 (26)	59 (29)
	Negative	1 (17)	1 (17)	1 (17)	141 (72)	147 (75)	141 (72)	142 (71)	148 (74)	142 (71)
ADP 1	Positive#	6 (100)	6 (100)	6 (100)	175 (90)	175 (90)	175 (90)	181 (90)	181 (90)	181 (90)
	Negative	0 (0)	0 (0)	0 (0)	20 (10)	20 (10)	20 (10)	20 (10)	20 (10)	20 (10)
ADP 2	Positive $	6 (100)	6 (100)	6 (100)	131 (67)	131 (67)	131 (67)	137 (68)	137 (68)	137 (68)
	Negative	0 (0)	0 (0)	0 (0)	64 (33)	64 (33)	64 (33)	64 (32)	64 (32)	64 (32)

MACE: major adverse cardiac event; ECG: electrocardiogram; TIMI: Thrombolysis-in-Myocardial-Infarction; hs-cTnI: high-sensitivity troponin I; ADP: Accelerated Diagnostic Protocol; ∞ ECG any new ischemia at 0h is positive; *TIMI ≥1 is positive; ** TIMI ≥2 is positive; ^^ hsTnI at 0 or 3 h > cut-off (^,~,~~) is positive; # Any new ischaemia at 0 h or 0- or 3 h hsTnI > cut-off (^,~, ~~) or TIMI ≥1 is positive; $ Any new ischaemia at 0 or 3 h or 0- or 3 h hsTnI > cut-off (^,~, ~~) or TIMI ≥2 is positive; ^ hsTnI at 0 or 3 h > 26.2 ng/L was positive; ~ Abbott gender-specific hsTnI cut-off [>15.6 ng/L (female) or >34.2 ng/L (male)]; ~~ Malaysian population gender-specific hsTnI cut-off [>18.6 ng/L (female) or >29.9 ng/L (male)]

TABLE 4: Diagnostic accuracy (95% CI) of ECG, hsTnI, TIMI, and ADP for the exclusion of MACE (Overall and Gender-specific hsTnI cut-offs)

	Sensitivity			Specificity			Negative Predictive Value			Positive Predictive Value		
	Overall	Gender-specific		Overall	Gender-specific		Overall	Gender-specific		Overall	Gender-specific	
	Abbott ^	Abbott ~	Malaysian ~~	Abbott ^	Abbott~	Malaysian ~~	Abbott ^	Abbott ~	Malaysian ~~	Abbott^	Abbott ~	Malaysian ~~
ECG ∞	16.7 (0.9- 63.5)	16.7 (0.9- 63.5)	16.7 (0.9- 63.5)	93.3 (88.6-96.2)	93.3 (88.6-96.2)	93.3 (88.6-96.2)	97.3 (93.5- 99.0)	97.3 (93.5- 99.0)	97.3 (93.5- 99.0)	7.1 (0.4-35.8)	7.1 (0.4-35.8)	7.1 (0.4-35.8)
TIMI = 0*	100 (51.7-100)	100 (51.7-100)	100 (51.7-100)	11.8 (7.8-17.4)	11.8 (7.8-17.4)	11.8 (7.8-17.4)	100 (82.2-100)	100 (82.2-100)	100 (82.2-100)	3.4 (1.4-7.5)	3.4 (1.4-7.5)	3.4 (1.4-7.5)
TIMI ≤ 1**	66.7 (24.1-94.0)	66.7 (24.1-94.0)	66.7 (24.1-94.0)	37.9 (31.2- 45.2)	37.9 (31.2- 45.2)	37.9 (31.2- 45.2)	97.4 (90.0-99.5)	97.4 (90.0-99.5)	97.4 (90.0-99.5)	3.2 (1.0-8.5)	3.2 (1.0-8.5)	3.2 (1.0-8.5)
hsTnI^^	83.3 (36.5-99.1)	83.3 (36.5-99.1)	83.3 (36.5-99.1)	72 .3 (65.4-78.3)	75.4 (68.7-81.1)	72 .3 (65.4-78.3)	99.3 (95.6-100)	99.3 (95.7-100)	99.3 (95.6-100)	8.5 (3.2-19.4)	9.4 (3.5-21.4)	8.5 (3.2-19.4)
ADP 1 #	100 (51.7-100)	100 (51.7-100)	100 (51.7-100)	10.2 (6.5-15.6)	10.2 (6.5-15.6)	10.2 (6.5-15.6)	100 (80.0-100)	100 (80.0-100)	100 (80.0-100)	3.3 (1.4-7.4)	3.3 (1.4-7.4)	3.3 (1.4-7.4)
ADP 2 $	100 (51.7-100)	100 (51.7-100)	100 (51.7-100)	32.8 (26.4-40.0)	32.8 (26.4-40.0)	32.8 (26.4-40.0)	100 (92.9-100)	100 (92.9-100)	100 (92.9-100)	4.4 (1.8-9.7)	4.4 (1.8-9.7)	4.4 (1.8-9.7)

MACE: major adverse cardiac event; ECG: electrocardiogram; TIMI: Thrombolysis-in-Myocardial-Infarction; hs-cTnI: high-sensitivity troponin I; ADP: Accelerated Diagnostic Protocol; ∞ ECG any new ischemia at 0h is positive; *TIMI ≥1 is positive; ** TIMI ≥2 is positive; ^^ hsTnI at 0 or 3 h > cut-off (^,~,~~) is positive; # Any new ischaemia at 0 h or 0- or 3 h hsTnI > cut-off (~, ~~) or TIMI ≥1 is positive; $ Any new ischaemia at 0 or 3 h or 0- or 3 h hsTnI > cut-off (~, ~~) or TIMI ≥2 is positive; ^ hsTnI at 0 or 3 h > 26.2 ng/L was positive; ~ Abbott gender-specific hsTnI cut-off [>15.6 ng/L (female) or >34.2 ng/L (male)]; ~~ Malaysian population gender-specific hsTnI cut-off [>18.6 ng/L (female) or >29.9 ng/L (male)]

hs-cTnI of <5 ng/L could had been used for their earlier discharge as shown in a rule-out AMI protocol based on a single test.[22] In this study, one of the six ADP-positive patients who developed 30-day MACE had a negative 0- and 3- hs-cTnI levels, based on either overall or gender-specific cut-offs. Interestingly, however, he had a detectable (above the LOD) 0-h hs-cTnI level of 18.9 ng/L. This was in keeping with previous findings of the reliability of such very low level of hs-cTn in identifying patients at risk of 30-day adverse effects.[23]

This study investigated the clinical utility of the hs-cTnI assay in a 3-h protocol for assessment of chest pain patients with possible AMI in ED. Incorporation of TIMI=0 categorised approximately 10% of ED chest pain patients as low risk of 30-day MACE; whilst that of TIMI≤1, trebled the number to about 30% of patients, while Sn and NPV remain the same in both protocols. Thus, suggesting that up to 30% of chest pain patients with possible ACS could be rapidly and safely discharged from ED and therefore helps to reduce ED overcrowding, utilisation of healthcare resources and patient inconvenience.[24] Similar pattern of results was seen in the previous study incorporating the two TIMI scores (either 0 or ≤1), ECG and hs-cTnI assay in a 2-hr protocol, whereby the proportion of low-risk patients almost doubled from about 20% to about 40% when using TIMI=0 and TIMI≤1, respectively.[18]

A previous study utilising TIMI score 0, identified 9.8% of subjects as low risk with a Sn for a 30-day MACE of 99.3% (95% CI: 97.9 to 99.8) and NPV of 99.1% (95% CI: 97.3 to 99.8).[16] The ADP, however, had utilised multiple cardiac biomarkers [contemporary troponin, myoglobin, creatine kinase-MB (CKMB)] on a point-of-care setting.[16] Another study which utilised a TIMI score 0 with a contemporary troponin assay classified 20% of subjects as low risk, with a Sn for 30-day MACE of 99.7% (95% CI: 98.1 to 99.9) and NPV of 99.7% (95% CI: 98.6 to 100).[17]

By using a TIMI score of 0, and a hs-cTnI, Cullen et al.[18] identified 19.6 % of subjects as low risk, none of whom had MACE. This ADP had a Sn of 100.0% (95% CI: 98.5 to 100) and NPV of 100% (95% CI: 98.5 to 100). In the same study, by incorporating a TIMI of ≤1 identified 41.5% of subjects as low risk, 2 of whom had MACE, resulting in a Sn of 99.2% (95% CI: 97.1 to 99.8) and NPV of 99.7% (95% CI: 98.9 to 99.9).[18] Similarly, a previous study using hs-cTnT and TIMI ≤1 which identified 34.5% and 45% of chest pain subjects in ED as low risk also yielded a Sn of 100% and 97.4%, in their derivation and validation cohort, respectively.[25]

In summary, although the Sn values achieved by contemporary troponin assay almost reached 100%, in some of these previous studies, it might be of higher cost as multiple biomarkers were included and of inferior diagnostic accuracy as contemporary troponin and point-of-care assay were used.[16,23,26] In contrast, incorporation of a hs-cTn assays into a clinical protocol for early ruling out an event has consistently shown a higher diagnostic accuracy performance.[10,18,25]

In this study, individual diagnostic parameter was not as effective at identifying patients who were at risk of MACE as using a combination of the parameters (TABLE 3). Interestingly, TIMI =0 yielded the same Sn and NPV values as both ADPs, albeit at a lower specificity (TABLE 4). However, gender-specific hs-cTnI cut-offs showed minimal effect on the performance of the ADPs, whereby the overall or both gender-specific cut-offs produced similar diagnostic accuracy for ruling out 30-days MACE in these patients (TABLE 4). Similar minimal impact of utilising gender-specific hs-cTnI cut-offs has been previously shown in several risk stratification ADPs.[10] Nevertheless, using the Abbott gender-specific gave rise to a less false positive rate (48 vs 54 by the overall or Abbott gender-specific cut-offs) (TABLE 4), with slightly higher Sp for 30-day MACE of 75.4 (95% CI: 68.7-81.1) (TABLE 3) compared with the overall or Malaysian population-based gender-specific cut-offs.

With several rule-out strategies being currently adopted, including accelerated diagnostic protocols in combination with a risk score, such as used in this study, harmonisation of clinical utilisation of hscTn has not yet been achieved.[23,27] Nevertheless, compared to the contemporary troponin assays, which require up to 6 hour or longer post-admission repeat testing, hscTn assays have significantly expedited the serial sampling interval, with most diagnoses achieved within 3 hour from initial testing.[23]

Although the use of gender-specific URL values has been endorsed by the international bodies,[12] with recent recommendation of the use of quality control (QC) levels covering these upper reference limits (URLs), their clinical utilities have yet to be fully proven, as discussed earlier and cited by Thygesen *et al*.,[12] Apple *et al*.,[23] and Wu *et al*.[28] Similarly, this study showed

that utilisation of the overall or either Abbott or a Malaysian population-based gender-specific hsTnI cut-off is equally accurate at ruling out 30-days MACE in chest pain patients in ED. Of note, since the determination of gender-specific URL in Malaysia by Lim *et al*.[20] more stringent international criteria of 300 participants of each gender, using a health questionnaire and surrogate biomarkers to detect underlying cardiovascular confounders, have been recommended.[20,28]

Strengths and Limitations

This study reported an observational experiment of incorporation of a hs-TnI assay into an accelerated diagnostic protocol in an ED setting at a local tertiary hospital in Malaysia. The study population displayed similar demographic features as compared to a recent ACS registry of the Malaysian population.[21] This study also prospectively included consecutive patients including those presented during out of hours, which would be applicable to an ED setting. Nevertheless, this was a single-center study in a tertiary cardiac referral hospital. The follow-up of MACE was carried out via telephone call, which might limit the information provided by patients. Despite all efforts, in this study, misclassification of NSTEMI and UA patients might occur given that the increment in cTn may be delayed in about 1% of the NSTEMI patients, as cited in Meller *et al*.[25] As the current study was an observational diagnostic study, future interventional studies utilising the protocol using hs-cTnI is recommended.

CONCLUSION

In conclusion, this study supported the use of hs-cTnI in a risk stratification accelerated diagnostic protocol to discharge ED chest pain patients safely and rapidly with proper outpatient follow-up. Except for its higher specificity for 30-day MACE, this study showed that in ruling out 30-day MACE, the use of gender-specific cut-offs were not superior to that of overall cut-off, as it did not improve diagnostic accuracy of hs-cTnI. In this study, hs-cTnI in combination with TIMI≤1 had the potential to reduce ED overcrowding by 32%, while maintaining >99% Sn and NPV. The high-risk study cohort, which was reflective of the Malaysian general population, thus supported the use of TIMI≤1 in an ED setting in Malaysia. Nevertheless, incorporation of any protocol will depend upon local clinical needs and logistical constraints such as availability of medical staffs or hs-cTn tests.

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