Original Article

Correlation of High-Sensitivity Cardiac Troponin T and SYNTAX Score in Stable Coronary Disease

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Background: Elevated high-sensitivity cardiac troponin T (hs-cTNT) in stable coronary artery disease (CAD) was associated with cardiovascular death and heart failure. The relationship of hs-cTNT and coronary anatomical complexity was investigated in a previous cross-sectional study, however, there was no previous data in Thailand. The authors used Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score to represent coronary anatomical complexity.

Objective: To assess the correlation of hs-cTNT and coronary anatomical complexity represented by SYNTAX scores in stable CAD patients.

Materials and Methods: An hs-cTNT in stable patients undergoing pharmacological stress testing study had been previously conducted. The present single center prospective cohort study enrolled 250 consecutive patients with suspected CAD who underwent pharmacological stress magnetic resonance imaging (MRI) between January 2010 and November 2013. It demonstrated pattern of troponin release during pharmacological stress testing, which was different according to the ischemic burden. The present study enrolled the patients from the previous cohort, whose baseline hs-cTNT were taken before pharmacological stress test, and underwent coronary angiography (CAG) within six months. The authors excluded the patients with significant valvular heart disease, hypertrophic cardiomyopathy, pulmonary embolism, clinically significant pulmonary hypertension, CKD stage 4 to 5, left ventricular ejection fraction (LVEF) of less than 30%, and previous CABG. The patients admitted for acute chest pain or having dynamic EKG change at rest within 30 days before enrollment were also excluded.

Results: Correlation coefficient between SYNTAX and hs-cTNT is 0.403 (r_s=0.09 to 0.64, p=0.013), which is a fair correlation. Using the hs-cTNT cutoff 5 ng/L, it had sensitivity of 80% and negative predictive value (NPV) of 80% to detect the high anatomical burden patients. The patients who were hospitalized due to angina had higher hs-cTNT of 17 versus 6 ng/L (p=0.032). Those who died had higher hs-cTNT of 25 versus 6 ng/L (p=0.012). All patients with hs-cTNT level lower than upper normal limit (13.5 ng/L) were alive at five years.

Conclusion: Hs-cTNT was fairly correlated with SYNTAX score and associated with worse clinical outcomes.

Keywords: High-sensitivity cardiac troponin T, SYNTAX score, Stable coronary artery disease

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High-sensitivity cardiac troponin T (hs-cTNT) is a cardiac biomarker used to detect myocardial necrosis. There are well established criteria using hs-cTNT to diagnose acute myocardial infarction[1]. Association between hs-cTNT level and severity of stable coronary artery disease (CAD) has been studied in stable CAD. A previous study found association between elevated hs-cTNT and cardiovascular death and heart failure in stable CAD[2].

Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score is a coronary angiographic scoring system used to evaluate anatomical complexity, which leads to appropriate mode of revascularization. Patients with high SYNTAX score are related to worse clinical outcome[3,4].

A previous study[5] investigated for relationship of hs-cTNT and coronary anatomical complexity by using SYNTAX score to determine the anatomical complexity. The study has shown patients with higher

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hs-cTNT had significantly higher SYNTAX score[5]. There was no previous data in Thailand.

Materials and Methods

Study population

A study of the hs-cTNT in stable patients undergoing a pharmacological stress testing had been previously conducted. The present study was a single center prospective cohort study that enrolled consecutive 250 patients with suspected CAD whom underwent pharmacological stress magnetic resonance imaging (MRI) between January 2010 and November 2013. It demonstrated the pattern of troponin release during pharmacological stress testing, which was different according to the ischemic burden[6]. The present study enrolled the patients from the previous cohort, whose baseline hs-cTNT was taken before the pharmacological stress test and underwent coronary angiography (CAG) within six months. The hs-cTNT is specific to myocardial injury, not specific to CAD. Some conditions may cause elevation of hs-cTNT such as cardiomyopathy, heart failure, chronic kidney disease (CKD), pulmonary embolism, pulmonary hypertension leading to exclusion criteria for the present study. Also excluded were the patients with significant valvular heart disease (severe valvular heart disease from echocardiography or cardiac MRI), hypertrophic cardiomyopathy (documented by echocardiography or cardiac MRI), pulmonary embolism, clinically significant pulmonary hypertension (clinical of right side heart failure with TR velocity greater than 3.4 m/second, PA systolic pressure greater than 50 mmHg from echocardiogram), CKD stage 4 to 5 (calculated eGFR by CKF-EPI formula of less than 30 ml/minute), left ventricular ejection fraction (LVEF) of less than 30% (measured by cardiac MRI), and previous coronary artery bypass graft (CABG). All patients were more than 18 years old and had suspected stable CAD. The patients hospitalized for acute chest pain or had dynamic EKG change at rest within 30 days before enrollment were also excluded. The Siriraj Institution Review Board approved the present study protocol and each participant provided inform consent. Investigations were in accordance with the Declaration of Helsinki.

High-sensitivity cardiac troponin T

Blood sample for hs-cTnT levels were obtained at baseline before the pharmacological stress testing. Serum hs-cTnT levels were measured by an immunoassay using electrochemiluminescence technology. It had a lower limit of significance of 5 ng/L and a coefficient of variation at the 99th percentile reference limit (13.5 ng/L) of 9%, which met the recommended guideline (less than 10% coefficient of variation at 99th percentile reference limit)[7].

Angiographic assessment and SYNTAX score calculation[8]

Based on coronary angiogram analysis, significant coronary lesion was defined as 50% or more diameter stenosis in vessel of 1.5 mm or more in diameter. SYNTAX score was calculated using algorithm at the SYNTAX website. SYNTAX scores were assessed by Pengchata P and Chunhamaneewat N. When there were discordant opinions, the lesions were assessed by Wongpraparut N independently. The analysis was blind to hs-cTNT level.

Primary outcome

The study was designed to demonstrate the correlation between hs-cTNT and SYNTAX score.

Clinical outcomes

The secondary outcomes were all cause mortality, myocardial infarction, and hospitalization due to angina in five years. For the patients who did not have follow-up visits at Siriraj Hospital, telephone follow-up interviews were obtained.

Statistical analysis

Continuous variables were expressed as median and interquartile range for non-normal distribution data and mean ± standard deviation (SD) for normal distribution data. Comparison of continuous variables were performed using the spearman range correlation. Mann-Whitney U test was used to identify the association between hs-cTNT, SYNTAX score and clinical events.

The patients were classified from angiographic data into two groups, high and low anatomical burden. High anatomical burden group was defined if SYNTAX score was more than 22 for non-left main disease and more than 32 for LM disease as per the 2014 ESC guideline for myocardial revascularization, for which CABG was recommended[10]. Pearson Chi-square test was used to evaluate the association between high SYNTAX score and hs-cTNT.

No previous study showed correlation coefficient of SYNTAX score and hs-cTNT. Correlation between SYNTAX score and percent ischemic defect score from ^{99m}Tc-sestamibi SPECT was r=0.647 from the previous study[9]. As the authors estimated that the

correlation coefficient of SYNTAX score and hs-cTNT was 0.5, at power 90%, 38 patients were required to determine the statistical significance. Analyses were performed with IBM SPSS statistical version 20.0.

Results

Patient enrollment

The overall cohort had 250 patients. Among these, 44 patients underwent coronary angiogram and had hs-cTNT within six months (gap between coronary angiogram and hs-cTNT was two months). Four of them were excluded due to severe left ventricular systolic dysfunction. One patient had GFR of less than 30 ml/minute/1.73 m². One patient had severe aortic stenosis. One patient had history of CABG. Therefore, 37 patients enrolled in the present study.

- 250 patients (overall cohort)
- 44 patients (underwent CAG and had hs-cTNT drawn within six months)
- Exclusion (seven patients)

4 severe left ventricular systolic dysfunction (LVEF of less than 30%)

1 GFR of less than 30 ml/minute/1.73 m²

1 severe AS

1 prior CABG

- 37 patients (enrolled in our study)

Patient characteristics

The mean age was 65 years and 43.2% were males. The most frequent presenting symptom was angina (51%), followed by dyspnea on exertion (40%). The major comorbidities were hypertension (83.8%), dyslipidemia (75.7%), and diabetes (48.6%). Median of LVEF was 60% and median of eGFR was 60 ml/minute/1.73 m² (Table 1).

The range of hs-cTNT level was 0 to 190 ng/L, the median was 7 ng/l (0 to 15.5). Twenty-seven percent of the patients had hs-cTNT below limit of significance, 30% of the patients had hs-cTNT more than the 99 percentile of the reference limit. The median SYNTAX score was 17 (Figure 1).

Primary outcome

Correlation coefficient between SYNTAX and hs-cTNT was 0.403 (r_s=0.09 to 0.64, p=0.013) (Figure 2).

SYNTAX score was insignificantly higher in the patients with elevated hs-cTNT. Median of SYNTAX scores in the patients with hs-cTNT of 13.5 ng/L or more was 21 (19.25 to 31.25), and in the patients with hs-cTNT of less than 13.5 ng/L was 11 (2 to 24) with p-value of 0.103 (Figure 3).

Table 1. Baseline characteristics (n = 37)

	n (%)
Age (years), Mean±SD	65.7±9.9
Male	16 (43.2)
Presenting symptom	
Angina	19 (51.3)
Dyspnea on exertion	15 (40.5)
Other	3 (7.2)
Underlying disease	
Diabetes mellitus	18 (48.6)
Hypertension	31 (83.8)
Dyslipidemia	28 (75.7)
Prior PCI	4 (13.5)
Left ventricular ejection fraction, Median (25 to75 percentile)	60 (46.7 to 68)
Creatinine (mg/dl), Median (25 to75 percentile)	0.98 (0.8 to 1)
GFR (ml/minute/1.73 m²), Median (25 to75 percentile)	60.7 (47 to 78)
Medication prior to angiography, %	
Aspirin	83.8
Clopidogrel	37.8
Beta-blocker	64.9
ACEI	27.0
ARB	40.5
Calcium antagonist	21.6
Statin	78.4
SYNTAX score, Median (25 to75 percentile)	17 (5 to 27.5)
Coronary artery disease, %	
Left main disease	16.2
Single vessel disease	16.2
Double vessel disease	37.8
Triple vessel disease	29.7
Insignificant stenosis (<50%)	16.2
Revascularization, %	
PCI	43.2
CABG	16.2
hs-cTNT (ng/L), Median (25 to75 percentile)	7 (0 to 15.5)
Month between TNT and coronary angiogram, Median (25 to75 percentile)	2 (1 to 3)

SD=standard deviation; PCI=percutaneous coronary intervention; GFR=glomerular filtration rate; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; CABG=coronary artery bypass graft; hs-cTNT=high-sensitivity cardiac troponin T

Table 2. Detection the patient with high anatomical burden: SYNTAX >22 (non-left main disease) and >33 for LM disease[10]

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Odd ratio (95% CI)	p-value
hs-cTNT ≥5 ng/L	80 (79.2 to 80.8)	29.6 (29.1 to 30.2)	29.6 (29.1 to 30.2)	80 (79.2 to 80.8)	1.68 (0.291 to 9.75)	0.558
hs-cTNT ≥13.5 ng/L	40 (39.0 to 40.1)	74 (73.5 to 74.6)	36 (35.5 to 37.3)	76.9 (76.4 to 77.4)	1.9 (0.412 to 8.798)	0.406

CI=confidence interval; PPV=positive predictive value; NPV=negative predictive value; hs-cTNT=high-sensitivity cardiac troponin T

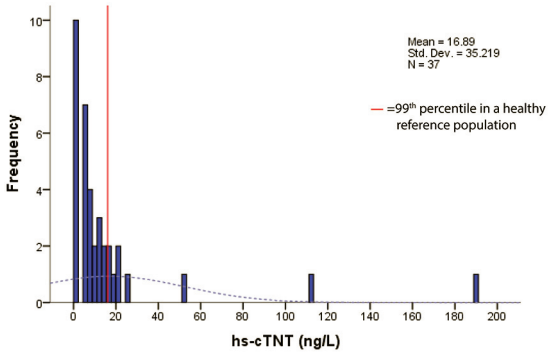

Figure 1. Distribution of high-sensitivity cardiac troponin T level. Troponin T level was below limit of significant in 10 patients (represent with 0 in the graph), higher than normal limit in 11 patients (30%).

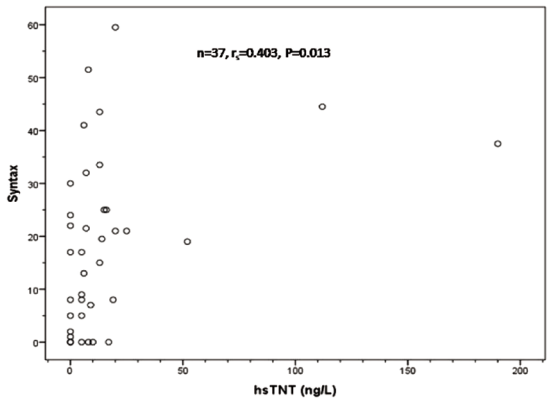

Figure 2. Distribution of hs-cTNT and SYNTAX score.

Using the hs-cTNT cutoff of 5 ng/L or greater, detecting the high anatomical burden patients had a sensitivity of 80% and negative predictive value (NPV) of 80% (Table 2, Figure 4).

5-year clinical outcome (n = 34)

At 5-year follow-up, the mortality for all causes was 8.8%, myocardial infarction was 5.8%, and hospitalization due to angina was 14.7%.

The patients who were hospitalized due to angina had higher hs-cTNT of 17 versus 6 ng/L (p=0.032). Those who died had higher hs-cTNT of 25 versus 6 ng/L (p=0.012). All patients with hs-cTNT level lower

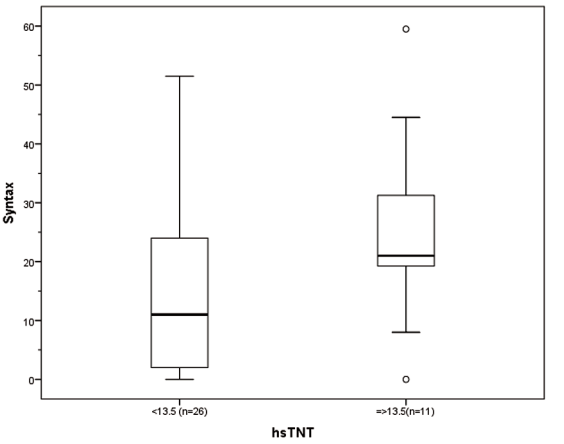

Figure 3. Box plot of SYNTAX score in the patient with or without hs-cTNT elevation.

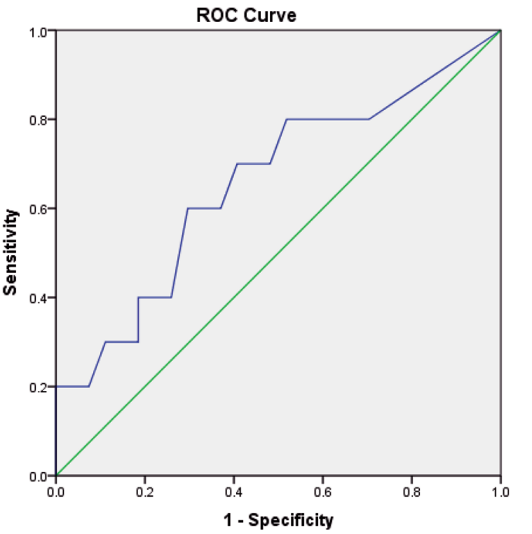

Figure 4. ROC curve of hs-cTNT and prediction of SYNTAX score >22 (non-LM disease) and >33 (LM disease=0.66).

Table 3. hs-cTNT and clinical outcome

	hs-cTNT (ng/L) Median (25 to 75 percentile)		p-value
	No event	Event	
All cause mortality	6 (0 to 13)	25 (22.5 to 68.5)	0.012
Myocardial infarction	6.5 (0 to 14.5)	61 (10 to 112)	0.139
Angina hospitalization	6 (0 to 13)	17 (10 to 20)	0.032

hs-cTNT=high-sensitivity cardiac troponin T

Table 4. SYNTAX score and clinical outcome

	SYNTAX Median (25 to 75 percentile)		p-value
	No event	Event	
All cause mortality	17 (5 to 24)	44 (32 to 52)	0.039
Myocardial infarction	18 (6 to 25)	22 (0 to 44.5)	1
Angina hospitalization	17 (7 to 25)	21 (0 to 21.5)	0.661

than upper normal limit (13.5 ng/L) were alive at five years (Table 3).

The patient who died within five years had significantly higher SYNTAX score of 44 versus 17 (p=0.039) (Table 4).

Discussion

Pathophysiological mechanisms of association between hs-cTNT and complexity of stable CAD are still unclear. There were potential mechanisms of troponin release in stable CAD patients. These mechanisms were related to myocardial ischemia such as cellular release of proteolytic troponin degradation product, increase cellular permeability, and formation and release of membranous blebs[11].

A previous study demonstrated the positive correlation of hs-cTNT level in patients with stable CAD with plaque burden found by coronary CTA. Elevation of hs-cTNT level might be due to silent coronary plaque rupture and spontaneous microembolization. Similar to the present study, there was positive correlation of hs-cTNT level and SYNTAX score that represented coronary complexity by coronary angiogram. This is currently used to determine the revascularization strategy[12].

Daněk et al[13] demonstrated significant correlation between the level of hs-cTNT and the presence of CAD but could not demonstrate correlation of the number of coronary arteries stenosis (stenosis of more than 70% in diameter) and level of hs-cTNT. The number of coronary artery stenosis does not represent the complexity of CAD as the SYNTAX score in the present study.

Yamazaki et al[5] found positive relationship between the SYNTAX score and the hs-cTNT. That study enrolled patients with ischemic heart disease, cardiomyopathy, and severe valvular heart disease who underwent coronary angiogram. Fifty-seven percent of the patients had CKD stage 3 to 5. The study found that cardiomyopathy, severe valvular heart disease, and renal insufficiency can cause hs-cTNT elevation[14]. The present study excluded cardiomyopathy, severe valvular heart disease, and CKD that might confound correlation of SYNTAX score and hs-cTNT. Therefore, the correlation of hs-cTNT and SYNTAX score in the present study was fair (Quantum 1974).

SYNTAX score was primarily used for revascularization selection. It is noteworthy that SYNTAX scores were calculated from every 50% or greater coronary stenosis. The scores were higher when complex lesion characteristics (such as bifurcation, trifurcation, calcification, and tortuosity) were present. Some hemodynamically insignificant, but complex lesions were included in the scoring system. Some patients with high SYNTAX scores might have low ischemic burden by functional testing.

Stable CAD patients were associated with low level of hs-cTNT[15]. Stable CAD patients with hs-cTNT level of less than 5 ng/L were associated with low anatomical complexity; therefore, might have lower chance to require CABG.

Elevated hs-cTNT was a prognostic implication for heart failure and cardiac death[2,12]. The authors' result was similar to previous studies. The patients who died within five years had significantly higher hs-cTNT and SYNTAX score. Stable CAD patients with high SYNTAX score was associated with higher mortality compared to those with low SYNTAX score.

Limitation

The present retrospective cohort study did not have adequate power for clinical outcomes. Because of our local practice, hs-cTNT and coronary angiogram was not done on the same day. There might be variation of hs-cTNT levels.

Conclusion

Stable CAD patients with elevated hs-cTNT level was associated with higher SYNTAX score, which represented higher anatomical complexity, and worse clinical outcomes.

What is already known on this topic?

High-sensitivity cardiac troponin T level was higher in the stable CAD with moderate to severe ischemic burden and associated with worse clinical outcome. However, correlation of hs-cTNT level and coronary anatomical complexity was not known.

What this study adds?

In stable CAD patient, hs-cTNT not only correlated with high ischemic burden and worse clinical outcome but also correlated with high coronary anatomical complexity.

Conflicts of interest

The authors declare no conflict of interest.

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