Clinical Significance of High-sensitivity Cardiac Troponin Measurement — Evaluation of HISCL High-sensitivity Troponin T Reagent and Comparison of AUCs Obtained on ROC Analysis of Reagents for Myocardial Biomarkers

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Measurement of myocardial biomarkers as objective diagnostic indicators of acute coronary syndrome (ACS) is becoming increasingly important. Because the selection of myocardial biomarkers is affected by the size of the laboratory and the environmental requirements, various myocardial biomarkers are currently used in different laboratories. In the present study, we used Automated Immunoassay System HISCL™ (HISCL; Sysmex Corporation, Kobe, Japan) and a special reagent for HISCL, HISCL High-sensitivity Troponin T Reagent, and examined its basic performance. Moreover, we examined the usefulness of measurement of high-sensitivity cardiac troponin T and I (hs-cTnT and hs-cTnI) in diagnosing ACS by comparing this method with measurement of heart-type fatty acid-binding protein (H-FABP) and creatinine kinase muscle and brain (CK-MB) mass. Patients with an acute chest pain visiting the emergency room of our hospital and comprehensively diagnosed with ACS were enrolled to this study. The basic performance of HISCL High-sensitivity Troponin T Reagent was satisfactory, and, according to receiver operating characteristic (ROC) analysis of the samples, the AUC values of hs-cTnI, hs-cTnT, H-FABP and CK-MB mass were 0.955, 0.946, 0.827 and 0.896 respectively, while their cutoff values were 0.156 ng/mL, 0.091 ng/mL, 25.6 ng/mL and 6.4 ng/mL respectively. According to the results of comparison between the AUC values of two markers, hs-cTnI and hs-cTnT showed higher diagnostic capability for ACS than H-FABP, and CK-MB mass was a myocardial biomarker with intermediate diagnostic capability. High-sensitivity cardiac troponin should be selected as a myocardial biomarker of first choice that contributes to an early diagnosis of ACS and immediate provision of appropriate treatment.

Key Words ⟩ Acute Coronary Syndrome (ACS), High-sensitivity Cardiac Troponin, Myocardial Biomaker, ROC Curve Comparison

INTRODUCTION

Acute coronary syndrome (ACS) is a general term for a group of diseases that cause acute myocardial ischemia due to severe coronary stenosis (acute myocardial infarction, unstable angina pectoris and acute sudden cardiac death). Generally, clinical symptoms and signs including chest pain, and an ECG waveform characterized by ST-segment change are used to diagnose ACS. According to an epidemiological study conducted in Japan, however, 40% of patients with ACS suffer from non-ST-segment elevation ACS [1]. Canto et al. [2] conducted a cohort study and reported one-third of patients with myocardial infarction did not complain of the symptom of chest pain. In this situation, measurement of a myocardial biomarker that serves as an objective diagnostic index has become increasingly important.

Since the selection of myocardial biomarkers is affected by the laboratory and the environmental need, various myocardial biomarkers are currently used among laboratories. According to the guidelines for ACS [3], high-sensitivity cardiac troponin measurement is recommended, and as the most reliable examination for diagnosing ACS this measurement has attracted attention. Recently, both sensitivity and speed of cardiac troponin measurement have improved, and a high-sensitivity system requiring just a short time for measurement has been developed. The automated immunoassay system HISCL-5000 (Sysmex, Kobe, Japan), which requires just 17 minutes for complete reaction of all parameters can

be used to measure hs-cTnT.

In the present study, we conducted a basic evaluation of the HISCL High-sensitivity Troponin T Reagent and examined the clinical usefulness of this method of high-sensitivity cardiac troponin measurement in comparison with measurement of conventional myocardial biomarkers including H-FABP and CK-MB mass. Patients with acute chest pain visiting the emergency room of our hospital and comprehensively diagnosed with ACS were enrolled in this study. The results are reported in this article.

SUBJECTS

1. Basic evaluation of HISCL Troponin T hs Assay Kit

The control sample used to determine accuracy provided by the manufacturer and the pooled plasma, adjusted to various concentrations according to the purposes of evaluation, were used.

2. Evaluation of myocardial biomarkers

The subjects included 118 patients who were brought to the Department of Emergency Medicine, Shizuoka General Hospital, with a chief complaint of acute chest pain, between September 2013 and February 2014. This included 34 patients diagnosed with ACS and 84 patients not diagnosed with ACS. Subjects underwent measurement of various myocardial biomarkers. Physical findings, ECG recording, echocardiogram, cardiac catheterization and chest X-ray films were used to make a diagnosis of ACS. After completing the final diagnoses, the patients were divided into ACS and non-ACS groups.

REAGENTS AND MEASUREMENT SYSTEMS

1. High-sensitivity cardiac troponin T (hs-cTnT)

The HISCL Troponin T hs Assay Kit (Sysmex Corporation) was used as a measurement reagent, while the HISCL-5000 was used as a measurement system.

2. High-sensitivity cardiac troponin I (hs-cTnI)

The ARCHITECT High Sensitive Troponin I ST (Abbott Japan, Co., Ltd.) was used as a measurement reagent, while the ARCHITECT Analyzer i-2000SR was used as a measurement system.

3. H-FABP

The Liblia H-FABP (DS Pharma Biomedical Co., Ltd.) was used as a measurement reagent, while the Hitachi LABOSPECT008 Automated Analyzer (Hitachi High-Technologies Corporation) was used as a measurement system.

4. CK-MB mass

The L-type Wako CK-MB mass (Wako Pure Chemical Industries, Ltd.) was used as a measurement reagent, while the Hitachi LABOSPECT008 Automated Analyzer was used as a measurement system.

All measurements were conducted according to the protocols specified by the manufacturers.

EXAMINATION METHODS

1. Basic evaluation of HISCL troponin T hs Assay Kit

Among the items used for basic evaluation of the reagent, those closely reflecting sensitivity and reproducibility were selected.

1) Within-run reproducibility
The control sample used to determine accuracy at two different concentrations provided by the manufacturer and the pooled plasma adjusted to the level around the upper limit of criteria range were used. After 20 consecutive measurements of each sample, the mean, standard deviation (SD) and coefficient of variation (CV) were calculated.

2) Between-run reproducibility
Samples were prepared to test the within-run reproducibility . They were measured twice a day for five days, and the mean, SD and CV were calculated.

3) Limit of blank (LoB), limit of detection (LoD)
The samples showing zero point of calibrator were used as blank samples, while pooled plasma samples adjusted to six concentrations were used for the LoD.
- LoB: The blank sample was measured 10 times a day for five days, and the LoB was obtained.
- Six LoD samples were measured twice a day for five days, and the synthetic standard deviation was calculated.
- The LoB and the synthetic standard deviation were used to calculate the LoD.

4) Limit of quantitation (LoQ)
- Ten pooled plasma samples at the concentrations around the predicted LoQ were used to conduct twice daily measurements for five days. The CV of each sample was calculated. The concentration corresponding to a CV of 10% was obtained using the approximate curve, and the value obtained was used as the LoQ.

2. ROC analysis of myocardial biomarkers for diagnosing ACS

According to the measurements of myocardial biomarkers, the ROC curves were plotted to obtain the area under the curve (AUC) values and cutoff values. The AUC values of two biomarkers were statistically compared with each other to make a comparison between myocardial biomarkers, in terms of capability to diagnose

ACS. A value of less than 0.05 was considered statistically significant ($p < 0.05$). EZR statistical analysis software (Ver. 1.31) was used for comparative analysis of AUC values. Statistical Analysis Software R (Ver. 3.2.2) and R Commander (Ver. 2.2-3) were also used in the present study [4].

3. Evaluation of sensitivity and specificity of myocardial biomarkers for diagnosing ACS

According to the cutoff values obtained on ROC analysis, the sensitivity, specificity, positive predictive and negative predictive value of myocardial biomarkers for

diagnosing ACS were estimated.

RESULTS

1. Basic evaluation of HISCL Troponin T hs Assay Kit

1) The CVs of within-run reproducibility ranged from 2.2% to 2.7%. The samples at the levels close to the upper limit of criteria range (0.016 ng/mL) also showed a satisfactory reproducibility as demonstrated by a CV of 2.7% (***Table 1***).

Table 1 *Within-run reproducibility*

			(ng/mL)
	Pool plasma	QC Low	QC High
1	0.017	0.114	1.993
2	0.018	0.112	2.010
3	0.017	0.114	1.996
4	0.018	0.115	2.013
5	0.017	0.110	2.023
6	0.017	0.114	2.030
7	0.017	0.113	1.943
8	0.018	0.115	1.936
9	0.017	0.112	1.980
10	0.017	0.114	2.005
11	0.018	0.109	1.906
12	0.017	0.108	1.938
13	0.017	0.109	1.918
14	0.018	0.108	1.930
15	0.017	0.111	1.900
16	0.017	0.112	1.893
17	0.017	0.108	1.968
18	0.017	0.109	1.936
19	0.018	0.108	1.944
20	0.017	0.110	1.915
Mean	0.0173	0.1113	1.9589
SD	0.0005	0.0026	0.0441
CV (%)	2.72	2.29	2.25

2) The CVs of between-run reproducibility ranged from 1.9% to 4.5%. The samples at the levels close to the upper limit of criteria range (0.016 ng/mL) also showed a relatively satisfactory reproducibility as demonstrated by a CV of 4.5% (***Table 2***).

Table 2 *Between-run reproducibility*

				(ng/mL)
Days		Pool plasma	QC Low	QC High
1day	1	0.018	0.112	2.054
	2	0.019	0.112	2.038
2day	1	0.017	0.110	2.072
	2	0.018	0.111	2.060
3day	1	0.019	0.115	1.950
	2	0.018	0.113	1.941
4day	1	0.018	0.114	1.959
	2	0.018	0.110	1.953
5day	1	0.018	0.113	1.962
	2	0.017	0.115	2.019
6day	1	0.018	0.116	1.958
	2	0.019	0.115	2.054
7day	1	0.019	0.118	1.982
	2	0.020	0.114	2.072
8day	1	0.018	0.113	1.856
	2	0.019	0.113	1.999
9day	1	0.019	0.115	2.106
	2	0.019	0.115	2.079
10day	1	0.019	0.111	2.083
	2	0.020	0.116	2.091
Mean		0.0185	0.1136	2.0144
SD		0.0008	0.0021	0.0666
CV (%)		4.47	1.88	3.31

3) The luminescence count value was used to obtain the LoB which turned out to be 3,442.9.

The luminescence count value was also used to obtain the LoD which turned out to be 4,091.4, and the concentration at this time was estimated to be 0.00088 ng/mL (**Table 3**).

Table 3 *Limit of blank (LoB: luminescence count), limit of detection (LoD: luminescence count)*

		1day	2day	3day	4day	5day
	1	3085	3087	3104	3315	3388
	2	3313	3166	3088	3285	3413
	3	3130	3246	3384	3256	3243
	4	3222	3168	2933	3334	3223
	5	3154	3082	3440	3360	3391
	6	3241	2904	3180	3384	3113
	7	3289	3160	3185	3245	3418
	8	3058	3083	3157	3231	3156
	9	3150	3109	3230	2988	3421
	10	2996	3164	3514	3372	3252
Mean		3163.8	3116.9	3221.5	3277	3301.8
SD		102.3	90.9	177.0	115.1	117.6
CV (%)		3.23	2.92	5.49	3.51	3.56
Mean of blank		3216.2				
SD of blank		137.8				
LoB		3442.9				

(ng/mL)

	Sample (1)	Sample (2)	Sample (3)	Sample (4)	Sample (5)	Sample (6)
1day	9938	9816	8709	4946	9253	5393
	9825	9814	8147	4952	8885	5367
2day	9585	9816	7874	4788	7975	5534
	9753	9715	8163	4892	8357	5384
3day	9456	10311	9855	5038	7828	5356
	9946	9785	7844	5204	8595	5280
4day	10235	10013	7731	4955	7960	5247
	9845	9681	8028	4832	7872	5270
5day	9400	9505	9310	5094	8290	5309
	9420	9128	8929	5217	8305	5449
Mean	9740.3	9758.4	8459	4991.8	8332.0	5358.9
SD	272.4	307.3	713.2	145.4	466.4	88.1
CV(%)	2.80	3.15	8.43	2.91	5.60	1.64
Mean of samples	7773.4					
Synthetic standard deviation	392.4					
LoD (luminescence count)	4091.4					
LoD (concentration: ng/mL)	0.00088					

4) According to the measurements of 10 different samples, the concentration showing a CV of 10% was obtained and the limit of quantitation (LoQ) was estimated to be 0.005 ng/mL (***Table 4***, ***Fig. 1***).

Table 4 *Limit of quantification (LoQ)*

(ng/mL)

|	Sample (1)	Sample (2)	Sample (3)	Sample (4)	Sample (6)	Sample (8)	Sample (9)	Sample (10)	Sample (11)	Sample (12)
1day	0.006	0.009	0.010	0.006	0.013	0.005	0.013	0.018	0.001	0.006
	0.006	0.008	0.010	0.006	0.013	0.005	0.013	0.018	0.001	0.005
2day	0.006	0.008	0.010	0.006	0.012	0.004	0.013	0.017	0.001	0.004
	0.006	0.009	0.010	0.006	0.012	0.005	0.013	0.018	0.001	0.005
3day	0.006	0.009	0.010	0.007	0.013	0.006	0.013	0.019	0.001	0.004
	0.006	0.008	0.010	0.006	0.012	0.004	0.013	0.018	0.002	0.005
4day	0.007	0.009	0.011	0.007	0.012	0.004	0.013	0.018	0.001	0.004
	0.006	0.009	0.010	0.006	0.013	0.004	0.012	0.018	0.001	0.004
5day	0.006	0.008	0.009	0.006	0.013	0.006	0.012	0.018	0.001	0.005
	0.006	0.008	0.009	0.006	0.012	0.005	0.012	0.017	0.002	0.005
Mean	0.0061	0.0085	0.0099	0.0062	0.0125	0.0048	0.0127	0.0179	0.0012	0.0047
SD	0.0003	0.0005	0.0006	0.0004	0.0005	0.0008	0.0005	0.0006	0.0004	0.0007
CV(%)	5.18	6.20	5.73	6.80	4.22	16.43	3.80	3.17	35.14	14.36
LoQ (CV10%)					0.0051					
LoQ (CV20%)					0.0024					
LoQ (CV7%)					0.0074					
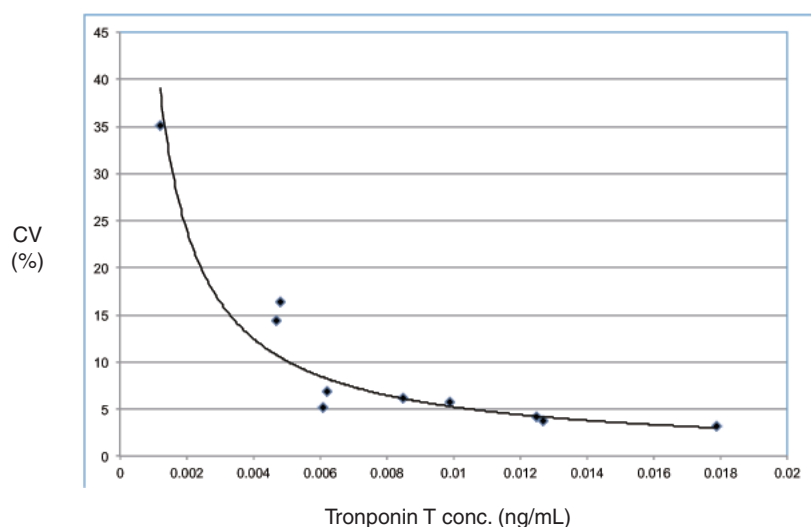
Fig. 1 *Limit of quantification (LoQ)*

2. ROC analyses of myocardial biomarkers for diagnosing ACS

According to the ROC analysis of myocardial biomarkers, the AUC values of hs-cTnI, hs-cTnT, H-FABP and CK-MB mass were 0.955, 0.946, 0.827 and 0.896 respectively. Their cutoff values were 0.156 ng/mL, 0.091 ng/mL, 25.6 ng/mL and 6.4 ng/mL respectively (***Fig. 2***). The differences in AUC value between myocardial biomarkers were examined, and a significant difference was recognized between hs-cTnI, hs-cTnT and H-FABP ($p < 0.001$). No significant difference was observed in the comparison of biomarkers in terms of other measurement items (***Fig. 3***).
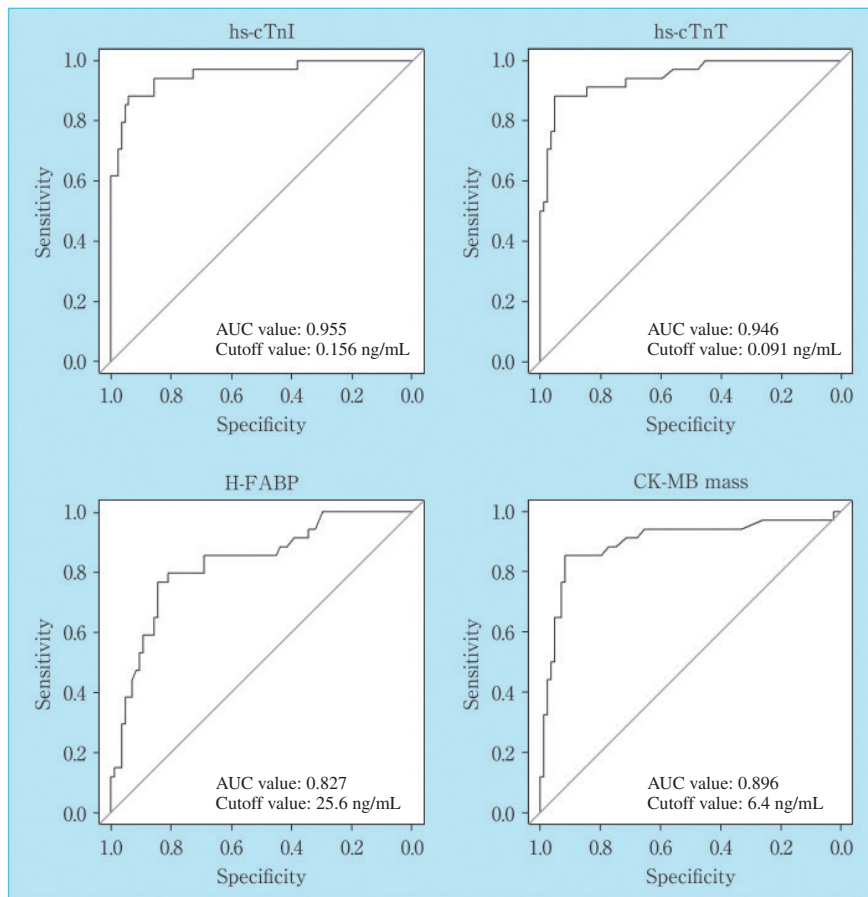

Fig. 2 *ROC curve analysis of each myocardial biomarker for ACS diagnosis in patients with acute chest pain visiting the emergency room of our hospital*
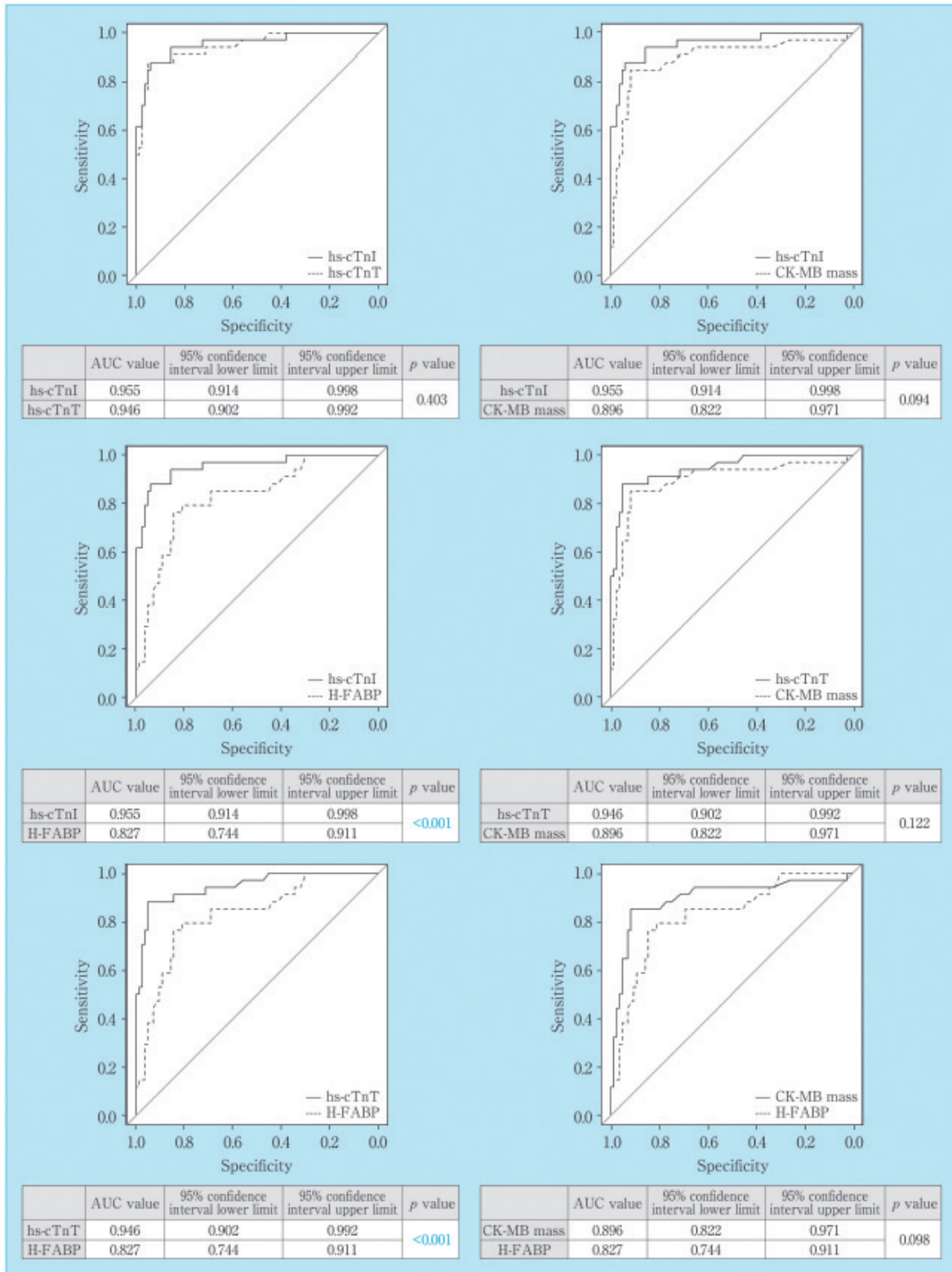
	AUC value	95% confidence interval lower limit	95% confidence interval upper limit	p value
hs-cTnI	0.955	0.914	0.998	0.403
hs-cTnT	0.946	0.902	0.992	

	AUC value	95% confidence interval lower limit	95% confidence interval upper limit	p value
hs-cTnI	0.955	0.914	0.998	0.094
CK-MB mass	0.896	0.822	0.971	

	AUC value	95% confidence interval lower limit	95% confidence interval upper limit	p value
hs-cTnI	0.955	0.914	0.998	<0.001
H-FABP	0.827	0.744	0.911	

	AUC value	95% confidence interval lower limit	95% confidence interval upper limit	p value
hs-cTnT	0.946	0.902	0.992	0.122
CK-MB mass	0.896	0.822	0.971	

	AUC value	95% confidence interval lower limit	95% confidence interval upper limit	p value
hs-cTnT	0.946	0.902	0.992	<0.001
H-FABP	0.827	0.744	0.911	

	AUC value	95% confidence interval lower limit	95% confidence interval upper limit	p value
CK-MB mass	0.896	0.822	0.971	0.098
H-FABP	0.827	0.744	0.911	

Fig. 3 Result of test of difference in AUC value between any two cardiac biomarkers

3. Evaluation of sensitivity and specificity of myocardial biomarkers for diagnosing ACS

Using the cutoff values obtained in the ROC analyses, hs-cTnI and hs-cTnT showed the highest sensitivity of 88% in diagnosing ACS, and H-FABP showed the lowest sensitivity of 76%. Moreover, hs-cTnT showed the highest specificity of 95%, while H-FABP showed the lowest specificity of 85%. Regarding the positive predictive value, hs-cTnT showed the highest rate of 88%, while H-FABP showed the lowest rate of 67%. All the markers showed a negative result prediction rate of more than 90% (***Table 5***).

DISCUSSION

In the present study, we evaluated the basic performance of the HISCL Troponin Ths Assay Kit and examined the clinical utility of high-sensitivity cardiac troponin measurement in diagnosing ACS by comparing high-sensitivity cardiac troponin with H-FABP and CK-MB mass in patients who were brought to the Department of Emergency Medicine, Shizuoka General Hospital, with a chief complaint of acute chest pain.

The HISCL Troponin Ths Assay Kit has excellent performance and shows high sensitivity and reproducibility as demonstrated by an LoQ of 0.0051 ng/mL at CV 10%.

On the basis of the AUC values of myocardial biomarkers obtained from ROC analyses, the biomarkers were ranked in the following order (from the most accurate): hs-cTnI, hs-cTnT, CK-MB mass and H-FABP. The differences in AUC value between myocardial biomarkers were examined, and the results showed that hs-cTnI and hs-cTnT had better capability to diagnose ACS than H-FABP, and that CK-MB mass was a myocardial biomarker with an intermediate diagnostic capability. Since the AUC values of hs-cTnI and hs-cTnT were 0.955 and 0.946 respectively, measurement of high-sensitivity cardiac troponin measurement seemed to be highly useful in diagnosing ACS. Due to the positive predictive values of hs-cTnI and hs-cTnT at 86% and 88% respectively, a diagnosis of ACS can be made with a probability of 90% as long as the sample tests positive for high-sensitivity cardiac troponin. Therefore, the ability to make a diagnosis of ACS can be improved remarkably by combining clinical symptoms and ECG changes. ACS can be ruled out with a probability of about 95% as long as the sample tests are negative for high-sensitivity cardiac troponin, because the negative result prediction rates of hs-cTnI and hs-cTnT were 95% respectively. Accordingly, high-sensitivity cardiac troponin is regarded as a useful marker for making a diagnosis of exclusion. It is imperative that critically ill patients brought to the Emergency Department are quickly and accurately assessed for ACS. High-sensitivity cardiac troponin measurement is a useful examination to quickly and accurately screen for ACS. In Japan, patients strongly suspected of suffering from ACS generally undergo cardiac catheterization even if they do not show ECG changes or elevation of myocardial biomarkers. Unnecessary invasive examinations should be avoided as much as possible, because cardiac catheterization is an invasive examination entailing some risk. The present study showed hs-TnI and hs-TnT had a sufficiently high diagnostic capability for ACS, suggesting that high-sensitivity cardiac troponin measurement might contribute to patients undergoing cardiac catheterization. Those patients who are strongly suspected of ACS should undergo high-sensitivity cardiac troponin measurement first. The measurement results will help guide appropriate and prompt patient treatment.

We also calculated the AUC values of conventional biomarkers including H-FABP and CK-MB mass. Of the AUC values of the myocardial biomarkers used in the present study, H-FABP showed the lowest value.

Table 5 *Evaluation of the sensitivity, specificity, positive predictive value, and negative predictive value for ACS diagnosis using the cutoff value of ROC curve analysis*

		ACS		sensitivity	specificity	positive predictive value	negative predictive value
		+	−				
hs-cTnI Cut off value 0.156 ng/mL	+	30	5	88%	94%	86%	95%
	−	4	79				
hs-cTnT Cut off value 0.091 ng/mL	+	30	4	88%	95%	88%	95%
	−	4	80				
H-FABP Cut off value 25.6 ng/mL	+	26	13	76%	85%	67%	90%
	−	8	71				
CK-MBmass Cut off value 6.4 ng/mL	+	29	7	85%	92%	81%	94%
	−	5	77				

N = 118

Because H-FABP is a low-molecular protein that is separated immediately after myocardial damage, it has been regarded as a useful marker for making an early diagnosis [5]. H-FABP, however, is affected by age and renal function, and the false-positive rate is high. Therefore, H-FABP is regarded as a marker with poor specificity and these drawbacks have been pointed out recently in the literature [6]. The positive predictive value of H-FABP was as low as 67% and thus limited importance is placed on measurement of H-FABP as long as high-sensitivity cardiac troponin can be measured. The AUC value of CK-MB mass was 0.896, third in performance after hs-TnI and hs-TnT. According to the guidelines of the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation (ESC/ACCF/AHA/WHF) Task Force, measurement of CK-MB mass is recommended if cardiac troponin cannot be measured [3]. A diagnosis of ACS can likely be made as long as the sample tests positive for CK-MB mass, because the positive predictive value of CK-MB mass was 81%. A potential concern is that the sensitivity of CK-MB mass is low in patients who experienced an episode within four hours [7] and thus the possibility of hyperacute ACS cannot be ruled out, even if the sample tests negative for CK-MB mass.

Although the selection of myocardial biomarkers differs depending on the size of the laboratory and the environmental requirements, high-sensitivity cardiac troponin I and T are regarded as myocardial biomarkers with excellent sensitivity and specificity. Either will result in the similar consequence in terms of evaluation of acute ischemic myocardial damage, because, in making a diagnosis of ACS, no difference was observed between high-sensitivity cardiac troponin I and T. Since high-sensitivity cardiac troponin, which rises immediately after onset of ACS, serves as a marker with excellent specificity [8,9], its measurement is indispensable for patients suspected of ACS.

If the laboratory environment does not allow measurement of high-sensitivity cardiac troponin, use of CK-MB mass as an alternative marker is recommended. In this case, CK-MB mass should be measured taking into account the fact that its sensitivity in diagnosing hyperacute ACS is low. The present study clearly demonstrated that the myocardial biomarker that best contributes toward a diagnosis of ACS is high-sensitivity cardiac troponin. Since improvement of high-sensitivity cardiac troponin measurement has enabled detection of minor myocardial damage, the possibility of its use as a marker to evaluate severity and prognosis of chronic heart failure arises and some researchers have emphasized the importance of cardiac troponin from this viewpoint [10]. Shimada, one of the authors of this article, and his colleagues analyzed the present data using Bayesian statistical methods. They calculated the post-test probability from the likelihood ratio and the pretest probability, and demonstrated that high-sensitivity troponin showed higher post-test probability in the examinations conducted at the Department of Emergency Medicine [11]. In the future, we should clinically apply high-sensitivity cardiac troponin measurement to patients with heart diseases other than ACS and conduct further study of differentiation between high-sensitivity troponin I and T. The laboratories that can introduce this system are limited, because high-sensitivity troponin measurement requires a special immunoserological system. Sufficient attention should be directed to the immunoserological systems which may differ considerably in terms of measurement time. Sysmex's HISCL system, which requires a relatively short period of 17 minutes for high-sensitivity troponin measurement, can be regarded as a beneficial and favorable system for emergency tests.

CONCLUSION

Although conventional myocardial biomarkers have a good capability for making a diagnosis of ACS, high-sensitivity cardiac troponin has a far better diagnostic capability. Since high-sensitivity cardiac troponin can be detected within a few hours after onset of ACS, it should be selected as the primary myocardial biomarker which can assist with an early diagnosis of ACS and allow for immediate appropriate treatment.

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