

[ ORIGINAL ARTICLE ]

## The Usefulness and Limitations of Point-of-care Cardiac Troponin Measurement in the Emergency Department

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### Abstract:

**Objective** This study was carried out to examine the usefulness of point-of-care (POC) cardiac troponin in diagnosing acute coronary syndrome (ACS) and to understand the limitations of a POC cardiac troponin I/T-based diagnoses.

**Methods** Patients whose cardiac troponin levels were measured in the emergency department using a POC system (AQT System; Radiometer, Tokyo, Japan) between January and December 2016 were retrospectively examined (N=1,449). Patients who were < 20 years of age or who were admitted with cardiopulmonary arrest were excluded. The sensitivity and specificity of the POC cardiac troponin levels for the diagnosis of ACS were determined.

**Result** One hundred and twenty of 1,449 total patients had ACS (acute myocardial infarction, n=88; unstable angina n=32). On comparing the receiver operating characteristic (ROC) curves, the area under the curve (AUC) values for POC cardiac troponin I and cardiac troponin T were 0.833 and 0.786, respectively. The sensitivity and specificity of POC cardiac troponin I when using the 99th percentile (0.023 ng/mL) as the diagnostic cut-off value were 69.0% and 88.1%, respectively. The sensitivity of POC cardiac troponin I (99th percentile) was higher in the patients sampled > 3 hours after symptom onset (83.3%) than in those sampled ≤ 3 hours after symptom onset (58.8%, p < 0.01).

**Conclusion** When sampled > 3 hours after the onset of symptoms, the POC cardiac troponin I level is considered to be suitable for use in diagnosing ACS. However, when sampled ≤ 3 hours after the onset of symptoms, careful interpretation of POC cardiac troponins is therefore required to rule out ACS.

**Key words:** point of care, cardiac biomarkers, acute coronary syndrome

(Intern Med 57: 1673-1680, 2018)

(DOI: 10.2169/internalmedicine.0098-17)

### Introduction

Rapid diagnostic techniques are needed in the emergency department, especially for acute coronary syndrome (ACS), as early coronary reperfusion can improve the prognosis of ACS (1, 2).

ACS should be diagnosed based on the symptoms and the results of electrocardiography (ECG), and ultrasound cardiography (UCG), and blood sampling. Many ACS patients

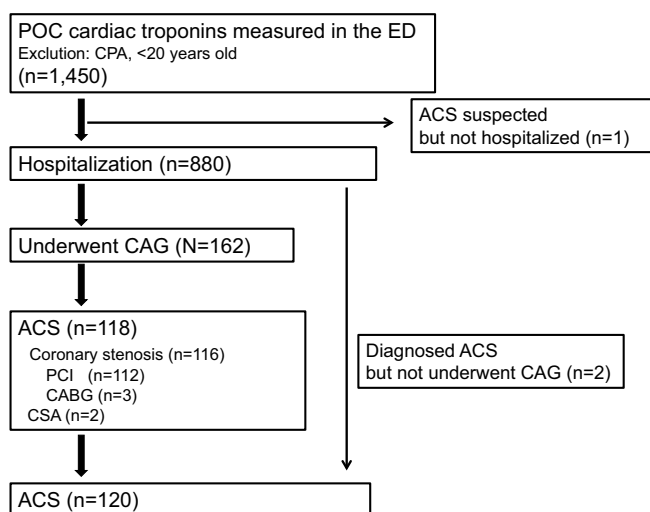
present with chest pain, but some do not (3-5). Care should therefore also be taken to correctly diagnose patients who do not present with chest pain. Furthermore, some patients do not show ECG changes and lack segmental asynergy on UCG. The recent development of biomarkers of cardiac injury can help in the diagnosis.

Troponin complex is a contractile element consisting of troponin C, I, and T (6). Each has skeletal and cardiac isoforms. When the membrane of cardiac muscle cells is injured, cardiac troponins flow from the cardiac muscle cells

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Received: August 19, 2017; Accepted: September 24, 2017; Advance Publication by J-STAGE: February 9, 2018

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**Figure 1.** Schematic illustration of the patients included in the present study. CPA: cardiopulmonary arrest, CAG: coronary angiography, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting

into the systemic circulation. At present, cardiac troponins T and I can be measured using commercially available antibodies.

The third universal definition of myocardial infarction recommends that the 99th percentile of cardiac troponin in a normal reference population be used as the cut-off value for the diagnosis of acute myocardial infarction (3). Recently, high-sensitive cardiac troponins have been developed, and their use has increased the sensitivity of the diagnosis of myocardial infarction. While the point-of-care (POC) measurement of cardiac troponins is less sensitive than using high-sensitive cardiac troponins (7, 8), the measurement can be performed very quickly (within approximately 15 min) at the bedside (7-9). However, clinical data on POC cardiac troponins are limited.

We therefore examined the usefulness of POC troponin in diagnosing ACS in order to clarify the limitations of a POC troponin I/T-based diagnosis.

## Materials and Methods

The study protocol was approved by the ethics committee of The Jikei University School of Medicine [28-366 (8609)] and the clinical research committee of The Jikei University Kashiwa Hospital.

The patients whose troponin levels were measured at the emergency department (ED) of The Jikei University Kashiwa Hospital (a tertiary-care center) from January 2016 to December 2016 were retrospectively reviewed. The POC cardiac troponin I/T levels at the time of admission were measured with a POC system (AQT90 Flex system, Radiometer, Tokyo, Japan). Patients who were <20 years of age and those with cardiopulmonary arrest on admission were excluded from the present study. The time of symptom onset was obtained from the medical records.

The patients were divided into two groups: patients with and without ACS. The diagnosis was determined retrospectively after discharge by one of the investigators. The following data (if appreciable) were taken into consideration in the diagnosis: the symptoms, physical findings, electrocardiogram findings, ultrasound echocardiography findings, chest X-ray findings, computed tomography findings, laboratory findings other than cardiac troponin levels, their response to the specific treatment and the follow-up in an outpatient clinic. ACS was confirmed by coronary angiography (CAG). In three cases of clinically suspected ACS, the patients did not undergo CAG. Two of these three cases were hospitalized, and the ACS diagnosis was confirmed during the course of hospitalization. However, in one case, the family refused hospitalization, so this case was excluded from the study. ACS was also categorized as ST-elevating myocardial infarction (STEMI), non-ST-elevating myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). Myocardial infarction was defined when a rapid increase or decrease in cardiac injury markers other than the cardiac troponins (creatinine kinase, creatine kinase MB isoform) was confirmed. Myocardial injury due to coronary artery spasm was categorized as myocardial infarction. Fig. 1 shows a schematic illustration of the patients included in the present study.

The age, sex and other laboratory findings of the two groups (ACS and non ACS) were compared. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation (10) coefficient modified for Japanese patients (11):  $eGFR = 194 \times Cr^{-1.094} \times age^{-0.287}$  ( $\times 0.739$  for female subjects for correction) ( $mL/min/1.73 m^2$ ). Continuous variables were expressed as the median [interquartile range (IQR)] and were compared using the Mann-Whitney test. Categorical variables were expressed as the number (percentage) and compared using the chi-squared test. A receiver-operating characteristic (ROC) curve analysis was performed to examine the sensitivity and specificity of the POC cardiac troponins in the diagnosis of ACS. The cut-off points where the sum of the sensitivity and specificity was highest were also shown.

It takes time for the biomarker levels to increase. Early admission can therefore lead to an increase in false-negative results. Thus, a histogram of the various cut-off values for ACS, based on the time between onset and the sampling, was created.

Renal failure is considered to be one of the reasons for false-positive results when cardiac troponins are used for the diagnosis of ACS. Thus, the false positive rate in non-ACS patients is shown in relation to the eGFR. The 99th percentile values of normal population supplied by the Radiometer were used as cut-off values (troponin T, > 0.017 ng/mL; troponin I, > 0.023 ng/mL). The false positive rate was compared between POC cardiac troponin I and T using the McNemar test for each renal function level. For this analysis, the non-ACS patients with available data for both POC cardiac troponin T and I were included. Multiplicity in sta-

**Table 1. The Final Diagnosis of the Patients Enrolled in This Study.**

ACS	120		
		STEMI	60 (50.0)
		NSTEMI	28 (23.3)
		UAP	32 (26.7)
Non-ACS	1,329		
		Aortic stenosis	4 (0.3)
		Takotsubo cardiomyopathy	4 (0.3)
		Heart failure	112 (8.4)
		Arrhythmias	74 (5.6)
		Aortic dissection	22 (1.7)
		Cerebral diseases	98 (7.4)
		Trauma	276 (20.8)
		Gastroentero- and hepatic diseases	110 (8.3)
		Respiratory disease	81 (6.1)
		Kidney disease	28 (2.1)
		Epilepsy	22 (1.7)
		Sepsis	9 (0.7)
		Others	489 (36.8)

Number in the parenthesis indicates percentage.

tistical tests was adjusted for using the hierarchical procedure. All statistical analyses were two-sided, and p values of <0.05 were considered to indicate statistical significance.

## Results

The final diagnoses of the patients are shown in Table 1. One hundred and twenty of a total 1,449 patients were diagnosed with ACS. The clinical characteristics of both groups are shown in Table 2. The eGFR values were higher in the ACS group, as were the serum creatinine kinase (CK) and creatine kinase MB isoform (CKMB) levels and the NT-pro brain natriuretic peptide (BNP) and POC cardiac troponin I/T levels. The frequency of chest pain was also higher in the ACS group; however, 32.5% of the ACS patients did not present with chest pain. The symptoms of the ACS patients without chest pain are shown in Table 3.

We performed an ROC curve analysis to examine the sensitivity and specificity of various POC cardiac troponin cut-off values in the diagnosis of ACS (Fig. 2). The area under the curve (AUC) for cardiac troponin I was 0.833, while that for cardiac troponin T was 0.786. POC cardiac troponin I was superior to troponin T, especially with regard to the specificity (Fig. 2). We drew an ROC curve for patients who were sampled at  $\leq 3$  hours after the onset of symptoms and those who were sampled at  $> 3$  hours after the onset of symptoms (Fig. 3). The AUC was higher when patients were sampled  $> 3$  hours after the onset of symptoms.

We next examined the sampling time-dependence of the sensitivity. Early sampling led to false-negative results; however, even when patients were sampled at  $> 6$  hours after the onset of symptoms, few cases were POC cardiac troponin I-negative (Fig. 4). All of these cases were diagnosed with

UAP.

We calculated the sensitivity and specificity of POC cardiac troponin I using several cut-off values for patients sampled at  $\leq 3$  hours or  $> 3$  hours after the onset of symptoms (in addition to the cut-off values for all patients). The sensitivity (using the 99th percentile as the cut-off value) was higher in patients sampled  $> 3$  hours after symptom onset (83.3%) than those sampled  $\leq 3$  hours after symptom onset (58.8%,  $p<0.01$ ) (Table 4).

The dependence of false-positive results on the renal function is shown in Table 5. When the eGFR was low, the false-positive rate increased in both POC cardiac troponin I and T. However, the false positive rate was much higher when POC cardiac troponin T was used, especially in patients with lower eGFR values.

## Discussion

The present study showed the following: 1) some patients with ACS do not experience chest pain; 2) POC cardiac troponin I was superior to POC cardiac troponin T for diagnosing ACS; and 3) POC cardiac troponin I was suitable for the diagnosis of ACS in the emergency department setting when sampling was performed at  $> 3$  hours after the onset of symptoms.

### *The diagnosis of acute coronary syndrome*

In the present study, ACS was diagnosed retrospectively based on clinical findings. Acute myocardial infarction (MI) was defined by rapid increases and decreases in biomarkers of cardiac injury.

Under the third definition of MI, the use of cardiac troponins and the 99th percentile of a normal reference popula-

**Table 2. The Characteristics of the Patients with and without ACS.**

	All	ACS	Non-ACS	p
N	[1,449]	[120]	[1,329]	
Gender Male n (%)	871 (60.1) [1,449]	93 (77.5) [120]	778 (58.5) [1,329]	<0.001
Age (years)	70 (55,79) [1,449]	71 (61,78) [120]	70 (54,80) [1,329]	NS
Chest pain n (%)	279 (19.3) [1,449]	81 (67.5) [120]	198 (14.9) [1,329]	<0.001
WBC (/μL)	7,600 (5,900-10,225) [1,446]	8,200 (6,830-10,500) [120]	7,500 (5,800-10,200) [1,326]	<0.05
CK (U/L)	110 (69-186) [1,445]	159 (100-365) [120]	107 (66-180) [1,325]	<0.001
CKMB (U/L)	10 (7-15) [1,114]	15 (10-34) [117]	10 (7-15) [997]	<0.001
eGFR (mL/min/1.73m <sup>2</sup> )	63.8 (43.1-80.9) [1,449]	60.3 (36.6-75.7) [120]	64.5 (43.5-81.3) [1,329]	<0.05
NT-proBNP (pg/mL)	223 (64-1,333) [956]	714 (149-4,000) [69]	204 (62-1,250) [887]	<0.001
Cardiac troponin I (μg/L)	<0.010 (<0.010-0.012) [1,399]	0.084 (0.014-0.963) [116]	<0.010 (<0.010-<0.010) [1,283]	<0.001
Cardiac troponin T (μg/L)	<0.010 (<0.010-0.017) [1,232]	0.059 (0.011-0.510) [94]	<0.010 (<0.010-0.015) [1,138]	<0.001

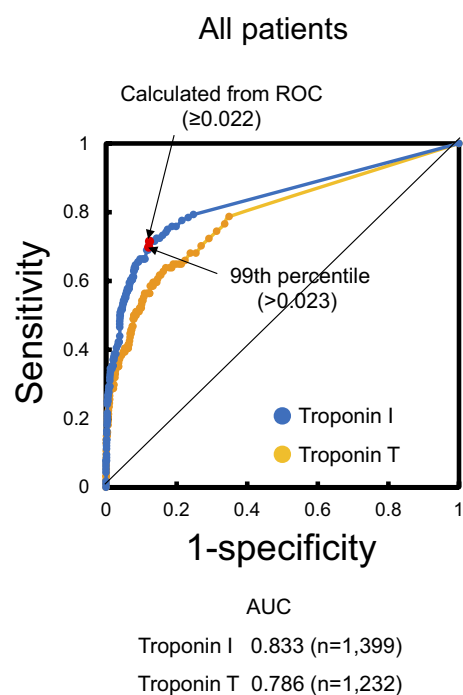
Continuous variables were expressed as the median (IQR). Categorical variables were expressed as the number (percentage). The number sampled was shown in [ ], as some cases were missed.

**Table 3. The Symptoms of the ACS Patients without Chest Pain.**

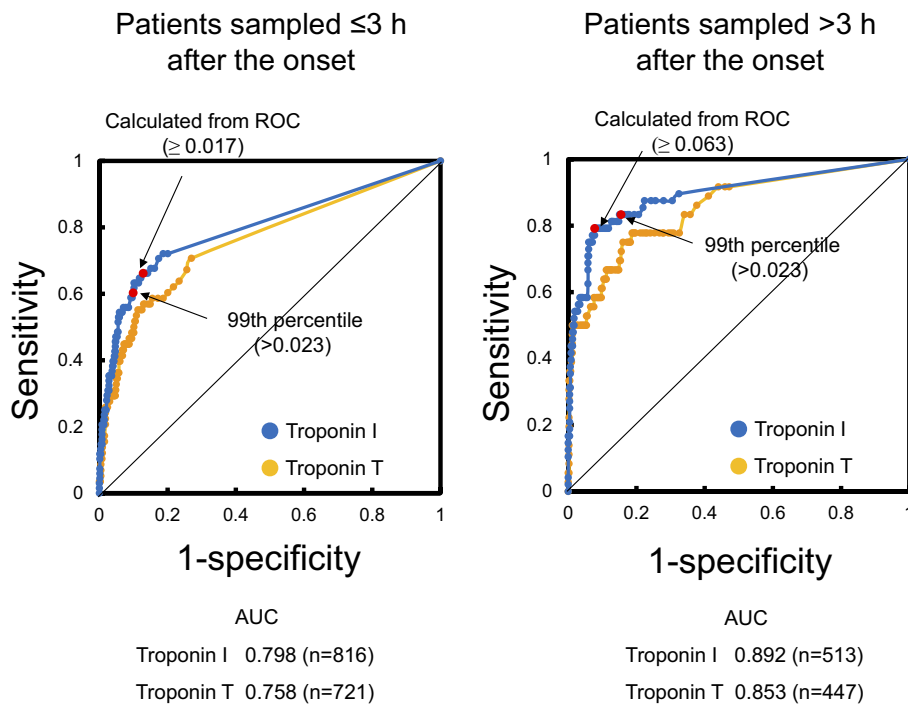
ACS without chest pain 39	
Chest discomfort	16 (41.0)
Dyspnea	18 (46.2)
Chest discomfort and/or dyspnea	30 (76.9)
Disturbance of consciousness	5 (12.8)
Drop	1 (2.6)
General fatigue	1 (2.6)
Palpitation	1 (2.6)
Neck pain	1 (2.6)

Number in the parenthesis indicates percentage.

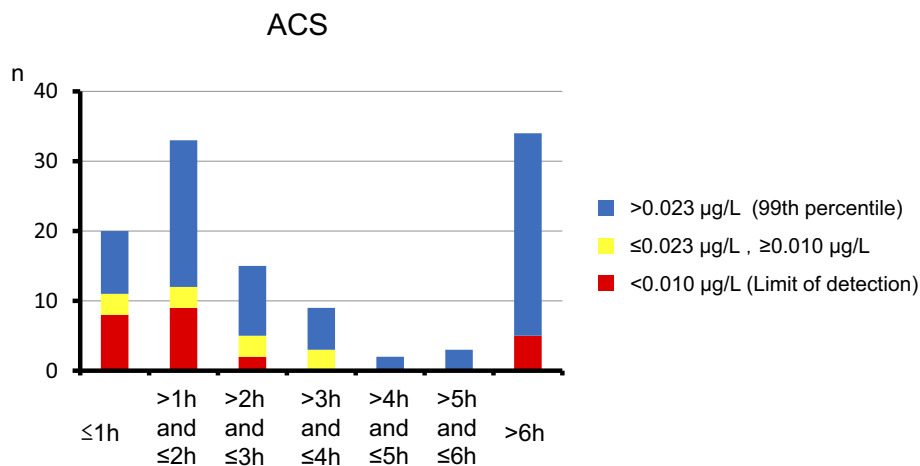
tion are recommended for the diagnosis (3). Furthermore, cardiac troponins are recommended when the coefficient of variation (CV) at the 99th percentile is  $\leq 10\%$  but should not be used when the CV at the 99th percentile is  $> 20\%$  (3). In the POC cardiac troponin used in the present study, the CV at the 99th percentile was 10-20%. Although POC cardiac troponins lack the sensitivity of the laboratory-measured high-sensitive troponins (7, 8), POC cardiac troponins can be measured very quickly at the bedside (7-9). Schneider et al. (7) reported that reducing the POC cardiac troponin cut-off value from the 99th percentile by half can increase the sensitivity. In the present study, the reduced cut-off value led to an increase in sensitivity (Table 4). In UAP, the diagnostic performance of high-sensitive cardiac

**Figure 2. The receiver-operating characteristic curves for the detection of ACS by POC troponins.**

troponins is not sufficient (12). Furthermore, in the present study, when measurements were performed at  $> 6$  hours, a small number of false negatives for UAP occurred. In cases involving very small amounts of myocardial damage, UAP is difficult to diagnose based solely on biomarkers of myo-



**Figure 3.** The receiver-operating characteristic curves for the detection of ACS by POC cardiac troponins in patients sampled at  $\leq 3$  hours or  $> 3$  hours after the onset of symptoms.



**Figure 4.** A histogram of the various cut-off values of POC cardiac troponin I for the diagnosis of ACS, according to the time between the onset of symptoms and sampling.

cardial injury.

### ACS without chest pain

In the present study, all of the patients who presented to the ED and in whom the POC cardiac troponin level was measured were included, as ACS without chest pain is not rare. Indeed, 24% of ACS patients do not experience chest pain (4). Myocardial infarction is not recognized in approximately 30% of cases (13). Silent myocardial infarction is related to hypertension, age, diabetes, sex (13), and renal dysfunction (5). Thus, care should be taken to detect ACS in patients who do not present with chest pain. The symptoms of the ACS patients without chest pain are listed in Table 3.

### Cardiac troponin T and I

The sensitivity of POC cardiac troponin I and T were similar. However, the specificity of POC cardiac troponin I was far superior to that of troponin T (Fig. 2). Cardiac troponin T mRNA is expressed in the skeletal muscle of patients with end-stage renal failure or Duchene muscle dystrophy but not in healthy skeletal muscle. In contrast, cardiac troponin I mRNA is not expressed in normal or diseased skeletal muscle (14). The plasma cardiac troponin T level is also increased in Pompe disease patients with skeletal damage (15). In the present study, the false-positive rate for POC cardiac troponin T was much higher than that for

**Table 4. The Sensitivity, Specificity, PPV, and NPV for Various Cut-off Values of POC Cardiac Troponin I.**

All the patients (n=1,399)					
Cut off		Sensitivity	Specificity	PPV	NPV
≥0.010 (μg/L)	Limit of detection	79.3	75.2	22.4	97.6
≥0.012 (μg/L)	Half 99th percentile	77.6	78.5	24.6	97.5
≥0.022 (μg/L)	Calculated from ROC	70.7	87.7	34.2	97.1
>0.023 (μg/L)	99th percentile	69.0	88.1	34.3	96.9
Patients sampled ≤3 hours after the onset (n=816)					
Cut off		Sensitivity	Specificity	PPV	NPV
≥0.010 (μg/L)	Limit of detection	72.1	79.9	24.6	96.9
≥0.012 (μg/L)	Half 99th percentile	70.6	82.6	27.0	96.9
≥0.017 (μg/L)	Calculated from ROC	66.2	87.2	31.9	96.6
>0.023 (μg/L)	99th percentile	58.8	90.4	35.7	96.0
Patients sampled >3 hours after the onset (n=513)					
Cut off		Sensitivity	Specificity	PPV	NPV
≥0.010 (μg/L)	Limit of detection	89.6	67.5	22.2	98.4
≥0.012 (μg/L)	Half 99th percentile	87.5	72.0	24.4	98.2
>0.023 (μg/L)	99th percentile	83.3	84.5	35.7	98.0
≥0.063 (μg/L)	Calculated from ROC	79.2	92.3	51.4	97.7

PPV: positive predictive value, NPV: negative predictive value

**Table 5. The False-positive Rates for POC Cardiac Troponin I and T in Relation to eGFR Values in Non-ACS Patients.**

Cut off	Raw data		Paired data		p
	Troponin I False positive n/N (%)	Troponin T False positive n/N (%)	Troponin I False positive n/N (%)	Troponin T False positive n/N (%)	
<15	27/91 (29.6)	69/76 (90.7)	21/72 (29.2)	65/72 (90.3)	<0.001
15–30	23/91 (25.3)	44/76 (57.9)	19/74 (25.7)	43/74 (58.1)	<0.001
30–45	31/154 (20.1)	44/134 (32.8)	25/127 (19.7)	42/127 (33.1)	0.001
45–60	31/229 (13.5)	43/202 (21.3)	24/195 (12.3)	43/195 (22.1)	0.001
60–75	15/279 (5.4)	16/244 (6.6)	7/233 (3.0)	16/233 (6.9)	0.035
75–90	20/239 (8.4)	20/219 (9.1)	17/209 (8.1)	20/209 (9.6)	NS
>90	6/200 (3.0)	7/187 (3.7)	6/182 (3.3)	7/182 (3.8)	-

-: statistical test was not performed due to hierarchical procedure

troponin I, especially in patients with a low renal function (Table 5). This result is consistent with the fact that the expression of cardiac troponin T, but not troponin I, is increased in the skeletal muscle of patients with end-stage renal failure.

### The time-dependence of the sensitivity of cardiac troponins

It takes a several hours for the biomarker levels to rise; thus, the concentration of POC cardiac troponin I was plotted against the time between the onset and the sample time (Fig. 4). In our hospital, some ACS patients were admitted very quickly, due to the efficiency of the ambulance service. In these cases, POC cardiac troponins were less sensitive

than high-sensitive troponins. However, at > 3 hours from the onset of symptoms, the sensitivity increased to reasonable levels. The repeated measurement of POC cardiac troponin can increase the accuracy, especially for patients who are admitted soon after the onset of symptoms.

### Japanese STEMI guideline

In the guideline for the management of patients with STEMI (JCS 2013) (16), the qualitative measurement of cardiac troponin or heart-type fatty acid-binding protein (H-FABP) with whole blood at bedside is recommended (Class I indication). The whole blood test at bedside takes only 15 minutes (17). Troponin T (qualitative measurement) increases > 4 hours after the onset of symptoms. H-FABP is a

low-molecular-weight protein that exists in the cytosol; it therefore increases earlier than cardiac troponin (16, 17). POC cardiac troponins in the present study showed a lower sensitivity than H-FABP, especially  $\leq 3$  hours after the onset. However, the specificity of H-FABP for myocardial infarction is around 50% (17). Therefore, when patients are admitted very quickly after symptom onset, the use of H-FABP is recommended.

### Serum cardiac troponin levels in non-ACS patients

In some patients without ACS, the levels of POC cardiac troponins exceeded the normal range. Several factors are involved in the increase in the serum concentration of cardiac troponins. Cardiac troponin is a heart-specific structural protein. However, when the cardiac muscle cells are injured, the proteins inside the cell flow into the systemic circulation. Thus, it is reasonable for the concentration of a biomarker of cardiac muscle injury to increase under certain conditions aside from acute myocardial infarction, including other cardiac diseases as well as non-cardiac diseases, such as myocarditis, arrhythmias, exposure to cardiotoxic agents, heart failure, Takotsubo cardiomyopathy, sepsis, renal failure, severe acute neurological diseases, and critical illness (3, 6, 18, 19).

### Study limitations

The present study is associated with several potential limitations. First, the sample size was small. Second, our hospital is a tertiary emergency medical facility. In addition to patients with chest pain, patients with traumatic injuries due to traffic accidents, whose POC cardiac troponin levels were measured frequently, were included in the analysis. The sensitivity and specificity were affected by the study population. Third, we only used the AQT system to measure the levels of POC cardiac troponins. The sensitivity and specificity depend on the antibodies and measuring system that are used. Thus, our data cannot be generalized to other POC systems. Despite these limitations, this study explained the usefulness and limitations of using the measurement of POC cardiac troponins to diagnose ACS in the ED.

### Conclusion

When sampled  $> 3$  hours after the onset of symptoms, the POC cardiac troponin I level is considered to be suitable for use in diagnosing ACS. However, when sampled  $\leq 3$  hours after the onset of symptoms, careful interpretation of POC cardiac troponins is required to rule out ACS. Increasing our understanding of the characteristics of POC cardiac troponins will aid in the diagnosis of ACS.

**The authors state that they have no Conflict of Interest (COI).**

### Acknowledgement

We would like to thank Prof. Masako Nishikawa, Clinical Research Support Center, The Jikei University School of Medicine,

for providing advice on the statistical analyses, and Dr. Brian Quinn, Japanese Medical Communication, for reading the manuscript.

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*Intern Med* 57: 1673-1680, 2018