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 POC cardiac troponin in diagnosing acute coronary syndrome (ACS) and to understand the limitations of a POC cardiac troponin I/T-based diagnosis.

[Methods] Patients whose cardiac troponin levels were measured in the emergency department using a POC system (AQT System; Radiometer, Tokyo) between January and December 2016 were retrospectively examined (N=1449). Patients who were <20 y.o. or who 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 twenty of the 1449 patients had ACS (acute myocardial infarction, n=88; unstable angina n=32). On comparing the ROC curves, the 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 patients sampled >3 h after the symptom onset (83.3%) than those sampled ≤3 h after the symptom onset (58.8%, P<0.01).

[Conclusion] When sampled >3 h after the onset of symptoms, the POC cardiac troponin I level is considered to be suitable for use in diagnosing ACS. On the other hand, when sampled ≤3 h after the onset of symptoms, careful interpretation of POC cardiac troponins should be needed

to rule out ACS.

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

Introduction

Rapid diagnostic techniques are needed in the emergency department, especially for acute coronary syndrome (ACS). 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). Thus, care should also be taken to correctly diagnose patients who do not present with chest pain. Moreover, 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 into the systemic circulation. At present, cardiac troponin T and I can be measured using commercially available antibodies.

The 3rd 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 their sensitivity in the diagnosis of myocardial infarction. The POC measurement of cardiac troponins is less sensitive than the

high sensitive cardiac troponins (7,8); however, the measurement can be performed very quickly (~15 min) at the bedside (7-9). However, the clinical data on POC cardiac troponins are limited. Thus, we carried out the present study to examine the usefulness of POC troponin in diagnosing ACS and to understand the limitations of a POC troponin I/T-based diagnosis.

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 point of care system (AQT90 Flex system, Radiometer, Tokyo, Japan). Patients who were younger 20 years of age and those with cardiopulmonary arrest on admission were excluded from the present study. The time of the symptom onset were 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, ultrasound echocardiography, chest X-ray, computed tomography, 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 3 cases of clinically suspected ACS, the patients did not undergo CAG. Two of 3 cases were hospitalized and ACS diagnosis was confirmed during the course of hospitalization. However, in one case, the family refused hospitalization, thus 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 of cardiac injury markers other than the cardiac troponins (creatine kinase, creatine kinase MB isoform) was confirmed. Myocardial injury due to coronary artery spasm was categorized as myocardial infarction. Figure 1 shows the schema 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): estimated GFR = $194 \times Cr^{-1.094} \times age^{-0.287}$ (mL/min/1.73 m^2). For female subjects, the estimated GFR was multiplied by a correction factor of 0.739. Continuous variables were expressed as the median (IQR) and were compared using the Mann-Whitney test. Categorical variables were expressed as the number (percentage), and were 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 sensitivity and specificity was the maximal were also shown.

It takes time for the levels of biomarkers 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 Radiometer were used as cut-off values (troponin T, >0.017 ng/mL; troponin I, >0.023 ng/mL). False positive rate was compared between POC cardiac troponin I and T using McNemar test for each renal function level. For this analysis, the non-ACS patients whose POC cardiac troponin T and I are both available were included. Multiplicity in statistical tests was adjusted using 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 twenty of

1,449 patients were diagnosed ACS. The clinical characteristics of both groups are shown in Table 2. The eGFR values were higher in the ACS group. The serum creatinine kinase (CK) and creatine kinase MB isoform (CKMB) levels were higher in the ACS group. The NT-proBNP and POC cardiac troponin I/T levels were higher in the ACS group. The frequency of chest pain was higher in the ACS group; however, 32.5% of the ACS patients did not present chest pain. The symptoms of the ACS patients without chest pain were 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 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 ≤3 h after the onset of symptoms and those who were sampled at >3 h after the onset of symptoms (Fig. 3). The AUC was higher when patients were sampled >3h 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 h after the onset of symptoms, few cases were POC cardiac troponin I-negative (Fig. 4). All of these cases were diagnosed as UAP.

We calculated the sensitivity and specificity of POC cardiac troponin I using several cut-off values for patients sampled at ≤3 h or >3 h after the onset of symptoms (in addition to

cut-off values for all patients). The sensitivity (using the 99th percentile as the cut-off value) was higher in patients sampled >3 h after the symptom onset (83.3%) than those sampled ≤3 h after the 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 h after the onset of symptoms.

The diagnosis of acute coronary syndrome

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

In the 3rd definition of MI, the use of cardiac troponins and the 99th percentile of a

normal reference population are recommended for the diagnosis (3). Moreover, cardiac troponins is recommended when a CV of the 99th percentile is ≤10%, but should not be used when a CV of the 99th percentile is >20% (3). In the POC cardiac troponin used in the present study, the CV at the 99th percentile is 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 to its half value 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 troponins is not sufficient (12). In the present study, when measurements were performed at >6 h, a small number of false negatives for UAP occurred. In cases involving very small amounts of myocardial damage, UAP is difficult to diagnose based on biomarkers of myocardial injury.

ACS without chest pain

In the present study, all of the patients who presented to the emergency department and in whom the POC cardiac troponin level was measured were included because ACS without chest pain is not rare. Twenty-four percent 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. On the other hand, 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 troponin I, especially in patients with a low renal function (Table 5). This result is consistent with the fact that 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, which is due to the

efficiency of the ambulance service. In these cases, POC cardiac troponins are 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 guidelines for the management of patients with ST-elevation acute myocardial infarction (JCS 2013) (16), qualitative measurement of cardiac troponin or heart-type fatty acid-binding protein (H-FABP) with whole blood at bedside are recommended (Class I indication). The whole blood test at bedside takes only 15 min (17). Troponin T (qualitative measurement) rise more than 4 hours after the onset. H-FABP is low molecular weight protein existed in the cytosol, thus H-FABP rises earlier than cardiac troponin (16,17). POC cardiac troponins in the present study showed sensitivity lower than H-FABP especially ≤3 h after the onset. However, Specificity of H-FABP for myocardial infarction is around 50% (17). Thus, when patients admitted very quickly after the symptom onset, use of H-FABP would be recommended.

The serum cardiac troponin levels in non-ACS patients.

In some patients without ACS, the levels of POC cardiac troponins were higher than the normal range. Several factors are involved in the increase in the serum concentration of cardiac troponins. Cardiac troponin is a heart-specific protein and is one of the structural proteins. 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 in various conditions other than acute myocardial infarction, including other cardiac diseases and non-cardiac diseases. These conditions include myocarditis, arrhythmias, exposure to cardiotoxic agents, heart failure, Takotsubo cardiomyopathy, sepsis, renal failure, severe acute neurological diseases, and critically 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 are 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 the using the measurement of POC cardiac troponins to diagnose ACS in the emergency department.

Conclusion

When sampled >3 h after the onset of symptoms, the POC cardiac troponin I level is considered to be suitable for use in diagnosing ACS. On the other hand, when sampled ≤3 h after the onset of symptoms, careful interpretation of POC cardiac troponins should be needed to rule out ACS. Increasing the understanding of the characteristics of POC cardiac troponins will help in the diagnosis of ACS.

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Legends

Fig. 1. The schema of the patients included in the present study.

CPA, cardiopulmonary arrest. CAG, coronary angiography. PCI, percutaneous coronary intervention. CAGB, coronary artery bypass grafting.

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

Fig. 3. The receiver-operating characteristic curves for the detection of ACS by POC cardiac troponins in patients sampled at ≤3 h or >3 h after the onset of symptoms.

Fig. 4. The 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.

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	1329		
		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.

Table 2. The characteristics of the patients with and without ACS

	All	ACS	Non-ACS	P
N	[1449]	[120]	[1329]	
Gender Male n (%)	871 (60.1) [1449]	93 (77.5) [120]	778(58.5) [1329]	<0.001
Age (years)	70 (55,79) [1449]	71 (61,78) [120]	70 (54,80) [1329]	NS
Chest pain n (%)	279 (19.3) [1449]	81 (67.5) [120]	198 (14.9) [1329]	<0.001
WBC (/μL)	7600 (5900-10225) [1446]	8200 (6830-10500) [120]	7500 (5800-10200) [1326]	<0.05
CK (U/L)	110 (69-186) [1445]	159 (100-365) [120]	107 (66-180) [1325]	<0.001
CKMB (U/L)	10 (7-15) [1114]	15 (10-34) [117]	10 (7-15) [997]	<0.001
eGFR (mL/min/1.73m2)	63.8 (43.1-80.9) [1449]	60.3 (36.6-75.7) [120]	64.5 (43.5-81.3) [1329]	<0.05
NT-proBNP (pg/mL)	223 (64-1333) [956]	714 (149-4000) [69]	204 (62-1250) [887]	<0.001
Cardiac troponin I (μg/L)	<0.010 (<0.010-0.012) [1399]	0.084 (0.014-0.963) [116]	<0.010 (<0.010-<0.010) [1283]	<0.001
Cardiac troponin T (μg/L)	<0.010 (<0.010-0.017) [1232]	0.059 (0.011-0.510) [94]	<0.010 (<0.010-0.015) [1138]	<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.

Table 4. The sensitivity, specificity, PPV, and NPV for various cut-off values of POC cardiac troponin I

All the patinets (N=1399)

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 h 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 h 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		
eGFR (mL/mim/1.73m^2)	Troponin I False positive n/N (%)	Troponin T False positive n/N (%)	Troponin I False positive n/N (%)	Troponin T False positive n/N (%)	P
<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.

Fig.1

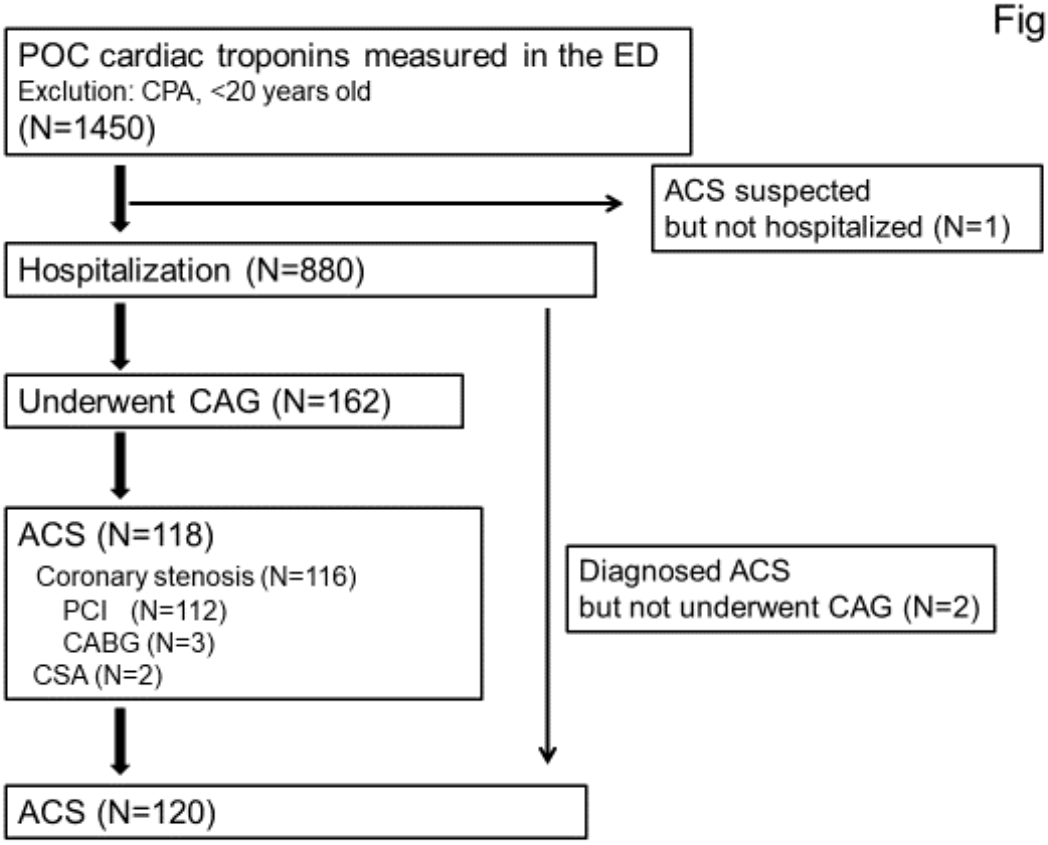
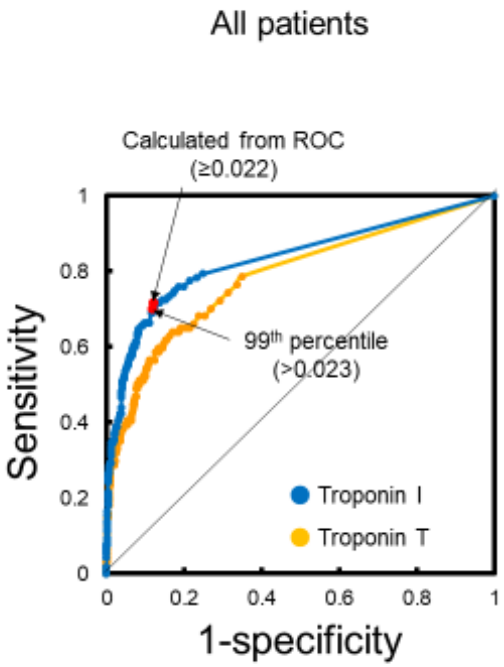

POC cardiac troponins measured in the ED
Exclution: CPA, <20 years old
(N=1450)
ACS suspected
but not hospitalized (N=1)
Hospitalization (N=880)
Underwent CAG (N=162)
ACS (N=118)
Coronary stenosis (N=116)
PCI (N=112)
CABG (N=3)
CSA (N=2)
Diagnosed ACS
but not underwent CAG (N=2)
ACS (N=120)

Fig.2



AUC

Troponin I 0.833 (N=1399)

Troponin T 0.786 (N=1232)

Fig.3

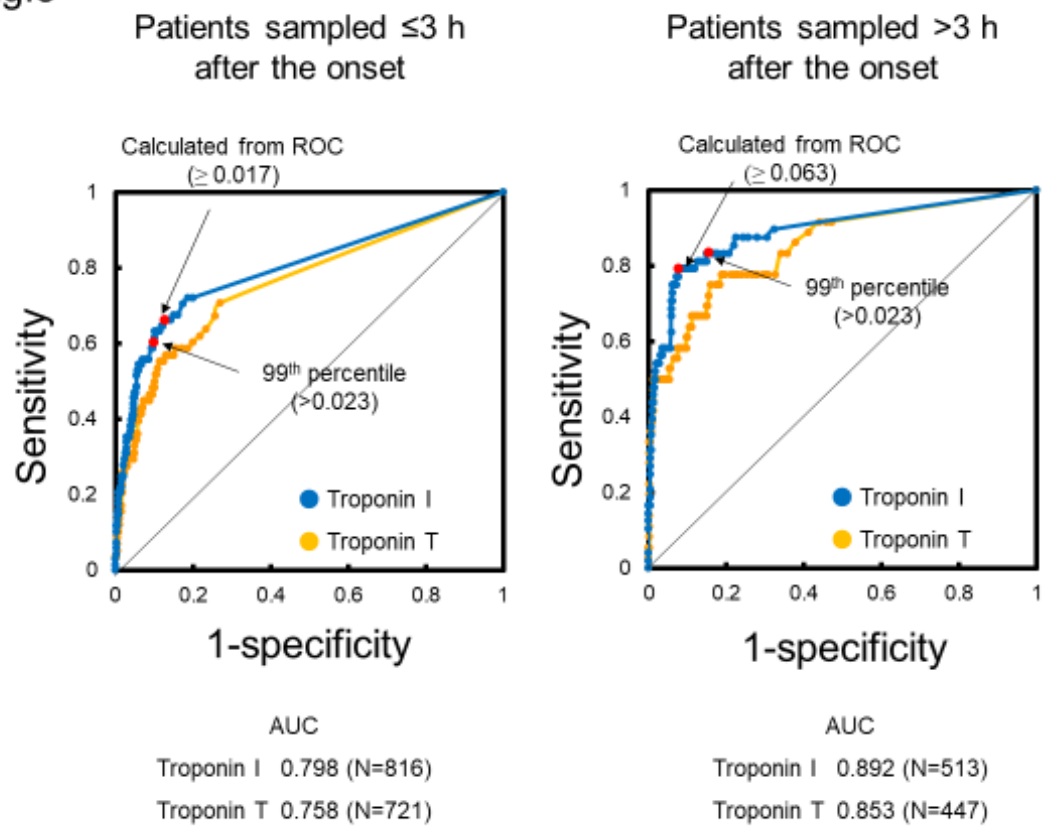
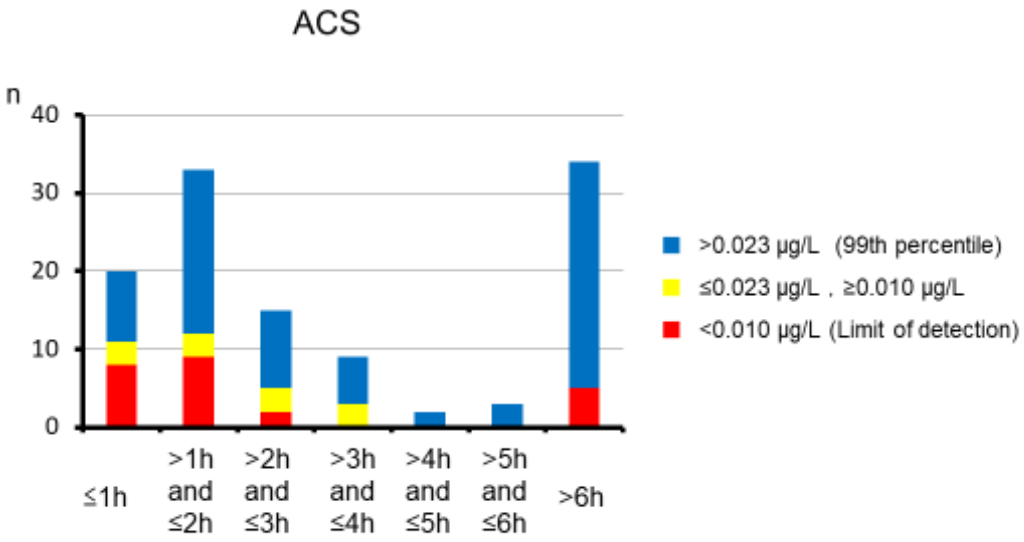

Patients sampled ≤3 h after the onset
Calculated from ROC (≥0.017)
99th percentile (>0.023)
Troponin I
Troponin T
Sensitivity
1-specificity
0
0.2
0.4
0.6
0.8
1
AUC
Troponin I 0.798 (N=816)
Troponin T 0.758 (N=721)
Patients sampled >3 h after the onset
Calculated from ROC (≥0.063)
99th percentile (>0.023)
Troponin I
Troponin T
Sensitivity
1-specificity
AUC
Troponin I 0.892 (N=513)
Troponin T 0.853 (N=447)

Fig.4


ACS
n
40
30
20
10
0
≤1h
>1h and ≤2h
>2h and ≤3h
>3h and ≤4h
>4h and ≤5h
>5h and ≤6h
>6h
>0.023 μg/L (99th percentile)
≤0.023 μg/L , ≥0.010 μg/L
<0.010 μg/L (Limit of detection)