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Original Article

Explanatory Power and Prognostic Implications of Factors Associated with Troponin Elevation in Acute Ischemic Stroke

Sung-Ho Ahn,[a] Ji-Sung Lee,[b] Mi-Sook Yun,[c] Jung-Hee Han,[d] Soo-Young Kim,[d] Young-Hak Kim,[e] Sang-Hyun Lee,[f] Min-Gyu Park,[a] Kyung-Pil Park,[a] Dong-Wha Kang,[d] Jong S. Kim,[g] Sun U. Kwon[d]

[a]Department of Neurology, Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Busan, Korea
[b]Clinical Research Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[c]Division of Biostatistics, Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Busan, Korea
[d]Department of Neurology, Asan Medical Center, University of Ulsan, College of Medicine, Seoul, Korea
[e]Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[f]Division of Cardiology, Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Busan, Korea
[g]Department of Neurology, Gangneung Asan Hospital, University of Ulsan, Gangneung, Korea

Background and Purpose We investigated the impact of comorbidity burden on troponin elevation, with separate consideration of neurological conditions, in patients with acute ischemic stroke (AIS).
Methods This prospective, observational cohort study consecutively enrolled patients with AIS for 2 years. Serum cardiac troponin I was repeatedly measured, and disease-related biomarkers were collected for diagnosis of preassigned comorbidities, including atrial fibrillation (AF), ischemic heart disease (IHD), myocardial hypertrophy (MH), heart failure (HF), renal insufficiency (RI), and active cancer. The severity of neurological deficits and insular cortical ischemic lesions were assessed as neurological conditions. Adjusted associations between these factors and troponin elevation were determined using a multivariate ordinal logistic regression model and area under the receiver operating characteristic curve (AUC). Cox proportional hazards model was used to determine the prognostic significance of comorbidity beyond neurological conditions.
Results Among 1,092 patients (66.5±12.4 years, 63.3% male), 145 (13.3%) and 335 (30.7%) had elevated (≥0.040 ng/mL) and minimally-elevated (0.040–0.010 ng/mL) troponin, respectively. In the adjusted analysis, AF, MH, HF, RI, active cancer, and neurological deficits were associated with troponin elevation. The multivariate model with six comorbidities and two neurological conditions exhibited an AUC of 0.729 (95% confidence interval [CI], 0.698–0.759). In Cox regression, AF, IHD, and HF were associated with adverse cardio-cerebrovascular events, whereas HF and active cancer were associated with mortality.
Conclusion Troponin elevation in patients with AIS can be explained by the burden of comorbidities in combination with neurological status, which explains the prognostic significance of troponin assay.

Keywords Troponin; Stroke; Comorbidity; Prognosis

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Introduction

Cardiac troponins are structural proteins of cardiomyocytes, and elevated serum troponin levels indicate myocardial injury. Thus, troponin elevation, especially above the 99th percentile of the upper reference limit (URL), has been used as a diagnostic and prognostic biomarker in acute coronary syndrome (ACS).[1] Furthermore, the use of the troponin assay has expanded the risk stratification in various patients, including those with stroke, stable coronary artery disease (CAD), atrial fibrillation (AF), heart failure (HF), myocardial hypertrophy (MH), renal insufficiency (RI), and even in the general population.[2]

However, the interpretative strategy of troponin elevation remains unclear,[3] especially in patients with acute ischemic stroke (AIS), owing to its complexity.[4] Patients with AIS frequently have various cardiac comorbidities, which can contribute to troponin elevation.[5] Furthermore, patients with AIS are mostly older adults and often have multiple comorbidities, including cardiac and non-cardiac comorbidities, which also contribute to troponin elevation, apart from the troponin elevation through neurogenic stress.[6] Thus, although international guidelines for AIS management recommend the measurement of the baseline troponin level in conjunction with electrocardiography (ECG) in all patients,[7] the practical application of the troponin assay is only available to assess a few specific conditions, such as concurrent ACS and cardiac arrhythmia, without a strategic approach.

Therefore, this study aimed to evaluate the influence of comorbidity burden on troponin elevation and prognostic significance, with separate consideration of neurological conditions in patients with AIS.

Methods

Study population

This study is a registered, prospectively enrolled, and observational study designed to investigate the prognostic significance[8] and the possible mechanisms of troponin elevation for enhancing the practical application of troponin measurement in patients with AIS (Clinical Research Information Service [CRIS]; KCT0000682; https://cris.nih.go.kr/cris).

All consecutive patients with AIS who visited the emergency room within 48 hours after the onset of acute neurological deficit at the Asan Medical Center in Korea between March 2013 and March 2015 were prospectively recruited. On admission, patients with suspected ACS were evaluated by cardiologists to determine the urgency of coronary angiographic assessment and excluded from this study. The Institutional Review Board of the Asan Medical Center approved this study (IRB no. 2012-

0561). Informed consent was obtained from each patient or their legal delegates.

Study protocol

Figure 1 shows the flow diagram of the study protocol. Registered patients routinely underwent measurements of serum cardiac troponin I level. The troponin level on the second day after stroke onset was designated as the reference value, considering the dynamic features of troponin release. The lower limit of detection of serum cardiac troponin I was 0.006 ng/mL, and the calculated 99th percentile of the URL was 0.040 ng/mL (Abbott Laboratories, Abbott Park, IL, USA). The patients were categorized into three groups: (1) troponin I level ≥0.040 ng/mL was defined as "elevated," (2) troponin I level between 0.040 and 0.010 ng/mL was interpreted as "minimally-elevated," and (3) troponin I level <0.010 ng/mL was defined as "non-detectable troponin."[8]

Based on prior research,[9,10] the disease-related biomarkers were prospectively collected to improve the diagnostic accuracy of troponin elevation-related comorbidities: (1) repeated 12-lead ECG (GE Healthcare, Waukesha, WI, USA), with the results processed using the Marquette 12SL ECG analysis program; (2) serum b-type natriuretic peptide (BNP) level measured on day 2 after stroke onset and repeated if patients had a borderline BNP elevation (i.e., >200 or >100 pg/mL in patients with or without RI, respectively);[11] (3) estimated glomerular filtration rate (GFR) at admission; and (4) serum D-dimer and fibrinogen at admission to assess coagulopathy, considering screening for cancer-related coagulopathy,[12] or pulmonary embolism.

Data collection

Clinical data, including demographic characteristics, conventional vascular risk factors, and laboratory data, were obtained. The pre-assigned comorbidities were defined based on the parameters of disease-related biomarkers, historical information, or both, as follows: (1) AF in the known history or positive on serial ECGs at least once; (2) ischemic heart disease (IHD) in the known history or positive ischemic-ECG changes (e.g., ST-segment elevation or depression, T-wave inversion, left bundle branch block [LBBB], or pathological Q-waves) on serial ECGs at least once; (3) MH in the known history or positive ventricular hypertrophy (VH) on serial ECGs at least once; (4) HF in the known history or an elevated BNP >500 pg/mL on serial measurements of BNP; (5) RI in the known history or an impaired GFR (<60 mL/min/1.73 m^2, calculated using the Modification of Diet in Renal Disease formula); and (6) active cancer (e.g., cancer within six months before enrollment, any treatment for cancer within the previous six months or recurrent or metastatic cancer, or newly diagnosed cancer after stroke). The stroke severity was assessed using the National
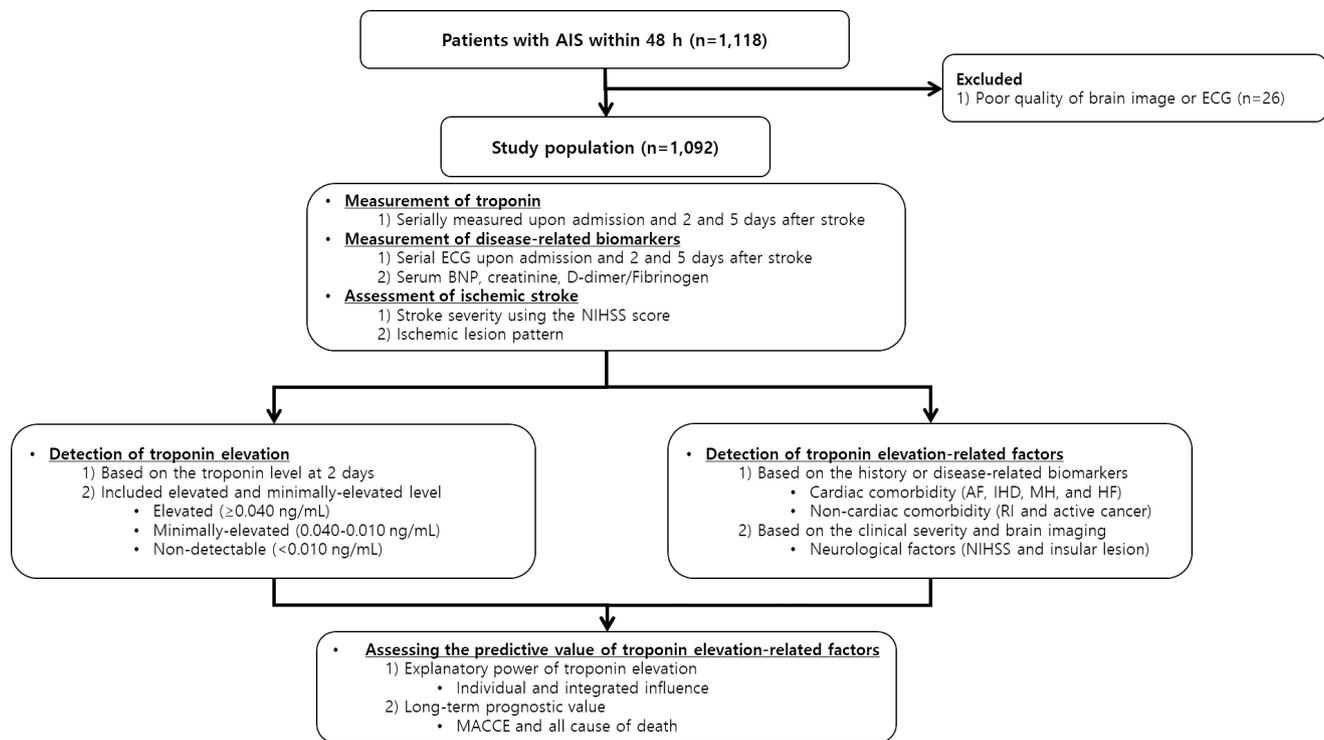
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┌─────────────────────────────────────────┐
│  Patients with AIS within 48 h (n=1,118) │
└─────────────────────────────────────────┘
                    │            ┌──────────────────────────────────────────┐
                    ├───────────→│ Excluded                                 │
                    │            │ 1) Poor quality of brain image or ECG    │
                    │            │    (n=26)                                │
                    ↓            └──────────────────────────────────────────┘
┌─────────────────────────────────────────┐
│       Study population (n=1,092)         │
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- **Measurement of troponin**
  1) Serially measured upon admission and 2 and 5 days after stroke
- **Measurement of disease-related biomarkers**
  1) Serial ECG upon admission and 2 and 5 days after stroke
  2) Serum BNP, creatinine, D-dimer/Fibrinogen
- **Assessment of ischemic stroke**
  1) Stroke severity using the NIHSS score
  2) Ischemic lesion pattern

- **Detection of troponin elevation**
  1) Based on the troponin level at 2 days
  2) Included elevated and minimally-elevated level
     - Elevated (≥0.040 ng/mL)
     - Minimally-elevated (0.040-0.010 ng/mL)
     - Non-detectable (<0.010 ng/mL)

- **Detection of troponin elevation-related factors**
  1) Based on the history or disease-related biomarkers
     - Cardiac comorbidity (AF, IHD, MH, and HF)
     - Non-cardiac comorbidity (RI and active cancer)
  2) Based on the clinical severity and brain imaging
     - Neurological factors (NIHSS and insular lesion)

- **Assessing the predictive value of troponin elevation-related factors**
  1) Explanatory power of troponin elevation
     - Individual and integrated influence
  2) Long-term prognostic value
     - MACCE and all cause of death

Figure 1. Flow diagram of the study protocol. Process of patient selection and classification according to the troponin level and diagnosis of troponin elevation-related factors to assess their predictive value. AIS, acute ischemic stroke; ECG, electrocardiography; BNP, b-type natriuretic peptide; NIHSS, National Institutes of Health Stroke Scale; AF, atrial fibrillation; IHD, ischemic heart disease; MH, myocardial hypertrophy; HF, heart failure; RI, renal insufficiency; MACCE, major adverse cardiac and cerebrovascular event.

Institutes of Health Stroke Scale (NIHSS)[13] score to define troponin elevation-related neurological factors, and the specific ischemic lesion location on the insular cortex was assessed on a diffusion-weighted magnetic resonance image.[14] Reperfusion therapy was defined as intravenous tissue plasminogen activator or intra-arterial reperfusion therapy, or both.

Follow-up information was obtained via a direct interview at the outpatient department or a telephone interview by the research coordinator, including major adverse cardiac and cerebrovascular events (MACCE, any cardiac or cerebrovascular death, nonfatal ACS, ischemic or hemorrhagic stroke, and coronary revascularization) and all causes of death to assess the long-term prognostic value.

Substudy for assessment of subclinical ACS risk

Considering underdetection of subclinical ACS risk, multidetector coronary computed tomography angiography (CTA) was prospectively performed for selected patients in the elevated, minimally-elevated, and non-detectable groups at a 1:2:2 ratio, after the exclusion of patients who were diagnosed with RI or those in whom performing coronary CTA was difficult (e.g., altered mental status, language dysfunction, and unstable medical conditions). CTA was performed using a dual-source scanner (SOMATOM Definition, Siemens, Erlangen, Germany), and 400 mg/mL iodine

(Iomeron 400, Bracco, Milan, Italy) was used. According to the guidelines, a 16-segment coronary artery tree model was used.

Furthermore, the possible etiology of high-risk patients with a troponin surge (>1.00 ng/mL, indicating extensive myocardial injury highly related to ACS) was assessed.

Statistical analysis

Baseline characteristics between the troponin I categories were compared using the chi-square test for categorical variables. Continuous variables were compared using Student's t-test or analysis of variance with Duncan's *post hoc* correction. To describe the influence of individual factors on troponin elevation (both elevated and minimally-elevated troponin levels), we obtained the odds ratio (OR) by multivariate ordinal logistic regression analysis using backward elimination (likelihood ratio test). Furthermore, to explore the integrated impact of the factors on troponin elevation, we incorporated them into the models in four ways to estimate the area under the receiver operating characteristic curve (AUC) for predicting troponin elevation: (1) six comorbidities; (2) six comorbidities and two neurological factors; (3) all independent factors related to troponin elevation besides the eight main variables; and (4) all variables in Table 1 except for reperfusion therapy.

After adjusting for all variables in Table 1 and the reference

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troponin value, the multivariate Cox proportional hazard model was used to determine the predictive value of individual comorbidity for long-term risk of MACCE and mortality. The results of the Cox analysis were reported as a hazard ratio (HR) and 95% confidence interval (CI). Statistical analysis was performed using the Statistical Package for the Social Sciences (version 17.0; SPSS Inc., Chicago, IL, USA).

Results

General characteristics

The mean age of 1,092 consecutive patients with AIS over 2 years was 66.5±12.4 years (range, 18–95 years), and 691 patients (63.3%) were men. The overall distribution of serum troponin levels peaked on day 2 after stroke onset, and almost half of patients with elevated (43.5%) and minimally-elevated (49.9%)

Table 1. Baseline characteristics according to the troponin value

Variable	Troponin level			P-value*
	Elevated (n=145)	Minimally-elevated (n=335)	Non-detectable (n=612)	
Age (yr)	71.8±12.1	70.3±11.7	63.2±11.8	<0.01
Male	84 (57.9)	212 (63.3)	395 (64.5)	0.33
Conventional risk factors				
Hypertension	109 (75.2)	245 (73.1)	388 (63.4)	<0.01
Diabetes mellitus	58 (40.0)	100 (29.9)	180 (29.4)	0.04
Hyperlipidemia	86 (59.3)	221 (66.0)	407 (66.5)	0.25
Current smoking	34 (23.4)	88 (26.3)	209 (34.2)	<0.01
Preassigned comorbidities				
AF	69 (47.6)	120 (35.8)	121 (19.8)	<0.01
IHD	57 (39.3)	100 (29.9)	119 (19.4)	<0.01
MH	47 (32.4)	97 (29.0)	117 (19.1)	<0.01
HF	36 (24.8)	37 (11.0)	15 (2.5)	<0.01
RI	59 (40.7)	88 (26.3)	69 (11.3)	<0.01
Active cancer	23 (15.9)	22 (6.6)	28 (4.6)	<0.01
Neurological status				
NIHSS score	8 [3, 14]	4 [2, 8]	3 [1, 6]	<0.01
Insular cortical lesions	58 (40.0)	71 (21.1)	84 (13.7)	<0.01
Main laboratory findings				
White blood cell (×10³/μL)	9.1±3.7	8.2±3.0	7.9±2.6	<0.01
Hemoglobin (g/dL)	13.4±2.2	14.1±2.1	14.2±1.8	<0.01
Platelet (×10³/μL)	202.9±92.4	218.9±76.9	232.6±60.8	<0.01
Prothrombin time (international normalized ratio)	1.1±0.3	1.1±1.0	1.0±0.8	0.43
Activated partial thromboplastin time (sec)	27.4±5.4	26.8±3.2	26.8±3.5	0.22
Glucose (mg/dL)	155.3±69.9	141.7±54.5	140.6±57.5	0.02
High-density lipoprotein (mg/dL)	50.5±17.5	48.7±14.2	51.3±18.9	0.10
Low-density lipoprotein (mg/dL)	98.1±50.1	104.3±39.3	114.8±39.4	<0.01
Homocysteine (mmol/mL)	19.3±8.5	18.2±7.5	17.5±7.1	0.03
C-reactive protein (mg/dL)	1.5±4.1	0.6±1.6	0.4±1.4	<0.01
Total bilirubin (mg/dL)	0.7±0.4	0.6±0.4	0.6±0.3	<0.01
Albumin (g/dL)	3.5±0.5	3.7±0.4	3.9±0.4	<0.01
Total protein (g/dL)	6.8±0.9	6.9±0.7	7.0±0.5	<0.01
Reperfusion therapy	45 (31.0)	74 (22.1)	125 (20.4)	0.02

Variables are presented as means±standard deviations, medians [interquartile range], or numbers (%).
AF, atrial fibrillation; IHD, ischemic heart disease; MH, myocardial hypertrophy; HF, heart failure; RI, renal impairment; NIHSS, National Institutes of Health Stroke Scale.
*P-values are calculated using one-way analysis of variance or Pearson's chi-square test, as appropriate.

troponin had newly detected troponin elevations compared to the baseline level (Supplementary Figure 1A and B).

A total of 480 (44.0%) patients had troponin elevation; 145 (13.3%) had elevated and 335 (30.7%) had minimally-elevated troponin. Patients with troponin elevation were older and had a higher prevalence of hypertension and diabetes but a lower prevalence of smoking than those with non-detectable troponin levels. Moreover, these patients had a higher prevalence of comorbidities, a higher severity of neurological deficits, and a higher prevalence of insular cortical lesions than those with non-detectable troponin levels. They received more reperfusion treatment than those with non-detectable troponin levels. Moreover, patients with troponin elevation showed a higher leukocyte count and higher glucose, homocysteine, C-reactive protein, and total bilirubin levels but lower hemoglobin, platelet, low-density lipoprotein, albumin, and total protein levels than those with non-detectable troponin levels (Table 1).

Influence of troponin elevation–related factors

Multivariate ordinal logistic regression analyses were performed to determine the contribution of individual factors to troponin elevation (Table 2). The comorbidities, including AF (OR, 1.41; 95% CI, 1.05–1.89), MH (OR, 1.97; 95% CI, 1.48–2.63), HF (OR, 2.65; 95% CI, 1.64–4.27), RI (OR, 1.89; 95% CI, 1.37–2.59), active cancer (OR, 1.92; 95% CI, 1.17–3.14), and neurological status such as NIHSS score (OR, 1.05; 95% CI, 1.02–1.07) were associated with troponin elevation. In addition, IHD and insular lesions tended to be related to troponin elevation. Moreover, age (OR, 1.04; 95% CI, 1.02–1.05 per 1-year increase), leukocyte count (OR, 1.10; 95% CI, 1.05–1.16), platelet count (OR, 0.96; 95% CI, 0.95–0.98), and albumin level (OR, 0.50; 95% CI, 0.36–0.70) were associated with troponin elevation.

Model 1, with six comorbidities, showed an AUC of 0.715 (95% CI, 0.684–0.745) for predicting troponin elevation. The accuracy of a diagnostic test for predicting troponin elevation was further improved to an AUC of 0.729 (95% CI, 0.698–0.759) after including two neurological factors on top of Model 1. Additionally, the estimated AUC of 0.772 (95% CI, 0.744–0.800) after the inclusion of other independent troponin elevation factors on top of model 2 was comparable to that of the final model with an AUC of 0.778 (95% CI, 0.749–0.806) (Table 3).

Prognostic value of troponin elevation–related factors

During a median follow-up of 18 months (interquartile range, 11–26 months), 179 (17.0%) patients experienced MACCE, and 132 (12.1%) died. The Cox proportional hazards analysis showed that AF (HR, 1.49; 95% CI, 1.05–2.10), IHD (HR, 1.54; 95% CI,

1.09–2.17), and HF (HR, 1.91; 95% CI, 1.24–2.93) are associated with increased risk of MACCE, and HF (HR, 1.73; 95% CI, 1.07–2.80) and active cancer (HR, 2.86; 95% CI, 1.69–4.83) with increased risk of all causes of death. In addition, IHD and MH were associated with an increased risk of all causes of death (Table 4).

Table 2. Ordinal logistic regression analysis of the contribution of factors related to troponin elevation along with elevated and minimally-elevated troponin levels

| Variables | For troponin elevation | | | |
| | Univariate | | Multivariate* | |
	OR	95% CI	OR	95% CI
Main variables				
AF	2.64	2.05–3.40	1.41	1.05–1.89
IHD	2.05	1.58–2.66	1.32	0.99–1.76
MH	1.77	1.36–2.30	1.97	1.48–2.63
HF	6.17	4.08–9.35	2.65	1.64–4.27
RI	3.47	2.61–4.61	1.89	1.37–2.59
Active cancer	2.60	1.65–4.11	1.92	1.17–3.14
NIHSS score	1.10	1.08–1.12	1.05	1.02–1.07
Insular lesion	2.62	1.97–3.50	1.34	0.94–1.91
Epidemiological information				
Age (yr)	1.06	1.04–1.07	1.04	1.02–1.05
Male	0.86	0.68–1.09	N/A	
Hypertension	1.60	1.24–2.07	N/A	
Diabetes mellitus	1.25	0.98–1.61	N/A	
Hyperlipidemia	0.86	0.68–1.10	N/A	
Current smoking	0.66	0.51–0.85	N/A	
Laboratory results				
White blood cell ($\times10^3/\mu L$)	1.08	1.04–1.13	1.10	1.05–1.16
Hemoglobin (g/dL)	0.86	0.81–0.91	N/A	
Platelet ($\times10^3/\mu L$)	0.95	0.94–0.97	0.96	0.95–0.98
Prothrombin time (international normalized ratio)	1.08	0.94–1.24	N/A	
Activated partial thromboplastin time (sec)	1.02	0.99–1.05	N/A	
Glucose (10 mg/dL)	1.02	1.00–1.04	N/A	
High-density lipoprotein (10 mg/dL)	0.95	0.87–1.02	N/A	
Low-density lipoprotein (10 mg/dL)	0.93	0.89–0.95	N/A	
Homocysteine (mmol/mL)	1.02	1.00–1.04	N/A	
C-reactive protein (mg/dL)	1.19	1.10–1.29	N/A	
Total bilirubin (mg/dL)	1.59	1.16–2.19	N/A	
Albumin (g/dL)	0.26	0.19–0.35	0.50	0.36–0.70
Total protein (g/dL)	0.67	0.55–0.81	N/A	

OR, odds ratio; CI, confidence interval; AF, atrial fibrillation; IHD, ischemic heart disease; MH, myocardial hypertrophy; HF, heart failure; RI, renal impairment; NIHSS, National Institutes of Health Stroke Scale; N/A, not applicable. *Adjustments were made for age, sex, conventional risk factors, and all laboratory results, besides the troponin elevation-related conditions, including six comorbidities and two neurological factors.

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Table 3. An AUC and goodness-of-fit test for the multivariate models for predicting troponin elevation

Models for prediction of elevated and minimally-elevated troponin levels				Diff.	*P*-value*	Diff.	*P*-value*	Diff.	*P*-value*
Description		AUC	95% CI						
Model 1	Six comorbidities	0.715	0.684–0.745	Ref.					
Model 2	Eight factors	0.729	0.698–0.759	0.014	0.06	Ref.			
Model 3	Eight factors and four other determinants	0.772	0.744–0.800	0.057	<0.01	0.043	<0.01	Ref	
Model 4	All variables (total of 27 variables)	0.778	0.749–0.806	0.063	<0.01	0.049	<0.01	0.006	0.50

Model 1 included six comorbidities, such as AF, IHD, MH, HF, RI, and active cancer. Model 2 included the NIHSS score and insular cortical lesions in addition to the factors included in model 1. Model 3 included age, leukocyte count, and low-density lipoprotein and albumin levels in addition to the factors included in model 2. Model 4 included age, sex, conventional risk factors, and all laboratory results mentioned in Table 1.
AUC, area under the receiver operating characteristic curve; CI, confidence interval; Diff., difference; Ref., reference; AF, atrial fibrillation; IHD, ischemic heart disease; MH, myocardial hypertrophy; HF, heart failure; RI, renal impairment; NIHSS, National Institutes of Health Stroke Scale.
*Comparing the AUC of paired data using the method by DeLong et al.[27]

Substudy for assessment of subclinical ACS risk

Among the 142 enrolled patients, no significant difference in the degree or number of CAD across the different troponin levels was observed. Almost half of the patients had no significant CAD, regardless of the troponin level (Table 5).

Only nine of the 29 patients with troponin surge (2.7%) were presumed to have symptomatic CAD (six cases with ACS and three cases with recent angina within 7 days). Among the remaining 20 patients, stress-induced cardiomyopathy (SICMP; six patients were in a comatose state, n=7), active cancer with extensive multiple metastases (all patients had D-dimer levels >25 μg/mL, n=5), and other medical conditions (n=8) were suspected as primary causes of troponin surge (Supplementary Table 1).

Discussion

This prospective study verified the overall influence of comorbidity burden on troponin elevation in AIS, with separate consideration of neurological status. In this study, the overall incidence of troponin elevation was not comparable with that observed in previous studies because our unique time point defined the troponin level two days after stroke onset as the reference level. Traditionally, the guidelines for AIS management recommend repeated troponin measurements in a few cases with the possibility of development of silent ischemia.[7] However, assessing dynamic changes in troponin levels is still important for differentiating the cause of cardiomyocyte damage and distinguishing acute elevations from chronic ones that are associated with a variety of chronic conditions,[1] which can be further clarified using a highly sensitive troponin assay for the deliberate detection of dynamic change.[3] In this context, our study shows that repeated troponin measurements using a highly sensitive troponin assay can enhance the detection and tracking of troponin elevation, including newly detected as well as minimally-elevated troponin (Supplementary Figure 1A and B), and the risk stratification

Table 4. Unadjusted and adjusted HR for the individual contribution of comorbidities to clinical outcomes during the 3-year follow-up

Variable	Unadjusted		Adjusted*	
	HR	95% CI	HR	95% CI
AF				
For MACCE	2.10	1.57–2.83	1.49	1.05–2.10
For all-cause of death	1.99	1.41–2.81	1.29	0.85–1.95
IHD				
For MACCE	1.93	1.42–2.60	1.54	1.09–2.17
For all-cause of death	1.55	1.08–2.22	1.42	0.93–2.18
MH				
For MACCE	1.09	0.78–1.52	1.01	0.70–1.45
For all-cause of death	1.42	0.98–2.50	1.41	0.92–2.17
HF				
For MACCE	3.67	2.55–5.27	1.91	1.24–2.93
For all-cause of death	3.85	2.56–5.78	1.73	1.07–2.80
RI				
For MACCE	1.88	1.36–2.60	1.09	0.74–1.62
For all-cause of death	2.15	1.50–3.10	0.83	0.51–1.34
Active cancer				
For MACCE	1.62	0.97–2.71	1.43	0.80–2.57
For all-cause death	5.31	3.56–7.90	2.86	1.69–4.83

HR, hazard ratio; CI, confidence interval; AF, atrial fibrillation; MACCE, major adverse cardiac and cerebrovascular events; IHD, ischemic heart disease; MH, myocardial hypertrophy; HF, heart failure; RI, renal insufficiency.
*Adjustments were made for all clinically relevant variables in Table 1, along with the reference troponin value measured on day 2 after stroke onset.

power to detect more high-risk patients with a higher burden of comorbidity and neurological deficits (Supplementary Figure 1C and D).

We verified the individual influence of six comorbidities on troponin elevation (Table 2), and their integrated influence on troponin elevation in combination with two neurological factors showed an AUC of 0.729 (Table 3). Therefore, troponin elevation in AIS can be explained by the burden of comorbidities in com-

Table 5. Coronary CTA according to troponin level

Variable	Cardiac troponin I among eligible patients*			P-value[†]
	Elevated (n=25 of 60)	Minimally-elevated (n=58 of 159)	Non-detectable (n=59 of 395)	
Age (yr)	68.3±12.6	68.3±10.7	64.8±9.5	0.17
Male	20 (80.0)	42 (72.4)	46 (78.0)	0.69
IHD (history or positive ischemic-ECG)	10 (40.0)	24 (41.4)	22 (37.3)	0.90
Obstructive disease				0.82
No CAD	4 (16.0)	11 (19.0)	9 (15.3)	
Non-obstructive CAD	10 (40.0)	20 (34.5)	27 (45.8)	
Obstructive CAD (>50% diameter stenosis)	11 (44.0)	27 (46.6)	23 (39.0)	
Number of CAD with >50% diameter stenosis				0.67
No	14 (56.0)	31 (53.4)	36 (61.0)	
1 or 2	6 (24.0)	20 (34.5)	17 (28.8)	
3 or left main disease	5 (20.0)	7 (12.1)	6 (10.2)	

Variables are presented as means±standard deviations or as numbers (%).
CTA, computed tomography angiography; IHD, ischemic heart disease; ECG, electrocardiography; CAD, coronary arterial disease.
*During evaluation of the CAD burden, 150 of 623 patients eligible for coronary CTA were initially enrolled, and eight had CTA failure; [†]P-values are calculated using analysis of variance, or Pearson's chi-square test or Fisher's exact test, as appropriate.

bination with neurological status, which, in turn, explains the prognostic value of the troponin assay in these patients when the prognostic significance of each comorbidity beyond neurological status is considered (Table 4). Troponin elevation indicates underlying cardiac comorbidities, which leads to an increased risk of cardiogenic embolic stroke with extensive ischemic lesions.[15] Furthermore, apart from the fatal impact of stroke, underlying comorbidities (i.e., AF,[16] HF,[17] IHD,[18] MH,[19] and RI[20]) also lead to poor outcomes. Therefore, despite the skeptical viewpoint on intensive cardiac monitoring in the recent AIS guidelines,[7] detecting troponin elevation-related comorbidities by measuring disease-related biomarkers can be a complementary tool for long-term risk stratification in patients with AIS.

In this study, the detection of subclinical ACS risk remains a diagnostic challenge, considering its fatal outcome. Patients with AIS are often older adults, and concomitant cardiac pathology is common; however, acquiring ACS symptoms is difficult due to cognitive dysfunction, aging, or neurological deficits. Thus, we attempted to define IHD based on the ischemic-ECG findings apart from the patients' medical history because elevated troponin levels caused by "silent ischemia" can be monitored using ischemic-ECG changes.[21] Finally, the overall IHD incidence (25.3%) was consistent with that reported in the literature (e.g., 20%–30% and 40% for symptomatic and asymptomatic IHD, respectively).[22] Additionally, among the 142 randomly selected patients, coronary CTA revealed no significant difference in grade or number of CAD across different troponin levels; half of the patients had no CAD (Table 5). This finding corroborates with those of a previous study that showed less frequent coronary culprit lesions in patients with AIS than in age- and sex-matched controls with

non-ST-segment elevation myocardial infarction (NSTEMI), despite similar baseline troponin levels.[23] Furthermore, of the 29 patients with a troponin surge, only nine were presumed to have symptomatic CAD (Supplementary Table 1). Therefore, troponin elevation indicates a burden of various ranges of cardiac and non-cardiac comorbidities in patients with AIS, even when subclinical ACS risk is considered.

Previously, we suggested the cerebrogenic myocardial injury (CMI) concept to explain the troponin elevation in AIS and could confirm it in this study (Supplementary Figure 2): synergistic interaction between vulnerable cardiac status (e.g., hypertrophic or damaged myocardium) and specific neurological conditions, leading to troponin elevation.[10] Finally, we proposed a diagnostic approach model for improving the practical application of the troponin assay in patients with AIS: (1) serial troponin measurements can improve the detection and tracking of the troponin level considering newly detected troponin elevation; (2) measurements of disease-related biomarkers can improve the detection of comorbidities, with the merit of long-term prognostic value beyond stroke severity; and (3) separate recognition of neurological status can show the interactive influence of neurogenic stress on comorbidity burden (Figure 2). Hence, stroke should be considered a systemic disease, and bidirectional interactions between the brain and peripheral organs should be considered for comprehensive therapeutics for AIS.[4]

Study limitations

This study has several limitations. First, this study was conducted at a single center; all patients were Asian. Second, the diagnostic accuracy of comorbidities based on disease-related biomarkers
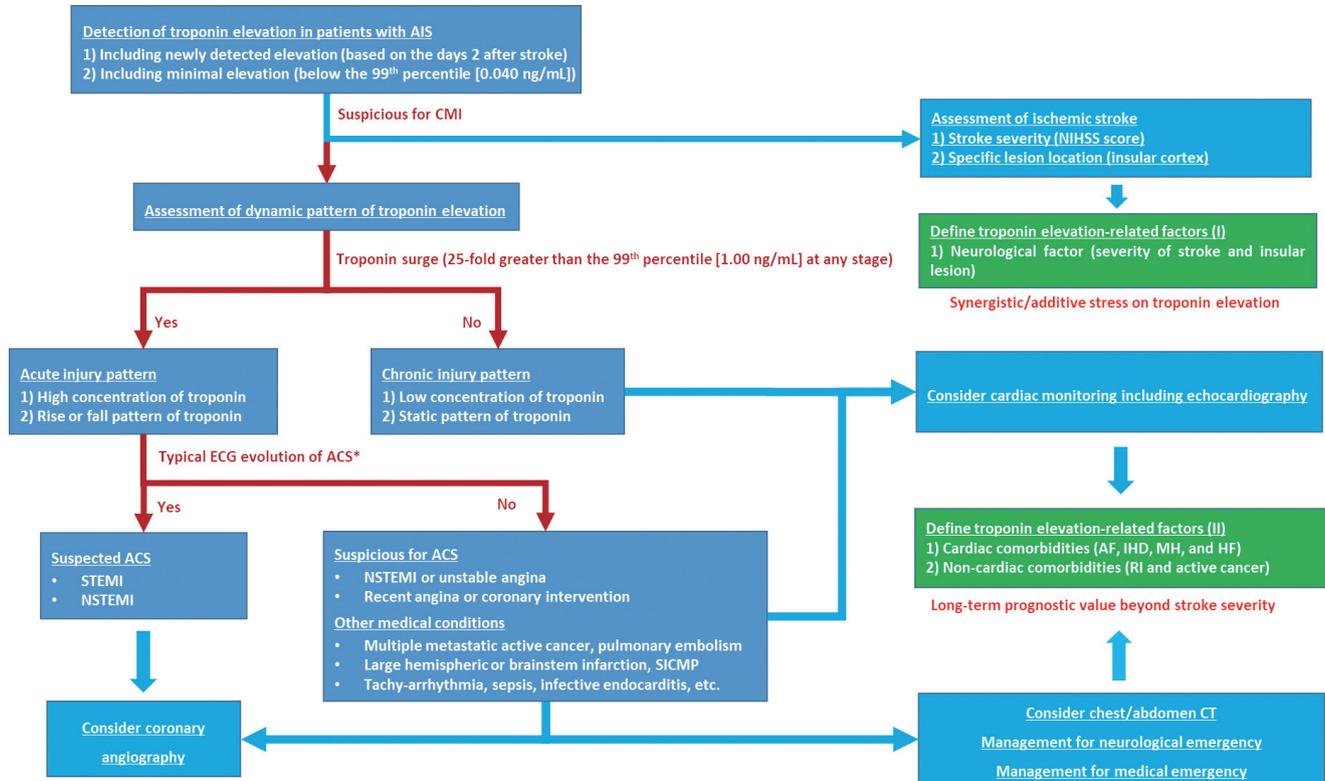
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Figure 2. Diagnostic approach model for assessing troponin elevation in patients with AIS. Process for detecting the troponin elevation (red line) and etiological evaluation of troponin elevation (blue line), including the recommendation of the clinical process (blue box) and diagnosis of the troponin elevation-related factors (green box). AIS, acute ischemic stroke; CMI, cerebrogenic myocardial injury; NIHSS, National Institutes of Health Stroke Scale; ECG, electrocardiography; ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; RI, renal insufficiency; SICMP, stress-induced cardiomyopathy; AF, atrial fibrillation; IHD, ischemic heart disease; MH, myocardial hypertrophy; HF, heart failure; RI, renal insufficiency; CT, computed tomography; LBBB, left bundle branch block. *ECG pattern, including (1) suspicious STEMI, which initially developed as an acute ischemic change (e.g., ST-segment elevation or LBBB), followed by newly developed Q-wave on serial ECG investigation; and (2) suspicious NSTEMI, which transiently/persistently developed as an acute ischemic change (e.g., ST-segment depression with or without T-wave inversion) on serial ECG investigation.

might remain limited; ischemic-ECG alone is often insufficient to diagnose IHD because it depends on various CAD conditions (e.g., size, arterial segment distribution, collateral vessels, location, extent, coronary stenosis severity, and prior myocardial necrosis) and may be observed in other conditions (e.g., acute pericarditis, VH, LBBB, the Brugada syndrome, SICMP, and early repolarization patterns).[21] HF diagnosis was difficult owing to limited diagnostic values, and the main terminology was based on the left ventricle ejection fraction measurement. ECG diagnostics of VH are based on the QRS voltage criteria for diagnosing MH; however, an increased QRS voltage in actual anatomical VH is not a consistent finding. Nonetheless, an alternative diagnostic approach in clinical practice includes serum level measurement of BNP as a "rule-out" test in HF diagnosis,[24] and the ECG criteria for VH are a strong independent predictor of cardiovascular morbidity and mortality.[25] Furthermore, when we applied more strict criteria for defining cardiac comorbidity based on the echocardiographic findings, such as IHD, MH, and HF,[26] the statistical significance of their individual influences on troponin elevation

and long-term prognostic value were still preserved, and their overall explanatory power for troponin elevation was further improved (Supplementary Tables 2-4). Third, the findings of coronary CTA have a generalization limitation because we only recruited 25% of eligible patients. However, the main confounders (e.g., age, sex, and prevalence of IHD) for determining the difference in CAD severity were similar across the troponin levels.

Conclusions

The elevation of serum troponin levels in patients with AIS is associated with the increasing burden of troponin elevation-related comorbidities, with a synergistic impact on the neurological status and a proportionally increased risk of long-term adverse outcomes. Thus, serum troponin levels, especially considering dynamic changes along with disease-related biomarkers, can be helpful in the risk stratification of patients with AIS.

Supplementary materials

Disclosure

Acknowledgments

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Supplemental Table 1. Presumptive diagnoses and outcomes of patients with troponin surge exceeding 1.00 ng/mL

| No | Troponin Baseline Days 2 Days 5 | Cardiac comorbidities | | | | Other comorbidities | | Neurological factors | | Consensus decision for a possible etiology |
		AF	IHD (WMIS)	MH (VMI)	HF (EF)	RI (GFR)	Cancer (D-dimer)	NIHSS score	Insular lesion	
1*	9.86 89.59 36.68	Y	Y (1.7)‡	N (144)‡	Y (35)‡	Y (47)	N (5.41)	16	Y	STEMI with HF history
2	0.34 22.23 2.34	Y	Y (1.0)	N (88)	Y (61)	Y (58)	N (3.90)	29	Y	R/O SICMP or NSTEMI with aggravated RI (comatose state)
3	0.02 12.94 5.61	Y	Y (1.0)	N (94)	Y (58)	Y (53)	Y (27.90)	2	N	Newly diagnosed hepatocellular cell carcinoma with metastasis
4*	0.23 9.14 5.27	N	Y (1.5)‡	Y (97)	N (53)	N (53)	N (0.37)	0	N	STEMI
5*	0.02 6.89 2.55	N	Y (2.0)‡	N (174)‡	Y (30)‡	N (89)	N (3.60)	10	N	STEMI with history of HF
6	8.85 6.29 3.47	N	N (1.0)	Y (186)‡	Y (61)	N (90)	N (0.48)	5	N	Marked sinus bradycardia due to multiple sinus pause
7	5.18 5.88 2.83	Y	N (1.0)	N (92)	N (56)	N (66)	Y (35.20)	5	N	Newly diagnosed cholangiocarcinoma with metastasis
8†	0.76 5.84 1.28	Y	Y (1.0)	Y (116)‡	N (52)	N (80)	N (0.90)	13	Y	NSTEMI
9†	0.36 4.98 2.32	N	Y (1.0)	N (77)	Y (66)	Y (8)	N (1.00)	23	Y	NSTEMI with septic shock and aggravated RI
10	2.68 4.88 1.33	Y	Y (1.0)	N (121)‡	Y (58)	Y (11)	N (2.13)	15	Y	Recent UA with end-stage RI
11	10.60 4.67 1.42	Y	N (1.2)‡	Y (149)‡	Y (60)	N (60)	N (13.08)	17	N	Infective endocarditis
12	3.24 4.08 6.01	N	N (1.3)‡	Y (100)‡	N (64)	Y (38)	N (1.28)	5	N	Other medical conditions (anemia and end-stage RI)
13	4.39 3.68 1.25	N	Y (1.0)	N (69)‡	N (64)	Y (53)	Y (6.22)	6	Y	Newly diagnosed non-small cell lung cancer with metastasis
14	5.05 2.80 0.56	Y	Y (1.0)	N (121)‡	N (60)	Y (59)	N (0.71)	1	N	Pulmonary hypertension due to left ventricular outflow tract obstruction
15	15.42 2.42 1.01	Y	N (2.0)‡	N (57)	Y (45)‡	N (84)	N (0.49)	11	Y	SICMP with apical ballooning
16	0.006 2.11 2.11	N	Y (1.0)	N (105)	Y (64)	N (60)	N (0.45)	2	N	Recent UA with 3-vessel coronary artery disease
17	0.03 1.50 0.06	N	Y (2.0)‡	N (107)	N (36)‡	N (80)	N (0.45)	22	Y	R/O SICMP with HF history (comatose state)

Supplemental Table 1. Continued

No	Troponin Baseline Days 2 Days 5	AF	IHD (WMIS)	MH (VMI)	HF (EF)	RI (GFR)	Cancer (D-dimer)	NIHSS score	Insular lesion	Consensus decision for a possible etiology
18	0.22 1.43 0.24	Y	Y (1.4)†	N (66)	Y (62)	N (75)	N (44.10)	18	Y	R/O SICMP and AF with SVR (comatose state)
19	1.23 1.31 N/A	N	Y (1.6)†	N (102)†	Y (44)†	Y (29)	Y (30.36)	15	N	Pancreatic cancer with metastasis and inferior vena cava thrombosis
20	1.10 1.24 0.14	N	N (1.0)	N (85)	N (62)	Y (58)	Y (27.80)	7	N	Cholangiocarcinoma with metastasis and DVT
21	0.01 1.21 N/A	Y	N (N/A)	Y (N/A)	N (N/A)	Y (58)	N (4.15)	17	N	R/O SICMP and AF with RVR (comatose state due to brainstem infarction)
22	0.01 1.20 0.006	N	N (1.0)	Y (116)†	N (58)	N (90)	N (0.34)	13	Y	R/O SICMP (neurological deterioration leading to craniectomy)
23	5.83 0.92 0.48	Y	Y (1.0)	N (131)†	N (61)	N (79)	N (2.88)	13	Y	R/O SICMP (neurological deterioration leading to craniectomy)
24	1.85 0.82 0.34	Y	N (1.0)	N (108)†	Y (59)	N (62)	N (4.10)	3	Y	AF with SVR
25	1.54 0.68 0.16	N	Y (1.0)	N (75)	N (67)	N (64)	N (0.37)	0	N	Other medical conditions (polycythemia vera with hyperkalemia)
26	1.47 0.62 N/A	N	N (1.0)	N (70)†	N (61)	N (82)	Y (24.09)	8	Y	Non-small cell lung cancer with metastasis and DVT
27	1.03 0.57 N/A	N	N (1.0)	Y (132)†	N (60)	N (75)	N (0.70)	3	N	New-onset UA with 3-vessel coronary artery disease
28*	0.11 0.36 4.26	N	Y (2.6)†	N (113)†	Y (34)†	Y (4)	Y (35.20)	11	N	Delayed onset STEMI with end-stage RI and renal cell carcinoma
29	0.03 0.03 4.32	Y	N (1.0)	Y (97)†	N (58)	N (66)	N (0.53)	13	N	AF with RVR

AF, atrial fibrillation; IHD, ischemic heart disease; WMIS, wall motion index score; MH, myocardial hypertrophy; VMI, ventricular mass index (g/m²); HF, heart failure; EF, ejection fraction (%); RI, renal impairment; GFR, glomerular filtration rate (mL/min/1.73 m²); NIHSS, National Institutes of Health Stroke Scale; STEMI, ST-segment elevation myocardial infarction; R/O, rule out; SICMP, stress-induced cardiomyopathy; NSTEMI, non-ST-segment elevation myocardial infarction; UA, unstable angina; SVR, slow ventricular response; DVT, deep vein thrombosis; RVR, rapid ventricular response; ECG, electrocardiography; LBBB, left bundle branch block; CAD, coronary arterial disease.
*ECG pattern suspicious of STEMI, which initially developed as an acute ischemic change (e.g., ST-segment elevation or LBBB), followed by newly developed Q-wave on serial ECG investigation; †ECG pattern suspicious of NSTEMI, which transiently/persistently developed as an acute ischemic change (e.g., ST-segment depression with or without T-wave inversion) on serial ECG investigation; ‡Echocardiographic abnormalities including (1) WMIS (>1 using a standard 16-segment model) compatible with CAD, (2) VMI (>95 g/m² for women and >115 g/m² for men), and (3) reduced EF (defined as <50%).

Supplemental Table 2. Recalculated ordinal logistic regression analysis of the contribution of factors related to troponin elevation along with elevated and minimally-elevated troponin levels

Variables	For troponin elevation			
	Univariate		Multivariate*	
	OR	95% CI	OR	95% CI
Main variables				
AF	2.64	2.05–3.40	1.31	0.97–1.76
IHD[†]	3.93	2.95–5.24	2.18	1.52–3.11
MH[†]	4.09	3.14–5.33	2.99	2.24–3.99
HF[†]	5.26	3.35–8.25	1.39	0.79–2.44
RI	3.47	2.61–4.61	1.94	1.31–2.48
Active cancer	2.60	1.65–4.11	1.96	1.17–3.21
NIHSS score	1.10	1.08–1.12	1.05	1.02–1.08
Insular lesion	2.62	1.97–3.50	1.30	0.91–1.86
Epidemiological information				
Age (years)	1.06	1.04–1.07	1.03	1.02–1.04
Male	0.86	0.68–1.09	N/A	
Hypertension	1.60	1.24–2.07	N/A	
Diabetes mellitus	1.25	0.98–1.61	N/A	
Hyperlipidemia	0.86	0.68–1.10	N/A	
Current smoking	0.66	0.51–0.85	N/A	
Laboratory results				
White blood cell ($\times 10^3$/μL)	1.08	1.04–1.13	1.11	1.06–1.16
Hemoglobin (g/dL)	0.86	0.81–0.91	N/A	
Platelet ($\times 10^3$/μL)	0.95	0.94–0.97	0.97	0.95–0.99
Prothrombin time (international normalized ratio)	1.08	0.94–1.24	N/A	
Activated partial thromboplastin time (seconds)	1.02	0.99–1.05	N/A	
Glucose (10 mg/dL)	1.02	1.00–1.04	N/A	
High-density lipoprotein (10 mg/dL)	0.95	0.87–1.02	N/A	
Low-density lipoprotein (10 mg/dL)	0.93	0.89–0.95	N/A	
Homocysteine (mmol/mL)	1.02	1.00–1.04	N/A	
C-reactive protein (mg/dL)	1.19	1.10–1.29	N/A	
Total bilirubin (mg/dL)	1.59	1.16–2.19	N/A	
Albumin (g/dL)	0.26	0.19–0.35	0.45	0.33–0.64
Total protein (g/dL)	0.67	0.55–0.81	N/A	

OR, odds ratio; CI, confidence interval; AF, atrial fibrillation; IHD, ischemic heart disease; MH, myocardial hypertrophy; HF, heart failure; RI, renal impairment; NIHSS, National Institutes of Health Stroke Scale; N/A, not applicable; CAD, coronary arterial disease.
*Adjustments were made for age, sex, conventional risk factors, and all laboratory results, besides the troponin elevation-related conditions, including six candidate comorbidities and two neurological factors; [†]Two-dimensional transthoracic echocardiography was conducted in patients who fulfilled the prescreening criteria: (1) suspected as having preassigned comorbidities; (2) suspected as having other cardiac comorbidities including arrhythmia and valvular or structural heart disease in the known history; (3) suspected as having potential embolic sources contributing to embolic stroke pattern; and (4) suspected as having medical conditions possibly contributing to embolism, including active cancer, hematologic or autoimmune disease, aortic problem, or other coagulopathic conditions. Finally, echocardiography was conducted on a total of 774 out of 1,092 patients. Then, cardiac comorbidity was redefined based on the echocardiographic abnormalities: (1) IHD was redefined as known history or having an echocardiographic wall motion abnormality which was defined as wall motion score index >1 using a standard 16-segment model compatible with CAD; (2) MH was redefined as known history or having echocardiographic ventricular hypertrophy which was defined as ventricular mass index >95 g/m^2 for women and >115 g/m^2 for men; and (3) HF was redefined as known history or having a reduced ejection fraction which was defined as <50%.

Supplemental Table 3. Redefined area under the ROC curve and goodness-of-fit test of the multivariate models for predicting troponin elevation

Models for prediction of elevated and minimally-elevated troponin levels				Diff.	P-value*	Diff.	P-value*	Diff.	P-value*
Description		AUC	95% CI						
Model 1	Six comorbidities[†]	0.745	0.716–0.774	Ref.					
Model 2	Eight factors[†]	0.760	0.731–0.789	0.015	0.032	Ref.			
Model 3	Eight factors and four other determinants[†]	0.794	0.767–0.821	0.049	<0.01	0.034	<0.01	Ref	
Model 4	All variables (total of 27 variables)[†]	0.804	0.777–0.831	0.059	<0.01	0.044	<0.01	0.010	0.038

Model 1 included six comorbidities, such as AF, IHD, MH, HF, RI, and active cancer. Model 2 included the NIHSS score and insular cortical lesions in addition to the factors included in model 1. Model 3 included age, leukocyte count, and LDL and albumin levels in addition to the factors included in model 2. Model 4 included age, sex, conventional risk factors, and all laboratory results mentioned in Table 1.

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; Diff., difference; Ref., reference; AF, atrial fibrillation; IHD, ischemic heart disease; MH, myocardial hypertrophy; HF, heart failure; RI, renal impairment; NIHSS, National Institutes of Health Stroke Scale; LDL, low-density lipoprotein; CAD, coronary artery disease.
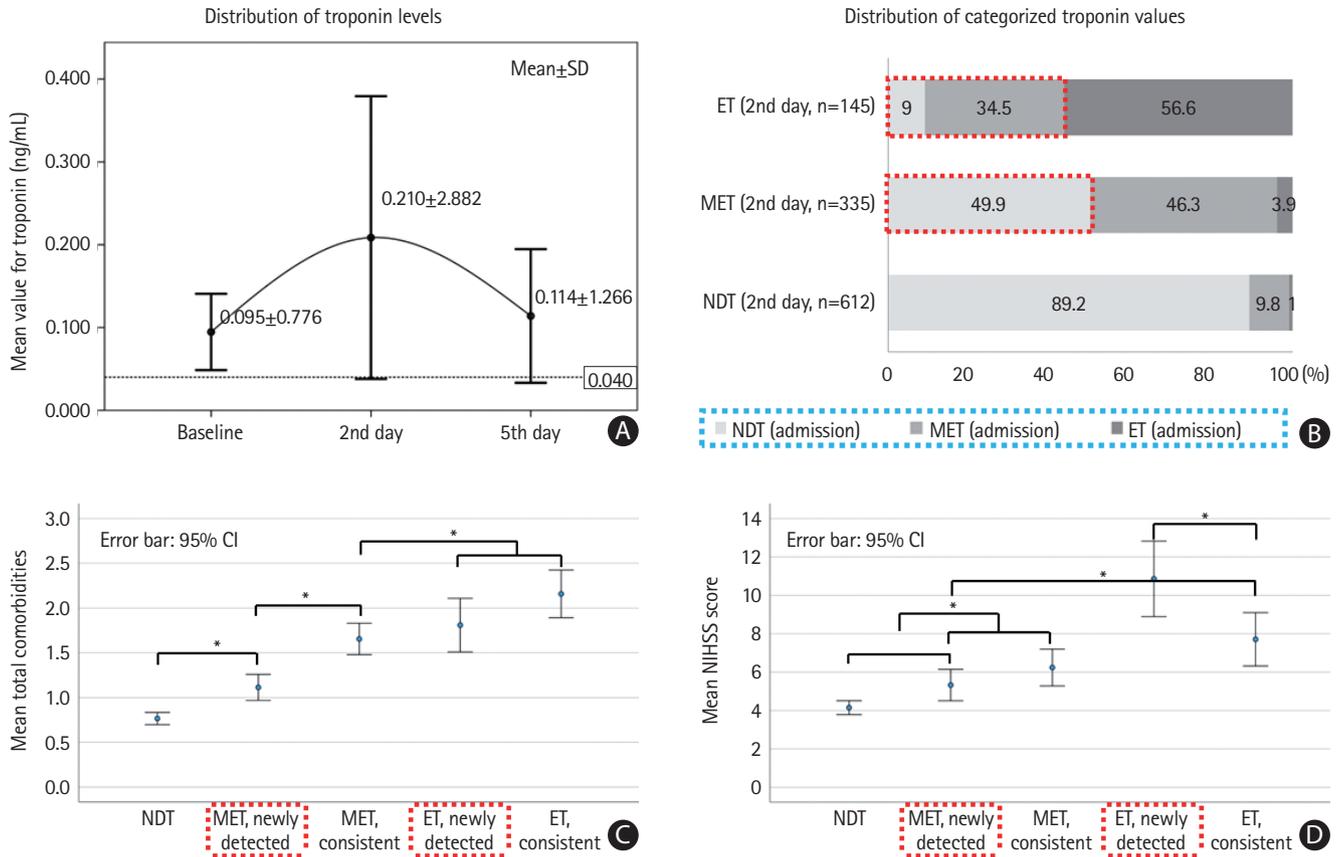
*Comparing the AUC of paired data ROC curves using the method of DeLong et al.[27]; [†]Two-dimensional transthoracic echocardiography was conducted on patients who fulfilled the prescreening criteria: (1) suspected as having preassigned comorbidities; (2) suspected as having other cardiac comorbidities including arrhythmia and valvular or structural heart disease in the known history; (3) suspected as having potential embolic sources contributing to embolic stroke pattern; and (4) suspected as having medical conditions possibly contributing to embolism, including active cancer, hematologic or autoimmune disease, aortic problem, or other coagulopathic conditions. Finally, echocardiography was conducted on a total of 774 out of 1,092 patients. Then, cardiac comorbidity was redefined based on the echocardiographic abnormalities: (1) IHD was redefined as known history or having an echocardiographic wall motion abnormality which was defined as wall motion score index >1 using a standard 16-segment model compatible with CAD; (2) MH was redefined as known history or having echocardiographic ventricular hypertrophy which was defined as ventricular mass index >95 g/m^2 for women and >15 g/m^2 for men; and (3) HF was redefined as known history or having a reduced ejection fraction which was defined as <50%.

Supplemental Table 4. Redefined unadjusted and adjusted HRs for the individual contribution of comorbidities to clinical outcomes during the 3-year follow-up

Variable	Unadjusted		Adjusted*	
	HR	95% CI	HR	95% CI
AF				
For MACCE	2.10	1.57–2.83	1.49	1.05–2.10
For all-cause of death	1.99	1.41–2.81	1.29	0.85–1.95
IHD[†]				
For MACCE	1.93	1.42–2.60	2.07	1.46–2.95
For all-cause of death	2.04	1.42–2.93	1.42	0.91–2.21
MH[†]				
For MACCE	1.09	0.78–1.52	1.28	0.92–1.78
For all-cause of death	2.22	1.57–3.13	1.41	0.92–2.17
HF[†]				
For MACCE	3.09	2.09–4.58	1.91	1.23–2.97
For all-cause of death	3.59	2.34–5.52	2.12	1.28–3.48
RI				
For MACCE	1.88	1.36–2.60	1.09	0.74–1.62
For all-cause of death	2.15	1.50–3.10	0.83	0.51–1.34
Active cancer				
For MACCE	1.62	0.97–2.71	1.43	0.80–2.57
For all-cause death	5.31	3.56–7.90	2.86	1.69–4.83

HR, hazard ratio; CI, confidence interval; AF, atrial fibrillation; MACCE, major adverse cardiac and cerebrovascular events; IHD, ischemic heart disease; MH, myocardial hypertrophy; HF, heart failure; RI, renal impairment; NIHSS, National Institutes of Health Stroke Scale; CAD, coronary artery disease.

*The multivariate Cox proportional hazards model was used to determine the prognostic significance of the individual impacts of six troponin elevation-related comorbidities for long-term risk of the MACCE, and mortality after adjusting for all clinically relevant variables, including age, sex, conventional risk factors, all laboratory findings, neurological status including the NIHSS score, and reperfusion therapy along with the reference troponin value measured on day 2 after stroke onset; [†]Two-dimensional transthoracic echocardiography was conducted in patients who fulfilled the pre-screening criteria: (1) suspected as having preassigned comorbidities; (2) suspected as having other cardiac comorbidities including arrhythmia and valvular or structural heart disease in the known history; (3) suspected as having potential embolic sources contributing to embolic stroke pattern; and (4) suspected as having medical conditions possibly contributing to embolism, including active cancer, hematologic or autoimmune disease, aortic problem, or other coagulopathic conditions. Finally, echocardiography was conducted on a total of 774 out of 1,092 patients. Then, cardiac comorbidity was redefined based on the echocardiographic abnormalities: (1) IHD was redefined as known history or having an echocardiographic wall motion abnormality which was defined as wall motion score index >1 using a standard 16-segment model compatible with CAD; (2) MH was redefined as known history or having echocardiographic ventricular hypertrophy which was defined as ventricular mass index >95 g/m^2 for women and >115 g/m^2 for men; and (3) HF was redefined as known history or having a reduced ejection fraction which was defined as <50%.

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Supplementary Figure 1. The dynamic pattern of serum troponin levels across time (A and B) and the burden of comorbidity and neurological status according to dynamic changes in categorized troponin levels (C and D). Newly detected troponin elevation (red dotted box) was compared with baseline troponin (blue dotted box) based on the categorized values. The burden of comorbidities was defined as the total number of predefined comorbidities, and the neurological burden as the mean NIHSS score. SD, standard deviation; ET, elevated troponin; MET, minimally-elevated troponin; NDT, non-detectable troponin; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale. *$P<0.05$ using analysis of variance with Duncan's *post hoc* test.
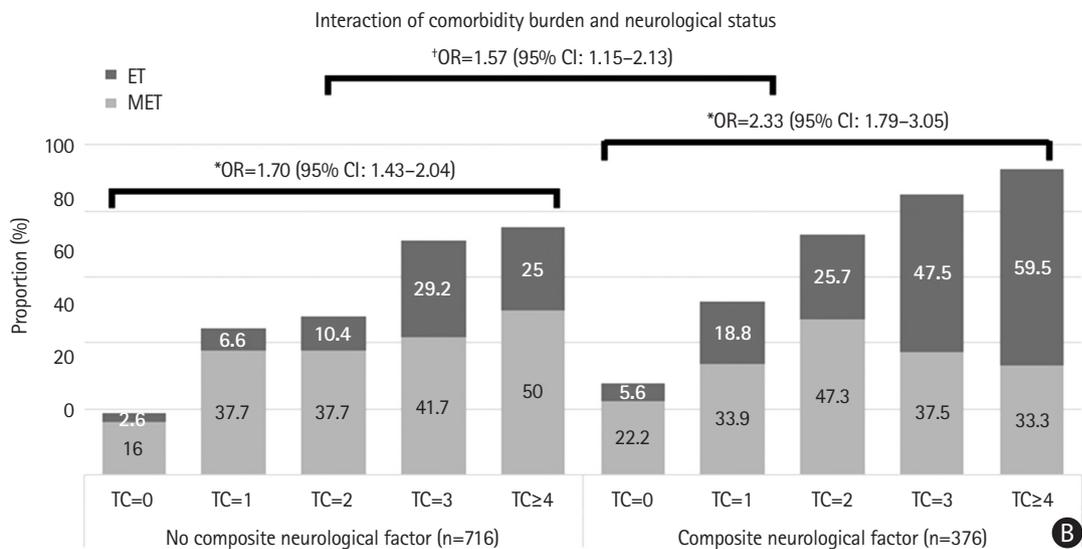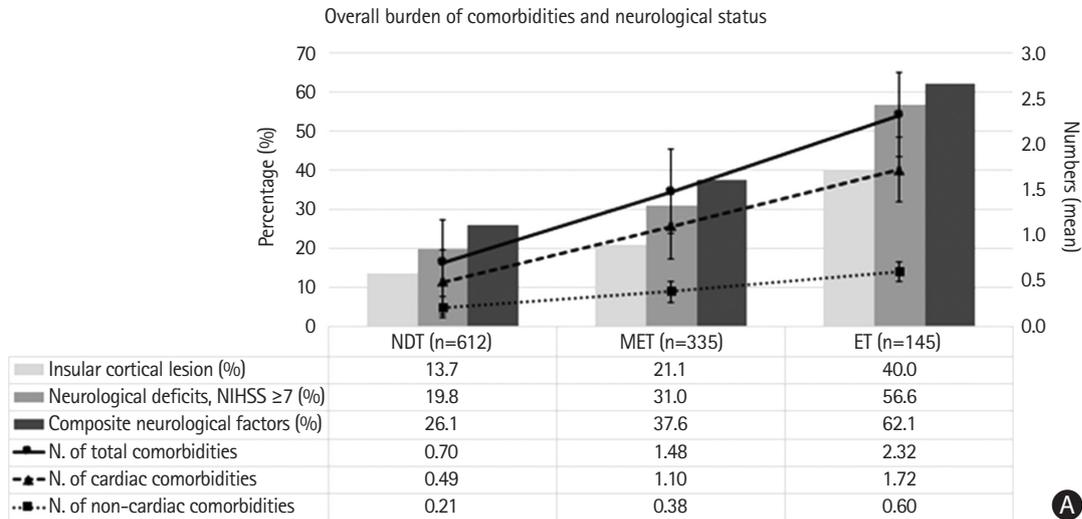
Supplementary Figure 2. Influence of comorbidity burden and neurological status on troponin elevation. (A) Comorbidity burden (defined as the total number of candidate comorbidities) and composite neurological conditions (defined as either moderate to severe deficit [NIHSS of ≥7 points], insular lesions, or both) increased linearly as the troponin level increased. (B) Conversely, the magnitude of troponin elevation increased linearly as the comorbidity burden increased, with rates being further higher in patients with a composite neurological status. NIHSS, National Institutes of Health Stroke Scale; N., number; NDT, non-detectable troponin; MET, minimally-elevated troponin; ET, elevated troponin; OR, odds ratio; CI, confidence interval; TC, total comorbidities. *$P < 0.05$ of OR for each number of TC after adjusting for age, sex, conventional risk factors, and all laboratory results; [†]$P < 0.05$ of OR of a composite neurological factor after adjusting for age, sex, conventional risk factors, all laboratory results, and the number of TC.