Troponin Levels and Outcomes in Patients with Embolic Stroke of Undetermined Source

Kang-Ho Choi,[a,b,]* Ja-Hae Kim,[c,]* Jae-Myung Kim,[a,b] Kyung-Wook Kang,[a,b] Joon-Tae Kim,[a]
Seong-Min Choi,[a] Man-Seok Park,[a] Ki-Hyun Cho[a]

[a]Department of Neurology, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea
[b]Department of Neurology, Chonnam National University Hwasun Hospital, Hwasun, Korea
[c]Molecular Imaging Center, Department of Nuclear Medicine, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea

*These authors contributed equally to the manuscript as first author.

Dear Sir:

A new clinical construct of embolic stroke of undetermined source (ESUS) has been proposed to group heterogeneous patients with embolism of undetermined cause despite recommended diagnostic workup.[1] Although the emboli in ESUS may originate from various potential embolic sources (PESs), cardioembolic sources may account for most PESs in ESUS.[1] Cardiac troponin (cTn) is a sensitive and specific marker of cardiac dysfunction.[2] Recent studies have suggested that elevated cTn levels are more common in patients with ESUS than in those with noncardioembolic stroke.[3] Elevated cTn levels may be associated with worse clinical outcomes and a higher risk of vascular events after stroke.[4,5] Therefore, we investigated the effectiveness of conventional cTn I (cTnI) and high-sensitivity cTn T (hs-cTnT) levels in predicting clinical outcomes in patients with ESUS.

This single-center retrospective cohort study used a prospective registry. Subjects were divided into normal and high troponin groups according to sex-specific 99th percentile upper reference limits (Supplementary Figure 1). The primary outcome measure was the first occurrence of major adverse cerebrovascular and cardiovascular events (MACCE) according to the baseline cTn levels over a 1-year period after ESUS. The secondary outcomes included constituents of MACCE. We enrolled 1,838 consecutive patients with ESUS admitted to our center (Supplementary Figure 1). The baseline patient characteristics and annual number of patients in the cTnI and hs-cTnT groups are presented in Supplementary Tables 1-4. Elevated cTnI and hs-cTnT levels were detected in 20.2% (209/1,037) and 21.2% (170/801) patients, respectively. Detailed methodical descriptions and outcomes of interest are provided in Supplementary methods and results.

The rates of vascular events were higher in the high cTnI (Figure 1) and hs-cTnT (Figure 2) groups than in the respective normal groups. Multivariate Cox regression analyses revealed that patients in the high cTnI group had a significantly increased risk of MACCE compared to those in the normal cTnI group (hazard ratio [HR], 1.97; 95% confidence interval [CI], 1.13 to 3.44; P=0.016) (Figure 3 and Supplementary Table 5) after adjustment for confounders. Similarly, patients with high hs-cTnT levels had a significantly increased risk of MACCE compared to those with normal hs-cTnT levels (HR, 2.69; 95% CI, 1.44 to 5.01; P=0.002) (Figure 3 and Supplementary Table 5). In sensitivity analyses, prognostic values of both cTnI and hs-cTnT for predicting the risk of MACCE remained unchanged when cTn levels were analyzed using the overall cTn cutoff levels without sex-specific differences (Supplementary Table 6).

Regarding secondary outcomes, high cTnI and hs-cTnT levels were also significantly associated with the risk of vascular death (Figure 3 and Supplementary Table 5). High hs-cTnT levels were significantly associated with the risk of recurrent ischemic stroke (HR, 2.62; 95% CI, 1.05 to 6.57; P=0.039); this association was not observed for cTnI levels (HR, 1.40; 95% CI,

JoS

Choi et al.   Troponin in Embolic Stroke of Undetermined Source

0.57 to 3.45; P=0.454) (Figure 3 and Supplementary Table 5). No significant differences were observed in the risk of acute myocardial infarction between the normal and high troponin groups (Figure 3 and Supplementary Table 5).

This is the first real-world cohort study on troponin levels in ESUS and validates the finding of a recent clinical trial substudy that the troponin level is a predictor of the risk of vascular events in patients with ESUS.[5] There is an urgent need to identify prognostic biomarkers related to potential cardiac dysfunction after ESUS.[1] In a recent randomized trial on ESUS, a high hs-cTnT level was associated with increased cardiovascular events.[5] Our data provide insights on the clinical significance of routine assessment of baseline troponin levels to predict vascular events after ESUS.

Our study has a few limitations. We were unable to perform all investigations for identifying PESs in ESUS, such as long-term cardiac monitoring, cardiac compound tomography, or magnetic resonance imaging. In addition, the predictive values of the two types of cTn were not compared. Since hs-cTnT assay has recently been introduced in clinical practice, patients who underwent hs-cTnT testing may have received more ad-

vanced treatment and better risk factor control than those who underwent cTnI testing. The risk of recurrent ischemic stroke was significantly associated with high hs-cTnT levels, but not with high cTnI levels. Further studies are needed to confirm whether hs-cTnT is superior to cTnI in predicting clinical outcomes and identify optimally tailored antithrombotics that reduce the risk of vascular events in patients with high cTn levels.

In conclusion, our findings suggest that high cTnI and hs-cTnT levels are significantly associated with MACCE and vascular death after ESUS. Our study also shows that high hs-cTnT levels are associated with a higher risk of recurrent ischemic stroke. Reducing the risk of MACCE after ESUS in individuals with high cTn levels is a challenge, and further studies are needed to improve patient care and clinical guidelines.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2021.00010.
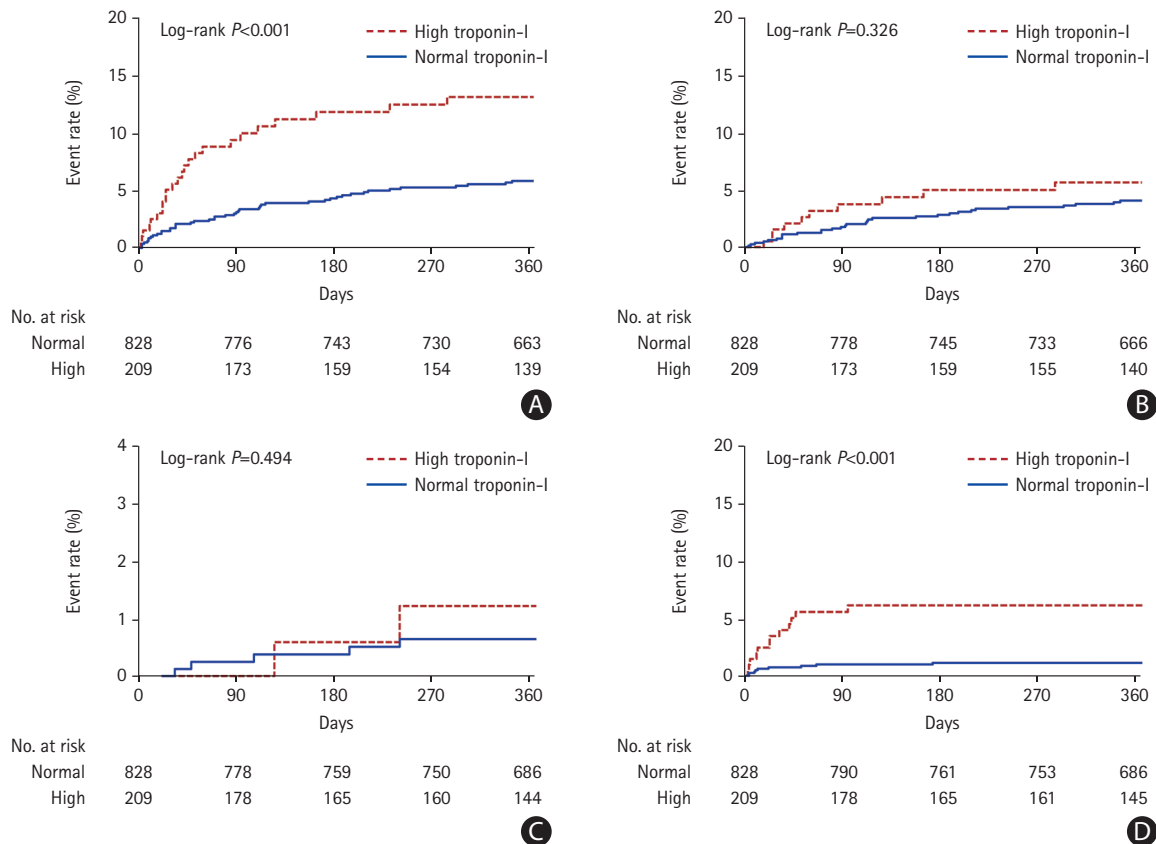
Figure 1. Vascular events based on conventional troponin I levels. (A) Major adverse cerebrovascular and cardiovascular event (MACCE), (B) recurrent stroke, (C) acute myocardial infarction, (D) vascular death.
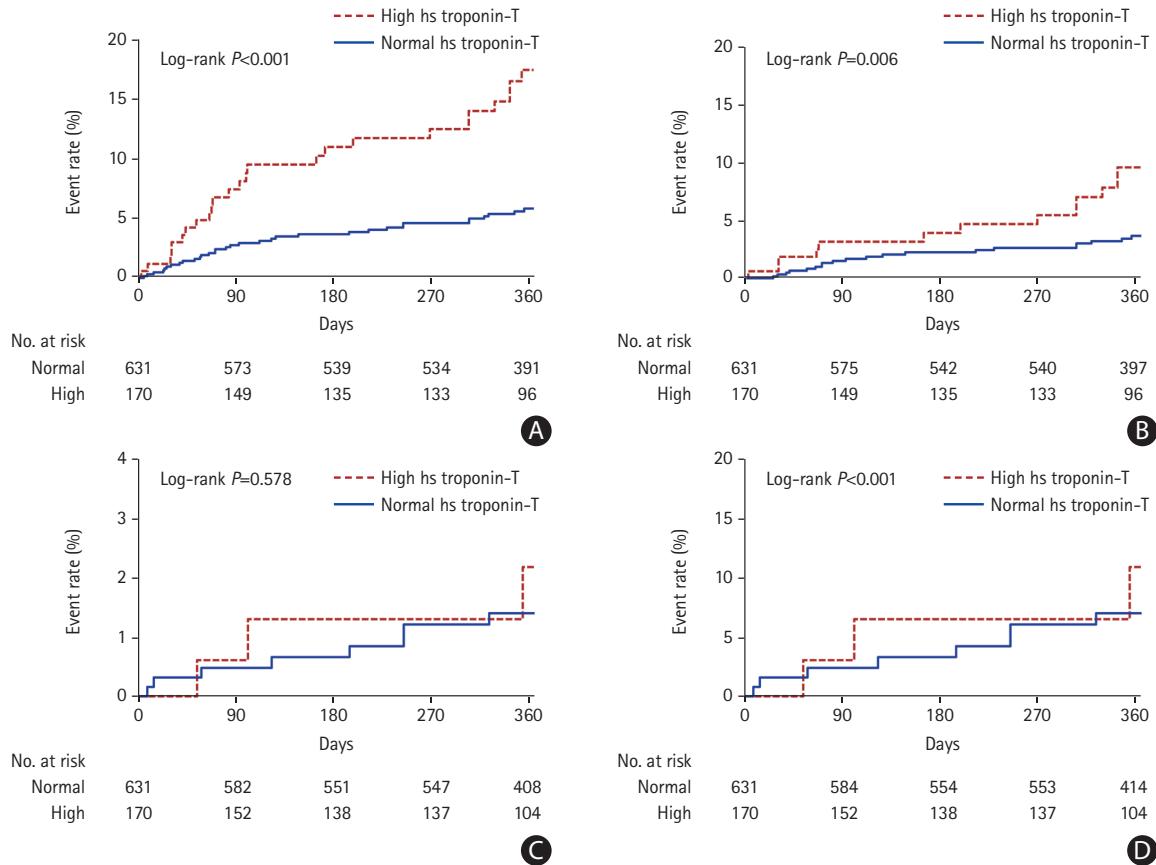
Figure 2. Vascular events based on high-sensitivity troponin T levels. (A) Major adverse cerebrovascular and cardiovascular event (MACCE), (B) recurrent stroke, (C) acute myocardial infarction, (D) vascular death.
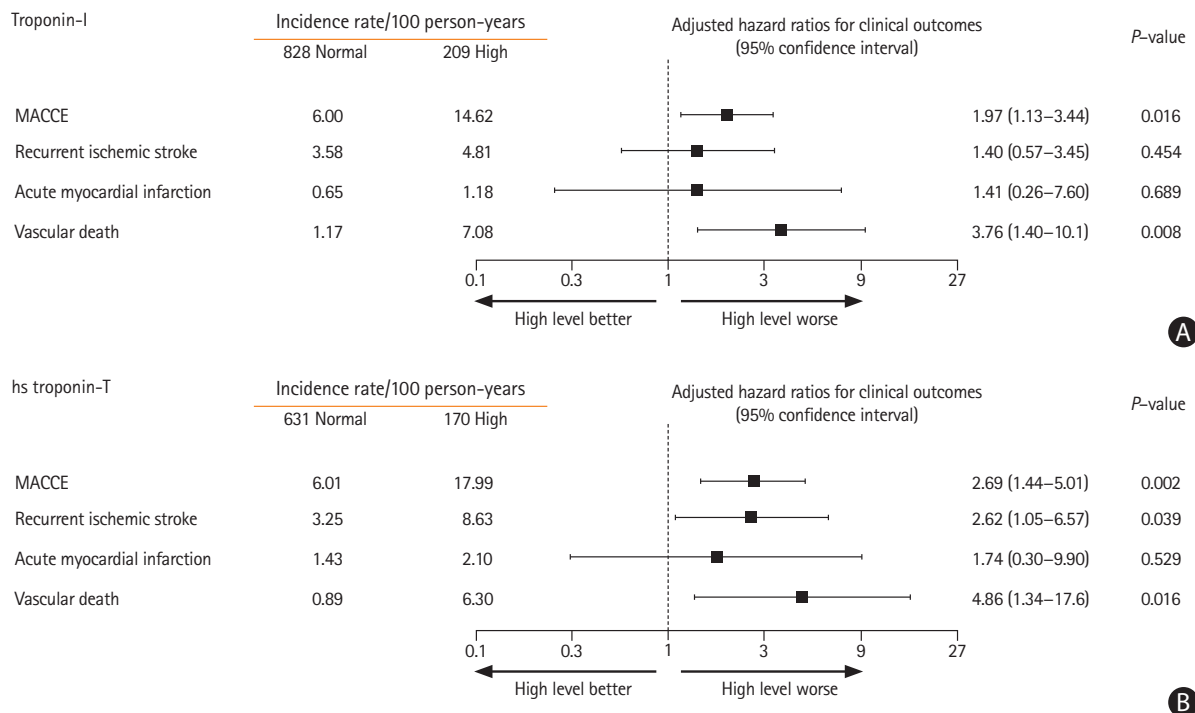
Figure 3. Association between cardiac troponin levels and clinical outcomes after embolic stroke of undetermined source. (A) Troponin I, (B) high-sensitivity troponin I (hs troponin-T). MACCE, major adverse cerebrovascular and cardiovascular event.

JoS

Choi et al.   Troponin in Embolic Stroke of Undetermined Source

References

1. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;13: 429-438.

2. McCarthy CP, Raber I, Chapman AR, Sandoval Y, Apple FS, Mills NL, et al. Myocardial injury in the era of high-sensitivity cardiac troponin assays: a practical approach for clinicians. *JAMA Cardiol* 2019;4:1034-1042.

3. Merkler AE, Gialdini G, Murthy SB, Salehi Omran S, Moya A, Lerario MP, et al. Association between troponin levels and embolic stroke of undetermined source. *J Am Heart Assoc* 2017;6: e005905.

4. Ahn SH, Lee JS, Kim YH, Kim BJ, Kim YJ, Kang DW, et al. Prognostic significance of troponin elevation for long-term mortality after ischemic stroke. *J Stroke* 2017;19:312-322.

5. Scheitz JF, Pare G, Pearce LA, Mundl H, Peacock WF, Czlonkowska A, et al. High-sensitivity cardiac troponin T for risk stratification in patients with embolic stroke of undetermined source. *Stroke* 2020;51:2386-2394.

Correspondence: Kang-Ho Choi
Department of Neurology, Chonnam National University Hospital, Chonnam National University Medical School, 42 Jebong-ro, Dong-gu, Gwangju 61469, Korea
Tel: +82-62-220-6137
Fax: +82-62-228-3461
E-mail: ckhchoikang@chonnam.ac.kr
https://orcid.org/0000-0001-8851-2104

Supplementary methods

Subjects and study design

In this single-center retrospective cohort study, we used a prospective registry of patients with acute ischemic stroke (AIS) who were admitted to our government-initiated comprehensive stroke center between January 2010 and May 2019. Patients were enrolled consecutively (1) if they had AIS and were admitted within 24 hours of onset of symptoms and (2) if the diagnosis of embolic stroke of undetermined source (ESUS) could be confirmed based on brain magnetic resonance imaging (MRI), 12-lead electrocardiography, cardiac monitoring for ≥24 hours, transthoracic echocardiography, and computed tomography (CT) or magnetic resonance angiography for the evaluation of extracranial and intracranial arteries. ESUS was defined as non-lacunar embolic ischemic stroke without evidence of a major-risk cardioembolic source, presence of ≥50% stenosis of the lumen of an extracranial or intracranial artery supplying the area of brain ischemia, or stroke without other specific causes, such as arteritis, dissection, migraine/vasospasm, or drug misuse. Cardiac troponin (cTn) levels were measured immediately after admission. The exclusion criteria were as follows: (1) patients who did not undergo baseline serum troponin level assessment on admission or (2) patients lost to follow-up whose clinical outcomes could not be investigated (Supplementary Figure 1). Data on baseline characteristics, underlying risk factors of stroke, and laboratory findings were collected from all subjects.

Subjects were categorized into normal or high troponin groups according to their baseline cTn levels (Supplementary Figure 1). We used sex-specific 99th percentile upper reference limits (URL) of cTn I (cTnI) and high-sensitivity cTn T (hs-cTnT) as thresholds for classifying groups. cTnI levels were measured using a sensitive assay on an automated platform (Dimension Vista, Siemens, Berlin, Germany), with a reported 99th percentile value of ≤30 ng/L for healthy males and ≤15 ng/L for healthy females. hs-cTnT levels were measured using a highly sensitive assay on an automated platform (Elecsys, Roche Diagnostics, Basel, Switzerland), with a reported 99th percentile value of ≤20 ng/L for healthy males and ≤13 ng/L for healthy females (Supplementary Figure 1). The limits of detection of the cTnI and hs-cTnT assays were 10 and 5 ng/L, respectively. At our center, hs-cTnT testing was performed since January 2015. Prior to January 2015, cTnI levels alone were tested. From January 2015, testing for a specific type of troponin (cTnI or hs-cTnT) depended on the physician's clinical judgment for each patient.

Clinical assessment and outcome measurements

The primary outcome measure was the first occurrence of major adverse cerebrovascular and cardiovascular events (MACCE; a composite of stroke, acute myocardial infarction [AMI], or death from a vascular cause) according to the baseline cTn levels over a 1-year period after ESUS. The key secondary outcomes included the incidence of recurrent ischemic stroke, intracerebral hemorrhage, AMI, and death from a vascular cause. Recurrent stroke was defined as a sudden development of a new focal neurologic deficit or worsening of an existing focal neurologic deficit after the index stroke event, with evidence of attributable new stroke lesions (ischemic or hemorrhagic stroke) on brain imaging (CT or MRI). The severity of the neurological deficit was assessed using the National Institutes of Health Stroke Scale (NIHSS). Paradoxical embolism suggesting right-to-left shunt was defined as the presence of microembolic signals on the transcranial Doppler bubble test conducted during hospitalization for all patients. Information regarding clinical outcomes was obtained from all patients during hospitalization, during routine clinic visits, or via telephone interviews with patients or their caregivers. The information was assessed by trained stroke physicians or nurses.

Statistical analysis

Differences between the groups were analyzed using one-way analysis of variance, the Kruskal-Wallis test, or the Mann–Whitney U test for continuous variables. The chi-square test or Fisher's exact test was used for non-continuous variables. Crude associations between cTn levels and the risk for clinical outcomes were analyzed over the study period using Kaplan-Meier curves with log-rank tests. Time-to-first event methods were used for the primary endpoint and for each secondary endpoint. Cox proportional hazard regression models were constructed to calculate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for clinical outcomes, according to the baseline cTn levels. Adjustments were performed for age; sex; presence of hypertension, dyslipidemia, diabetes mellitus, coronary heart disease, and cancer; current smoking; prior history of stroke or transient ischemic attack; initial NIHSS score; initial blood pressure; leukocyte counts; hemoglobin, creatinine, and C-reactive protein levels; and administration of reperfusion therapy (intravenous alteplase or mechanical thrombectomy) based on their clinical significance. We conducted additional sensitivity analyses using the overall 99th percentile URL cutoff levels of 21 ng/L for cTnI and 15 ng/L for hs-cTnT without a sex-specific difference. Statistical significance was set at $P<0.05$ in all analyses. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA), SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and R software version 3.3.1 (R Foundation, Vienna, Austria).

JoS

Choi et al.   Troponin in Embolic Stroke of Undetermined Source

Data availability and ethics statement

All supporting study data can be obtained from the corresponding author on reasonable request from a qualified investigator. Our Institutional Review Board approved the present study. Written informed consent was obtained from all patients or their legal representatives for inclusion in the prospective stroke registry. We used the acronym "TOP-ESUS" to define our research, which stands for cTn levels and outcomes in patients with ESUS. All clinical and laboratory investigations described in this study were conducted in accordance with the principles outlined in the Declaration of Helsinki.

Supplementary results

Patient characteristics

In this study, we included 1,838 consecutive patients with ESUS (Supplementary Figure 1). A total of 1,037 (56.4%) patients underwent cTnI testing and 801 (43.6%) patients underwent hs-cTnT testing. The mean time from symptom onset to cTn testing was 11.9 hours. The mean follow-up duration was 10.6 months. The clinical and biochemical characteristics of patients according to cTn levels are presented in Supplementary Tables 1 and 2. Elevated cTnI levels were detected in 209 (20.2%) of 1,037 patients tested for cTnI and elevated hs-cTnT levels were detected in 170 (21.2%) of 801 patients tested for hs-cTnT. Patients who underwent cTnI testing were more likely to have hypertension, while those who underwent hs-cTnT testing were more likely to have dyslipidemia and old myocardial infarction (Supplementary Table 3). Detailed information on the incidence of ESUS and cTn assays performed each year at our center is provided in Supplementary Table 4.

Clinical outcomes

Among patients who underwent cTnI and hs-cTnT testing, 69 and 58 patients experienced MACCE during follow-up. The annual rates of MACCE were higher in the high cTnI and hs-cTnT groups than in the respective normal groups (14.62% vs. 6.00% and 17.99% vs. 6.01%, respectively) (Supplementary Table 5). Kaplan-Meier analyses showed that the risk of MACCE was significantly higher in the high troponin groups than in the respective normal groups, regardless of the type of troponin test performed (log-rank $P<0.001$) (Figures 1 and 2). In multivariate Cox regression analyses, patients in the high cTnI group had a significantly increased risk of MACCE compared to those in the normal cTnI group (HR, 1.97; 95% CI, 1.13 to 3.44; $P=0.016$) (Figure 3 and Supplementary Table 5) after adjustment for confounders. Similarly, patients with high hs-cTnT levels had a significantly increased risk of MACCE compared to those with normal hs-cTnT levels (HR, 2.69; 95% CI, 1.44 to 5.01; $P=0.002$) (Figure 3 and Supplementary Table 5).

Regarding secondary outcomes, high cTnI and hs-cTnT levels were significantly associated with the risk of vascular death in patients with ESUS (HR, 3.76; 95% CI, 1.40 to 10.1; $P=0.008$ and HR, 4.86; 95% CI, 1.34 to 17.6; $P=0.016$, respectively) (Figure 3 and Supplementary Table 5). High hs-cTnT levels were significantly associated with the risk of recurrent ischemic stroke (HR, 2.62; 95% CI, 1.05 to 6.57; $P=0.039$); this association was not observed for cTnI levels (HR, 1.40; 95% CI, 0.57 to 3.45; $P=0.454$) (Figure 3 and Supplementary Table 5). No significant differences were observed in the risk of hemorrhagic stroke and AMI between the normal and high troponin groups (Figure 2 and Supplementary Table 5).

In the sensitivity analysis, we evaluated the association between elevated cTn levels and clinical outcomes using the overall cTn cutoff levels without sex-specific differences. The prognostic values of both cTnI and hs-cTnT for predicting the risk of MACCE were similar (Supplementary Table 6). High cTnI and hs-cTnT levels were significantly associated with a higher risk of MACCE (HR, 2.40; 95% CI, 1.39 to 4.14; $P=0.002$ and HR, 3.58; 95% CI, 1.87 to 6.86; $P<0.001$, respectively) and vascular death in patients with ESUS (Supplementary Table 6). The high hs-cTnT group, identified using the overall hs-cTnT cutoff levels, had a higher risk of recurrent ischemic stroke than the normal hs-cTnT group (HR, 2.96; 95% CI, 1.22 to 7.16; $P=0.016$) (Supplementary Table 6).

Supplementary Table 1. Baseline characteristics according to baseline cardiac troponin levels

Characteristic	Conventional troponin I			High-sensitivity troponin T		
	Normal (n=828)	High (n=209)	P	Normal (n=631)	High (n=170)	P
Age in years	63.8±13.4	71.0±11.7	<0.001	63.6±13.5	73.4±10.8	<0.001
Male sex	535 (64.6)	95 (45.5)	<0.001	432 (68.5)	73 (42.9)	<0.001
Comorbidities						
Hypertension	434 (52.4)	124 (59.3)	0.087	288 (45.6)	98 (57.6)	0.007
Diabetes mellitus	201 (24.3)	55 (26.3)	0.602	147 (23.3)	49 (28.8)	0.165
Dyslipidemia	120 (14.5)	29 (13.9)	0.907	121 (19.2)	23 (13.5)	0.112
Cancer	100 (12.1)	34 (16.3)	0.134	56 (8.9)	25 (14.7)	0.036
Current smoking	211 (25.5)	28 (13.4)	<0.001	147 (23.3)	17 (10.0)	<0.001
Coronary heart disease	46 (5.6)	17 (8.1)	0.218	43 (6.8)	22 (12.9)	0.015
Prior stroke or TIA	149 (18.0)	27 (12.9)	0.100	101 (16.0)	36 (21.2)	0.140
Cardiac markers						
Troponin (ng/L)	14.4±3.5	285.2±794.3	<0.001	8.9±5.7	42.4±53.0	<0.001
NT-pro BNP (ng/mL)	0.9±3.3	4.5±9.2	<0.001	0.9±3.4	2.6±6.5	0.054
CK-MB (ng/mL)	3.9±9.0	7.0±16.6	0.335	2.0±3.7	3.1±2.4	0.004
Myoglobin (µg/mL)	0.2±0.3	0.5±1.3	0.158	0.2±0.4	0.3±0.6	0.555
Biochemical variables						
Total cholesterol (mg/dL)	180.4±43.1	173.1±48.9	0.057	177.3±43.3	173.4±45.7	0.333
LDL-C (mg/dL)	118.2±54.3	111.0±41.9	0.054	113.4±57.8	107.8±38.0	0.164
Triglyceride (mg/dL)	116.7±70.3	108.9±59.5	0.108	118.6±70.0	115.7±60.1	0.614
HDL-C (mg/dL)	45.1±12.1	43.9±14.3	0.330	46.0±16.9	45.4±14.3	0.664
Fasting blood sugar (mg/dL)	122.1±46.3	127.8±51.5	0.154	124.8±48.1	119.5±43.5	0.230
Glycated hemoglobin (%)	6.1±1.3	6.1±1.2	0.861	6.2±1.4	6.2±1.3	0.684
Hemoglobin (g/dL)	13.7±1.9	12.7±2.0	<0.001	13.9±1.9	12.9±1.9	<0.001
Leukocyte counts (×10⁹/L)	8.7±3.1	9.0±3.4	0.309	8.4±3.0	8.1±2.7	0.369
Creatinine (mg/dL)	0.8±0.6	1.0±1.1	0.016	0.9±0.4	1.1±1.1	0.009
C-reactive protein (mg/dL)	0.7±2.0	1.2±2.5	0.003	0.7±2.2	1.2±2.0	0.005
Initial NIHSS	2 (0–7)	3 (1–9)	0.008	2 (0–5)	3 (1–8)	0.003
Systolic blood pressure (mm Hg)	137.8±23.0	136.9±23.7	0.606	136.4±22.6	139.3±21.6	0.160
Diastolic blood pressure (mm Hg)	83.6±13.3	81.4±14.5	0.039	82.5±14.1	81.8±15.4	0.601
Intravenous alteplase	145 (17.5)	25 (12.0)	0.067	64 (10.1)	21 (12.4)	0.490
Mechanical thrombectomy	56 (6.8)	16 (7.7)	0.763	61 (9.7)	17 (10.0)	1.000
Lesion territory			0.954			1.000
Anterior circulation	547 (66.1)	137 (65.6)		416 (65.9)	112 (65.9)	
Posterior circulation	281 (33.9)	72 (34.4)		215 (34.1)	58 (34.1)	

Values are presented as mean±standard deviation, number (%), or median (interquartile range).

TIA, transient ischemic attack; NT-pro BNP, N-terminal pro B-type natriuretic peptide; CK-MB, creatine kinase myocardial band; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale.

JoS

Choi et al.   Troponin in Embolic Stroke of Undetermined Source

Supplementary Table 2. Transcranial and echocardiographic findings according to cardiac troponin levels

Variable	Conventional troponin I			High-sensitivity troponin T		
	Normal (n=828)	High (n=209)	P	Normal (n=631)	High (n=170)	P
Transcranial Doppler						
Paradoxical embolism	301 (36.4)	72 (34.4)	0.781	256 (40.6)	68 (40.0)	0.963
Holter monitoring						
Atrial tachycardia	70 (8.5)	29 (13.9)	0.024	44 (7.0)	18 (10.6)	0.160
Transthoracic echocardiography						
Old myocardial infarction	29 (3.5)	19 (9.1)	0.001	36 (5.7)	21 (12.4)	0.005
Left atrial enlargement	8 (1.0)	9 (4.3)	0.002	6 (1.0)	5 (2.9)	0.108
Left ventricular hypertrophy	23 (2.8)	18 (8.6)	<0.001	19 (3.0)	13 (7.6)	0.012
Ejection fraction <50%	88 (10.6)	28 (13.4)	0.311	79 (12.5)	32 (18.8)	0.047
Aortic valve stenosis	62 (7.5)	33 (15.8)	0.002	67 (10.6)	20 (11.8)	0.285
Pulmonary hypertension	160 (19.3)	68 (32.5)	<0.001	112 (17.7)	59 (34.7)	<0.001
Diastolic dysfunction	613 (74.0)	159 (76.1)	0.076	482 (76.4)	137 (80.6)	0.016

Values are presented as number (%).

Supplementary Table 3. Baseline characteristics according to troponin type

Characteristic	Troponin-I (n=1,037)	High-sensitivity troponin-T (n=801)	Total (n=1,838)	P
Age in years	65.2±13.4	65.7±13.6	65.4±13.5	0.433
Male sex	630 (60.8)	505 (63.0)	1,135 (61.8)	0.340
Risk factors				
Hypertension	558 (53.8)	386 (48.2)	944 (51.4)	0.019
Diabetes mellitus	256 (24.7)	196 (24.5)	452 (24.6)	0.958
Dyslipidemia	149 (14.4)	144 (18.0)	293 (15.9)	0.042
Cancer	134 (12.9)	81 (10.1)	215 (11.7)	0.074
Current smoking	239 (23.0)	164 (20.5)	403 (21.9)	0.206
Coronary heart disease	63 (6.1)	65 (8.1)	128 (7.0)	0.107
Prior stroke or TIA	176 (17.0)	137 (17.1)	313 (17.0)	0.991
Cardiac markers				
NT-pro BNP (ng/mL)	1.5±5.1	1.4±4.6	1.5±4.9	0.707
CK-MB (ng/mL)	5.1±12.6	2.3±3.5	2.8±6.5	0.051
Myoglobin (µg/mL)	0.3±0.8	0.2±0.5	0.3±0.7	0.625
Biochemical variables				
Total cholesterol (mg/dL)	178.9±44.4	176.5±43.8	177.9±44.1	0.267
LDL-C (mg/dL)	116.8±52.2	112.2±54.1	114.8±53.1	0.090
Triglyceride (mg/dL)	115.2±68.3	118.0±68.0	116.3±68.2	0.403
HDL-C (mg/dL)	44.8±12.6	45.8±16.4	45.3±14.3	0.190
Fasting blood sugar (mg/dL)	123.2±47.4	123.7±47.1	123.4±47.3	0.839
Glycated hemoglobin (%)	6.1±1.3	6.2±1.4	6.1±1.3	0.097
Initial NIHSS	2 (1–7)	2 (0–6)	2 (1–7)	0.064
Reperfusion therapies	203 (19.6)	131 (16.4)	334 (18.2)	0.086
Paradoxical embolism	373 (36.0)	324 (40.4)	697 (37.9)	0.094
Atrial tachycardia	99 (9.5)	62 (7.7)	161 (8.8)	0.202
Transthoracic echocardiography				
Old myocardial infarction	48 (4.6)	57 (7.1)	105 (5.7)	0.029
Left atrial enlargement	17 (1.6)	11 (1.4)	28 (1.5)	0.787
Left ventricular hypertrophy	41 (4.0)	32 (4.0)	73 (4.0)	1.000
Aortic valve stenosis	95 (9.2)	87 (10.9)	182 (9.9)	0.631
Pulmonary hypertension	228 (22.0)	171 (21.3)	399 (21.7)	0.970
Diastolic dysfunction	772 (74.4)	619 (77.3)	1,391 (75.7)	0.149

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
TIA, transient ischemic attack; NT-pro BNP, N-terminal pro B-type natriuretic peptide; CK-MB, creatine kinase myocardial band; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale.

Supplementary Table 4. The number of enrolled patients during cTn assays performed each year in this study

Year	All AIS	ESUS	Enrolled	cTnI	hs-cTnT
2010	1,137	199	189	189	-
2011	1,071	141	134	134	-
2012	1,146	150	145	145	-
2013	1,118	201	196	196	-
2014	1,083	218	211	211	-
2015	1,070	224	220	73	147
2016	1,089	215	209	25	184
2017	974	212	207	29	178
2018	985	211	198	21	177
2019*	456	136	129	14	115
Total	10,255	1,907	1,838	1,037	801

cTn, cardiac troponin; AIS, acute ischemic stroke; ESUS, embolic stroke of undetermined source (admitted within 24 hours of the onset of symptoms); hs-cTnT, high-sensitivity cTn T.
*Until May 2019.

Supplementary Table 5. Event rates and association estimates from Cox proportional hazard model according to baseline cardiac troponin levels

Clinical outcome	Conventional troponin I			High-sensitivity troponin T		
	Normal (n=828)	High (n=209)	P	Normal (n=631)	High (n=170)	P
Primary outcome						
MACCE						
Incidence per 100 person-years	6.00	14.62		6.01	17.99	
Adjusted HR (95% CI)*	Reference	1.97 (1.13–3.44)	0.016	Reference	2.69 (1.44–5.01)	0.002
Secondary outcomes						
Recurrent ischemic stroke						
Incidence per 100 person-years	3.58	4.81		3.25	8.63	
Adjusted HRs (95% CI)*	Reference	1.40 (0.57–3.45)	0.454	Reference	2.62 (1.05–6.57)	0.039
Intracerebral hemorrhage						
Incidence per 100 person-years	0.52	1.19		0.36	0.70	
Adjusted HRs (95% CI)*	Reference	4.12 (0.60–28.2)	0.149	Reference	2.03 (0.14–29.0)	0.600
Acute myocardial infarction						
Incidence per 100 person-years	0.65	1.18		1.43	2.10	
Adjusted HRs (95% CI)*	Reference	1.41 (0.26–7.60)	0.689	Reference	1.74 (0.30–9.90)	0.529
Death from vascular causes						
Incidence per 100 person-years	1.17	7.08		0.89	6.30	
Adjusted HR (95% CI)*	Reference	3.76 (1.40–10.1)	0.008	Reference	4.86 (1.34–17.6)	0.016

MACCE, major adverse cerebrovascular and cardiovascular events; HR, hazard ratio; CI, confidence interval.
*Adjusted variables: age, sex, hypertension, dyslipidemia, diabetes mellitus, coronary heart disease, cancer, current smoking, prior history of stroke or transient ischemic attack, initial National Institutes of Health Stroke Scale score, initial blood pressure, hemoglobin, leukocyte counts, creatinine, C-reactive protein, and reperfusion therapies.

Supplementary Table 6. Association between high cardiac troponin levels using the overall 99th percentile upper reference cutoff level and clinical outcomes

Independent variable	Adjusted HR (95% CI)*				
	MACCE	Recurrent IS	ICH	AMI	Vascular death
Conventional troponin-I					
Normal	Reference	Reference	Reference	Reference	Reference
High	2.40 (1.39–4.14)	1.80 (0.78–4.10)	2.86 (0.45–18.19)	3.11 (0.27–35.12)	3.52 (1.23–10.02)
High-sensitivity troponin-T					
Normal	Reference	Reference	Reference	Reference	Reference
High	3.58 (1.87–6.86)	2.96 (1.22–7.16)	1.96 (0.14–27.48)	1.86 (0.42–8.08)	4.92 (1.34–17.98)

HR, hazard ratio; CI, confidence interval; MACCE, major adverse cerebrovascular and cardiovascular events; IS, ischemic stroke; ICH, intracerebral hemorrhage; AMI, acute myocardial infarction.
*Adjusted variables: age, sex, hypertension, dyslipidemia, diabetes mellitus, coronary heart disease, cancer, current smoking, prior history of stroke or transient ischemic attack, initial National Institutes of Health Stroke Scale score, initial blood pressure, hemoglobin, leukocyte counts, creatinine, C-reactive protein, and reperfusion therapies.
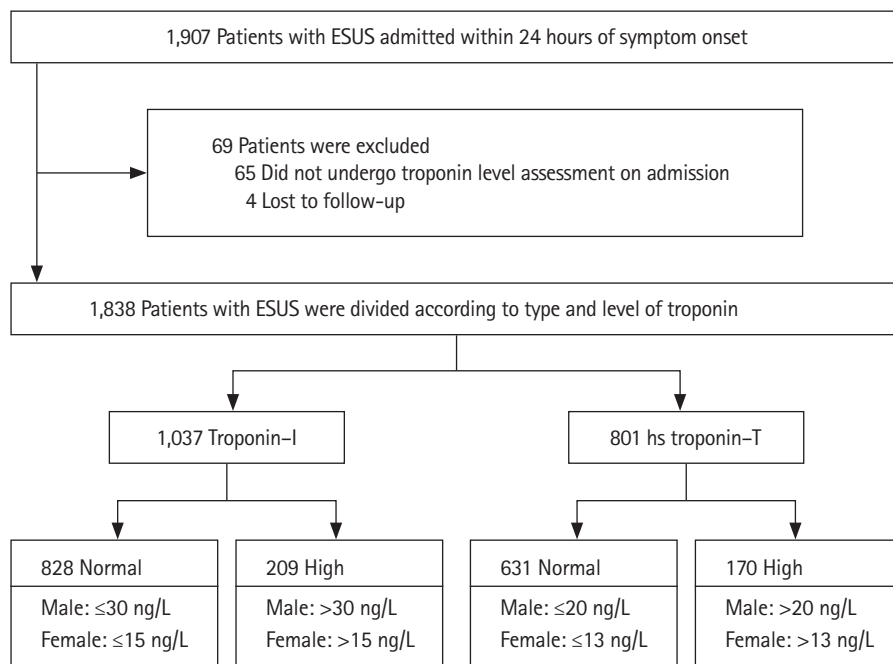
Supplementary Figure 1. Subject enrollment and clinical outcome measures. ESUS, embolic stroke of undetermined source; hs, high-sensitivity.