

Letters

Troponin I Levels and Long-Term Outcomes in Acute Ischemic Stroke Patients



Cardiac troponins are sensitive and specific biomarkers of cardiac injury, and the elevation of serum troponin is frequently identified in patients with acute ischemic stroke (AIS) (1). However, the clinical significance of elevated troponin in AIS is still uncertain due to insufficient adjustment for the adverse effect of troponin-releasing comorbidities, including concomitant ischemic heart disease, atrial fibrillation, congestive heart failure, ventricular hypertrophy, chronic kidney disease, and active cancer. The current study aimed to assess the relationship between the magnitudes of troponin levels and adverse long-term outcomes in AIS patients after adjusting for possible confounders.

This is a registered, prospectively-enrolled, observational study (Clinical Research Information Service number [KCT0000682](#)). All consecutive AIS patients who were admitted within 48 h after onset to the Asan Medical Center in Korea were prospectively recruited from 2013 to 2015. Registered patients underwent the repeated measurements of cardiac troponin I (Abbott Laboratories, Abbott Park, Illinois) at admission and at 2 and 5 days after stroke onset, if possible. Troponin level at day 2 was designated as the reference value, and categorized into elevated (≥ 0.040 ng/ml), minimally elevated (0.039 to 0.010 ng/ml), and nondetectable (< 0.010 ng/ml) (2). Based on previous results (2,3), disease-specific biomarkers were routinely measured: 1) repeated 12-lead electrocardiography (ECG) in conjunction with troponin measurements; 2) serum B-type natriuretic peptide at day 2 and repeated (i.e., borderline elevation > 200 or > 100 pg/ml with or without renal insufficiency); 3) serum creatinine at admission; and 4) serum D-dimer/fibrinogen at admission, to assess coagulopathy particularly attributed to cancer.

Demographic characteristics, conventional risk factors, the National Institutes of Health Stroke Scale score (i.e., surrogate for stroke severity), and

reperfusion therapy were obtained. A total of 6 candidate troponin-releasing comorbidities were defined: 1) atrial fibrillation in known history or positive ECG at least once; 2) ischemic heart disease in known history or positive ischemic-ECG changes (e.g., ST-segment elevation/depression, T-wave inversion, left bundle branch block, or pathological Q-waves) at least once; 3) ventricular hypertrophy in known history or positive ECG at least once; 4) congestive heart failure in known history or elevated serum B-type natriuretic peptide > 500 pg/ml; 5) chronic kidney disease in known history or impaired glomerular filtration rate < 60 ml/min/1.73 m²; and 6) active cancer in known history within 6 months or newly diagnosed during hospitalization.

The adverse outcomes were major adverse cardiac and cerebrovascular event (MACCE) (any cardiac or cerebrovascular death, nonfatal myocardial infarction, ischemic or hemorrhagic stroke, and coronary revascularization) and all-cause mortality. Follow-up information was obtained via direct or telephone interview by a blinded research coordinator (J.H.H. or S.Y.K.). The multivariable Cox proportional hazards model was used to determine the relationship between the troponin categories and adverse outcomes. Adjustments were made for all clinically relevant variables. Hazard ratios (HRs) are reported with 95% confidence intervals (CIs).

During a 2-year period, 26 patients were excluded due to inadequate quality of data, and 1,092 of 1,118 patients were eligible for the analysis. The mean age was 66.5 ± 12.4 years (range 18 to 95 years), and 691 patients (63.3%) were male. Over a median follow-up of 18 months (interquartile range: 11 to 26 months), 179 patients (17.0%) experienced MACCE, and 132 patients (12.1%) died.

The overall rate of MACCE and all-cause mortality was proportionally increased by an increased troponin level. Cox regression revealed that minimally elevated and elevated troponin were independently correlated with an increased risk of MACCE (HR: 1.58; 95% CI: 1.08 to 2.32 for minimally elevated troponin; and HR: 2.76; 95% CI: 1.76 to 4.33 for elevated troponin) and all-cause death (HR: 1.77; 95% CI: 1.07 to 2.91 for minimally elevated troponin; and HR: 3.63; 95% CI: 2.13 to 6.19 for elevated troponin) (Table 1).

TABLE 1 Incidence Rate per 100 Person-Years and Hazard Ratios for Troponin Levels to Predict Adverse Long-Term Outcomes

	Patients With Event, % (Events/Patients)	Incidence Rate		Unadjusted		Adjusted*	
		Rate	95% CI	HR	95% CI	HR	95% CI
MACCE							
Nondetectable	9.8 (60/612)	6.49	5.04-8.36	Reference		Reference	
Minimally elevated	19.1 (64/335)	14.52	11.37-18.56	2.20	1.55-3.13	1.59	1.08-2.32
Elevated	37.9 (55/145)	39.10	30.02-50.93	5.53	3.82-7.80	2.76	1.76-4.33
All-cause of death							
Nondetectable	4.7 (29/612)	2.97	2.07-4.28	Reference		Reference	
Minimally elevated	13.4 (45/335)	9.66	7.21-12.94	3.09	1.94-4.93	1.77	1.07-2.91
Elevated	40.0 (58/145)	38.22	29.55-49.44	11.21	7.16-17.54	3.63	2.13-6.19
*Adjustments were made for all clinically relevant variables, including age, sex, conventional risk factors (i.e., hypertension, diabetes, hyperlipidemia, and smoking), pre-defined 6 comorbidities (i.e., active cancer, atrial fibrillation, congestive heart failure, chronic kidney disease, ischemic heart disease, and ventricular hypertrophy), the National Institutes of Health Stroke Scale score at admission, and reperfusion therapy (i.e., including intravenous or intra-arterial reperfusion therapy). CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular events.							

This prospective study verified the relationship between the magnitudes of serum troponin levels and long-term adverse outcomes after adjusting for potential biases, such as the timing of troponin measurement and comorbid illness affecting troponin level. We found a dose-response relationship between the troponin levels and risk of MACCE and all-cause mortality.

This study is the first to reveal the clinical significance of troponin elevation, even including minimally elevated troponin below the 99th percentile of the upper reference limit, after adjusting various troponin-releasing conditions. In recent years, multiple studies have shown the clinical significance of minimally elevated troponin in a wide array of acute/chronic medical conditions, and even in healthy subjects (4).

In conclusion, serum troponin level is significantly associated with long-term adverse outcomes in a dose-dependent manner, and consequently, can be useful for risk stratification in AIS.

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REFERENCES

1. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. *J Am Coll Cardiol* 2018;18:36941-9.
2. Ahn SH, Lee JS, Kim YH, et al. Prognostic significance of troponin elevation for long-term mortality after ischemic stroke. *J Stroke* 2017;19:312-22.
3. Ahn SH, Kim YH, Shin CH, et al. Cardiac vulnerability to cerebrogenic stress as a possible cause of troponin elevation in stroke. *J Am Heart Assoc* 2016;5:e004135.
4. Popp RL. Troponin: messenger or actor? *J Am Coll Cardiol* 2013;61:611-4.

Use of Direct Oral Anticoagulants Among Patients With Limited Income and Resources



The direct oral anticoagulants (DOAC) are safer and easier to use than warfarin. Little is known about DOAC use among socioeconomically disadvantaged populations, for whom DOAC cost (out-of-pocket cost of \$387 to \$525 for a 1-month supply) (1) may be prohibitive. We characterized DOAC use patterns among 74 million Medicaid beneficiaries in the United States between 2010 and 2017.

We used current and deprecated National Drug Codes to query the State Drug Utilization Database between October 2010 and December 2017 for warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban. We calculated the number of prescriptions over time for all oral anticoagulants and for each