



## Brief Communication

# Association Between Stroke Severity and Serum Troponin in Acute Stroke

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**ABSTRACT:** Serum troponin is often elevated in patients with acute stroke and its mechanism is unknown. In a retrospective single-center cohort study, we evaluated the association between stroke severity and serum troponin in 187 patients with acute stroke using multivariable modified Poisson models. A one-point increase in the National Institutes of Health Stroke Scale (measure of stroke severity) was associated with a marginally higher serum troponin level in adjusted models (aIRR 1.03; 1.01–1.05,  $P = 0.001$ ). The modest, yet potentially independent, association between stroke severity and serum troponins could suggest a neurogenic basis for a cardiac injury in patients with acute stroke.

**RÉSUMÉ :** Association entre la gravité des AVC et la troponine sérique dans le cas d'AVC en phase aiguë. La troponine sérique apparaît souvent élevée chez des patients victimes d'un AVC en phase aiguë tandis que son mécanisme demeure inconnu. Dans une étude de cohorte monocentrique rétrospective, nous avons cherché, au moyen de modèles de Poisson modifiés à variables multiples, à évaluer l'association entre la gravité d'un AVC et la troponine sérique chez 187 patients victimes d'un AVC en phase aiguë. Une augmentation d'un point au *National Institutes of Health Stroke Scale* (NIHSS), outil mesurant la gravité des AVC, a ainsi été associée à un taux de troponine sérique légèrement plus élevé dans le cas de modèles ajustés (rapport du taux d'incidence ajusté ou RTIa : 1,03 ; 1,01-1,05 ;  $p = 0,001$ ). De plus, l'association modeste, mais potentiellement indépendante, entre la gravité des AVC et les troponines sériques pourrait suggérer la présence d'une lésion cardiaque d'origine neurogène chez les patients victimes d'un AVC en phase aiguë.

**Keywords:** Stroke; severity; troponin; negative binomial

(Received 13 July 2023; final revisions submitted 6 November 2023; date of acceptance 1 December 2023; First Published online 6 December 2023)

There is a bidirectional association between cardiac disease and stroke, with one leading to the other. Among patients with acute stroke, adverse cardiac events are associated with worse survival in both the short- and long-term.<sup>1</sup> Assessment of cardiac biomarkers, specifically high-sensitivity troponin, has been recommended by American Heart Association/American Stroke Association (AHA/ASA) guidelines,<sup>2</sup> and prior reports have found higher risk of disability and death among those with elevated troponin compared to those with normal levels.<sup>3</sup> However, whether the elevation in serum troponin is an independent biomarker of poor stroke outcomes or a consequence of having severe strokes (i.e., a neurogenic basis for minor cardiac injury) is unclear.<sup>3</sup> Our objective was to evaluate if greater stroke severity was associated with a higher rise in the serum troponin levels in adults with acute stroke.

We conducted a single-centre retrospective cohort study in Toronto, Canada. We randomly selected patients (aged  $\geq 40$  years) admitted between January 1, 2018 and December 31, 2018 to Sunnybrook Health Sciences Centre, a quaternary hospital in Toronto, Canada with a discharge diagnosis of ischemic stroke (ICD-10 code H34.1, I63.x, I64.x) or intracerebral hemorrhage (ICD-

10 I61.x). This validated definition has high sensitivity and specificity.<sup>4</sup> The Sunnybrook Hospital Ethics Review Board approved this study (SUN-5185). Due to limited funding and the COVID-19 pandemic, we had to restrict data collection to a random sample of participants.

Our primary exposure of interest was the stroke severity at the time of admission, measured using the National Institutes of Health Stroke Scale (NIHSS) by a physician. Patients that developed a subacute stroke during their hospital stay, and subsequently did not have recorded NIHSS, were excluded ( $n = 32$ ).

Our primary outcome was high-sensitivity serum troponin measured at the time of the stroke diagnosis or within the first 24 hours. We excluded those without information on serum troponin ( $n = 15$ ) and those with levels greater than 500 ng/dL (outliers,  $n = 3$ ). There were no major differences in those with and without missing troponins in our dataset (e-Table 1). All patients with acute stroke get a serum troponin level tested at this center; however, those with subacute stroke, especially on a non-stroke unit, may not get this information.

We compared baseline characteristics between those with elevated troponin ( $> 15$  ng/dL) vs. normal ( $\leq 15$  ng/dL) troponin

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**Cite this article:** Kuczynski AM, Rzyczniak G, Cheong GHL, Famiyeh P, and Vyas MV. (2024) Association Between Stroke Severity and Serum Troponin in Acute Stroke. *The Canadian Journal of Neurological Sciences* 51: 848–850, <https://doi.org/10.1017/cjn.2023.323>

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**Table 1:** Baseline characteristics of patients with acute stroke at a stroke center in Toronto, Canada

	Elevated Troponin ( $\geq 15$ ng/dL) <i>n</i> = 96 (51.3)	Normal Troponin (<15 ng/dL) <i>n</i> = 91 (48.7)	<i>P</i> value
Age, years	83 (72–87)	70 (62–80)	<0.001
Female	41 (42.7)	48 (52.8)	0.17
Previous stroke or transient ischemic attack	30 (31.6)	23 (25.3)	0.34
Hypertension	84 (88.4)	63 (69.2)	0.001
Diabetes	27 (28.4)	21 (23.1)	0.41
Hyperlipidemia	53 (55.8)	41 (45.6)	0.16
Median serum creatinine, $\mu$ mol/L	90 (74–124)	77 (65–91)	<0.001
ST elevation on EKG	2 (2.13)	1 (1.14)	0.60
Congestive heart failure	23 (24.2)	11 (12.1)	0.03
Stroke type			0.56
Ischemic stroke	86 (89.6)	79 (86.8)	
Intracerebral hemorrhage (ICH)	10 (10.4)	12 (13.2)	
Median Admission NIHSS	8 (3–16)	4 (2–10)	0.012
Stroke severity (NIHSS range)			0.02
Mild (< 5)	38 (39.6)	46 (50.6)	
Moderate (5–10)	30 (31.3)	33 (36.3)	
Severe ( $\geq 10$ )	28 (29.2)	12 (13.2)	

Continuous variable as median (Q1–Q3); categorical variable as *n* (%).

levels using Wilcoxon rank sum test for continuous and chi-square test for binary variables. Given the right-skewed distribution of serum troponin levels in patients with stroke (e-figure 1), in our primary analysis, we operationalized troponin levels as a variable that followed a negative binomial distribution. We used age- and sex-adjusted and multivariable-adjusted negative binomial regression models to calculate adjusted incidence rate ratio of higher serum troponin for every one-point increase in NIHSS. We accounted for the following variables in the multivariable analyses: age, sex, stroke type (ischemic stroke vs. intracerebral hemorrhage), serum creatinine level, presence of ST elevation on electrocardiogram, hypertension, and congestive heart failure (details on how the variables were operationalized in the models is listed in Table 1). In secondary analyses, we performed multivariable modified Poisson models with troponin level dichotomized as a binary variable, adjusting for the same covariates as before. We conducted stratified analyses by sex and stroke type to ensure that our findings were robust. All analyses were conducted using Stata/MP version 16.1 (StataCorp LLC, College Station, Texas, USA).

We included 187 patients [median age 76 years (Q1–Q3, 66–84), and 89 were female (47.6%)] with complete information on both exposure and outcome. The median NIHSS was 6 (2–13), with 84 patients (44.9%) having a minor stroke (NIHSS < 5) (Table 1). The mean serum troponin was  $44.8 \pm 137$  ng/dL. Compared to those with normal levels, those with elevated serum troponin were older, had higher serum creatinine, and were more likely to have hypertension and congestive heart failure (Table 1).

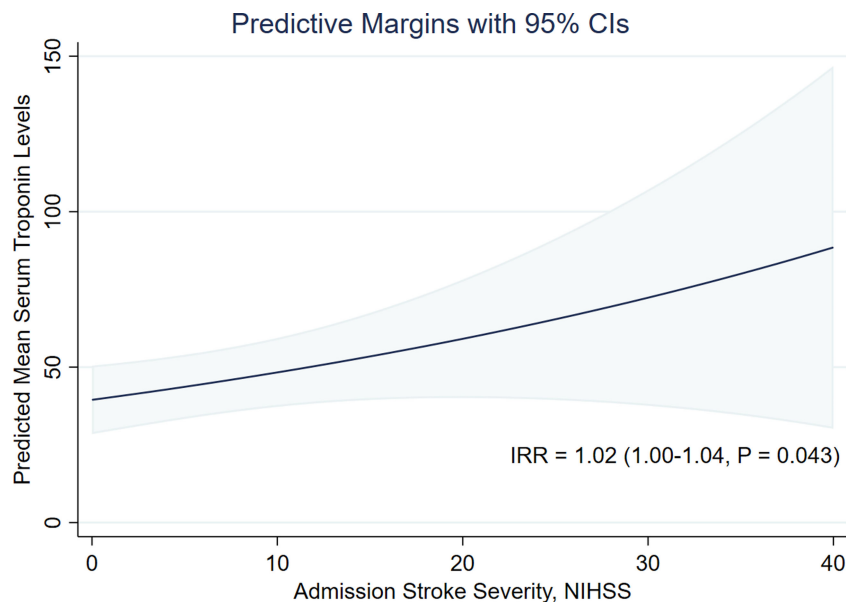
In multivariable-adjusted models, a one-point increase in NIHSS was associated with a 3% higher serum troponin (aIRR 1.03; 1.01–1.05,  $P = 0.001$ ) (Fig. 1 and e-Table 1). This association was not modified by sex ( $P = 0.281$ ) or stroke type ( $P = 0.61$ ) (e-Table 2). When operationalized as a binary variable, a one-point

increase in NIHSS was associated with a 2% higher adjusted risk of elevated serum troponin, albeit with confidence intervals that included the null value (aRR 1.02; 1.00–1.03,  $P = 0.067$ ).

Using physician-rated stroke severity in patients with acute ischemic and hemorrhagic stroke, we found that greater stroke severity, measured using NIHSS, was associated with higher serum troponin levels irrespective of stroke type or sex.

Elevations in serum troponin have been identified in acute neurological conditions including seizure, transient global amnesia, traumatic brain injury, and stroke. Previous studies have identified an association between elevated troponin and the presence of atherosclerosis on coronary angiography<sup>5</sup> and ischemic lesions on cardiac MRI<sup>6</sup> in patients with ischemic stroke further suggesting that cardiac injury may occur in relation to neurogenic insult. In a study of patients with ischemic stroke in the US, where serum troponin was dichotomized, the odds of having high troponin level were associated with a higher NIHSS score (OR 1.05; 1.03–1.07)<sup>7</sup>; however, converting a continuous variable into a binary leads to loss of power as demonstrated in our findings. Taken together, these findings add to the growing literature on minor cardiac injury in those with stroke,<sup>8</sup> suggesting it to be a function of the primary event itself.<sup>9</sup>

As this was a single-center study, future multicenter prospective work using representative patients on whom data on NIHSS and troponin is collected systematically is required to delineate the cause of elevated troponins in acute stroke, including differences in severity between ischemic and hemorrhagic stroke associated with troponin elevations. In addition, we were unable to account for baseline troponin levels or a history of coronary artery disease which could influence our findings. We were also unable to evaluate the change in troponin over time, which could help delineate if the troponin rise after stroke is transient or sustained. We suggest exercising caution when generalizing these findings



**Figure 1:** Association between admission National Institutes of Health Stroke Scale (NIHSS) and serum troponin among acute stroke patients admitted to a stroke center in Toronto, Canada using negative binomial regression.

given the possible selection bias introduced by selecting patients with stroke in whom serum troponin was available. Despite these limitations, our work highlights the importance of selecting appropriate regression models when evaluating exposure-outcome relationship with skewed distribution of the outcome.<sup>10</sup>

In conclusion, greater stroke severity was associated with a marginal, yet independent increase in the serum troponin in acute stroke, suggesting the need for further work to understand the prognostic value of elevated serum troponin by appropriately accounting for stroke severity.<sup>10</sup> This association between troponin rise and increased stroke severity raises the possibility of using serum cardiac troponins as a pre-hospital biomarker to identify severe stroke or those with large vessel occlusion, where specific hyperacute treatments could be administered to improve functional outcomes for patients with stroke.

**Supplementary material.** The supplementary material for this article can be found at <https://doi.org/10.1017/cjn.2023.323>.

**Competing interests.** None.

**Statement of authorship.** AMK, GR, and MVV were involved in the concept and design. AMK, GL, PF, and MVV were involved in data acquisition. AMK and MVV performed statistical analyses and interpreted the results. All authors contributed to the manuscript writing.

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