Association Between Cardiac Enzyme Elevation and Clinical Prognosis of Neurosurgical and Neurocritically Ill Patients

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Abstract

To investigate whether cardiac troponin (cTn) elevation is associated with in-hospital mortality and major adverse cardiac events (MACEs) in neurosurgical and neurocritically ill patients. Among neurosurgical patients admitted to the intensive care unit (ICU) from January 2013 to December 2019, those whose serum cTnI levels were obtained within 7 days after ICU admission were included. Propensity score matching was used. Each patient with cTnI elevation was matched to one of control patients. The primary endpoint was in-hospital mortality and the secondary outcome was MACE. cTnI elevation was shown in 702 (11.7%) of 6,004 patients. After propensity score matching, 617 pairs of data were generated by 1:1 individual matching without replacement. In multivariable analysis of overall and propensity score-matched population, cTnI elevation were associated with in-hospital mortality (adjusted odds ratio [OR]: 2.78, 95% confidence interval [CI]: 1.95 – 3.95 and adjusted OR: 1.77, 95% CI: 1.20 – 2.62, respectively). In addition, cTnI elevation were associated with MACE (adjusted OR: 3.75, 95% CI: 2.43 – 5.78 and adjusted OR: 4.04, 95% CI: 2.24 – 7.29, respectively). In this study, cTnI elevation was associated with in-hospital mortality and MACEs in neurosurgical and neurocritically ill patients.

Introduction

Perioperative myocardial injury is associated with major adverse cardiac events (MACEs) and clinical prognosis of patients with non-cardiac or non-vascular surgeries[1]. Many surgical patients experience MACEs during the perioperative period and the first year after surgery[1–4]. Especially, postoperative cardiac troponin (cTn) elevation is important to predict prognosis of these surgical patients[1]. In addition, cTn elevation is associated with increased mortality and hospitalization in critically ill patients [5]. Regardless of the associated cardiovascular disease, cTn is a specific marker of myocardial injury and a predictor of prognosis[6–8].

Most morbidity and mortality of neurosurgical patients might be due to neurosurgical or neurocritically illness, although cardiac injury might also contribute to their poor clinical prognosis[9–11]. cTn elevation is also associated with prognosis of neurocritically ill patients with intracerebral hemorrhage or subarachnoid hemorrhage[9,11–13].

A limited number of studies have reported that clinical outcomes of neurosurgical and neurocritically ill patients are associated with cTn elevation[9,10,13]. Therefore, the objective of this study was to investigate whether cTn elevation might be associated with in-hospital mortality and MACEs in patients admitted to neurosurgical intensive care unit (ICU). In addition, we evaluated whether cTn elevation *per se* was associated with poor prognosis when severity and factors other than cTn elevation were controlled by propensity score matching.

Methods

Study population and design. This was a retrospective, single-center, observational study. Patients who were admitted to the neurosurgical ICU in a tertiary referral hospital (Samsung Medical Center, Seoul, Republic of Korea) from January 2013 to December 2019 were eligible. This study was approved by the Institutional Review Board of Samsung Medical Center (approval number: SMC 2020-09-082). The requirement for informed consent was waived by the Institutional Review Board of Samsung Medical Center due to its retrospective nature. Included criteria were: (1) patients who were hospitalized in the neurosurgical ICU due to postoperative management or neurocritical illness, and (2) those whose serum cTnI levels were obtained within seven days after ICU admission. Exclusion criteria were: (1) those with insufficient medical records, (2) those who had 'do not resuscitation' order, (3) those who were admitted to departments other than neurosurgery, and (4) those who were transferred to other hospitals or with unknown prognoses (Fig. 1).

Definitions and endpoints. In this study, baseline characteristics such as comorbidities, ICU management, and laboratory data were collected retrospectively using Clinical Data Warehouse. Our center constructed the "Clinical Data Warehouse Darwin-C" designed for investigators to search and retrieve de-identified medical records from electronic archives. It contains data pertaining to more than four million patients. Clinical and laboratory data were extracted from the Clinical Data Warehouse Darwin-C after finalizing the patient list in this study. Risk of surgery was defined according to the 2014 European Society of Cardiology/European Society of Anesthesiology (ESC/ESA) guidelines[14]. Perioperative management of patients followed institutional protocols based on current guidelines[6,14]. According to the institutional guideline, perioperative cTnI was measured for patients with more than moderate risk or undergoing moderate- to high-risk surgeries[14]. It was also measured at the discretion of attending clinician for patients with mild risks[6,14]. An automated analyzer (Advia Centaur XP; Siemens Healthcare Diagnostics, Erlangen, Germany) with a highly sensitive immunoassay was used for cTnI measurement. The lowest limit of detection was 6 ng/L. In this study, cTnI elevation was defined as an increase in cTnI above 0.0 6μg/L within 7 days after ICU admission[15]. Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated based on the worst value recorded during the initial 24 h in the ICU admission[16,17]. If the patient was intubated, the verbal score of Glasgow Coma Scale (GCS) was estimated using eye and motor scores as reported previously[18]. MACEs were defined as non-fatal cardiac arrest, emergent coronary revascularization, acute coronary syndrome, stroke, congestive heart failure, atrial fibrillation (new onset or destabilization of pre-existing atrial fibrillation), major arrhythmia, cardiovascular death, and rehospitalization for cardiovascular reasons[1]. The primary endpoint was in-hospital mortality and the secondary outcome was MACE.

Statistical analyses. All data are presented as means ± standard deviations for continuous variables and frequencies and proportions for categorical variables. Data were compared using Student's *t*-test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. Propensity score matching was used to control the selection bias and the confounding factor detected in this observational study. Each patient with cTnI elevation was matched to one control patient with the nearest neighbor matching within calipers determined by the propensity score. A caliper width of 0.2 of the

standard deviation of the logit of the propensity score was used for the matching[19]. To determine the effectiveness of propensity score matching for controlling the differences between patients with and without cTnI elevation, standardized mean differences (SMDs) were calculated for each variable before and after matching. SMDs less than 10% indicated successful propensity scores matching and balancing between the two groups. To evaluate whether there is a difference in in-hospital mortality and MACEs according to the cTnI elevation, we performed multiple logistic regression with stepwise variable selection in the overall and matched population. In the overall population, we tried to obtain the result of correcting confounding through regression adjustment, and in the matching dataset, we perform doubly robust estimation to additionally correct the bias that still exits after propensity score matching. The variables included in the multiple analyses were age, sex, comorbidities, cause of ICU admission, utilization of organ support modalities, including mechanical ventilators, continuous renal replacement therapy and vasopressors, ICP monitoring devices, hyperosmolar therapy, GCS, and APACHE II score on ICU admission. Cumulative mortality was calculated by Kaplan–Meier estimate and compared using a log-rank test. All tests were two-sided and *p* values less than 0.05 were considered statistically significant. All statistical analyses were performed with R Statistical Software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics. A total of 12,743 patients were admitted to the neurosurgical ICU during the study period and 6,004 patients were included in the final analysis. In the overall study population, cTnI elevation was shown in 702 (11.7%) patients (Fig. 1). The mean age of all patients was 55.8 ± 15.6 years. There were 2,698 (44.9%) male patients. Malignancy (50.5%) and hypertension (34.8) were the most common comorbidities. Elective vascular surgery (37.1%) and brain tumors (36.0%) were the most common reasons for ICU admission (Table 1). In the overall population, there were significantly differences for variables of baseline characteristics between the two groups except for current smoking and the use of mannitol (Table 1). The mean value of maximum cTnI level was higher in the cTnI elevation group than in the normal cTnI group (5.1 ± 34.3 μg/L vs. 0 ± 0 μg/L, $p < 0.001$). After propensity score matching, 617 pairs of data were generated by 1:1 individual matching without replacement. No significant imbalance was found in baseline characteristics between matched pairs (Table 1).

Table 1
Baseline characteristics of study population

	Overall study population				Propensity score-matched population			
	No elevation (n = 5302)	Elevation (n = 702)	P value	SMD	No elevation (n = 617)	Elevation (n = 617)	P value	SMD
Patient demographics								
Age (year)	54.94 ± 15.31	62.05 ± 15.97	< 0.001	0.454	60.89 ± 15.51	61.92 ± 15.91	0.248	0.066
Sex, male	2341 (44.2)	357 (50.9)	0.001	0.135	319 (51.7)	308 (49.9)	0.569	0.036
Comorbidities								
Malignancy	2724 (51.4)	306 (43.6)	< 0.001	0.156	291 (47.2)	290 (47.0)	0.999	0.003
Hypertension	1751 (33.0)	339 (48.3)	< 0.001	0.315	293 (47.5)	302 (48.9)	0.649	0.029
Diabetes mellitus	598 (11.3)	131 (18.7)	< 0.001	0.208	114 (18.5)	116 (18.8)	0.942	0.008
Chronic kidney disease	168 (3.2)	81 (11.5)	< 0.001	0.325	58 (9.4)	67 (10.9)	0.450	0.048
Cardiovascular disease	103 (1.9)	77 (11.0)	< 0.001	0.374	52 (8.4)	57 (9.2)	0.688	0.029
Chronic liver disease	102 (1.9)	28 (4.0)	0.001	0.122	22 (3.6)	24 (3.9)	0.881	0.017
Behavioral risk factors								
Current alcohol consumption	1285 (24.2)	144 (20.5)	0.033	0.089	141 (22.9)	128 (20.7)	0.408	0.051
Current smoking	586 (11.1)	81 (11.5)	0.748	0.015	83 (13.5)	76 (12.3)	0.610	0.034

Data are presented as numbers (%) or means ± standard deviations.

*Some patients received more than one hyperosmolar agent.

†Variables are not retained in propensity score matching

APACHE II Acute Physiology and Chronic Health Evaluation, *ICP* intracranial pressure, *ICU* intensive care unit, *SMD* standardized mean difference.

	Overall study population				Propensity score-matched population			
	No elevation (n = 5302)	Elevation (n = 702)	P value	SMD	No elevation (n = 617)	Elevation (n = 617)	P value	SMD
Cause of ICU admission			< 0.001	1.175			0.935	0.098
Brain tumor	2006 (37.8)	155 (22.1)			160 (25.9)	154 (25.0)		
Elective vascular surgery	2162 (40.8)	68 (9.7)			67 (10.9)	68 (11.0)		
Intracerebral hemorrhage	265 (5.0)	129 (18.4)			121 (19.6)	105 (17.0)		
Traumatic brain injury	247 (4.7)	129 (18.4)			105 (17.0)	106 (17.2)		
Subarachnoid hemorrhage	211 (4.0)	135 (19.2)			101 (16.4)	110 (17.8)		
Spinal surgery	217 (4.1)	25 (3.6)			21 (3.4)	24 (3.9)		
Central nervous system infection	41 (0.8)	10 (1.4)			9 (1.5)	10 (1.6)		
Cerebral infarction	33 (0.6)	14 (2.0)			14 (2.3)	14 (2.3)		
Others	120 (2.3)	37 (5.3)			19 (3.1)	26 (4.2)		
APACHE II score on ICU admission	3.26 ± 4.35	7.87 ± 8.03	< 0.001	0.713	6.72 ± 6.58	7.06 ± 7.50	0.399	0.048
Glasgow coma scale on ICU admission	14.60 ± 1.61	12.02 ± 4.33	< 0.001	0.79	12.79 ± 3.63	12.47 ± 4.05	0.151	0.082
ICU management								

Data are presented as numbers (%) or means ± standard deviations.

*Some patients received more than one hyperosmolar agent.

†Variables are not retained in propensity score matching

APACHE II Acute Physiology and Chronic Health Evaluation, *ICP* intracranial pressure, *ICU* intensive care unit, *SMD* standardized mean difference.

	Overall study population				Propensity score-matched population			
	No elevation (n = 5302)	Elevation (n = 702)	P value	SMD	No elevation (n = 617)	Elevation (n = 617)	P value	SMD
Use of vasopressors	127 (2.4)	88 (12.5)	< 0.001	0.393	69 (11.2)	71 (11.5)	0.928	0.010
Mechanical ventilation	842 (15.9)	437 (62.3)	< 0.001	1.080	358 (58.0)	352 (57.1)	0.773	0.020
Continuous renal replacement therapy	13 (0.2)	44 (6.3)	< 0.001	0.344	12 (1.9)	21 (3.4)	0.158	0.091
ICP monitoring	403 (7.6)	143 (20.4)	< 0.001	0.375	133 (21.6)	123 (19.9)	0.527	0.040
Use of mannitol*	2304 (43.5)	295 (42.0)	0.497	0.029	270 (43.8)	268 (43.4)	0.954	0.007
Use of glycerin*	549 (10.4)	226 (32.2)	< 0.001	0.554	200 (32.4)	189 (30.6)	0.540	0.038
Clinical outcomes†								
In-hospital mortality	176 (3.3)	208 (29.6)	< 0.001		115 (18.6)	159 (25.8)	0.003	
28-day mortality	161 (3.0)	206 (29.3)	< 0.001		104 (16.9)	159 (25.8)	0.000	
ICU mortality	100 (1.9)	150 (21.4)	< 0.001		77 (12.5)	109 (17.7)	0.014	
ICU length of stay (day)	59.6 ± 332.7	127.6 ± 185.7	< 0.001		171.0 ± 901.3	124.5 ± 181.4	0.210	
Hospital length of stay (day)	23.5 ± 93.7	46.0 ± 222.3	0.008		58.4 ± 251.5	34.0 ± 43.0	0.018	

Data are presented as numbers (%) or means ± standard deviations.

*Some patients received more than one hyperosmolar agent.

†Variables are not retained in propensity score matching

APACHE II Acute Physiology and Chronic Health Evaluation, *ICP* intracranial pressure, *ICU* intensive care unit, *SMD* standardized mean difference.

	Overall study population				Propensity score-matched population			
	No elevation (n = 5302)	Elevation (n = 702)	P value	SMD	No elevation (n = 617)	Elevation (n = 617)	P value	SMD
Major adverse cardiac events			< 0.001				< 0.001	
New onset arrhythmia	55 (1.0)	22 (3.1)			13 (2.1)	19 (3.1)		
Heart failure	3 (0.1)	14 (2.0)			1 (0.2)	11 (1.8)		
Acute coronary syndrome	1 (0.02)	12 (1.7)			0 (0)	9 (1.5)		
Cardiac arrest	1 (0.02)	5 (0.7)			1 (0.2)	5 (0.8)		
Cardiovascular death	0 (0)	15 (2.1)			0 (0)	11 (1.8)		
Data are presented as numbers (%) or means ± standard deviations.								
*Some patients received more than one hyperosmolar agent.								
†Variables are not retained in propensity score matching								
APACHE II Acute Physiology and Chronic Health Evaluation, *ICP* intracranial pressure, *ICU* intensive care unit, *SMD* standardized mean difference.								

Clinical outcomes. In the overall study population, rates of in-hospital mortality and ICU mortality were higher in patients with cTnI elevation than in those without cTnI elevation (29.6% vs. 3.3% and 21.4% vs. 1.9%, both $p < 0.001$) (Table 1). Lengths of stay in the ICU and hospital were prolonged in patients with cTnI elevation than in those without cTnI elevation ($p < 0.001$ and $p = 0.008$, respectively). Clinical outcomes in the propensity score-matched population were similar to those of the entire population. In the propensity score-matched population, rates of in-hospital mortality and ICU mortality were also higher in the elevated cTnI group than in the normal cTnI group (25.8% vs. 18.6% and 17.7% vs. 12.5, $p = 0.003$ and $p = 0.014$, respectively). MACEs were more common in patients with cTnI elevation than in those without cTnI elevation in the overall population and the propensity score-matched population (9.7% vs. 1.1% and 8.9% vs. 2.4%, both $p < 0.001$) (Table 1).

In multivariable analysis of the overall and propensity score-matched population, cTnI elevation were associated with in-hospital mortality (adjusted odds ratio [OR]: 2.78, 95% confidence interval [CI]: 1.95–3.95 and adjusted OR: 1.77, 95% CI: 1.20–2.62, respectively). In addition, cTnI elevation were associated with MACE (adjusted OR: 3.75, 95% CI: 2.43–5.78 and adjusted OR: 4.04, 95% CI: 2.24–7.29, respectively) (Table 2).

Table 2
The relationship between elevated cardiac troponin I (cTnI) and clinical outcomes of the overall and propensity score-matched population

cTnI elevation within 7 days	*Adjusted odds ratio (95% CI)	*P* value
In-hospital mortality		
Overall population	2.78 (1.95–3.95)	< 0.001
Propensity score-matched population	1.77 (1.20–2.62)	0.004
Major adverse cardiac events		
Overall population	3.75 (2.43–5.78)	< 0.001
Propensity score-matched population	4.04 (2.24–7.29)	< 0.001
* Adjusted for age, sex, comorbidities, cause of ICU admission, utilization of organ support modalities, use of invasive ICP monitoring device, hyperosmolar therapy, and APACHE II score on ICU admission		
CI confidence interval, *APACHE* Acute Physiology and Chronic Health Evaluation, *ICP* intracranial pressure, *ICU* intensive care unit		

In survival analysis, the mortality rate of patients with cTnI elevation was significantly higher than that of patients without cTnI elevation in the propensity score-matched population (28.8% vs. 19.3%, log-rank test, $p < 0.001$) (Fig. 2).

Discussion

In this study, we investigated whether cTn elevation was associated with mortality and MACEs in patient admitted to neurosurgical ICU. Major findings of this study were as follows. First, elevated cTnI level was shown in about one-tenth of neurosurgical patients in the overall population. Second, rates of in-hospital mortality and ICU mortality were higher in patients with cTnI elevation than in those without cTnI elevation in the overall study population and the propensity score-matched population. The length of hospitalization was also prolonged in patients with cTnI elevation than in those without cTnI elevation in both populations Finally, multivariable analysis revealed that cTnI elevation were associated with in-hospital mortality and MACE in overall and propensity score-matched population.

cTn is a regulatory protein that can lead to myocardial contraction by controlling calcium-mediated interaction with actin and myosin[5,20]. Destroyed cardiomyocytes can release cTn into the blood which can be detected using a commercially available immunoassay[5]. Postoperative myocardial injury is an independent predictor of cardiovascular complications and mortality within 30 days and one year in patients undergoing orthopedic or abdominal surgeries[1]. Especially, cTn elevation is associated with worse cardiac outcomes after major surgeries[21]. In addition, elevated cTn measurements among critically ill patients are associated with increased mortality and ICU length of stay[5].

In patients with subarachnoid hemorrhage, electrocardiographic abnormalities, including prolongation of QT interval and repolarization abnormalities, are commonly detected[9,12]. Especially, cTn elevation has been found in one-third of patients with subarachnoid hemorrhage known to be associated with increased mortality[9,13]. cTn elevation is also associated with mortality in patients with surgically treated intracerebral hemorrhage and traumatic brain injury[9,22]. Under stressful conditions such as acute brain injury, stimulation of the hypothalamic paraventricular nucleus as the main control center of the hypothalamic-pituitary-adrenal axis can activate sympathetic output and lead to electrocardiographic abnormalities, arrhythmia, and myocardial injury[23]. In addition, activation of this axis after acute brain injury can cause a significant increase in catecholamines. The catecholamine surge hypothesis is the most widely accepted mechanism of brain-heart interaction[23]. Recent histological studies have shown that catecholamine-mediated myocardial injury may be a major pathophysiology of neurocritical illness[9–11, 24]. Therefore, cardiac injury could be accompanied by neurosurgical or neurocritical illness. It is known to be associated with clinical prognosis[9–11, 22,24].

Neurosurgical patients with severe brain injury are more likely to develop cardiac injury and MACEs compared to those with benign diseases. Therefore, it is not easy to determine whether elevated cTn itself is associated with a poor prognosis or neurosurgical patients with elevated cTn will show poor prognosis because of their neurocritical illness. Therefore, a propensity score matching method was used to adjust for this confounder in this study. In brief, cTnI elevation was significantly associated with poor clinical outcomes of neurosurgical and neurocritically ill patients. Finally, the majority of morbidity and mortality could be arising from neurocritical illness, although other studies have suggested that cardiac injury might also be a contributing factor[9–11].

This study has several limitations. First, this was a retrospective review of medical records and data extracted from Clinical Data Warehouse. The nonrandomized nature of registry data might have resulted in a selection bias. Second, laboratory tests including cTnI levels were protocol-based for patients with perioperative neurosurgery. They were performed occasionally by non-protocol methods for neurocritically ill patients without neurosurgery. Third, the pathophysiology of acute coronary syndrome could not be determined for a few patients. Cardiac catheterization was not performed in these sick patients because intrahospital transport was impossible due to severe illness. Finally, the distribution of neurosurgical diseases differed from that of the general neurosurgical ICU and the proportion of patients with brain tumors was particularly high.

Conclusions

In this study, cTnI elevation was associated with in-hospital mortality and cardiac complications in neurosurgical and neurocritically ill patients. In addition, the length of hospitalization was prolonged for patients with cTnI elevation than that for those without cTnI elevation. Finally, perioperative or neurocritical illness-associated cardiac injury could be associated with clinical outcomes of neurosurgical and neurocritically ill patients.

Declarations

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Contributions

JHL contributed to the study design, data collection, drafting of the manuscript, and statistical analysis. YIL contributed to the data collection and statistical analysis. JA contributed to the study design and statistical analysis. JAR contributed to the study conception and design, data collection, and drafting of the manuscript. All authors read and approved the final manuscript.

Ethics declarations

This study was approved by the Institutional Review Board of Samsung Medical Center (approval number: SMC 2020-09-082). Patients' records were reviewed and published according to the Declaration of Helsinki. The requirement for informed consent was waived by the Institutional Review Board of Samsung Medical Center due to its retrospective nature.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable. This study did not contain individual or personal data in any form (including individual details, images, or videos).

Data availability

Our data are available on Harvard Dataverse Network (http://dx.doi.org/10.7910/DVN/9HU70P).

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Figures

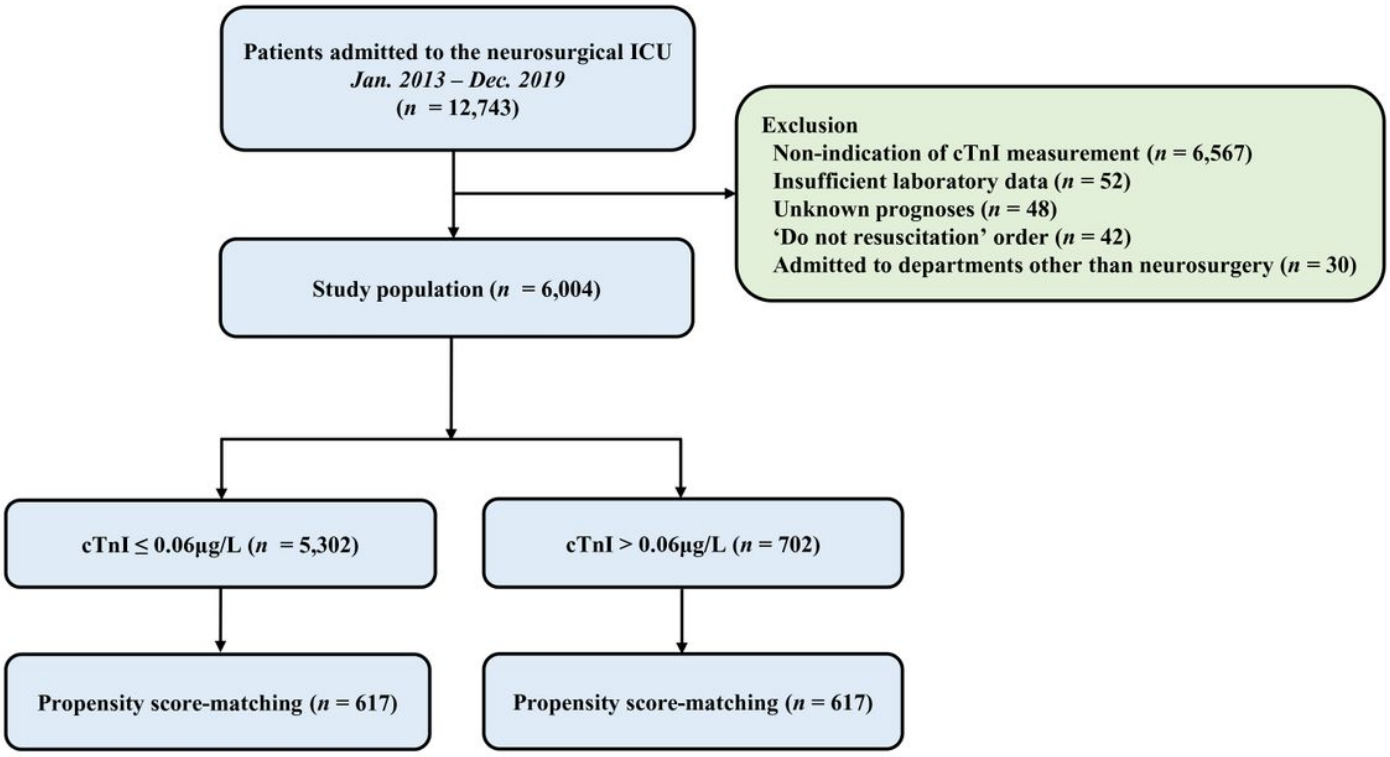

Figure 1

Study flow chart. ICU, intensive care unit; ICU, intensive care unit; cTnI, cardiac troponin I.

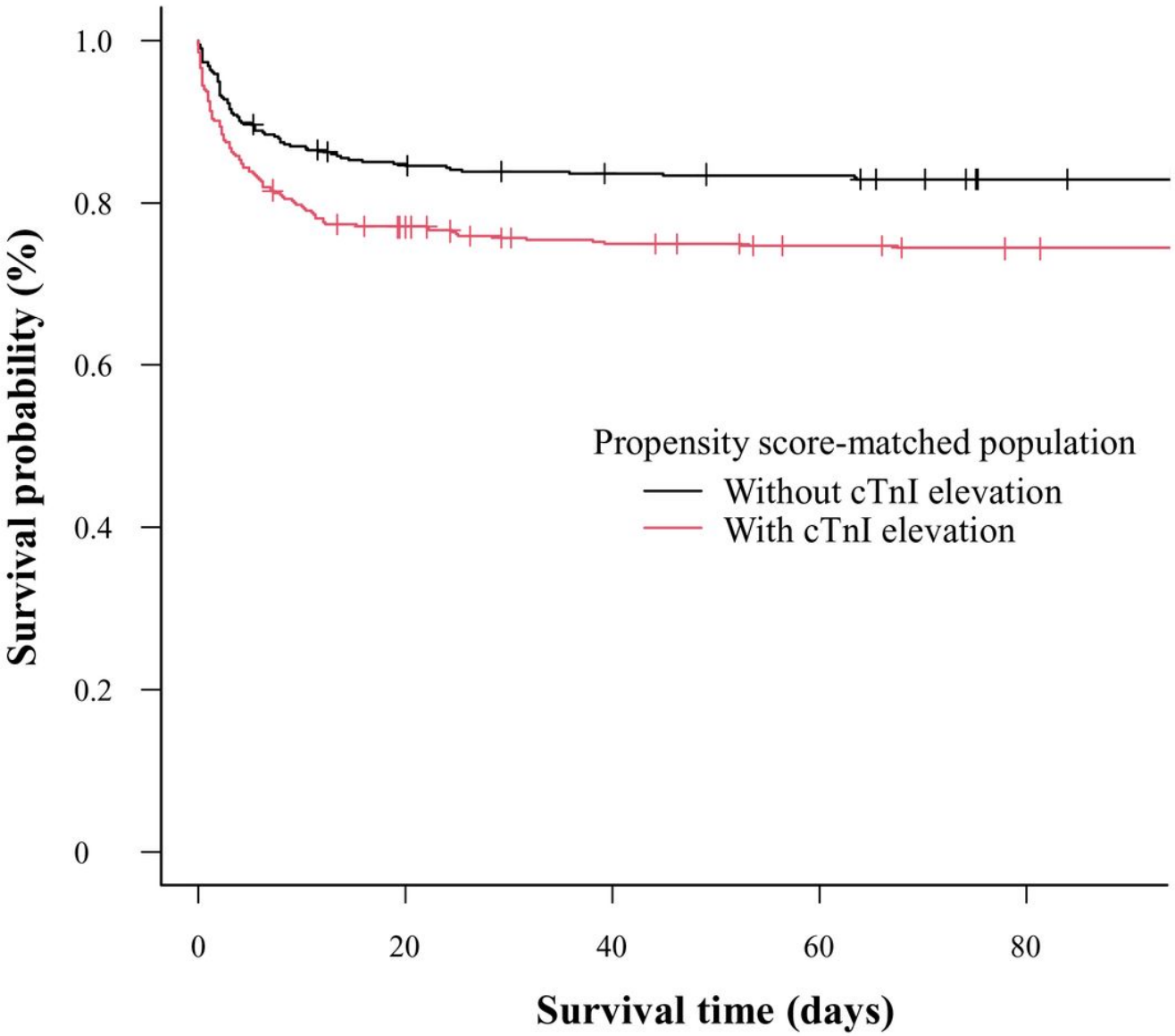

Figure 2

Kaplan Meier survival analyses of propensity score-mached population. The mortality rate of patients with cardiac troponin I (cTnI) elevation was significantly higher compared with those without cTnI elevation (28.8% vs. 19.3%, log-rank test, $p < 0.001$).