学位論文

Serum Neuron-Specific Enolase Level as Predictor of Neurologic Outcome after Aortic Surgery

（大血管手術後における神経学的予後予測因子としての血清神経特異的エノラーゼ値）

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Abstract

Background: This study aimed to evaluate the significance of serum neuron-specific enolase (NSE) level as a predictor of neurologic injury in thoracic aortic surgery.

Methods: We neurologically assessed 60 consecutive patients who underwent thoracic aortic surgery for thoracic aortic aneurysm (n = 26) and aortic dissection (n = 34). Using moderate hypothermic circulatory arrest with antegrade cerebral perfusion, total arch replacement and hemiarch replacement were performed in 37 and 23 patients, respectively. Serum NSE levels in venous blood samples drawn before surgery and at 1 day after surgery were measured. Severity of neurologic injury was categorized as either uncomplicated (n = 48), temporary neurologic dysfunction (TND, n = 5), or permanent neurologic dysfunction (PND, n = 7). The extent of stroke was estimated on computed tomography or magnetic resonance imaging.

Results: The NSE level significantly differed among the three groups (PND > TND > uncomplicated) on the first postoperative day. ROC curve analysis showed that the cutoff value of NSE level was 34.14 ng/mL for neurologic injury (sensitivity, 0.769; specificity, 0.851) and 43.56 ng/mL for PND (sensitivity, 1.000; specificity, 0.963). The NSE level significantly correlated with the extent of stroke ($r = 0.61$, $p < 0.001$).

Conclusion: Serum NSE level is a significant predictor of adverse neurologic outcomes and extent of stroke after thoracic aortic surgery.

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Keywords: serum neuron-specific enolase; thoracic aortic surgery; temporary neurologic dysfunction; permanent neurologic dysfunction; neurologic injury

Introduction

The gamma subunit of the glycolytic enzyme enolase—commonly referred to as neuron-specific enolase (NSE)—is a well-known marker of central nervous system (CNS) cell damage following brain ischemia owing to its location in the neuronal and axonal processes and its leakage into the spinal fluid and blood in the event of nerve damage [1]. Despite the extensive use of NSE as a tumor marker for neuroblastoma [2] and small-cell lung cancer [3], the fact that it leaks into the spinal fluid after CNS damage has led to recent attempts to measure NSE levels in various neurologic and cerebrovascular disorders and has resulted in its usage as a marker of CNS injury [4,5]. Other reported quantitative markers of CNS injury in the blood and spinal fluid include brain-type creatine phosphokinase found in neurons [6] and S-100 protein in glial cells [7]. In the present study, we selected NSE as a marker that could easily be measured in the perioperative period and investigated the relationship between neurologic injury and serum NSE level. This study aimed to evaluate the significance of serum NSE level as a predictor of neurologic injury in thoracic aortic surgery.

Materials and Methods

Patients

From October 2012 to February 2015, 273 consecutive patients underwent cardiac operations in our institution. Among them, patients who underwent thoracic aortic surgery were reviewed. Preoperative and postoperative data (included serum NSE) were corrected from the institutional database. The study population included 60 consecutive patients (43 men, 17 women; mean age, 70 ± 11 years). Preoperative factors are summarized in Table 1. Thoracic aortic surgery was elective in 37 patients, urgent in 7 patients, and emergent in 16 patients. Aortic etiologies were categorized as either true thoracic aortic aneurysm (n = 26) or aortic dissection (n = 34); patients with aortic dissection comprised 22 patients with acute type A aortic dissection, 9 patients with chronic type A aortic dissection, and 3 patients with chronic type B aortic dissection. For acute

type A aortic dissection, emergency operation was performed in 15 patients with patent false lumen or unstable hemodynamics, and urgent operation was performed in 7 patients with thin thrombosed false lumen and stable hemodynamics. History of hypertension, diabetes mellitus, hyperlipidemia, smoking, chronic obstructive pulmonary disease (COPD), and Marfan syndrome prior to surgery was recorded by history taking for all patients. The renal function of all patients was evaluated by obtaining a blood sample and measuring serum creatinine concentration prior to surgery.

The preoperative cardiac function of all patients was assessed and recorded using transthoracic echocardiography or transesophageal echocardiography (TEE), and the results were classified as good (>60%), adequate (30–60%), or poor (<30%). Furthermore, the severity of aortic valve insufficiency was categorized into stages 0 to IV.

Neurologic Assessment

Neurologic findings prior to surgery were recorded. Elective patients underwent preoperative cranial computed tomography (CT), magnetic resonance imaging (MRI), or carotid ultrasonography, and the resulting images were evaluated by a radiologist for head and neck vascular stenosis and old cerebral infarction. Conversely, urgent and emergent patients underwent carotid ultrasonography for the evaluation of cranial blood flow.

After surgery, neurologic findings upon emergence from anesthesia were recorded and evaluated for signs of neurologic injury. Patients with suspected neurologic injury underwent brain CT or MRI as soon as possible, and a stroke team was consulted before commencing therapy or rehabilitation.

Infarction location was determined by a radiologist blinded to patients' NSE level. Infarction volume was estimated using the frequently used ABC/2 method for measuring intracerebral hematoma volume based on CT and MRI images [8-11] (Fig. 1). The two longest perpendicular linear diameters (A and B) on the section in which the abnormality on CT or MRI appeared the

largest were measured. Taking into account these diameters, the product of section thickness and total number of sections containing the lesion (C) was determined, and infarction volumes were calculated using the following formula: volume = ABC/2. The total infarction volume in patients with multiple infarction sites was calculated by adding the estimated volume of each area.

We evaluated the severity of neurologic injury using the definition of distinct neurologic endpoints reported by Ergin et al. [12]. Temporary neurologic dysfunction (TND) was defined as the occurrence of postoperative confusion, agitation, delirium, prolonged obtundation, or transient parkinsonism without any localizing neurologic signs. Findings on CT or MRI performed in these patients were usually normal. Permanent neurologic dysfunction (PND) was defined as the presence of permanent neurologic deficits that were focal (stroke) or global (parkinsonism, coma, gait disturbance) in nature and persisting at discharge from the hospital. When these permanent deficits were associated with strokes, CT or MRI showed corresponding focal defects.

NSE Evaluation

Venous blood samples were collected before and at 24 h after surgery and were subsequently centrifuged at 3000 rpm for 10 min within 1 h of collection. The serum component was used as the NSE measurement sample. NSE measurement was performed using electrochemiluminescence immunoassay with a commercially available biotinylated anti-NSE antibody and $Ru(bpy)_3$-labeled antibody (cobas immunoassay analyzer; Roche Diagnostics GmbH, Mannheim, Germany). This method enables NSE measurement within the range of 0.05–370 ng/mL. If measurement could not be immediately performed, serum samples were stored at −30°C and subsequently thawed prior to measurement.

Surgical Procedure

Anesthesia was induced by intravenous infusion of remifentanil and propofol, and a muscle relaxant was administered before endotracheal intubation. Anesthesia was maintained by infusion

of fentanyl and continuous infusion of remifentanil and propofol. A central venous line and Swan–Ganz catheter were inserted via the right internal jugular vein. The TEE probe was inserted to evaluate cardiac function during surgery.

All surgeries were performed using the median sternotomy approach. Depending on the condition of the ascending aorta, cardiopulmonary bypass (CPB) was established by utilizing a combination of the ascending, axillary, and femoral arteries as arterial inflow sites and by draining blood via the superior and inferior vena cava. Blood was transmitted by a centrifugal pump and drained by negative pressure. Blood cardioplegia was employed for myocardial protection.

After establishing CPB, hypothermic circulatory arrest was induced at moderate hypothermia (i.e., rectal temperature of 20–28°C), and selective cerebral perfusion was initiated while performing distal anastomosis using the open distal method. When performing total arch replacement, the elephant trunk procedure was used for distal anastomosis, and the thoracic aorta was repaired using woven Dacron grafts with four branches. When performing hemiarch replacement, the artery was repaired using woven Dacron grafts with a single branch.

Duration of surgery, CPB, cardiac arrest, circulatory arrest, selective cerebral perfusion, and minimal rectal temperature were recorded for all patients.

Statistical Analysis

All data were analyzed using SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). Data obtained from this study were expressed as mean ± SD. Nonparametric Mann–Whitney U test and Tukey's HSD test were used to compare mean values. The relationships between the NSE level and the infarction volume and operative factors (i.e., duration of surgery, CPB, aortic cross-clamp time, selective cerebral perfusion, and minimal rectal temperature) were evaluated using linear regression analysis.

To determine the cutoff value for NSE level as a predictor of postoperative neurologic injury onset, evaluation was performed using receiver operating characteristic (ROC) curves. A statistically

significant difference was deemed present at $p < 0.05$.

Results

Patient Characteristics

Patient characteristics prior to surgery are shown in Table 1. No significant differences in age, sex, percentage of aortic dissections, or percentages of urgent and emergent surgeries were observed between the uncomplicated group and the neurologic injury group. Furthermore, there were no significant differences in preoperative history of hypertension, diabetes mellitus, hyperlipidemia, smoking, COPD, Marfan syndrome, myocardial ischemia, shock, aortic valve insufficiency, or serum creatinine level between both groups. Cerebral malperfusion occurred in 5 patients with acute type A aortic dissection. A significantly higher number of patients in the neurologic injury group had a preoperative history of cerebral infarction induced by cerebral malperfusion ($p = 0.004$).

Patient characteristics during surgery are shown in Table 2. No significant difference in the percentage of total arch or hemiarch replacement procedures was noted between both groups. With respect to concomitant procedures, there was no significant difference in the percentage of patients who underwent valve-sparing aortic root replacement, aortic valve replacement, or valvuloplasty; however, the percentage of patients who also underwent coronary artery bypass grafting in the neurologic injury group was significantly higher ($p = 0.03$).

There were no significant differences in the duration of surgery, aortic cross-clamp time, or circulatory arrest time between both groups.

Outcomes

Four of the patients died within 30 days of surgery owing to mediastinitis (n = 1), respiratory complications (n = 2), and multiple organ failure due to multiple systemic embolism (n = 1). However, no significant intergroup difference in mortality was observed, with two deaths each in

the uncomplicated group and the neurologic injury group. There were two in-hospital deaths due to mediastinitis (n = 1) and acute lower limb arterial occlusion (n = 1) in the uncomplicated group but none in the neurologic injury group.

Neurologic injury occurred in 12 patients (20%); with respect to the severity of neurologic injury, 5 and 7 patients had TND and PND, respectively. Preoperative cerebral malperfusion was observed in two patients with TND and one patient with PND. Postoperative imaging showed infarctions in 7 patients, with a mean infarction volume of 9.217 ± 10.468 cm^3. As regards imaging technique, MRI was performed in 3 patients at 11.7 ± 5.9 days after surgery, whereas CT was performed in 4 patients at 4.3 ± 5.3 days after surgery.

Aside from neurologic injury, the following major complications were particularly observed in 12 patients (20%): re-exploration for bleeding (n = 4), renal failure (n = 4), respiratory failure (n = 3), mediastinitis (n = 2), and acute lower limb ischemia (n = 1).

The mean postoperative intensive care unit stay was significantly longer in the neurologic injury group than in the uncomplicated group (13.1 ± 11.8 days versus 5.1 ± 4.5 days; $p < 0.001$).

NSE

Figure 2 illustrates a comparison of NSE levels in blood samples obtained before surgery and at 1 day after surgery in each group. The mean NSE level was significantly higher on the day after surgery than on the day before surgery in the uncomplicated group (27.8 ± 9.0 ng/mL versus 25.2 ± 33.0 ng/mL; $p < 0.001$, Mann–Whitney) and neurologic injury group (55.4 ± 34.5 ng/mL versus 16.5 ± 5.1 ng/mL; $p < 0.001$, Mann–Whitney), as well as in the TND group (35.6 ± 13.7 ng/mL versus 16.4 ± 3.9 ng/mL; $p = 0.028$, Mann–Whitney) and PND group (80.9 ± 34.6 ng/mL versus 16.6 ± 6.0 ng/mL; $p = 0.002$, Mann–Whitney) (Fig. 2).

Figure 3 shows a comparison of NSE levels in blood samples obtained at 1 day after surgery according to the presence or absence of neurologic injury and the severity of neurologic injury. The mean NSE level was significantly higher in the neurologic injury group than in the

uncomplicated group (55.4 ± 34.5 ng/mL versus 27.8 ± 9.0 ng/mL; p = 0.001, Mann–Whitney). With respect to severity, the mean NSE level was significantly higher in the PND group (80.9 ± 34.6 ng/mL) than in the TND group (35.6 ± 13.7 ng/mL) or uncomplicated group (27.8 ± 9.0 ng/mL) ($p < 0.001$, Tukey's HSD) (Fig. 3).

The mean NSE level of 5 patients with preoperative cerebral malperfusion was 17.5 ± 3.2 ng/mL before surgery and 43.2 ± 29.9 ng/mL at 1 day after surgery. The mean NSE level of two TND patients with cerebral malperfusion were 17.68 ng/mL and 12.54 ng/mL before surgery, 58.95 ng/mL and 21.33 ng/mL at 1 day after surgery. The NSE level of one PND patient with cerebral malperfusion was 20.2 ng/mL before surgery, 88.67 ng/mL at 1day after surgery.

The cutoff values for the onset of neurologic injury and severe neurologic injury were estimated using ROC curves (Fig. 4). Specifically, the cutoff value for neurologic injury was estimated to be 34.14 ng/mL with a sensitivity of 0.769 and specificity of 0.851 (AUC, 0.791 [95% CI, 0.617–0.964]), whereas the cutoff value for PND was estimated to be 43.56 ng/mL with a sensitivity of 1.000 and specificity of 0.963 (AUC, 0.985 [95% CI, 0.957–1.000]). Serum NSE level at 1 day after surgery exhibited a very high level of sensitivity and specificity, and the statistical power was particularly high for PND.

The correlation between serum NSE level and infarction volume at 1 day after surgery was investigated using linear regression analysis. The results of this analysis (Fig. 5) indicated a significant correlation between serum NSE level and infarction volume ($r = 0.61$, $p < 0.001$). Similar analyses for NSE level and duration of surgery, CPB, circulatory arrest time, and selective cerebral perfusion did not reveal any significant correlations (Fig. 6).

Discussion

This study showed that serum NSE level at 1 day after thoracic aortic surgery was a significant predictor of adverse neurologic outcomes and correlated with stroke volume. Several studies have reported NSE as a biomarker of neurologic injury. However, no studies have indicated serum NSE

level as a biomarker for the prediction of neurologic injury severity after thoracic aortic surgery.

Neurologic injury is a serious surgical complication in thoracic aortic surgery. Selim et al. reported that the incidence rate of postoperative neurologic injury was 3–8% for valve replacement and 8–15% for thoracic aortic surgery [13]. In particular, the incidence of neurologic injury is higher in thoracic aortic surgery than in other procedures owing to the involvement of hemodynamic factors in the form of embolisms caused by surgical manipulation of cervical branches and reduction in systemic blood pressure due to the use of CPB. Therefore, early therapeutic intervention is essential to minimize the sequelae of these dangerous complications. However, the early perioperative period in thoracic aortic surgery is typically concerned with ensuring the patient's respiration and circulation and inserting various drains and lines, making it difficult to establish a precise early diagnosis using diagnostic imaging techniques such as CT and MRI. Hence, biomarkers that indicate the extent of CNS cell damage based on intracerebral enzymes and brain-specific proteins leaking from the spinal fluid may be useful in establishing an early diagnosis of neurologic injury [10].

A number of studies have investigated these biomarkers, including brain-type creatine phosphokinase (CK-BB) [6], S-100 protein in glial cells [7], neurofilaments [14], glial fibrillary acidic protein [15], and tau protein [16]. Enolase is a glycolytic enzyme that catalyzes cytoplasmic ATP production reactions. It has a molecular weight of approximately 100,000 Da and is not affected by sex or age differences or smoking. Enolase is a dimer comprising three subunits—alpha, beta, and gamma—that can combine to form five different isoenzymes, namely the αα, ββ, and γγ homodimers and the αβ and αγ hybrid types [17,18]. The γγ and αγ isoenzymes containing the γ-subunit are particularly abundant in the CNS tissue (approximately 20 μg/mg protein) but are very scarce in other tissues (0.1–0.4 μg/mg protein). In the CNS tissue, the γ-subunit is located in the neurons and axons and is absent from glial cells, hence the name "NSE" [19]. In the present study, we used NSE in the neurons and axons as a biomarker of neurologic injury.

Roine et al. reported that serum NSE level at 24 h after resuscitation was significantly higher

among patients in a vegetative or brain-dead post-resuscitation state than among those who regained consciousness [1]. Moreover, Georgiadis et al. showed that NSE and S-100β levels in blood samples drawn during the first 24 h after cardiac surgery were useful indicators of adverse neurologic outcomes [20]. Moreover, several studies have reported significantly higher NSE levels in the spinal fluid than in serum [6,7]. Based on these study findings, we measured and investigated NSE levels in blood samples collected within 24 h of surgery using peripheral blood to minimize the patient's burden.

Hardemark et al. correlated NSE concentrations in the cerebrospinal fluid with the development and size of infarcts in rats by sampling the fluid before and after middle cerebral artery occlusion over several days [21]. Jonsson et al. reported the correlation between S-100β concentration and the size and severity of infarction [22]. However, in the present study, we observed a positive correlation between NSE and infarction volume. The increase in serum NSE concentration was attributed to extracellular effusion caused by the ischemic breakdown of the blood–brain barrier. Therefore, our finding of a positive correlation in which the NSE level increased in conjunction with the size of the infarct is highly logical. Upon comparing NSE levels according to the severity of neurologic injury, we observed that the NSE level was higher in the PND group than in the TND group or uncomplicated group. This finding could be attributed to the fact that larger infarctions lead to greater blood–brain barrier disruption.

The study findings showed that postoperative serum NSE levels were higher than preoperative serum NSE levels in the three groups; nonetheless, they failed to reveal any correlation between NSE level and duration of surgery, CPB, aortic cross-clamp time, and selective cerebral perfusion. However, lengthening the duration of CPB increases the time that red blood cells (RBCs) are in contact with the oxygenator and centrifugal pump, which inevitably leads to hemolysis due to the destruction of the said RBCs [23]. As RBCs contain NSE [24], hemolysis is therefore thought to increase NSE concentration, as reported in several previous studies [25,26]. Hence, prolonging CPB presumably increases the serum NSE concentration, which could explain why these two

factors appear to be correlated. The lack of such finding in the present study could be attributed to the fact that hemolysis induced by RBC destruction occurred in the study patients during CPB but the duration of CPB was not very long for the correlation between NSE level and duration of CPB because of the improved performance of recent oxygenators and centrifugal pumps.

Immediately measuring the serum NSE level after aortic surgery is a new strategy aimed at detecting neurologic injury in the acute stage. If hypothermic cerebroprotection was applied to patients with increasing serum NSE level, the neurologic outcomes of these patients may be improved. These study findings are very important for the improvement in neurologic outcomes.

The present study has limitations, including its retrospective design, small study population, and low incidence of neurologic injury. As such, we cannot discount the possibility of various biases in the results, and a larger patient population is required to confirm our findings. In addition to this point, this study cohort is heterogenous including acute and chronic as well as several underlying pathologies. This heterogeneity may reduce the potential to draw meaningful conclusions. Nevertheless, perioperative variables were no significant differences between uncomplicated group and neurologic injury group excluding concomitant CABG. Therefore, these study findings are reliable for drawing meaningful conclusions.

In conclusion, the present study showed that serum NSE level within 24 h of surgery is a useful predictor of neurologic injury onset and severity. The involvement of various factors in thoracic aortic surgery can make it difficult to establish a precise diagnosis using diagnostic imaging techniques; therefore, early intervention using serum NSE level as a diagnostic criterion may be capable of mitigating the sequelae that can arise from postoperative neurologic injury.

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Figure legends

Figure 1.

The formula ABC/2 was used, where A is the largest stroke diameter on CT or MRI, B is the diameter 90° to A, and C is the approximate number of CT or MRI slices with stroke multiplied by slice thickness. A and B are denoted by orange and blue lines, respectively.

Figure 2.

The mean NSE level was significantly higher on the day after surgery than on the day before surgery. PND, permanent neurologic dysfunction; Post, postoperative; Pre, preoperative; TND, temporary neurologic dysfunction.

Figure 3.

The mean NSE level was significantly higher in the neurologic injury group than in the uncomplicated group; similarly, it was significantly higher in the PND group than in the TND group or uncomplicated group. PND, permanent neurologic dysfunction; TND, temporary neurologic dysfunction.

Figure 4.

Serum NSE level at 1 day after surgery exhibited a very high level of sensitivity and specificity. AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

Figure 5.

There was a significant correlation between serum NSE level and infarction volume ($r = 0.61$, $p < 0.001$). NSE, neuron-specific enolase.

Figure 6.

There was no significant correlation between serum NSE level and duration of surgery, CPB, circulatory arrest time, or selective cerebral perfusion. ACP, antegrade cerebral perfusion; CPB, cardiopulmonary bypass; NSE, neuron-specific enolase.

Tables

Table 1. Preoperative variables

	All (n = 60)	Uncomplicated (n = 48)	Neurologic injury (n = 12)	p-value
Age	70.4 ± 11.6	70.3 ± 11.5	70.7 ± 11.7	0.926
Gender, male	43 (71.7%)	35 (72.9%)	8 (66.6%)	0.667
Aortic dissection	34 (56.7%)	28 (58.3%)	6 (50.0%)	0.602
Emergent/urgent	23 (38.3%)	17 (35.4%)	6 (50.0%)	0.688
Hypertension	56 (93.3%)	46 (95.8%)	10 (83.3%)	0.271
Diabetes mellitus	8 (13.3%)	7 (14.9%)	1 (8.3%)	0.737
Hyperlipidemia	24 (40.0%)	20 (41.7%)	4 (33.3%)	0.795
Smoking history	22 (36.7%)	19 (39.9%)	3 (25.0%)	0.538
COPD	18 (30.0%)	15 (31.3%)	3 (25.0%)	0.673
Marfan syndrome	1 (1.7%)	1 (2.1%)	0 (0.0%)	0.614
Myocardial ischemia	3 (5.0%)	2 (4.2%)	1 (8.3%)	0.554

Brain ischemia	**3 (5.0%)**	**0 (0.0%)**	**3 (25.0%)**	**0.004**
Shock/tamponade	**2 (3.3%)**	**1 (2.1%)**	**1 (8.3%)**	**0.498**
Grade 3 or 4 aortic regurgitation	**11 (18.3%)**	**9 (18.8%)**	**2 (16.7%)**	**0.868**
Creatinine (mg/dL)	**1.13 ± 1.14**	**0.98 ± 0.47**	**1.69 ± 2.37**	**0.325**

Abbreviation: COPD, chronic obstructive pulmonary disease

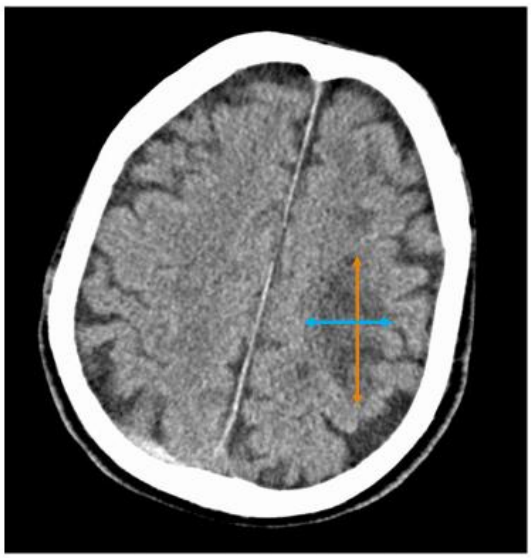
Table 2. Operative and postoperative data

	All (n = 60)	Uncomplicated (n = 48)	Neurologic injury (n = 12)	p-value
TAR	37 (61.7%)	29 (60.4%)	8 (66.7%)	0.795
Aortic root replacement	3 (5.0%)	2 (4.2%)	1 (8.3%)	0.554
Valve-sparing root replacement	3 (5.0%)	3 (6.2%)	0 (0.0%)	0.374
CABG	7 (11.7%)	3 (6.2%)	4 (33.3%)	0.003
Aortic valve replacement or repair	6 (10.0%)	5 (10.4%)	1 (8.3%)	0.796
Operation time (min)	426.2 ± 130.3	420.4 ± 132.7	449.3 ± 122.7	0.482
Aortic cross-clamp time (min)	123.5 ± 43.5	122.6 ± 42.7	127.4 ± 48.1	0.754
Circulatory arrest time (min)	50.5 ± 19.6	49.4 ± 19.4	54.83 ± 20.8	0.427
Intensive care unit stay	6.7 ± 7.2	5.1 ± 4.5	13.1 ± 11.8	<0.0001

Operative mortality (<30 days)	**4 (5.0%)**	**2 (4.2%)**	**2 (16.7%)**	**0.103**
Major complications (excluding stroke)	**12 (20%)**	**8 (16.7%)**	**4 (33.3%)**	**0.197**

Abbreviations: CABG, coronary artery bypass grafting; TAR, total arch replacement

Fig 1



A is orange line, and B is blue line

Fig 2

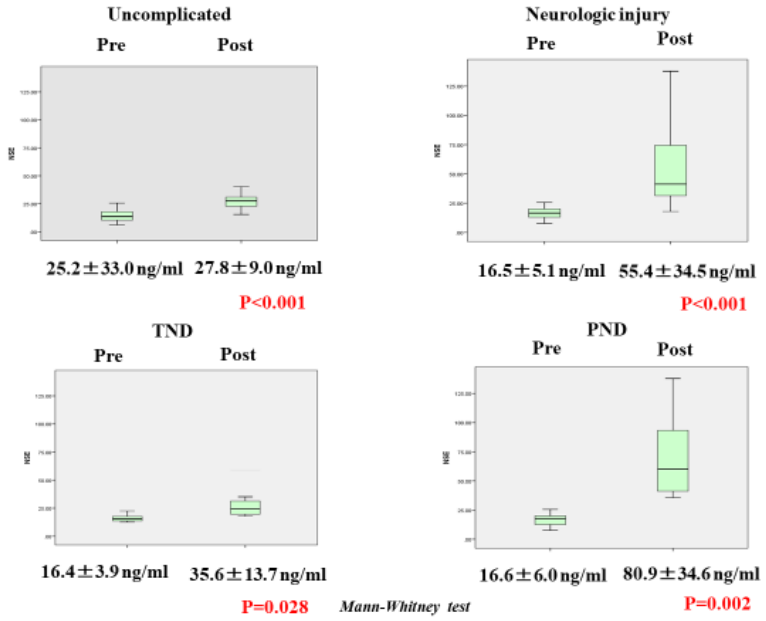

Uncomplicated
Pre
Post
25.2±33.0 ng/ml
27.8±9.0 ng/ml
P<0.001
Neurologic injury
Pre
Post
16.5±5.1 ng/ml
55.4±34.5 ng/ml
P<0.001
TND
Pre
Post
16.4±3.9 ng/ml
35.6±13.7 ng/ml
P=0.028
PND
Pre
Post
16.6±6.0 ng/ml
80.9±34.6 ng/ml
P=0.002
Mann-Whitney test

Fig 3

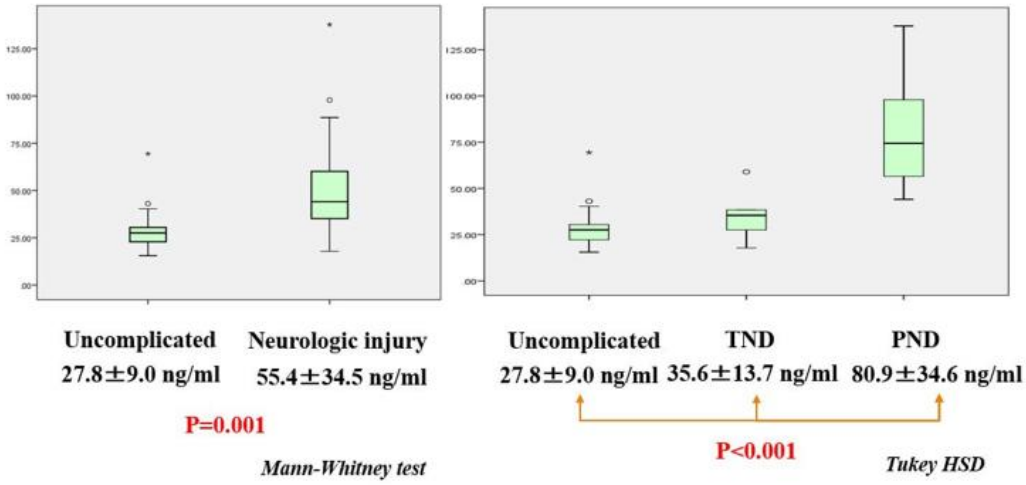

125.00
100.00
75.00
50.00
25.00
.00
Uncomplicated
27.8±9.0 ng/ml
Neurologic injury
55.4±34.5 ng/ml
P=0.001
Mann-Whitney test
Uncomplicated
27.8±9.0 ng/ml
TND
35.6±13.7 ng/ml
PND
80.9±34.6 ng/ml
P<0.001
Tukey HSD

Fig 4

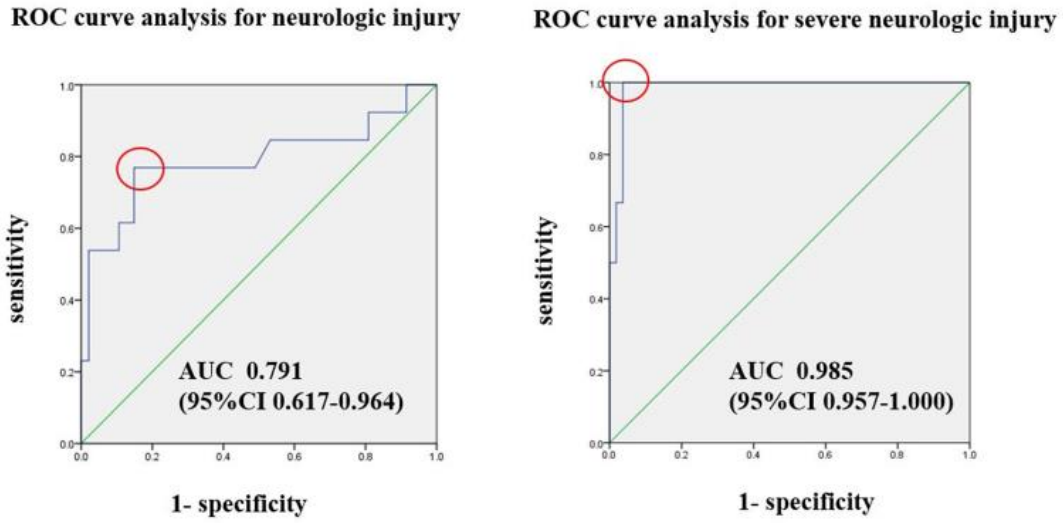

ROC curve analysis for neurologic injury
sensitivity
1- specificity
AUC 0.791
(95%CI 0.617-0.964)
ROC curve analysis for severe neurologic injury
sensitivity
1- specificity
AUC 0.985
(95%CI 0.957-1.000)

Fig 5

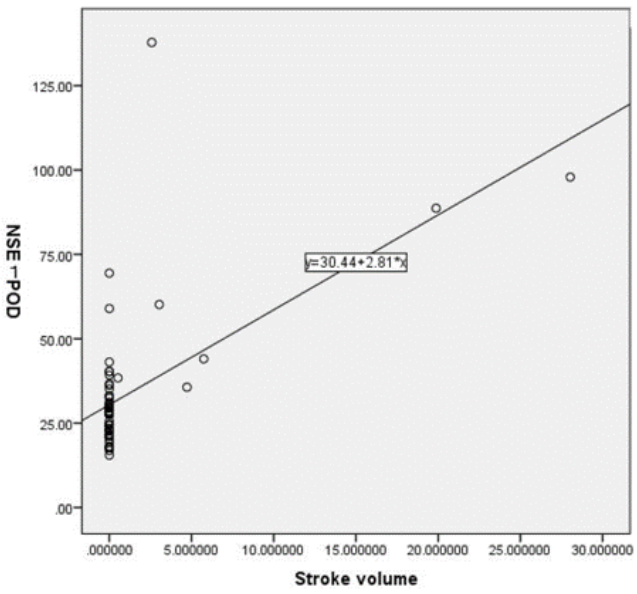
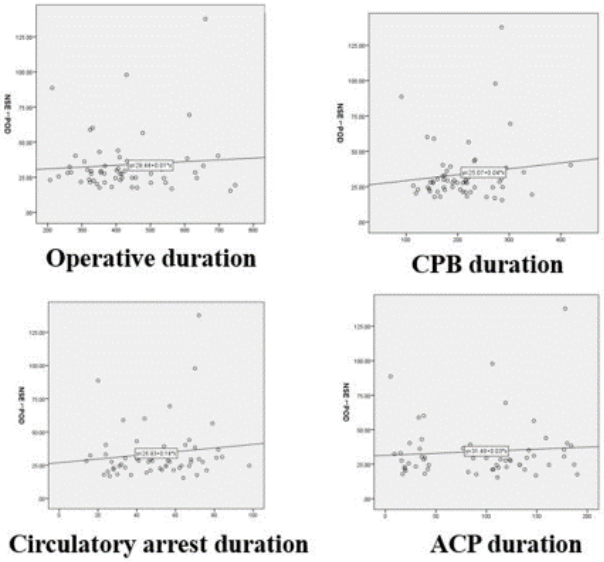

125.00
100.00
75.00
50.00
25.00
.00
NSE 1-POD
y=30.44+2.81*x
.000000
5.000000
10.000000
15.000000
20.000000
25.000000
30.000000
Stroke volume

Fig 6


Operative duration
CPB duration
Circulatory arrest duration
ACP duration