Elevation of troponin I in acute ischemic stroke

Yu-Chin Su, Kuo-Feng Huang, Fu-Yi Yang, Shinn-Kuang Lin

Background. Cardiac morbidities account for 20% of deaths after ischemic stroke and is the second commonest cause of death in acute stroke population. Elevation of cardiac troponin has been regarded as a prognostic biomarker of poor outcome in patients with acute stroke.

Methods. This retrospective study enrolled 871 in-patients with acute ischemic stroke from August 2010 to March 2015. Data included vital signs, laboratory parameters collected in the emergency department, and clinical features during hospitalization. National Institutes of Health Stroke Scale (NIHSS), Barthel index, and modified Rankin Scale (mRS) were used to assess stroke severity and outcome.

Results. Elevated troponin I (TnI) > 0.01 μg/L was observed in 146 (16.8%) patients. Comparing to patients with normal TnI, patients with elevated TnI were older (median age 77.6 years vs 73.8 years), had higher median heart rates (80 bpm vs 78 bpm), higher median white blood cells (8.40 vs 7.50 1000/m^3) and creatinine levels (1.40 mg/dL vs 1.10 mg/dL), lower median hemoglobin (13.0 g/dL vs 13.7 g/dL) and hematocrit (39% vs 40%) levels, higher median NIHSS scores on admission (11 vs 4) and at discharge (8 vs 3), higher median mRS scores (4 vs3) but lower Barthel index scores (20 vs 75) at discharge ($p < 0.001$). Multivariate analysis revealed that age ≧ 76 years (OR 2.25, CI 1.59-3.18), heart rate ≧ 82 bpm (OR 1.47, CI 1.05-2.05), evidence of clinical deterioration (OR 9.45, CI 4.27-20.94), NIHSS score ≧ 12 on admission (OR 19.52, CI 9.59-39.73), and abnormal TnI (OR 1.98, CI 1.18-3.33) were associated with poor outcome. Significant factors for in-hospital mortality included male gender (OR 3.69, CI 1.45-9.44), evidence of clinical deterioration (OR 10.78, CI 4.59-25.33), NIHSS score ≧ 12 on admission (OR 8.08, CI 3.04-21.48), and elevated TnI level (OR 5.59, CI 2.36-13.27). *C*-statistics revealed that abnormal TnI improved the predictive power of both poor outcome and in-hospital mortality. Addition of TnI > 0.01 ug/L or TnI > 0.1 ug/L to the model-fitting significantly improved *c*-statistics for in-hospital mortality from 0.887 to 0.926 ($p = 0.019$) and 0.927 ($p = 0.028$), respectively.

Discussion. Elevation of TnI during acute stroke is a strong independent predictor for both poor outcome and in-hospital mortality. Careful investigation of possible concomitant cardiac disorders is warranted for patients with abnormal troponin levels.

Elevation of Troponin I in Acute Ischemic Stroke

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Abstract

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49 **Key words**: troponin I; acute ischemic stroke; cardiac enzyme; poor outcome; in-hospital
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61 **Introduction**

62 Heart disease and stroke are the second and third leading causes of death after cancer in
63 Taiwan. Cerebrovascular and coronary artery diseases share many of the same risk factors.
64 Cardiac mortality accounts for 20% of deaths and is the second commonest cause of death in the
65 acute stroke population, second only to neurologic deaths as a direct result of the incident stroke
66 (Bounds et al., 1981; Prosser et al., 2007). Prevalence of symptomatic and asymptomatic
67 ischemic heart disease in acute stroke has been reported to be 20 to 30% and 40%, respectively
68 (Adams et al., 2003). Cardiac troponins are important biomarkers of acute myocardial infarction
69 and are routinely studied in the setting of ischemic heart disease. Abnormal levels of cardiac
70 troponins have also been reported to be associated with poor clinical outcome in patients with
71 acute cerebrovascular diseases, including ischemic stroke (Di Angelantonio et al., 2005; Scheitz
72 et al., 2012; Provideˆncia, Barra & Paiva, 2013; Faiz et al., 2014) , intracerebral hemorrhage
73 (Hays & Diringer, 2006), and spontaneous subarachnoid hemorrhage (Deibert et al., 2003).
74 Common risk factors for vascular diseases, such as hypertension, diabetes, heart disease,
75 and hyperlipidemia, are well known comorbidities of stroke. Most previous studies emphasized
76 the correlation of these comorbidities with stroke and clinical outcomes. However, the definition
77 of each risk factor is usually not identical and the duration of these risk factors is not well
78 described. The impact of a poorly controlled risk factor on the severity and outcome of stroke is
79 not the same as that of a well-controlled one. Available laboratory parameters and clinical
80 features as well as biomarkers during acute stroke provide valuable information when
81 investigating the clinical outcomes after stroke. In this study, we investigated whether certain
82 clinical features and laboratory parameters including troponin I (TnI) that are commonly
83 measured on admission to the emergency department are predictive of outcome in patients with

acute stroke.

Materials & Methods

Study Population and Data Collection

Patients who were treated for stroke in the neurological ward from August 2010 to March 2015 were retrospectively selected from the stroke registry database. Inclusion criteria included a diagnosis of acute ischemic stroke that was confirmed by clinical presentation and proof of an ischemic lesion and/or absence of a corresponding intracranial lesion other than infarction by brain computed tomography or magnetic resonance study, and an available serum TnI study conducted in the emergency department within 48 hours of symptom onset. TnI is considered as a routine study for patients with acute stroke by some but not all emergency physicians. Thus, measurement of TnI became a partial randomization study in the emergency department. Data integrated for analysis in this study included the sex and age of the patients, clinical data such as blood pressure and heart rate, and hematological parameters including the white blood cell count, hemoglobin, hematocrit, blood urea nitrogen, creatinine and TnI levels on arrival in the emergency department, and the severity of stroke evaluated on admission.

Definitions

TnI was measured using a conventional VIDAS Troponin I Ultra assay (bioMerieux, Marcy L'Etoile, France) in the hospital's central laboratory. The analytical limit of detection and the 99th percentile upper reference limit was 0.01 μg/L. Abnormal elevation of TnI was defined as a TnI blood level > 0.01 μg/L. Patients were stratified into two groups according to the TnI level, the normal group ($\leqq$ 0.01μg/L) and the abnormal group (> 0.01μg/L). Patients with abnormal TnI levels were further stratified into two relatively equal-sized groups, the low-positive group (0.02-0.1μg/L) and the high-positive group (> 0.1μg/L) (Scheitz et al., 2014). Stroke severity was

assessed on admission according to the National Institutes of Health Stroke Scale (NIHSS). The etiology of stroke was classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria (Adams et al., 1993). Clinical deterioration was defined in patients who demonstrated an increase of two or more points in the NIHSS score during the acute stage of stroke (Siegler et al., 2013; Umemura et al., 2014). Outcomes were evaluated using the NIHSS, the Barthel index and the modified Rankin Scale (mRS) at discharge. An mRS score > 2 was considered to indicate a poor outcome. All causes of death during hospitalization were registered as in-hospital mortality.

Statistical Analysis

Continuous variables are presented as median with interquartile range (IQR) or mean ± standard deviation. TnI values and mRS scores were analyzed as continuous and dichotomous variables. The chi-square test and Fisher's exact test were used for categorical comparisons of data. Group comparisons of continuous variables were performed using Mann–Whitney U and Kruskal-Wallis H tests for independent samples. Significant predictors in the univariate analyses were transferred to dichotomous variables with the cut-off level according to the mean values of poor outcome, and were subsequently included in a multiple logistic-regression model to identify the most important factors associated with poor outcome, and in a stepwise logistic-regression model with in-hospital death. The predictive performance of the variables including TnI was compared using *c*-statistics. We compared basic models for poor outcome and in-hospital mortality including clinical variables to models that also included information on TnI levels. Comparisons of *c*-statistics were done according to the method of DeLong (DeLong et al. 1988). A p value of less than 0.05 was considered to indicate statistical significance. All statistical

analyses were performed with the statistical package SPSS (Version 17, SPSS Inc, Chicago, IL). The ROC curve comparisons were calculated using R software (version 2.15.3, pROC package). This study was approved by the Institutional Review Board of the Taipei Tzu Chi Hospital 04-XD40-107.

Results

During the study period, a total of 2,307 patients presented to our emergency department with acute ischemic stroke. Only 871 of those patients had valid data on TnI levels because during that period, measurement of TnI level was not routinely performed in the emergency department for patients with acute stroke. The average age of the 871 patients with valid TnI data was about 1.2 years older than that of all 2,307 patients (72.3 ± 13.6 vs 71.1 ± 13.4 years, p = 0.02, Mann-Whitney test). Other baseline characteristics of the 871 patients with valid TnI data, including male-to-female ratio (1.13 vs 1.21), percentage of patients with cardioembolism (15% vs 13%), average blood pressure, heart rate, laboratory data, and NIHSS on admission (8.3 vs 7.8), did not differ from those of the total 2,307 patients. The median age of the 871 patients enrolled in the study was 74.5 years (IQR 62.7-82.8) and 46.8% of them were women. The women were significantly older and had lower diastolic blood pressure, hemoglobin levels and hematocrit levels (p <0.001) than the men. The women had higher NIHSS (p = 0.024) and mRS scores as well as lower Barthel index scores at discharge, and poorer outcomes (p < 0.001) than the men. The mortality rate was significantly higher in the men (p = 0.017). Elevated TnI levels were observed in 146 of the 871 patients (16.8%). Of these, 77 (8.8%) had high-positive levels and 69 (7.9%) had low-positive levels. Table 1 shows the comparison of clinical features, laboratory data, severity of stroke, and outcomes of patients with different levels of TnI. Abnormal TnI levels were more common in patients with stroke due to large artery atherosclerosis (54/232 = 23%), cardioembolism (38/131 = 29%), and undetermined etiology (5/17 = 29%) than in patients with stroke due to small vessel occlusion (48/482 = 10%) and other determined etiology (1/9 = 11%) according to the TOAST classification. Patients with abnormal TnI levels were significantly older (p < 0.001) than patients with normal TnI levels and had

199 significantly higher heart rates ($p = 0.018$), white blood cell counts ($p = 0.025$), and creatinine
200 levels ($p < 0.001$) and significantly lower hemoglobin ($p = 0.006$) and hematocrit levels ($p =$
201 0.025). In addition, patients with abnormal TnI levels had higher median NIHSS scores on
202 admission (11, IQR 5-21) and at discharge (8, IQR 4-22) than patients with normal TnI levels (4,
203 IQR 2-9 and 3, IQR 1-4, respectively) ($p < 0.001$). The median Barthel index was lower (20, IQR
204 0-75) and the mRS was higher (4, IQR 3-5) in patients with abnormal TnI than in patients with
205 normal TnI (75, IQR 35-100 and 3, IQR 1-4, respectively) ($p < 0.001$). Poor outcomes were
206 observed in 509 (58%) of the 871 patients and death occurred in 31 (3.6%) patients. Patients with
207 abnormal TnI levels had longer hospital stays (16 days vs 9 days), higher rates of clinical
208 deterioration (18% vs 9%, $p = 0.005$), poor outcome (79% vs 54%, $p < 0.001$), and death (14%
209 vs 2%, $p < 0.001$) than patients with normal TnI levels. All the differences were more prominent
210 in the high-positive group. There were mor poor outcomes (85%) and deaths (21%) in the high-
211 positive group than in the low-positive group (74% and 6%, respectively).
212 Univariate analyses of continuous variables revealed that patients with poor outcomes were
213 older, and had higher heart rates, TnI levels, white blood cell counts, creatinine levels, and
214 NIHSS scores on admission and at discharge, and higher mRS scores at discharge but lower
215 hemoglobin levels, hematocrit levels, and Barthel index scores than those with better outcomes
216 (Table 2). Analysis of dichotomous variables revealed that female gender, cardioembolism,
217 abnormal TnI levels, and evidence of clinical deterioration were associated with poor outcomes.
218 In-hospital death was associated with high systolic blood pressure, high heart rate, high TnI level,
219 high white blood cell count, and high NIHSS score on admission, and longer length of stay.
220 Dichotomous analysis showed significant correlation of male gender, abnormal TnI levels, and
221 evidence of clinical deterioration with in-hospital death. Age was not associated with in-hospital

222 death.

223 Table 3 showed the regression analysis of the significant dichotomous variables with the
224 cut-off levels according to the mean values of poor outcome in Table 2. Multivariate logistic
225 regression analysis revealed that age ≧ 76 years ($p < 0.001$), heart rate ≧ 83 bpm ($p = 0.001$),
226 evidence of clinical deterioration ($p < 0.001$), NIHSS score ≧ 14 on admission ($p < 0.001$) , and
227 abnormal TnI level (odds ratio [OR]: 1.98; 95% confidence interval [CI]: 1.18-3.33; $p = 0.01$)
228 were significant predictors of poor outcome. A stepwise backward regression analysis showed
229 male gender ($p = 0.006$), evidence of clinical deterioration ($p < 0.001$), NIHSS score ≧ 12 on
230 admission ($p < 0.001$), and abnormal TnI level (OR: 5.59; 95% CI: 2.36-13.27; $p < 0.001$) were
231 significant predictors of in-hospital mortality.

232 *C*-statistics of regression models for detection of poor outcome and death for each factor are
233 shown in Table 4. *C*-statistics for detection of poor outcome was 0.691 for NIHSS score ≧12 on
234 admission. The addition of age ≧ 76 years, evidence of clinical deterioration, and TnI ≧ 0.01
235 ug/L to the regression model resulted in significant improvement of the *c*-statistics to 0.787 ($p <$
236 0.05). The addition of TnI > 0.01 ug/L or TnI > 0.1 ug/L to a model-fitting including significant
237 factors in logistic regression (NIHSS score on admission ≧12, age ≧ 76 years, evidence of
238 clinical deterioration, heart rate ≧ 82 bpm) did not improve the predictive value foro poor
239 outcome. Similar results were observed for detection of death. *C*-statistics for detection of death
240 was 0.790 for an NIHSS score ≧12 on admission. The addition of TnI ≧ 0.01 ug/L and
241 evidence of clinical deterioration to the regression model resulted in significant improvement of
242 the *c*-statistics to 0.912 ($p < 0.05$). The addition of TnI > 0.01 ug/L or TnI > 0.1 ug/L to a model-
243 fitting including NIHSS ≧ 12 on admission, evidence of deterioration and male gender
244 significantly improved the predictive value for death from 0.887 to 0.926 and 0.927, respectively

($p < 0.05$).

268 **Discussion**

269 TnI is a highly sensitive and specific marker of acute myocardial infarction. Elevated TnI is
270 characteristic of a number of cardiac diseases as well such as heart failure, pericarditis,
271 myocarditis, atrial fibrillation and tachycardia (Tanindi & Cemri, 2011). Elevated TnI has also
272 been found in patients with chronic renal failure, sepsis, critical illness, pulmonary embolism,
273 chronic obstructive pulmonary disease, and stroke (Tanindi & Cemri, 2011; Mannu, 2014).
274 Elevated levels of cardiac troponin have been reported in 10–34% of patients with acute stroke.
275 Kerr et al conducted a systematic review of studies measuring troponin within 7 days of
276 symptom onset in acute stroke patients and found that more than 18% of patients had a high
277 troponin level (Kerr et al., 2009). Some studies reported that elevated troponin levels were more
278 common in patients with stroke due to cardioembolism who also had evidence of atrial
279 fibrillation, ischemic heart or heart failure (Etgen et al., 2005; Faiz et al., 2014). Abnormal TnI
280 levels were observed in 16.8% patients in our study. We found that patients with abnormal TnI
281 were more likely to have large artery atherosclerosis, cardioembolism and undetermined etiology.
282 Patients who had risks from both atrial fibrillation and stenotic cerebral arteries were grouped
283 into undetermined etiology with conflicting data when categorizing the subtype of stroke. This
284 could explain why there was a similarly higher percentage of elevated TnI levels in patients with
285 undetermined etiology. Patients with elevated TnI levels were older and had higher heart rates
286 and creatinine levels but lower hemoglobin levels and hematocrits than patients with normal TnI
287 levels. Patients with elevated TnI presented with more severe initial stroke severity and showed a
288 greater degree of clinical deterioration during hospitalization. Worse outcomes and higher in-
289 hospital mortality were observed in patients with abnormal TnI as well. All of the above
290 differences were most prominent in patients with high-positive TnI levels. These findings are

291 similar to those reported by Di Angelantonio et al, who found a dose-response relationship
292 between the three TnI groups (normal, low-positive, and high-positive) and clinical features (Di
293 Angelantonio et al., 2005).

294 Mechanisms for elevated TnI during acute ischemic stroke may be separated into 2 major
295 groups, (1) ischemic myocardial injury (ie, because of coronary ischemia) and (2) nonischemic
296 (noncoronary) myocardial injury (Scheitz et al. 2015a). Coronary plaque rupture or mismatch
297 between oxygen demand and supply (such as in tachyarrhythmia, hypertensive crisis, or
298 respiratory failure) may cause ischemic myocardial injury. Nonischemic myocardial injury
299 comprises neurogenic heart syndrome and noneurogenic conditions (severe infection or sepsis,
300 heart or renal failure, pulmonary embolism). In neurogenic heart syndrome, acute stroke-related
301 increased sympathetic activity with excessive catecholamine release results in coagulative
302 myocytolysis (also known as contraction band necrosis or myofibrillar degeneration) or
303 cardiomyopathy. Myocytolysis surrounding patches of subendocardial hemorrhage or swollen
304 myocytes surrounding epicardiac nerves during early acute stroke has been suggested to be the
305 cause of cardiac injury (Oppenheimer & Hachinski, 1992). Barber et al found that raised TnI was
306 associated with elevation of circulating epinephrine in patients with acute ischemic stroke
307 (Barber et al., 2007). Involvement of the parietal lobe or insular cortex has also been associated
308 with elevated cardiac troponin levels due to the imbalance of sympathetic and parasympathetic
309 autonomic control (Ay et al., 2006; Rincon et al., 2008; Scheitz et al., 2015b). Not all patients in
310 our study underwent brain magnetic resonance imaging to indentify the precise location of the
311 stroke; therefore, we were not able to analyze the involvement of the insular or parietal cortex.
312 Cardiac cell damage with elevated troponins in acute stroke may be enhanced by the stress-
313 related inflammatory response as well as the cytokine response pathways (Christensen et al.,

2004). The etiologies of elevated troponin levels other than acute coronary syndrome in renal failure include subclinical myocardial damage (micro-infarctions) and decreased renal troponin excretion (Freda et al., 2002; Jensen et al., 2007; Faiz et al., 2014). Serum troponin T is increased more frequently than TnI in patients with renal failure, and TnI has been reported to be a more sensitive and specific biomarker of cardiac damage than Troponin T in patients with end-stage renal failure (Freda et al., 2002; Mannu, 2014).

There is no doubt that advanced age, higher NIHSS score on admission, and evidence of clinical deterioration during hospitalization are associated with a worse outcome and higher death rate at discharge. The average age of patients with abnormal TnI, patients with poor outcome, and patients who died in the hospital in this study was approximately 76 years. Faiz et al also reported that age $\geqq$ 76 years was independently associated with elevated troponin levels in patients with acute ischemic stroke (Faiz et al., 2014). A high heart rate was associated with worse outcomes, in particular death, in a long-term follow-up study of patients with vascular diseases (Erdur et al., 2014). In our study, a higher heart rate was observed in patients with abnormal TnI (83 bpm), in those with poor outcome (82 bpm), and in those who died before discharge (87 bpm) than those without these factors. Multivariate analysis revealed that heart rate $\geqq$ 82 bpm was also an independent risk factor for poor outcome. Erdur et al reported that heart rate $\geqq$ 83 bpm on admission was independently associated with in-hospital mortality in acute ischemic stroke patients, suggesting early negative effects of autonomic imbalance (Erdur et al., 2014).

With the exception of the NIHSS score on admission and subsequent deterioration during hospitalization, only elevated TnI was a strong independent predictor of both poor outcome and death. Abnormal TnI had an OR of 1.98 for poor outcome and an OR of 5.59 for in-hospital

337 mortality. A meta-analysis of 2901 patients from 15 studies with different definitions and
338 sampling times for troponin by Kerr et al revealed that elevated troponin is associated with poor
339 outcome; however, they did not fully establish whether elevated troponin is an independent
340 prognostic factor (Kerr et al., 2009). Recent studies with multivariate models including age and
341 some measures of stoke severity have concluded that a positive level of troponin is associated
342 with an overall increased risk of both death and disability (Jensen et al., 2007; Faiz et al., 2014a;
343 Faiz et al., 2014b). In the present study, *c*-statistics revealed that abnormal TnI improved the
344 predictive power of both poor outcome and in-hospital mortality. Although the predictive
345 performance of abnormal TnI for poor outcome was relative low in a categorized model with
346 strong predictors, such as NIHSS score≧ 12 on admission and evidence of deterioration, both
347 low-positive and high-positive TnI significantly increased the discriminative power of the model
348 for in-hospital death. The American Stroke Association recommends the routine checking of
349 markers of cardiac ischemia during acute stroke (Adams et al., 2007). Whether troponin should
350 be routinely checked is still under deliberation. Nevertheless, recognition and careful
351 investigation of possible concomitant cardiac disorders in patients with acute ischemic stroke is
352 warranted for patients with elevated troponin levels.
353 The newly developed high-sensitivity assay of troponin allows for precise detection of
354 troponin even at concentrations 10-fold lower than conventional assays (Wu & Jaffe, 2008). A
355 high-sensitivity troponin test improves the diagnosis of patients with acute myocardial infarct.
356 However, reduction of specificity comes with improvement in sensitivity. In Scheitz's series,
357 troponin T elevation above the 99th percentile was detected with a high-sensitivity assay in more

than 50% of patients with acute ischemic stroke, and even moderately elevated troponin T was associated with an unfavorable outcome (Scheitz et al,. 2014). The presence of high positive or dynamic change troponin levels might indicate ischemic myocardial injury. Stroke patients with dynamic changes in troponin levels (>50%) within 24 hours showed a higher risk for in-hospital mortality than patients with increased troponin levels who were stable over time (Scheitz et al., 2014). Serial measurements should be performed to establish whether troponin is acutely or chronically elevated. For patients with non-acute elevation of troponin levels, out-patients evaluation for structural or coronary heart disease is recommended. For patients with high positive or a dynamic pattern of elevated troponin levels, prompt measures for prevention of cardiovascular disease should be intensified or reevaluated. Noninvasive echocardiography, cardiac magnetic resonance imaging or computed tomography may help to identify possible unstable coronary disease, heart failure, or cardiomyopathy. Invasive coronary angiography may be indicated for patients with acute myocardial infarction (Scheitz et al. 2015a).

This study has a number of limitations. First, this study was retrospective in nature. There was selection bias exits because of only a small group of patents received TnI measurement. Second, TnI was checked only once in each patient in the emergency room without an exact time period of onset-of-symptoms to troponin measurement. Dynamic change measurement of TnI might provide more prognostic relevance in acute ischemic stroke. Third, the low number of patients with the outcome “death” might limit meaningfulness although stepwise logistic

377 regression analysis was used. Finally, we did not perform a follow-up study after discharge.
378 Notwithstanding these limitations, our data extend the current understanding of the implications
379 of troponin positivity in acute ischemic stroke.
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Conclusions

Troponin I provide better information than age and other laboratory parameters in prediction of outcome of stroke, even after adjustment for the strong impact factors of stroke severity and presence of clinical deterioration. Elevation of TnI during acute stroke is a strong independent predictor of both poor outcome and in-hospital mortality. Both neurologists and cardiologists need to pay more attention to possible concomitant cardiac disorders in patients with abnormal troponin levels during acute stroke.

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523 Table 1. Correlation of clinical features and troponin I level in 871 patients with acute ischemic stroke

Characteristics	Troponin I test [a]			Troponin I level (ug/L) [b]			
	Abnormal (>0.01 ug/L) (n = 146)	Normal (n = 725)	*P* value	> 0.1 (n = 77)	0.02-0.1 (n = 69)	≦0.01 (n = 725)	*P* value
Median age (years)	77.6 (66.2-85.6)	73.8 (61.6-82.2)	<0.001	77.7 (67.2-84.9)	77.5 (65.4-85.9)	73.8 (61.6-82.2)	0.003
Systolic pressure (mmHg)	160 (144-192)	162 (144-184)	0.972	157 (140-188)	164 (145-195)	162 (144-184)	0.615
Diastolic pressure (mmHg)	87 (76-103)	90 (79-101)	0.294	87 (74-102)	87 (76-106)	90 (79-101)	0.567
Heart rate (bpm)	80 (73-90)	78 (67-89)	0.015	84 (71-94)	80 (74-88)	78 (67-89)	0.029
White blood cells (1000/mm^3)	8.40 (6.48-7.03)	7.50 (6.11-9.53)	0.025	9.10 (7.11-11.01)	7.44 (5.81-9.14)	7.50 (6.11-9.53)	<0.001
Hemoglobin (g/dL)	13.0 (11.1-14.8)	13.7 (12.3-14.9)	0.006	12.9 (10.9-15.2)	13.1 (11.2-14.6)	13.7 (12.3-14.9)	0.021
Hematocrite (%)	39.0 (34.0-43.2)	40.0 (36.0-43.0)	0.025	38.0 (33.8-44.0)	39.0 (34.0-43.0)	40.0 (36.0-43.0)	0.074
Glucose (mg/dL)	144 (115-118)	139 (112-185)	0.612	156 (123-213)	133 (113-158)	139 (112-185)	0.065
Creatinine (mg/dL)	1.40 (1.00-2.20)	1.10 (0.90-1.30)	<0.001	1.40 (1.00-2.40)	1.30 (1.0-2.0)	1.10 (0.90-1.30)	<0.001
NIHSS score (on admission)	11 (5-21)	4 (2-9)	<0.001	11 (6-23)	10 (4-20)	4.0 (2-9)	<0.001
NIHSS score (at discharge)	8 (4-22)	3 (1-7)	<0.001	11 (4-32)	6 (3-15)	3 (1-7)	<0.001
Barthel index score	20 (0-75)	75 (35-100)	<0.001	18 (0-66)	30 (5-85)	75 (35-100)	<0.001
modified Rankin Scale	4 (3-5)	3 (1-4)	<0.001	5 (4-5)	4 (1-5)	3 (1-4)	<0.001
Length of stay (days)	16 (8-29)	9 (5-24)	<0.001	19 (9-29)	14 (6-28)	9 (5-24)	<0.001
Deterioration [c]	26 (18%)	68 (9%)	0.005	16 (21%)	10 (15%)	68 (9%)	0.006
mRS > 2 [c]	116 (79%)	393 (54%)	<0.001	65 (85%)	50 (74%)	393 (54%)	<0.001
Death [c]	20 (14%)	11 (2%)	<0.001	16 (21%)	4 (6%)	11 (2%)	<0.001

524 Notes.

525 NIHSS, National Institute of health Stroke Scale; mRS, modified Rankin Scale; a, Mann-Whitney U test; b, Kruskal-Wallis test; c, Chi-square test.

526 Data are expressed as median (IQR) or n (%)

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528

529 Table 2. Correlation of clinical features and outcomes in 871 patients with acute ischemic stroke

	Poor outcome (mRS > 2) [a]					Death [a]		
	Mean		Median		*P*	Median		*P*
Characteristics	Y (n = 509)	N (n = 362)	Y (n = 509)	N (n = 362)	value	Y (n = 31)	N (n = 840)	value
Age (years)	75.7±12.5	67.4±13.5	78.0 (67.3-85.1)	66.9 (57.5-78.3)	<0.001	78.0 (69.3-84.3)	74.5 (62.5-82.7)	0.180
Systolic pressure (mmHg)	165±32	164±29	162 (144-186)	163 (144-184)	0.904	182 (150-200)	162 (144-184)	0.034
Diastolic pressure (mmHg)	89±18	92±18	88 (77-102)	91 (80-101)	0.114	86 (72-106)	89 (79-101)	0.972
Heart rate (bpm)	82±17	77±16	80 (69-92)	76 (66-85)	<0.001	84 (78-97)	78 (67-89)	0.019
Troponin I (ug/L)	0.119±0.656	0.022±0.101	0.01 (0.01-0.01)	0.01 (0.01-0.01)	<0.001	0.09 (0.01-0.65)	0.01 (0.01-0.01)	<0.001
White blood cells ($1000/mm^3$)	8.32±3.03	7.84±2.65	7.81 (6.20-9.98)	7.40 (6.19-9.26)	0.039	9.00 (6.71-11.80)	7.60 (6.20-9.61)	0.022
Hemoglobin (g/dL)	13.1±2.2	13.9±2.0	13.3 (11.7-14.5)	14.0 (12.7-15.2)	<0.001	13.5 (11.3-14.9)	13.6 (12.2-14.9)	0.698
Hematocrite (%)	38.7±5.9	40.7±5.1	39 (35-43)	41 (38-44)	<0.001	39 (35-43)	40 (36-43)	0.631
Glucose (mg/dL)	169±88	164±84	144 (115-195)	134 (109-187)	0.054	162 (136-205)	139 (113-194)	0.130
Creatinine (mg/dL)	1.52±1.47	1.30±1.02	1.2 (0.9-1.5)	1.1 (0.9-1.3)	0.032	1.5 (1.1-2.0)	1.1 (0.9-1.4)	<0.001
NIHSS score (on admission)	12.2±9.0	2.9±3.0	9 (5-18)	2 (1-4)	<0.001	25 (20-32)	5 (2-10)	<0.001
NIHSS score (at discharge)	11.7±11.4	1.4±1.6	7 (4-16)	1 (0-2)	<0.001	-	-	
Barthel index score	34.5±28.9	95.7±9.3	35 (5-60)	100 (95-100)	<0.001	-	-	
modified Rankin Scale	4.2±0.9	0.9±0.6	4 (4-5)	1 (1-1)	<0.001	-	-	
Length of stay (days)	23.2±16.8	6.8±5.2	20 (10-30)	5 (4-8)	<0.001	9 (3-24)	11 (5-25)	0.213
Male gender [b]			243 (48%)	220 (61%)	<0.001	23 (74%)	440 (52%)	0.017
Cardioembolism [b]			95 (19%)	36 (10%)	<0.001	7 (23%)	124 (15%)	0.301
Abnormal troponin I [b]			116 (23%)	30 (8%)	<0.001	20 (65%)	126 (15%)	<0.001
Deterioration [b]			86 (17%)	8 (2%)	<0.001	18 (58%)	76 (9%)	<0.001

530 Notes.

531 mRS, modified Rankin Scale; IQR, interquartile range; NIHSS, National Institute of health Stroke Scale; a, Mann-Whitney U test; b, Chi-square test.

532 Data are expressed as mean±sd, median (IQR) or n (%)

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534 Table 3. Regression model of factors influencing outcomes and mortality in 871 patients with acute ischemic stroke

	Poor outcome (mRS > 2) [a]		Death [b]	
Characteristics	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male gender	0.75 (0.53-1.06)	0.108	3.69 (1.45-9.44)	0.006
Age ≧ 76 years	2.25 (1.59-3.18)	<0.001		
Heart rate ≧ 82 bpm	1.47 (1.05-2.05)	0.026		
White blood cells ≧ 8320 uL	1.21 (0.86-1.70)	0.264		
Hemoglobin ≦ 13.1 g/dL	1.44 (0.78-2.65)	0.245		
Hematocrite ≦ 38.7 %	1.22 (0.68-2.23)	0.508		
Creatinine ≧ 1.52 mg/dL	1.05 (0.67-1.64)	0.848		
Cardioembolism	0.85 (0.50-1.46)	0.573		
Deterioration	9.45 (4.27-20.94)	<0.001	10.78 (4.59-25.33)	<0.001
NIHSS score (admission) ≧12	19.52 (9.59-39.73)	<0.001	8.08 (3.04-21.48)	<0.001
Troponin I > 0.01ug/L	1.98 (1.18-3.33)	0.010	5.59 (2.36-13.27)	<0.001

535 Notes.

536 NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; OR, odds ratio; CI, confidence

537 interval; [a] multiple logistic regression; [b] stepwise backward regression.

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Table 4. C-statistics for prediction of poor outcome and in-hospital mortality

Poor outcome (mRS > 2) [a]			Death [b]		
Characteristics	C-statistics (95% CI)	*P**	Characteristics	C-statistics (95% CI)	*P**
NIHSS score (admission) ≧ 12	0.691 (0.657-0.725)		NIHSS score (admission) ≧ 12	0.790 (0.707-0.872)	
includes age ≧ 76 years	0.748 (0.717-0.780)	<0.001	includes troponin I > 0.01ug/L	0.860 (0.799-0.921)	0.001
further includes deterioration	0.778 (0.748-0.808)	<0.001	further includes deterioration	0.912 (0.859-0.965)	0.018
further includes troponin I > 0.01ug/L	0.787 (0.758-0.817)	0.006	further includes male gender	0.926 (0.884-0.969)	0.134
further includes heart rate ≧ 82 bpm	0.796 (0.767-0.825)	0.057			
Model 1	0.790 (0.761-0.819)	*P***	Model 2	0.887 (0.829-0.946)	*P***
+ Troponin I > 0.01ug/L	0.796 (0.767-0.825)	0.155	+ Troponin I > 0.01ug/L	0.926 (0.884-0.969)	0.019
+ Troponin I ≧ 0.1ug/L	0.798 (0.769-0.826)	0.106	+ Troponin I ≧ 0.1ug/L	0.927 (0.886-0.968)	0.028

Notes.

mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; CI, confidence interval; [a] multiple logistic regression; [b] stepwise backward regression; * compared with previous one; ** compared with Model 1 or 2

Model 1 includes NIHSS score (admission)≧12, age≧76 years, deterioration, heart rate≧82 bpm

Model 2 includes NIHSS score (admission)≧12, deterioration, male gender