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Original Article

Characteristics of blood tests in patients with acute cerebral infarction who developed symptomatic intracranial hemorrhage after intravenous administration of recombinant tissue plasminogen activator

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Objective Patients suspected as having acute ischemic stroke usually undergo blood tests, including coagulation-related indexes, because thrombocytopenia and coagulopathy are contraindications for recombinant tissue plasminogen activator (rtPA) administration. We aimed to identify blood test indexes associated with symptomatic intracranial hemorrhage (sICH) in patients with acute ischemic stroke who received intravenous rtPA.

Methods This retrospective observational study included patients diagnosed with acute ischemic stroke who were treated with intravenous rtPA at the emergency department of a tertiary hospital in Seoul between February 2008 and January 2018. Blood test indexes were compared between the sICH and non-sICH groups. Logistic regression and receiver-operating characteristic curve analyses were performed.

Results In this study, 375 patients were finally included. Of 375 patients, 42 (11.2%) showed new intracranial hemorrhage on follow-up brain computed tomography, of whom 14 (3.73%) had sICH. Platelet count, aspartate aminotransferase and lactate dehydrogenase levels were significantly different between the sICH and non-sICH groups, and platelet count showed statistical significance in the regression analysis. Significantly lower platelet counts were observed in the sICH group than in the non-sICH group (174,500 vs. 228,000/mm^3, P=0.020). The best cutoff platelet count was 195,000/mm^3, and patients with platelet counts of <195,000/mm^3 had a 5.4-times higher risk of developing sICH than those with platelet counts of ≥195,000/mm^3.

Conclusion Platelet count was the only independent parameter associated with sICH among the blood test indexes. Mild thrombocytopenia may increase the risk of sICH after intravenous administration of rtPA.

Keywords Cerebral infarction; Thrombolytic therapy; Intracranial hemorrhages; Hematologic tests

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Capsule Summary

What is already known

Previous studies reported that hyperglycemia, increased neutrophil-to-lymphocyte ratio, and decreased glomerular filtration rate are associated with the occurrence of symptomatic intracranial hemorrhage (sICH) after use of intravenous thrombolytic agents in patients with acute ischemic stroke.

What is new in the current study

Platelet count was the only independent parameter associated with the development of sICH. Mild thrombocytopenia may increase the risk of sICH after intravenous administratino of thrombolytic agents.

INTRODUCTION

Since 2010, the American Heart Association (AHA) and American Stroke Association (ASA) have recommended that recombinant tissue plasminogen activator (rtPA) be administered to patients within 4.5 hours of acute ischemic stroke onset.[1] Although intravenous (IV) rtPA is an important and effective medical therapy that improves the prognosis of patients with an acute ischemic stroke,[2-5] hemorrhagic transformation occurs more frequently in the rtPA-treated group than in the placebo group.[2,3,5,6] Hemorrhagic transformation is divided into petechial hemorrhage (scattered or spotty distribution) and parenchymal hemorrhage (hematoma) according to the configuration of hemorrhage on brain computed tomography (CT).[3] Small petechial hemorrhages in infarcted tissue are not associated with poor prognosis; however, large parenchymal hematomas are associated with delayed recanalization and often result in neurological deterioration and poor outcome (symptomatic intracranial hemorrhage, sICH).[7] Although sICH is defined slightly differently among previous studies, sICH occurred in 1.7% to 7.6% of patients treated with rtPA.[2-5,8] The incidence of large intracranial hemorrhage (parenchymal hemorrhage type 2) reported in a recent pooled analysis study was 5.2%.[9]

Patients suspected as having acute ischemic stroke usually undergo blood tests, including coagulation-related indexes such as platelet count, activated partial thromboplastin time (aPTT), and international normalized ratio of prothrombin time, because thrombocytopenia (platelet count $<100,000/mm^3$) and coagulopathy (international normalized ratio >1.7, abnormal aPTT) are contraindications for rtPA administration.[10] However, considering that time is critical in patients with acute ischemic stroke, rtPA is sometimes administered before blood test results are obtained.[10] Therefore, clinicians may face a dilemma of choosing between "rapid rtPA administration" and "confirming laboratory contraindications for rtPA" in the treatment decision of acute ischemic stroke. Naturally, coagulation-related blood test indexes may be associated with sICH occurrence. However, platelet count and aPTT were not included as risk factors of sICH.[11] In contrast, non-coagulation-related blood test indexes, such as hyperglycemia,[11-13] increased neutrophil-to-lymphocyte ratio (NLR),[14] and decreased glomerular filtration rate (GFR),[15] were correlated with sICH.

This study began with the question of whether the blood test indexes included in the contraindications for rtPA are associated with sICH. This study aimed to investigate blood test indexes associated with sICH in Korean patients who had an acute ischemic stroke that was treated with rtPA and determine whether hematological indexes could predict sICH occurrence.

METHODS

Study design and subjects

This retrospective observational study included patients diagnosed with acute ischemic stroke and treated with IV rtPA at the emergency department (ED) of a tertiary hospital in Seoul between February 2008 and January 2018. An average of 34,000 patients visit the ED annually. Approximately 380 patients were diagnosed as having acute ischemic stroke per year during the study period.

Adult patients diagnosed with acute ischemic stroke and receiving IV rtPA in the ED were identified. The exclusion criteria were a pre-stroke modified Rankin Scale score >1, rtPA administration >4.5 hours after symptom onset, and no follow-up brain imaging within 36 hours after rtPA administration. This study was conducted according to the research ethics guidelines of our hospital after obtaining institutional review board approval (2015-12-041). Written informed consent was exempted by the institutional review board. To protect the patients' personal information, the patient name, hospital number, date of birth, and social security number were deleted after assigning a serial number to each patient.

Intravenous thrombolytic therapy

In the ED where this study was performed, the so-called "stroke fast track protocol" was applied consistently for patients suspected as having an acute ischemic stroke within 6 hours of symptom onset to prevent treatment delay regardless of the patient's ED arrival order. If the stroke fast track protocol is applied, an on-call physician (emergency medicine resident or neurology resident) is immediately called from the triage. After a brief, focused medical history taking and neurological examination by the physician, immediate blood tests and brain imaging (CT or magnetic resonance imaging) are performed according to the physician's order. If IV administration of rtPA is indicated, 10% of the 0.9-mg/kg dose of rtPA (Actilyse, Boehringer-Ingelheim, Ingelheim, Germany) is administered as a bolus, and the remaining 90% of the dose is administered over 60 minutes. All patients who received rtPA were admitted to the stroke care unit, and follow-up brain non-contrast CT was routinely performed within 24 to 36 hours. All scans were performed using a 4th-generation CT scanner, with a 5-mm-thick slice.

Data collection

Data of all the patients were collected by reviewing the electronic medical records and order communication system. The data collected and analyzed for the study were age; sex; medical history; initial vital signs; initial National Institutes of Health Stroke Scale (NIHSS) score; intravenous administration of rtPA; results of the initial blood test at the ED, including complete blood count; prothrombin time (PT); aPTT; levels of glucose, aspartate aminotransferase (AST), alanine amino transferase, total bilirubin, blood urea nitrogen, creatinine, creatinine phosphokinase, lactate dehydrogenase (LDH), electrolyte, and C-reactive protein; initial brain imaging (brain CT or magnetic resonance imaging); and follow-up brain CT.

Hemorrhagic transformation was considered to occur when ICH was newly observed in the follow-up CT. Hemorrhagic transformation was further divided into 4 subtypes according to the definition of the European Cooperative Acute Stroke Study (ECASS) as follows: HI1, small petechial hemorrhage along the margins of the infarct; HI2, confluent petechiae within the infarcted area but no space-occupying effect; PH1, hematoma covering ≤30% of the infarcted area with some space-occupying effect; and PH2, hematoma covering >30% of the infarcted area with substantial space-occupying effect.[3] sICH was defined as "any hemorrhage with neurological deterioration concomitant with an NIHSS score of ≥4 points or any hemorrhage leading to death" according to ECASS II.[3] All brain images were reviewed by the emergency physician with reference to the radiologist's readings.

Statistical analyses

Statistical analyses were performed, first, to identify variables with statistically significant differences between the two groups, among hematologic, demographic, and clinical indexes. The Mann-Whitney U-test was used for continuous variables, and the chi-square test or Fisher exact test was used for nominal variables. Data were presented as medians and interquartile ranges. Further logistic regression analyses were performed for all laboratory and clinical parameters. Receiver-operating characteristic curve analysis was performed for continuous variables with statistical significance in the logistic regression analysis to analyze the predictability of sICH. Multivariate logistic regression analysis was performed for all variables with statistical significance in the logistic regression analysis. We used Stata ver. 13.0 (StataCorp., College Station, TX, USA) for our statistical analyses, and the statistical significance was based on a P-value <0.05.

RESULTS

During the study period, 420 patients received IV rtPA upon diagnosis of acute ischemic stroke in the ED. After excluding 45 patients, 375 patients were finally included. Ten patients were excluded because rtPA was administered after 4.5 hours from symptom onset. Twenty-seven patients who did not undergo follow-up brain CT after IV rtPA were also excluded, and another 8 patients were excluded because of a lack of electronic medical record data. Of 375 patients, 42 (11.2%) had a new intracranial hemorrhage on follow-up brain CT. Twenty-eight patients (7.4%) had hemorrhagic transformation without significant symptoms (non-sICH), and 14 (3.7%) had significant symptoms (sICH). All the patients in the sICH group had a PH2 subtype (Fig. 1). Four patients in the non-sICH group had an HI1 subtype; 13, an HI2 subtype; 10, a PH1 subtype; and 1, a PH2 subtype (Fig. 1).

Comparison of patient characteristics between the sICH and non-sICH groups

The patients in the post-rtPA sICH group were older than those in the non-sICH group, but the difference was not statistically significant (74 vs. 70 years, P=0.734). The incidence of sICH was higher in patients taking aspirin than in those not taking aspirin, but the difference was not statistically significant (9.42% vs. 21.43%, P=0.150). Initial systolic blood pressure (SBP), NIHSS score, and prevalence of atrial fibrillation were significantly higher in the post-rtPA sICH group than in the non-sICH group (SBP: 175 vs. 152 mmHg, P=0.041; NIHSS: 18 vs. 10, P<0.001; atrial fibrillation: 64.29% vs. 34.07%, P=0.02). The demographic and clinical features of the two groups are summarized in Table 1.

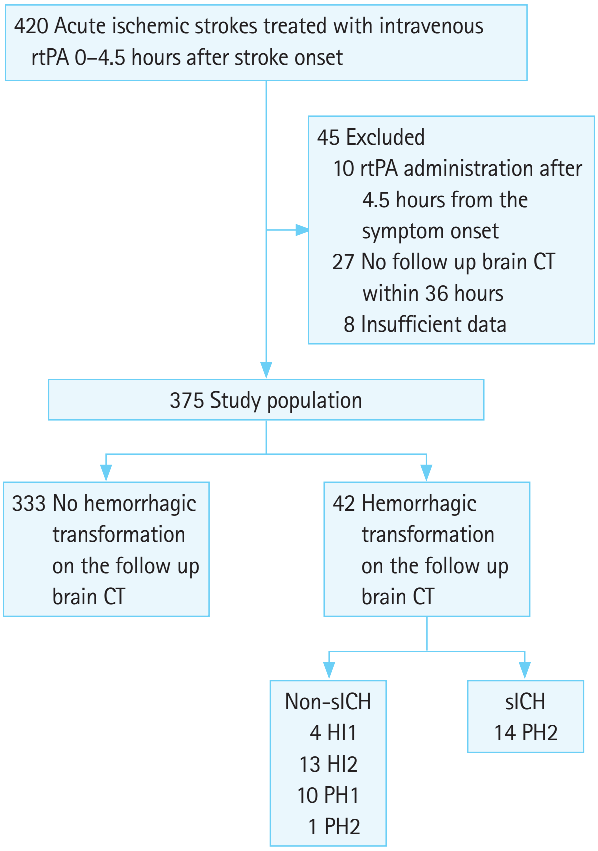

Fig. 1. Study flow diagram. rtPA, recombinant tissue plasminogen activator; CT, computed tomography; sICH, symptomatic intracranial hemorrhage; HI1, small petechial hemorrhage along the margins of the infarct; HI2, confluent petechiae within the infarcted area but no space-occupying effect; PH1, hematoma covering ≤30% of the infarcted area with some space-occupying effect; PH2, hematoma covering >30% of the infarcted area with substantial space-occupying effect.

Comparison of blood test indexes between the sICH and non-sICH groups

Among the blood test indexes, platelet count, AST level, and LDH level were significantly different between the sICH and non-sICH groups. The platelet count was lower, and AST and LDH levels were higher in the sICH group than in the non-sICH group (174,500 vs. 228,000/mm^3, P=0.02; 31 vs. 24 IU/L, P=0.022; and 296 vs. 395 IU/L, P=0.05, respectively). NLR, serum glucose level, and creatinine level were not statistically different between both the groups. The blood test indexes of both the groups are comparatively summarized in Table 2.

Parameters to predict post-rtPA sICH

In the univariate logistic regression analysis, SBP (odds ratio [OR], 1.018; 95% confidence interval [CI], 1.001 to 1.034; P=0.032), NIHSS score (OR, 1.163; 95% CI, 1.061 to 1.275; P=0.001), presence of atrial fibrillation (OR, 3.483; 95% CI, 1.142 to 10.618; P=0.028), and platelet count (OR, 0.988; 95% CI, 0.978 to 0.998; P=0.018) showed statistically significant correlations with sICH development (Table 3).

In the receiver-operating characteristic analysis, SBP and platelet count showed poor predictability (area under the curve [AUC], 0.661; 95% CI, 0.510 to 0.811; AUC, 0.684; 95% CI, 0.503 to 0.865, respectively) for sICH. NIHSS score showed fair predictability for sICH (AUC, 0.780; 95% CI, 0.713 to 0.848). The best cutoff SBP was

Table 1. Summary of the patients' characteristics

Characteristics	Non-sICH (n=361)	sICH (n=14)	P-value
Age (yr)	70 (60–77)	74 (60–76)	0.734
≥80	68 (18.84)	1 (7.14)	0.481
Male	226 (62.6)	7 (50)	0.340
Body weight (kg)	62 (55–70)	58.5 (45–64)	0.083
Clinical parameters (prior to rtPA)			
Systolic blood pressure (mmHg)			
Initial	152 (131–178)	175 (156–197)	0.041[a]
Immediately before rtPA	150 (130–162)	161.5 (138–177)	0.126
Diastolic blood pressure (mmHg)			
Initial	84 (74–93)	92.5 (78–101)	0.269
Immediately before rtPA	80 (70–90)	80.5 (67–100)	0.630
Heart rate (initial) (counts/min)	80 (70–91)	82.5 (76–88)	0.489
NIHSS (initial)	10 (6–16)	18 (15–19)	<0.001[a]
Onset to rtPA time (min)	108 (85–147)	106.5 (90–132)	0.895
eGFR (mL/min/1.73 m^2)	80.7 (68.1–101)	75.75 (57.3–91)	0.394
History			
Hypertension	210 (58.17)	8 (57.14)	0.939
Diabetes mellitus	80 (22.16)	3 (21.43)	1.000
Hypercholesterolemia	32 (8.86)	0 (0)	0.619
Atrial fibrillation	123 (34.07)	9 (64.29)	0.020[a]
Smoking	87 (24.1)	1 (7.14)	0.203
Previous stroke	48 (13.3)	1 (7.14)	1.000
Previous intracranial hemorrhage	1 (0.28)	1 (7.14)	0.073
mRS 0–1 before stroke	356 (98.61)	14 (100)	1.000
rtPA dose (mg)	55.8 (49–63)	51.5 (40.5–58)	0.067
Antithrombotic drugs	86 (23.82)	4 (28.57)	0.750
Aspirin monotherapy	34 (9.42)	3 (21.43)	0.150
Clopidogrel monotherapy	14 (3.88)	0 (0)	1.00
Aspirin and clopidogrel	17 (4.71)	1 (7.14)	0.504
Warfarin	16 (4.43)	0 (0)	1.000
Apixaban	1 (0.28)	0 (0)	1.000
Triflusal	2 (0.55)	0 (0)	1.000
Cilostazol	2 (0.55)	0 (0)	1.000

Values are presented as median (interquartile range) or number (%). The eGFR was calculated using the 4-variable Modification of Diet in Renal Disease formula: eGFR (mL/min/1.73 m^2) = 186 × (serum creatinine$^{-1.154}$) × age$^{-0.203}$ × (1.210 if black) × 0.742 (if female).
sICH, symptomatic intracranial hemorrhage; rtPA, recombinant tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale.
[a]Statistical significance, according to a Mann-Whitney U-test.

Table 2. Comparison of blood test indexes between the sICH and non-sICH groups

Blood test index	Non-sICH (n = 361)	sICH (n = 14)	P-value
WBC (×1,000/mm³)	7.8 (6.42–9.5)	7.8 (6.2–9.6)	0.859
Neutrophil (%)[a]	56.1 (47–64.3)	55.55 (40.1–71.3)	0.898
Lymphocyte (%)[b]	33.6 (24.5–41.3)	35.95 (21.9–46.5)	0.822
Monocyte (%)[c]	56.1 (47–64.3)	55.55 (40.1–71.3)	0.898
Hemoglobin (g/dL)	13.9 (12.5–15.1)	13 (12.6–14.1)	0.203
Hematocrit (%)	41.6 (38–44.8)	39.65 (37.1–42.9)	0.252
MCV (fL)	92.4 (89.2–95.7)	93.5 (90.1–95.7)	0.574
MCH (pg)	31 (30–32.1)	31.4 (30.4–32.1)	0.551
MCHC (g/dL)	33.5 (32.9–34.1)	33.4 (32.7–34)	0.737
RDW (%)	13.3 (12.8–13.9)	13.55 (13.2–14.1)	0.145
Platelet (×1,000/mm³)	228 (190–269)	174.5 (140–251)	0.020[d]
NLR	1.66 (1.14–2.63)	1.555 (0.86–3.26)	0.825
LMR	0.6 (0.38–0.88)	0.65 (0.31–1.16)	0.813
PLR	91.06 (69.03–124.65)	62.03 (50.58–129.68)	0.072
PT (INR)	1.01 (0.96–1.07)	1.035 (0.98–1.1)	0.488
aPTT (sec)	29.7 (27.4–32.2)	29.4 (28.8–32.9)	0.390
Blood urea nitrogen (mg/dL)	17.4 (13.9–20.8)	20.2 (16.5–23.4)	0.143
Creatinine (mg/dL)	0.9 (0.8–1.1)	1 (0.8–1.2)	0.565
Aspartate transaminase (IU/L)	24 (19–28)	31 (23–38)	0.022[d]
Alanine aminotransferase (IU/L)	19 (14–25)	22 (13–30)	0.551
Bilirubin (mg/dL)	0.72 (0.54–0.92)	0.805 (0.69–1.135)	0.169
Sodium (mmol/L)	140 (139–142)	140 (139–141)	0.799
Potassium (mmol/L)	4 (3.7–4.2)	3.85 (3.8–4.3)	0.986
Chloride (mmol/L)	105 (103–107)	104 (102–107)	0.698
Glucose (mg/dL)	130 (111–161)	136.5 (118–170)	0.403
Creatine phosphokinase (IU/L)	87.5 (62–123)	79.5 (65–106)	0.530
Lactate dehydrogenase (IU/L)	296 (221–379)	395 (287–436)	0.050
Osmolality (mOsm/kg)	299 (295–304)	299 (297–300)	0.853
C-reactive protein (md/dL)	0.5 (0.5–0.6)	0.5 (0.5–0.55)	0.735

Values are presented as median (interquartile range).
sICH, symptomatic intracranial hemorrhage; WBC, white blood cell count; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time.
[a]Proportion (%) of neutrophils in the WBC. [b]Proportion (%) of lymphocytes in the WBC. [c]Proportion (%) of monocytes in the WBC. [d]Statistical significance, according to the Mann-Whitney test.

170 mmHg, with a sensitivity, specificity, positive predictive value, and negative predictive value of 64.29%, 66.76%, 6.98%, and 97.97%, respectively. The best cutoff platelet count was 195,000/mm³, with a sensitivity, specificity, positive predictive value, and negative predictive value of 71.43%, 73.13%, 9.35%, and 98.51%, respectively. The best cutoff NIHSS score was 15 points, with a sensitivity, specificity, positive predictive value, and negative predictive value of 78.57%, 69.53%, 9.09%, and 98.82%, respectively.

In the multivariate regression analysis, SBP ≥170 mmHg, NIHSS score ≥15, and platelet count <195,000/mm³ showed adjusted ORs (95% CI) of 3.247 (0.998 to 10.571, P=0.050), 7.020 (1.816 to 27.134, P=0.005), and 5.389 (1.491 to 19.481, P=0.010) (Table 4), respectively. The probabilities of sICH according to SBP, NIHSS score, and platelet count are displayed in Fig. 2 with their predictive margins.

DISCUSSION

In this study, we identified blood test indexes that were associated with sICH in patients with acute ischemic stroke who received IV rtPA. Platelet count was the only independent parameter associated with sICH among all the blood test indexes. In addition, mild thrombocytopenia could increase the risk of sICH after IV administration of rtPA.

Some blood test indexes, such as hyperglycemia,[11-13] increased NLR,[14] and decreased GFR,[15] are associated with post-rtPA sICH. Surprisingly, coagulation-related blood test indexes, such as plate-

Table 3. Univariate logistic regression analysis of clinical and laboratory parameters

Variable	Unadjusted OR (95% CI)	P-value
Clinical parameters		
Age	1.006 (0.964–1.049)	0.784
Male	0.597 (0.205–1.740)	0.345
Body weight	0.958 (0.918–1.001)	0.055
Initial SBP	1.018 (1.001–1.034)	0.032[a]
Initial DBP	1.015 (0.985–1.046)	0.332
NIHSS	1.163 (1.061–1.275)	0.001[a]
Onset to rtPA time	0.998 (0.987–1.010)	0.755
eGFR	0.999 (0.981–1.018)	0.941
Hypertension	0.959 (0.326–2.820)	0.939
Diabetes mellitus	0.958 (0.261–3.517)	0.948
Atrial fibrillation	3.483 (1.142-10.618)	0.028[a]
rtPA dose	0.953 (0.908–1.000)	0.051
Aspirin monotherapy	2.623 (0.698–9.864)	0.154
Aspirin and clopidogrel	1.557 (0.192–12.603)	0.678
Laboratory parameters		
White blood cell count	0.946 (0.751–1.193)	0.639
Neutrophil	1.000 (0.959–1.042)	0.985
Hemoglobin	0.889 (0.697–1.134)	0.344
Hematocrit	0.959 (0.878–1.048)	0.356
RDW	1.092 (0.831–1.435)	0.526
Platelet	0.988 (0.978–0.998)	0.018[a]
NLR	1.036 (0.806–1.331)	0.784
PLR	0.999 (0.990–1.008)	0.793
PT (INR)	2.047 (0.015–277.702)	0.775
aPTT	1.074 (0.930–1.240)	0.331
Glucose fasting	1.002 (0.995–1.009)	0.636
Bilirubin total	2.582 (0.534–12.490)	0.238
Aspartate transaminase	1.009 (0.991–1.028)	0.318
Alanine aminotransferase	1.004 (0.974–1.036)	0.780
Blood urea nitrogen	1.038 (0.977–1.103)	0.228
Creatinine	0.805 (0.213–3.044)	0.749
Lactate dehydrogenase	1.003 (0.999–1.006)	0.110

OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue plasminogen activator; eGFR, estimated glomerular filtration rate; RDW, red blood cell distribution width; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time.
[a]Statistical significance.

let count, PT, and aPTT, are not related to post-rtPA sICH. Unlike the results of previous studies, our results showed that serum glucose level, NLR, and GFR were not significantly different between the sICH and non-sICH groups. Rather, platelet count was the only independent parameter that predicted sICH development. The best cutoff platelet count was 195,000/mm^3. When we divided subjects into groups of <195,000/mm^3 and ≥195,000/mm^3 according to the platelet count, the median platelet count in the <195,000/mm^3 group was 164,000/mm^3 and 9.4% (10/107) had sICH. The median platelet count was 250,500/mm^3 and 1.5% (4/268) had sICH in the >195,000/mm^3 group. Patients with platelet counts of <195,000/mm^3 had a 5.4-times higher risk of developing sICH than those with platelet counts of ≥195,000/mm^3.

Table 4. Multivariate logistic regression analysis of clinical and laboratory parameters

Variable	Adjusted OR (95% CI)[a]	P-value
Initial SBP	1.017 (1.000–1.034)	0.050
Initial SBP ≥185 vs. <185 mmHg[b]	2.124 (0.632–7.145)	0.223
Initial SBP ≥170 vs. <170 mmHg[c]	3.247 (0.998–10.571)	0.050
NIHSS	1.160 (1.046–1.286)	0.005
NIHSS ≥15 vs. <15[d]	7.020 (1.816–27.134)	0.005
Atrial fibrillation	2.032 (0.618–6.680)	0.243
Platelet count	0.992 (0.982–1.002)	0.117
Platelet <100,000/mm^3 vs. ≥100,000/mm^3	40.905 (1.954–856.466)	0.017
Platelet <195,000/mm^3 vs. ≥195,000/mm^3[e]	5.389 (1.491–19.481)	0.010

OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; NIHSS, National Institutes of Health Stroke Scale.
[a]Adjusted for initial SBP, NIHSS, atrial fibrillation, platelet count, lactate dehydrogenase. [b]The exclusion criteria for recombinant tissue plasminogen activator within 4.5 hours from stroke onset by the American Heart Association and the American Stroke Association. [c]The best cutoff value of SBP. [d]The best cutoff value of the NIHSS score. [e]The best cutoff value of platelet count.

Our main finding suggests that mild thrombocytopenia may not be a contraindication for rtPA as long as the platelet count is >100,000/mm^3 but may still increase the risk of post-rtPA sICH. This main result regarding platelet count may have significant clinical implications and may be controversial. In the AHA/ASA guidelines, rtPA is contraindicated for patients with platelet counts of <100,000/mm^3,[10] but in the real world, it may be administered before confirming platelet counts. Mowla et al.[16] reported no significant difference in the incidence of post-rtPA sICH between patients with platelet counts of <100,000/mm^3 and those with platelet counts of >100,000/mm^3 (7.7% vs. 6.04%, P=0.73). However, their study included only a few cases (five cases plus 21 cases reported in previous studies), which are insufficient to make definitive conclusions. In our study, two patients had a platelet count of <100,000/mm^3, and sICH occurred in one (50%). One patient who had sICH was a 75-year-old woman with an initial NIHSS score of 13 who received IV rtPA 71 minutes after symptom onset. Her platelet count was 87,000/mm^3. The other patient was an 85-year-old man who did not have sICH but had an initial NIHSS score of 16. He received rtPA 90 minutes after symptom onset, and his platelet count was 99,000/mm^3. In this study, patients with a platelet count <100,000/mm^3 showed a 40.9-times higher risk of developing sICH than those with a platelet count >100,000/mm^3. Therefore, we recommend upholding the platelet count of <100,000/mm^3 as an absolute contraindication for IV

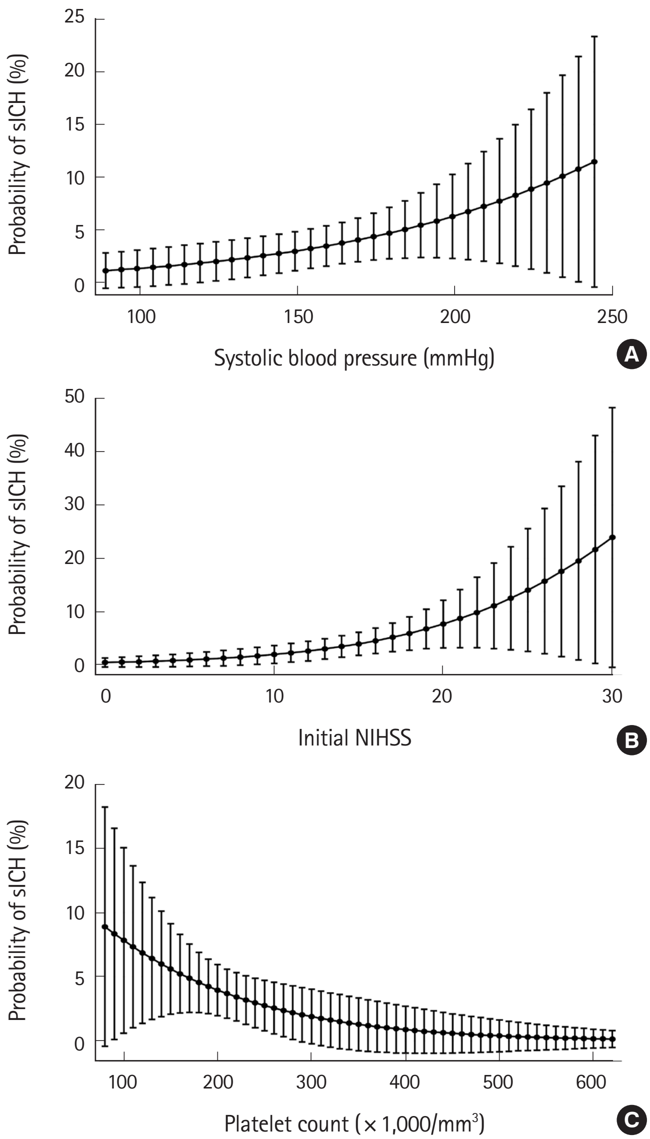

Fig. 2. Graphs of the probability of symptomatic intracranial hemorrhage (sICH) with predictive margins. Predictive probability of sICH according to systolic blood pressure (A), initial National Institutes of Health Stroke Scale (NIHSS) score (B), and platelet count (C).

rtPA administration.

In addition, the increased risk of sICH should not be ignored in cases within the lower normal range (mild thrombocytopenia). The 2018 AHA/ASA guidelines recommend intra-arterial thrombectomy for treating acute ischemic stroke caused by a documented large artery occlusion in the proximal anterior circulation.[17] Second-generation mechanical thrombectomy devices (retrievable stents) are safe and effective for reducing disability and are superior to standard treatment with IV thrombolysis alone for treating acute ischemic stroke. Although it is beyond the scope of this study, it may be desirable to substitute endovascular thrombectomy for IV or intra-arterial administration of rtPA in patients with low platelet counts, if possible.

Although AST and LDH levels were significantly different between the sICH and non-sICH groups, they may not be clinically related to sICH occurrence. In the logistic regression analysis, AST and LDH levels were statistically significant and therefore cannot be used as a predictor of post-rtPA sICH. However, we could not explain why AST and LDH levels were elevated in the sICH group.

Among the clinical risk factors, SBP and NIHSS score were independently associated with sICH in this study, and these results are consistent with those of previous studies. Perini et al.[18] reported that higher SBP significantly increases the frequency of sICH in rtPA-treated patients. In the ECASS II study, the baseline SBP before rtPA administration showed a significant correlation with sICH (OR, 1.02; 95% CI, 1.00 to 1.03, $P=0.02$).[12] The results of this study also showed that a higher initial SBP was independently associated with sICH among patients who received IV rtPA. Interestingly, the initial SBP at the ED was more strongly associated with the incidence of sICH than SBP just before administering IV rtPA. The best cutoff initial SBP for an increased risk of sICH was 170 mmHg. Although high blood pressure may theoretically be advantageous to improve regional cerebral blood flow,[19] it may be desirable to maintain SBP at <170 mmHg to prevent sICH occurrence.

NIHSS score correlates with infarct volume and is the most commonly used stroke outcome scale.[20] In previous studies, higher initial NIHSS scores were associated with sICH,[11,21] and similar results were obtained in this study. In this study, NIHSS score turned out to be the most reliable predictor of sICH among the other parameters assessed. Patients with NIHSS scores ≥15 had a 7-times higher risk of sICH than those with NIHSS scores <15. If a patient with an acute stroke has an NIHSS score ≥15, the physician must be cautious in using rtPA and should check the patient's platelet count and strictly control SBP.

Previous studies do not agree on the association between age and sICH. In the meta-analysis by Whiteley et al.,[11] age was associated with post-rtPA sICH (OR, 1.03; 95% CI, 1.01 to 1.04, $P<0.001$). However, in the prospective cohort study by Sylaja et al.,[22] older age in carefully selected patients did not increase the risk of post-rtPA sICH. In the current study, 69 patients (18.4%) were aged >80 years, and age and sICH were not statistically correlated.

This study has some limitations. First, it was conducted at a single tertiary hospital. As the research hospital is located in an urban area and the study was conducted by Asian people, care should be taken in comparing the results with those of previous studies because regional and racial characteristics may act as sources of bias. Second, although we analyzed the data for 10 years, the number of sICH patients was only 14. Nevertheless, the sample size of this study was relatively larger than those of other single-center studies. However, the small sample size is one of the major weaknesses of this study. Third, this study did not include all possible clinical and brain imaging findings, such as infarction volume, hyperdense cerebral artery sign, and presence of visible hypodensity, owing to the natural limitation of retrospective studies. This study merely analyzed the blood test results of patients with sICH on their follow-up brain CT. However, the primary goal of this study was to determine the laboratory features of patients with sICH, so this limitation did not significantly affect the main outcome of this study. This study is meaningful in that it analyzed the association between sICH and various laboratory parameters that have not been well-studied previously.

In conclusion, among the blood tests indexes, platelet count was the only independent predictor of sICH after administering rtPA within 4.5 hours from the onset of acute ischemic stroke symptoms. Physicians should be aware of the increased risk of sICH in patients with mild thrombocytopenia. If patients with mild thrombocytopenia have other concomitant risk factors, such as an NIHSS score ≥15 or SBP ≥170 mmHg, physicians should be aware of the potential risk of post-rtPA sICH and should strictly control the blood pressure.

CONFLICT OF INTEREST

No author has any conflict of interest.

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