ASSOCIATION OF THE TYPE OF INTRACEREBRAL HEMORRHAGE WITH SERIOUS COMPLICATIONS AND PREDICTIVE FACTORS FOR HEMORRHAGIC TRANSFORMATION AFTER THROMBOLYTIC TREATMENT IN PATIENTS WITH ACUTE ISCHEMIC STROKE

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Abstract

Background: Accurate classification of postthrombolytic intracerebral hemorrhage (ICH) subtypes is vital for predicting stroke outcomes and managing ICH. Currently, the recommended classification criteria are the European Cooperative Acute Stroke Study III criteria, including two primary categories: hemorrhagic infarction (HI) and parenchymal hematoma (PH).

Objectives: The primary objective of this study was to assess the contribution of various ICH subtypes to serious complications, with the secondary aim to identify associated predictors.

Methods: The study examined medical records of patients with acute ischemic stroke receiving thrombolysis at Saraburi Hospital from 2014 to 2022. The logit model with the margins command assessed the association of ICH subtypes with serious complications, and multinomial logistic regression identified potential predictors for HI and PH.

Results: Among 345 patients, HI-1, HI-2, PH-1 and PH-2 had prevalence rates of 3.2, 7.8, 4.9 and 7.5%, respectively, while 76.5% did not have ICH. PH-2 demonstrated the strongest correlation with inhospital mortality (adjusted risk ratio [RR] 2.83, 95% CI 1.56-5.13), invasive mechanical ventilator requirement (adjusted RR 3.93, 95% CI 2.09-7.39) and hematoma evacuation (adjusted RR 4.58, 95% CI 1.17-17.95) compared with patients of non-ICH. HI demonstrated a significant prolongation of hospitalization. (adjusted RR 3.30, 95% CI 1.53-7.12). Multinomial logistic regression analysis revealed that prior use of antiplatelet drugs, antihypertensive treatment before rt-PA, white blood cell count ≥11,750 cells/mm^3 and baseline Alberta stroke program early CT scores ≤7 were independent predictors for PH. The adjusted odds ratios were 3.06 (95% CI, 1.23-7.57), 6.95 (95% CI, 2.62-18.45), 6.01 (95% CI, 2.17-16.65) and 5.01 (95% CI, 2.00-12.60), respectively.

Conclusion: The PH-2 subtype was associated with the highest mortality, while our study demonstrated that the HI subtype, previously considered relatively benign with successful early recanalization, showed a significant prolongation of hospitalization compared with that of patients of non-ICH. High-risk patients of ICH require intensive monitoring to reduce complications.

Keywords: Intracerebral hemorrhage, Acute stroke, Thrombolysis, Mortality, Complications

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Introduction

Intravenous recombinant tissue plasminogen activator (rt-PA), approved in 1996 for acute ischemic stroke (AIS)[1], intricately leads to intracerebral hemorrhage (ICH) by disrupting the blood-brain barrier and causing damage to the extracellular matrix, impaired cerebral autoregulation and increased vascular permeability.[2] The incidence of ICH among patients with AIS typically occurs within seven days after thrombolysis, reported in 3 to 10% of cases with symptomatic intracerebral hemorrhage (sICH) and associated with serious complications, resulting in high mortality. The cumulative 12-month risk of death among patients with postthrombolytic ICH was increased approximately three fold.[3, 4]

Based on related studies regarding the relationship between ICH subtypes and poststroke complications, the primary focus has been on studying outcomes related to mortality and disability.[5-7] However, limited information remains concerning the specific association between ICH subtypes, as classified by radiographic classifications according to the European Cooperative Acute Stroke Study II (ECASS II) and the occurrence of postthrombolytic severe complications across different fields. Emphasizing that radiographic signs of ICH on follow-up imaging do not always correspond with rapidly occurring clinical deterioration is critical; therefore, characterizing the ICH subtypes to help predict clinical outcomes and guide therapeutic choices after rt-PA administration is essential. Consequently, the definition of "thrombolysis-related sICH" can be problematic. The impact of the ICH subtypes on short and long term outcomes among patients with AIS continues being debated.[7] Identifying pretreatment predictors of ICH can help improve patient selection and counseling. Stroke severity, advanced age, heart disease, high blood pressure and early non-contrast computed tomography (NCCT) abnormalities have been shown to predict ICH after stroke, but the results are considered controversial. [[8]

The primary objective of this study aimed to assess the impact of ICH subtypes on short term prognoses including inhospital mortality (IHM), stroke-associated pneumonia (SAP), length-of-stay (LOS) ≥14 days, invasive mechanical ventilation (IMV) requirement, hematoma evacuation and septicemia among patients with AIS who underwent thrombolysis. The secondary objective was identifying potential predictors for PH (parenchymal hemorrhage), HI (hemorrhagic infarction), and any ICH.

Methods

Study population

This retrospective observational study included patients with acute anterior circulation ischemic stroke (AACIS) receiving thrombolysis and admitted to Saraburi Hospital, located in central Thailand, a tertiary care hospital with 700 beds. The study comprised 345 consecutive patients enrolled between 1 January, 2015 and 31 July, 2022. The guidelines for the early management of patients with AIS 2019 determined the indications and contraindications for thrombolytic treatment. [9] After 24 hours, patients without evidence of ICH or large hemispheric infarction were administered antiplatelet or oral anticoagulant therapy. The Human Research Ethics Committee of Saraburi Hospital approved this study (EC061/2565), and the patient flowchart is depicted in **Figure 1.**

Data collection

Data were collected from electronic medical records to determine patient demographics,

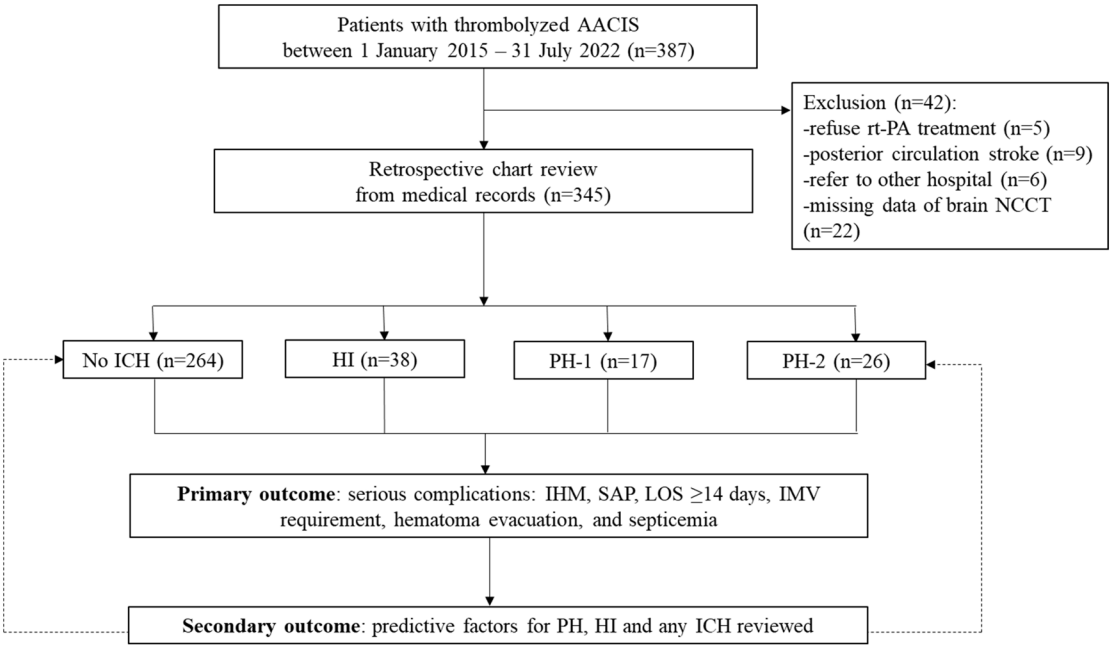

Figure 1. Patient flow chart.

comorbidities, prestroke functional status, time from symptom onset to thrombolysis, National Institutes of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early CT Score (ASPECTS), laboratory results, ICH subtypes and complications. After 24 hours of thrombolysis, a neurologist and neuroradiologist examined the brain NCCT. Our assessment focused on the occurrence of ICH within seven days following rt-PA treatment. The ICH subtypes and ASPECTS were determined independently by each reader. Disagreements were resolved consensually by mutual discussion between the neurologist and neuroradiologist to ensure accurate results. A follow-up NCCT was performed to detect ICH after thrombolysis. The International Classification of Diseases, 10th Revision, Clinical Modification (I63) was used to confirm a diagnosis of AIS, and the mortality data were categorized using information obtained from death certificates.

Criteria and Definition

Regarding the radiological classification of ICH subtypes after thrombolysis, we used the ECASS II. HI and PH are the two main radiographic classifications for identifying postthrombolytic ICH. HI type 1 (HI-1) is characterized by scattered petechiae without mass effect, while HI-2 is characterized by confluent petechiae without mass effect. Additionally, PH was classified in two groups: parenchymal hemorrhage type 1 (PH-1), referring to a hematoma within infarcted tissue occupying less than 30% without significant mass effect, and PH-2, representing a hematoma occupying more than 30% of infarcted tissue with mass effect. [5, 6]

Regarding other definitions, diabetes mellitus (DM) criteria were: (i) random plasma glucose ≥200 mg/dl, (ii) fasting plasma glucose ≥126 mg/dl, or (iii) HbA1c ≥6.5% (≥48 mmol/mol).[10] Chronic kidney disease (CKD) was defined as kidney damage or a glomerular filtration rate <60 mL/min/1.73 m^2 for three months or more, irrespective of cause.[11] Myocardial infarction (MI) is diagnosed when at least two of the following criteria are met: (i) symptoms of ischemia; (ii) new ST-segment changes or a left bundle branch block; (iii) the presence of pathologic Q waves on the electrocardiogram; (iv) a new regional wall motion abnormality on the echocardiography or (v) the presence of an intracoronary thrombus at angiography.[12] Congestive heart failure (CHF) diagnosis relies on the Framingham Diagnostic Criteria, requiring two major criteria or one major and two minor criteria. Major criteria encompass acute pulmonary edema, cardiomegaly, hepatojugular reflux, neck vein distention, paroxysmal nocturnal dyspnea or orthopnea, pulmo-

nary rales and the third heart sound (S3 gallop). Minor criteria include ankle edema, dyspnea on exertion, hepatomegaly, nocturnal cough, pleural effusion and tachycardia (heart rate >120 beats per minute). [13]

Outcomes

The primary outcome measures included serious complications of thrombolytic treatment to investigate the impact of ICH subtypes on IHM, SAP, LOS ≥14 days, IMV requirement, hematoma evacuation and septicemia. The secondary outcomes were PH, HI, and any ICH after thrombolytic treatment, which were analyzed to identify predictors for thrombolysis in AACIS. Additional analyses included the association between the frequency of ICH subtypes and functional outcomes at hospital discharge, which were evaluated using the modified Rankin Scale (mRS), assessed by neurologists and stroke-trained nurses. A favorable outcome was defined as an mRS score of 0 to 1, while a score of 6 represented death. NCCT examination was performed using a TOSHIBA-160 slice Aquilion Prime scanner by Canon Medical Systems in Otawara, Japan. The examination covered continuous cross-sections from the entire base of the skull to the vertex, parallel to the inferior orbitomeatal line, with a 3 mm axial slice thickness, 120 kV and 240 mA. The interpretation involved assessing all cross-sectional images of the brain. We employed NCCT to identify the radiologic classification of ICH subtypes and assess ASPECTS before administering rt-PA.

Statistical analysis

We used Stata (Version 16.0; Stata Corp., College Station, TX, USA) for statistical analysis. Categorical data were analyzed using frequency and percentage, mean and standard deviation for normally distributed continuous data, and median and interquartile range (IQR) for non-normally distributed continuous data. Fisher exact or chi-square test was conducted to compare categorical variables, while the Mann–Whitney U or Student's t-test was employed to compare continuous variables. We used the logit model with the margins command to estimate the risk ratio (RR) with 95% confidence intervals (CIs) for the association between ICH subtypes and serious stroke complications. The unadjusted model involved univariable analysis. In the adjusted analysis, we further adjusted for age, sex, the Trial of ORG 10172 in Acute Stroke Treatment classification, NIHSS, baseline ASPECTS ≤7, DM, CKD, MI, CHF and a history of malignancy, which comprised potential confounders. The cumulative incidence of IHM according to ICH subtypes and non-ICH groups was evaluated using the Kaplan-Meier method, and statistical significance was determined through the log-rank test. Multinomial logistic regression was used to assess potential risk factors for HI and PH. Variables with p-values <0.2 from univariable analysis were included in the multivariable multinomial logistic regression for the final model, presenting results as odds ratios (ORs) with 95% CIs.

Results

Clinical features of patients with different types of postthrombolytic ICH

This retrospective study included 387 individuals receiving thrombolysis for AACIS at Saraburi Hospital from 1 January, 2015, to 31 July, 2022. We excluded 42 patients for the following reasons: five declined rt-PA treatment, nine presented posterior circulation AIS, six were referred to other hospitals and 22 had incomplete brain NCCT images **(Figure 1).** A cohort of 345 patients participated in the study, and 81 developed postthrombolytic ICH. HI-1 was diagnosed among 11 patients (3.2%), HI-2 among 27 patients (7.8%), PH-1 among 17 patients (4.9%) and PH-2 among 26 patients (7.5%), while 264 patients (76.5%) were without ICH. The patients' mean age was 62, and 47.0% were men. The patients' LOS ranged from 1 to 91 days with a median of 5 days (IQR: 3 to 9). Sixty-five of 345 (18.8%) patients with thrombolysis in AACIS who were admitted to the stroke unit died. Patients with postthrombolytic ICH were more likely to have prior use of antiplatelet drugs, swallowing dysfunction, aphasia, gaze paresis, higher mRS score for pre-stroke functional status, time of onset of symptoms to rt-PA of 3 to 4.5 h, higher NIHSS score, cardioembolic stroke, antihypertensive treatment before thrombolysis and lower baseline ASPECTS **(Table 1).**

Impact of the ICH subtypes on serious complications

Associations between the ICH subtypes and IHM

In adjusted models, PH-2 was significantly associated with IHM during stroke unit hospitalization (adjusted RR 2.83; 95% CI, 1.56 to 5.13). **Figure 2** depicts Kaplan-Meier curves for IHM according to ICH subtypes and patients of non-ICH. The cumulative incidence of IHM was highest in PH-2 (p<0.001). The cumulative incidence curves for IHM demonstrated a sharp increase in PH-2 within the initial 10–20 days from admission. However, we did not find a significant relationship among HI, PH-1 and IHM **(Table 2).**

Associations between the ICH subtypes and SAP

We found an association between ICH subtypes (PH-1, PH-2 and any ICH) and the risk of SAP in adjusted models. The adjusted RRs were 2.58 (95% CI, 1.14 to 5.87), 2.01 (95% CI, 1.04 to 3.88), and 2.02 (95% CI, 1.17 to 3.49) in the adjusted model compared with those of the patients of non-ICH, respectively. We did not find a significant correlation between HI and SAP in the adjusted model. However, HI tended to increase the risk of SAP compared with that of patients of non-ICH (adjusted RR 1.77, 95% CI 0.86 to 3.65) **(Table 2).**

Associations between the ICH subtypes and LOS ≥14 days

In adjusted models, HI, PH-1 and any ICH were associated with LOS ≥14 days. The adjusted RRs were 3.30 (1.53 to 7.12), 4.63 (1.88 to 11.38), and 2.97 (1.59 to 5.54) for HI, PH-1 and any ICH, respectively. However, we did not determine a relationship between PH-2 and LOS ≥14 days in the adjusted model **(Table 2).**

Associations between the ICH subtypes and IMV requirement

PH-1, PH-2 and any ICH showed significant associations with IMV requirement in the adjusted models compared with those of patients of non-ICH **(Table 2).** The adjusted RRs for PH-1, PH-2 and any ICH compared with patients of non-ICH were 3.70 (95% CI, 1.55 to 8.80), 3.93 (95% CI, 2.09 to 7.39) and 3.14 (95% CI, 1.77 to 5.57), respectively. While the association between HI and IMV requirement was not statistically significant, our data indicated a trend suggesting an increased risk of IMV requirement with HI (adjusted RR 1.88, 95% CI 0.84 to 4.19).

Associations between the ICH subtypes and hematoma evacuation

Only PH-2 was significantly associated with hematoma evacuation in the adjusted model (adjusted RR 4.58; 95% CI, 1.17 to 17.95). Nevertheless, no significant association was observed between HI, PH-1, any ICH and hematoma evacuation, as indicated in **Table 2.**

Associations between the ICH subtypes and septicemia

In adjusted models, the PH-1 and any ICH groups showed a significantly higher association with septicemia compared with that of patients of non-ICH, with adjusted RRs of 4.40 (95% CI, 1.13 to 17.16) and 2.71 (95% CI, 1.05 to 6.98), respectively. However, the adjusted models found no relationship between HI, PH-2 and septicemia **(Table 2).**

A bar graph illustrating the functional outcomes of patients with different ICH subtypes at hospital discharge is presented using the mRS score **(Figure 3).** Notably, 92.3% of patients with PH-2 died during hospitalization **(Table 3 and Figure 3)**. The rates of SAP were significantly higher in HI-1 (36.36%), HI-2 (29.63%), PH-1 (58.82%) and PH-2 (61.54%) compared with patients of non-ICH (12.12%). Specifically, the rates of SAP were approximately 3.0 to 5.0 times higher, and the rates of IMV requirement were about 3.0 to 10.0 times higher in these ICH groups. Hematoma evacuation was predominantly performed among patients with PH-2 (23.08%), occurring at a 10.0 fold higher frequency than in that of patients of non-ICH (2.27%). Septicemia rates were approximately 6.0 times higher in PH-1 (23.53%) and PH-2 groups (23.08%) than those of non-ICH (3.79%) **(Table 3 and Supplemental Figure 2).**

Predictive factors for PH after thrombolytic treatment

Univariable multinomial regression analysis revealed that prior use of antiplatelet drugs (OR 2.83, 95% CI 1.39 to 5.75), atrial fibrillation (OR 2.83, 95% CI 1.39 to 5.75), mRS score for pre-stroke functional status ≥1 (OR 4.08, 95% CI 1.60 to 10.43), time of symptom onset to rt-PA 3 to 4.5 hours (OR=2.16, 95% CI 1.12 to 4.14), diastolic blood pressure ≥110 mmHg (OR 2.50, 95% CI 1.20 to 5.21), NIHSS at admission ≥16 (OR 5.85, 95% CI 2.92 to 11.72), antihypertensive treatment before rt-PA (OR 2.83, 95% CI 1.39 to 5.75), admission white blood cell count (WBC) ≥11,750 cells/mm^3 (OR 6.91; 95% CI 3.16 to 15.10), admission blood glucose ≥120 mg/dL (OR 2.14, 95% CI 1.09 to 4.19) and baseline ASPECTS ≤7 (OR 9.49, 95% CI 4.67 to 19.29) were statistically significant predictors of PH **(Supplementary Table 1).** The best cutoff value for the WBC count in the cohort, as revealed by receiver operating characteristic analysis and Youden index analysis, was 11,750 cells/mm^3. Multivariable multinomial logistic regression analysis revealed that prior use of antiplatelet drugs, antihypertensive treatment before rt-PA, WBC count ≥11,750 cells/mm^3 and baseline ASPECTS ≤7 were independent predictors for PH. The adjusted ORs were 3.06 (95% CI, 1.23 to 7.57), p=0.016; 6.95 (95% CI, 2.62 to 18.45), p<0.001; 6.01 (95% CI, 2.17 to 16.65), p=0.001 and 5.01 (95% CI, 2.00 to 12.60), p= 0.001, respectively **(Table 4).**

Discussion

This study found that PH-2 exhibited the highest risk of IHM, IMV requirement, and hematoma evacuation compared with patients of non-ICH. Furthermore, PH-1 demonstrated the highest association with SAP, prolonged hospitalization and septicemia. This underscores the importance of comprehending the risk of complications associated with each ICH subtype, enabling the physician to strategize surveillance and treatment interventions to minimize these complications. Patients developing PH presented significant, prior use of antiplatelet drugs, antihypertensive treatment before rt-PA, WBC count ≥11,750 cells/mm^3 and baseline ASPECTS ≤7. Early prediction among high risk patients with PH can guide prompt treatment, preventing complications and death among patients with postthrombolytic ICH.

Our study found that 23.5% (81/345) of patients with thrombolysis in AACIS had ICH, and 44.4% (36/81) of patients with ICH died during the study period. Serious complications frequently accompany postthrombolytic ICH and carry a high overall mortality rate. Recent studies have shown that the incidence of ICH following thrombolysis among patients with AIS ranges from 10 to 50%.[14–16] Our study found an ICH occurrence rate of 23.5% after thrombolysis, higher than the NINDS study but slightly lower than the ECASS III trial.[16] Related research in Thailand by Dharmaraja et al.[17] reported an incidence rate of 5.36% (14/216) using the NINDS definition. In 2013, Watanawong et al.[18] reported an incidence rate of sICH of 20.7% (18/103) according to the NINDS criteria. The mean time from onset to thrombolysis was 142.0±57.2 min, lower than that reported by the ECASS III study. The median NIHSS score at admission was 11 (IQR, 8–17), consistent with the ECASS II study but lower than that reported by the NINDS study.[19,20] Our study revealed lower incidence proportions of HI-1 and HI-2 compared with those of the ECASS II study, while the incidences of PH-1 and PH-2 were closely similar. This could be attributed to the differences in the study populations: our cohort focused on patients receiving rt-PA within 3 to 4.5 hours, whereas the ECASS II study included patients receiving rt-PA within six hours of symptom onset. Ringleb et al.[21] observed a slightly higher incidence of ICH within the six-hour time window than the three-hour time window (ORs: 3.23 vs. 2.68). The time window for rt-PA administration and stroke severity varied across studies, potentially impacting the incidence of ICH differently.[4]

It has been well established that PH is strongly associated with an elevated likelihood of unfavorable outcomes.[17, 22, 23] Hematoma expansion is a mortal predictor among patients with ICH.[24] Our study's results aligned with these findings,

Table 1. Patient characteristics of postthrombolytic ICH by ICH subtypes.

Characteristic	All patients (n=345)	Non-ICH (n=264)	Type of intracerebral hemorrhage		
			HI (n=38)	PH-1 (n=17)	PH-2 (n=26)
Age, years					
18-59	151(43.77)	122(46.21)	15(39.47)	4(23.53)	10(38.46)
60-69	81(23.48)	58(21.97)	13(34.21)	4(23.53)	6(23.08)
70-79	62(17.97)	48(18.18)	6(15.79)	4(23.53)	4(15.38)
>=80	51(14.78)	36(13.64)	4(10.53)	5(29.41)	6(23.08)
Sex					
Male	162(46.96)	121(45.83)	21(55.26)	9(52.94)	11(42.31)
Female	183(53.04)	143(54.17)	17(44.74)	8(47.06)	15(57.69)
Vascular risk factors and comorbidities					
Smoking	123(35.65)	99(37.50)	10(26.32)	4(23.53)	10(38.46)
Alcohol	142(41.16)	114(43.18)	11(28.95)	3(17.65)	14(53.85)
Prior use of the antiplatelet drugs	66 (19.13)	42 (15.91)	9 (23.68)	7 (41.18)	8 (30.77)
Atrial fibrillation	102(29.57)	69(26.14)	13(34.21)	9(52.94)	11(42.31)
Myocardial infarction	29(8.41)	25(9.47)	1(2.63)	1(5.88)	2(7.69)
Congestive heart failure	37(10.72)	26(9.85)	4(10.53)	3(17.65)	4(15.38)
Valvular heart disease	22(6.38)	14(5.30)	6(15.79)	0(0)	2(7.69)
Diabetes mellitus	93(26.96)	66(25.00)	14(36.84)	7(41.18)	6(23.08)

Table 1. Patient characteristics of postthrombolytic ICH by ICH subtypes. (cont.)

Characteristic	All patients (n=345)	Non-ICH (n=264)	Type of intracerebral hemorrhage		
			HI (n=38)	PH-1 (n=17)	PH-2 (n=26)
Hypertension	243(70.43)	184(69.70)	26(68.42)	14(82.35)	19(73.08)
Chronic kidney disease	44(12.75)	34(12.88)	3(7.89)	2(11.76)	5(19.23)
Dyslipidemia	141(40.87)	109(41.29)	14(36.84)	8(47.06)	10(38.46)
History of malignancy	8(2.32)	6(2.27)	1(2.63)	0(0)	1(3.85)
History of RRT	5(1.45)	4(1.52)	1(2.63)	0(0)	0(0)
Clinical presentation					
Hemiparesis	341(98.84)	262(99.24)	38(100.00)	16(94.12)	25(96.15)
Dysarthria	275(79.71)	207(78.41)	35(92.11)	11(64.71)	22(84.62)
Swallowing dysfunction	129(37.39)	73(27.65)	23(60.53)	10(58.82)	23(88.46)
Ataxia	37(10.72)	24(9.09)	6(15.79)	2(11.76)	5(19.23)
Hemianopia	23(6.67)	17(6.44)	3(7.89)	2(11.76)	1(3.85)
Aphasia	132(38.26)	89(33.71)	17(44.74)	7(41.18)	19(73.08)
Neglect	62(17.97)	40(15.15)	11(28.95)	4(23.53)	7(26.92)
Cranial nerve disorder	12(3.48)	7(2.65)	2(5.26)	1(5.88)	2(7.69)
Gaze paresis	112(32.46)	65(24.62)	17(44.74)	7(41.18)	23(88.46)
mRS score for pre-stroke functional status, n (%)					
0	320(92.75)	250(94.70)	35(92.11)	13(76.47)	22(84.62)
1	6(1.74)	5(1.89)	0(0)	0(0)	1(3.85)
2-3	19(5.51)	9(3.41)	3(7.89)	4(23.53)	3(11.54)

Table 1. Patient characteristics of postthrombolytic ICH by ICH subtypes. (cont.)

Characteristic	All patients (n=345)	Non-ICH (n=264)	Type of intracerebral hemorrhage		
			HI (n=38)	PH-1 (n=17)	PH-2 (n=26)
Time to rt-PA					
< 3 hours	313(90.72)	242(91.67)	35(92.11)	16(94.12)	20(76.92)
3-4.5 hours	32(9.28)	22(8.33)	3(7.89)	1(5.88)	6(23.08)
SBP, mmHg —median (IQR)	159.20±28.87	157.07±28.12	165.18±26.38	167.23±32.64	166.84± 35.14
DBP, mmHg —median (IQR)	92.34±19.15	90.71±19.12	93.68±19.11	102.23±18.13	100.38±16.86
NIHSS at admission					
4-15	232(67.25)	195(73.86)	23(60.53)	9(52.94)	5(19.23)
16-20	76(22.03)	46(17.42)	10(26.32)	5(29.41)	15(57.69)
>20	37(10.72)	23(8.71)	5(13.16)	3(17.65)	6(23.08)
TOAST classification					
Large-artery atherosclerosis	76(22.03)	49(18.56)	15(39.47)	2(11.76)	10(38.46)
Cardioembolism	119(34.49)	76(28.79)	18(47.37)	10(58.82)	15(57.69)
Small-vessel occlusion	134(38.84)	125(47.35)	4(10.53)	4(23.53)	1(3.85)
Stroke of other determined etiology	9(2.61)	7(2.65)	1(2.63)	1(5.88)	0(0)
Stroke of undetermined etiology	7(2.03)	7(2.65)	0(0)	0(0)	0(0)

Table 1. Patient characteristics of postthrombolytic ICH by ICH subtypes. (cont.)

Characteristic	All patients (n=345)	Non-ICH (n=264)	Type of intracerebral hemorrhage		
			HI (n=38)	PH-1 (n=17)	PH-2 (n=26)
Length of stay, days	5(3, 9)	4(3, 7)	8(6, 17)	13(8, 24)	6(3, 15)
Antihypertensive treatment before rt-PA	97(28.12)	50(18.94)	20(52.63)	10(58.82)	17(65.38)
Laboratory findings					
WBC (×10⁶/mL) —median (IQR)	9.02±3.22	8.83±3.16	9.44±3.58	9.24±2.64	10.20±3.54
NLR— median (IQR)	2.21(1.53, 3.67)	2.19(1.50, 3.57)	2.15(1.56, 3.25)	3.09(1.62, 4.29)	2.80(1.55, 5.26)
Hb (g/dL) — median (IQR)	12.55±2.13	12.60±2.18	12.43±1.65	12.22±2.17	12.41±2.21
Hct (%) — median (IQR)	38.18±6.29	38.27±6.44	38.05±5.25	37.55±5.46	37.91±6.83
Platelet (×10⁶/mL) — median (IQR)	251.51± 81.35	251.64±75.59	247.73±99.81	250.47±115.26	256.34±87.56
INR, median (IQR)	0.97±0.13	0.96±0.12	0.97±0.10	0.95±0.31	1.02±0.12
Cr (mg/dL) — median (IQR)	0.95(0.78, 1.15)	0.95(0.78, 1.16)	0.93(0.70, 1.15)	0.97(0.84, 1.13)	0.95(0.82, 1.13)
Admission blood glucose (mg/dL) — median (IQR)	138.26±62.36	133.28±60.18	156.50±71.54	153.35±63.12	152.30±64.56
Workflow time					
Onset to door time, min) — median (IQR)	90(60, 120)	90(60, 120)	90(60, 120)	96(70, 120)	120(60, 150)
Door to needle time, min) — median (IQR)	42(28, 63)	43(28, 65)	39(25, 59)	39(32, 66)	40.50(28, 58)

Table 1. Patient characteristics of postthrombolytic ICH by ICH subtypes. (cont.)

Characteristic	All patients (n=345)	Non-ICH (n=264)	Type of intracerebral hemorrhage		
			HI (n=38)	PH-1 (n=17)	PH-2 (n=26)
Time of the onset of thrombolysis, min	141.99±57.16	141.01±56.63	134.23±51.42	153±56.52	156.11±69.74
ASPECTS					
Baseline ASPECTS	8.84±1.55	9.21±1.30	8.00±1.69	8.00±1.70	6.96±1.58

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; Cr, creatinine; DBP; diastolic blood pressure; HI, hemorrhagic infarction; Hb, hemoglobin; Hct, hematocrit; ICH, intracerebral hemorrhage; INR, international normalized ratio; mRS, modified Rankin Scale; NLR, neutrophil to lymphocyte ratio; NIHSS, National Institute of Health Stroke Scale; PH, parenchymal hemorrhage; RRT, renal replacement therapy; rt-PA, recombinant tissue plasminogen activator; SBP; systolic blood pressure; TOAST classification, the trial of ORG 10172 in acute stroke treatment; WBC, white blood cell count.

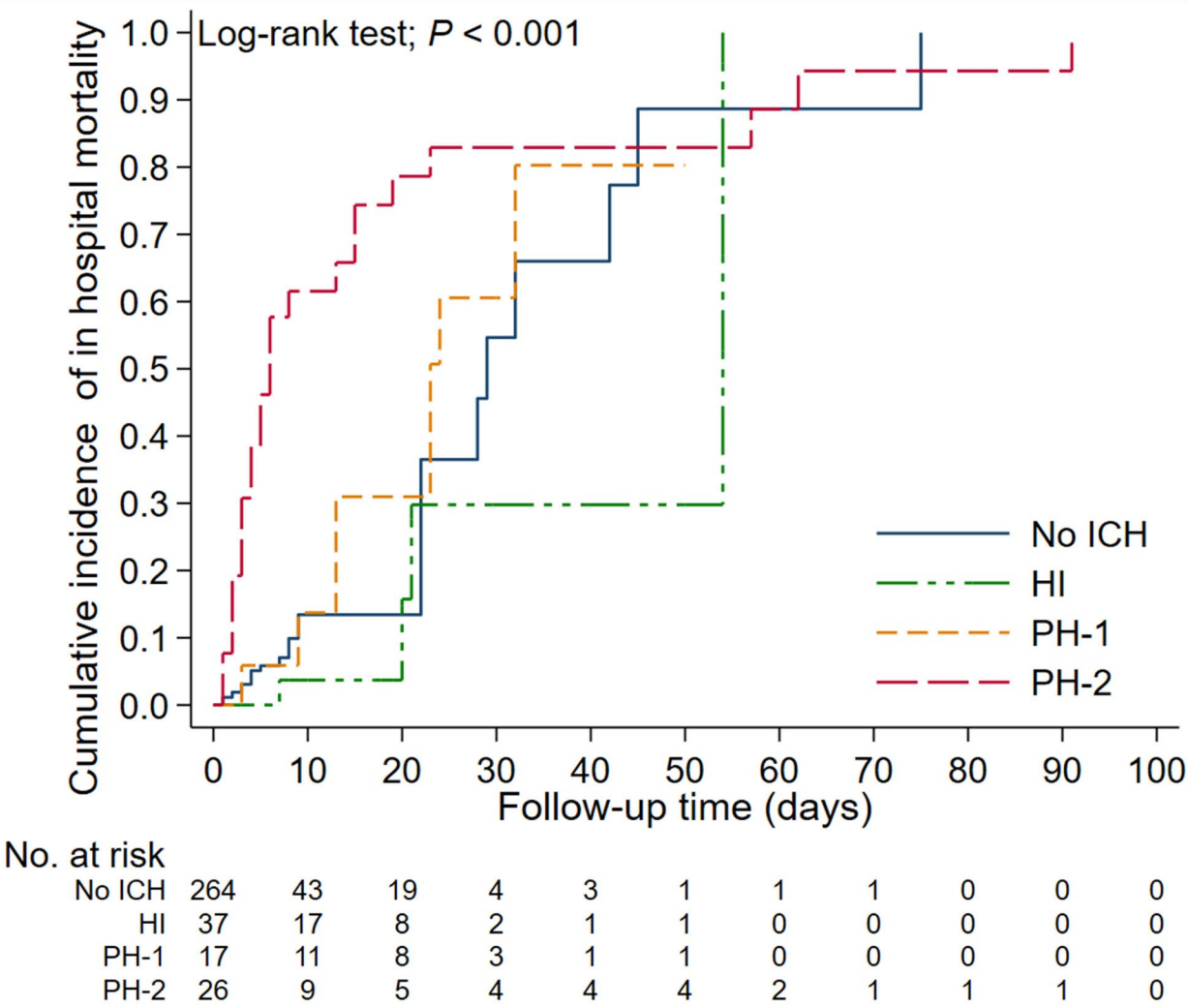

Figure 2. Kaplan-Meier estimates the cumulative incidence of IHM according to ICH subtypes and non-ICH groups.

which indicated that PH-2 strongly correlated with IHM and hematoma evacuation. Furthermore, a significant association was noted between PH-1 and stroke complications including SAP, prolonged hospitalization, IMV requirement and septicemia. This consistency with related research underscores the need for intensive care for patients with ICH, who are prone to complications, particularly pneumonia. Prolonged hospital stays are associated with hospital-acquired pneumonia (HAP) and functional decline, especially among the elderly, with HAP in the ICU carrying an approximate 20% mortality rate.[25, 26] Ventilated patients, managed for respiratory failure or to control increasing intracranial pressure, face an increased risk of airway bacterial colonization and subsequent lung infection. This risk arises from microbial colonization in the lower respiratory tract, continuous micro-aspiration and compromised lung defense mechanisms. Consequently, pneumonia is strongly linked to the duration of mechanical ventilation and hospital stays. The need for tracheostomy among patients requiring prolonged IMV significantly elevates the risk of ventilator-associated pneumonia. Bacterial colonization during the tracheostomy procedure serves as a reservoir for lower airway colonization, further heightening the risk of pneumonia and subsequent septicemia among patients with ICH. [27]

HI has been acknowledged as a successful recanalization sign and predicted favorable functional outcomes among patents with AIS

Table 2. Risk ratio of IHM, SAP, LOS ≥14 days, IMV requirement, hematoma evacuation and septicemia with any ICH after thrombolytic treatment among patients with acute ischemic stroke compared with that of patients of non-ICH.

	IHM (n=65) RR (95%CI)	SAP (n=70) RR (95%CI)	LOS ≥14 days (n=54) RR (95%CI)	IMV requirement (n=67) RR (95%CI)	Hematoma evacuation (n=15) RR (95%CI)	Septicemia (n=24) RR (95%CI)
HI						
Unadjusted analysis	1.24 (0.48-3.21)	2.61 (1.34-5.06)	3.21 (1.62-6.35)	2.89 (1.38-6.05)	2.32 (0.48- 11.09)	2.78 (0.87-8.86)
Adjusted analysis	0.68 (0.25-1.83)	1.77 (0.86-3.65)	3.30 (1.53-7.12)	1.88 (0.84-4.19)	1.46 (0.24-8.81)	2.09 (0.59-7.42)
PH-1						
Unadjusted analysis	4.44 (2.02-9.73)	4.85 (2.39-9.87)	4.78 (2.16-10.55)	5.82 (2.71-12.53)	2.59 (0.33-20.36)	6.21 (1.95-19.81)
Adjusted analysis	2.14 (0.87-5.27)	2.58 (1.14-5.87)	4.63 (1.88-11.38)	3.70 (1.55-8.80)	1.38 (0.13-14.75)	4.40 (1.13-17.16)
PH-2						
Unadjusted analysis	8.70 (5.05-15.01)	5.08 (2.79-9.25)	3.12 (1.41-6.90)	10.15 (5.77-17.88)	10.15 (3.52-29.28)	6.09 (2.21-16.76)
Adjusted analysis	2.83 (1.56-5.13)	2.01 (1.04-3.88)	1.98 (0.83-4.70)	3.93 (2.09-7.39)	4.58 (1.17-17.95)	2.72 (0.90-8.22)
Any ICH						
Unadjusted analysis	4.31 (2.64-7.04)	3.87 (2.42-6.19)	3.51 (2.06-5.99)	5.84 (3.54-9.62)	4.89 (1.74-13.74)	4.56 (2.03-10.27)
Adjusted analysis	1.94 (1.11-3.38)	2.02 (1.17-3.49)	2.97 (1.59-5.54)	3.14 (1.77-5.57)	2.66 (0.78-9.09)	2.71 (1.05-6.98)

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; RR, risk ratio; CHF, congestive heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; HI, hemorrhagic infarction; IHM, in-hospital mortality ICH, intracerebral hemorrhage; IMV, invasive mechanical ventilator; LOS, length of stay; MI, myocardial infarction; NIHSS, National Institute of Health Stroke Scale; PH, parenchymal hemorrhage; SAP, stroke associated pneumonia; TOAST classification, the trial of ORG 10172 in acute stroke treatment.Variables adjusted for are as follows: age, sex, TOAST classification, NIHSS, baseline ASPECTS ≤7, DM, CKD, MI, CHF, and history of malignancy.

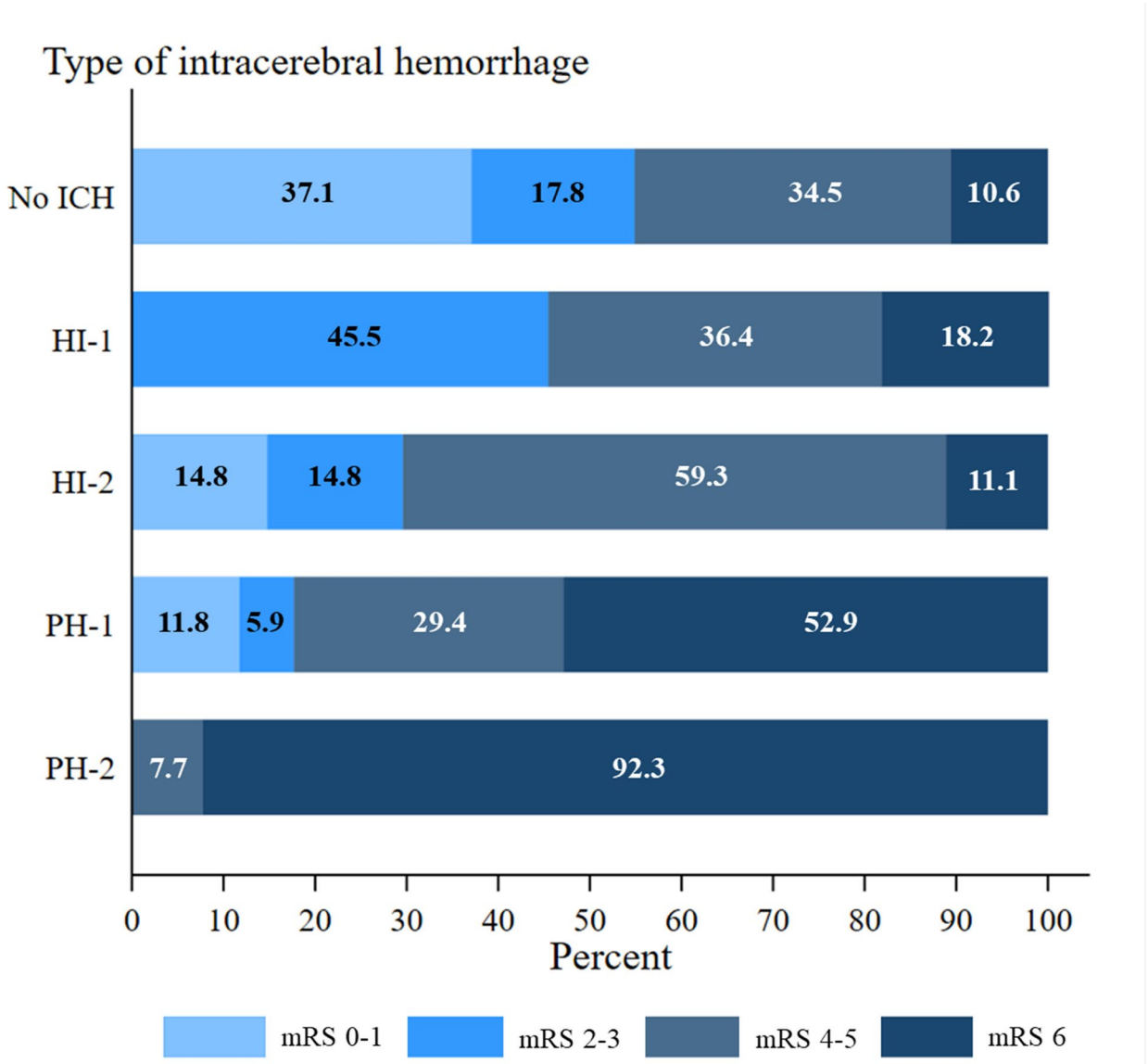

Figure 3. Functional outcomes of patients with different ICH subtypes of postthrombolytic ICH using the mRS at the time of hospital discharge.

receiving thrombolytic therapy.[14, 15, 28] Conversely, our analysis revealed that HI significantly prolonged hospitalization. Although HI showed a non-significant increase in the risk of SAP and IMV requirement compared with that of patients of non-ICH, a trend indicated elevated risk, according to our data. This result might have negatively impacted long term outcomes. The relationship between HI and SAP could be attributed to the significantly higher prevalence of swallowing dysfunction among patients with HI compared with that of patients of non-ICH (60.53% vs. 27.65%, p<0.001). Swallowing dysfunction significantly raises the risk of aspiration pneumonia, particularly among patients with ICH. It occurs when respiratory pathogens colonize the oropharynx, leading to the inhalation of infectious particles. The bedside swallow screen is vital for early dysphagia identification among patients with ICH.[29] It enables effective early-stage swallowing rehabilitation including aspiration monitoring, modifying dietary consistency or texture, oral hygiene and appropriate posture for swallowing to reduce aspiration.

Notably, the prior use of antiplatelets, antihypertensive treatment before rt-PA and a WBC count at admission ≥11,750 cells/mm^3 were ex-

Table 3. Serious complications among patients with acute ischemic stroke after thrombolytic treatment, categorized by ICH subtypes.

Serious complications	All patients (n=345)	ICH subtypes					*p*-value
		Non-ICH (n =264)	HI-1 (n=11)	HI-2 (n=27)	PH-1 (n=17)	PH-2 (n=26)	
In-hospital mortality	65(18.84%)	28(10.61)	2 (18.18)	3 (11.11)	8 (47.06)	24(92.31)	<0.001
Stroke associated pneumonia	70 (20.29)	32 (12.12)	4 (36.36)	8 (29.63)	10 (58.82)	16 (61.54)	<0.001
LOS≥14 days	54 (15.65)	26 (9.85)	4 (36.36)	8 (29.63)	8 (47.06)	8 (30.77)	<0.001
IMV requirement	67 (19.42)	24 (9.09)	3 (27.27)	7 (25.93)	9 (52.94)	24 (92.31)	<0.001
Hematoma evacuation	15 (4.35)	6 (2.27)	0 (0)	2 (7.41)	1 (5.88)	6 (23.08)	0.001
Septicemia	24 (6.96)	10 (3.79)	1 (9.09)	3 (11.11)	4 (23.53)	6 (23.08)	<0.001

Abbreviations: HI, hemorrhagic infarction; ICH, intracerebral hemorrhage; LOS, length of stay; PH, parenchymal hemorrhage

Table 4. Multivariable analysis of predictive factors for PH, HI and any ICH after thrombolytic treatment.

Predictors	PH (PH-1 and PH-2) (n=43)	95% CI	HI (HI-1 and HI-2) (n=38)	95% CI	Any ICH (n=81)	95% CI
	OR* (*p*-value)		OR* (*p*-value)		OR† (*p*-value)	
Alcohol consumption	#	#	0.41 (0.026)	0.18-0.90	0.67 (0.241)	0.35-1.30
Prior use of antiplatelet drugs	3.06 (0.016)	1.23-7.57	#	#	2.08 (0.046)	1.01-4.28
Atrial fibrillation	1.65 (0.248)	0.71-3.88	#	#	1.44 (0.288)	0.73-2.84
mRS score for pre-stroke functional status ≥1	2.27 (0.194)	0.66-7.78	#	#	1.39 (0.534)	0.49-3.94
Time to rt-PA						
< 3 hours	Reference	-	Reference	-	#	#
3-4.5 hours	1.00 (0.236)	0.35-2.89	#	#	#	#
DBP ≥110 mmHg	1.69 (0.994)	0.71-4.03	#	#	0.79 (0.574)	0.34-1.82
NIHSS at admission ≥16	1.88 (0.177)	0.75-4.68	0.92 (0.840)	0.40-2.12	1.15 (0.696)	0.57-2.34
Antihypertensive treatment before rt-PA	6.95 (<0.001)	2.62-18.45	#	#	6.55 (<0.001)	3.22-13.36
Admission WBC count ≥11750 cells/mm^3	6.01 (0.001)	2.17-16.65	#	#	2.84 (0.020)	1.18-6.83
Admission blood glucose ≥120 mg/dL	1.51 (0.332)	0.66-3.48	1.83 (0.104)	0.88-3.80	1.55 (0.167)	0.83-2.89
Baseline ASPECTS ≤7	5.01 (0.001)	2.00-12.60	6.44 (<0.001)	2.69-15.43	5.71 (<0.001)	2.69-12.11

* Odds ratio from multinomial logistic regression

† Odds ratio from binary logistic regression

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; DBP; diastolic blood pressure; OR, odds ratios; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PH, parenchymal hemorrhage; rt-PA, recombinant tissue plasminogen activator; TOAST classification, trial of ORG 10172 in acute stroke treatment; WBC, white blood cell count.

not included; † multinomial logistic regression; ‡ multivariable logistic regression.

clusively observed in the PH subgroup, not in the HI group. This finding supports a related study indicating that a higher total WBC count is associated with a larger baseline hematoma volume and intraventricular growth among patients with ICH.[30] Hematoma enlargement occurs due to an augmented systemic inflammatory response, disrupting the blood-brain barrier and facilitating molecular exchange.[31] The inflammatory response occurred 4 to 6 hours after onset, starting with leukocytic infiltration. Cytokines such as interferon-γ, interleukin-6 and tumor necrosis factor-α affected cellular integrity, and blood-brain barrier breakdown was often associated with responses to acute cerebral insults, including ICH.[32] Moreover, new-onset hypertension was associated with an inflammatory response and poor neurological outcomes.[23] According to our study, an ASPECTS ≤7 was associated with PH. These results were consistent with numerous studies demonstrating the association between early ischemic changes (EICs) on NCCT and the risk of ICH after thrombolysis.[8, 33, 34] Ischemic change in NCCT is a key predictor of sICH, particularly in cases with a larger infarct core undergoing thrombolytic therapy. However, its sensitivity and specificity are constrained. Evaluating blood-brain barrier damage, measured through permeability using computed tomography and magnetic resonance perfusion imaging, can directly serve as a tool to predict ICH following thrombolysis.[35]

Related studies have found that heavy alcohol consumption (≥5 drinks/day) was linked to an increased ICH risk, while rare (<1 drink/month) and moderate alcohol intake (≥1 drink/month and ≤2 drinks/day) were associated with a decreased risk of ICH. The protective effect is hypothesized to be associated with increased HDL concentration from rare and moderate alcohol consumption, contributing to vascular integrity maintenance, although the mechanism remains unclear.[36] In our study, as we only collected information on the history of binary information on alcohol consumption due to the retrospective observational nature of this study, we lacked sufficient detailed data regarding the level of alcohol consumption (quantity of drinks daily). Therefore, our multivariable analysis revealed that alcohol was a protective factor against HI (adjusted OR 0.41; 95% CI, 0.18 to 0.90), a finding that should be considered cautiously.

Our study's primary strength lies in its emphasis on examining the correlation between ECASS II ICH subtypes and comprehensive clinical outcomes. To the best of our knowledge, this study constitutes the first to shed light on the comprehensive exploration of the relationship between ICH subtypes and various stroke complications. However, this study also encountered several limitations. First, our results may need to be more generalizable because this study, limited to a single-center setting, requires additional research to validate its results. Second, as our study focused on the short term consequences, the information on long term outcomes still needs to be evaluated. Third, magnetic resonance imaging with diffusion-weighted imaging (DWI) is highly sensitive for EICs, but due to its cost and limited availability, we used NCCT-based ASPECTS instead. However, when evaluating EICs among patients with early symptoms of disability within six hours of onset, the differences between NCCT and DWI in visualizing EICs were minimal.[29] Lastly, the impact of alcohol consumption on ICH risk was assessed based on the number of drinks.[36] Despite the unavailability of detailed data on exact amounts from a retrospective review of electronic medical records, we collected alcohol consumption data in binary information. Future research should investigate the correlation between the level of alcohol consumption and the risk of ICH in a prospective observational study in the Thai population, as the need for further investigation remains.

Conclusion

The PH-2 subtype exhibits the highest increase in mortality compared with that of patients of non-ICH. The HI subtype, considered relatively benign with successful early recanalization, showed a significant prolongation of hospitalization compared with that of patients of non-ICH in our exploratory research. Prior use of antiplatelet drugs, antihypertensive treatment before thrombolysis, elevated admission WBC and baseline ASPECTS ≤7 were independent

predictors of PH. Early identification of ICH after thrombolysis is urgently required.

To enhance the comprehensiveness of the research article, we propose augmenting the details within the Funding, Acknowledgments, Competing Interests, Availability of Data and Materials, and Author Contributions sections following the conclusion. The specifics are as follows:

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Competing interests

The authors declare they have no conflicts of interest directly relevant to the content of this article.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

Every author in this study made substantial contributions, thoroughly reviewed, and provided approval for the final manuscript. SK provided the original idea and layout, conducted information gathering and data analysis. Data interpretation was performed by SK, WN, SS, and NA. SK and NA were involved in ASPECTS and ICH classification for NCCT interpretation. The initial version of the paper was authored by SK, WN, and SS. All authors participated in drafting, reviewing, and editing the manuscript.

Supplementary Material

The Supplementary Material for this article can be found online at: https://jseamed.org/index.php/jseamed/article/view/186

Supplementary Table 1: Univariable and multivariable multinomial logistic regression analyses of predictive factors for PH after thrombolytic treatment.

Supplementary Figure 1: Impact of the ICH subtypes on IHM, Note: the IHM percentages pertained to patients with any ICH.

Supplementary Figure 2: Effect of ICH subtypes impact on serious complications (SAP, LOS ≥14 days, IMV requirement, hematoma evacuation and septicemia). Significant differences (p<0.001) were observed in comparisons (chi-squared test) among no ICH, HI-1, HI-2, PH-1 and PH-2 groups.

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