

# Simple Estimates of Symptomatic Intracranial Hemorrhage Risk and Outcome after Intravenous Thrombolysis Using Age and Stroke Severity

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## Dear Sir:

Several models have been developed to predict the risk of symptomatic intracranial hemorrhage (SICH) and functional outcome in patients treated with intravenous tissue plasminogen activator (IV-TPA). Although a more complex model provides more precise estimates, its application to a practice setting requiring emergent decision and swift treatment is limited.<sup>1-10</sup> Among numerous clinical and imaging variables, age and stroke severity are immediately accessible and powerful predictors of SICH risk and functional outcome after IV-TPA treatment. We aimed to provide simple estimates of SICH risk and good functional outcome, based on the patients' age and initial National Institute of Health Stroke Scale (NIHSS) score.

The current study utilized data from the Clinical Research Center for Stroke-5 registry, which is a prospective registry of patients with acute ischemic stroke admitted to 15 academic centers in Korea. The registry was approved by the Institutional Review Boards of all participating centers. Informed consent from individual patients or their legally authorized representatives was waived due to the anonymity of individual patient data and minimal risk to patients. However, the study was additionally approved by the Institutional Review Board of the center where the principal investigator is affiliated.

The current study included patients treated with IV-TPA within 4.5 hours of stroke onset, between April 2008 and March 2015. The exclusion criteria included endovascular therapy added to IV-TPA, a pre-stroke modified Rankin Scale (mRS) score >2, TPA

**Table 1.** Symptomatic intracranial hemorrhage risk according to 20 strata based on age and initial NIHSS score

NIHSS score	Age					Total (n=1,991)
	≤49 (n=201)	50-59 (n=360)	60-69 (n=446)	70-79 (n=655)	≥80 (n=329)	
0-5 (n=637)	0.00 (0.00-4.02) (0/90)	0.64 (0.02-3.52) (1/156)	2.61 (0.72-6.56) (4/153)	2.14 (0.59-5.39) (4/187)	7.84 (2.18-18.88) (4/51)	2.04 (1.09-3.46) (13/637)
6-10 (n=576)	1.67 (0.04-8.94) (1/60)	4.35 (1.43-9.85) (5/115)	0.79 (0.02-4.31) (1/127)	2.04 (0.56-5.14) (4/196)	2.56 (0.31-8.96) (2/78)	2.26 (1.21-3.83) (13/576)
11-15 (n=405)	0.00 (0.00-10.58) (0/33)	3.85 (0.47-13.21) (2/52)	3.37 (0.70-9.54) (3/89)	4.29 (1.59-9.09) (6/140)	5.49 (1.81-12.36) (5/91)	3.95 (2.27-6.34) (16/405)
>15 (n=373)	5.56 (0.14-27.29) (1/18)	0.00 (0.00-9.49) (0/37)	7.79 (2.91-16.19) (6/77)	10.61 (5.92-17.15) (14/132)	6.42 (2.62-12.78) (7/109)	7.51 (5.05-10.67) (28/373)
Total (n=1991)	1.00 (0.12-3.55) (2/201)	2.22 (0.96-4.33) (8/360)	3.14 (1.73-5.21) (14/446)	4.27 (2.86-6.12) (28/655)	5.47 (3.27-8.51) (18/329)	3.52 (2.75-4.42) (70/1991)

Values are presented as % (95% confidence interval) and n/N (n is the number of patients with symptomatic intracranial hemorrhage and N is the patient number included in each cell).

NIHSS, National Institute of Health Stroke Scale.

administration at outside hospitals, and the unavailability of mRS score at discharge. The safety outcome was SICH, which was defined as any hemorrhagic transformation with an NIHSS score worsening  $\geq 4$  points. The efficacy outcome was a good functional outcome, defined by an mRS score of  $\leq 2$  at discharge. The patient age was categorized as  $\leq 49$ , 50-59, 60-69, 70-79, and  $\geq 80$  years, and the initial NIHSS score was categorized as  $\leq 5$ , 6-10, 11-15, and  $> 15$ . Linear regression was used to assess changes in the risk of SICH and proportion of patients achieving a discharge mRS score of  $\leq 2$ , with each increasing level in the age or NIHSS score ordinal categories. Five age categories and four NIHSS score categories yielded 20 different groups, for which we calculated the crude estimates of the SICH risk and the proportion of patients achieving a discharge mRS score of  $\leq 2$ . The exact Clopper-Pearson method for binomial proportions was used to calculate the 95% confidence intervals (CIs) of individual estimates. Using an interaction term, we assessed whether age and NIHSS score affected SICH risk and mRS outcome heterogeneously between men and women.

During the study period, 34,917 patients with acute ischemic stroke were enrolled, and 3,148 patients were treated with IV-TPA alone. After excluding 1,157 patients (i.e., 350 patients with pre-stroke mRS score  $> 2$ , 361 receiving IV-TPA treatment at outside hospitals, 440 treated with IV-TPA beyond 4.5 hours, and 6 with unavailable discharge mRS scores), the final study cohort included 1,991 patients. The mean age was  $67.0 \pm 13.0$  years, 38.6% were female, the median baseline NIHSS was 8 (interquartile range, 5-14), and the median time from onset to IV-TPA treatment was 120 min (interquartile range, 87-168 min). Cardioembolism was the most common subtype (33.3%), followed by large artery atherosclerosis (32.0%), undetermined etiology (22.8%), small vessel occlusion (10.2%), and other determined etiology (1.7%).

For all patients, the crude estimate (95% CI) of the SICH risk

was 3.52% (2.75-4.42%). The SICH risk monotonically increased with increasing age or NIHSS score category levels. On average, the SICH risk increased by 1.1% and 1.8%, with each level increase of the age and NIHSS score categories, respectively. Across 20 strata combining the age and NIHSS categories, the SICH risk substantially varied, ranging between 0% and 10.6% (Table 1). The SICH risk did not differ between men and women (3.03% [2.14-4.15%] versus 4.29% [2.97-5.97%], respectively; unadjusted  $P=0.136$ ), and there were no interaction between sex and age (interaction  $P=0.875$ ) or sex and NIHSS score (interaction  $P=0.537$ ) for the SICH risk.

For all patients, the crude estimate of a discharge mRS  $\leq 2$  outcome was 52.4% (50.2-54.7%). The proportion achieving the mRS  $\leq 2$  outcome monotonically decreased with increasing levels of the age or NIHSS score ordinal categories; on average, the proportion decreased by 8.3% and 18.5% with each level increase on the age and NIHSS score categories, respectively. Across 20 strata, the proportion of patients with a discharge mRS score of  $\leq 2$  substantially varied, ranging between 12.8% and 81.1% (Table 2). More men than women were likely to achieve the mRS  $\leq 2$  outcome (57.5% [54.7-60.3%] versus 44.3% [40.8-47.9%]; unadjusted  $P<0.001$ ). The effect of the NIHSS score on the mRS  $\leq 2$  outcome was not heterogeneous between men and women (interaction  $P=0.836$ ). However, the effect of age on the mRS  $\leq 2$  outcome differed between men and women (interaction  $P=0.004$ ); the effect was more consistent among men than among women.

The current study has some limitations. Our results were based on a Korean patient cohort treated in stroke centers experienced in thrombolysis and ensuring organized stroke care, which limits the generalizability of our findings. Overall, the SICH risk monotonically increased with increasing age and increasing stroke severity. However, when patients were further stratified by age and

**Table 2.** Proportion of patients achieving mRS 0–2 at discharge according to 20 strata based on age and initial NIHSS score

NIHSS score	Age					Total (n=1991)
	≤49 (n=201)	50–59 (n=360)	60–69 (n=446)	70–79 (n=655)	≥80 (n=329)	
0–5 (n=637)	81.1 (71.5–88.6) (73/90)	73.1 (65.4–79.9) (114/156)	79.7 (72.5–85.8) (122/153)	73.8 (66.9–79.9) (138/187)	64.7 (50.1–77.6) (33/51)	75.4 (71.8–78.7) (480/637)
6–10 (n=576)	66.7 (53.3–78.3) (40/60)	63.5 (54.0–72.3) (73/115)	60.6 (51.6–69.2) (77/127)	53.6 (46.3–60.7) (105/196)	55.1 (43.4–66.4) (43/78)	58.7 (54.5–62.7) (338/576)
11–15 (n=405)	57.6 (39.2–74.5) (19/33)	51.9 (37.6–66.0) (27/52)	42.7 (32.3–53.6) (38/89)	27.9 (20.6–36.1) (39/140)	26.4 (17.7–36.7) (24/91)	36.3 (31.6–41.2) (147/405)
>15 (n=373)	38.9 (17.3–64.3) (7/18)	21.6 (9.8–38.2) (8/37)	24.7 (15.6–35.8) (19/77)	23.5 (16.6–31.7) (31/132)	12.8 (7.2–20.6) (14/109)	21.2 (17.1–25.7) (79/373)
Total (n=1991)	69.2 (62.3–75.5) (139/201)	61.7 (56.4–66.7) (222/360)	57.4 (52.7–62.0) (256/446)	47.8 (43.9–51.7) (313/655)	34.7 (29.5–40.1) (114/329)	52.4 (50.2–54.7) (1044/1991)

Values are presented as % (95% confidence interval) and n/N (n is the number of patients achieving mRS 0–2 at discharge and N is the patient number included in each cell).

mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.

NIHSS categories, the relatively small sample in each cell resulted in a less uniform trend. In addition, the small sample size of several strata resulted in wide confidence intervals, jeopardizing the precision of estimates. Thus, we could not provide the estimates for men and women separately, but merely explored the sex effect statistically. Finally, our findings are applicable to patients treated with IV-TPA alone, but not applicable to those receiving additional endovascular therapy or endovascular therapy alone.

The risks and benefits of IV-TPA varied substantially according to the patients' age and stroke severity. Our simplified age-based and stroke severity-based estimates, which are summarized in Tables 1 and 2, and immediately accessible online or offline, would help clinicians discuss the individualized expected risks and benefits with patients and their family to make a well-informed, expedited decision in an emergent setting.

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