J Korean Med Sci. 2025 Apr 7;40(13):e49
https://doi.org/10.3346/jkms.2025.40.e49
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Neuroscience

Association of Age, Sex and Education With Access to the Intravenous Thrombolysis for Acute Ischemic Stroke

Yoona Ko,[1] **Beom Joon Kim**,[2] **Youngran Kim**,[3] **Jong-Moo Park**,[4] **Kyusik Kang**,[5] **Jae Guk Kim**,[6] **Jae-Kwan Cha**,[7] **Tai Hwan Park**,[8] **Kyungbok Lee**,[9] **Jun Lee**,[10] **Keun-Sik Hong**,[11] **Byung-Chul Lee**,[12] **Kyung-Ho Yu**,[12] **Dong-Eog Kim**,[13] **Joon-Tae Kim**,[14] **Jay Chol Choi**,[15] **Jee Hyun Kwon**,[16] **Wook-Joo Kim**,[16] **Kyu Sun Yum**,[17] **Sung-Il Sohn**,[18] **Hyungjong Park**,[18] **Sang-Hwa Lee**,[19] **Kwang-Yeol Park**,[20] **Chi Kyung Kim**,[21,22] **Sung Hyuk Heo**,[23] **Moon-Ku Han**,[2,24] **Anjail Z. Sharrief**,[25] **Sunil A. Sheth**,[25] **Hee-Joon Bae**,[2,24] **and on behalf of CRCS-K Investigators**

[1]Department of Neurology, Seoul National University Bundang Hospital, Seongnam, Korea
[2]Department of Neurology and Cerebrovascular Center, Seoul National University Bundang Hospital, Seongnam, Korea
[3]Department of Management, Policy & Community Health, School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX, USA
[4]Department of Neurology, Uijeongbu Eulji Medical Center, Eulji University, Uijenongbu, Korea
[5]Department of Neurology, Nowon Eulji Medical Center, Eulji University School of Medicine, Seoul, Korea
[6]Department of Neurology, Daejeon Eulji Medical Center, Eulji University School of Medicine, Daejeon, Korea
[7]Department of Neurology, Dong-A University Hospital, Busan, Korea
[8]Department of Neurology, Seoul Medical Center, Seoul, Korea
[9]Department of Neurology, Soonchunhyang University Seoul Hospital, Seoul, Korea
[10]Department of Neurology, Yeungnam University Medical Center, Daegu, Korea
[11]Department of Neurology, Inje University Ilsan Paik Hospital, Goyang, Korea
[12]Department of Neurology, Hallym University Sacred Heart Hospital, Anyang, Korea
[13]Department of Neurology, Dongguk University Ilsan Hospital, Goyang, Korea
[14]Department of Neurology, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea
[15]Department of Neurology, Jeju National University Hospital, Jeju, Korea
[16]Department of Neurology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea
[17]Department of Neurology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea
[18]Department of Neurology, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, Korea
[19]Department of Neurology, Hallym University Chuncheon Sacred Heart Hospital, Chuncheon, Korea
[20]Department of Neurology, Chung-Ang University Hospital, Seoul, Korea
[21]Department of Neurology, Korea University College of Medicine, Seoul, Korea
[22]Department of Neurology, Korea University Guro Hospital, Seoul, Korea
[23]Department of Neurology, Kyung Hee University Hospital, Seoul, Korea
[24]Department of Neuroscience, Seoul National University College of Medicine, Seoul, Korea
[25]Department of Neurology, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA

Received: Aug 23, 2024
Accepted: Oct 18, 2024
Published online: Dec 9, 2024

Address for Correspondence:
Beom Joon Kim, MD, PhD
Department of Neurology and Cerebrovascular Center, Seoul National University Bundang Hospital, Office #8710, 82 Gumi-ro 173-beon-gil, Bundang-gu, Seongnam 13620, Republic of Korea.
Email: Kim.BJ.Stroke@gmail.com

ORCID iDs
Yoona Ko
https://orcid.org/0009-0002-7688-495X
Beom Joon Kim
https://orcid.org/0000-0002-2719-3012
Youngran Kim
https://orcid.org/0000-0002-2063-5017
Jong-Moo Park
https://orcid.org/0000-0002-4199-3024
Kyusik Kang
https://orcid.org/0000-0002-4021-4439
Jae Guk Kim
https://orcid.org/0000-0003-1418-0033
Jae-Kwan Cha
https://orcid.org/0000-0002-1049-5196
Tai Hwan Park
https://orcid.org/0000-0002-5148-1663

ABSTRACT

Background: Barriers to treatment with intravenous thrombolysis (IVT) for patients with acute ischemic stroke (AIS) in South Korea remain incompletely characterized. We analyze a nationwide prospective cohort to determine patient-level features associated with delayed presentation and non-treatment of potential IVT-eligible patients.

Kyungbok Lee
https://orcid.org/0000-0003-2663-7483
Jun Lee
https://orcid.org/0000-0001-8643-0797
Keun-Sik Hong
https://orcid.org/0000-0002-4684-6111
Byung-Chul Lee
https://orcid.org/0000-0002-3885-981X
Kyung-Ho Yu
https://orcid.org/0000-0002-8997-5626
Dong-Eog Kim
https://orcid.org/0000-0002-9339-6539
Joon-Tae Kim
https://orcid.org/0000-0003-4028-8339
Jay Chol Choi
https://orcid.org/0000-0002-3550-2196
Jee Hyun Kwon
https://orcid.org/0000-0002-5894-3146
Wook-Joo Kim
https://orcid.org/0000-0001-5290-0623
Kyu Sun Yum
https://orcid.org/0000-0001-9815-7652
Sung-Il Sohn
https://orcid.org/0000-0002-6900-1242
Hyungjong Park
https://orcid.org/0000-0002-6112-2939
Sang-Hwa Lee
https://orcid.org/0000-0002-0609-1551
Kwang-Yeol Park
https://orcid.org/0000-0003-4570-3538
Chi Kyung Kim
https://orcid.org/0000-0002-0423-7297
Sung Hyuk Heo
https://orcid.org/0000-0002-9215-5119
Moon-Ku Han
https://orcid.org/0000-0003-0166-387X
Anjail Z. Sharrief
https://orcid.org/0000-0002-9814-6715
Sunil A. Sheth
https://orcid.org/0000-0003-0602-8509
Hee-Joon Bae
https://orcid.org/0000-0003-0051-1997

Funding

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI22C0454).

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Ko Y, Kim BJ. Data curation: Ko Y, Kim BJ, Kim Y, Park JM, Kang K, Kim JG,

Methods: We identified consecutive patients with AIS from 01/2011 to 08/2023 from a multicenter and prospective acute stroke registry in Korea. Patients were defined as IVT candidates if they presented within 4.5 hours from the last known well, had no lab evidence of coagulopathy, and had National Institute of Health Stroke Scale (NIHSS) ≥ 4. Multivariable generalized linear mixed regression models were used to investigate the associations between their characteristics and the IVT candidates or the use of IVT among the candidates.
Results: Among 84,103 AIS patients, 41.0% were female, with a mean age of 69 ± 13 years and presentation NIHSS of 4 [interquartile range, 1–8]. Out of these patients, 13,757 (16.4%) were eligible for IVT, of whom 8,179 (59.5%) received IVT. Female sex (adjusted risk ratio [RR], 0.90; 95% confidence interval [CI], 0.86–0.94) and lower years of education (adjusted RR, 0.90; 95% CI, 0.84–0.97 for 0–3 years, compared to ≥ 13 years) were associated with a decreased likelihood of presenting as eligible for IVT after AIS; meanwhile, young age (adjusted RR, 1.12; 95% CI, 1.01–1.24 for ≤ 44 years, compared to 75–84 years) was associated with an increased likelihood of being an IVT candidate. Among those who were eligible for IVT, only age was significantly associated with the use of IVT (adjusted RR, 1.09; 95% CI, 1.03–1.16 for age 65–74 and adjusted RR, 0.83; 95% CI, 0.76–0.90 for ≥ 85 years, respectively).
Conclusion: Most patients with AIS present outside IVT eligibility in South Korea, and only 60% of eligible patients were ultimately treated. We identified increased age, female sex and lower education as key features on which to focus interventions for improving IVT utilization.

Keywords: Disparity; Stroke; Intravenous Thrombolysis; South Korea

INTRODUCTION

Ischemic stroke remains a leading cause of disability and mortality worldwide, and South Korea is no exception.[1] The incidence rate of ischemic stroke in South Korea is estimated to be approximately 100,000 annually.[2] Recanalization therapies, including intravenous thrombolysis (IVT) and endovascular recanalization, have been established as fundamental components of the therapeutic strategy for ischemic stroke.[3] Despite its clinical importance, the real-world application of IVT is often suboptimal: 9% in the United States and 11% in South Korea.[4,5] Overall, reasons for the low rate of utilization have been investigated, including patients' delayed presentation to the hospital, geographical propensity of healthcare facilities, limitation of human resources, and insufficient hospital support.[6-9]

The overall process of the acute stroke chain of survival, encompassing the onset of stroke symptoms to the hospital treatment, can be delineated into the initial and secondary phases.[10] The initial phase involves the recognition of stroke symptoms by the patient or a caregiver and the subsequent decision to seek immediate medical attention, understanding the urgency of timely intervention for stroke with the pre-existing knowledge for immediate action. The secondary phase commences upon the patient's arrival at the emergency department, where the hospital's hyperacute stroke protocol is activated, leading to rapid diagnostic imaging to determine eligibility for IVT.[11] At present, the effectiveness and efficacy of this sequential process in South Korea remain incompletely characterized.

To address this issue, we analyzed a nationwide prospective acute ischemic stroke (AIS) registry in Korea. We identified patient characteristics associated with performance metrics in the pre-hospital and hospital settings, namely the proportion of AIS patients who would be IVT candidates, and the proportion of candidate patients treated with IVT. By delineating

Cha JK, Park TH, Lee K, Lee J, Hong KS, Lee BC, Yu KH, Kim DE, Kim JT, Choi JC, Kwon JH, Kim WJ, Yum KS, Sohn SI, Park H, Lee SH, Park KY, Kim CK, Heo SH, Han MK, Bae HJ. Formal analysis: Ko Y, Kim BJ. Methodology: Kim BJ. Supervision: Kim BJ. Visualization: Ko Y. Writing - original draft: Ko Y. Writing - review & editing: Kim BJ, Kim Y, Sharrief AZ, Sheth SA.

factors associated with IVT underutilization, subsequent targeted interventions can be designed.[12]

METHODS

Clinical Research Collaboration for Stroke in Korea (CRCS-K)

This study was conducted based on the CRCS-K registry. The CRCS-K is a prospective, ongoing, nationwide, multicenter registry dedicated to the recruitment of patients with AIS or transient ischemic attack admitted within seven days of symptom onset.[1] Initiated in 2008 within nine centers, the registry has expanded to nineteen by 2023, encompassing a mix of university hospitals and tertiary referral centers across South Korea.[12] The participating centers are tasked with delivering comprehensive stroke care to the region. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study participants

In the CRCS-K registry, ischemic stroke patients were diagnosed and managed by experienced vascular neurologists at participating centers, adhering to the most current guidelines and institutional protocols and at the discretion of attending physicians.[3,13,14] Case registration in the CRCS-K is performed within 48 business hours of admission or ER arrival for acute stroke patients. The information generated during hospitalization is entered within one month of discharge, and data integrity is maintained through repeated audits at three months and one year.

A total of 113,832 case records were registered to the CRCS-K registry between April 2008 and August 2023. We included 97,381 cases whose ischemic lesions were documented on the relevant neuroimaging. We further limited the analysis to 88,645 cases admitted between January 2011 and August 2023, considering the change of database structure made on January 2011. We excluded 4542 cases due to the following reasons: 1) admitted 1 week after onset (n = 3,400), 2) IVT before arrival (n = 1,099), and 3) no information on the time of IVT (n = 43). The included cohort contains 84,103 cases of ischemic stroke patients (**Fig. 1**).

Measurements

We retrieved baseline demographic and clinical information from the CRCS-K registry database for all the study participants, including sex, age, education, pre-stroke functional independence, and stroke characteristics such as initial National Institute of Health Stroke Scale (NIHSS) score, stroke subtype, vascular risk factors, pre-stroke medications, acute stroke treatments, time metrics, and functional recovery. Pre-stroke functional dependence was defined as a modified Rankin Scale (mRS) score of equal or greater than one. The level of education was self-reported by the patients or their next of kin. Functional recovery was ascertained either through routine clinical follow-up or structured telephone interviews conducted by trained study coordinators at participating hospitals. Details of clinical definitions have been published and are referred to elsewhere.[15]

Study outcomes are being considered for the IVT candidates among all study participants and for the receipt of IVT among those identified as IVT candidates. A patient was defined as an IVT candidate if they met the following criteria: AIS patients who 1) arrived within 4.5 hours from the time last known well, 2) had an initial NIHSS score of 4 or higher, and

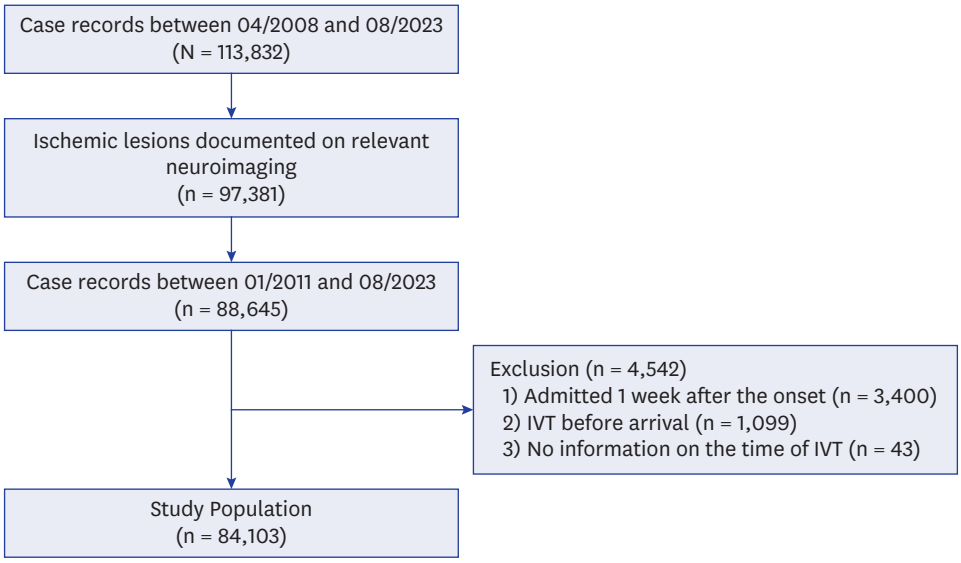

Fig. 1. Flow diagram of study inclusion/exclusion.
IVT = intravenous thrombolysis.

3) a prothrombin time – international normalization ratio at arrival of less than 1.7. Additional contraindications for IVT were not included due to the paucity of information.

Statistical analysis

Baseline clinical characteristics of included patients were summarized as frequencies (percentages), mean ± standard deviations, or medians [interquartile ranges; IQRs] and were compared by treatment of IVT using a χ^2 test for categorical variables and *t*-test or a one-way ANOVA for continuous variables, as appropriate. The associations between study outcomes and potential predictors were evaluated using multivariable generalized linear mixed models, taking the year of admission and treating centers as random variables and the following variables as fixed terms: age, sex, education, pre-stroke functional independency, baseline NIHSS, hypertension, diabetes, dyslipidemia, atrial fibrillation, smoking, pre-stroke antiplatelet use, and pre-stroke anticoagulant use. Last known well (LKW) to arrival time was only included in a multivariable model for IVT use among the IVT candidates because of its strong correlation with the use of IVT in the general ischemic stroke cohort.

All data analyses were conducted using R version 4.3.2 (R Core Team, 2023; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at two-tailed *P* values < 0.05.

Ethics statement

The Institutional Review Board (IRB) of the Seoul National University Bundang Hospital and participating centers approved acquisition, analysis and publication of this study (B-1710-429-102; B-2307-841-303). Informed consent from patients or their next of kin was obtained for the prospective stroke registry under the approval of the IRB from participating centers (IRB #B-1706-403-303). The ethics committee approved the secondary use of the registry data with a waiver for additional informed consent, considering the anonymity of the dataset and minimal risk to the participants (IRB #B-2401-877-001). The dataset supporting the conclusions of this article is available upon reasonable request to the corresponding author,

pending ethical committee approval. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies.

RESULTS

Study population

A total of 84,103 patients with AIS admitted between January 2011 and August 2023 were included in the study. The population was predominantly male (59.0%) with a mean age of 69 ± 13 years. The initial median NIHSS was 4 [IQR, 1–8], and the median LKW to arrival time was 13 [IQR, 3–34] hours. Pre-stroke functional dependency was reported in 21% of the cohort. The 13,757 (16.4%) patients were deemed eligible for IVT, and 8,179 (59.5%) of the IVT candidates were treated with IVT. The total number of IVT cases from the cohort was 9,670 (11.5%). Those who had IVT out of the supposed candidacy presented with minor neurological deficits. Endovascular recanalization treatment was performed in 7,589 (9.0%) patients. Overall, 37,599 (46.0%) showed an mRS score of 0–1 at 3 months after stroke and 5,749 (7.0%) patients were deceased at 3 months (missing mRS score in 2,347 cases). AIS patients who had IVT were predominantly male, lower age at onset, with higher pre-stroke functional independence, and had arrived earlier (**Table 1**).

Presenting as IVT candidate and IVT use among the candidate showed stability over the years (**Supplementary Table 1**) but showed variability across centers (**Supplementary Table 2**).

IVT candidate: metric of the pre-hospital stage

Among 84,103 patients with AIS, 13,757 (16.4%) patients were deemed eligible for IVT. Patients eligible for IVT were generally older, predominantly male, and had lower levels of education compared to their ineligible counterparts. Additionally, this group exhibited higher initial NIHSS and a greater prevalence of vascular risk factors (**Table 2**). Despite yearly fluctuations in the proportion of patients meeting the definition of IVT candidate, the overall trend remained stable, ranging from 14% to 18% of all ischemic stroke patients (**Supplementary Table 1**). Variations in the IVT candidates across participating hospitals were not noticeable, varying from 12% to 19% (**Supplementary Table 2**).

Multivariable models adjusting for baseline characteristics showed that age, sex, and education level were significantly associated with an increased likelihood of presenting to the hospital as an IVT candidate (**Table 2**). The likelihood of presenting as IVT candidates increased in the group of ≤ 44 years by 12%, 45–64 years by 11%, and 65–74 years by 8%, compared to the 75–84 years group. This younger cohort tended to present with lower baseline NIHSS than their older counterparts (**Supplementary Table 3**).

Patients with lower years of education were at a decreased risk of being an IVT candidate compared to those with more than 13 years of education. Specifically, the likelihood of presenting as IVT candidates decreased in the group of ischemic stroke patients with 0–3 years by 10%, 4–6 years by 8%, 7–9 years by 7%, and 10–12 years by 7%, compared to the group of more than 13 years of education. Lower educational levels were correlated with delayed presentation after onset; the median of the LKW to arrival was 13.5 hours in 0–3 years compared to a median of 11.2 hours in the ≥ 13 years group (**Supplementary Table 4**).

https://doi.org/10.3346/jkms.2025.40.e49

Table 1. Baseline characteristics of included patients

Characteristics	All cohort (N = 84,103)	No IVT (n = 74,433)	IVT (n = 9,670)	*P* value
Demographic information				
Age, yr	69 ± 13	69 ± 13	68 ± 13	< 0.001
Female sex	34,479 (41.0)	30,753 (41.3)	3,726 (38.5)	< 0.001
Year of education				< 0.001
0–3	11,395 (13.5)	10,274 (13.8)	1,121 (11.6)	
4–6	16,819 (20.0)	14,896 (20.0)	1,923 (19.9)	
7–9	12,490 (14.9)	11,032 (14.8)	1,458 (15.1)	
10–12	22,663 (26.9)	19,950 (26.8)	2,713 (28.1)	
≥ 13	14,087 (16.7)	12,349 (16.6)	1,738 (18.0)	
No information	6,649 (7.9)	5,932 (8.0)	717 (7.4)	
Pre-stroke functional dependence	17,897 (21.3)	16,483 (22.1)	1,414 (14.6)	< 0.001
Acute stroke information				
NIHSS score at presentation	4 [1–8]	3 [1–7]	9 [5–15]	< 0.001
LKW to arrival, hr	13 [3–34]	15 [6–41]	1.3 [0.7–2.4]	< 0.001
Intravenous thrombolysis	9,670 (11.5)	-	9,670 (100.0)	
Endovascular recanalization	7,589 (9.0)	4,388 (5.9)	3,201 (33.1)	< 0.001
Stroke subtype				
LAA	29,686 (35.3)	26,970 (36.2)	2,716 (28.1)	< 0.001
SVO	15,198 (18.1)	14,344 (19.3)	854 (8.8)	< 0.001
CE	17,968 (21.4)	14,346 (19.3)	3,622 (37.5)	< 0.001
ODE	2,963 (3.5)	2,723 (3.7)	240 (2.5)	< 0.001
UDE	18,288 (21.7)	16,050 (21.6)	2,238 (23.1)	< 0.001
Vascular risk factors and pre-stroke management				
Hypertension	56,317 (67.0)	50,143 (67.4)	6,174 (63.8)	< 0.001
Diabetes	28,235 (33.6)	25,559 (34.3)	2,676 (27.7)	< 0.001
Dyslipidemia	26,615 (31.6)	23,854 (32.0)	2,761 (28.6)	< 0.001
Atrial fibrillation	17,875 (21.3)	14,398 (19.3)	3,477 (36.0)	< 0.001
Smoking	29,508 (35.1)	25,988 (34.9)	3,520 (36.4)	0.004
Pre-stroke antiplatelet use	23,906 (28.4)	21,286 (28.6)	2,620 (27.1)	0.002
Pre-stroke anticoagulants use	5,633 (6.7)	5,140 (6.9)	493 (5.1)	< 0.001
Functional recovery after stroke				
mRS score at 3 mon[a]				< 0.001
0	18,024 (22.0)	16,336 (22.6)	1,688 (17.9)	
1	19,575 (23.9)	17,650 (24.4)	1,925 (20.5)	
2	12,992 (15.9)	11,485 (15.9)	1,507 (16.0)	
3	10,613 (13.0)	9,345 (12.9)	1,268 (13.5)	
4	8,964 (11.0)	7,724 (10.7)	1,240 (13.2)	
5	5,839 (7.1)	4,987 (6.9)	852 (9.1)	
6	5,749 (7.0)	4,818 (6.7)	931 (9.9)	

Values are presented as mean ± standard deviation, median [interquartile range], or number (%).
IVT = intravenous thrombolysis, NIHSS = National Institute of Health Stroke Scale, LKW = last known well, LAA = large artery atherosclerosis, SVO = small vessel occlusion, CE = cardioembolism, ODE = other determined etiologies, UDE = undetermined etiologies, mRS = modified Rankin Scale.
[a]mRS score at 3 months is available in 81,756 (97.2%) cases.

IVT use among the candidates: metric of the hospital stage

Among the 13,757 AIS patients identified as IVT candidates, 8,179 (59.5%) received IVT. Relative to those who fulfilled the definition for IVT candidates but did not have IVT, IVT recipients were generally younger, more often male, had higher levels of education, and had functional independence before the index stroke. While the baseline NIHSS was comparable between the two groups, the interval from the LKW to arrival was significantly reduced in those who had IVT treatment (**Table 3**). Variability was observed in the actual administration of IVT among the candidates, ranging from 48% to 75% across different hospitals (**Supplementary Table 2**).

There were no noticeably associated factors with the actual utilization of IVT except 65–74-year-old group (adjusted risk ratio [RR], 1.09; 95% CI, 1.03–1.16 compared to the

https://doi.org/10.3346/jkms.2025.40.e49

Table 2. Patients' characteristics associated with the probability of being an IVT candidate

Characteristics	IVT candidates		*P* value	Bivariate analyses	Multivariate analyses
	No (n = 70,346)	Yes (n = 13,757)		Crude RR (95% CI)	Adjusted RR (95% CI)
Age, yr	69 ± 13	71 ± 13	< 0.001	1.009 (1.008–1.011)	
Age group, yr			< 0.001		
≤ 44	3,055 (4.3)	494 (3.6)		0.79 (0.72–0.87)	1.12 (1.01–1.24)
45–64	21,200 (30.1)	3,516 (25.6)		0.81 (0.77–0.84)	1.11 (1.05–1.17)
65–74	18,998 (27.0)	3,584 (26.1)		0.90 (0.86–0.94)	1.08 (1.03–1.13)
75–84	20,834 (29.6)	4,463 (32.4)		Reference	Reference
≥ 85	6,259 (8.9)	1,700 (12.4)		1.21 (1.15–1.28)	1.00 (0.94–1.06)
Female sex	28,609 (40.7)	5,870 (42.7)	< 0.001	1.08 (1.03–1.11)	0.90 (0.86–0.94)
Year of education			< 0.001		
0–3	9,292 (13.2)	2,103 (15.3)		1.22 (1.15–1.30)	0.90 (0.84–0.97)
4–6	13,901 (19.8)	2,918 (21.2)		1.15 (1.09–1.21)	0.92 (0.86–0.98)
7–9	10,492 (14.9)	1,998 (14.5)		1.06 (0.996–1.13)	0.93 (0.88–0.996)
10–12	19,200 (27.3)	3,463 (25.2)		1.01 (0.96–1.07)	0.93 (0.88–0.98)
≥ 13	11,958 (17.0)	2,129 (15.5)		Reference	Reference
No information	5,503 (7.8)	1,146 (8.3)		1.14 (1.06–1.23)	1.11 (1.06–1.16)
Pre-stroke functional dependence	14,710 (20.9)	3,187 (23.2)	< 0.001	1.12 (1.08–1.16)	0.82 (0.78–0.85)
NIHSS score	3 [1–6]	11 [6–16]	< 0.001	1.104 (1.102–1.107)	1.11 (1.102–1.107)
Hypertension	47,262 (67.2)	9,055 (65.8)	0.002	0.95 (0.92–0.98)	0.98 (0.94–1.02)
Diabetes	24,236 (34.5)	3,999 (29.1)	< 0.001	0.81 (0.78–0.84)	0.86 (0.83–0.90)
Dyslipidemia	22,770 (32.4)	3,845 (27.9)	< 0.001	0.84 (0.81–0.87)	0.96 (0.92–1.001)
Atrial fibrillation	12,555 (17.8)	5,320 (38.7)	< 0.001	2.34 (2.26–2.42)	1.39 (1.33–1.44)
Smoking	25,163 (35.8)	4,345 (31.6)	< 0.001	0.85 (0.82–0.89)	0.96 (0.92–1.005)
Pre-stroke antiplatelet use	19,974 (28.4)	3,932 (28.6)	0.662	1.01 (0.97–1.05)	1.05 (1.01–1.09)
Pre-stroke anticoagulants use	4,332 (6.2)	1,301 (9.5)	< 0.001	1.46 (1.37–1.54)	0.91 (0.86–0.97)

Values are presented as mean ± standard deviation, median [interquartile range], or number (%).
IVT = intravenous thrombolysis, RR = risk ratio, CI = confidence interval, NIHSS = National Institute of Health Stroke Scale.

Table 3. Patients' characteristics by actual IVT use among the candidates and multivariable models

Characteristics	IVT use among the candidates		*P* value	Bivariate analyses	Multivariable analyses
	No (n = 5,578)	Yes (n = 8,179)		Crude RR (95% CI)	Adjusted RR (95% CI)
Age, yr	73 ± 13	69 ± 13	< 0.001	0.990 (0.989–0.992)	
Age group, yr			< 0.001		
≤ 44	152 (2.7)	342 (4.2)		1.29 (1.15–1.44)	1.01 (0.90–1.15)
45–64	1,131 (20.3)	2,385 (29.2)		1.26 (1.19–1.34)	1.06 (0.99–1.13)
65–74	1,258 (22.6)	2,326 (28.4)		1.21 (1.14–1.28)	1.09 (1.03–1.16)
75–84	2,063 (37.0)	2,400 (29.3)		Reference	Reference
≥ 85	974 (17.5)	726 (8.9)		0.79 (0.73–0.86)	0.83 (0.76–0.90)
Female sex	2,671 (47.9)	3,199 (39.1)	< 0.001	0.86 (0.83–0.90)	1.00 (0.94–1.05)
Year of education			< 0.001		
0–3	1,103 (19.8)	1,000 (12.2)		0.71 (0.66–0.77)	0.92 (0.83–1.01)
4–6	1,259 (22.6)	1,659 (20.3)		0.85 (0.79–0.91)	0.98 (0.91–1.06)
7–9	778 (13.9)	1,220 (14.9)		0.91 (0.85–0.99)	0.98 (0.90–1.06)
10–12	1,229 (22.0)	2,234 (27.3)		0.96 (0.90–1.03)	0.99 (0.92–1.06)
≥ 13	704 (12.6)	1,425 (17.4)		Reference	Reference
No information	505 (9.1)	641 (7.8)		0.84 (0.76–0.92)	0.93 (0.84–1.03)
Pre-stroke functional dependence	1,935 (34.7)	1,252 (15.3)	< 0.001	0.60 (0.56–0.64)	0.69 (0.65–0.74)
NIHSS score	10 [6–16]	11 [6–16]	0.148	0.998 (0.995–1.002)	1.00 (0.997–1.01)
LKW to arrival, hr	2.0 [1.0–3.4]	1.2 [0.7–2.2]	< 0.001	0.81 (0.79–0.83)	0.82 (0.81–0.84)
Hypertension	3,831 (68.7)	5,224 (63.9)	< 0.001	0.92 (0.88–0.96)	0.99 (0.95–1.04)
Diabetes	1,753 (31.4)	2,246 (27.5)	< 0.001	0.92 (0.80–0.97)	0.98 (0.93–1.03)
Dyslipidemia	1,536 (27.5)	2,309 (28.2)	0.384	1.01 (0.97–1.06)	1.01 (0.96–1.06)
Atrial fibrillation	2,264 (40.6)	3,056 (37.4)	< 0.001	0.95 (0.91–0.99)	1.08 (1.02–1.13)
Smoking	1,436 (25.7)	2,909 (35.6)	< 0.001	1.20 (1.14–1.25)	1.06 (1.01–1.12)
Pre-stroke antiplatelet use	1,698 (30.4)	2,234 (27.3)	< 0.001	0.94 (0.89–0.99)	0.95 (0.90–0.995)
Pre-stroke anticoagulants use	891 (16.0)	410 (5.0)	< 0.001	0.51 (0.46–0.56)	0.51 (0.46–0.57)

Values are presented as mean ± standard deviation, median [interquartile range], or number (%).
IVT = intravenous thrombolysis, RR = risk ratio, CI = confidence interval, NIHSS = National Institute of Health Stroke Scale, LKW = last known well.

https://doi.org/10.3346/jkms.2025.40.e49

75–84-year group). Female sex and year of education were not associated with the actual use of IVT. Additionally, prior use of antiplatelet agents (adjusted RR, 0.95; 95% CI, 0.90–0.995) and pre-stroke anticoagulants use (adjusted RR, 0.51; 95% CI, 0.46–0.57) were associated with decreased likelihood of IVT.

DISCUSSION

Our study analyzed case records of 84,103 patients with AIS from a nationwide registry to identify factors associated with the use of IVT. We found that female sex and lower years of education were associated with decreased likelihood of presenting as IVT candidates. However, among those deemed eligible for IVT, the likelihood of actual IVT was associated mostly with their functional status, prior use of medication and earlier arrival rather than their social or demographic background. Although age and educational attainment were both correlated, each independently associated with the likelihood of being an IVT candidate.

The stroke chain of survival outlines key steps from recognizing symptoms to administering treatment, highlighting the importance of quick identification of stroke symptoms, rapid emergency responses, and swift transport to fully equipped hospitals for recanalization and subsequent in-hospital care.[10] This model encourages collaboration among the public, emergency services, and healthcare professionals to improve patient outcomes, including their chances of having recanalization treatments and achieving functional recovery. In evaluating the model's overall performance, the study utilized a nationwide multicenter database in Korea, distinguishing between pre-hospital and in-hospital phases. The proportion of presenting as IVT candidates was chosen as a performance metric for the pre-hospital phases, assessing awareness and immediate actions regarding stroke by patients or their caregivers. The actual IVT use among these candidates was selected as a performance metric for the in-hospital phases, focusing on the swift and effective response by emergency or neurology staff to evaluate the patients and administer IVT.

The incidence of ischemic stroke is increasingly prevalent among the elderly, as confirmed by analyses of the Get With The Guideline for Stroke data and national inpatient samples.[16-18] Despite a rise in the eligibility for IVT in the elderly, our study showed that its usage remained significantly lower, with the probability of ischemic stroke patients ≥ 85 years old receiving IVT 17% less than those aged 75–84. Our study diverges from previous ones by specifically examining IVT candidates with alleged onset time and neurological deficits, suggesting there should be no hesitancy in starting IVT except for serious medical contraindications. In addition, physicians may be reluctant to provide potentially harmful treatment for dependent elderly patients aggressively.[19,20]

In our study of a representative ischemic stroke cohort from South Korea, we found that educational attainment was a significant predictor of IVT candidates, with lower educational levels correlating with a lower likelihood of presenting as IVT candidates. Delayed arrival in these groups may be partially associated with the disparity. Unlike previous studies that focused on income or social class, the authors used years of education as a proxy for socioeconomic status. This approach is particularly relevant given that the majority of stroke patients are elderly and typically not actively employed, which makes direct income less of a reliable indicator.[21] Furthermore, in Korea, where the geographic segregation by economic and social class is not pronounced,[22] education may serve as a more applicable indicator of socioeconomic status.

https://doi.org/10.3346/jkms.2025.40.e49

Although educational attainment and sex were associated with presenting as IVT candidates, these were not significant factors in the actual IVT among the candidates. This indicates that once patients are admitted to a hospital, their socioeconomic status does not hinder their access to IVT treatment. South Korea's universal healthcare insurance system may play a crucial role in this by providing comprehensive coverage to nearly all residents, regardless of economic status, region, or age.[23] The affordability of alteplase, which costs approximately USD 320, and the overall direct medical cost of an acute stroke admission, typically around USD 3,000—with patients paying only about 5% of these costs in acute stroke—significantly lowers financial barriers to accessing healthcare resources for stroke patients.[24-26]

Previous studies have identified several factors contributing to disparities in the use of IVT, including sex, race, age, income, and geography.[27,28] These disparities are shaped by a complex interplay of social, economic, historical, cultural, and political influences that affect the behaviors of patients, caregivers, stakeholders, and medical professionals.[29] In contrast, South Korea's relatively compact geography and homogeneous population, coupled with a government-operated single-payer healthcare system, mean that the inequality factors influencing IVT utilization may differ from those in other countries in the world.

Since the National Institute of Neurological Disorders and Stroke trial in 1995, IVT for AIS has become the standard of care globally.[3,30] However, according to our study, approximately 40% of AIS patients are not receiving treatment despite being IVT candidates in terms of time and neurological deficit. This underscores a significant missed opportunity, especially for the elderly population and those with lower educational attainment. Despite the universal healthcare system, which minimizes access limitations to acute stroke care, inequalities in the real world persist in South Korea.[31] Potential contributing factors to the disparity may include unconscious hesitancy on the part of healthcare providers to provide the IVT in elderly patients,[32] lower awareness of stroke among lower socioeconomic status individuals with lower education levels,[33] non-specific stroke presentation in females with unconscious bias in evaluating female patients,[34] delayed detection in elderly patients who live alone,[35] and potential nihilism of physicians in managing dependent elderly.[36]

There are a few points that need further clarification. Conducted in South Korea, a nation distinguished by its universal healthcare system, the findings of our study must be contextualized carefully when extrapolated to regions with different healthcare systems. The study's timeframe, 2011 to 2023, coincided with evolving guidelines for acute stroke management, potentially influencing the interpretation of IVT utilization trends over time. The exclusion criteria utilized in European Cooperative Acute Stroke Study III may still have an impact on clinical practice as reflected in the dataset used in this study, particularly in the earlier period.[37] In our study, we observed a lower proportion of IVT administration among patients with prior antiplatelet use before stroke onset. This may imply the presence of residual confounding factors that were not fully adjusted for, such as baseline differences in age, educational attainment or comorbidities.

It is important to note that the analysis did not encompass every contraindication for IVT as outlined in clinical practice guidelines, which could affect the applicability of our findings. The source database of our study originated from multicenter and prospective registry, but its coverage may not cover the whole stroke incidence cases in Korea. Additionally, the dataset had 8% missing information on the education level. We defined neurological deficit eligible to IVT as NIHSS score ≥ 4.[38]

In conclusion, our study examined a nationwide prospective stroke registry in South Korea and discovered that factors such as age, sex and educational attainment influenced the likelihood of presenting as IVT candidates for ischemic stroke patients. However, these factors did not significantly affect whether these candidates received IVT. Our findings highlight the need for targeted public awareness campaigns to improve awareness of stroke symptoms and the urgency of immediate transfer and treatment, particularly among the geriatric population and those from lower socioeconomic status. Additionally, our results suggest that there is a need to investigate hospital- and provider-level factors that may affect IVT utilization among eligible individuals. Such initiatives could significantly enhance IVT utilization across South Korea, contributing to better global health outcomes and reducing disparities in stroke care.

ACKNOWLEDGMENTS

A list of all researchers participating in the CRCS-K: Yong Soo Kim, MD; Do Yeon Kim, MD; Jun Yup Kim, MD; Jihoon Kang, MD, PhD (Seoul National University College of Medicine, Seoul National University Bundang Hospital); Kang-Ho Choi, MD; Hyunsoo Kim, MD (Chonnam National University Hospital); Dong-Ick Shin, MD, PhD (Chungbuk National University Hospital); Yoonkyung Lee, MD; Dae-Hyun Kim, MD, PhD (Dong-A University Hospital); Dong-Seok Gwak, MD, PhD (Dongguk University Ilsan Hospital); Sangil Park, MD; Dongwhan Lee, MD (Uijeongbu Eulji Medical Center, Eulji University); Michelle Sojung Youn, MD (Nowon Eulji Medical Center, Eulji University School of Medicine); Do-Hyung Kim, MD; Soo Joo Lee, MD, PhD (Eulji University Daejeon Eulji Medical Center); Minwoo Lee, MD, PhD; Mi-Sun Oh, MD (Hallym University Sacred Heart Hospital); Hong-Kyun Park, MD; Yong-Jin Cho, MD, PhD (Inje University Ilsan Paik Hospital); Chul-Hoo Kang, MD; Joong-Goo Kim, MD (Jeju National University Hospital); Jeong-Ho Hong, MD, PhD (Keimyung University Dongsan Hospital); Sang-Soon Park, MD (Seoul Medical Center); Jeong-Yoon Lee, MD (Soonchunhyang University Seoul Hospital); Doo Hyuk Kwon, MD (Yeungnam University Medical Center); Jung Hoon Han, MD; Keon-Joo Lee MD; Kyungmi Oh, MD, PhD (Korea University Guro Hospital); Chulho Kim, MD, PhD (Hallym University Chuncheon Sacred Heart Hospital); Chan-Young Park, MD; Hae-Bong Jeong, MD (Chung-Ang University Hospital); Ho Geol Woo, MD, PhD (Kyung Hee University Hospital); Ji Sung Lee, PhD; Jae-Sung Lim, MD (Asan Medical Center), Juneyoung Lee, PhD (Department of Biostatistics, Korea University College of Medicine); Jonguk Kim, MD (Inha University Hospital).

This manuscript is based on part of the first author (Y Ko)'s master's thesis submitted to Seoul National University, College of Medicine.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Number of patients by study periods

Supplementary Table 2
Number of patients by participating centers

https://doi.org/10.3346/jkms.2025.40.e49

Supplementary Table 3

Baseline characteristics by age group

Supplementary Table 4

Baseline characteristics by educational attainment

REFERENCES

1. Kim JY, Kang K, Kang J, Koo J, Kim DH, Kim BJ, et al. Executive summary of stroke statistics in Korea 2018: a report from the Epidemiology Research Council of the Korean Stroke Society. *J Stroke* 2019;21(1):42-59. PUBMED | CROSSREF
2. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 2021;20(10):795-820. PUBMED | CROSSREF
3. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019;50(12):e344-418. PUBMED | CROSSREF
4. Suolang D, Chen BJ, Wang NY, Gottesman RF, Faigle R. Geographic and regional variability in racial and ethnic disparities in stroke thrombolysis in the United States. *Stroke* 2021;52(12):e782-7. PUBMED | CROSSREF
5. Kim JY, Lee KJ, Kang J, Kim BJ, Kim SE, Oh H, et al. Acute stroke care in Korea in 2013-2014: national averages and disparities. *J Korean Med Sci* 2020;35(20):e167. PUBMED | CROSSREF
6. Eissa A, Krass I, Bajorek BV. Barriers to the utilization of thrombolysis for acute ischaemic stroke. *J Clin Pharm Ther* 2012;37(4):399-409. PUBMED | CROSSREF
7. Baatiema L, Otim ME, Mnatzaganian G, de-Graft Aikins A, Coombes J, Somerset S. Health professionals' views on the barriers and enablers to evidence-based practice for acute stroke care: a systematic review. *Implement Sci* 2017;12(1):74. PUBMED | CROSSREF
8. Faigle R, Urrutia VC, Cooper LA, Gottesman RF. Individual and system contributions to race and sex disparities in thrombolysis use for stroke patients in the United States. *Stroke* 2017;48(4):990-7. PUBMED | CROSSREF
9. Otite FO, Saini V, Sur NB, Patel S, Sharma R, Akano EO, et al. Ten-Year trend in age, sex, and racial disparity In tPA (Alteplase) and thrombectomy use following stroke in the United States. *Stroke* 2021;52(8):2562-70. PUBMED | CROSSREF
10. Zachrison KS, Nielsen VM, de la Ossa NP, Madsen TE, Cash RE, Crowe RP, et al. Prehospital stroke care Part 1: Emergency medical services and the stroke systems of care. *Stroke* 2023;54(4):1138-47. PUBMED | CROSSREF
11. Wang CJ, Gu HQ, Zong LX, Zhang XM, Zhou Q, Jiang Y, et al. Effectiveness of a quality improvement intervention on reperfusion treatment for patients with acute ischemic stroke: a stepped-wedge cluster randomized clinical trial. *JAMA Netw Open* 2023;6(6):e2316465. PUBMED | CROSSREF
12. Bae HJ; CRCS-K Investigators. David G. Sherman lecture award: 15-year experience of the nationwide multicenter stroke registry in Korea. *Stroke* 2022;53(9):2976-87. PUBMED | CROSSREF
13. Ko SB, Park HK, Kim BM, Heo JH, Rha JH, Kwon SU, et al. 2019 Update of the Korean clinical practice guidelines of stroke for endovascular recanalization therapy in patients with acute ischemic stroke. *J Stroke* 2019;21(2):231-40. PUBMED | CROSSREF
14. Park HK, Ko SB, Jung KH, Jang MU, Kim DH, Kim JT, et al. 2022 Update of the Korean clinical practice guidelines for stroke: antithrombotic therapy for patients with acute ischemic stroke or transient ischemic attack. *J Stroke* 2022;24(1):166-75. PUBMED | CROSSREF
15. Kim BJ, Park JM, Kang K, Lee SJ, Ko Y, Kim JG, et al. Case characteristics, hyperacute treatment, and outcome information from the clinical research center for stroke-fifth division registry in South Korea. *J Stroke* 2015;17(1):38-53. PUBMED | CROSSREF
16. George BP, Asemota AO, Dorsey ER, Haider AH, Smart BJ, Urrutia VC, et al. United States trends in thrombolysis for older adults with acute ischemic stroke. *Clin Neurol Neurosurg* 2015;139:16-23. PUBMED | CROSSREF
17. Schwamm LH, Ali SF, Reeves MJ, Smith EE, Saver JL, Messe S, et al. Temporal trends in patient characteristics and treatment with intravenous thrombolysis among acute ischemic stroke patients at Get With The Guidelines-Stroke hospitals. *Circ Cardiovasc Qual Outcomes* 2013;6(5):543-9. PUBMED | CROSSREF

18. Sun P, Zheng L, Lin M, Cen S, Hammond G, Joynt Maddox KE, et al. Persistent inequities in intravenous thrombolysis for acute ischemic stroke in the United States: results from the nationwide inpatient sample. *J Am Heart Assoc* 2024;13(9):e033316. PUBMED | CROSSREF
19. Kim BJ, Cho YJ, Hong KS, Lee J, Kim JT, Choi KH, et al. Treatment intensification for elevated blood pressure and risk of recurrent stroke. *J Am Heart Assoc* 2021;10(7):e019457. PUBMED | CROSSREF
20. Daugherty SL, Powers JD, Magid DJ, Masoudi FA, Margolis KL, O'Connor PJ, et al. The association between medication adherence and treatment intensification with blood pressure control in resistant hypertension. *Hypertension* 2012;60(2):303-9. PUBMED | CROSSREF
21. Darin-Mattsson A, Fors S, Kåreholt I. Different indicators of socioeconomic status and their relative importance as determinants of health in old age. *Int J Equity Health* 2017;16(1):173. PUBMED | CROSSREF
22. Lim U, Kim DH. Do birds of a feather flock together? Exploring the geography of educational segregation in Seoul, Korea. *Studies in Regional Science* 2010;40(2):479-94. CROSSREF
23. WHO Regional Office for the Western Pacific. *Republic of Korea Health System Review: WHO Regional Office for the Western Pacific*. Manila, Philippines: WHO Regional Office for the Western Pacific; 2015.
24. Health Insurance Review & Assessment Service (HIRA). *Korea Health Insurance Review and Assessment Service (HIRA) Releases 'Current Status of Cerebrovascular Disease Treatment'*. Wonju, Korea: HIRA; 2023.
25. Hong KS, Kim SE, Bae HJ. Five-year cumulative cost saving with thrombolysis in Korea: 3-month disability-based estimation. *J Stroke* 2020;22(2):262-5. PUBMED | CROSSREF
26. Kim SE, Lee H, Kim JY, Lee KJ, Kang J, Kim BJ, et al. Three-month modified Rankin Scale as a determinant of 5-year cumulative costs after ischemic stroke: an analysis of 11,136 patients in Korea. *Neurology* 2020;94(9):e978-91. PUBMED | CROSSREF
27. Denny MC, Rosendale N, Gonzales NR, Leslie-Mazwi TM, Middleton S. Addressing disparities in acute stroke management and prognosis. *J Am Heart Assoc* 2024;13(7):e031313. PUBMED | CROSSREF
28. Trifan G, Gallo LC, Lamar M, Garcia-Bedoya O, Perreira KM, Pirzada A, et al. Association of unfavorable social determinants of health with stroke/transient ischemic attack and vascular risk factors in Hispanic/Latino adults: results from Hispanic Community Health Study/Study of Latinos. *J Stroke* 2023;25(3):361-70. PUBMED | CROSSREF
29. Dawes DE. *The Political Determinants of Health*. Baltimore, MD, USA: Johns Hopkins University Press; 2020.
30. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333(24):1581-7. PUBMED | CROSSREF
31. Organisation for Economic Co-operation and Development (OECD). *OECD Reviews of Public Health: Korea*. Paris, France: OECD; 2020.
32. Kapral MK, Devon J, Winter AL, Wang J, Peters A, Bondy SJ. Gender differences in stroke care decision-making. *Med Care* 2006;44(1):70-80. PUBMED | CROSSREF
33. Pan Y, Chen R, Li Z, Li H, Zhao X, Liu L, et al. Socioeconomic status and the quality of acute stroke care: the China national stroke registry. *Stroke* 2016;47(11):2836-42. PUBMED | CROSSREF
34. Labiche LA, Chan W, Saldin KR, Morgenstern LB. Sex and acute stroke presentation. *Ann Emerg Med* 2002;40(5):453-60. PUBMED | CROSSREF
35. Foerch C, Misselwitz B, Humpich M, Steinmetz H, Neumann-Haefelin T, Sitzer M, et al. Sex disparity in the access of elderly patients to acute stroke care. *Stroke* 2007;38(7):2123-6. PUBMED | CROSSREF
36. Hall WJ, Chapman MV, Lee KM, Merino YM, Thomas TW, Payne BK, et al. Implicit racial/ethnic bias among health care professionals and its influence on health care outcomes: a systematic review. *Am J Public Health* 2015;105(12):e60-76. PUBMED | CROSSREF
37. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359(13):1317-29. PUBMED | CROSSREF
38. Fugate JE, Rabinstein AA. Absolute and relative contraindications to IV rt-PA for acute ischemic stroke. *Neurohospitalist* 2015;5(3):110-21. PUBMED | CROSSREF