Original Article

Comorbid Diseases and 1-Year Mortality in Acute Ischemic Stroke: A National Database Study

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Objective: To study the association between comorbid diseases and long-term mortality in acute ischemic stroke patients with and without an intravenous recombinant tissue plasminogen activator (rt-PA) treatment using a national database.

Materials and Methods: The present study was a retrospective cohort study. The database used in the present study was a Universal Health Coverage (UHC) insurance of Thailand. The inclusion criteria were consecutive adult patients diagnosed as acute ischemic stroke and admitted to the hospital. The study period was between October 1st, 2011 and September 30th, 2014. Mortality was defined as a 1-year mortality after acute ischemic stroke. We analyzed if comorbid diseases associated with the 1-year mortality with regards of the rt-PA treatment.

Results: During the study period, there were 120,545 patients met the study criteria. Of those, 4,610 patients (3.8%) received rt-PA. The 1-year mortality rate in the rt-PA group and no rt-PA group were 1,129 (24.5%) and 30,910 (26.7%), respectively (*p*-value = 0.001). The rt-PA group had significantly higher proportions of eight comorbid diseases than the no rt-PA group; mostly cardiovascular diseases such as hypertension, coronary artery disease, heart failure, or atrial fibrillation.

Conclusion: The 1-year mortality rate in acute ischemic stroke was significantly lower if treated with the rt-PA. Cardiovascular comorbid diseases may increase risk of mortality if treated with the rt-PA.

Keywords: Intravenous recombinant tissue plasminogen activator, Hypertension, Cardiovascular disease

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Acute ischemic stroke is the most common stroke type: accounted for 87% of stroke[1]. Since 1995, a study by the National Institutes of Neurological Disorders and Stroke (NINDS) showed that a recombinant tissue plasminogen activator (rt-PA) significantly improved physical status compared with placebo (odds ratio of 1.7; 95% confidence interval of 1.2 to 2.6)[2]. However, a meta-analysis published in 2014 found that a 90-day mortality rate in the thrombolytic therapy group was slightly higher than the control group (17.9% vs. 16.5%) but not significant (hazard ratio 1.11, 95% confidence interval 0.99 to 1.25)[3].

Even though the rt-PA treatment is recommended for acute ischemic stroke patients, there are some factors associated with mortality particularly comorbid diseases. Previous studies found that glomerular filtration rate or hyperglycemia may affect mortality or disability of acute ischemic stroke patients who received the rt-PA treatment[4-6]. Acute hyperglycemia was significantly increasing in-hospital mortality by 68% (95% confidence interval 1.57, 1.80)[6]. However, there is limited data on other comorbid diseases on long-term mortality and on whether receiving the rt-PA treatment particular in Thai population.

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Materials and Methods

The present study was a retrospective cohort study and conducted by using the national database of the Universal Health Coverage (UHC). The inclusion criteria were consecutive adult patients diagnosed and admitted to the hospital with acute ischemic stroke. The study period was between October 1st, 2011 and September 30th, 2014.

The eligible patients were evaluated for baseline characteristics, comorbid diseases, history of rt-PA treatment, and 1-year mortality. The comorbid diseases were retrieved by using the ICD10 and ICD9 search terms as follows: coronary artery disease (I25), diabetes mellitus (E11), obesity (E66.x), hyperthyroidism (E05.0-E05.9), dyslipidemia (E78.0 to E78.9), congestive heart failure (I50.0 to I50.9), rheumatic heart disease (I34.x to I39.x, Q22.x to Q23.x), atrial fibrillation (I48), chronic kidney disease (N18.1 to N18.9), cirrhosis

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(K70.3, K71.7, K74), previous history of stroke (I63.0 to I63.9), previous history of TIA (I65.0 to I66.9), HIV infection (B20.0 to B22.9, B24.0 to B24.9, R75, Z21), and peripheral artery disease (I73.0 to I74.9). The previous history of stroke defined by evidence of stroke documented by the computed tomography or magnetic resonance imaging of the brain in the past three years. For those who received more than one time of the rt-PA treatment, data of the first rt-PA treatment was used for the analysis. The one-year mortality was retrieved from national registry database, Household Registration Division, Ministry of Interior of Thailand.

The eligible patients were divided into two groups by the rt-PA treatment at baseline and at one year. At one year, the studied variables were evaluated for those who died and categorized by the rt-PA treatment. Descriptive statistics were used to compute the studied variables. Differences between groups by rt-PA treatment were compared by the Fisher Exact test: https://statpages.info/ctab2x2.html. A statistical significance was defined by a *p*-value less than 0.05.

Results

During the study period, there were 120,545 patients met the study criteria. Of those, 4,610 patients (3.8%) received rt-PA. The mean (SD) age of the patients was 65.8 (13.1) years with the highest proportion at age range of 65 to 74 years (27.6%). There was no difference on sex (male patients: 54.4%). The most common comorbid disease was hypertension (48.0%) (Table 1).

The 1-year mortality rate in the rt-PA group and no rt-PA group were 1,129 (24.5%) and 30,910 (26.7%), respectively (*p*-value = 0.001). There were 10 comorbid diseases which were significantly different between those who received and did not receive the rt-PA treatment (Table 2). The rt-PA group had significantly higher proportions of eight comorbid diseases than the no rt-PA group. Only the proportions of chronic kidney disease and cirrhosis were significantly lower in the rt-PA group than the no rt-PA group (*p*-value <0.001 and 0.012), respectively (Table 3).

Discussion

Regarding acute ischemic stroke mortality, the ECASS III found that the mortality rates at 90-day in the rt-PA group and no rt-PA group were comparable at 7.7% vs. 8.4%[7]. In the meta-analysis, these numbers were reverse but not significant at 17.9% vs. 16.5%[3]. The present study found similar results with the ECASS III but significantly different. The 1-year mortality rate in the rt-PA group was significantly lower than the no rt-PA group (24.5% vs. 26.7%). This difference was only 2.2% but it may be significant due

Table 1. Characteristics of acute ischemic stroke patients who registered in the universal coverage database from October 1, 2011 to September 30, 2014 categorized by a recombinant tissue plasminogen activator (rt-PA)

Factors	rt-PA (n = 4,610)	No rt-PA (n = 115,935)	Total (%) (n = 120,545)
Mean (SD) age, years	63.1 (13.1)	65.9 (13.1)	65.8 (13.1)
Age range, years			
<35	88 (1.9)	1,529 (1.3)	1,617 (1.3)
35 to 44	292 (6.3)	5,360 (4.6)	5,652 (4.7)
45 to 54	777 (16.9)	16,438 (14.2)	17,215 (14.3)
55 to 64	1,190 (25.8)	27,425 (23.7)	28,615 (23.7)
65 to 74	1,354 (29.4)	31,924 (27.5)	33,278 (27.6)
75 to 84	801 (17.4)	26,143 (22.6)	26,944 (22.4)
>85	108 (2.3)	7,116 (6.1)	7,224 (6.0)
Male sex	2,509 (54.4)	63,035 (54.4)	65,544 (54.4)
Comorbid disease			
Coronary artery disease	194 (4.2)	4,120 (3.6)	4,314 (3.6)
Hypertension	2,126 (46.1)	55,697 (48.0)	57,823 (48.0)
Diabetes	636 (13.8)	20,867 (18.0)	21,503 (17.84)
Obesity	14 (0.3)	124 (0.1)	138 (0.1)
Hyperthyroidism	56 (1.2)	808 (0.7)	864 (0.7)
Dyslipidemia	1,548 (33.6)	35,654 (30.8)	37,202 (30.9)
Heart failure	147 (3.2)	2,357 (2.0)	2,504 (2.1)
Rheumatic heart disease	227 (4.9)	2,707 (2.3)	2,934 (2.4)
Atrial fibrillation	995 (21.6)	10.858 (9.4)	11,853 (9.8)
Chronic kidney disease	193 (4.2)	7,521 (6.5)	7,714 (6.4)
Cirrhosis	10 (0.2)	691 (0.6)	701 (0.6)
Previous stroke	152 (3.3)	2,371 (2.1)	2,523 (2.1)
Previous transient ischemic attack	22 (0.5)	258 (0.2)	280 (0.2)
HIV infection	13 (0.3)	451 (0.4)	464 (0.4)
Peripheral artery disease	10 (0.2)	143 (0.1)	153 (0.1)

Table 2. Characteristics of acute ischemic stroke patients who died within one year categorized by a recombinant tissue plasminogen activator (rt-PA)

Factors	rt-PA (n = 1,129)	No rt-PA (n = 30,910)	*p*-value
Male sex	531 (47.0)	15,304 (49.5)	0.108
Age range, years			0.442
<35	8 (0.8)	194 (0.7)	
35 to 44	25 (2.2)	746 (2.4)	
45 to 54	98 (8.7)	2,270 (7.3)	
55 to 64	204 (18.1)	4,983 (16.1)	
65 to 74	391 (34.6)	8,311 (26.9)	
75 to 84	347 (30.7)	10,415 (33.7)	
>85	56 (4.9)	3,991 (12.9)	
Comorbid disease			
Coronary artery disease	78 (6.9)	1,550 (5.0)	0.007
Hypertension	572 (50.7)	14,543 (47.0)	0.018
Diabetes	211 (16.7)	6,190 (20.0)	0.289
Obesity	1 (0.08)	21 (0.06)	0.546
Hyperthyroidism	20 (1.7)	278 (0.9)	0.006
Dyslipidemia	252 (22.3)	6,233 (20.1)	0.083
Heart failure	86 (7.6)	1,466 (4.7)	<0.001
Rheumatic heart disease	80 (7.1)	1,099 (3.5)	<0.001
Atrial fibrillation	370 (32.8)	5,482 (17.7)	<0.001
Chronic kidney disease	81 (7.1)	3,446 (11.1)	<0.001
Cirrhosis	5 (0.4)	387 (1.2)	0.012
Previous stroke	45 (4.0)	847 (2.7)	0.016
Previous transient ischemic attack	9 (0.8)	94 (0.3)	0.011
HIV infection	4 (0.4)	146 (0.5)	0.823
Peripheral artery disease	5 (0.4)	96 (0.3)	0.409

Table 3. Factors associated with one-year mortality in acute ischemic stroke patients

Factors	Adjusted odds ratio	95% confidence interval	*p*-value
rTPA	0.91	(0.85, 0.98)	0.014
Female sex	1.10	(1.07, 1.13)	<0.001
Age range, years			
<35	1.00		
35 to 44	1.15	(0.97, 1.36)	0.107
45 to 54	1.21	(1.04, 1.42)	0.016
55 to 64	1.65	(1.42, 1.93)	<0.001
65 to 74	2.56	(2.19, 2.99)	<0.001
75 to 84	4.77	(4.09, 5.57)	<0.001
>85	9.19	(7.84, 10.78)	<0.001
Comorbid disease			
Coronary artery disease	1.26	(1.18, 1.35)	<0.001
Hypertension	0.88	(0.86, 0.91)	<0.001
Diabetes	1.48	(1.42, 1.53)	<0.001
Obesity	0.95	(0.59, 1.53)	0.840
Hyperthyroidism	1.09	(0.94, 1.27)	0.266
Dyslipidemia	0.55	(0.54, 0.57)	<0.001
Heart failure	3.24	(2.96, 3.54)	<0.001
Rheumatic heart disease	1.21	(1.11, 1.31)	<0.001
Atrial fibrillation	2.37	(2.27, 2.48)	<0.001
Chronic kidney disease	2.15	(2.05, 2.27)	<0.001
Cirrhosis	4.34	(3.70, 5.09)	<0.001
Previous stroke	1.47	(1.34, 1.61)	<0.001
Previous transient ischemic attack	1.63	(1.25, 2.12)	<0.001
HIV infection	3.17	(2.59, 3.88)	<0.001
Peripheral artery disease	4.10	(2.83, 5.93)	<0.001

to large sample size (120,545 patients). Note that the mortality rate in our study was quite higher than previously reported[3,7]. The differences may be from different study population or stroke care. The meta-analysis and the ECASS III study had study population of 6,756 participants and 821 patients, respectively. Stroke care in Thailand may be also different from the Western countries. These data may indicate that stroke care in Thailand may need some improvements.

For comorbid diseases and 1-year mortality, those who received the rt-PA treatment and had prior cardiovascular diseases including hypertension, coronary artery disease, atrial fibrillation, previous stroke/TIA, or rheumatic heart disease tend to have higher mortality rate than those who did not receive the rt-PA treatment (Table 2). These findings may explain by more severe cardiovascular conditions may increase risk of mortality. One possible factor is post rt-PA intracerebral hemorrhage. The ECASS III study found that the rt-PA treatment significantly increased risk of intracranial bleeding compared with control treatment (7.9% vs. 3.5%; $p<0.1$)[7]. The post rt-PA intracranial bleeding was moderately correlated with mortality ($r = 0.401$, $p = 0.050$)[8]. In contrast, those who did not have the rt-PA treatment had significantly higher mortality rate at one year than those who received the rt-PA treatment if they had chronic kidney disease or cirrhosis as a comorbid disease. These findings were different from the previous report that low glomerular filtration rate below 45 was associated with poor outcome in rt-PA treatment[5]. Therefore, these findings should be further investigated.

The main advantage of the present study was large sample size and mortality was documented by the official registry database. However, there are some limitations. The UHC database did not provide treatment details or personal details such as treatments other than rt-PA or duration of hypertension. And, the analysis in this study was not computed for the model. Only descriptive statistics were used to evaluate the association between comorbid diseases and 1-year mortality. Confounding factors may exist.

In conclusion, the 1-year mortality rate in acute ischemic stroke was significantly lower if treated with the rt-PA. Cardiovascular comorbid diseases may increase risk of mortality if treated with the rt-PA.

What is already known on this topic?

The mortality rate after an intravenous recombinant tissue plasminogen activator (rt-PA) therapy in acute ischemic stroke is controversial. Data on association of comorbid diseases and acute ischemic stroke is limited.

What this study adds?

An intravenous recombinant tissue plasminogen activator (rt-PA) therapy had benefits on 1-year mortality reduction according to the national database. Comorbid diseases of cardiovascular conditions may increase risk of 1-year mortality in the rt-PA treatment.

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Potential conflicts of interest

The authors declare on conflict of interest.

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โรคร่วมและอัตราการเสียชีวิตในหนึ่งปีในผู้ป่วยโรคหลอดเลือดสมองชนิดขาดเลือดเฉียบพลัน: ฐานข้อมูลระดับชาติ

อภิรักษ์ ทีรฆพงศ์, นิศา วรสูต, นรงฤทธิ์ เกษมทรัพย์, สมศักดิ์ เทียมเก่า, กิตติศักดิ์ สวรรยาวิสุทธิ์, กรรณิการ์ คงบุญเกียรติ

วัตถุประสงค์: เพื่อศึกษาความเกี่ยวข้องระหว่างโรคร่วมและอัตราการเสียชีวิตระยะยาวในผู้ป่วยโรคหลอดเลือดสมองชนิดขาดเลือดเฉียบพลันที่ได้รับและไม่ได้รับยา recombinant tissue plasminogen activator (rt-PA) ทางหลอดเลือดดำโดยการใช้ฐานข้อมูลระดับชาติ

วัสดุและวิธีการ: การศึกษานี้เป็นการศึกษาแบบ cohort ย้อนหลัง ฐานข้อมูลได้จากสำนักงานหลักประกันสุขภาพแห่งชาติในประเทศไทย ข้อบ่งชี้ในการรับเข้าการศึกษาคือผู้ป่วยผู้ใหญ่ที่ได้รับการวินิจฉัยเป็นโรคหลอดเลือดสมองชนิดขาดเลือดเฉียบพลันที่ได้รับการรับเข้านอนโรงพยาบาลตามลำดับ การศึกษานี้ใช้ข้อมูลตั้งแต่วันที่ 1 ตุลาคม พ.ศ. 2554 ถึง 30 กันยายน พ.ศ. 2557 อัตราการเสียชีวิตหมายถึงการเสียชีวิตภายใน 1 ปี หลังเป็นโรคหลอดเลือดสมองชนิดขาดเลือดเฉียบพลัน โดยจะวิเคราะห์โรคร่วมกับอัตราการเสียชีวิต แบ่งตามการได้รับยา rt-PA

ผลการศึกษา: ในช่วงเวลาที่ทำการศึกษาพบว่ามีผู้ป่วยเข้าข้อบ่งชี้ของการศึกษา 120,545 ราย โดย 4,160 ราย (ร้อยละ 3.8) ได้รับยา rt-PA อัตราการเสียชีวิตใน 1 ปีในผู้ป่วยที่ได้รับและไม่ได้รับยา rt-PA มีจำนวน 1,129 ราย (ร้อยละ 24.5) และ 30,910 ราย (ร้อยละ 26.7) ตามลำดับ ($p = 0.001$) กลุ่มที่ได้รับ rt-PA มีสัดส่วนโรคร่วม 8 โรคสูงกว่ากลุ่มที่ไม่ได้รับยา rt-PA โดยเฉพาะโรคกลุ่มหัวใจและหลอดเลือด ได้แก่ ความดันโลหิตสูง โรคหลอดเลือดหัวใจ โรคหัวใจวาย และ หัวใจเต้นผิดจังหวะ atrial fibrillation

สรุป: อัตราการเสียชีวิตใน 1 ปี ในผู้ป่วยโรคหลอดเลือดสมองชนิดขาดเลือดเฉียบพลันพบว่ามีอัตราต่ำกว่าอย่างมีนัยสำคัญในกลุ่มที่ได้รับยา rt-PA โรคร่วมกลุ่มหัวใจและหลอดเลือด อาจจะเพิ่มอัตราการเสียชีวิตในกลุ่มที่ได้รับการรักษาด้วยยา rt-PA