The Impact of Comorbidities on In-hospital Mortality of Acute Stroke: An Analysis from Thailand's National Database

Chuleeporn Sirijaichingkul,
Suranut Charoensri,
Somsak Tiamkao,
Kannikar Kongbunkiat,
Nisa Vorasoot,
Narongrit Kasemsap

Abstract

Background: Stroke remains a major public health concern and is a leading cause of mortality worldwide. Comorbidities often complicate management and influence outcomes in stroke patients, yet their specific impact on in-hospital mortality in Thailand's acute stroke population remains underexplored.

Objective: To evaluate the influence of various comorbidities on in-hospital mortality among patients with acute ischemic and hemorrhagic stroke in Thailand.

Methods: A retrospective analysis was conducted using data from Thailand's national stroke database. Comorbidities based on International Classification of Diseases, 10th Revision (ICD-10) codes were assessed for their association with in-hospital mortality using multivariable logistic regression models.

Results: Comorbidities including leukemia, coronary artery disease, atrial fibrillation, peripheral artery disease, heart failure, diabetes, chronic kidney disease, liver disease, and human immunodeficiency virus (HIV) infection were significantly associated with increased in-hospital mortality across stroke subtypes. In contrast, peptic ulcer disease and underlying malignancies, including solid tumors and lymphoma, were significant predictors of mortality in ischemic stroke but not in hemorrhagic stroke.

Conclusions: Comorbidities play a critical role in determining in-hospital mortality in stroke patients, with variations observed between ischemic and hemorrhagic subtypes. These findings underscore the need for individualized management strategies

Chuleeporn Sirijaichingkul[1], Suranut Charoensri[2], Somsak Tiamkao[1], Kannikar Kongbunkiat[1], Nisa Vorasoot[1], Narongrit Kasemsap[1]
[1] Division of Neurology, Department of Medicine, Faculty of Medicine. Khon Kaen University, Thailand.
[2]Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine. Khon Kaen University, Thailand.

Corresponding author:
Narongrit Kasemsap
Division of Neurology, Department of Medicine, Faculty of Medicine, Khon Kaen University, THAILAND. 40002
Email: naroka@kku.ac.th

รับต้นฉบับ 3 เมษายน 2568, ปรับปรุงต้นฉบับ 2 สิงหาคม 2568, ตอบรับต้นฉบับตีพิมพ์ 14 สิงหาคม 2568

that address comorbid conditions to optimize stroke outcomes.

Keywords: Comorbidities, In-hospital Mortality, Acute Stroke, Thailand's National Database

Introduction

Stroke is a significant public health concern, ranking as the second leading cause of mortality globally[1]. Its incidence demonstrates a yearly rise, particularly pronounced in developing countries compared to their counterparts in Europe, America, and Australia. Approximately 70% of stroke incidence and 87% of stroke-related mortalities are concentrated in nations with low to middle socioeconomic status, including Asian countries.[2] Data regarding stroke mortality varies significantly among Asian populations, ranging from 50 -160 per 100,000 population.[3] In Thailand, the mortality rate due to stroke has also shown an upward trend, increasing from 3.7 per 100,000 population in 1950 to 11.8 per 100,000 population in 1983.[4] A data from the Ministry of Public Health during 2008 to 2012 also showed the increasing in mortality rate of stroke in Thailand from 20.8 in the year 2008 to 30.7 per 100,000 populations in the year 2012.[5] A study conducted by Tiamkao et al. during 2016 to 2022 in Thailand reported an overall stroke incidence rate of 330.72 per 100,000 population, with 222.19 cases classified as ischemic stroke and 88.38 as hemorrhagic stroke. Furthermore, the study documented a mortality rate of 10.92%.[6] This suggests that despite the incorporation of recombinant tissue plasminogen activator (rt-PA) administration within the Universal Coverage Scheme as per Thailand's national policy since 2009, improvements in mortality rates of ischemic stroke have not been evident.

The mortality risk associated with acute stroke has been attributed to various factors including patients' demographics, behavioral factors, comorbidities, and in-hospital complications. A study using hospital databases in USA identified several factors associated with mortality, including patient age, female gender, absence of Medicare insurance, and the presence of comorbid diseases.[7] Another study in Asia indicated that atrial fibrillation, ischemic heart disease, diabetes, and a history of smoking were significant risk factors for mortality upon discharge from the hospital in patients with ischemic stroke. Notably, diabetes was specifically associated with mortality upon discharge in patients with intracerebral hemorrhage.[8] A meta-analysis conducted in Ethiopia highlighted hypertension as the foremost contributor to in-hospital mortality in stroke cases, followed by atrial fibrillation and diabetes mellitus.[9] Racial disparities in stroke outcomes are well-documented, with African Americans exhibiting elevated mortality rates associated with stroke compared to Caucasians.[10] Medical complications during stroke admission such as septicemia, pulmonary embolism, pneumonia, myocardial infarction, status epilepticus, and heart failure were also identified as significant factors associated with stroke mortality[11].

Comorbidities significantly influence short-term mortality following hospital admission for stroke.[12] Certain comorbid conditions may hinder or delay standard thrombolytic interventions. Alternatively, comorbidities themselves can directly or indirectly contribute to post-stroke complications, including an elevated risk of bleeding, thrombosis, or and increased susceptibility to infections.[13,14] Recognizing the impact of comorbidities on stroke mortality is essential for optimizing post-stroke outcomes by

tailoring interventions to specific comorbid conditions. However, limited data are available regarding the impact of comorbidities on in-hospital mortality among patients with acute stroke in Thailand. The most recent national study examining risk factors for acute stroke in Thailand was conducted during 2009–2010, prior to the widespread adoption of thrombolytic therapy.[11] The subsequent incorporation of rt-PA administration within the Universal Coverage Scheme starting in 2009 may have significantly influenced stroke outcomes.[6] Consequently, the risk factors identified during that period may no longer accurately reflect the current clinical landscape in Thailand. This study aims to address this gap by identifying comorbidities associated with in-hospital mortality among patients admitted with acute stroke in the post rt-PA era. Additionally, we aim to quantify the impact of individual comorbidities on in-hospital mortality, stratified by stroke subtypes, including ischemic stroke, ischemic stroke treated with rt-PA, and hemorrhagic stroke.

Materials and Methods.

Study Design and Setting

This retrospective cohort study utilized data from Thailand's Universal Coverage Scheme (UCS) database, covering the period from October 1, 2018, to September 30, 2023. Data from the UCS database, managed by the National Health Security Office (NHSO), were verified electronically using a computerized program that detects errors based on predefined conditions and screening criteria agreed upon by data auditors.

Study Population

Adult patients aged over 18 years old with a primary diagnosis of stroke were identified using the International Classification of Diseases, 10th Revision (ICD-10) codes I61 and I63 recorded on patient reimbursement forms. Patients admitted primarily for rehabilitation, coded as Z50.0–Z50.9, were excluded.

Study variables and outcomes

The primary outcome of this study was in-hospital mortality, defined as discharge status coded as "death" in patient reimbursement forms. This outcome was analyzed as a dichotomous variable (death vs. alive, including discharge against medical advice). Comorbidities included in the analysis were based on the 19 diseases listed in the Charlson Comorbidity Index (CCI),[15] along with additional comorbidities of interest. These were identified using ICD-10 codes recorded in the comorbidities section of patient reimbursement forms. (Table 1) Patients who received rt-PA for the treatment of ischemic stroke were identified using International Classification of Diseases, 9th Revision (ICD-9) procedure code 9910, as recorded in the procedures section of patient reimbursement forms.

Table 1: Diagnosis codes based on the International Classification of Diseases, 10th Revision (ICD-10) codes.

Diagnosis	ICD-10 codes
Ischemic stroke	I63
Hemorrhagic stroke	I61
Hypertension	I10-I15
Diabetes mellitus	E10-14
Coronary artery disease	I20-I25
Peripheral artery disease	I70-79
Atrial fibrillation and flutter	I48
Dyslipidemia	E78
Heart failure	I50
Chronic pulmonary disease	J44.0, J44.1, J44.8, J44.9
Connective tissue disease	M30-36, M06
Liver disease	B18-B19, K70-K77
Chronic kidney disease	N18-N19
Dementia	F01-F03, G30
Peptic ulcer disease	K25, K26, K27, K28
Non metastatic cancer	C00-41, C43-C75
Metastatic cancer	C76-C80
Lymphoma	C81-C90
Leukemia	C91-C95
Human immunodeficiency virus (HIV) infection	B20-B24

Statistical analysis

Statistical analysis was performed using the R program. Descriptive statistics were used to analyze demographic data (age, sex), prevalence of in-hospital stroke mortality, and comorbidities for each cohort. Categorical variables were reported as percentages, while continuous variables were reported as mean and standard deviation for normally distributed data or as median and inter-quartile range for non-normally distributed data. Analytical statistics were used to assess differences between patients discharged alive and those who died during hospitalization, using t-tests, Chi-square tests, Wilcoxon rank-sum tests, or Fisher's exact tests, as appropriate. The effect of each potential comorbidity on in-hospital mortality was examined using univariate logistic regression, and multivariable logistic regression was performed to adjust for potential confounders.

Results

Overall population (ischemic stroke and hemorrhagic stroke)

A total of 648,781 hospitalized patients with acute stroke were included in the analysis, comprising 499,330 cases of ischemic stroke (77%) and 149,451 cases of hemorrhagic stroke (23%). Female patients were more prevalent among those with ischemic stroke (45.8%) compared to hemorrhagic stroke (38%, p-value<0.001). The median age of

ischemic stroke patients was significantly higher than that of hemorrhagic stroke patients (66 years vs. 61 years, p-value<0.001). Hypertension was the most common comorbidity in both ischemic and hemorrhagic stroke patients. However, diabetes ranked second in ischemic stroke patients, followed by dyslipidemia. In contrast, among hemorrhagic stroke patients, dyslipidemia was the second most prevalent comorbidity, with diabetes ranking third. Most comorbidities were observed more frequently in ischemic stroke patients; however, hypertension and liver disease were more commonly reported in hemorrhagic stroke patients. The in-hospital mortality rate among the overall population was 8.6%, with significant differences between ischemic stroke (4.0%) and hemorrhagic stroke (23.8%, p<0.001). Hemorrhagic stroke patients exhibited a higher median length of hospital stay compared to ischemic stroke patients (5 vs. 4 days, p-value <0.001). (Table 2) Multivariable logistic regression analysis identified several comorbidities that were significantly associated with increased in-hospital mortality across stroke subtypes. Among hemorrhagic stroke patients, leukemia (OR 4.48; 95% CI 3.31-6.09) was the most strongly associated with mortality, followed by coronary artery disease (OR 1.69; 95% CI 1.55-1.83), atrial fibrillation (OR 1.61; 95% CI 1.52-1.70), chronic kidney disease (OR 1.59; 95% CI 1.52-1.66), liver disease (OR 1.49; 95% CI 1.38-1.60), peripheral artery disease (OR 1.37; 95% CI 1.08-1.72), heart failure (OR 1.33; 95% CI 1.18-1.50), human immunodeficiency virus (HIV) infection (OR 1.22; 95% CI 1.02-1.44), and diabetes (OR 1.15; 95% CI 1.11-1.19). For ischemic stroke patients, the significant predictors of mortality included leukemia (OR 3.91; 95% CI 2.46-5.96), atrial fibrillation (OR 3.10; 95% CI 3.00-3.20), heart failure (OR 2.75; 95% CI 2.60-2.92), metastatic cancer (OR 2.66; 95% CI 2.11-3.33), peripheral artery disease (OR 2.59; 95% CI 2.23-3.00), liver disease (OR 2.57; 95% CI 2.34-2.82), coronary artery disease (OR 2.08; 95% CI 1.98-2.19), HIV infection (OR 2.04; 95% CI 1.66-2.49), peptic ulcer disease (OR 1.91; 95% CI 1.47-2.43), lymphoma (OR 1.81; 95% CI 1.16-2.70), nonmetastatic cancer (OR 1.71; 95% CI 1.53-1.91), chronic kidney disease (OR 1.36; 95% CI 1.30-1.42), and diabetes (OR 1.22; 95% CI 1.18-1.26). (Figure 1)

Table 2: Baseline characteristics of stroke patients

	Hemorrhagic stroke (n=149,451)	Ischemic stroke (n=499,330)	p-value
Demographics			
Female, n (%)	567,86 (38.0)	228,781 (45.8)	<0.001
Age (years), median [IQR]	61 [51, 71]	66 [57, 75]	<0.001
Comorbidities, n (%)			
Hypertension	107,283 (71.8)	284,393 (57.0)	<0.001
Dyslipidemia	25,539 (17.1)	207,694 (41.6)	<0.001
Atrial fibrillation	6,193 (4.1)	54,893 (11.0)	<0.001
Coronary artery disease	2,829 (1.9)	20,328 (4.1)	<0.001
Heart failure	1,323 (0.9)	9,846 (2.0)	<0.001
Peripheral artery disease	341 (0.2)	1,716 (0.3)	<0.001

	Hemorrhagic stroke (n=149,451)	Ischemic stroke (n=499,330)	p-value
Diabetes	24,366 (16.3)	154,012 (30.8)	<0.001
COPD	1,786 (1.2)	8,766 (1.8)	<0.001
Connective tissue disease	486 (0.3)	2,468 (0.5)	<0.001
Liver disease	3,332 (2.2)	5,630 (1.1)	<0.001
Chronic kidney disease	10,931 (7.3)	41,540 (8.3)	<0.001
Dementia	378 (0.3)	2,141 (0.4)	<0.001
Peptic ulcer disease	105 (0.1)	834 (0.2)	<0.001
Non metastatic cancer	1,046 (0.7)	5,161 (1.0)	<0.001
Metastatic cancer	189 (0.1)	772 (0.2)	0.015
Lymphoma	41 (0.03)	318 (0.1)	<0.001
Leukemia	177 (0.1)	182 (0.04)	<0.001
HIV infection	660 (0.4)	2,223 (0.4)	0.873
Treatment / outcomes			
Receiving rt-PA, n (%)	0 (0.0)	36,842 (7.4)	<0.001
Length of hospital stay (days), median [IQR]	5 [3,10]	4 [3,6]	<0.001
In-hospital death, n (%)	35,622 (23.8)	20,108 (4.0)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; rt-PA, recombinant tissue plasminogen activator; IQR, interquartile range

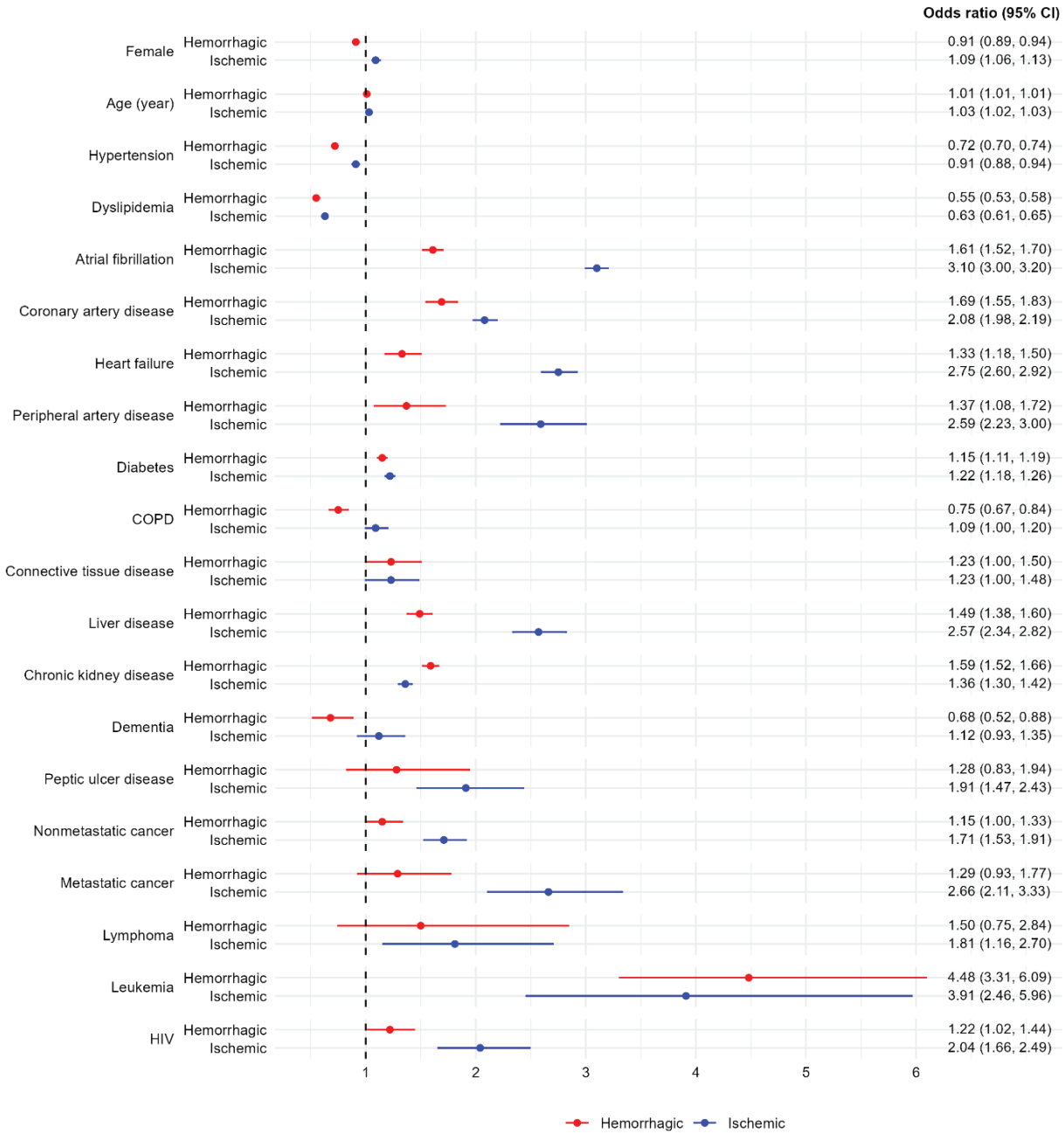

Figure 1: Adjusted odds ratio of each comorbidity on in-hospital mortality, stratified according to stroke subtypes.
Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.

Subgroup analysis of patients with ischemic stroke who received rt-PA

Among patients with ischemic stroke, 38,642 (7.4%) received rt-PA. These patients had a higher percentage of certain comorbidities such as dyslipidemia, atrial fibrillation, coronary artery disease, heart failure, peripheral artery disease, and chronic obstructive pulmonary disease compared to those who did not receive rt-PA. Conversely, conditions such as diabetes, liver disease, chronic kidney disease, and dementia were less prevalent in this group. Additionally, patients who received rt-PA

experienced higher mortality rates (6.7% vs. 3.8%, p < 0.001) and longer hospital stays compared to those who did not receive rt-PA treatment. (Table 3) Multivariable logistic regression analysis in this subgroup identified peripheral artery disease (OR 2.23; 95% CI 1.44-3.34), heart failure (OR 2.21; 95% CI 1.90-2.56), atrial fibrillation (OR 2.17; 95% CI 1.98-2.37), liver disease (OR 2.05; 95% CI 1.47-2.81), diabetes (OR 1.40; 95% CI 1.27-1.54), and chronic kidney disease (OR 1.38; 95% CI 1.20-1.58) as significant predictors of in-hospital mortality. (Figure 2)

Table 3: Characteristics of patients with ischemic stroke, stratified by rt-PA treatment

	Received rt-PA treatment (n=36,842)	No rt-PA treatment (n=462,488)	p-value
Demographics			
Female, n (%)	16,512 (44.8)	212,269 (45.9)	<0.001
Age (years), median [IQR]	66 [56, 74]	66 [57, 75]	<0.001
Comorbidities, n (%)			
Hypertension	21,011 (57.0)	263,382 (56.9)	0.77
Dyslipidemia	16,054 (43.6)	191,640 (41.4)	<0.001
Atrial fibrillation	7,892 (21.4)	47,001 (10.2)	<0.001
Coronary artery disease	2,114 (5.7)	18,214 (3.9)	<0.001
Heart failure	1,431 (3.9)	8,415 (1.8)	<0.001
Peripheral artery disease	165 (0.4)	1,551 (0.3)	<0.001
Diabetes	9,389 (25.5)	144,623 (31.3)	<0.001
COPD	777 (2.1)	7,989 (1.7)	<0.001
Connective tissue disease	179 (0.5)	2,289 (0.5)	0.84
Liver disease	352 (1.0)	5,278 (1.1)	0.001
Chronic kidney disease	2,449 (6.6)	39,091 (8.5)	<0.001
Dementia	83 (0.2)	2,058 (0.4)	<0.001
Peptic ulcer disease	47 (0.1)	787 (0.2)	0.06
Non metastatic cancer	351 (1.0)	4,810 (1.0)	0.12
Metastatic cancer	48 (0.1)	724 (0.2)	0.24
Lymphoma	26 (0.1)	292 (0.1)	0.66
Leukemia	7 (0.02)	175 (0.04)	0.09
HIV infection	162 (0.4)	2,061 (0.4)	0.90
Outcomes			
Length of hospital stay (days), median [IQR]	5 [4,7]	4 [3,5]	<0.001
In-hospital death, n (%)	2,475 (6.7)	17,633 (3.8)	<0.001

Abbreviations: rt-PA, recombinant tissue plasminogen activator; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; rt-PA, recombinant tissue plasminogen activator; IQR, interquartile range

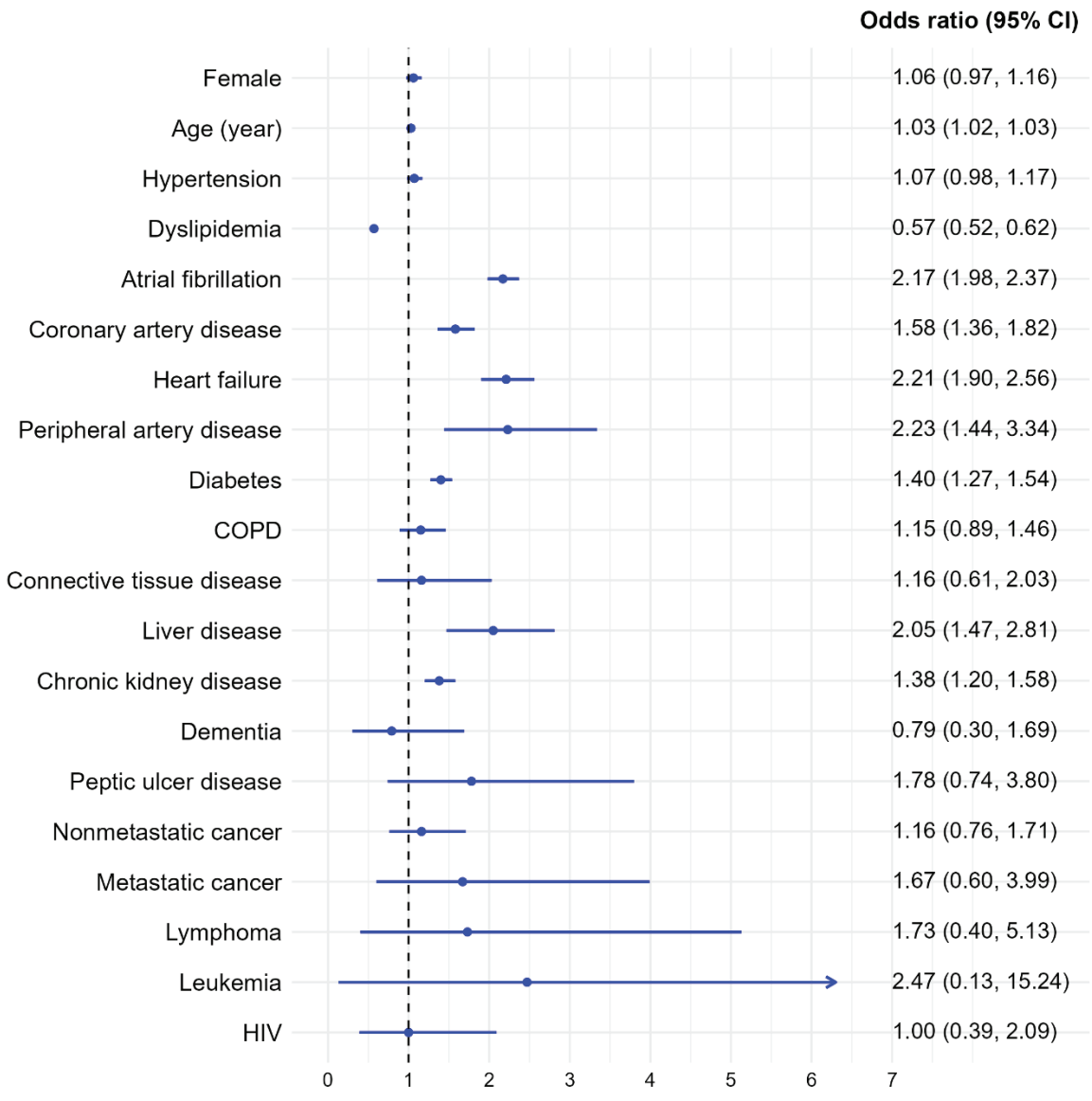

Figure 2: Adjusted odds ratio of each comorbidity on in-hospital mortality among ischemic stroke patients receiving rt-PA treatment.

Abbreviations: rt-PA, recombinant tissue plasminogen activator; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.

Discussion

The current study provides critical insights into the impact of comorbidities on in-hospital mortality among patients with acute stroke, utilizing a large national database in Thailand. The findings reveal substantial variability in mortality predictors between ischemic and hemorrhagic stroke subtypes.

The overall in-hospital mortality rate for stroke patients in this study was 8.6%, with significant differences between ischemic and hemorrhagic strokes. Mortality was notably lower for ischemic strokes at 4.0% compared to 23.8% for hemorrhagic strokes. Additionally, patients with hemorrhagic strokes experienced significantly longer hospital stays than those with ischemic strokes.

These findings highlight the greater severity of hemorrhagic strokes compared to ischemic strokes, consistent with global trends. Epidemiological data indicate that intracerebral hemorrhage is the leading cause of death among stroke patients, particularly within the first three months following the event, while ischemic stroke being the primary cause of years lived with disability.[16,17] Studies have shown that intracerebral hemorrhage carries a 30-day mortality rate of 40% to 50%, approximately twice that of ischemic stroke,[18] with only 27% of survivors achieving functional independence at 90 days.[19] This elevated severity of hemorrhagic stroke is largely attributed to its acute pathophysiological effects, the limited availability of effective treatments, and the high likelihood of secondary injuries.[20]

Our study showed that comorbidities played a pivotal role in determining in-hospital stroke outcomes, with leukemia demonstrated as the strongest predictor of mortality in both hemorrhagic and ischemic strokes. Consistent with previous research, patients with active acute myeloid leukemia who experience cerebrovascular accidents have a fivefold increased risk of mortality.[21] The heightened mortality risk associated with leukemia may be attributed to thrombocytopenia and coagulopathy, which can result from bone marrow failure or as adverse effects of chemotherapy, further intensifying bleeding risk after stroke events. Moreover, leukemia is frequently linked to agranulocytosis, which increases susceptibility to infections and complicates recovery in the acute stroke setting, contributing to poorer outcomes. Other significant comorbidities contributing to in-hospital mortality in both stroke subtypes include coronary artery disease, atrial fibrillation, peripheral artery disease, heart failure, diabetes, chronic kidney disease, liver disease, and HIV infection. These conditions are critical comorbidities that can compromise treatment effectiveness, restrict therapeutic options, and increase susceptibility to secondary complications, such as nosocomial infections or hemodynamic instability, which can substantially worsen stroke outcomes. Consistent with our findings, a previous study in Thailand identified myocardial infarction, atrial fibrillation, congestive heart failure, chronic kidney disease, and HIV infection as significant factors associated with hospital mortality in patients with cerebral infarction.[11]

Interestingly, our study revealed that patients with underlying malignancies, including lymphoma, had an increased risk of hospital mortality in ischemic stroke; however, this association was not clearly observed in hemorrhagic stroke. Similar findings from the Japan Stroke Data Bank demonstrated that ischemic stroke patients with cancer experienced significantly higher in-hospital mortality compared to those without cancer, with this effect being more pronounced than in hemorrhagic stroke.[22] This disparity may be attributed to cancer-induced hypercoagulable states, which predominantly increase the risk of thromboembolic events leading to vascular occlusion rather than bleeding. Furthermore, cancer treatments such as chemotherapy and radiotherapy can promote atherosclerosis, exacerbating the progression of ischemic stroke in these patients.[23–25]

Peptic ulcer disease is another condition associated with an increased risk of in-hospital mortality in ischemic stroke patients, a relationship that was not clearly observed in those with hemorrhagic stroke. This disparity may be attributed to the frequent use of thrombolytic, antiplatelet, or

anticoagulant therapies in ischemic stroke patients to prevent recurrent stroke. While these treatments are essential, they can significantly increase the risk of gastrointestinal bleeding in patients with underlying peptic ulcers, potentially leading to worse outcomes.

Patients who received rt-PA experienced longer hospital stays and higher overall mortality rates compared to those not treated with rt-PA. These observations could reflect the higher baseline severity of strokes in patients selected for rt-PA treatment, as well as the inherent risks associated with thrombolytic therapy. However, this study lacked data on functional outcomes, neurological status, or recovery among patients who survived after rt-PA treatment. It is crucial to interpret these results within the broader context of the established long-term clinical benefits of rt-PA, which has been shown to significantly improve functional status and enhance long-term survival in eligible patients, despite its associated risks.[26,27]

Consistent with findings from the overall ischemic stroke population, comorbidities such as coronary artery disease, peripheral artery disease, heart failure, atrial fibrillation, diabetes, liver disease, and chronic kidney disease were associated with increased mortality in the subgroup of patients receiving rt-PA treatment. In contrast, peptic ulcer disease, HIV infection, and underlying malignancies, including solid tumors and hematologic cancers, were not statistically significant predictors of mortality in this subgroup. This lack of significance is likely attributed to the very small number of patients with these conditions who received rt-PA. Such patients are frequently excluded from rt-PA therapy due to their generally poor prognosis and restriction to treatment eligibility. This underrepresentation likely resulted in insufficient statistical power to detect significant associations between these conditions and mortality in the rt-PA-treated subgroup.

The strength of this study lies in its large sample size and utilization of a national database, which significantly enhances the generalizability of its findings to the Thai population. Nevertheless, the study has certain limitations. The reliance on administrative data introduces the potential for misclassification of diagnoses or outcomes, which could affect the accuracy of the findings. Moreover, the database extracted from the patient reimbursement forms lacks critical clinical details, such as stroke severity metrics e.g., the National Institutes of Health Stroke Scale (NIHSS) and detailed outcomes like functional status or the modified Rankin Scale (mRS). Incorporating these parameters would provide a deeper understanding of how comorbidities influence both short- and long-term stroke outcomes

Conclusion

Our study demonstrates that leukemia, liver disease, chronic kidney disease, diabetes, HIV infection and cardiovascular conditions—such as atrial fibrillation, heart failure, coronary artery disease, and peripheral artery disease—are significant predictors of in-hospital mortality in patients with acute ischemic and hemorrhagic stroke. In contrast, peptic ulcer disease and malignancies were identified as significant predictors of mortality in ischemic stroke but not in hemorrhagic stroke. These findings underscore the complex interplay between comorbid conditions and treatment outcomes. Future research should explore deeper into these interactions to guide more personalized and effective therapeutic decision-making processes

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