Original Article

In-hospital direct costs for thromboembolism and bleeding in Chinese patients with atrial fibrillation

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Abstract

Objective: Limited data are available on the direct costs of hospitalization owing to thromboembolism and bleeding in patients with atrial fibrillation (AF) in China. Such data are essential for policy development, service planning, and cost-effectiveness analysis of new therapeutic strategies. This study aimed to provide detailed data regarding in-hospital direct costs for these patients, compare the costs at different scenarios, and identify independent factors that may predict the costs.

Methods: We collected data regarding in-hospital direct costs among patients with AF who were hospitalized owing to ischemic stroke (IS), transient ischemic attack (TIA), intracranial hemorrhage (ICH), or major gastrointestinal bleeding. All data were collected from 7 representative tertiary referral hospitals and 3 secondary care hospitals from December 2009 to October 2014.

Results: In total, 312 eligible patients with thromboembolism and 143 patients with major bleeding were identified, and their hospital charts were reviewed. The median in-hospital direct costs were 17,857 Chinese Yuan (CNY) for IS and 16,589 CNY for TIA (equivalent to 2907 US dollars and 2701 US dollars, respectively). For patients with major bleeding, the costs were 27,924 CNY for ICH and 18,196 CNY for major gastrointestinal bleeding (equivalent to 4546 US dollars and 2962 US dollars, respectively). The direct costs were mainly driven by medications, which accounted for approximately 33.4%−36.1% in different groups of patients. The direct costs were highly related to the hospital level and National Institutes of Health Stroke Scale scores in patients with thromboembolism; in patients with ICH, the factors included hospital level, warfarin treatment before admission, and prior hospitalization for stroke.

Conclusions: Given the high prevalence, AF-related thromboembolism and bleeding impose considerable economic burden on the Chinese society. Efforts to improve the management of AF may confer substantial economic benefits.

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Introduction

Atrial fibrillation (AF) is one of the most common causes of stroke, conferring a five-times higher risk of stroke on patients compared to the risk in the general population.[1] AF-related stroke is nearly twice as likely to be fatal as non-AF stroke, and functional deficits are likely to be more severe among survivors.[2] Several prior studies have reported that the mean costs of ischemic stroke (IS) were significantly higher for patients with AF than for those without AF.[3–6] Two national database studies in Europe[7,8] estimated the mean costs for intracranial hemorrhage, gastrointestinal bleeding, and other major bleeding events in patients with AF. The acute care costs were 7331, 3601, 3941 Euros (EUR), and the average 3-year societal costs were 27,627, 17,868, and 12,384 EUR, respectively, suggesting that bleeding events also conferred a substantial economic burden on patients with AF.

With the wide adoption of new treatments among patients with AF for stroke prevention, such as non-vitamin K antagonist oral anticoagulants (NOACs) and left atrial appendage occlusion procedures, it is important to evaluate the costs of these new treatments on the healthcare system and the money they will save by providing more effective stroke prevention and reducing the adverse events of bleeding.[9,10] Hence, accurate data on hospitalization costs related to AF-associated stroke and bleeding are essential for informed policies and decision making.

However, the available data on the health economics of patients with AF-related stroke and bleeding are scarce, especially for the healthcare system in Asian countries such as China. This study aimed to provide detailed data regarding in-hospital direct costs for patients with AF who are hospitalized owing to acute thromboembolism and bleeding events, compare the costs at different scenarios, and identify independent factors that may predict the costs.

Methods

Data source

This cost-of-illness study was conducted in 7 representative tertiary hospitals and 3 secondary care hospitals in Beijing. Tertiary hospitals were referral hospitals providing high-level medical services to several geographic regions. Secondary care hospitals usually provide general medical care in the regions where they are located. In all the participating hospitals, electronic medical records and detailed medical costs during hospitalization were available, and data were abstracted through chart review.

Data of all patients with a diagnosis of AF and of those hospitalized owing to new-onset stroke or transient ischemic attack (TIA) from January 2012 to March 2014 were collected. As major bleeding-induced hospitalization was less common, we expanded the data collection window to December 2009 to October 2014, to increase our sample size.

Study population

Eligible patients were ≥18 years of age, and the diagnoses were identified by the International Classification of Diseases, 10th Revision (ICD-10), coded by the discharging hospital.

For patients with thromboembolism, the inclusion criteria were as follows: (1) hospitalization owing to IS or TIA; and (2) a history of AF or newly diagnosed AF during the index hospitalization.

For patients with major bleeding, the inclusion criteria were as follows: (1) hospitalization owing to intracranial hemorrhage (ICH) or major gastrointestinal bleeding (major gastrointestinal bleeding was defined as bleeding leading to transfusion of at least two units of whole blood or erythrocytes, requiring hospitalization or surgery, resulting in permanent disability); and (2) a history of AF or newly diagnosed AF during the index hospitalization.

Patients were excluded if they satisfied the following criteria: (1) transient or reversible AF; (2) diagnosis of rheumatic mitral stenosis or mitral valve prostheses; (3) hospital discharge against physician advice or transfer to another hospital; (4) bleeding related to tumors, trauma, immunodeficiency, and pregnancy.

Patient consent forms were exempted as this study was a retrospective study using data from medical records. In addition, no individualized patient data were published or revealed. The Ethics Committee of Beijing Anzhen Hospital, the Capital Medical University approved the study protocol.

Data collection

The data abstracted from medical records included sociodemographic characteristics, medical history, information on smoking and alcohol consumption, and variables related to hospitalization. Medication usage information, including that on preadmission warfarin, antiplatelet agents, non-steroidal anti-inflammatory drugs, and steroids, was also obtained. Stroke severity, evaluated by the National Institutes of Health Stroke Scale (NIHSS), was also abstracted.

In-hospital direct costs

Data on costs were collected from medical records. All costs during hospitalization were classified into 8 categories, namely medication (administered during hospitalization and prescribed at discharge; usage of traditional Chinese herbs was also included), medical treatment (such as monitoring or infusion expenditure), laboratory testing (all blood tests or other sample tests within laboratories, such as routine blood testing or biochemistry tests), imaging exam (such as MRI and CT), costs of provided healthcare materials, nursing care, bed costs, and warming and other add-on costs.

Considering the impact of inflation, all costs were expressed in the year 2014 in Chinese Yuan (CNY), with a 5% discount rate applied. A conversion of 6.14 (central parity rate in 2014) was applied to express the costs in US Dollars.

Statistical analysis

Patient characteristics and cost data were reported according to the diagnosis (IS, TIA, ICH or major gastrointestinal bleeding). Patient characteristics were summarized using descriptive statistics. Categorical variables were shown as n (%), whereas continuous variables were shown as mean ± standard deviation (SD).

Owing to the skewed distribution of costs and length-of-stay (LOS) data, the medians of total direct costs, direct costs per day, and each of the eight direct-cost components were reported. In-hospital direct costs were also depicted across the possible factors to compare the costs in specific subgroups. Multiple linear regression analysis was performed to determine the predictors of higher hospitalization costs; all the baseline variables were included in the analysis, and the dependent variable in the regression analyses was $\log_{10}$ transformed. A P value < 0.05 was considered statistically significant. All analyses were conducted using SAS software (version 9.2, SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Overall, 312 eligible patients with thromboembolism and 143 patients with bleeding were reviewed. Baseline characteristics of the study population are shown in Table 1. About 72.4% of patients with thromboembolism were treated in tertiary hospitals. The mean ages of patients with TIA and IS were 77.2 and 75.6 years, respectively. About 88% of patients with major bleeding were treated in tertiary hospitals, with the mean ages of patients with ICH and major gastrointestinal bleeding being 72.6 and 73.8 years, respectively.

In-hospital direct costs

The median in-hospital direct costs for each patient were 17,857 CNY for IS, 16,589 CNY for TIA, 27,924 CNY for ICH, and 18,196 CNY for major gastrointestinal bleeding (equivalent to 2908, 2702, 4548, 2964 US Dollars, respectively) (Table 2). The highest in-hospital costs were observed in patients with ICH. When dividing the total direct costs by the LOS, the direct costs per day remained the highest in patients with ICH, followed by major gastrointestinal bleeding, IS, and TIA. The major drivers of direct costs were medication costs using Western drugs.

In-hospital direct costs in different subgroups

In-hospital direct costs stratified by demographic, clinical variables, preadmission treatment, and stroke severity are shown in Table 3. As the number of patients with TIA was limited, the TIA and IS groups were combined as the thromboembolism group.

Table 1
Baseline characteristics of patients on admission.

Characteristics	Thromboembolism		Bleeding	
	TIA ($n = 20$)	IS ($n = 292$)	ICH ($n = 92$)	Major gastrointestinal bleeding ($n = 51$)
Age, years, mean ± SD	77.2 ± 10.2	75.6 ± 9.6	72.6 ± 10.8	73.8 ± 10.3
Female, %	70.0	48.6	35.9	35.3
Tertiary hospital, %	90.0	71.2	82.6	98.0
AF history, years, mean ± SD	5.4 ± 5.1	8.0 ± 9.9	5.9 ± 6.7	5.5 ± 5.6
AF history, years, median	4.0	4.0	3.5	3.0
NIHSS scores, mean ± SD	NA	7.5 ± 8.2	NA	NA
CHA$_2$DS$_2$-VASc, mean ± SD	4.4 ± 1.6	4.4 ± 1.7	3.3 ± 1.4	3.6 ± 1.7
HAS-BLED score, mean ± SD	2.3 ± 0.6	2.9 ± 1.1	2.6 ± 1.3	3.1 ± 1.2
Preadmission warfarin treatment, %	5.6	11.1	11.2	20.4
Preadmission antiplatelet treatment, %	40.0	33.5	23.3	40.0
INR on admission, mean ± SD	1.2 ± 0.3	1.1 ± 0.5	1.1 ± 0.3	1.3 ± 0.7
Prior hospitalization owing to stroke, %	15.0	37.8	19.5	29.4
AF type, %				
Paroxysmal	35.0	22.3	29.4	37.3
Persistent	45.0	47.3	45.7	47.1
Unspecified	20.0	30.5	25.0	15.7
Comorbidities, %				
Hypertension	70.0	73.9	81.5	70.6
Diabetes mellitus	50.0	32.5	25.0	43.1
Congestive heart failure	20.0	24.0	13.2	25.5
Prior bleeding	10.0	9.6	12.0	19.6
Prior thromboembolism	15.0	43.2	32.6	43.1
Vascular disease	45.0	25.4	14.1	25.0
Abnormal liver function	0	2.7	1.1	5.9
Abnormal renal function	0	2.4	3.3	11.8
Smoking, %	25.0	24.0	19.6	33.3
Excessive alcohol, %	15.0	15.5	15.2	17.7

TIA: transient ischemic attack; IS: ischemic stroke; ICH: intracranial hemorrhage; AF: atrial fibrillation; NIHSS: National Institutes of Health Stroke Scale; INR: international normalization ratio; SD: standard deviation; HAS-BLED: Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; NA: not applicable.

Table 2
In-hospital direct costs in CNY for all patients of thromboembolism and bleeding groups.

Variables	Thromboembolism group		Bleeding group	
	TIA ($n = 20$)	IS ($n = 292$)	ICH ($n = 92$)	Major gastrointestinal bleeding ($n = 51$)
Length of stay, days	17	15	18	14
Direct costs per day, CNY	934	1211	1647	1435
Total direct costs, CNY	16,589	17,857	27,924	18,196
Bed, CNY(%)	444 (2.0)	390 (1.6)	538 (1.7)	432 (2.0)
Laboratory test, CNY(%)	2383 (10.9)	2113 (8.8)	2335 (7.3)	2468 (11.4)
Imaging, CNY(%)	3125 (14.3)	1794 (7.4)	2009 (6.3)	1505 (6.9)
Doctor service, CNY(%)	829 (3.8)	1043 (4.3)	3352 (10.5)	912 (4.2)
Nursing care, CNY(%)	143 (0.7)	135 (0.6)	171 (0.5)	117 (0.5)
Healthcare material, CNY(%)	1322 (6.0)	1030 (4.3)	2329 (7.3)	1754 (8.1)
Medication, CNY(%)	7423 (33.9)	8705 (36.1)	10,608 (33.4)	7256 (33.5)
Chinese drugs, CNY(%)	402 (1.8)	982 (4.1)	49 (0.2)	0
Western drugs, CNY(%)	5376 (24.5)	7577 (31.4)	10,117 (31.8)	7004 (32.3)
Others, CNY(%)	463 (2.1)	328 (1.4)	273 (0.9)	224 (1.0)

Data are presented as median or median (%). CNY: Chinese Yuan; TIA: transient ischemic attack; IS: ischemic stroke; ICH: intracranial hemorrhage.

Table 3
In-hospital direct costs in different subgroups.

Subgroups	Thromboembolism			ICH			Major gastrointestinal bleeding		
	n	LOS, days	Direct costs, CNY	n	LOS, days	Direct costs, CNY	n	LOS, days	Direct costs, CNY
Age, years									
<65	42	15.0	15,742	20	19.0	31,667	10	14.5	17,407
65−74	71	17.0	17,944	25	17.0	26,004	16	14.5	18,739
≥75	199	15.0	16,608	47	20.0	22,565	25	14.0	13,986
Gender									
Male	156	15.0	16,161	59	20.0	35,470	33	14.0	16,504
Female	156	15.0	17,288	33	17.0	22,224	18	14.5	16,491
AF type									
Paroxysmal	72	15.0	17,420	27	20.0	31,924	19	15.0	18,311
Persistent	147	16.0	16,011	42	18.0	22,025	24	14.5	17,416
Unspecified	93	15.0	16,742	23	17.0	47,574	8	10.0	12,814
Hospital level									
Secondary care hospital	86	18.0	13,201	16	19.5	15,692	1	14.0	78,748
Tertiary referral hospital	226	14.0	17,330	76	18.0	26,909	50	14.0	16,146
Stroke severity									
Mild (NIHSS 1−4)	120	15.0	15,151	NA	NA	NA	NA	NA	NA
Moderate (NIHSS 5−15)	76	15.0	19,487	NA	NA	NA	NA	NA	NA
Moderately severe (NIHSS 16−20)	25	21.0	31,298	NA	NA	NA	NA	NA	NA
Severe (NIHSS 21−42)	25	18.0	39,272	NA	NA	NA	NA	NA	NA
Preadmission warfarin treatment									
No	264	15.5	16,854	79	18.0	26,115	39	14.0	15,788
Yes	32	15.0	14,719	10	13.5	22,395	10	14.0	15,816
Preadmission antiplatelet treatment									
No	205	15.0	15,883	69	20.0	24,649	30	15.0	16,491
Yes	105	16.0	17,607	21	17.0	26,004	20	12.0	17,058
History of hospitalization owing to stroke									
≥Twice	113	16.0	19,036	14	17.0	46,377	15	15.0	19,199
First time	198	15.0	15,465	77	18.0	24,552	36	14.0	14,887
Chronic heart failure									
No	228	15.0	16,836	79	18.0	26,004	38	14.5	16,146
Yes	74	15.0	17,034	12	16.0	22,818	13	12.0	18,327
Hypertension									
No	81	14.0	14,741	17	23.0	40,111	15	14.0	15,788
Yes	229	16.0	17,186	75	17.0	22,224	36	14.0	18,422
Diabetes mellitus									
No	205	15.0	17,285	69	18.0	31,924	29	13.0	13,809
Yes	105	16.0	16,047	23	17.0	18,417	22	15.0	18,986
Prior thromboembolism									
No	182	15.0	15,246	62	19.5	26,059	29	14.0	13,986
Yes	129	16.0	18,897	30	16.0	23,607	22	15.0	18,905
Vascular disease									
No	225	15.0	16,608	79	20.0	31,924	36	15.0	15,245
Yes	82	16.5	17,657	13	13.0	16,778	12	12.0	18,986
Prior bleeding									
No	169	15.0	16,608	38	16.0	23,222	22	14.0	13,415
Yes	30	17.5	23,820	11	17.0	13,201	10	14.0	16,593

LOS: length of stay; CNY: Chinese Yuan; ICH: intracranial hemorrhage; AF: atrial fibrillation; NIHSS: National Institutes of Health Stroke Scale; NA: not applicable.

Factors independently associated with in-hospital costs

The association between patient characteristics and in-hospital costs was assessed using multivariate linear regression analysis. In patients with thromboembolism, the direct costs were significantly related to the hospital level and NIHSS scores. The equation can be represented as: Log_{10} (in-hospital costs) = 3.714 + 0.127 ×(hospital level) + 0.015 × (NIHSS score).

Similarly, the direct costs were related to the hospital level, preadmission warfarin treatment, and prior hospitalization for stroke in patients with ICH, and the equation is: Log_{10} (in-hospital costs) $= 3.315 + 0.377 \times$ (hospital level) $- 0.458$ (preadmission warfarin treatment [yes $= 1$; no $= 0$]) $+ 0.520 \times$ (prior hospitalization for stroke [yes $= 1$; no $= 0$]). In patients with major gastrointestinal bleeding, the regression analysis showed no linear association.

Estimated economic benefits of oral anticoagulation treatment for patients with AF

Based on the incidence of events from randomized clinical trials for warfarin and NOACs,[11–14] and the costs data in the present study, we conducted a simplified simulation analysis to estimate the economic benefits of oral anticoagulation treatment for patients with AF (Table 4).

Discussion

The results of the present study provide novel data on in-hospital direct costs in a cohort of Chinese patients with AF. The median in-hospital direct cost per patient per discharge was 17,857 CNY for patients with IS and 16,589 CNY for patients with TIA. For patients with ICH and major gastrointestinal bleeding, the costs were 27,924 CNY and 18,196 CNY, respectively. The major drivers of direct costs were medications, which accounted for about one-third of the total direct costs in

the different groups. The direct costs were highly related to hospital level and NIHSS scores in patients with thromboembolism. Likewise, the predictors of total direct costs in patients with ICH were hospital level, preadmission warfarin treatment, and prior hospitalization for stroke. These findings suggest the huge medical resources consumed by AF complications in China.

In 2014, the average annual disposable income for a Chinese household was 65,814 CNY, and the median was 46,000 CNY.[15] Quantitatively, the healthcare expenditure of AF-related complications could be catastrophic, given that it exceeds a 40% threshold percentage of a household's annual expenditure excluding expenditure for food.[16,17] Insights into these data are essential for healthcare reimbursement policy and other policy-making decisions.

Treatment decisions for patients with AF depend on balancing the risk of IS *vs.* the increased rate of bleeding with anticoagulation. In real world clinical practice, the economic costs should also be accounted for.[18] In previous studies, therapeutic warfarin was associated with reduced severity of IS at presentation and reduced disability or death at discharge in patients with AF,[19,20] which is consistent with the current study. We also found that the direct costs for patients with IS who had undergone warfarin treatment before admission were less than those for patients who did not undergo warfarin treatment.

In our simulation analysis, we found that warfarin significantly reduces stroke, with a modest increase in bleeding rate compared with that observed using

Table 4
Simulation study on the costs imposed or saved by anticoagulation therapy.

Study	Drug	Ischemic stroke incidence[a], %	ICH incidence[a], %	Major gastrointestinal bleeding incidence[a], %	Direct costs due to ischemic stroke, ICH and major gastrointestinal bleeding per 100 AF patients (CNY)	Economic net benefits per 100 patients with AF[b]
Meta-analysis of RCTs[15]	Warfarin	1.96	0.30	0.90	59,753.30	Warfarin is associated
	Placebo	5.89	0.10	0.60	118,887.70	with 59,134.40 CNY-lower cost than that of placebo
RE-LY[16]	Warfarin	1.20	0.74	1.02	60,652.10	Dabigatran is associated
	Dabigatran (110 mg)	1.34	0.23	1.12	50,730.40	with 9921.70 CNY (110 mg) or 8370.50 CNY (150 mg)-lower
	Dabigatran (150 mg)	0.92	0.30	1.51	52,281.60	cost than that of warfarin
ROCKET[17]	Warfarin	1.42	0.70	1.37	69,832.30	Rivaroxaban is associated
	Rivaroxaban	1.34	0.50	2.00	74,282.40	with 4450.10 CNY-higher cost than that of warfarin

ICH: Intracranial hemorrhage; AF: atrial fibrillation; CNY: Chinese Yuan; RCT: randomized controlled trial.
The costs of the anticoagulant agents and international normalization ratio (INR) testing were not included in the analysis.
  [a] Incidence per year, based on the data in previous randomized controlled trials (RCTs).
  [b] The larger costs minus the smaller costs per 100 patients with AF.

placebo, resulting in net economic benefits (Table 4). Compared to warfarin, dabigatran was associated with lower direct costs while rivaroxaban was associated with moderately higher direct costs in treating patients with AF, not accounting for the costs of the drugs per se and those of international normalization ratio (INR) testing.

Of note, the direct costs of in-hospital treatment of AF-associated complications are high, compared to the average income of the Chinese population. If improperly managed, AF would impose a substantial burden on the society. Further, the prevalence of AF is expected to rise in the future because of the aging population and emerging risk factors in this country [21]; thus, the importance of stroke prevention with anticoagulation treatment should be emphasized more in China, given that the treatment is considerably underused despite some improvements in recent years.[22]

Data are lacking with regard to the costs that NOACs will impose on the medical care system, despite the fact that clinical studies have shown their efficacy in reducing the risk of AF-related stroke, compared with warfarin.[23,24] In China, all these NOACs are not covered by medical insurance, and the current data on in-hospital direct costs can be applied in budget impact analysis to assess the affordability of health technologies within specific healthcare settings.[25,26] Hence, the current data are important for further decision-analytic models and cost-effectiveness studies in China.[27]

The LOS is an independent determinant of in-hospital direct costs.[28,29] In the current study, the median LOS for each condition was greater than 2 weeks, suggesting the need for improvement in treatment and rehabilitation effectiveness in Chinese hospitals. Further studies to reduce the in-hospital direct costs are required. The current study provides information on in-hospital direct costs, which shows that the highest proportion of in-hospital direct costs are related to Western medicine. Nonetheless, avoiding medical therapy without evidence for prognostic benefit, such as Chinese herbs, may help further reduce total in-hospital direct costs.

Several internal factors may also influence in-hospital direct costs, including medical insurance system, medical referral system, specific hospital management, and the financial status of the patients. In China, although there are different types of medical insurance, patients from other provinces can only receive a portion of the reimbursement. Patients in good financial condition typically pursue better medical care, and since the medical referral system has not been well established, patients can directly go to tertiary hospitals without referral, regardless of the severity of the disease. These factors can also be regulatory targets for the government to reduce the economic burden in China.

This study has several limitations. First, patients with only TIA or IS, ICH, and major gastrointestinal bleeding were included in this study. Second, the study population was recruited from selected service providers located in Beijing, a relatively developed area in China, and, thus, may not be expected to be representative of the whole country. In addition, we acknowledge that in-hospital direct costs may provide limited information, as the resource utilization of the whole chain of care is not considered. Costs incurred after discharge may be even higher, owing to rehabilitation, long-term care, and impairment of work capacity or daily activities. Although the costs were inflated to a common price year from different calendar years, it may not necessarily reflect the current treatment mix.

Despite these limitations, the present study still provides detailed data on in-hospital direct costs of AF-related thromboembolism and bleeding, and reveals the economic burden of AF-related complications in China. These data are essential for policy development, service planning, and cost-effectiveness analyses for new therapeutic agents.

Conclusion

Given the high prevalence,[30] AF-related thromboembolism and bleeding events impose considerable economic burden on the Chinese society. Efforts to improve the management of AF may confer substantial economic benefits.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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