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ORIGINAL RESEARCH

Impact of Beta-Blockers on Pneumonia, Mortality and Functional Outcomes of Patients with Intracerebral Hemorrhage-A Retrospective Multicenter Study

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Purpose: Given the current lack of research on the impact of beta-blockers (BB) on clinical outcomes in patients with intracerebral hemorrhage (ICH). This study aimed to evaluate the effect of BB on pneumonia, functional outcomes, and mortality in adult patients with primary ICH.

Patients and Methods: This was a retrospective study of a registry cohort of patients with ICH from 13 stroke centers in Beijing, China. Patients aged 18 years or older with first-time primary ICH admitted within 72 h after onset were included. Main exclusion criteria including previous ICH, previous mRS≥3, primary intraventricular hemorrhage, missing of baseline data or lost of follow-up. BB group was defined as any use of beta-blockers pre-existing or initiated after onset of ICH, those without any use of beta-blockers were defined as non-BB group. The clinical outcomes were in-hospital pneumonia, mortality and functional outcome (favorable outcome defined as a modified Rankin Score of 0–3) at 90 d.

Results: The study included 947 patients (657 males [69.38%]; mean [standard deviation] age, 57.67 [13.68] years). Two hundred and thirty of 809 patients (28.43%) in the non-BB group and 64 of 138 patients in the BB group were diagnosed with pneumonia (46.38%). Multivariate analysis confirmed that patients in the BB group were likely to have an increased risk of pneumonia after adjusting for confounders (odds ratio [OR], 1.806; 95% confidence interval [CI]:1.139–2.862; P=0.0119). No statistical difference was observed in the proportion of favorable outcome (P=0.9289) or mortality (P=0.2120) at 90 d between the two groups.

Conclusion: The results of this cohort study suggest that any use of BB is associated with an increased risk of pneumonia post-ICH. Randomized clinical trials are needed to evaluate the effects of non-selective BB on the prevention of pneumonia post-ICH.

Keywords: beta-blockers, intracerebral hemorrhage, pneumonia, outcome, mortality

Introduction

Stroke is the second leading cause of death globally and the third leading cause of death or disability.[1] Intracerebral hemorrhage (ICH) is the most severe type of stroke, with a mortality rate exceeding 36% within 1 month and 50% within 1 year.[2–4] Survivors often experience residual disabilities including motor and cognitive impairments.[3,5] The most common infectious complication of stroke includes pneumonia, which has been reported in 16.8% of patients with ICH.[6] Pneumonia is a major risk factor for a poor prognosis in ICH and is correlated with a high mortality rate.[7]

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The post-ICH pneumonia is related to immunosuppression induced by continuous activation of the sympathetic nervous system. The post-ICH pneumonia relates to the poor outcomes of ICH.[8] Preclinical experiments demonstrated that blocking the sympathetic nervous system with beta-blockers can prevent pneumonia and significantly reducing post-ICH mortality.[9–13]

Some clinical studies have demonstrated that beta-blocker (BB) use is linked to decreased mortality and risk of pneumonia associated with ICH.[8,14–16] Other studies discovered that BB use was associated with an increased risk of pneumonia in patients with ICH.[17–19] Otherwise, some studies reported that BB use was unrelated to the risk of pneumonia in patients with ICH.[20] Given the conflicting results from limited clinical studies on the use of BB in pneumonia and outcomes post-ICH, we conducted a retrospective study based on a Chinese multicenter prospective registry of ICH to analyze the impact of BB on pneumonia, mortality and functional outcomes of patients with ICH.

Methods

Study Design and Participants

This study included patients diagnosed with ICH at 13 stroke centers in Beijing, China. Participants were prospectively enrolled between June 2014 and September 2016, with a follow-up period of 1 year. A total of 1964 individuals were initially recruited and all participants provided written informed consent. The study adhered to the ethical principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (KY2014-023-02).

The inclusion criteria were admitted to the hospital within 72 h of symptom onset, age 18 years or older, a diagnosis of primary ICH confirmed via computed tomography (CT) in accordance with the World Health Organization guidelines and signed informed consent from either the patient or a family member.

Patients were excluded if they had a prior history of ICH, a pre-ICH modified Rankin Scale (mRS) score of 3 or higher, or if they were diagnosed with primary intraventricular hemorrhage (IVH). Patients with incomplete baseline data or lost of follow-up records were also excluded. From the initial cohort of 1964 patients with ICH, 82 patients were excluded for the time from onset to admission exceeded 72 hours, 2 patients were excluded for aged younger than 18 years old, 47 patients were excluded for previous ICH, 59 were excluded due to pre-existing disabilities (mRS $\geq$ 3), 53 patients were excluded for primary IVH, 289 patients were excluded for missing of baseline imaging data of head CT, 90 patients were excluded for missing of baseline clinical data, 214 patients were excluded for missing of data of dysphagia screening, 181 patients were excluded for missing of pneumonia or 90-d functional outcome. Finally, 947 patients were included in the final analysis (Figure 1). BB group was defined as any use of beta-blockers pre-existing or initiated after onset of ICH, meanwhile, non-BB group was defined as the absence of recorded use of beta-blockers.

Collection of Data

The analysis included variables such as age, sex, and blood pressure (systolic and diastolic) on admission. Medical history was documented, including conditions such as hypertension, diabetes mellitus, prior stroke, myocardial infarction, and atrial fibrillation. Lifestyle factors, including smoking and drinking were also recorded. The pre-admission functional status was evaluated using the mRS. The timing of admission from symptom onset was categorized into three intervals: within 6 hours, between 6 and 24 h, and between 24 and 72 h.

Stroke severity on admission was assessed using the National Institutes of Health Stroke Scale (NIHSS), which ranged from 0 to 42, with high scores indicating significant neurological impairment. The Glasgow Coma Scale (GCS) score, ranging from 3 to 15, was applied to evaluate consciousness, with low scores suggesting severe alterations. Swallowing function was assessed through dysphagia screening, categorizing patients as with or without dysphagia. In-hospital surgical interventions including decompressive craniectomy, hematoma aspiration, craniotomy for hematoma evacuation, and lateral ventriculopuncture drainage were documented. Data of pre-admission medication were collected, including antidiabetic drugs, lipid-lowering drugs, antiplatelet drugs, and antihypertensive drugs, specifically angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs).

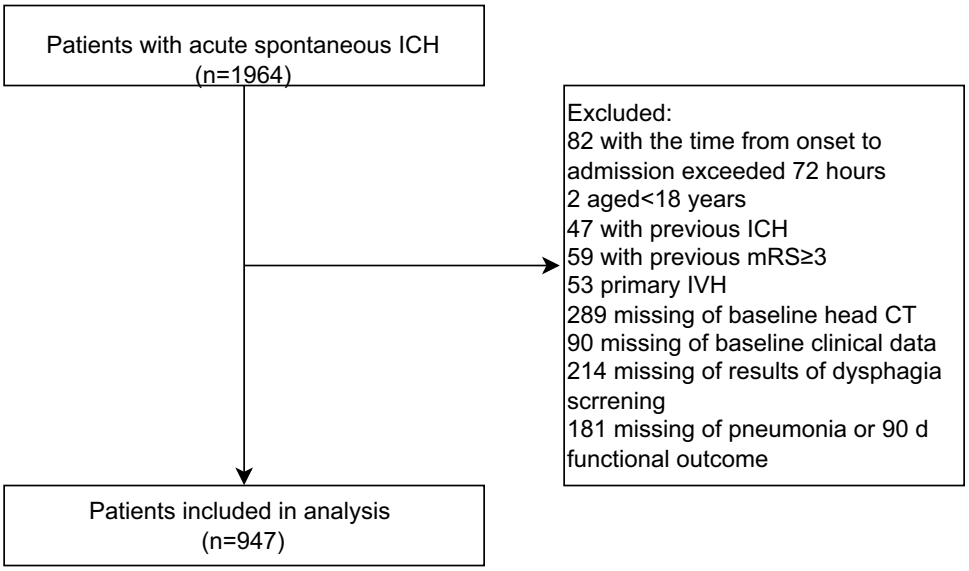


Figure 1 Flow chart for selection of study patients.
Abbreviations: ICH, intracerebral hemorrhage; mRS, modified Rankin Score; IVH, primary intraventricular hemorrhage; CT, computed tomography.

Characteristics of ICH

The analysis of ICH charcteristics was performed using digital CT imaging for centrally evaluation. The hematoma volume was determined using the ABC/2 formula[21] based on initial CT scans. Additional factors assessed included the location of the hematoma (cerebral lobe, basal ganglia, thalamus, brainstem, and cerebellum) and the extension of the hematoma into the intraventricular or subarachnoid spaces.

Outcome Evaluation and Follow-up

The in-hospital pneumonia diagnosed by the criteria Centers for Disease Control and Prevention (CDC) and the data of outcome was retrieved from the study database.[22] The participants were subsequently followed up through structured telephone interviews conducted 3 months after the onset of ICH. The follow-up data were collected directly from the patients or from their legal representatives if they were unable to provide information.

To minimize bias, these evaluations were performed by trained personnel who were blinded to the patient's baseline characteristics. Functional outcomes were assessed using the mRS, a validated measure of stroke outcomes, with scores ranging from 0 (no symptoms) to 6 (death). In this study, favorable outcomes were defined as an mRS score of 0–3.

Statistical Analysis

Data analysis was conducted using Statistical Analysis Software Studio version 9.4 (SAS Institute, Cary, North Carolina, USA). For continuous variables following a normal distribution, the results are expressed as mean ± standard deviation (SD). Non-normally distributed continuous variables are reported as median values and interquartile ranges (IQR). Moreover, categorical variables are summarized as frequencies and percentages.

Comparisons between groups for continuous variables were performed using *t*-tests when the data were normally distributed or Mann-Whitney *U*-tests for non-normally distributed data. The chi-square test was utilized to analyze categorical variables. Multivariate logistic regression models were employed to assess the association between groups and the occurrence of pneumonia or 90-d mRS. Additionally, multivariate Cox proportional hazards models were utilized to evaluate the effect of BB on 90-d mortality.

Variables included in the multivariate models were selected based on both univariate analysis ($P<0.05$) and a review of the relevant literature. The correlations and collinearity among these variables were assessed to ensure robustness. We predefined the subgroup analysis including age (<60y and ≥60y), sex (male and female), hematoma volume (less than 10, 10–30, and greater than 30 mL) and dysphagia (with and without dysphagia) based on the previous studies. Subgroup

analyses followed similar analytical approaches using the same adjustment variables as those applied to the outcomes. Results from both the crude and adjusted regression models were reported as odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical tests were two-sided, and significance was defined as P<0.05.

Results

Baseline Characteristics of Total Patients

A total of 947 patients were included in this study (flow chart displayed in Figure 1) comprising 657 males and 290 females, with a male-to-female ratio of 2.27:1. The age ranged from 18 to 92 years, with a mean age of 57.67±13.68 years. A total of 619 patients (65.36%) arrived at the hospital within 6 h of symptom onset, and 833 patients (87.96%) arrived within 24 h. Six hundred and sixty-three (70.01%) patients had a history of hypertension, 141 (14.89%) were diagnosed with diabetes mellitus, 10 (1.06%) had atrial fibrillation, 15 (1.58%) were identified with myocardial infarction, 136 (14.36%) had a stroke, 436 (46.04%) smoking, and 337 (33.59%) drinking. A total of 831 patients (87.75%) had a prior mRS score of 0. The average systolic blood pressure (SBP) on admission was 165 (148–186) mmHg, and the average diastolic blood pressure (DBP) was 96 (82–109) mmHg. The median baseline NIHSS score was 11 (4–19), and the median baseline GCS score was 14 (9–15). The median baseline hematoma volume was 15.52 (6.00–36.98) mL.

Comparison of Baseline Characteristics Between Patients in the Non-BB Group and BB Group

Baseline characteristics of patients in the non-BB and BB groups were presented in Table 1. The non-BB group included 809 patients (85.43%), whereas the BB group included 138 patients (14.57%). The non-BB group had a lower proportion of hypertension (67.86% vs 82.61%, P=0.0005) and prior antiplatelet (14.96% vs 23.19%, P=0.0152) than those in the BB group. Patients in the non-BB group had a low SBP (163 [147–184] vs 179.5 [153–200], P<0.0001) and DBP (95 [82–107] vs.100

Table 1 Comparison of Baseline Characteristics Between ICH Patients with Any Use of Beta-Blockers Pre-Existing or Initiated After Onset of ICH (BB Group) and Those Without (Non-BB Group)

Variable	Non-BB group (n=809)	BB group (n=138)	P-value
Age, years, mean ± SD	57.69±13.59	57.54±14.27	0.6910
Male, n (%)	561 (69.34)	96 (69.51)	0.9586
Hypertension, n (%)	549 (67.86)	114 (82.61)	0.0005
Diabetes mellitus, n (%)	118 (14.59)	23 (16.67)	0.5257
Atrial fibrillation, n (%)	6 (0.74)	4 (2.9)	0.0657
Myocardial infarction, n (%)	12 (1.48)	3 (2.17)	0.8167
Prior stroke, n (%)	116 (14.34)	20 (14.49)	0.9620
Smoking, n (%)	373 (46.11)	63 (45.65)	0.9212
Drinking, n (%)	295 (36.46)	42 (30.43)	0.1715
Prior mRS score, n (%)			0.5592
0	713 (88.13)	118 (85.51)	
1	76 (9.39)	17 (12.32)	
2	20 (2.47)	3 (2.17)	
Medication history			
Prior Antidiabetic, n (%)	72 (8.9)	15 (10.87)	0.4590
Prior lipid-lowering, n (%)	40 (4.94)	12 (8.7)	0.0738
Prior antiplatelet, n (%)	121 (14.96)	32 (23.19)	0.0152
Prior ACEI, n (%)	39 (4.82)	2 (1.45)	0.0721
Prior ARB, n (%)	43 (5.32)	10 (7.25)	0.3616
Prior CCB, n (%)	133 (16.44)	27 (19.57)	0.3652

(*Continued*)

Table 1 (Continued).

Variable	Non-BB group (n=809)	BB group (n=138)	P-value
Time from onset to admission			0.5282
≤6 h, n (%)	523 (64.65)	96 (69.57)	
6<time≤24 h, n (%)	187 (23.11)	27 (19.57)	
24<time≤72 h, n (%)	99 (12.24)	15 (10.87)	
SBP, mmHg, median (IQR)	163 (147–184)	179.5 (153–200)	<0.0001
DBP, mmHg, median (IQR)	95 (82–107)	100 (89–117)	0.0003
Dysphagia, n (%)	327 (40.42)	81 (58.70)	<0.0001
Severity of ICH			
GCS on admission, median (IQR)	14 (9–15)	12 (8–15)	0.0414
NIHSS on admission, median (IQR)	10 (4–22)	12.5 (8–22)	0.1708
Location of hematoma			0.4406
Lobar, n (%)	209 (25.83)	46 (33.33)	
Basal ganglia, n (%)	394 (48.70)	58 (42.03)	
Thalamus, n (%)	114 (14.09)	18 (13.04)	
Brain stem, n (%)	48 (5.93)	9 (6.52)	
Cerebellum, n (%)	44 (5.44)	7 (5.07)	
Extension into the ventricle, n (%)	300 (37.08)	69 (50.00)	0.0040
Extension into subarachnoid, n (%)	120 (14.83)	22 (15.94)	0.7359
Hematoma volume, mL, median (IQR)	15 (5.85–36.75)	20 (7.4–39.47)	0.1253
Surgical intervention, n (%)	170 (21.01)	35 (25.36)	0.2516

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; mRS, modified Rankin score; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; IQR, interquartile range; SD, standard deviation.

[89–117], P=0.0003) than those in the BB group. Patients in the non-BB group had a low frequency of dysphagia (40.42% vs 58.70%, P<0.0001) and extension into the ventricle (37.08% vs 50.00%, P=0.0040). Patients in the non-BB group had higher GCS scores on admission (14 [9–15] vs 12 [8–15], P=0.0414) than those in the BB group. Patients in both the BB and non-BB groups had similar distributions of age, sex, diabetes mellitus, atrial fibrillation, myocardial infarction, prior stroke, smoking, drinking, prior mRS score, prior antidiabetic, prior lipid-lowering, prior ACEI, prior ARB and prior CCB. Additionally, no significant differences were observed between the groups regarding the time from ICH onset to admission, NIHSS score on admission, hematoma location, hematoma volume, extension into the subarachnoid, and surgical intervention (all P>0.05).

Association Between BB and Pneumonia

Association between BB and pneumonia was shown in Table 2. The overall rate of pneumonia was 31.05%. Two hundred and thirty of 809 patients (28.43%) in the non-BB group and 64 of 138 patients in the BB group were diagnosed with pneumonia (46.38%). Logistic regression analysis revealed a significant difference in the risk of pneumonia between the BB and non-BB groups, with a significantly higher risk of pneumonia in the BB group than in the non-BB group (OR: 2.177; 95% CI: 1.507–3.145; P<0.0001). Subsequently, multivariate analysis verified that patients in the BB group were likely to have an increased risk of pneumonia after adjustment for sex, age, hypertension, atrial fibrillation, drinking, prior ACEI, prior ARB, prior CCB, prior lipid-lowering, prior antiplatelet, time from onset to admission, SBP, DBP, dysphagia, GCS on admission, NIHSS on admission, hematoma location, extension into the ventricle, hematoma volume, and surgical intervention (OR: 1.806; 95% CI: 1.139–2.862; P=0.0119).

Association Between BB and 90 d mRS

Association between BB and 90 d mRS was shown in Table 2. The overall rate of favorable outcome (mRS 0–3) at 90 d was 62.09%. In the non-BB group, 511 of the 809 patients had a favorable outcome at 90 d (63.16%), whereas 77 of

Table 2 Impact of Beta-Blockers on Clinical Outcomes

Clinical Outcome	No. of Events (%)		Unadjusted		Adjusted*	
	No-BB Group (n=809)	BB Group (n=138)	OR/HR (95% CI)	P-value	OR/HR (95% CI)	P-value
Pneumonia[a]	230/809(28.43)	64/138(46.38)	2.177 (1.507–3.145)	<0.0001	1.806 (1.139–2.862)	0.0119
90 d mRS 0–3[a]	511/809(63.16)	77/138(55.80)	1.358 (0.943–1.957)	0.1000	0.977 (0.579–1.646)	0.9289
90 d death[b]	118/809(14.59)	21/138(15.22)	1.209 (1.008–1.450)	0.0410	1.131 (0.932–1.371)	0.2120

Notes: [a]Analyzed by multivariable logistic regression models. [b]Analyzed by multivariable Cox proportional hazard models. *Adjusted for sex, age, hypertension, atrial fibrillation, drinking, prior angiotensin-converting enzyme inhibitors, prior angiotensin receptor blockers, prior calcium channel blockers, prior lipid-lowering, prior antiplatelet, time from onset to admission, systolic blood pressure, diastolic blood pressure, dysphagia, Glasgow Coma Scale on admission, National Institutes of Health Stroke Scale on admission, hematoma location, extension into the ventricle, hematoma volume, and surgical intervention.

Abbreviations: BB group, patients with any use of beta-blockers pre-existing or initiated after onset of ICH; Non-BB group, patients without any use of beta-blockers; mRS, modified Rankin Score; OR, odd ratio; HR, hazard ratio; CI, conffdence interval.

the 138 patients in the BB group had a favorable outcome at 90 d (55.80%). Logistic regression analysis identified no statistical difference in the frequency of favorable outcome at 90 d between the non-BB and the BB groups (OR: 1.358; 95% CI: 0.943–1.957; P=0.100). Further multivariate analysis, adjusted for factors as same as above also demonstrated no significant difference (OR: 0.977; 95% CI: 0.579–1.646; P=0.9289).

Association Between BB and 90 d Mortality

Association between BB and 90 d mortality was shown in Table 2. Overall 90 d mortality rate was 14.68%, with 118 of 809 in the non-BB group (14.59%) and 21 of 138 in the BB group (15.22%). Cox proportional hazard models report higher mortality at 90 d in the BB group than in the non-BB group (HR: 1.209; 95% CI: 1.008–1.450; P=0.0410). However, no statistical difference was observed between the two groups after adjusting for multivariables (HR: 1.131; 95% CI: 0.932–1.371; P=0.2120).

Subgroup Analysis of the Impact of BB on Pneumonia, mRS, and Mortality at 90 d

We conducted a stratified analysis as illustrated in Figure 2. The relationship between BB and the high rate of pneumonia in patients with ICH remained significant after adjusting for multivariables. This association was observed across all age groups (<60 years or 60 years and older), those with large baseline hematoma volume (> 30 mL) or in patients without dysphagia. Subgroup analysis of the distribution of favorable outcome (mRS 0–3) at 90 d between the two groups revealed no statistical difference after adjusting for multivariables. In the subgroup analysis of 90 d mortality, unexpectedly females in the BB group exhibited a significantly increased mortality rate at 90 d after adjusting for multivariables (BB group vs non-BB group = 19.05% vs 13.71%; HR:1.614; 95% CI: 1.119–2.327; P=0.0104; P for interaction: 0.0426).

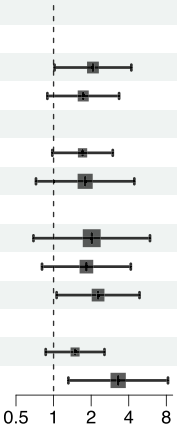
Discussion

This study was based on a Chinese multicenter registry of ICH and investigated the relationship between the use of BB and the risk of pneumonia, 90-d neurological functional outcomes, and 90-d mortality. Our study confirmed that, compared to individuals in the non-BB group, those in the BB group had a significantly increased risk of pneumonia, especially those with a larger hematoma volume or those without dysphagia. Although the risk of pneumonia increased in the BB group, this did not affect their 90-d neurological outcomes. The 90-d mortality rate in individuals in the BB group was similar to that of the individuals in the non-BB group. However, among female patients, the mortality risk was significantly higher in those receiving BB compared to those not receiving BB.

Preclinical studies have demonstrated that activation of the sympathetic nervous system post ICH induces immunosuppression, which facilitates the development of pneumonia. Furthermore, administration of BB has been demonstrated to reverse this process, thereby reducing the risk of pneumonia and mortality. However, as first-line treatment for hypertension and coronary artery disease and commonly prescribed for diseases such as migraines, and anxiety, prior use of BB potentially altering sympathetic tone combined with the presence of cardiovascular comorbidities may contribute

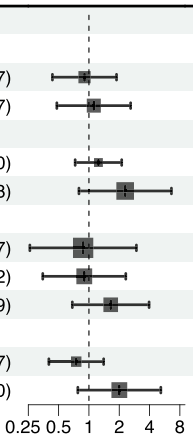
pneumonia [a]

Variable	No. of patients	No. /Total No. (%) Non–BB (n = 809)	BB (n = 138)	Adjusted * OR (95% CI)	P	p for interaction
All Patients	947	809	138			
Age						0.8421
Age < 60y	523	108/445(24.27)	32/78(41.03)	2.067(1.018–4.197)	0.0445	
Age ≥ 60y	424	122/364(33.52)	32/60(53.33)	1.728(0.892–3.348)	0.0464	
Sex						0.8191
Male	657	165/561(29.41)	44/96(45.83)	1.706(0.977–2.979)	0.0604	
Female	290	65/248(26.21)	20/42(47.62)	1.791(0.723–4.435)	0.2078	
Hematoma volume						0.9700
Hematoma volume < 10mL	351	48/308(15.58)	12/43(27.91)	2.021(0.690–5.918)	0.1994	
10mL ≤ Hematoma volume ≤ 30mL	317	68/271(25.09)	20/46(43.48)	1.832(0.808–4.155)	0.1475	
Hematoma volume > 30mL	279	114/230(49.57)	32/49(65.31)	2.272(1.058–4.880)	0.0354	
Dysphagia						0.5149
With Dysphagia	408	183/327(55.96)	53/81(65.43)	1.487(0.865–2.557)	0.1514	
Without Dysphagia	539	47/482(9.75)	11/57(19.30)	3.292(1.314–8.250)	0.0110	



90d mRS (0-3) [a]

Variable	No. of patients	No. /Total No. (%) Non–BB (n = 809)	BB (n = 138)	Adjusted * OR (95% CI)	P	p for interaction
All Patients	947	809	138			
Age						0.9403
Age < 60y	523	316/445(71.01)	52/78(66.67)	0.904(0.434–1.880)	0.7863	
Age ≥ 60y	424	195/364(53.57)	25/60(41.67)	1.118(0.482–2.596)	0.7951	
Sex						0.1252
Male	657	361/561(64.35)	60/96(62.50)	1.243(0.730–2.116)	0.3492	
Female	290	150/248(60.48)	17/42(40.48)	2.291(0.796–6.596)	0.1244	
Hematoma volume						0.8394
Hematoma volume < 10mL	351	252/308(81.82)	34/43(79.07)	0.876(0.259–2.961)	0.8314	
10mL ≤ Hematoma volume ≤ 30mL	317	171/271(63.10)	26/46(56.52)	0.899(0.348–2.323)	0.8266	
Hematoma volume > 30mL	279	88/230(38.26)	17/49(34.69)	1.646(0.684–3.957)	0.2657	
Dysphagia						0.1736
With Dysphagia	408	100/327(30.58)	31/81(38.27)	0.748(0.400–1.400)	0.3642	
Without Dysphagia	539	411/482(85.27)	46/57(80.70)	2.004(0.776–5.176)	0.1508	



90d death [b]

Variable	No. of patients	No. /Total No. (%) Non–BB (n = 809)	BB (n = 138)	Adjusted * HR (95% CI)	P	p for interaction
All Patients	947	809	138			
Age						0.1853
Age < 60y	523	57/445(12.81)	8/78(10.26)	0.943(0.722–1.232)	0.6677	
Age ≥ 60y	424	61/364(16.76)	13/60(21.67)	1.329(0.984–1.796)	0.0637	
Sex						0.0426
Male	657	84/561(14.97)	13/96(13.54)	1.031(0.814–1.306)	0.8007	
Female	290	34/248(13.71)	8/42(19.05)	1.614(1.119–2.327)	0.0104	
Hematoma volume						0.3360
Hematoma volume < 10mL	351	15/308(4.87)	3/43(6.98)	1.339(0.946–1.894)	0.0997	
10mL ≤ Hematoma volume ≤ 30mL	317	36/271(13.28)	6/46(13.04)	1.047(0.728–1.507)	0.8036	
Hematoma volume > 30mL	279	67/230(29.13)	12/49(24.49)	1.000(0.722–1.385)	0.9988	
Dysphagia						0.4262
With Dysphagia	408	106/327(32.42)	21/81(25.93)	1.167(0.902–1.510)	0.2407	
Without Dysphagia	539	12/482(2.49)	0/57(0)	1.060(0.786–1.431)	0.7021	

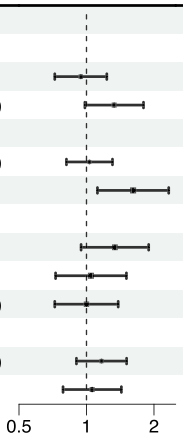


Figure 2 Subgroup analysis to evaluate the relationship of the use of beta-blockers on pneumonia, functional outcome and mortality in ICH patients of different age (< 60 years or ≥ 60 years), gender, baseline hematoma volume (30 mL) and swallowing function. [a]Analyzed by multivariable logistic regression models. [b]Analyzed by multivariable Cox proportional hazard models. *Adjusted for sex, age, hypertension, atrial fibrillation, drinking, prior angiotensin-converting enzyme inhibitors, prior angiotensin receptor blockers, prior calcium channel blockers, prior lipid-lowering, prior antiplatelet, time from onset to admission, systolic blood pressure, diastolic blood pressure, dysphagia, Glasgow Coma Scale on admission, National Institutes of Health Stroke Scale on admission, hematoma location, extension into the ventricle, hematoma volume, and surgical intervention.

Abbreviations: BB group, patients with any use of beta-blockers pre-existing or initiated after onset of ICH; Non-BB group, patients without any use of beta-blockers; mRS, modified Rankin Score; OR, odd ratio; HR, hazard ratio; CI, confidence interval.

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to poor outcomes of ICH. Our findings suggest that the unfavorable outcome was more strongly associated with pneumonia than with 90-d functional outcomes (mRS).

The volume of hematoma is closely related to immune status, and it is also an important predictor of pneumonia.[23,24] For patients with smaller hematoma volumes, the risk of pneumonia is relatively low, and therefore, the impact of BB on pneumonia is not significant. Our study confirmed that in patients with larger hematoma volumes (>30mL), the risk of pneumonia in BB group is significantly higher than that in Non-BB group. Furthermore, dysphagia are also an important predictor of pneumonia.[24] In our subgroup analysis, the increased risk of pneumonia in BB group was significant only in patients without dysphagia, while no statistical difference was found in patients with dysphagia. This may be related to the higher inherent risk of pneumonia in patients with dysphagia (55.96% in Non-BB group and 65.43% in BB group, separately).

Our study is the first to report an association between the use of β-blockers and an increased mortality rate in female patients. Previous studies have confirmed that the mortality rate among female stroke patients in specific age groups is higher than that of male patients, suggesting that physiological differences between genders, particularly estrogen, may play an important regulatory role in ICH mortality.[25,26] Similarly, it can be hypothesized that estrogen may influence the effects of β-blockers on ICH patients of different genders.

As pneumonia can significantly increase the mortality rate and risk of stroke recurrence in patients with ICH, it is reasonable to assume that the incidence of pneumonia is closely associated with poor prognosis and higher mortality.[7,27] However, in our study, despite the significantly elevated risk of pneumonia in the BB group, it was not associated with mortality or functional outcome. A possible explanation for this could be the protective effects of BB on both the cardiovascular and nervous systems were offset as the influence of imbalanced comorbidities between the two groups.[8,28] Additionally, our study did not include other infectious diseases, such as urinary tract infections or sepsis, which could also contribute to the lack of association between BB and mortality or poor prognosis.

Our research found that both pre- and post- onset BB use increased risk of pneumonia, are similar to those of some previous studies. Starr et al's study discovered that the post-onset BB use significantly increased the risk of pneumonia but did not affect in-hospital mortality or mRS at discharge.[18] Westendorp et al found patients with pre-onset BB use have a higher rate of pneumonia in ischemic stroke and ICH.[19]

Notably, most studies focused on selective β_1 receptor antagonists, such as atenolol. In preclinical studies, non-selective BB that inhibits β_2 receptors has been demonstrated to reverse post-stroke immunosuppression and reduce the risk of pneumonia and mortality.[9–12] Given the widespread distribution of β_2 receptors (rather than β_1 receptors or β_3 receptors), which are expressed by most immune cells and their potential immunomodulation, non-selective BB may play a key role in alleviating post-stroke immunosuppression and preventing pneumonia.[29–32] Therefore, early initiating (within 24 h) administration of non-selective BB-propranolol which could reserve cardiovascular benefits as well as reverse immunosuppression and prevent pneumonia, has the potential to reduce the risk of pneumonia post-ICH. An ongoing randomized controlled clinical trials to determine whether propranolol can be used to prevent stroke-associated pneumonia post-ICH (NCT05419193).[33]

The strengths of our study was based on a large prospective multicenter ICH cohort from China and explored the impact of BB use on the risk of in-hospital pneumonia, 90-d functional outcomes, and mortality. Additionally, we adjusted for imbalances in baseline variables between the two groups as well as for all potential risk factors related to the outcomes.

The limitations of this study hinder the generalizability of our conclusions. First, our study did not differentiate between the types, duration, or dosages of BB or whether the medication was administered before or after the onset of ICH. Second, as a retrospective study, the definition of pneumonia was based on the CDC criteria, which differed from the newest diagnostic criteria of strokeassociated pneumonia, which define stroke-associated pneumonia as a lower respiratory tract infection within 7 d after a stroke.[34]

Conclusion

The use of BB was associated with an increased risk of pneumonia but had no impact on 90-d mRS of 0–3 scores. Additionally, BB use in females was associated with an elevated 90-d mortality risk. Randomized controlled clinical trials are urgently needed to evaluate the effectiveness of propranolol in preventing stroke-associated pneumonia post-ICH.

Data Sharing Statement

Data may be shared by writing to the corresponding author.

Ethical Approval

The study was approved by the ethics committees of Beijing Tiantan Hospital, Capital Medical University (KY2014-023-02). All study procedures were conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Informed Consent

Written informed consent was obtained from all patients or legal surrogates.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest.

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