Impact of Prior Ischemic Stroke on Outcomes in Patients With Heart Failure

— A Propensity-Matched Study —

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Background: Whether ischemic stroke per se, rather than older age or additional comorbidities, accounts for the adverse prognosis of heart failure (HF) is uncertain. The present study examined the intrinsic association of ischemic stroke with outcomes in a propensity-matched cohort.

Methods and Results: Of 1,351 patients hospitalized with HF, 388 (28.7%) had prior ischemic stroke. Using propensity score for prior ischemic stroke, estimated for each patient, a matched cohort of 379 pairs of HF patients with and without prior ischemic stroke, balanced on 32 baseline characteristics was assembled. At 30 days, prior ischemic stroke was associated with significantly higher risks of the combined endpoint of all-cause death or readmission (hazard ratio [HR]: 1.91; 95% confidence interval [CI]: 1.38 to 2.65; $P < 0.001$), all-cause death (HR: 2.08; 95% CI: 1.28 to 3.38; $P = 0.003$), all-cause readmission (HR: 2.67; 95% CI: 1.78 to 4.01; $P < 0.001$), and HF readmission (HR: 2.11; 95% CI: 1.19 to 3.72; $P = 0.010$). Prior ischemic stroke was associated with a significantly higher risk of all 4 outcomes at both 6 months and 1 year.

Conclusions: Prior ischemic stroke was a potent and persistent risk predictor of death and readmission among patients with HF after accounting for clinical characteristics.

Key Words: Death; Heart failure; Ischemic stroke; Propensity score; Readmission

Heart failure (HF) is predominantly a complex disease of older adults with extensive comorbidities that have substantial implications for prognosis.^{1–3} Stroke, especially ischemic stroke responsible for the majority of strokes, is a common comorbidity in patients with HF.^{4,5} There is a general perception that the interaction between ischemic stroke and HF deteriorates the outcomes of HF because the 2 diseases share common risk factors and pathophysiological mechanisms.⁶

To date, there is a paucity of studies investigating the effect of prior ischemic stroke on outcomes in real-world patients with HF, and several large cohorts failed to identify stroke as a significant predictor of HF prognosis in

Western populations.^{7–9} Associations between stroke and poor outcomes of HF have often been concealed by the bias of older age and higher prevalence of additional comorbidities that affected HF prognosis. Further, the bias is unable to be adjusted using traditional regression-based multivariable risk models because of the limitation of lack of procedural transparency, confounders that may not be balanced at baseline, and strong and often untenable model assumptions.¹⁰ Accordingly, whether stroke per se, rather than age or comorbidities, accounts for adverse prognosis is uncertain. Propensity score matching, on the other hand, is designed to assemble cohorts in which patients are balanced on all measured baseline covariates

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and investigators are blinded to study outcomes.^{11–14} The use of propensity scores to perform adjustment also allows investigators to assess the extent to which stroke has an independent association with poor outcomes.

Therefore, the objective of the present study was to examine the association of prior ischemic stroke with outcomes in a propensity score-matched cohort of patients with HF in which those with and without stroke would be well balanced on all measured baseline covariates. An understanding of this association could have important implications for future prevention strategies in these particular patients with HF.

Methods

Study Population

This was a prospective observational cohort study of patients hospitalized in the Heart Failure Center of China-Japan Friendship Hospital between January 1, 2015, and January 30, 2018. All patients aged 18 years or older admitted to the department with a diagnosis of HF were enrolled. Patients with HF were identified by the clinical practice guideline of the Chinese Society of Cardiology, with diagnostic criteria that are similar to the recommendations of the European Society of Cardiology.^{15,16} Cases of missing data or lost to follow-up were excluded. The patient selection process is shown in **Figure 1**. The Ethics Committee of the China-Japan Friendship Hospital approved the overall protocol.

Definition of Prior Ischemic Stroke

Prior ischemic stroke was clinically ascertained according to

the guidelines of the American Heart Association/American Stroke Association with minor modification because patients had the ischemic stroke 6–60 months prior, with stable neuropathological, neuroimaging, and/or clinical evidence of permanent injury.¹⁷ In 388 patients, prior ischemic stroke was diagnosed.

Data Collection

Variables collected in the present study included demographics (age, sex, and history of smoking), echocardiographic and biochemical data (albumin, B-type natriuretic peptide, blood urea nitrogen, etc.), the etiology of HF (ischemic heart disease, cardiomyopathy, etc.), comorbidities (cardiac and non-cardiac) at admission, and medications (angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin-receptor blockers [ARBs], β -blockers, mineralocorticoid receptor antagonists [MRAs], calcium-channel blockers [CCBs], statins, diuretics, nitrates, digoxin, antiplatelets, and anticoagulants) at admission and discharge.

Assembly of a Balanced Cohort

First, we analyzed the factors related to 30-day all-cause readmission or death in the 388 hospitalized HF patients with prior ischemic stroke. Briefly, in the univariable analysis for 30-day all-cause readmission or death, age, DBP, N-terminal pro-B-type natriuretic peptide (NT-proBNP), hemoglobin, total hospital length of stay, white-cell count, neutrophil-to-lymphocyte ratio serum albumin, serum sodium, serum potassium, triglycerides, thyroid stimulating hormone, triiodothyronine, anemia, dyslipidemia, infection, thyroid disease, ACEIs/ARBs, β -blockers,

Table 1. Baseline Characteristics of Patients With HF by History of Ischemic Stroke Before and After Propensity Matching

Variable	Entire cohort			Propensity score-matched cohort		
	No prior ischemic stroke (n=963)	Prior ischemic stroke (n=388)	P value	No prior ischemic stroke (n=379)	Prior ischemic stroke (n=379)	P value
Age, years	66.7±14.3	75.6±10.1	<0.001	75.0±9.5	77.6±16.2	0.508
Female	372 (38.6)	161 (41.5)	0.330	211 (55.7)	220 (58.0)	0.509
SBP, mmHg	129.0±22.0	130.7±24.4	0.218	133.4±24.5	131.1±23.9	0.190
DBP, mmHg	74.9±13.2	74.5±14.8	0.600	73.6±13.8	74.5±14.5	0.747
Heart rate, beats/min	79.1±15.9	77.8±16.2	0.155	78.3±16.7	77.6±16.2	0.552
BMI, kg/m²	24.7±5.8	24.8±3.0	0.594	24.7±4.5	24.90±3.9	0.589
History of smoking	453 (47.0)	147 (37.9)	0.088	133 (35.1)	140 (36.9)	0.864
Past medical history						
CAD	607 (63.0)	282 (72.7)	0.001	260 (68.6)	273 (72.0)	0.301
Hypertension	687 (71.3)	322 (83.0)	<0.001	314 (82.8)	316 (83.4)	0.846
Dyslipidemia	451 (46.8)	222 (57.2)	0.001	229 (60.4)	220 (58.0)	0.506
Diabetes mellitus	351 (36.4)	166 (42.8)	0.031	161 (42.5)	164 (43.3)	0.760
Atrial fibrillation	302 (31.4)	145 (37.4)	0.035	139 (36.7)	138 (36.4)	0.940
Anemia	309 (32.1)	153 (39.4)	0.010	152 (40.1)	146 (38.5)	0.655
CKD	277 (28.8)	101 (26.0)	0.309	87 (23.0)	100 (26.4)	0.273
Cancer	176 (18.3)	92 (23.7)	0.025	86 (22.7)	86 (22.7)	1.000
COPD	170 (17.7)	47 (12.1)	0.010	44 (11.6)	46 (12.1)	0.822
Thyroid dysfunction	52 (5.4)	27 (7.0)	0.277	25 (6.6)	27 (7.1)	0.774
Laboratory findings						
Hemoglobin, g/L	125.3±24.5	119.6±21.3	<0.001	118.6±23.3	119.9±21.3	0.431
eGFR, mL/min/1.73 m ²	76.3±30.6	66.9±28.4	<0.001	66.4±29.6	67.1±28.3	0.756
Glucose, mmol/L	7.2±3.1	7.7±3.5	0.023	7.6±3.4	7.62±3.5	0.805
BNP, pg/mL*	580.5 (366.0, 1,064.0)	485.5 (267.5, 843.0)	<0.001	530.0 (281.0, 933.0)	494.0 (267.0, 847.0)	0.319
LVEF, %	51.6±12.9	53.54±9.6	0.002	50.97±8.5	51.38±7.0	0.463
Medications at admission						
ACEIs/ARBs	633 (65.7)	262 (67.5)	0.527	252 (66.5)	251 (66.2)	0.939
β-blockers	663 (68.8)	256 (66.0)	0.308	263 (69.4)	256 (67.5)	0.584
MRAs	402 (41.7)	139 (35.8)	0.044	138 (36.4)	138 (36.4)	1.000
Statins	374 (38.8)	169 (43.6)	0.110	164 (43.3)	168 (44.3)	0.770
Loop diuretics	789 (81.9)	335 (86.3)	0.046	328 (86.5)	335 (88.4)	0.442
Nitrates	485 (50.4)	210 (54.1)	0.211	193 (50.9)	201 (53.0)	0.561
Digoxin	254 (26.4)	79 (20.4)	0.019	80 (21.1)	79 (20.8)	0.929
Antiplatelet drugs	507 (52.6)	226 (58.2)	0.061	210 (55.4)	223 (58.8)	0.340
Anticoagulants	213 (22.1)	52 (13.4)	<0.001	55 (14.5)	47 (12.4)	0.394
CCBs	279 (29.0)	139 (35.8)	0.014	130 (34.3)	139 (36.7)	0.494

Values are mean±standard deviation or number (%) unless indicated otherwise. *Median [interquartile range]. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CCB, calcium-channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure.

nitrates, antiplatelets, statins and CCBs (all $P<0.05$) (Supplementary Table 1).

Due to the imbalance in baseline covariates and additional covariates that affected HF prognosis, propensity score matching was used to assemble a cohort in which patients with and without prior ischemic stroke would be balanced on key measured baseline covariates. A notable strength of using the propensity score approach is that the process of cohort assembly is outcome-blinded as in a randomized controlled trial, and the balanced baseline characteristics can be displayed in a tabular form.^{11,12} We estimated the propensity score for prior ischemic stroke for each of 1,351 patients using a non-parsimonious multi-variable logistic regression model.^{18–20} In the model, prior

ischemic stroke was the dependent variable and 32 baseline characteristics (Table 1) were the covariates. Using a matching protocol, we matched 379, or 97.7%, of the 388 patients who had prior ischemic stroke, with another 379 patients without prior ischemic stroke, but with a similar probability or propensity score as the patients with prior ischemic stroke. The distribution of propensity scores is shown in Figure 2. As propensity score models are sample-specific adjusters and are not intended to be utilized for out-of-sample prediction or estimation of coefficients, the measures of fitness and discrimination are not important for the assessment of the model's effectiveness.²¹ Hence, to quantify pre-match imbalances and post-match balances, we assessed our propensity score model by calculating the

A

B

Figure 2. Results of propensity score-matched, by prior ischemic stroke. **(A)** Distribution of propensity scores for the cohort before and after matching, by prior ischemic stroke. **(B)** Histograms of the density of propensity scores for the cohort before and after matching, by prior ischemic stroke.

pre- and post-match absolute standardized differences for the 32 measured baseline characteristics, with an absolute standardized difference value of 0% indicating no residual bias and values <10% suggesting inconsequential bias.

Study Outcomes

We examined the following outcomes: the combined endpoint of all-cause readmission or death, all-cause death, all-cause readmission, and HF readmission. We performed follow-up interviews regularly and all outcome events of death or readmission at 30 days, 6 months, and 1 year were documented into the China Heart Failure Center Reporting Platform (<http://data.chinahfc.org>). Only the

first readmission occurring at any time after the index admission and throughout the follow-up period of the study was considered to be a qualifying readmission.

Statistical Analysis

Normally distributed continuous variables are expressed as mean±standard deviation, non-normally distributed continuous variables are expressed as median and interquartile range, and categorical variables are expressed as n (%). Pearson chi-square and Wilcoxon rank sum tests were used for the comparisons of baseline characteristics between patients with and without prior ischemic stroke, as appropriate. All outcome analyses were conducted

Table 2. Clinical Outcomes in the Propensity Score-Matched Cohort

	Events (%)		HR (95% CI)	P value
	No prior ischemic stroke (n=379)	Prior ischemic stroke (n=379)		
30-day outcomes				
HF readmission	18 (4.7)	35 (9.2)	2.11 (1.19–3.72)	0.010
All-cause readmission	33 (8.7)	81 (21.4)	2.67 (1.78–4.01)	<0.001
All-cause death	25 (6.6)	48 (12.7)	2.08 (1.28–3.38)	0.003
All-cause death or readmission	57 (15.0)	100 (26.4)	1.91 (1.38–2.65)	<0.001
6-month outcomes				
HF readmission	54 (14.2)	71 (18.7)	1.51 (1.06–2.15)	0.023
All-cause readmission	86 (22.7)	147 (38.8)	1.95 (1.49–2.54)	<0.001
All-cause death	38 (10.0)	70 (18.5)	2.06 (1.39–3.05)	<0.001
All-cause death or readmission	123 (32.5)	174 (45.9)	1.60 (1.27–2.02)	<0.001
1-year outcomes				
HF readmission	70 (18.5)	91 (24.0)	1.54 (1.13–2.10)	0.007
All-cause readmission	110 (29.0)	183 (48.3)	1.95 (1.54–2.47)	<0.001
All-cause death	39 (10.3)	86 (22.7)	2.51 (1.72–2.67)	<0.001
All-cause death or readmission	148 (39.1)	212 (55.9)	1.67 (1.35–2.06)	<0.001

CI, confidence interval; HF, heart failure; HR, hazard ratio.

using matched data. Cumulative risk for outcomes was estimated by Kaplan-Meier survival curves and compared using the Cox regression analysis. Hazard ratio (HR) and 95% confidence interval (CI) expressed the risk of events of patients with prior ischemic stroke compared with patients without prior ischemic stroke. Subgroup analyses were performed to determine whether the association between prior ischemic stroke and the combined endpoint of all-cause death or readmission was homogeneous across various subgroups of the matched cohort. Two-sided tests with $P<0.05$ were considered statistically significant. Statistical analysis was conducted using SPSS for Windows (version 25.0, SPSS Inc., Chicago, IL, USA) and the R programming language and environment version 3.6.0 (<http://cran.r-project.org>).

Results

Baseline Characteristics of Entire Cohort and Propensity Score-Matched Cohort

The 758 matched patients had a mean age of 75.3 ± 9.8 years and 43.1% were female. Before matching, 388 (28.7%) patients had a prior ischemic stroke. Patients with prior ischemic stroke were older, had a greater burden of comorbidities, more HF was caused by coronary artery disease and fewer received MRAs compared with those without prior ischemic stroke (Table 1, Supplementary Table 2). After propensity score matching, all imbalanced baseline characteristics between patients with and without prior ischemic stroke were well balanced so that no significant differences remained (Table 1, Supplementary Table 2). The median (IQR) duration of ischemic stroke of the enrolled patients was 4 years ([3–8] years). The ischemic stroke duration of nearly 80% patients enrolled in the present study ranged from 3 to 8 years.

30-Day Outcomes

Prior ischemic stroke was associated with significantly higher risks of the combined endpoint of all-cause death or readmission (HR: 1.91; 95% CI: 1.38 to 2.65; $P<0.001$),

all-cause death (HR: 2.08; 95% CI: 1.28 to 3.38; $P=0.003$), all-cause readmission (HR: 2.67; 95% CI: 1.78 to 4.01; $P<0.001$), and HF readmission (HR: 2.11; 95% CI: 1.19 to 3.72; $P=0.010$) (Table 2, Figure 3). The results showed that the duration of ischemic stroke in patients with and without 30-day readmission or death was 61.1 ± 34.1 months and 60.8 ± 34.7 months, respectively ($P=0.291$). There was no significant difference in the duration of ischemic stroke between the 2 groups, which suggested that stroke per se rather than duration of disease accounted for the poor clinical outcomes in patients with HF.

The major causes of 30-day readmission were non-HF rather than HF (56.8% vs. 43.2%) in patients with prior ischemic stroke (Supplementary Figure A). The 3 most common non-cardiovascular causes were pneumonia (32.6%), renal disorders (28.3%), and injury (19.6%) (Supplementary Figure B).

6-Month and 1-Year Outcomes

Prior ischemic stroke was associated with higher risks of the combined endpoint of all-cause death or readmission, all-cause death, all-cause readmission, and HF readmission at 6 months and 1 year (Table 2, Figure 3). At 1-year readmission, the proportion of non-HF causes was similar to HF cause (24.3% vs. 24.0%) in patients with prior ischemic stroke.

Subgroup Analysis in the Matched Cohort

According to the analyses of outcomes, prior ischemic stroke had a higher weight on adverse outcomes at 30 days compared with 6 months and 1 year. Subgroup analyses for the combined endpoint of 30-day all-cause death or readmission were performed to identify factors that may deteriorate prognosis (Figure 4). The association between prior ischemic stroke and the combined endpoint of all-cause death or readmission at 30 days was homogeneous among various clinically relevant subgroups of patients, except by age and statin use at admission. The HRs (95% CIs) for the 30-day combined endpoint associated with prior ischemic stroke in the subgroups aged ≥ 75 years and

Figure 3. Cumulative risk of outcomes in patients with heart failure (HF), by prior ischemic stroke. Cumulative risk for all-cause death or readmission (A), all-cause death (B), all-cause readmission (C), and HF readmission (D).

<75 years were 2.59 (1.71 to 3.93; $P<0.001$) and 1.11 (0.65 to 1.92; $P=0.697$), respectively (P for interaction=0.016), and for receiving and not receiving statins were 0.93 (0.47 to 1.85; $P=0.842$) and 2.50 (1.71 to 3.64; $P<0.001$), respectively (P for interaction=0.013).

Discussion

Findings from the present study demonstrated that prior ischemic stroke in patients with HF was associated with a significantly higher risk of poor outcomes. The associations with all-cause death or readmission became significant during the first 30 days and lasted for 1 year. To the best of our knowledge, this is the first study to compare the risks of death and readmission in HF patients with and without a history of ischemic stroke through one-to-one propensity score matching, which suggested that ischemic stroke remains a strong predictor of unfavorable outcomes after eliminating the greater proportion of potential confounding variables. These findings complement and

extend knowledge about prognosis in the presence of ischemic stroke among patients with HF.

There is a general perception that the presence of stroke is associated with a higher burden of comorbidity and poor outcomes in patients with HF. However, several large cohorts of HF patients did not identify stroke as a significant predictor of death or readmission in Western populations (Europe and the USA).⁷⁻⁹ Whether stroke per se, rather than additional comorbidities or older age, accounts for the adverse prognosis is a great uncertainty. The intrinsic association between stroke and outcomes of HF may be concealed by the bias of higher prevalence of additional comorbidities affecting HF prognosis; furthermore, the bias cannot be diminished by traditional regression-based multivariable risk adjustment models.¹⁰ In the present study, the findings were distinct from those of previous studies because of our use of a robust propensity-score matching design, which was likely the best study design to allow us to assess directly the extent to which stroke has an independent association with outcomes in HF. A notable

Figure 4. Forest plots for subgroup analysis of all-cause death or readmission, by prior ischemic stroke. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CI, confidence interval; MRA, mineralocorticoid receptor antagonist.

advantage of propensity score matching is to design observational studies as similar to randomized clinical trials in several critical ways. First, it allowed us to assemble a study cohort in which patients with and without prior ischemic stroke were well balanced on all measured covariates.¹² Second, we could measure the achieved balance objectively in the matched cohort.¹¹ Third, and perhaps most importantly, propensity score matching makes it possible to do both of these procedures without knowledge of, or access to, outcomes data, as investigators of a randomized clinical trial would not know the outcomes of the trial during its design.^{13,14} Therefore, the process of cohort assembly is outcome-blinded as in a randomized clinical trial.

Noteworthy findings of this study were that prior ischemic stroke had a robust effect on all-cause death and readmission in patients with HF, and the effects became significant during the first 30 days and lasted for 1 year.

Ischemic stroke, as an important comorbidity in patients with HF, may promote increasing dysfunction, diminished quality of life and inadequate recovery after HF aggravation.^{4,6,22} Although there is a paucity of studies in both clinical and experimental research investigating the mechanisms of ischemic stroke-induced cardiac dysfunction, several mechanisms are thought to underlie the worsening outcomes of ischemic stroke in patients with HF. Activation of the hypothalamic-pituitary-adrenal (HPA) axis after ischemic stroke causes a significant increase in catecholamines, which can cause cardiac hypertrophy or myocardial ischemia.²³⁻²⁶ It is also possible that ischemic stroke could disrupt the blood-brain barrier (BBB) and increased permeability.⁴ In a vicious cycle, disruption of the BBB facilitates the entry of brain-derived antigens and extracellular vesicles derived from injured brain cells to enter the blood stream and encounter peripheral immune cells, which could indirectly induce cardiac dysfunction.²⁷

Moreover, the complex interplay of the local and systemic inflammatory responses after stroke involves many immune cell types and circulating signals and is important in both infection and secondary cardiac damage.^{4,28} In addition, the role of microvesicles released by damaged astrocytes, neurons and microglia after stroke in mediating cardiac damage warrants future investigation. Thus, HF and prior ischemic stroke are linked by pathophysiological mechanisms that promote the progression of each other, and in turn substantially contribute to poor outcomes in HF patients with prior ischemic stroke.

Prior ischemic stroke has particular relevance for the treatment of HF. HF patients with prior ischemic stroke have complex treatment regimens that can disproportionately lead to polypharmacy and worsen the prognosis of HF patients. However, although prior ischemic stroke has a definite effect on the clinical outcomes of HF, appropriate treatment has not determined in these particular patients with HF. The findings from our subgroup analyses are also important because they help identify the subset of HF patients who are at increased risk of poor outcomes. We observed that the stroke-associated increased risk of death or readmission was higher in those not receiving statins. The evidence regarding the beneficial effects of statin therapy remained contradictory in the general HF population. Currently, the European Society of Cardiology HF guidelines and the American College of Cardiology/American Heart Association HF guidelines do not recommend initiation of statins in most patients with HF.^{16,29} These recommendations are based mainly on the findings of the CORONA and GISSI-HF studies that were large-scale placebo-controlled trials of statin treatment in patients with HF.^{30,31} No significant decrease in the primary composite mortality/morbidity endpoint was seen in actively treated subjects in either trial.^{30,31} Nonetheless, statins therapy for secondary prevention of ischemic stroke has been recommended by the American Heart Association /American Stroke Association Ischemic Stroke guidelines.³² Recently, results from the Treat Stroke to Target trial also suggested intense statin therapy in patients with ischemic stroke of atherosclerotic origin, despite the limitations of the trial.³³ Statins have multiple cholesterol-independent pleiotropic effects, including the improvement of endothelial function, inhibition of inflammation and thrombosis, promotion of angiogenesis and neuroprotection, and stabilization of atherosclerotic plaques. Pretreatment with a statin is associated with greater neurological improvement and better survival in large artery atherosclerotic stroke. In addition, use of statins may exert a neuroprotective benefit in patients with ischemic stroke through reduction in cholesterol and a number of the pleiotropic effects, which may in turn improve the prognosis of HF.³⁴ One of the main protective mechanisms elicited by statin administration is the increase in nitric oxide bioavailability, which regulates cerebral perfusion and improves endothelial function, but others include antioxidant properties, the inhibition of inflammatory responses, immunomodulatory actions, the regulation of progenitor cells, and stabilization of atherosclerotic plaques. Many of these effects are due to the inhibited synthesis of isoprenoid intermediates, which serve as lipid attachments for a variety of intracellular signaling molecules.³⁵ Although the data from the present study do not support a change in the existing guidelines and we cannot specifically recommend statin treatment, our results add to evidence that statin therapy has addi-

tional prognostic value and may be a treatment option for patients with HF combined with ischemic stroke. To ensure the plausibility and validity of these results, further well-designed controlled trials are needed to fully understand the optimal treatment strategy for this patient population.

Our results identified that the causes of 30-day readmission in patients with HF and prior ischemic stroke were more likely to be non-HF, for which there are several explanations. First, patients with prior ischemic stroke are prone to dysphagia-related pulmonary aspiration, which is the most common reason for infection, and are admitted into different departments, which may lead to incomplete treatment.³⁶ Second, patients with prior ischemic stroke often have unfavorable physical activity levels are thus are prone to physical function impairment,³⁷ which can complicate treatment regimens.^{38,39} Third, cognitive impairment after ischemic stroke in many survivors and is a considerable burden to patients and their caregivers, often leading to poor compliance and adherence by the patient.⁴⁰

Our subgroup analyses also found that prior ischemic stroke had a greater effect on HF with preserved ejection fraction (HFpEF) compared with reduced EF (HFrEF). The pathophysiology underlying HFpEF is heterogeneous and no treatment has yet been shown, convincingly, to reduce morbidity or mortality. Therefore, HFpEF patients should be managed with interventions that have been shown to improve symptoms and outcome related to comorbidities. However, our results showed that the treatment of prior ischemic stroke in HFpEF patients was inadequate. First, the use of statins was lower in HFpEF compared with HFrEF patients. Statins may control hyperlipidemia and have pleiotropic effects such as improving vascular endothelial function, inhibition of oxidative stress pathways, and anti-inflammatory actions.^{41,42} Accumulating clinical evidence suggests that statins also have a beneficial effect on enhanced cerebral repair in patients with ischemic stroke.⁴³ Second, fewer patients with HFpEF appeared to receive β -blockers compared with patients with HFrEF. Ischemic stroke is a condition associated with a robust stress response with sympathetic activation, which is in turn responsible for increased morbidity and mortality after stroke.^{44,45} Beta-blocker therapy has been suggested to have neuroprotective properties, through reducing the increased sympathetic tone after ischemic stroke.⁴⁶

Study Limitations

Several limitations need to be considered. Given the observational nature of the study, despite a rigorous propensity score matched design to assemble cohorts that were well balanced on all measured baseline covariates, hidden bias may remain because of the influence of potential unmeasured confounders. The conditions associated with stroke, such as disability, cognitive impairment, and frailty, could potentially influence the outcomes of patients with HF, and unfortunately, these conditions were not adequately assessed in our study. Results of subgroup analyses should be interpreted with caution because they may be false positive due to multiple comparisons and false negative due to inadequate power.

Conclusions

After accounting for clinical characteristics, prior ischemic stroke was a potent and persistent risk predictor of death and readmission among patients with HF. Given the complex pattern of ischemic stroke and HF, innovative models of integrated multidisciplinary care and further studies on optimal management are warranted specifically in this patient population.

Ethics Approval

The study was approved by the Ethics Committee of China-Japan Friendship Hospital (No. 2019-83-K54).

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Disclosures

The authors declare no conflicts of interest.

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Supplementary Files

Please find supplementary file(s);
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