



# Association between Heart Failure and Clinical Prognosis in Patients with Acute Ischemic Stroke: A Retrospective Cohort Study

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**Background and Purpose** Ischemic stroke is a common cause of death worldwide. In clinical practice it is observed that many individuals who have experienced an ischemic stroke also suffer from simultaneous comorbidities such as heart failure, which could be directly associated with a worse clinical prognosis. Therefore, this study analyzed outcomes in terms of the severity of the event, inhospital mortality, duration of hospital stay, and inhospital recurrence of the episode, in order to determine the implications resulting from the presentation of both pathologies.

**Methods** This was a retrospective-cohort, hospital-based study.

**Results** The study included 110 subjects with heart failure (exposed) and 109 subjects without heart failure (nonexposed). The incidence of inhospital mortality was 27.27% in exposed patients and 9.17% in nonexposed patients ( $p<0.001$ ), and the presence of heart failure increased the risk of death by 92% ( $p=0.027$ ). According to scores on the National Institutes of Health Stroke Scale, the median severity was worse in exposed than nonexposed patients (16.1 vs. 9.2,  $p=0.001$ ). The median hospital stay was 9 days in subjects with heart failure and 7 days in nonexposed patients ( $p=0.011$ ). The rate of inhospital stroke did not differ significantly between exposed and nonexposed patients (1.82% vs. 0.92%,  $p=0.566$ ).

**Conclusions** Individuals with heart failure who suffer from an acute ischemic stroke show worse clinical outcomes in terms of mortality, event severity, and duration of hospital stay.

**Key Words** stroke, heart failure, mortality, prognosis.

## INTRODUCTION

The World Health Organization defines a stroke as a medical emergency of abrupt onset that lasts for longer than 24 hours and characterized by a neurological focal deficit. Stroke is caused by either a vascular obstruction in the case of events of ischemic origin or an arterial wall injury in the case of events of hemorrhagic origin, which results in the suspension of brain blood flow.<sup>1,2</sup> Strokes are the second most common cause of death worldwide. Around 5.5 million people died from stroke in 2016, with 2.7 million of them suffering from an ischemic stroke.<sup>3</sup>

In clinical practice it is evident that many individuals diagnosed with acute ischemic stroke (AIS) also have a history of heart failure (HF). The latter is an important condition since it represents a predisposing factor for proximal brain vasculature obstruction; it has been reported that the risk of developing AIS is two- to threefold higher in patients with HF than in patients without HF.<sup>4</sup> This relationship is biologically plausible due to the hemodynamic changes that are typical of HF. However, the association between HF and the clinical prog-

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nosis in patients with stroke has not been studied and that is the reason why the development of this research study has been proposed.

## METHODS

An observational, analytical, retrospective-cohort, hospital-based study was performed. The study included patients diagnosed with AIS who were treated at Fundación Clínica Shaio in the city of Bogotá, Colombia, from January 1, 2008 to December 31, 2017. An AIS event was defined as a focal neurological deficit lasting for between 24 hours and 7 days, with radiological proof of cerebral infarction. The study excluded patients with concomitant neurological diseases that may alter the clinical course of AIS, such as transient ischemic attack, epilepsy, migraine, somatomorphic disorders, and clinical conditions that emulate AIS. An exposed patient was defined as any patient with AIS and a diagnosis of HF, the latter being defined by the patient's pathological history or by an estimated decrease of <40% in the ejection fraction of the left ventricle according to the electrocardiogram measured when the patient was admitted into the health institution. Nonexposed patients were defined as patients with AIS who did not have HF as a comorbidity.

The required sample size was determined based on estimating possible risk factors with the formula used for the normal asymptotic method with  $\alpha=0.05$ ,  $\beta=0.2$ , and an assignment rate of 1:1. The number of individuals to be included was 218, comprising 109 exposed patients and 109 nonexposed patients. However, for convenience it was decided to increase the number of exposed individuals to 110. The subjects were identified from the electronic records of the clinic over the above-mentioned time frame. Inclusion and exclusion criteria were applied to establish to which group each subject belonged. Once the variables of interest were defined, medical records that had been made and diagnostic tests that had been performed during patient hospitalization were reviewed, and that information was recorded on a database created on the REDCap platform.<sup>5</sup>

In order to compare the exposed and nonexposed groups, a mean-difference Z test was applied to continuous variables conforming to a normal distribution, with a Wilcoxon rank-sum test applied to other continuous variables. Dichotomic qualitative variables were compared between two groups using a Z test of proportion differences. For polytomous variables, a chi-square test or Fisher's exact test was performed depending on the case.

The risk versus time was modeled using Kaplan-Meier survival analysis, which was stratified according to each cohort. A logarithmic rank test and a Wilcoxon test were used to de-

termine the differences between the produced survival curves. The association between HF and inhospital mortality was estimated using the hazard ratio (HR) along with the 95% confidence interval (CI) in a crude estimate and a multivariate analysis with a nonconditioned Cox proportional-hazards model with right censoring, adjusted by covariables (variables that are described in the literature as modifying the effect or those that were found to differ significantly between the two groups). Regressive variables were selected using a stepwise technique with input and output probabilities of 10% and 15%, respectively. The specification for this association model was tested through re-estimation link test methods. The proportional-hazards assumption was assessed using graphic methods such as log-log plots [-ln(-survival function) vs. ln(t)] in order to look for parallel curves and Schoenfeld residuals and thereby achieve a global assessment as well as an assessment of each variable included in the model (looking for the absence of slopes in the plots). Statistical results were considered significant at  $p \leq 0.05$ , with 95% CIs also being used. Statistical analysis was performed with Stata software (version 15 SE, StataCorp., College Station, TX, USA).<sup>6</sup>

The present research was approved by the research ethics committee of the local institution.

## RESULTS

This study included 219 subjects: 110 subjects with HF (exposed) and 109 subject without HF (nonexposed). Table 1 summarizes the characteristics of the subjects included in each cohort as well as the statistical differences and similarities found among them.

No significant differences were found between the exposed and nonexposed cohorts in age, sex, mean arterial pressure, or history of atherosclerosis, small-vessel disease, cardioembolic disease, diabetes mellitus, neurological disease, ischemic stroke, arterial hypertension, platelet antiaggregation, or smoking. However, histories of atrial fibrillation (AF) and anticoagulation were significantly more frequent in exposed than nonexposed subjects. Moreover, the body mass index (BMI) was significantly higher in the nonexposed group than the exposed group, and the left-ventricle ejection fraction was significantly worse in the exposed group. The subtypes of AIS present during the event and the corresponding to the TOAST classification also differed significantly between the two groups. The most-frequent AIS subtype in both groups was large-vessel atherosclerosis, while the second-most-frequent origin was the cardioembolic subtype in the exposed group and small-vessel occlusion in the nonexposed group.

Regarding the outcomes of interest, the median severity as quantified using the National Institutes of Health Stroke

**Table 1.** Sociodemographic and anthropometric variables and clinical history in the case and control groups

Variable	Exposed (n=110)	Nonexposed (n=109)	p
Age, years	78.1 [70.4–84.5]	76.3 [65.4–83.6]	0.191*
Sex			0.457 <sup>†</sup>
Male	53 (48.18)	58 (53.21)	
Female	57 (51.82)	51 (46.79)	
BMI, kg/m <sup>2</sup>	24.4 [22.0–26.2]	25.7 [22.9–28.7]	0.006*
History of atherosclerosis			0.782 <sup>†</sup>
Yes	44 (40.37)	42 (38.53)	
No	65 (59.63)	67 (61.47)	
History of small-vessel disease			0.212 <sup>†</sup>
Yes	5 (4.55)	1 (0.93)	
No	105 (95.45)	107 (99.07)	
History of cardioembolic disease			0.113 <sup>†</sup>
Yes	14 (12.73)	7 (6.42)	
No	96 (87.27)	102 (93.58)	
History of atrial fibrillation			0.001
Yes	51 (46.36)	24 (22.02)	
No	59 (53.64)	85 (77.98)	
History of type II diabetes mellitus			0.825 <sup>†</sup>
Yes	21 (19.09)	19 (17.92)	
No	89 (80.91)	87 (82.08)	
History of Parkinson's disease			0.999 <sup>†</sup>
Yes	2 (1.82)	2 (1.83)	
No	108 (98.18)	107 (98.17)	
History of anticoagulation			0.001 <sup>†</sup>
Yes	37 (33.64)	9 (8.26)	
No	73 (66.36)	100 (91.74)	
History of ischemic stroke			0.374 <sup>†</sup>
Yes	31 (28.18)	25 (22.94)	
No	79 (71.82)	84 (77.06)	
History of arterial hypertension			0.080 <sup>†</sup>
Yes	94 (86.24)	84 (77.06)	
No	15 (13.76)	25 (22.94)	
History of platelet antiaggregation			0.170 <sup>†</sup>
Yes	34 (31.19)	25 (22.94)	
No	75 (68.81)	84 (77.06)	
History of smoking			0.844 <sup>†</sup>
Yes	25 (22.73)	26 (23.85)	
No	85 (77.27)	83 (76.15)	
Duration of hospital stay, days	9 [5–15]	7 [4–11]	0.011*
Inhospital stroke recurrence			0.566 <sup>§</sup>
Yes	2 (1.82)	1 (0.92)	
Subtype of AIS according to the TOAST classification			0.001 <sup>†</sup>
Large-artery atherosclerosis	92 (83.64)	87 (79.82)	
Cardioembolism	12 (10.91)	3 (2.75)	
Small-vessel occlusion	4 (3.64)	18 (16.51)	
Stroke of undetermined etiology	2 (1.82)	1 (0.92)	
Mean arterial pressure at entry, mm Hg	98.7 [91.7–116.7]	106.3 [95.3–116.3]	0.132*
Left-ventricle ejection fraction, %	37 [30–45]	58 [55–60]	0.001*

Data are median [interquartile range] or n (%) values.

\*Wilcoxon rank-sum test, <sup>†</sup>Pearson's chi-square test, <sup>‡</sup>Fisher's exact test, <sup>§</sup>Z test of proportion differences.

AIS: acute ischemic stroke, BMI: body mass index, NIHSS: National Institutes of Health Stroke Scale.

Scale (NIHSS) score was worse in exposed than nonexposed patients (16.1 vs. 9.2,  $p < 0.0001$ ). The mean hospital stay was 9 days in exposed patients and 7 days in nonexposed patients ( $p = 0.0117$ ). The recurrence rate of in-hospital stroke did not differ significantly between exposed and nonexposed patients (1.82% vs. 0.92%,  $p = 0.5664$ ). These results are presented in Table 2.

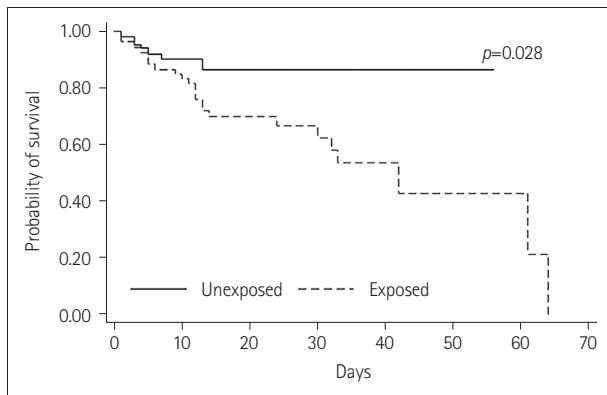
**Comparison of survival curves**

Survival functions were similar in the two groups during the first 3 days. On day 8 of follow-up, the probability of survival was 86.39% for patients with AIS and HF and 90.26% for patients with AIS and without HF. The nonexposed cohort

**Table 2.** Comparison of NIHSS score, duration of hospital stay, and recurrence of in-hospital stroke between exposed and nonexposed cohorts

Variable	Exposed (n=110)	Nonexposed (n=109)	p
NIHSS score at admission			<0.0001
Median (IR)	16.1 [10.9–21]	9.2 [4–16]	
Duration of hospital stay, days			
Median (IR)	9 [5–15]	7 [4–11]	0.011*
In-hospital stroke recurrence			
Yes	2 (1.82)	1 (0.92)	0.566 <sup>†</sup>

Data are median [interquartile range] or n (%) values. \*Wilcoxon rank-sum test, <sup>†</sup>Z test of proportion differences. NIHSS: National Institutes of Health Stroke Scale.



**Fig. 1.** Kaplan–Meier survival curves.

**Table 3.** Association between HF and in-hospital mortality

Intrahospital mortality	Exposed (n=110)	Nonexposed (n=109)	Crude model		Adjusted model*	
			HR [95% CI]	p	HR [95% CI]	p
No	80 (72.73)	99 (90.83)	1 [reference]	–	–	–
Yes	30 (27.27)	10 (9.17)	2.19 [1.05–4.52]	0.034	1.92 [1.21–2.63]	0.027

Data are n (%) or HR [95% CI] values. \*Adjusted by age at admission, BMI, NIHSS score at admission, history of cardioembolic disease, AF, anticoagulation, and arterial hypertension, and stroke subtypes. AF: atrial fibrillation, BMI: body mass index, HR: hazard ratio, NIHSS: National Institutes of Health Stroke Scale.

showed a slight reduction in survival probability by day 36, to 86.34%, whereas the exposed cohort showed a significant reduction, to 53.57%. These trends are reflected in the Kaplan-Meier survival curves in Fig. 1, which shows that the survival function on most of the follow-up days was significantly lower for the exposed cohort than the nonexposed group. The survival curves were significantly different in a logarithmic rank test ( $\chi^2 = 4.79$ ,  $p = 0.0286$ ).

**Association between HF and in-hospital mortality in patients with AIS**

A Cox proportional-hazards model was constructed to assess the relationship between HF and in-hospital mortality. Table 3 reports the crude HRs estimated for that association. The risk of death was significantly higher in the exposed group than the nonexposed group. The presence of HF increased the risk of death by 119% (95% CI=5–352%). When adjusting the model for variables such as the age at admission, BMI, NIHSS score at admission, stroke subtypes, and history of cardioembolic disease, AF, anticoagulation, and arterial hypertension, the risk of death decreased by 92% (95% CI=21–163%). These results indicate that the presence of HF is a significant risk factor for death in patients with AIS.

**DISCUSSION**

HF is a highly prevalent disease worldwide and hence is considered a major public health issue. Comorbidities underlying HF are becoming increasingly prominent and frequent, which requires comprehensive interdisciplinary health care to be provided to patients with this condition. Ischemic stroke is an important comorbidity for individuals with HF, since the possibilities of suffering from this event increase by two- to threefold due to the structural and functional changes occurring during the natural course of HF.<sup>7</sup> However, few studies have investigated the relationship between the presence of HF in individuals who have suffered from an ischemic stroke and the increase in the risk of death caused by this event.<sup>8</sup>

The present study found that HF was associated with an increased risk of death (HR=1.92,  $p = 0.027$ ), which is consistent with a meta-analysis published in 2007 suggesting that

HF associated with an ischemic stroke episode doubles the risk of death.<sup>9</sup> No previous study has compared the severity of AIS between patients with and without HF; the present study found that the median NIHSS score was significantly higher in AIS patients with HF than in those without this condition (16.1 vs. 9.2,  $p=0.001$ ). These results suggest that there are intrinsic factors that cause HF to trigger the onset of thrombotic events, which in turn results in a greater loss of basic neurological functions. This is reflected in worse clinical outcomes, which increases the NIHSS score for these events, and thus the risk of death.

It is worth mentioning that one of the factors that most influences the clinical prognosis of patients with AIS is brain collateral circulation, which is a vascular network that ensures perfusion toward brain tissue when there are alterations in the primary vascular channels.<sup>10,11</sup> Once an ischemic stroke takes place, neurons located in the affected brain mass can only survive if there is optimal collateral flow. A defective collateral system produces a worse outcome and a progressive extension of brain infarction.<sup>12</sup> Sufficiency of the collateral circulation depends mainly on the cerebral blood flow, which is significantly altered by the decrease in perfusion pressure caused by HF.<sup>13-15</sup> There have even been suggestions that HF exacerbation results in a significant decrease in blood flow through the carotid and basilar arteries, which in turn leads to a greater impairment of brain blood flow that would subsequently affect collateral recruitment.<sup>16</sup>

Besides the brain collateral circulation, AF is a condition shared by many patients with HF, and it is directly associated with worse clinical outcomes in AIS patients.<sup>8</sup> Some authors suggest that AF is the main cause of strokes in patients with a history of HF, since this kind of arrhythmia causes contractile dysfunction and stasis, which increases the risk of thromboembolism, results in structural remodeling of the atrium thus aggravating the auricular condition, and further increases the risk of small-vessel occlusion.<sup>17</sup> The present study found significant differences in outcomes according to the history of AF in both the exposed and nonexposed groups, with AF recurring more often in individuals with HF, which suggests that increases in mortality and NIHSS scores are related to the presence of AF.

As stated above, individuals with HF who suffer from AIS exhibit multiple intrinsic factors that lead to worse clinical outcomes regarding mortality and severity. These conditions are probably the underlying cause of the results obtained in this work regarding the duration of hospital stay, whose median was longer in patients with HF (9 days) than in patients without this condition (7 days).

This study has provided clear evidence that clinical outcomes of an individual who has experienced AIS are worse

if they present with underlying HF. This indicates the importance of identifying this condition properly, so that therapeutic strategies for the maintenance of adequate cardiac function and the promotion of brain tissue recovery can be applied.

In conclusion, individuals who experience AIS have worse clinical outcomes if they have been diagnosed with HF, in terms of the severity of the event, mortality risk, and the duration of hospital stay. These effects are explained by the loss of collateral brain circulation in patients with HF. It should be highlighted that the triad of HF, AF, and the onset of AIS are associated with worse in-hospital clinical outcomes. However, their implications in early clinical outcomes over a 90-day follow-up still need to be determined.

### Author Contributions

Conceptualization: Jose Luis Lozano Villanueva, Fabián Cortés Muñoz, Jenny Carolina Sánchez Casas. Data curation: Luis Alfonso Barragán Pedraza. Formal analysis: Fabián Cortés Muñoz, Jenny Carolina Sánchez Casas. Methodology: Jose Luis Lozano Villanueva, Javier Francisco Torres Zafra, Fernán del Cristo Mendoza Beltrán. Writing—review & editing: Jose Luis Lozano Villanueva, Javier Francisco Torres Zafra, Fernán del Cristo Mendoza Beltrán, Luis Alfonso Barragán Pedraza.

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### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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### REFERENCES

- Grysiewicz RA, Thomas K, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. *Neurol Clin* 2008;26:871-895.
- Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation* 2016; 133:e38-e360.
- GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;18:439-458.
- Witt BJ, Brown RD Jr, Jacobsen SJ, Weston SA, Ballman KV, Mevreden RA, et al. Ischemic stroke after heart failure: a community-based study. *Am Heart J* 2006;152:102-109.
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven meth-

- odology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377-381.
6. StataCorp LLC. Stata statistical software: release 15. College Station, TX: StataCorp LLC; 2017.
  7. Haeusler KG, Laufs U, Endres M. Chronic heart failure and ischemic stroke. *Stroke* 2011;42:2977-2982.
  8. Sharma JC, Fletcher S, Vassallo M, Ross I. Cardiovascular disease and outcome of acute stroke: influence of pre-existing cardiac failure. *Eur J Heart Fail* 2000;2:145-150.
  9. Witt BJ, Gami AS, Ballman KV, Brown RD Jr, Meverden RA, Jacobsen SJ, et al. The incidence of ischemic stroke in chronic heart failure: a meta-analysis. *J Card Fail* 2007;13:489-496.
  10. Bang OY, Goyal M, Liebeskind DS. Collateral circulation in ischemic stroke: assessment tools and therapeutic strategies. *Stroke* 2015;46:3302-3309.
  11. Ginsberg MD. The cerebral collateral circulation: relevance to pathophysiology and treatment of stroke. *Neuropharmacology* 2018;134(Pt B):280-292.
  12. Jung S, Wiest R, Gralla J, McKinley R, Mattle H, Liebeskind D. Relevance of the cerebral collateral circulation in ischaemic stroke: time is brain, but collaterals set the pace. *Swiss Med Wkly* 2017;147:w14538.
  13. Jefferson AL, Liu D, Gupta DK, Pechman KR, Watchmaker JM, Gordon EA, et al. Lower cardiac index levels relate to lower cerebral blood flow in older adults. *Neurology* 2017;89:2327-2334.
  14. Roy B, Woo MA, Wang DJJ, Fonarow GC, Harper RM, Kumar R. Reduced regional cerebral blood flow in patients with heart failure. *Eur J Heart Fail* 2017;19:1294-1302.
  15. Meng L, Hou W, Chui J, Han R, Gelb AW. Cardiac output and cerebral blood flow: the integrated regulation of brain perfusion in adult humans. *Anesthesiology* 2015;123:1198-1208.
  16. Mamalyga ML, Mamalyga LM. Violation of cerebral hemodynamics in the cardiac dysfunction caused by chronic heart failure. *Zh Nevrol Psikiatr Im S S Korsakova* 2015;115:106-111.
  17. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial fibrillation and mechanisms of stroke: time for a new model. *Stroke* 2016;47:895-900.