Predictors of in-hospital mortality after ischemic stroke: A prospective, single-center study

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Abstract
Background and Aims: Stroke is the second leading cause of death around the globe. Studies examining the predictors of in-hospital mortality and the impact of complications on early outcome of acute ischemic stroke are scant. The aim of this study was to identify predictors of in-hospital mortality in patients with acute ischemic stroke.

Methods: This was a prospective, single-center study of patients with acute ischemic stroke consecutively admitted to the Neurology Department of a general hospital during a 2-year period (from January 1, 2010 to December 31, 2011). Prospective data from this single-center study included variables related to sociodemographics, comorbidities, and medical complications, together with in-hospital mortality. Since stroke mortality may impact differently by sex and is also influenced by hospital length of stay, we proceeded to stratify by these variables.

Results: Six-hundred and seventy-three patients were included. Overall, in-hospital mortality rate was 7.13%. Stratifying by length of stay in-hospital (< 7 days and ≥ 7 days), we observed that within the first week, overall mortality was related to a history of previous stroke, higher stroke severity, and to cardiovascular and respiratory complications. After 7 days, the main factor independently associated with overall in-hospital mortality was stroke severity (National Institutes of Health Stroke Scale [NIHSS] ≥ 14, odds ratio [OR]: 17.15; 95% CI, 3.06-96.07). Stratifying by sex, we observed that females had a worse outcome if there was a history of prior stroke (OR: 3.29; 95% CI, 1.19-9.10), higher stroke severity (NIHSS ≥ 14, OR: 16.63; 95% CI, 4.66-59.31), and cardiovascular complications (OR: 29.70; 95% CI, 5.70-154.8). Among men, stroke severity (NIHSS ≥ 14, OR: 23.19; 95% CI, 5.69-94.56), respiratory infections (OR: 3.84; 95% CI, 1.32-11.20), and older age had significant negative impact.

Conclusions: Stroke severity and potentially modifiable complications (respiratory infections and cardiovascular complications) confer an increased risk of in-hospital death in both women and men, particularly during the first week of admission.
INTRODUCTION

Stroke is the second leading cause of death around the globe.1 The incidence of stroke in Spain is 187 cases per 100,000 persons per year for a first ever stroke or transient ischemic attack (TIA).2

In the last decades, stroke incidence and mortality have decreased, and the approach to acute ischemic stroke has been deeply transformed.3 Specialized stroke units and early rehabilitation have contributed to reduce stroke morbidity and mortality, and the adoption of reperfusion strategies of cerebral ischemic tissue such as intravenous thrombolysis, and more recently mechanical thrombectomy, have clearly contributed to improve outcomes in these patients.4 However, the majority of patients do not arrive at the hospital soon enough to receive emergency stroke treatment.5 In addition, worldwide data suggest that in the next decades, the incidence of ischemic stroke will increase as a result of increased longevity.6

Despite improvements in acute stroke care, prognosis remains somber for a significant proportion of patients, with early-case (21 days to 1 month after stroke) fatality rate for ischemic stroke ranging from 13% to 23% in high-income countries.7 Monitoring the trends and patterns of in-hospital stroke mortality allows for the identification of factors associated with mortality that may help reduce death rates by selecting those patients at higher risk who require more intensive resources.

Prior studies have shown that mortality predictors differ between males and females8; a systematic review of 98 studies found that stroke was more severe in women, with a higher mortality as compared with men.9 Furthermore, clear sex differences according to stroke subtypes, severity, risk factors, and outcome have been reported.10,11

Stroke mortality is also influenced by the length of stay (LOS) in-hospital, and those predictors for stays of 7 days or less differ from those for longer stays.12-14 Indeed, stroke mortality exhibits a bimodal distribution, with the first peak during the initial 7 days.13 Yet, despite a large body of literature on stroke prognosis, studies examining the predictors of in-hospital mortality and the impact of medical and neurological complications on early outcome in general neurology clinical practice are scant.

In this study, we sought to identify factors associated with in-hospital mortality after ischemic stroke. Due to the aforementioned evidence for an influence of LOS and sex on mortality, the initial mortality analysis was followed by a stratification according to these two variables.

METHODS

We identified all patients with acute ischemic stroke consecutively admitted to the Neurology Department (stroke unit) of our hospital over a 24-month period (from January 1, 2010 to December 31, 2011). Our hospital is a 439-bed hospital in northern Spain serving a population of 300,000 inhabitants. It belongs to the network of the Spanish public health care system, which provides free unrestricted care to the population. Our Department of Neurology has a stroke unit with urgent neuroimaging resources, sonography, and staff on call available 24 hours a day. This was a single-center study.

Data were collected through the Hospital Stroke Database, a prospective stroke registry that contains sociodemographic characteristics, comorbid conditions, clinical, laboratory, and radiological findings, hospital management, medical and neurological complications, treatment regimen, and outcomes. The database collects the information of all stroke patients admitted to our hospital.

2.1 Study population and data selection

2.1.1 Inclusion criteria

The major inclusion criterion was admission to the hospital with the main diagnosis of acute ischemic stroke, as defined by the updated definition of stroke for the 21st century.15 We only included acute stroke patients when admission was done within 1 week after symptom onset. The diagnosis of cerebral infarction was confirmed in each patient by computed tomography or magnetic resonance imaging. The combination of symptoms lasting less than 24 hours with evidence of acute vascular lesions on neuroimaging was also catalogued as stroke in this study. Only patients greater than or equal to 18 years old were eligible in this study.

2.1.2 Exclusion criteria

Patients with TIA or with intracerebral and subarachnoid hemorrhage were excluded from the present analysis since their prognosis differs significantly from ischemic stroke.16,17 Also, in-hospital strokes were excluded.

2.2 Definition of variables

The variables evaluated in this study had been selected a priori, based on existing literature and clinical judgment.9,14

2.2.1 Patient data

Patients' age on admission and sex were recorded, as were the following comorbidities: smoking (active or not); arterial hypertension, defined by a history of antihypertensive treatment before admission, or systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg for longer than 48 hours after admission; diabetes mellitus, assessed as known diabetes on admission or if plasma glucose was greater than 200 mg/dL (11.1 mmol/L) on admission or during hospital stay; history of dyslipidemia if total cholesterol level was greater than or equal to 200 mg/dL or low-density lipoprotein (LDL) cholesterol > 150 mg/dL; previous atrial fibrillation known and atrial fibrillation de novo documented by electrocardiogram or Holter monitoring; previous stroke, defined as evidence for acute neurologic deficit of more than or equal to 24 hours before current event or history of ischemic cardiomyopathy or peripheral arteriopathy.
2.2.2 | Ischemic stroke classification

Patients were classified (1) according to the size and location of infarction, by the Oxfordshire Classification of Stroke (OCSP), (2) etiologically, by Trial of Org 10172 in Acute Stroke Treatment classification (TOAST),18 and (3) based on severity, by the National Institutes of Health Stroke Scale (NIHSS).19 OCSP is a topographic, four-category classification composed by total anterior circulation (TACI), partial anterior circulation (PACI), Posterior Circulation (POCI), and lacunar (LACI). TOAST defines a five-option classification: small artery (lacunar) atherosclerotic; large artery atherosclerotic (atherothrombotic), including artery to artery embolism; cardioembolic; stroke of other determined cause; and stroke of undetermined cause. NIHSS score at admission is a 15-item neurologic examination stroke scale used to provide a quantitative measure of stroke-related neurologic deficit, ranging from 0 (asymptomatic) to 42 points (maximum score) (categorized a priori as less than 7, 7-13, and greater than or equal to 14 points based on previous studies20). Finally, functional impairment at discharge was evaluated according to the modified Rankin Scale (mRS), where favorable outcome was defined when patient was independent (mRS 0-2), and poor outcome was defined as dependence (mRS 3-5) or death (mRS 6).21 In-hospital mortality was defined as mRS 6.

During hospitalization, information on the following medical and neurological complications was collected: (1) cardiovascular complications, including acute myocardial infarction, heart failure, ventricular arrhythmias, cardiac arrest, and pulmonary embolism; (2) respiratory infection, assessed clinically by the presence of respiratory crackles, combined with at least one of the following: temperature greater than 38°C, new purulent sputum, or positive chest radiograph that occurred during hospital stay22; (3) urinary infection, defined by clinical findings combined with pyuria18; and (4) symptomatic seizures, defined as nonepileptic patients who developed focal or general seizures in the context of stroke.22 It was also recorded whether the patient received therapy with t-PA. LOS was determined by the time from admission to discharge; it was evaluated as a continuous variable and was also categorized as less than or equal to 7 days and greater than 7 days based on prior reports investigating in-hospital mortality,12 and taking into account that the main clinical decisions are made during the first week of admission.23 Patients remained admitted until they were independent to return home or stable enough to be transferred to a rehabilitation center.

2.3 | Ethics

This study was approved by the Ethics Committee of our institution. Written informed consent was obtained from all patients or their relatives when the patient was not able to communicate properly.

2.4 | Statistical analyses

An exploratory analysis of the studied sample was initially performed, which included mean and standard deviations for continuous data, and frequencies and percentages for qualitative data. The Kolmogorov-Smirnov test was used to verify the normality of continuous variables.

To assess potential predictors of in-hospital mortality, a univariable analysis was undertaken. Age, comorbidities, OCSP, NIHSS score, and complications were considered. Student's t-test and ANOVA (or the Wilcoxon test and Kruskal-Wallis if data was not normally distributed) were used. For categorical variables, the Chi-square test or the Fisher's exact test was used.

As mentioned in the introduction, this procedure was performed stratified by sex, since there is a large body of evidence in the literature indicating that mortality predictors may impact differently according to sex.8-11 It was also stratified by LOS (less than or equal to 7 days and greater than or 7 days), since the main clinical decisions are made during the first week of admission and mortality predictors may differ depending on the LOS.12-14

In the multivariable analysis, we developed logistic regression models with backward elimination method to build models to predict in-hospital mortality. Those variables with a P value < 0.20 in the univariable analysis were considered for the multivariable analysis. Covariates that showed a P value < 0.05 remained in the final model. We assessed the discrimination ability of the multivariable model developing a receiver operating characteristic (ROC) curve and calculating its area under curve (AUC). A model with an AUC value higher than 0.7 is considered to have good discrimination ability.24 Furthermore, the Hosmer-Lemeshow statistical method was applied to test the goodness-of-fit of the final multivariable models. A P value > 0.05 in that test was taken to reflect good calibration.

These analyses were performed in the overall sample, and in that stratified by sex of the patient and length of stay (less than or equal to 7 days and greater than 7 days). All the statistical procedures were done using SAS System v9.4. A two-sided P value < 0.05 was deemed statistically significant.

3 | RESULTS

3.1 | Study sample and main variables associated with mortality

Six hundred and seventy-three patients met the inclusion criteria out of 953 patients admitted to the Neurology Department with stroke during the study period. Two hundred and eighty patients were excluded, either for not fulfilling the inclusion criteria (39 patients) or for having exclusion criteria (54 hemorrhagic strokes and 187 TIAs).

Sociodemographics and clinical features are described in Table 1. The median age of the patients was 78 (interquartile range [IQR]: 71-84). Thirty-five patients (5.2%) were aged less than or equal to 55 years, 369 patients (54.8%) were between 56 to 80 years, and 269 patients (39.97%) were greater than 80 years. The most common comorbidities were hypertension (469 patients, 69.6%), dyslipemia (236, 35%), smoking (225, 33.4%), and a history of atrial fibrillation (191, 28.3%). The most common medical complication during hospital admission was respiratory infection (62, 9.2%). The etiology of stroke included atherothrombosis (232, 35%), cardioembolism (199, 29.5%), small vessel disease (139, 20.6%), stroke of other determined cause (8,
1.19%), and stroke of undetermined cause (95, 14.1%). Twenty patients had stroke of unusual etiology: underlying neoplasia (8), hematological disorders (2), infection (5), autoimmune disease (1), and miscellaneous causes (4). Only 8 of them met the inclusion criteria. The median LOS was 5 days (IQR, 4-7). Five-hundred eleven (75.9%) patients were discharged within the first week after admission. The NIHSS at admission was greater than or equal to 6 in 420 (62.4%) patients, 7 to 13 in 126 (18.7%) patients, and greater than or equal to 14 in 127 (18.8%) patients, with a median score of 4 (IQR: 2-10). Of the 673 patients, 33 (4.9%) received thrombolytic

| TABLE 1 | Patient’s sociodemographic and clinical features according to the overall in-hospital mortality. |
|---------|--------------------------------------------------------------------------------------------------|
| Alive (n= 626) | Dead (n= 47) | Total (n = 673) | p-value* |
| **Sex, n (%)** | | | 0.45 |
| Men | 335 (53.51) | 22 (46.81) | 357 (53.05) |
| Women | 291 (46.49) | 25 (53.19) | 316 (46.95) |
| **Age, mean ±SD** | 75.73±10.95 | 81.70±9.39 | 76.14±10.95 | <0.001 |
| **Age, n (%)** | | | <0.001 |
| ≤55 | 34 (5.43) | 1 (2.23) | 35 (5.20) |
| 56-80 | 354 (56.55) | 15 (31.91) | 369 (54.83) |
| >80 | 238 (38.02) | 31 (65.96) | 269 (39.97) |
| **Prior atrial fibrillation, n (%)** | 168 (26.84) | 23 (48.94) | 191 (28.38) | 0.026 |
| **Smoking, n (%)** | 213 (34.03) | 12 (25.53) | 225 (33.43) | 0.26 |
| **HTA, n (%)** | 436 (69.65) | 14 (29.79) | 450 (66.99) | 0.93 |
| **Diabetes, n (%)** | 143 (22.84) | 14 (29.79) | 157 (23.33) | 0.29 |
| **Dyslipemia, n (%)** | 223 (35.62) | 13 (27.66) | 236 (35.07) | 0.34 |
| **Previous strokes, n (%)** | 115 (18.37) | 16 (34.04) | 131 (19.47) | 0.01 |
| **Ischemic cardiopathy, n (%)** | 74 (11.82) | 7 (14.89) | 81 (12.04) | 0.49 |
| **Peripheral arterial disease, n (%)** | 25 (3.99) | 2 (4.26) | 27 (4.01) | 0.71 |
| **Cardiovascular complications, n (%)** | 17 (2.72) | 10 (21.28) | 27 (4.01) | <0.0001 |
| **Respiratory infection, n (%)** | 42 (6.71) | 20 (42.55) | 62 (9.21) | <0.0001 |
| **Urinary infection, n (%)** | 20 (3.19) | 1 (2.13) | 21 (3.12) | 0.68 |
| **Seizures, n (%)** | 12 (1.92) | 0 (0.00) | 12 (1.78) | 0.34 |
| **OCSP, n (%)** | | | <0.0001 |
| TACI | 107 (17.09) | 38 (80.85) | 145 (21.55) |
| PACI | 269 (42.97) | 2 (4.26) | 271 (40.27) |
| POCI | 113 (18.05) | 6 (12.77) | 119 (17.68) |
| LACI | 137 (21.88) | 1 (2.13) | 138 (20.51) |
| **TOAST classification, n (%)** | | | 0.0003 |
| Cardiembolic | 173 (27.64) | 26 (55.32) | 199 (29.57) |
| Atherothrombosis | 219 (34.98) | 13 (27.66) | 232 (34.47) |
| Lacunar | 138 (22.04) | 1 (2.13) | 139 (20.65) |
| Unusual origin | 8 (1.28) | 0 (0.00) | 8 (1.19) |
| Undetermined | 88 (14.06) | 7 (14.89) | 95 (14.12) |
| **Length of stay, median (IQR)** | 5 (4.7) | 7 (4.9) | 5 (4.7) | 0.04 |
| **Length of stay, n (%)** | | | 0.01 |
| ≤7 | 483 (77.16) | 28 (59.57) | 511 (75.93) |
| >7 | 143 (22.84) | 19 (40.43) | 162 (24.07) |
| **NIHSS, median (IQR)** | 4 (2.9) | 22 (19.30) | 10 (4.30) | <0.001 |
| **NIHSS, n (%)** | | | <0.0001 |
| ≤6 | 415 (66.29) | 5 (10.64) | 420 (62.41) |
| 7-13 | 121 (19.33) | 5 (10.64) | 126 (18.72) |
| ≥14 | 90 (14.38) | 37 (78.72) | 127 (18.87) |
| **t-PA therapy, n (%)** | 31 (4.95) | 2 (4.26) | 33 (4.90) | 0.83 |

Abbreviations: LACI, lacunar infarct; NIHSS, National Institutes of Health Stroke Scale; OCSP: Oxfordshire Classification of Stroke (see text). TACI: total anterior circulation infarct; PACI: partial anterior circulation infarct; POCI: posterior circulation infarct; LACI: lacunar infarct. IQR: Interquartile range. TOAST: Trial of Org 10172 in Acute Stroke Treatment (see text).

*Chi-square test or Fisher’s Exact method was used to test the association between categorical variables. The T-test or the non-parametric Wilcoxon test was applied for evaluating the mean/median comparison between the studied groups, respectively.*
therapy. Overall, 6% of the patients had symptomatic brain hemorrhages after t-PA therapy.

The overall in-hospital mortality rate was 7.13% (95% CI, 5.31%-9.35%). In-hospital mortality among men was 6.16% (3.90%-9.18%) and in women it was 8.23% (95% CI, 5.45%-11.82%) (P = 0.36, Fisher’s exact test). Out of 48 deaths, 26 were of neurological origin. Female patients were older than male patients (median [IQR] age 80 [73.5-85] vs. 74.08 [68-82] P < 0.001, Wilcoxon test). Males exhibited higher prevalence of smoking (54.3 vs 9.8%, P < 0.0001, Fisher’s exact test) and symptomatic seizures (2.80% vs 0.63%, P < 0.04, Fisher’s exact test), but arterial hypertension was more common in females. Stroke severity was higher in females (NIHSS) (Median [IQR]: 5 [2-12] vs 4 [2-9], P < 0.01, Fisher’s exact test).

Despite the lack of a significant effect of sex on mortality in the univariable analysis, prior evidence in the literature indicates that several of the analyzed mortality predictors may impact differently according to sex.

In addition, stroke mortality has also been reported to be influenced by the LOS, and those predictors for stays of 7 days differ from those for longer stays. For these reasons, after an initial global mortality analysis, we proceeded to further analyze data stratified by both sex and LOS.

Table 2 shows the sociodemographic and clinical features according to mortality stratified by sex. Among females, prior atrial fibrillation, previous strokes, cardiovascular complications, and respiratory infections during hospital stay were associated with higher mortality. In males, age, dyslipemia, and respiratory infections were associated with higher mortality. A higher NIH score was associated with mortality in both sexes.

Table 3 displays the results obtained from the stratified analysis by LOS. Among those patients with a LOS > 7, only those with respiratory infection showed a higher mortality risk. In contrast, prior atrial fibrillation, previous strokes, and cardiovascular complications were associated to mortality in those patients with shorter stays.

These differences led us to perform separate predictive models stratified by sex and by LOS (Table 4).

### 3.2 In-hospital mortality stratified by sex

A multivariable analysis to investigate potential predictors of in-hospital mortality by sex showed that prior strokes, cardiovascular complications, and stroke severity were independent predictors of in-hospital death among women (Table 4).

Advanced age, stroke severity, and respiratory infections during hospitalization had a significantly negative impact on outcome among men.

### 3.3 In-hospital mortality stratified by length of stay

To investigate potential predictors of in-hospital mortality by length of stay, a multivariable logistic regression model was developed (Table 4), which revealed that during the first week, mortality was associated with a history of previous stroke, higher stroke severity, and both cardiovascular and respiratory complications during hospitalization.

After a LOS of 7 days, the main factor independently associated with in-hospital mortality was stroke severity.

Our models showed good goodness-of-fit properties in terms of calibration and discrimination (Table 4). In all models, AUC values were above 0.80 and the P values obtained from the Hosmer-Lemeshow tests applied were greater than 0.05.

### 3.4 In-hospital mortality in the overall sample

For completeness, we also performed a multivariable logistic regression model in the overall sample (n = 673), without any stratification, and the results are shown in Table S1. In this sample, the presence of (1) previous strokes; (2) cardiovascular complications during hospitalization, and (3) respiratory infection during hospital stay, were associated with higher in-hospital mortality risk.

### 4 DISCUSSION

This prospective, single-center study evaluated the in-hospital mortality in a sample of patients consecutively admitted for ischemic stroke. On the basis of our findings and on previous reports, the analysis was then performed after stratification by sex and by length of stay during hospital admission.

Our results show that the most relevant independent factor associated with in-hospital mortality in ischemic stroke patients are stroke severity (in the overall sample and on each of the analyzed strata, as measured by the NIH scores), as well as respiratory infections (overall sample, in men, and in patients with a LOS ≤ 7 days) and cardiovascular complications (overall sample in women and in patients with a LOS ≤ 7 days), the two latter representing potentially modifiable conditions. The risk of death conferred by these conditions was particularly important during the first week of admission.

The overall mortality rate in this study (7.13%) falls within the range of previous global studies (from 3% to 15.6%) and are close to the 6% described recently in another Spanish cohort. Our data confirm that the main factor with an independent impact on in-hospital mortality is stroke severity in both women and men, and in both short and long stays. This finding is consistent with previous studies.

The present study shows that potentially modifiable factors such as respiratory infections present in a similar rate of patients as described in prior studies were independently associated to in-hospital mortality only in men (OR: 3.84; 95% CI, 1.32-11.20), in accordance with other study. However, cardiovascular complications were associated with poorer outcome only in women (OR: 29.70; 95% CI, 5.70-154.8).

The association between clinical variables and stroke in-hospital mortality has previously been analyzed. However, most studies were retrospective and did not differentiate ischemic and hemorrhagic strokes. In contrast, the present study was conducted prospectively, only including ischemic stroke patients to improve the homogeneity of the sample, and was carried out in the neurology practice of a general hospital. In our study, ischemic stroke was more frequent among men, but women were older and are with a more severe stroke,
consistent with previous studies. In contrast, we did not find sex differences between the different subtypes of stroke.

Our findings show that older age represents an important independent predictor of death risk only in men, in agreement with Heuschmann et al. On the other hand, and contrary to previous studies that have demonstrated that prior stroke history was an independent predictor in men, our study only found a significant negative impact in outcome in women (OR: 3.29; 95% CI, 1.19-9.10). In the future, with women’s greater life expectancy, these differences may be exacerbated.

Since 1984, early mortality after stroke has been shown to exhibit a bimodal distribution, with the first peak during the initial 7 days. Since most clinical interventions are decided during the first week, we decided to compare stroke death variables impact among patients

| TABLE 2 | Univariable analysis of the association between risk factors and mortality, stratified by sex. |
|---------|------------------------------------------------------------------------------------------|
|         | Female (n=316)                                                                           | Male (n=357) |
|         | Dead (n=26) Alive (n=289) P value* Dead (n=22) Alive (n=335) P value* |
| Age, mean ±SD | 80.28±9.90 78.32±10.18 0.486 | 83.32±8.72 73.47±11.10 <.0001 |
| Age, n (%) | 0.61 | <0.001 |
| ≤55      | 0 (0) 8 (100) | 1 (3.70) 26 (96.30) |
| 56-80    | 11 (7.28) 140 (92.72) | 4 (1.83) 214 (98.17) |
| >80      | 14 (8.92) 143 (91.08) | 17 (15.18) 995 (84.82) |
| Prior atrial fibrillation, n (%) | 14 (14.74) 81 (85.26) 0.006 | 9 (9.38) 87 (90.63) 0.140 |
| Smoking, n (%) | 1 (3.23) 30 (96.77) 0.49 | 11 (5.67) 183 (94.33) 0.826 |
| Arterial hypertension, n (%) | 20 (8.55) 214 (91.45) 0.636 | 13 (5.53) 222 (94.47) 0.49 |
| Diabetes mellitus, n (%) | 8 (11.43) 62 (88.57) 0.216 | 6 (6.90) 81 (93.10) 0.80 |
| Dyslipemia, n (%) | 11 (9.17) 109 (90.83) 0.53 | 2 (1.72) 114 (98.28) 0.017 |
| Previous strokes, n (%) | 11 (17.74) 51 (82.26) 0.001 | 5 (7.25) 64 (92.75) 0.78 |
| Ischemic cardioathy, n (%) | 2 (6.45) 29 (93.55) 0.75 | 5 (10) 45 (90) 0.21 |
| Peripheral arterial disease, n (%) | 1 (10) 9 (90) 0.57 | 1 (5.88) 16 (94.12) 0.96 |
| Cardiovascular complications, n (%) | 7 (63.64) 4 (36.36) <0.001 | 3 (18.75) 13 (81.25) 0.067 |
| Respiratory infection, n (%) | 8 (32) 17 (68) <0.001 | 12 (32.43) 25 (67.57) <0.001 |
| Urinary infection, n (%) | 1 (7.14) 13 (92.86) 0.91 | 0 (0) 7 (100) 0.49 |
| Seizures, n (%) | 0 (0) 2 (100) 0.68 | 0 (0) 10 (100) 0.41 |
| OCSP, n (%) | <0.001 | <0.001 |
| TACI     | 22 (25.58) 64 (74.42) | 16 (27.12) 43 (72.88) |
| PACI     | 0 (0) 126 (100) | 2 (1.38) 143 (98.62) |
| POCI     | 3 (6.52) 43 (93.48) | 3 (4.11) 70 (95.89) |
| LACI     | 0 (0) 58 (100) | 1 (1.25) 79 (98.75) |
| TOAST, n (%) | 0.01 | 0.075 |
| Cardioembolic | 15 (14.56) 88 (85.44) | 11 (11.46) 85 (88.54) |
| Atherothrombotic | 6 (5.36) 106 (94.64) | 7 (5.83) 113 (94.17) |
| Lacunar   | 0 (0) 58 (100) | 1 (1.23) 80 (98.77) |
| Unusual origin | 0 (0) 2 (100) | 0 (0) 6 (100) |
| Undetermined | 4 (9.76) 37 (90.24) | 3 (5.56) 51 (94.44) |
| Length of stay, median (IQR) | 6 (4.8) 5 (3.7) 0.26 | 7.5 (4.10) 5 (4.8) 0.069 |
| Length of stay, n (%) | 0.197 | 0.02 |
| ≤7       | 17 (6.80) 233 (93.20) | 11 (4.21) 250 (95.79) |
| >7       | 8 (12.12) 58 (87.88) | 11 (11.46) 85 (88.54) |
| NIHSS, median (IQR) | 20 (14.22) 4 (2.10) <0.001 | 18.5 (15.21) 4 (2.7) <0.001 |
| NIHSS, n (%) | <0.001 | <0.001 |
| ≤6       | 3 (1.72) 171 (98.28) | 2 (0.81) 244 (99.19) |
| 7-13     | 3 (4.41) 65 (95.59) | 2 (3.45) 56 (96.55) |
| ≥14      | 19 (25.68) 55 (74.32) | 18 (33.96) 35 (66.04) |
| t-PA therapy, n (%) | 1 (5.88) 16 (94.12) 0.75 | 1 (6.25) 15 (93.75) 0.99 |

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; OCSP: Oxfordshire Classification of Stroke (see text). TACI: total anterior circulation infarct; PACI: partial anterior circulation infarct; POCI: posterior circulation infarct; LACI: lacunar infarct. IQR: Interquartile range

TOAST: Trial of Org 10172 in Acute Stroke Treatment (see text)

*Chi-square test or Fisher’s Exact method was used to test the association between categorical variables. The T-test or the non-parametric Wilcoxon test was applied for evaluating the mean/median comparison between the studied groups, respectively.
with LOS \( \leq 7 \) days, and with longer stays. Our patients with LOS > 7 days were older, with higher stroke severity, more frequent cardiovascular complications, respiratory and urinary infections, and seizures. In those with LOS \( \leq 7 \) days, previous strokes, cardiovascular and respiratory complications, and stroke severity had an independent effect on death risk. In longer stays, only stroke severity was a significant predictor.

Our data confirm that in patients with a LOS \( \leq 7 \) days, pneumonia, one of the most frequent medical complications of stroke and the most common cause of fever within the first 48 hours after stroke, was also the most frequent medical complication. However, a prior German study found that in patients with shorter LOS, poor outcome and early death was attributed to nonmodifiable predictors such as stroke severity on admission or age. Conversely, modifiable

### Table 3

Univariable analysis of the association between risk factors and mortality, stratified by length of stay (LOS).

|                      | LOS <7days (n=511) | LOS ≥7days (n=162) |
|----------------------|--------------------|--------------------|
|                      | Dead (n=29)        | Alive (n=482)      | P value\(^a\) |
|                      |                    |                    | Dead (n=19)  | Alive (n=143) | P value\(^a\) |
| Sex, n (%)           | 0.24               | 0.90               | 0.02        | 0.32         |
| Men                  | 11 (4.21)          | 250 (95.79)        | 11 (11.46)  | 85 (88.54)   |
| Women                | 17 (6.80)          | 233 (93.20)        | 8 (12.12)   | 58 (87.88)   |
| Age, mean ±SD        | 83 ±8.15           | 75.34±10.93        | <0.001      | 79.79 ±10.93 | 0.19          |
| Age, n (%)           | 0.002              | 0.32               | 0.016       | 0.77         |
| ≤55                  | 0 (0)              | 27 (100)           | 1 (12.50)   | 7 (87.50)    |
| 56-80                | 9 (3.08)           | 283 (96.92)        | 6 (7.79)    | 71 (92.21)   |
| >80                  | 19 (9.90)          | 173 (90.10)        | 12 (15.58)  | 65 (84.42)   |
| Prior atrial fibrillation, n (%) | 14 (10.07) | 125 (89.93) | 0.016 | 9 (17.31) | 43 (82.69) | 0.189 |
| Smoking, n (%)       | 7 (4.07)           | 165 (95.93)        | 5 (9.43)    | 48 (90.57)   |
| Arterial hypertension, n (%) | 21 (5.97) | 331 (94.03) | 0.837 | 13 (11.11) | 104 (88.89) | 0.79 |
| Diabetes mellitus, n (%) | 8 (6.72) | 111 (93.28) | 0.651 | 6 (15.79) | 32 (84.21) | 0.39 |
| Dyslipemia, n (%)    | 10 (5.49)          | 172 (94.51)        | 4 (7.41)    | 50 (92.59)   |
| Previous strokes, n (%) | 10 (10.99) | 81 (89.01) | 0.023 | 6 (15) | 34 (85) | 0.57 |
| Ischemic cardioathy, n (%) | 5 (8.20) | 56 (91.80) | 0.373 | 2 (10) | 18 (90) | 0.80 |
| Peripheral arterial disease, n (%) | 1 (5.26) | 18 (94.74) | 0.937 | 1 (12.50) | 7 (87.50) | 0.94 |
| Cardiovascular complications, n (%) | 7 (53.85) | 6 (46.15) | <0.001 | 3 (21.43) | 11 (78.57) | 0.215 |
| Respiratory infection, n (%) | 12 (44.44) | 15 (55.56) | <0.001 | 9 (25.71) | 26 (74.29) | 0.007 |
| Urinary infection, n (%) | 1 (12.50) | 7 (87.50) | 0.376 | 0 (0) | 13 (100) | 0.367 |
| Seizures, n (%)      | 0 (0)              | 6 (100)            | 0 (0)       | 6 (100)      |
| OCSP, n (%)          | 23 (28.75)         | 57 (71.25)         | 16 (24.62)  | 49 (75.38)   |
| TACI                 | 2 (0.93)           | 212 (99.07)        | 0 (0)       | 57 (100)     |
| PACI                 | 4 (4.49)           | 85 (95.51)         | 2 (6.67)    | 28 (93.33)   |
| LACI                 | 0 (0)              | 128 (100)          | 1 (10)      | 9 (90)       |
| TOAST, n (%)         | 0.002              | 0.70               | 0.001       | <0.001      |
| Cardioembolic        | 15 (11.63)         | 114 (88.37)        | 11 (15.71)  | 59 (84.29)   |
| Atherothrombotic     | 10 (5.43)          | 174 (94.57)        | 4 (8.33)    | 44 (91.67)   |
| Lacunar              | 0 (0)              | 128 (100)          | 1 (9.09)    | 10 (90.91)   |
| Unusual origin       | 0 (0)              | 5 (100)            | 0 (0)       | 3 (100)      |
| Undetermined         | 4 (6.15)           | 61 (93.85)         | 3 (10)      | 27 (90)      |
| NIHSS, median (IQR)  | 19 (11.5,21)       | 3 (2,7)            | <0.001      | 19 (15,23)   | 9 (4.15) | <0.001 |
| NIHSS, n (%)         | <0.001             | <0.001             | 0.001       | 0.001       |
| ≤6                   | 4 (1.11)           | 355 (98.89)        | 1 (1.64)    | 60 (98.36)   |
| 7-13                 | 5 (5.81)           | 81 (94.19)         | 0 (0)       | 40 (100)     |
| ≥14                  | 20 (30.30)         | 46 (69.70)         | 18 (29.51)  | 43 (70.49)   |
| t-PA therapy, n (%)  | 0 (0)              | 20 (100)           | 0.620       | 2 (15.38)    | 11 (84.62) | 0.65 |

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; OCSP: Oxfordshire Classification of Stroke (see text). TACI: total anterior circulation infarct; PACI: partial anterior circulation infarct; POCI: posterior circulation infarct; LACI: lacunar infarct. IQR: Interquartile range.

TOAST: Trial of Org 10172 in Acute Stroke Treatment (see text).

\(^a\)Chi-square test or Fisher’s Exact method was used to test the association between categorical variables. The T-test or the non-parametric Wilcoxon test was applied for evaluating the mean/median comparison between the studied groups, respectively.
factors, as respiratory infection, were of major importance in longer stays. However, unlike ours, this prospective multicenter study, studied patients with stroke without differentiating their ischemic or hemorrhagic origin. Our findings are in line with Vargas et al who found that respiratory infections were associated with higher mortality during the first week.

Our study has several strengths. First, all data were collected in a prospective, uniform manner, and only data from ischemic stroke patients were analyzed. Second, it was based on a general neurology clinical practice setting. On the basis of our findings, we believe that there is enough evidence to develop and evaluate a predictive model to identify high-risk ischemic stroke patients in future investigations.

Among the study limitations, the fact that we employed a tissue-based definition of TIA, which has been proven more accurate than the time-based definition for predicting recurrent stroke, may have resulted in a higher number of minor strokes being identified as compared with a time-based definition. Our study was based on data acquired in a single hospital, and therefore, may not be readily comparable to the patterns of in-hospital stroke mortality in multicenter studies collecting information from the routine clinical care of acute stroke. In addition, we only observed hospitalization time, and therefore, factors influencing early mortality could differ from variables predicting outcome after discharge from hospital.

In summary, our findings show that prior atrial fibrillation, previous strokes, cardiovascular complications, and respiratory infections during hospital stay were associated with a higher mortality particularly in women, whereas age, dyslipemia, and respiratory infections were associated with a higher mortality in men. Stroke severity was associated with mortality in both sexes. Prevention and appropriate management of these conditions is paramount to improve the prognosis of patients with ischemic stroke.

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**CONFLICTS OF INTEREST**
The authors declare no conflicts of interest.

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**TABLE 4** Summary statistics of multivariable logistic regression analysis for risk of in-hospital mortality, by sex and length of stay (LOS)

| Sex          | Length of stay (LOS) | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value |
|--------------|----------------------|-------------|---------|-------------|---------|-------------|---------|-------------|---------|
|              | ≤7 days              | >7 days     |         |
| Age          | Men                  | Women       |         |
| ≤80          | Reference            | -           |         | -           | -       | -           | -       | -           | -       |
| >80          | 3.67 (1.21, 11.16)   | 0.02        |         | -           | -       | -           | -       | -           | -       |
| Previous stroke | No                  | Reference   |         | Reference   | -       | -           | -       | -           | -       |
|              | -                    | -           |         | 3.29 (1.19, 9.10) | 0.02 | 2.80 (1.01, 7.72) | 0.04 | -           | -       |
| Respiratory infection | No                  | Reference   |         | Reference   | -       | -           | -       | -           | -       |
|              | -                    | -           |         | 3.84 (1.32, 11.20) | 0.01 | 5.82 (1.97, 17.18) | 0.001 | -           | -       |
| Cardiovascular complications | No                  | Reference   |         | Reference   | -       | -           | -       | -           | -       |
|              | -                    | -           |         | 29.70 (5.70, 154.8) | <0.001 | 15.33 (3.38, 69.60) | <0.001 | -           | -       |
| NIH          | ≤6                   | Reference   | 2.22 (0.36, 13.70) | 0.39 | 1.53 (0.28, 8.20) | 0.62 | 3.57 (0.91, 14.08) | 0.07 | 0.50 (0.02, 13.00) | 0.68 |
|              | 7-13                 | Reference   | 16.63 (4.66, 59.31) | <0.001 | 22.99 (7.04, 75.02) | <0.001 | 17.15 (3.06, 96.07) | 0.0001 |
|              | ≥14                  | Reference   | 23.19 (5.69, 94.56) | <0.001 | 23.19 (5.69, 94.56) | <0.001 | 23.19 (5.69, 94.56) | <0.001 | 23.19 (5.69, 94.56) | <0.001 |
| Model performance | AUC (95% CI)          | 0.951 (0.950, 0.952) |         | 0.902 (0.899, 0.904) | 0.941 (0.940, 0.942) | 0.831 (0.830, 0.833) |
|              | H-L test             | 0.238       | 0.89    | 0.519       | 0.419   | 0.519       | 0.419   |

Abbreviations: ‐, Variable not entered in the final multivariable logistic regression. OR (95% CI): Odds ratios with their 95% confidence intervals. AUC (95% CI): area under the ROC curve with its own confidence interval. H-L test: Hosmer-Lemeshow test.
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