**Cumulative rehospitalizations and implications for subsequent mortality after first-ever ischemic stroke**

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**ABSTRACT**

**Introduction:** Clinical implications of readmission following initial hospitalization for acute ischemic stroke (AIS) are not known. We examined predictors of readmissions and impact of readmissions on subsequent mortality after first-ever AIS.

**Materials and methods:** Adults aged ≥18 years who survived to discharge after hospitalization for first-ever AIS from 2003 to 2019 were included in the study. For each patient, the overall burden of hospitalizations was measured as total number of hospitalizations and aggregate days spent hospitalized during follow-up. We used Poisson regression to estimate incident rate ratios (IRR) for predictors of re-hospitalization and time-dependent Cox regression to estimate hazard ratios (HR) for mortality.

**Results:** Of 908 AIS survivors, 537 died, 669 had 2,645 readmissions over 4,535 person-years follow-up. Adjusted independent predictors of cumulative readmission included being white (IRR 1.21, 95% CI 1.03–1.42), dependency on discharge (IRR 1.27, 95% CI 1.17–1.38), cardio-embolism (IRR 1.35, 95% CI 1.18–1.45), smoking (IRR 1.21, 95% CI 1.08–1.35), anemia (IRR 1.40, 95% CI 1.24–1.57), arthritis (IRR 1.20, 95% CI 1.10–1.31), coronary artery disease (IRR 1.34, 95% CI 1.23–1.47), cancer (IRR 1.96, 95% CI 1.64–2.30), chronic kidney disease (IRR 1.36, 95% CI 1.21–1.57), COPD (IRR 1.18, 95% CI 1.04–1.34), depression (IRR 1.50, 95% CI 1.37–1.66), diabetes mellitus (IRR 1.48, 95% CI 1.36–1.48), and heart failure (IRR 1.17, 95% CI 1.03–1.34). Conversely, hyperlipidemia was associated with a lower risk of readmission (IRR 0.79, 95% CI 0.71–0.88). Mortality was significantly increased with each hospitalization and cumulative days spent in hospital.

**Conclusions:** Among survivors of AIS hospitalization, certain sociodemographic indicators, stroke-specific features, and several key comorbid conditions were associated with increased risk of readmissions, which in turn correlated with increased mortality. Therefore, lifestyle modification and optimal treatment of comorbidities are likely to improve the outcome after AIS.

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**Introduction**

Acute ischemic stroke (AIS) is among the leading causes of hospitalization and disability in the United States [1]. Patient with AIS who survived hospitalization are at increased risk for readmission and death after discharge [2–6]. In general, readmission following any acute care hospitalization is associated with increased mortality, healthcare cost, and a negative impact on quality of life [7–9]. For conditions such as heart failure, pneumonia, and acute myocardial infarction, a large proportion of readmissions were unrelated to index hospitalization and, yet, lead to increased risk of subsequent death [10,11].

Published data on readmission following AIS are limited, with most clinical trials focused on short- or intermediate-term outcomes and on restricted conditions such as recurrent stroke or cardiovascular events [3,12,13]. Most studies focused on first readmission following index AIS hospitalization even though more hospital readmission can occur beyond the first in each patient when followed over a longer-period of time. Therefore, an understating of overall burden of hospitalization provides a better estimate of morbidity among AIS survivors. To date, data are limited on studies examining the predictors of readmission. A recent systematic review of 16 clinical trials showed that factors associated with readmission were inconsistent across studies [3]. Previous studies have investigated predictors of a single or first hospitalization mainly for recurrent stroke or stroke-related event. However, the predictors of cumulative all-cause readmissions which contribute to high morbidity and substantial burden on inpatient healthcare cost have not been determined. It is not known whether the burden of recurrent hospitalization after AIS is predictive of subsequent death. Thus, among survivors of AIS, the cumulative long-term burden of readmissions, determinants of readmission, and clinical consequences of readmission after the index event represent critical knowledge gaps that need to be addressed.
To address these critical knowledge gaps, we aimed to investigate 1) the cumulative incidence of readmission; 2) patient at risk for readmission, 3) the effect of readmission on subsequent mortality; and 4) whether days spent hospitalized during follow-up is predictive of subsequent mortality.

Materials and methods

Study design

A retrospective cohort study.

Data source

Data on consecutive patients hospitalized for first-ever AIS at Mayo Clinic, Rochester, Minnesota, were initially extracted by professional abstractors using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10 codes. The electronic medical records of each patient were subsequently reviewed by the study investigators who added missed data points and excluded patients who did not meet inclusion criteria. Further details of data extraction are published elsewhere [4]. ICD codes were previously reported to have high specificity for AIS [14]. The look-back period extended to 1 January 1994 to ensure validity of first-ever event. The Mayo Clinic also serves as a primary care facility for the residents of Olmsted County in the US state of Minnesota, which has a population of 158,293 as of 2019. The current study population was restricted to Olmsted County residents to ensure all hospital readmissions were accounted for.

Study population

Adults aged ≥18 years with a new AIS who were discharged alive from Mayo Clinic, Rochester, Minnesota, between 1 January 2003 and 25 December 2019 were included in the study. We excluded patients with uncertain AIS diagnosis, stroke prior to 1 January 2003, and those declined participation in research. The Mayo Clinic Institutional Review Board approved the study, and the need for informed consent was waived. All the supporting data are provided within the article and its online supplementary files.

Ascertainment of diagnosis of acute ischemic stroke

The diagnosis of AIS was based on documentation by a neurologist. Three study investigators settled the principal discharge diagnosis by manual review of admission and discharge summaries of each patient. Patients with AIS stroke were classified into 5 etiological subtypes based on Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria (Large artery atherosclerosis [LAA], cardio-embolism, small vessel occlusion [SVO], other determined etiology, undetermined etiology) [15].

Ascertainment of National Institute of Health stroke scale (NIHSS) score

For each patient, the severity of neurological deficit on admission was assessed by National Institutes of Health Stroke Scale (NIHSS) score from 0 to 42, with higher score indicating greater stroke severity. The NIHSS score was retrospectively calculated using comprehensive neurological examination findings by the attending neurologist in patients with missing NIHSS scores [16]. Previous studies provided evidence for the accuracy and reliability of retrospective assessment of NIHSS score from medical record [17].

Ascertainment of disability on dismissal

Disability was measured on the modified Rankin Scale (mRS) [18,19] on day of dismissal. The mRS score was calculated (6-point disability scale from 0, indicating no symptoms, to 6, indicating death) for each patient based on retrospective analysis of functional assessment data (feeding, bathing, grooming, dressing, toileting, transfers, mobility, ambulation, stair climbing) provided by physical and occupational therapists in their documentation. Disability was defined as estimated score ≥3 on mRS.

Ascertainment of covariates

The covariates for multivariable models were selected based on expert opinion and data from previous studies [4,20–22]. Comorbid conditions included preexisting chronic disease conditions or new diagnosis during index hospitalization. Patients were screened for anemia [23] and a panel of 20 chronic conditions specified by the US Department of Health

| Table 1. Baseline clinical characteristics of study population, n = 908. | Values |
|-----------------------------|--------|
| Sociodemographics | Age, mean (SD) years |
| Male n = (%) | 410 (45) |
| White n = (%) | 838 (92) |
| Stroke-specific characteristics | Cigarette smoking n = (%) |
| Anterior, n = (%) | 140 (15) |
| mRS ≥3, n = (%) | 499 (55) |
| TOAST classification (Etiology of stroke) | LAA, n = (%) |
| Cardio-embolic, n = (%) | 292 (32) |
| Undetermined, n = (%) | 275 (30) |
| Determined, n = (%) | 38 (5) |
| Comorbidities | Hypertension, n = (%) |
| Hyperlipidemia, n = (%) | 557 (61) |
| Depression, n = (%) | 176 (19) |
| Diabetes mellitus, n = (%) | 225 (25) |
| CAD, n = (%) | 252 (28) |
| Heart failure, n = (%) | 122 (13) |
| COPD, n = (%) | 75 (8) |
| CKD, n = (%) | 123 (13) |
| Arthritis, n = (%) | 242 (27) |
| Osteoporosis, n = (%) | 110 (12) |
| Dementia, n = (%) | 106 (12) |
| Cancer, n = (%) | 50 (5) |
| Anemia, n = (%) | 104 (11) |
| Physiological variable | Systolic blood pressure, mmHg, Mean (SD) |
| Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LAA, large artery atherosclerosis; mRS, modified Rankin score; SD, standard deviation; SVO, small vessel occlusion; TOAST, Trial of OBG 10172 in Acute Stroke Treatment. | 151 (23) |
and Human Services [24]. Comorbidities with <3% prevalence were excluded from the analysis. Baseline variables are listed in Table 1. The covariate selection is described with a flow chart on page 2 in the supplement.

Outcomes
The pre-specified co-primary outcomes were the occurrence of readmissions or death until censoring date of 25 December 2019. Both hospitalizations and deaths were sub-grouped according to the following categories: all cause, recurrent stroke, cardiovascular (CV), and non-cardiovascular (non-CV). CV causes of readmission or death included all cardiac and vascular events including recurrent strokes.

Ascertainment of readmission
Readmission was defined as all in-patient hospitalizations up until death or until censoring date following discharge from the index AIS admission. For each patient, the overall burden of hospitalization was measured as total number of hospitalizations and aggregate days spent hospitalized during the follow-up. Recurrent hospitalizations were classified as hospitalization from any condition, recurrent stroke, CV, or non-CV condition. Once readmission was ascertained, three study investigators settled the principal discharge diagnosis and time to readmission by manual review of electronic medical records. Only readmissions to hospital, not emergency room visits, were included in analysis.

Ascertainment of mortality
The time to death was assessed from index hospitalization to censoring on 25 December 2019. Mortality data were abstracted from electronic medical records, which were constantly updated for mortality by respective primary care providers across the Mayo Clinic and Mayo Clinic Health System. The cause of death was identified from official death certificates and classified into four main categories: all-cause, CV, non-CV, and recurrent stroke.

Follow-up
Patients were followed from date of discharge until death or censoring date of 25 December 2019, whichever occurred first.

Statistical analysis
We reported continuous variables as means and standard deviations (SD) and categorical variables as frequencies and proportions. The independent predictors of cumulative readmissions were assessed by Poisson regression models with no concern for overfitting because of high number of events. We constructed separate Poisson regression models to estimate incident rate ratio (IRR) for all-cause, cardiovascular (CV), and non-CV hospitalizations. The time-dependent Cox proportional regression models were developed to determine hazard ratio (HR) and 95% confidence intervals (CI) for each readmission category (all-cause, CV, and non-CV) separately for all-cause or stroke, cardiovascular, or non-cardiovascular mortality. To avoid overfitting of the Cox regression models, we used maximum total variance data reduction technique. We replicated time-dependent Cox proportional models to assess HR and 95% CIs for mortality from all-cause, cardiovascular, non-cardiovascular, or stroke associated with days and each percentage of follow-up time spent hospitalized from discharge to death or censoring date. Poisson regression and Cox regression models were adjusted for baseline characteristics shown in Table 1. We performed data analysis using SAS version 9.4 (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA). A P < 0.05 was considered as statistically significant.

Results
Study cohort
Supplemental Figure illustrates the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flow diagram for selection of final study cohorts. The look-back period was extended to 9 years to ensure first-ever stroke of the final cohort. The final study cohort consisted of 908 patients with a first-ever AIS and who survived to discharge with a median follow-up of 4.3 years (interquartile range 1.5 –7.6 years; range 0.003 –16.7 years). Of total 908 patients, 816 (90%) were admitted to stroke unit and cared exclusively by stroke neurologist as the primary care provider. The remaining of the patients were admitted to other services including hospital medicine, general internal medicine, and family medicine, and most of these patients were treated in consultation with stroke neurology service. The baseline characteristics of the study population are presented in Table 1.

Time to event
During 4,535 person-years of follow-up, 669 (74%) patients had 2,645 readmissions from any condition corresponding to 12,089 days in hospital; 0.73% follow-up time spent hospitalized for any-condition; 238 (26%) patients were never hospitalized. Most readmissions were from non-CV conditions (non-CV 1,944 [73%] vs CV 715 [27%]). The remaining 238 patients (26%) were free of readmission during the follow-up period. For readmitted patients, the average number of hospitalizations was 4 and corresponding aggregate mean number of days hospitalized was 18. During a median follow-up of 4.3 years, 537 patients (59%) died from any cause including 244 (45%) CV deaths and 293 (55%) non-CV deaths, with 371 patients (41%) surviving to censoring date.

Analysis of cumulative readmission
Figure 1 shows the Poisson regression models for association between candidate predictors and readmission according to the category of cause, which included all-cause, CV, and non-CV conditions, represented as IRR with 95% CI and forest plot. Of 24 patient-level characteristics, we noted statistically significant association in 13 indicators for increased rates of all-cause readmission [white race, functional dependency on discharge, cardio-embolism as the etiology of AIS, current smoking status on admission, presence of anemia, arthritis, coronary artery disease (CAD), cancer, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), depression, diabetes mellitus, and heart failure]; 7 candidate predictors for increased rates of CV readmissions (white race,
Results of multivariable Poisson regression models, independent predictors of readmission from any condition, cardiovascular condition, and non-cardiovascular condition.

| Candidate predictors | All-cause | Cardiovascular | Non-cardiovascular |
|----------------------|-----------|----------------|-------------------|
|                      | IRR (95% CI) | Forrest plot | IRR (95% CI) | Forrest plot | IRR (95% CI) | Forrest plot |
| Age, years           | 1.01 (1.00 – 1.02) | Forrest plot | 1.01 (1.00 – 1.02) | Forrest plot | 1.01 (1.01 – 1.02) | Forrest plot |
| Male vs female       | 1.05 (0.97 – 1.14) | Forrest plot | 1.08 (0.92 – 1.27) | Forrest plot | 1.03 (0.94 – 1.13) | Forrest plot |
| White vs non-white   | 1.21 (1.03 – 1.42) | Forrest plot | 1.44 (1.05 – 2.03) | Forrest plot | 1.12 (0.94 – 1.34) | Forrest plot |
| Mean SBP             | 1.00 (0.99 – 1.00) | Forrest plot | 1.00 (0.99 – 1.01) | Forrest plot | 0.99 (0.99 – 0.99) | Forrest plot |
| mRS x2 vs x1         | 1.27 (1.17 – 1.38) | Forrest plot | 0.96 (0.81 – 1.13) | Forrest plot | 1.41 (1.28 – 1.56) | Forrest plot |
| Anterior vs posterior | 1.06 (0.97 – 1.16) | Forrest plot | 0.92 (0.78 – 1.10) | Forrest plot | 1.13 (1.02 – 1.26) | Forrest plot |
| LAA                  | 1.06 (0.92 – 1.21) | Forrest plot | 0.88 (0.66 – 1.16) | Forrest plot | 1.17 (1.00 – 1.37) | Forrest plot |
| Cardio-embolism      | 1.31 (1.18 – 1.45) | Forrest plot | 1.40 (1.14 – 1.71) | Forrest plot | 1.31 (1.15 – 1.48) | Forrest plot |
| SVD                  | 1.11 (0.99 – 1.23) | Forrest plot | 1.07 (0.87 – 1.31) | Forrest plot | 1.14 (1.01 – 1.30) | Forrest plot |
| Determined cause     | 1.08 (0.87 – 1.34) | Forrest plot | 0.99 (0.64 – 1.49) | Forrest plot | 1.07 (0.82 – 1.37) | Forrest plot |
| Smoker vs non-smoker | 1.21 (1.08 – 1.35) | Forrest plot | 1.16 (0.93 – 1.43) | Forrest plot | 0.99 (0.99 – 0.99) | Forrest plot |
| Anemia               | 1.40 (1.24 – 1.57) | Forrest plot | 1.16 (0.91 – 1.47) | Forrest plot | 1.52 (1.33 – 1.73) | Forrest plot |
| Arthritis            | 1.20 (1.10 – 1.31) | Forrest plot | 1.18 (0.99 – 1.40) | Forrest plot | 1.23 (1.11 – 1.36) | Forrest plot |
| CAD                  | 1.34 (1.23 – 1.47) | Forrest plot | 1.53 (1.29 – 1.82) | Forrest plot | 1.32 (1.19 – 1.47) | Forrest plot |
| Cancer               | 1.96 (1.64 – 2.30) | Forrest plot | 1.62 (1.12 – 2.28) | Forrest plot | 1.95 (1.62 – 2.34) | Forrest plot |
| CKD                  | 1.36 (1.21 – 1.57) | Forrest plot | 1.49 (1.19 – 1.84) | Forrest plot | 1.30 (1.14 – 1.48) | Forrest plot |
| COPD                 | 1.18 (1.04 – 1.34) | Forrest plot | 0.80 (0.59 – 1.05) | Forrest plot | 1.30 (1.13 – 1.50) | Forrest plot |
| Dementia             | 0.93 (0.79 – 1.10) | Forrest plot | 0.71 (0.48 – 1.02) | Forrest plot | 0.97 (0.80 – 1.17) | Forrest plot |
| Depression           | 1.50 (1.37 – 1.66) | Forrest plot | 1.24 (1.01 – 1.51) | Forrest plot | 1.56 (1.41 – 1.76) | Forrest plot |
| Diabetes mellitus    | 1.48 (1.36 – 1.46) | Forrest plot | 1.41 (1.19 – 1.68) | Forrest plot | 1.50 (1.35 – 1.66) | Forrest plot |
| Hyperlipidemia       | 0.79 (0.71 – 0.86) | Forrest plot | 0.75 (0.62 – 0.91) | Forrest plot | 0.94 (0.84 – 1.04) | Forrest plot |
| Hypertension         | 1.04 (0.92 – 1.16) | Forrest plot | 0.96 (0.76 – 1.20) | Forrest plot | 1.08 (0.94 – 1.25) | Forrest plot |
| Heart failure        | 1.17 (1.03 – 1.34) | Forrest plot | 1.11 (0.85 – 1.44) | Forrest plot | 1.15 (0.98 – 1.34) | Forrest plot |

Figure 1. Forest plot for incidence rate ratio (IRR) and confidence intervals (CI) for readmission by category of cause.

Cardio-embolism as the etiology of AIS, CAD, cancer, CKD, depression, and diabetes); and 13 candidate predictors for non-CV readmission (age, mRS, anterior circulation stroke, cardio-embolism as the cause of AIS, current smoking status, presence of anemia, arthritis, CAD, cancer, CKD, COPD, depression, or diabetes), implying considerable overlap among predictors for different categories of readmission. There was no sex- or hypertension-related differences in rates of hospitalization, whereas hyperlipidemia showed an inverse association with all-cause and CV readmissions.

Analysis of death

Post-discharge incident hospitalization regardless of time to admission or cause (all-cause, CV, non-CV, recurrent stroke) significantly increased the subsequent risk for all-cause, CV, non-CV, or stroke-specific mortality after adjusting for age, sex, race, smoking status, NIHSS score, etiology of stroke according to TOAST classification, concomitant hyperlipidemia, hypertension, depression, CAD, COPD, CKD, heart failure, dementia, anemia, and statin therapy. The magnitudes of estimated HRs for CV, non-CV, and stroke-specific deaths were broadly similar. When burden of hospitalization was further quantified according to number of days or percentage of follow-up time interval spent hospitalized, mortality (all-cause, CV, non-CV, stroke-specific) increased by 1% and 2 to 5% for each day and each 1% percentage, respectively, of follow-up time interval spent hospitalized. Figure 2 illustrates HR with 95% CI derived from time-dependent Cox regression analysis and corresponding forest plots for all-cause, CV, non-CV, and stroke-specific deaths. Mortality data were stratified according to each hospitalization for any cause, CV, non-CV, and stroke-specific cause and each day or each 1 percentage point of follow-up interval spent hospitalized.

Discussion

Main Findings

This cohort study has demonstrated that stroke survivors were at high risk of subsequent cumulative readmission with 3 in 4 patients hospitalized over a median follow-up of 4.3 years. The cumulative burden of hospitalization following AIS was substantial, with readmitted patients having an average of 4 hospitalizations and the corresponding aggregate mean number of days being hospitalized were 18 days. Analysis of hospital readmission by category of cause demonstrated that recurrent hospitalization from non-CV diagnoses occurred nearly three times as often as recurrent stroke and other related CV conditions combined. Similarly, among survivors of AIS, mortality from non-CV conditions was greater than that from CV conditions. These trajectories suggest that non-CV conditions are quantitatively more important as the cause of hospital readmission and subsequent mortality than stroke and CV conditions in the longer-term follow-up. We found that several candidate predictors obtained during initial hospitalization were independently associated with subsequent cumulative hospitalizations: all-cause, CV, and non-CV.
To the best of our knowledge, this is the first study that determined the magnitude of mortality risk associated with the burden of readmission, measured as total number of hospitalizations, aggregate number of days, and percentage of follow-up time interval spent hospitalized after index AIS hospitalization. After adjusting for covariates, the number of hospitalizations was an independent predictor of subsequent long-term mortality with each additional readmission, regardless of time to occurrence or cause, leading to a 12% increase in all-cause, 7% increase in CV, and an 8% increase in death from recurrent stroke. Furthermore, each day and each percentage follow-up time interval being hospitalized after discharge from AIS was associated with 1% and 4% increased risk of death from any cause, respectively. Similar rates of increased post-stroke mortality from other categories of causes were observed in association with corresponding causes of readmission.

### Literature in the Clinical Context

Stroke survivors, matched to a non-stroke cohort, were at high risk of hospitalizations and mortality that persisted for long-term after index hospitalization [25]. Previous studies of AIS patients reported varied estimates of re-hospitalization rates at 30 days [26], 1 year [27,28], and 5 year [25,29] after index hospitalization for AIS [26]. Overall, the rates of rehospitalizations were unacceptably high. The finding of the present study that non-cardiovascular hospitalizations exceeded hospitalizations for combined recurrent stroke and cardiovascular conditions were consistent with readmission pattern from previously published reports in stroke and other cardiovascular diseases such as heart failure [26,28,29]. Predictors of readmission following AIS have not been well established. Although a range of patient-level and process-of-care-level characteristics have been investigated, a systematic review and meta-analysis provided inconclusive data due to considerable heterogeneity among studies in the selection of patient-level characteristics to predict readmission [3]. We found sociodemographic indicators, stroke-specific characteristics, and several comorbidities as independent predictors of cumulative readmissions following first AIS hospitalization with considerable overlap among the determinants of all-cause, CV, and non-CV hospitalizations. Remarkably, hyperlipidemia was associated with a lower risk of cumulative readmission independent of statin therapy, consistent with a recent report of similar inverse association between hyperlipidemia and 30-day post-stroke readmission [26].

The results of the present study underscore the importance of burden of hospitalization (measured as number of hospitalizations, number of days and percentage of follow-up time interval hospitalized) on subsequent mortality after initial AIS, which is in concordance with previous reports in heart failure [30] and stroke [31] and our own previous research in transient ischemic attack [20,22].

| Death from any cause | HR (95% CI) | P |
|----------------------|-------------|---|
| Per hospitalization from any condition | 1.12 (1.10-1.14) | <0.0001 |
| Per hospitalization from cardiovascular condition | 1.27 (1.20-1.34) | <0.0001 |
| Per hospitalization from non-cardiovascular condition | 1.12 (1.10-1.15) | <0.0001 |
| Hospitalization for stroke | 1.92 (1.48-2.49) | <0.0001 |
| Per day spent hospitalized | 1.01 (1.01-1.01) | <0.0001 |

| Cardiovascular death | HR (95% CI) | P |
|----------------------|-------------|---|
| Per hospitalization from any condition | 1.07 (1.03-1.11) | 0.002 |
| Per hospitalization from cardiovascular condition | 1.25 (1.15-1.43) | <0.0001 |
| Per hospitalization from non-cardiovascular condition | 1.05 (1.00-1.11) | 0.05 |
| Hospitalization for stroke | 1.62 (0.91-2.87) | 0.10 |
| Per day spent hospitalized | 1.01 (1.00-1.11) | 0.03 |

| Non-cardiovascular death | HR (95% CI) | P |
|--------------------------|-------------|---|
| Per hospitalization from any condition | 1.07 (1.04-1.11) | <0.0001 |
| Per hospitalization from cardiovascular condition | 1.10 (1.00-1.21) | 0.04 |
| Per hospitalization from non-cardiovascular condition | 1.09 (1.05-1.13) | <0.0001 |
| Hospitalization for stroke | 1.39 (0.94-2.06) | 0.10 |
| Per day spent hospitalized | 1.01 (1.00-1.01) | <0.0001 |

| Death from recurrent stroke | HR (95% CI) | P |
|-----------------------------|-------------|---|
| Per hospitalization from any condition | 1.08 (1.02-1.14) | 0.01 |
| Per hospitalization from cardiovascular condition | 1.36 (1.16-1.59) | 0.0001 |
| Per hospitalization from non-cardiovascular condition | 1.07 (1.00-1.14) | 0.05 |
| Hospitalization for stroke | 14.84 (8.47-25.99) | <0.0001 |
| Per day spent hospitalized | 1.01 (1.01-1.02) | <0.0001 |

Figure 2. Forest plot for hazard ratios (HR) and 95% confidence intervals (CI) of death by category of cause using time-dependent multivariable Cox regression models.
Strengths and limitations

Strengths of the present study included large, consecutive, well-characterized patient population with neurologist-confirmed diagnosis of AIS and having comprehensive data and near complete follow-up. The severity of stroke was rated by the neurologist, and all comorbid conditions were diagnosed by physicians.

The multivariable Poisson and Cox regression models in current study were accounted for several important covariates not available in previous reports based on administrative data. The Mayo Clinic has one of the oldest patient records-keeping system in the United States, thus, ensuring high level of case ascertainment for incident stroke and mortality updates [32]. The current study has the following limitations. The study population is biased toward specialized stroke services and the patient population is predominantly white, reflecting the overall composition of the local population in the southeast Minnesota, which may limit generalizability to AIS patients in the community. The study has specific limitations inherent to its retrospective design.

Conclusions

Among survivors of first-ever AIS hospitalization, being white, active smoking, cardioembolic stroke subtype, dependency at discharge, and several key comorbid conditions were associated with increased risk of readmissions, which in turn correlated with increased mortality following AIS. These findings highlight the importance of lifestyle modification and optimal treatment of coexisting conditions to improve readmissions and mortality among patients hospitalized for AIS.

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