Predictors of Recurrent Hospitalizations and the Importance of These Hospitalizations for Subsequent Mortality After Incident Transient Ischemic Attack

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Background: We examined predictors of recurrent hospitalizations and the importance of these hospitalizations for subsequent mortality after incident transient ischemic attacks (TIA) that have not yet been investigated. *Methods:* Adults hospitalized for TIA from 2000 through 2017 were examined for recurrent hospitalizations, days, and percentage of time spent hospitalized and long-term mortality. *Results:* Of 266 patients hospitalized for TIA, 122 died, 212 had 826 anycondition hospitalization (59 from TIA-related conditions) corresponding to 3384 inpatient days during 1693 person-years of follow-up. Of 42 patient-level characteristics, age greater than or equal to 65 years (Incidence rate ratio [IRR] 1.75, 95% confidence interval [CI] 1.19-2.55), current smoking (IRR 2.15, 95% CI 1.39-3.33), concurrent heart failure (IRR 1.81, 95% CI 1.17-2.80) or anemia (IRR 1.90, 95% CI 1.40-2.48), and no prescription statin (IRR 1.45, 95% CI 1.04-2.03, $P = .0289$) emerged as significant predictors of anycondition rehospitalization. All these variables except heart failure remained significant predictors of TIA-related rehospitalizations. All-cause mortality was significantly increased after each hospitalization from anycondition (hazard ratio [HR] 1.32, 95% CI 1.26-1.39), TIA-related condition (HR 1.72; 95% CI 1.28-2.30), and per each day (HR 1.05, 95% CI 1.04-1.05) and per 1% of follow-up time spent hospitalized from anycondition (HR 1.45, 95% CI 1.34-1.58). *Conclusions:* Older age, current tobacco smoking, concurrent heart failure or anemia, and no prescription statin, easily measured patient-level characteristics, identifies patients with TIA at high risk for recurrent hospitalizations and the burden of these hospitalizations predicts subsequent mortality.

Key Words: Readmission—mortality—transient ischemic attack

Readmission from any condition following an acute care hospitalization is associated with increased mortality, healthcare cost, and a negative impact on patients' quality of life.[1-3] With an annual incidence of 240000, transient ischemic attack (TIA) is a common cause of emergency department visits and short-term hospitalizations in the United States.[4] Although, TIA represents a reversible neurovascular event with relatively low in-hospital mortality, it increases the risk of subsequent hospitalizations from diverse conditions and decreases the long-term survival.[5-13] However, among patients with incident TIA, unlike in other cardiovascular conditions,[14,15] the predictors of

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recurrent hospitalization and importance of these hospitalizations for subsequent mortality have not been determined.

We, therefore, aimed at examining cumulative incident hospitalizations from anycondition or TIA-related conditions, length of each hospitalization, and long-term mortality by category of cause after incident TIA. First, we assessed predictors of anycondition or TIA-related recurrent hospitalization using patient-level characteristics obtained during index hospitalization. Second, we explored the association between long-term mortality by category of cause (all-cause, cardiovascular disease-, cancer-, noncardiovascular, and noncancer-related) following incident TIA and the burden of hospitalization measured as number of hospitalizations and days and percentage of follow-up time spent hospitalized.

Methods

Study Design and Population

We conducted a retrospective analysis of adults aged greater than or equal to 18 years who were hospitalized for the first TIA at Mayo Clinic, Rochester, Minnesota, a comprehensive stroke center, from January 1, 2000 to October 29, 2017. The initial TIA cohort was identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code (433.10) until September 2015 and ICD-10 code (G45.9) until October 2017. Previous studies have demonstrated a high positive predictive value of ICD-9-CM codes for the discharge diagnoses of stroke and TIA.[16,17] The diagnosis was confirmed by review of medical records for documentation by a stroke neurologist. The details of data extraction have been previously published.[13] Three study investigators reviewed electronic health records of individual study patients to collect the data points. The study was approved by the Mayo Clinic Institutional Review Board and the need for patient consent was waived.

Definition of Transient Ischemic Attack

TIA was defined as a brief episode of neurological dysfunction, caused by focal brain or retinal ischemia of less than 24 hours with no evidence of acute infarction on neuroimaging.[18] Patients with previous history of stroke or TIA documented in medical records, hypertensive encephalopathy, reversible cerebral vasoconstriction syndrome, diagnostic uncertainty, on dialysis, on transplant list, organ transplant recipients, or recipients of left ventricular assist device were all excluded because their mortality was less likely to be influenced by index TIA event. The first TIA was defined as 1 listed as the primary discharge diagnosis with no documentation in secondary diagnoses or past medical history and no previous hospitalization for TIA since 1994. Only the first hospitalization was included in analysis in patients, who had multiple TIA-related hospitalizations.

Study Outcomes and Definitions

Recurrent Hospitalization

In each patient, we assessed all hospitalizations from initial admission for incident TIA until death or until censoring at October 29, 2017. Overall burden of hospitalization was measured as the number of hospitalizations, days, and percentage of follow-up time spent hospitalized. Recurrent hospitalizations were classified as hospitalization from anycondition or to TIA-related condition-composite of recurrent TIA and incident stroke. To ensure inclusiveness of all readmissions following discharge from index hospitalization, only patients residing in Olmsted County, Minnesota at enrollment and during follow-up were included in the study. Patients with incomplete follow-up per medical records were excluded.

Mortality

The time to death was measured from index hospitalization to censoring at October 29, 2017. The cause of death was identified from official death certificates and classified into 4 main categories: all-cause, cardiovascular disease-, cancer (the most common cause of death in Minnesota), noncardiovascular and noncancer-related.

Measures of Covariates

We categorized: age as less than 65 years and greater than or equal to 65 year, body mass index (BMI) less than 30 and greater than or equal to 30 kg/m^2, tobacco use as current smoker, ex-smoker, and never smoker, systolic blood pressure less than 140 mmHg and greater than or equal to 140 mmHg, hemoglobin less than 10 g/dl and greater than or equal to 10 g/dl, creatinine less than 1.5 mg/dl and greater than or equal to 1.5 m/dl, high-density lipoprotein cholesterol greater than or equal to 45 mg /dl and less than 45 mg/dl, low-density lipoprotein cholesterol less than 100 mg/dl and greater than or equal to 100 mg /dL. Blood pressure and laboratory variables were collected from first measurements obtained during index hospitalization. First blood pressure measurement was disregarded as an error if it showed very low or very high value and that a second measurement that was in agreement with other sequential measurements was selected. Comorbid conditions were assessed at the time of discharge. Comorbid conditions with frequency of less than 5% were excluded from the analysis. Etiology of TIA was categorized into 5 groups: (1) large artery atherosclerosis (LAA), (2) cardio-embolism, (3) small vessel occlusion, (4) other determined cause, and (5) undetermined cause.[19] The

anatomical distribution of TIA was classified as anterior and posterior circulation based on predominant symptom complexes as documented by admitting physicians and suggested by previous studies.[20,21]

Statistical Analysis

Continuous variables were reported as means and standard deviations and categorical variables as frequencies and proportions. Poisson regression models were generated to determine independent predictors of repeat hospitalization with no concern for overfitting because of high number of events (hospitalizations). Separate multiple Cox proportional regression models were constructed to estimate adjusted hazard ratio (HR) for all-cause mortality and mortality stratified by the category of cause (cardiovascular disease-, cancer, noncancer and noncardiovascular disease-related) with anycondition repeat hospitalization as time-dependent variable. Because of concern related to model overfitting, Cox models were further adjusted for relevant covariates using the maximum total variance data reduction technique. This technique avoids overfitting, since a limited number of summary variables, each made up of a linear combination of the original covariates, are used in the fitted models. We then developed multiple time-dependent Cox proportional regression models to estimate HR for all-cause mortality associated with each rehospitalization, each day and percentage of follow-up of time spent hospitalized between discharge and death or censoring date.

A subgroup analysis was performed with focus on TIA-related rehospitalization. A separate Poisson regression model was generated to identify predictors of TIA-related repeat hospitalization. Similarly, a separate time-dependent Cox regression model was generated to evaluate the association between TIA-related hospitalization and all-cause mortality.

Both Poisson regression and Cox regression models were adjusted for 42 baseline characteristics measured on admission. The analyses were performed using SAS version 9.4 (Statistical Analysis System, SAS Institute Inc., Cary, NC). For all analyses, a 2-side *P* less than .05 was regarded as statistically significant.

Results

Baseline Characteristics

As presented in Fig 1, of 680 patients screened for eligibility, 414 were excluded for various reasons resulting in a final study cohort of 266 patients with first-ever TIA who remained in Olmsted County from index hospitalization to death or censoring date. A total of 122 (46%) patients had died by the end of follow-up. The baseline

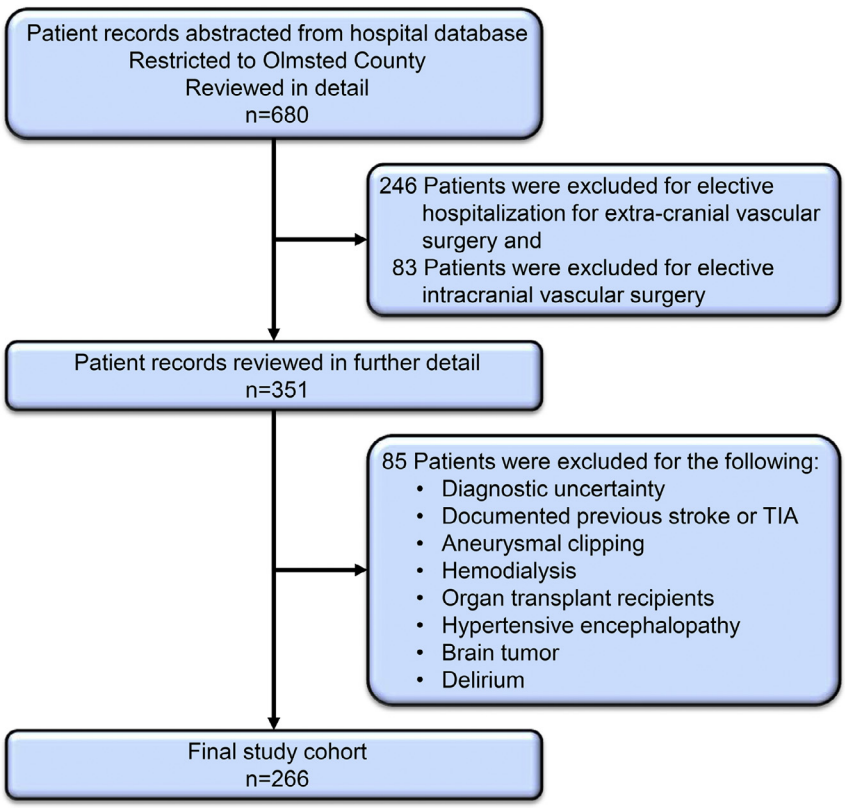

Figure 1. *Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flow diagram of the process of selection of study cohorts.*

Table 1. *Baseline characteristics of study population*

Patient characteristics		Values
Age in years		73.4 ± 15.1
Sex	Male	132 (50%)
Race	Whites	251 (94%)
Admission type	Stroke service	195 (73%)
LOS (days)		2 (1-3)
Tobacco smoking	Current	33 (13%)
	Past	92 (36%)
	Never	132 (51%)
Blood pressure	SBP (mmHg)	151 ± 27
	DBP (mmHg)	78 ± 15
	PP (mmHg)	72 ± 23
Anthropometry	BMI (kg/m^2)	27.8 ± 5.7
Key laboratory findings	Hb (g/dL)	13.2 (12.1-14.3)
	BUN (mg/dL)	20.8 ± 12.6
	Creatinine (mg/dL)	1.1 ± 0.3
	HDL-C (mg/dL)	50.4 ± 15.4
	LDL-C (mg/dL)	99.1 ± 35.4
Drugs	Antiplatelets	235 (88%)
	Statin	145 (55%)
	Beta-blocker	117 (44%)
	ACEI/ARBs	103 (39%)
Comorbid conditions	Hyperlipidemia	132 (50%)
	Hypertension	203 (76%)
	Depression	50 (19%)
	Diabetes	55 (21%)
	Arthritis	81 (30%)
	Cancer	41 (15%)
	Atrial fibrillation	58 (22%)
	CAD	83 (31%)
	COPD	25 (9%)
	Osteoporosis	30 (11%)
	CKD	34 (13%)
	Heart failure	30 (11%)
	Dementia	25 (9%)
	Anemia	63 (24%)
Imaging studies	CT-head	254 (95%)
	MR-brain	172 (65%)
	MRA-head and neck	123 (46%)
	Carotid duplex US	184 (69%)
	TTE/TEE	177 (66%)
Etiology of TIA	LAA	44 (17%)
	Cardio-embolism	55 (21%)
	SVO	62 (23%)
	Other determined cause	9 (3%)
	Undetermined cause	96 (36%)
Arterial territory of TIA	Anterior circulation	210 (78%)
	Posterior circulation	61 (22%)

Abbreviations: ACEI/ARBs, angiotensin converting enzyme inhibitor/ angiotensin II receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, computerized tomography; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LAA, large artery atherosclerosis; LDL-C, Low-density lipoprotein cholesterol; LOS, length of hospital stay; MR, magnetic resonance; MRA, magnetic resonance angiography; SBP, systolic blood pressure; SVO, small vessel occlusion; PP, pulse pressure; TIA, transient ischemic attack; TTE/TEE, transthoracic echocardiogram/ transesophageal echocardiogram.

characteristics of the study population are described in Table 1. Asthma, illicit drug use, schizophrenia, autism spectrum disorders, HIV/AIDS were all excluded from analysis, because of very low prevalence rate (<4%) in the study population. Anemia was added to comorbidities based on its prognostic implications in previously published studies.

Table 2. *Results of multivariable Poisson regression model for identifying independent predictors of recurrent hospitalization*

Hospital readmissions	Covariates	IRR	95% CI	*P* value
Anycondition	Age ≥ 65 versus < 65 years	1.75	1.19-2.55	.0040
	Current smoking versus no/past smoking	2.15	1.39-3.33	.0006
	No statin Rx versus statin Rx	1.45	1.04-2.03	.0289
	Heart failure versus no heart failure	1.81	1.17-2.80	.0079
	Anemia versus no anemia	1.90	1.40-2.48	< .0001
TIA-related conditions (composite of recurrent TIA and incident stroke)	Age ≥ 65 versus < 65 years	2.04	1.03-4.04	.0412
	Current smoking versus no/past smoking	3.36	1.56-7.25	.0019
	No statin Rx versus statin Rx	2.15	1.11-4.15	.0222
	Anemia versus no anemia	2.30	1.16 -4.56	.0165
	LAA as the cause of index TIA	2.66	1.22-5.75	.0134
	Determined cause for index TIA	5.96	1.73-20.54	.0047

Abbreviations: CI, confidence interval; IRR, incident rate ratio; LAA, large artery atherosclerosis; TIA, transient ischemic attack.

Multivariable Poisson regression models were adjusted for 42 prespecified covariates with no concern for overfitting because of high number of events (hospitalizations).

Burden of Hospitalization

During 1693 person-years of follow-up, 212 patients had 826 hospitalizations from anycondition corresponding to 3384 cumulative inpatient days and 54 patients were never hospitalized. Of total readmissions following initial TIA, 59 were from composite of recurrent TIA and incident stroke (7 patients had 2 and 2 patients had 3 recurrent TIA-related hospitalization during follow-up)

Predictors of Repeat Hospitalizations

The results of multivariable Poisson regression model for identifying independent predictors of repeat hospitalization from any condition or TIA-specific condition are represented in Table 2.

Repeat Hospitalization and Mortality

There were 122 deaths from anycondition including 8 deaths among 54 patients who did not have recurrent hospitalization during the study period. Based on Cox regression model anycondition hospitalization was associated with increased mortality from anycondition, cardiovascular disease, cancer, and noncardiovascular noncancer. In subgroup analysis, TIA-specific hospitalization was also associated with increased mortality from anycondition. Results of these analyses are presented as adjusted HR, 95% CI, and respective *P* values in Table 3.

Burden of Hospitalization and Long-term Mortality

Of total of 266 patients with TIA, 212 had a cumulative 3384 inpatient days or 0.55% follow-up time spent

Table 3. *Results of multivariable time-dependent Cox proportional regression models for HR for mortality by category of cause and per incident rehospitalization, number of days or percentage of follow up time spent hospitalized between TIA discharge and death or censoring date*

Mortality categories			HR (95% CI)	*P* value
All-cause	Per hospitalization	Anycondition	1.32 (1.26-1.39)	<.0001
	Follow-up time spent hospitalized after incident TIA	Per day	1.04 (1.03-1.05)	<.0001
		Per one percentage point	1.45 (1.34-1.58)	<.0001
Cardiovascular disease-related	Per hospitalization	Anycondition	1.38 (1.22-1.56)	<.0001
	Follow-up time spent hospitalized after incident TIA	Per day	1.04 (1.02-1.05)	<.0001
		Per one percentage point	1.37 (1.20-1.56)	<.0001
Cancer-related	Per hospitalization	Anycondition	1.38 (1.40-1.68)	.0011
	Follow-up time spent hospitalized after incident TIA	Per day	1.05 (1.02-1.07)	<.0001
		Per one percentage point	1.40 (1.13-1.74)	<.0001
Noncardiovascular and noncancer-related mortality	Per hospitalization	Anycondition	1.58 (1.40-1.78)	<.0001
	Follow-up time spent hospitalized after incident TIA	Per day	1.05 (1.03-1.06)	< .0001
		Per one percentage point	1.55 (1.37-1.76)	< .0001

Abbreviations: CI, confidence interval; HR, hazard ration; TIA, transient ischemic attack.

Cox models measuring the association between hospitalization and death were adjusted for a number of covariates using the maximum total variance data reduction technique. This technique avoids overfitting since a limited number of summary variables, each made up of a linear combination of the original covariates, are used in the fitted models.

hospitalized for anycondition. Overall mortality increased by 4% for each hospitalized day from anycondition and by 45% for each 1% follow-up time spent hospitalized. Table 3 illustrates adjusted Cox HRs for mortality by category of cause and number of days or percentage of time spent hospitalized between index hospitalization and death or censoring date.

Discussion

Main Findings

This study evaluated patient-level characteristics associated with cumulative hospitalizations and the influence of these hospitalizations on subsequent mortality after index hospitalization for a first TIA. First, we identified age greater than or equal to 65 years, tobacco smoking, and concurrent heart failure and anemia on admission and no statin prescription on dismissal as independent predictors of recurrent hospitalization from anycondition after incident TIA. All these variables except heart failure remained significant predictors of TIA-related recurrent hospitalizations. Additionally, LAA and a determined cause for TIA were also found as significant predictors of TIA-related recurrent hospitalizations. Second, patients with repeat hospitalization from anycondition or TIA-related condition were at high risk for subsequent death, a hazard significantly associated with the burden of hospitalization, measured as number of rehospitalizations and days and percentage of follow-up time spent hospitalized. The association between anycondition hospitalization and mortality remained significant and of broadly of similar magnitude even when mortality was stratified according to category of cause as cardiovascular disease-, cancer, and noncardiovascular and noncancer-related.

Comparative Studies

A limited number of studies examined the predictors of hospital readmissions after a stroke and TIA and results were inconclusive.[22,23] We demonstrated that, after index hospitalization, readmission from TIA-related conditions accounted for only a minority of all readmissions (7%). In comparison, in other acute conditions such as heart failure, pneumonia, and acute myocardial infarction, readmissions were frequently from disease-specific conditions (40%-53.4%).[24-27] There are a few possible explanations for these divergent findings. First, there was a documented decline in the occurrence of TIA-related events.[5] Second, a higher mean age of our study population compared to those from national TIA registry.[5] Finally a high prevalence of comorbidities among our study patients as reported previously.[13]

Older age has a consistent association with an elevated risk of recurrent hospitalization for a wide range of acute conditions,[28-30] a finding in concordance with our results for patients with TIA. Although tobacco smoking is 1 of the leading risk factors for incident cardiovascular disease including stroke and overall death in the United States,[31,32] the findings of its association with readmission for non-TIA acute conditions were mixed.[33-36] We found that among patients with TIA, tobacco smoking compared to never smoking or past smoking conferred a greater risk for recurrent hospitalization from anycondition or TIA-related conditions, possibly from increased susceptibility for cardiovascular or respiratory events as previously reported.[37] Comorbidities are prevalent in hospitalized patients with TIA and stroke.[13] Heart failure is 1 of the leading causes of initial and recurrent hospitalizations [25,30,38,39] and not surprisingly our findings also demonstrated a strong association with recurrent hospitalizations from any condition but not with TIA-related condition after initial TIA. While, comorbid effect of anemia on readmissions after index acute care hospitalization is not fully understood with published reports providing contradictory data,[40-42] we observed an increase in risk of recurrent hospitalization after initial TIA with concurrent anemia. In this study, patient hospitalized for TIA due to LAA and a determined cause were at greater rehospitalization risk for TIA-related conditions, possibly owing to multiple reasons as previously described.[5,43,44] Statin therapy initiated after incident TIA or stroke results in improved clinical outcome and strongly recommended by American Heart Association and American Stroke Association.[45-48] Our results support these recommendations and show that lack of statin therapy on discharge significantly increases the risk of recurrent hospitalization from any or TIA-related conditions, regardless of mechanism of TIA.

No previous studies assessed the effect of hospital readmission on subsequent mortality after index hospitalization for TIA. Nonetheless, the association between hospital readmission and mortality was investigated in patients with a number of non-TIA conditions such as acute myocardial infarction, heart failure, pneumonia, and chronic obstructive pulmonary disease and many reports yielded inconsistent findings.[24,27,49,50] For instance, in a large medicare patient population, Krumholz and colleagues examined the relationship between readmission and mortality in acute myocardial infarction, heart failure, and pneumonia and found no association.[49] In comparison, Setoguchi et al investigated the effect of repeat heart failure hospitalizations and found that the number of readmissions were independent predictors of mortality among heart failure patients in the community.[27] These findings were further supported by a more recent report in heart failure with preserved ejection fraction.[24] We extended these observations to patients hospitalized for new TIA.

Clinical Implications

Our findings allow identification of subgroups of patients who might benefit from life-style modification and optimization of medical treatment to reduce the burden of recurrent hospitalization following initial TIA, a

supposition that merits further evaluation in randomized clinical studies. The mechanisms underlying recurrent hospitalization may be complex and multifactorial. Understanding a broad spectrum of conditions associated with recurrent hospitalization throughout post-discharge period and identification of high-risk patients potentially allows initiation of preemptive strategies to reduce the risk of subsequent readmission. Assessment of number of repeat hospitalizations and length of time spent hospitalized permit recognition of TIA patients at high risk of subsequent mortality.

Limitations and Strengths

We acknowledge several limitations and strengths in the present study. The study population is biased toward specialized stroke services and may not represent TIA patients in the community presenting to general medical clinics and emergency departments. Despite the limitations inherent in a retrospective design, the study included well characterized patient population with regards to primary and secondary diagnosis. Furthermore, patients were reliably classified into etiological subgroups based on imaging studies and medical record documentation. The electronic medical record system at Mayo Clinic, Rochester, Minnesota is 1 of the oldest in the country with documented efficiency and a high level of case ascertainment for incident TIA and prompt mortality updates.[51]

Conclusions

In summary, older age, current tobacco smoking, concurrent heart failure and anemia, and prescription statin on dismissal are easily measured patient-level characteristics with strong association with recurrent hospitalization after a first TIA. The burden of these hospitalizations measured as number of readmissions and days and percentage of follow-up time spent hospitalized increased subsequent mortality independent of patient-level characteristics. Identification of patients at high-risk for recurrent hospitalizations and subsequent mortality after incident TIA allow provision of targeted interventions to improve the outcome.

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