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Trends in ischemic stroke outcomes in a rural population in the United States

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ABSTRACT

Introduction: The stroke mortality rate has gradually declined due to improved interventions and controlled risk factors. We investigated the associated factors and trends in recurrence and all-cause mortality in ischemic stroke patients from a rural population in the United States between 2004 and 2018.

Methods: This was a retrospective cohort study based on electronic health records (EHR) data. A comprehensive stroke database called "Geisinger NeuroScience Ischemic Stroke (GNSIS)" was built for this study. Clinical data were extracted from multiple sources, including EHR and quality data.

Results: The cohort included in the study comprised of 8561 consecutive ischemic stroke patients (mean age: 70.1 ± 13.9 years, men: 51.6%, 95.1% Caucasian). Hypertension was the most prevalent risk factor (75.2%). The one-year recurrence and all-cause mortality rates were 6.3% and 16.1%, respectively. Although the one-year stroke recurrence increased during the study period, the one-year stroke mortality rate decreased significantly. Age > 65 years, atrial fibrillation or flutter, heart failure, and prior ischemic stroke were independently associated with one-year all-cause mortality in stratified Cox proportional hazards model. In the Cause-specific hazard model, diabetes, chronic kidney disease and age < 65 years were found to be associated with one-year ischemic stroke recurrence.

Conclusion: Although all-cause mortality after stroke has decreased, stroke recurrence has significantly increased in stroke patients from rural population between 2004 and 2018. Older age, atrial fibrillation or flutter, heart failure, and prior ischemic stroke were independently associated with one-year all-cause mortality while diabetes, chronic kidney disease and age less than 65 years were predictors of ischemic stroke recurrence.

1. Introduction

A recent study by the Centers for Disease Control and Prevention (CDC) indicated that the four-decade decline in stroke death rates in the United States (US) has slowed down, stalled, or in some cases, reversed in recent years [1]. Substantial variations exist in terms of the timing and magnitude of this unfavorable change. The rural-urban disparities in life expectancy widened between 1969 and 2009, with 7% of the disparity due to stroke [2]. Additionally, the incidence of stroke in rural areas of the US remains high [3] mainly due to a lower socioeconomic status and a higher prevalence of risk factors [3,4], including obesity [5], smoking [6], and lower rates of physical activity [7].

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Defining disparities in stroke risk factors, outcomes, and geography that might be driving the unfavorable outcome could lead to the implementation of targeted interventions to reduce stroke burden among vulnerable populations [8]. Yet very few studies have reported the trends in stroke outcomes among a large rural population in the US (Supplemental Table 1). The goal of this study was to define trends in stroke outcomes of all-cause mortality and recurrence among ischemic stroke patients from a rural population of central Pennsylvania between 2004 and 2018 and evaluate the factors that are associated with these stroke outcomes.

2. Methods

2.1. Data source and study population

This was retrospective cohort study based on extracted data from multiple sources including Geisinger's Electronic Health Record (EHR) system, Geisinger Quality database, as well as the Social Security Death database. These data sources were used to build a comprehensive stroke database called "Geisinger NeuroScience Ischemic Stroke (GNSIS)". GNSIS includes demographic, clinical, genetic, and laboratory data of 8929 ischemic stroke patients from September 2003 to May 2019. Geisinger is a fully integrated health system and the largest rural health maintenance organization (HMO) in the country. Geisinger serves a predominantly Caucasian population of 2.6 million people living in 43 counties, outside of the major metropolitan regions, in northeastern and central Pennsylvania with a very low (<5%) outmigration rate (Supplemental Fig. 1) [9,10]. The study was reviewed and approved by the Geisinger Institutional Review Board.

2.2. GNSIS population and data processing

2.2.1. GNSIS population

To build the GNSIS database, we first created a high-fidelity, data-driven, in-house phenotype definition for ischemic stroke. Multiple manual validations were carried out to finalize the phenotype and fine-tune the data pull criteria. The patients were included in the GNSIS database if they had (1) a primary hospital discharge diagnosis of ischemic stroke, (2) a brain magnetic resonance imaging (MRI) performed during the same encounter to confirm the diagnosis, and (3) an overnight stay in the hospital. Brain MRI is part of stroke order-set for all stroke patients with no contraindications (cardiac defibrillator, foreign body, etc.). The Current Procedural Terminology (CPT) 4 codes for brain MRIs are available in Supplemental Table 2a. The diagnosis of ischemic stroke and other health conditions was based on the International Classification of Diseases Clinical Modification, Ninth or Tenth Revision, (ICD-9-CM or ICD-10-CM) codes (Supplemental Table 2b). The manual validation of 125 randomly selected patients, including reviewing the MR imaging, indicated a specificity of 100% ensuring all patients in the GNSIS database had an accurate diagnosis of acute ischemic stroke.

In cases of multiple encounters due to recurrent cerebral infarcts, the first hospital encounter was considered as the index event. The data from all encounter types were extracted and processed to ensure the comprehensiveness of the follow-up information. This database interfaces with the Social Security Death Index to reflect updated information on the vital status.

2.2.2. Data processing

As part of data pre-processing, steps were taken to ensure the integrity and validity of the data. For instance, units were verified and reconciled if needed; distributions of variables were assessed over time to ensure data stability. The range for the variables was defined according to expert knowledge and available literature—outliers were assessed, replaced, or capped based on clinical data. As part of the de-identification process, the age of patients older than 89 years old was masked and changed to 89. Filters were applied to ensure that the relevant variables were captured within the desired time frame and that the order of events was maintained. The last encounter of patients was also recorded to ensure that patients were active. The admission National Institute of Health Stroke Scale (NIHSS) was extracted from the quality data and merged with the EHR data using medical record numbers.

2.3. Trends in stroke outcomes - Cohort and outcome definitions

For the current study, we included data from 2004 to 2018 as the full-year data for the year 2003 and 2019, and follow-up data for 2019 were not available in this study. As a result, 8561 out of 8929 ischemic stroke patients from GNSIS were included in the study. Genetic data was not used for this study as it was only available for approximately 20% of the patients. Supplemental Table 2c includes the full descriptions of the data elements included in the study. The outcome measures were the rate of one-year ischemic stroke recurrence and all-cause mortality following the ischemic stroke event. The stroke recurrence for each year was calculated by dividing the number of ischemic stroke patients during that year who had a recurrence within one year from the initial stroke event, by the total number of ischemic stroke patients who completed one-year follow-up. Patients who had follow-up of less than one year or died within a year without a stroke recurrence were not included in the calculation. One-year all-cause mortality rate was calculated by dividing the total number of patients who died within one year after the initial stroke event, by the total number of stroke patients with at least one year of follow-up. Patients from 2018 were not part of the analysis of the trends in the outcomes as majority of patients from 2018 did not have a one-year follow-up data but were included in the survival analysis. The ischemic stroke patients were also grouped into five-year intervals: 2004–2008 (interval A), 2009–2013 (interval B), and 2014–2018 (interval C).

The follow-up time for ischemic stroke recurrence was defined as the time between index stroke date and last encounter date in the electronic health record. The follow-up time for all-cause mortality was defined as the time between index stroke date and the end of study period (May 20, 2019) because mortality information from Social Security Death Index till this date was included in the study.

2.4. Statistical analysis

All continuous variables were summarized as mean ± standard deviation or median with inter-quartiles [IQR]), and categorical variables as count and percentage. For comparison between groups, the chi-square test was used for the categorical variables and analysis of variance (ANOVA) or Kruskal-Wallis test was used for continuous variables. A post-hoc analysis was performed with Bonferroni correction to determine the difference between subgroups. Correlation between variables was assessed using the Spearman correlation coefficient (between numerical variables), Cramer's V (between categorical variables), and Point-biserial correlation coefficient (between categorical and numerical variables).

Cochrane-Armitage test for trend was used to analyze the time trends in acute stroke care and stroke outcomes. One-year ischemic stroke recurrence was assessed using the cumulative incidence function in which mortality was considered a competing risk. Fine-Gray sub-distribution hazard model and cause-specific hazard model were also employed to examine ischemic stroke recurrence. The former allows for estimating the effect of covariates on absolute risk of outcome over time and whereas the latter is appropriate for causal analysis of competing risk [11]. One-year all-cause mortality was assessed using the Kaplan-Meier estimator and Cox proportional hazards model. The Log-rank test and Gray's test were used to compare groups in the Kaplan-Meier estimator and cumulative incidence function, respectively. The proportional hazards assumptions were tested using the Schoenfeld residuals test and the variables not meeting the proportional hazards

assumption were used to stratify the models. For all analyses, $p < 0.05$ was considered statistically significant.

All statistical analyses were performed using R version 3.6.2 [12] using R libraries *car* [13], *DescTools* [14], *ltm* [15], *rcompanion* [16], *cmprsk* [17], *survival* [18], *survminer* [19] *and tidyverse* [20].

3. Results

3.1. Patient population and clinical characteristics

The study cohort included 8561 consecutive patients of ischemic stroke (mean age: 70.1 ± 13.9 years, men: 51.6%, Caucasian: 95.1%) who presented to one of the six Geisinger Health System centers from 2004 to 2018. The majority of patients (7354; 85.9%) were older than 55 years at the index event and 66.3% of patients were older than 65 years at index event. Twenty-seven (0.3%) patients were younger than

Table 1
Demographics, comorbidities and outcomes of ischemic stroke patients included in the study.

Total Number of Patients in Each Group	Total Population 2004–2018	Interval A 2004–2008	Interval B 2009–2013	Interval C 2014–2018	*p*-Value
Number of patients, n	8561	1587	2514	4460	
Age at index ischemic stroke, mean (SD)	70.1 (13.9)	70.1 (13.7)	69.5 (13.9)	70.4 (14.0)	0.040
Age at index ischemic stroke, median [IQR]	71.6 [61.0, 81.2]	72.7 [61.4, 80.6]	70.9 [60.6, 80.6]	71.7 [61.0, 81.9]	0.025
Age categories					
≤ 55 years, n (%)	1207 (14.1)	239 (15.1)	377 (15.0)	591 (13.3)	<0.001
55.1–65 years, n (%)	1677 (19.6)	280 (17.6)	506 (20.1)	891 (20.0)	
65.1–75 years, n (%)	2142 (25.0)	382 (24.1)	629 (25.0)	1131 (25.4)	
75.1–85 years, n (%)	2241 (26.2)	494 (31.1)	653 (26.0)	1094 (24.5)	
>85 years	1294 (15.1)	192 (12.1)	349 (13.9)	753 (16.9)	
Men, n (%)	4421 (51.6)	830 (52.3)	1311 (52.1)	2280 (51.1)	0.601
National Institutes of Health Stroke Scale (NIHSS)[a], median [IQR]	4 [2, 7]	NA [NA, NA]	5 [2, 8]	4 [2, 7]	0.004
Atrial fibrillation, n (%)	1810 (21.1)	235 (14.8)	516 (20.5)	1059 (23.7)	<0.001
Atrial flutter, n (%)	229 (2.7)	34 (2.1)	71 (2.8)	124 (2.8)	0.344
Atrial fibrillation or flutter, n (%)	1858 (21.7)	241 (15.2)	531 (21.1)	1086 (24.3)	<0.001
Hypertension, n (%)	6441 (75.2)	936 (59.0)	1938 (77.1)	3567 (80.0)	<0.001
Myocardial infarction, n (%)	993 (11.6)	157 (9.9)	316 (12.6)	520 (11.7)	0.033
Diabetes, n (%)	2776 (32.4)	397 (25.0)	834 (33.2)	1545 (34.6)	<0.001
Dyslipidemia, n (%)	5321 (62.2)	729 (45.9)	1562 (62.1)	3030 (67.9)	<0.001
Heart failure, n (%)	1153 (13.5)	158 (10.0)	330 (13.1)	665 (14.9)	<0.001
Hypercoagulable states, n (%)	114 (1.3)	13 (0.8)	46 (1.8)	55 (1.2)	0.016
Chronic liver disease, n (%)	258 (3.0)	13 (0.8)	57 (2.3)	188 (4.2)	<0.001
Chronic lung diseases, n (%)	1823 (21.3)	250 (15.8)	533 (21.2)	1040 (23.3)	<0.001
Rheumatic diseases, n (%)	345 (4.0)	51 (3.2)	97 (3.9)	197 (4.4)	0.098
Chronic kidney disease, n (%)	1614 (18.9)	131 (8.3)	427 (17.0)	1056 (23.7)	<0.001
History of neoplasm, n (%)	1318 (15.4)	256 (16.1)	374 (14.9)	688 (15.4)	0.554
Peripheral vascular diseases, n (%)	1375 (16.1)	206 (13.0)	420 (16.7)	749 (16.8)	0.001
History of ischemic stroke, n (%)	814 (9.5)	86 (5.4)	220 (8.8)	508 (11.4)	<0.001
History of hemorrhagic stroke, n (%)	556 (6.5)	31 (2.0)	133 (5.3)	392 (8.8)	<0.001
Smoking Status[b]					<0.001
Never Smoker, n (%)	2693 (31.6)	423 (26.7)	744 (29.7)	1526 (34.3)	
Current Smoker, n (%)	1241 (14.5)	155 (9.8)	348 (13.9)	738 (16.6)	
Former Smoker, n (%)	2103 (24.6)	310 (19.6)	566 (22.6)	1227 (27.6)	
Unknown, n (%)	2497 (29.3)	694 (43.9)	848 (33.8)	955 (21.5)	
Family history of heart disease, n (%)	3052 (35.7)	541 (34.1)	968 (38.5)	1543 (34.6)	0.002
Family history of stroke, n (%)	1160 (13.5)	191 (12.0)	361 (14.4)	608 (13.6)	0.103
Prior Medications Use					
Antiplatelets, n (%)	855 (10.0)	104 (6.6)	230 (9.1)	521 (11.7)	<0.001
Warfarin, n (%)	718 (8.4)	114 (7.2)	196 (7.8)	408 (9.1)	0.024
Other oral anticoagulants, n (%)	64 (0.7)	0 (0.0)	2 (0.1)	62 (1.4)	<0.001
Statins, n (%)	2570 (30.0)	406 (25.6)	725 (28.8)	1439 (32.3)	<0.001
Antihypertensives, n (%)	2650 (31.0)	504 (31.8)	753 (30.0)	1393 (31.2)	0.402
Type of health insurance[c]					<0.001
Commercial, n (%)	1834 (21.8)	265 (16.8)	509 (20.5)	1060 (24.3)	
Health maintenance organization, n (%)	2415 (28.7)	345 (21.8)	682 (27.5)	1388 (31.8)	
Medicaid, n (%)	452 (5.4)	77 (4.9)	221 (8.9)	154 (3.5)	
Medicare, n (%)	3588 (42.6)	886 (56.1)	1037 (41.9)	1665 (38.1)	
Self-pay, n (%)	10 (0.1)	0 (0.0)	2 (0.1)	8 (0.2)	
Special Billing, n (%)	50 (0.6)	5 (0.3)	10 (0.4)	35 (0.8)	
Veteran Affairs, n (%)	72 (0.9)	1 (0.1)	16 (0.6)	55 (1.3)	
Mechanical thrombectomy	175 (2.0)	2 (0.1)	22 (0.9)	151 (3.4)	<0.001
Intravenous thrombolysis	543 (6.3)	15 (0.9)	142 (5.6)	386 (8.7)	<0.001
One-year stroke recurrence[d], n (%)	343/5444 (6.3) [e]	62/1162 (5.3)	91/1841 (4.9)	190/2441 (7.8) [e]	<0.001
One-year all-cause mortality[f], n (%)	1216/7563 (16.1) [e]	270/1587 (17.0)	434/2514 (17.3)	512/3462 (14.8) [e]	0.019

[a] NIHSS available for 2016 patients (0, 205, 1811 patients in intervals A, B and C respectively).
[b] Smoking status for 8534 patients aged 18 years and above (1582, 2506, 4446 patients in intervals A, B and C respectively).
[c] Health insurance type available for 8421 patients (1579, 2477, 4365 patients in intervals A, B and C respectively).
[d] Recurrent stroke rate calculated for 5444 patients with at least one-year follow-up (1162, 1841, 2441 patients in intervals A, B and C respectively).
[e] Data from patients in 2018 were not part of the analysis in the recurrence and all-cause mortality rate.
[f] All-cause mortality rate calculated for 7563 patients with at least one-year follow-up (1587, 2514, 3462 patients in intervals A, B and C respectively).

18 years old. While the annual median of age at the index stroke remained stable (Supplemental Fig. 2A) during the 15 years, the proportion of patients in age-groups 55.1–65 years and > 85 years increased while the proportion of patients in age groups ≤55 years and 75.1–85 years decreased over the years (Table 1, Supplemental Fig. 2B). The median admission NIHSS was 4 [IQR: 2–7] among the 2016 (23.5%) available records. The patients' characteristics and clinical information are summarized in Table 1. The variables NIHSS (76%), and insurance data (2%) suffered from missingness.

Among the patient cohort, hypertension was the most prevalent comorbidity (75.2%) followed by dyslipidemia (62.2%), and diabetes (32.4%). Out of 8561 patients, 2028 (23.7%) had all the three risk factors. A past medical history of ischemic stroke, atrial fibrillation or flutter, and hypercoagulable state was seen in 9.5%, 21.7% and 1.3% patients respectively (Table 1). When considering the most common comorbidities, there was a significant difference among the three intervals (A, B, and C; Table 1). Post-hoc analyses demonstrated that hypertension, atrial fibrillation, dyslipidemia, history of hemorrhagic and ischemic stroke, chronic liver disease, and chronic kidney disease were significantly different between all three intervals. Heart failure, peripheral vascular disease, and chronic lung diseases (asthma, chronic obstructive pulmonary disease, and occupational lung diseases) were significantly lower in interval A but there were no significant differences in these comorbidities between intervals B and C (Supplemental Table 3).

Among the 8534 adult patients, 14.5% of patients reported to be current smokers at their index date, and 24.6% were former smokers when asked at their stroke index date. Due to the proportion of patients who did not report their smoking status (29.3%), a meaningful conclusion regarding the smoking status pattern over time could not be established.

Among all patients, 31.0% were taking antihypertensives, 30.0% were on statins, and 9.1% were taking an oral anticoagulant before the index stroke. There was a significant increase in the use of statins from time interval A, to interval B and C (25.6%, 28.8%, and 32.3%; $p < 0.001$). However, no significant difference was observed in antihypertensives use over the same period (31.8%, 30.0%, and 31.2% $p = 0.402$). A significant increase was observed in the use of warfarin (7.2%, 7.8%, and 9.1% $p = 0.024$) and new oral anticoagulants (0.0%, 0.1%, and 1.4% $p \leq 0.001$) (Table 1). It was observed that warfarin was underutilized but showed gradual increase over the years. Warfarin utilization still increased despite wide availability of newer oral anticoagulants after 2010 possibly due to the cost of the newer oral anticoagulants.

3.2. Acute stroke care

Among the study cohort, there was an increasing trend in the rate of intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) (Supplemental Table 4). The Cochrane-Armitage test for trend showed increasing trend for both IVT ($p < 0.0001$) and mechanical thrombectomy ($p < 0.0001$). Less than 1% patients in the cohort received IVT in interval A; the rate of IVT increased to 5.6% in interval B and 8.7% in interval C. Similarly, the rate of mechanical thrombectomy was less than 1% in intervals A and B but significantly increased to 3.4% in interval C.

3.3. One-year ischemic stroke recurrence

Out of 8561 ischemic stroke patients, patients who were lost to follow-up or died within a year without a stroke recurrence and patients from the year 2018 were excluded from recurrence trend analysis. Thus 5444 patients were included in the trend analysis. Out of 5444 patients, 343 (6.3%) had a recurrence within the first year following the index stroke. Compared to intervals A (5.3%) and B (4.9%), there was a significant increase in one-year stroke recurrence in interval C (7.8%, $p = 0.001$). The annual rates of ischemic stroke recurrence till year 2017 is given in Supplemental Fig. 3. The Cochrane-Armitage test for trend showed increasing trend for ischemic stroke recurrence ($Z = -3.6558$, $p = 0.0001$).

The difference between patients with and without one-year ischemic stroke recurrence is given in Table 2. The rates of myocardial infarction, diabetes, chronic kidney disease, prior ischemic stroke was significantly higher in patients with one-year stroke recurrence compared to those without recurrence.

All 8561 patients were included in analysis of cumulative incidence function, Fine-Gray subdistribution model and cause-specific hazard model. Ischemic stroke recurrence was estimated by cumulative incidence function to be 1.9% (95% confidence interval (CI): 1.6–2.2), 3% (95% CI: 2.6–3.3) and 5% (95% CI: 4.5–5.5) at 30 days, 90 days and one year, respectively (Supplemental Fig. 4A). When grouped by five-year intervals, ischemic stroke recurrence was higher in interval C (2014–2018) than in intervals A (Gray's test: $p = 0.002$) and B (Gray's test: $p < 0.001$; Fig. 1A).

In the Fine-Gray subdistribution model for one-year ischemic stroke recurrence, diabetes was associated with an increase in relative incidence of recurrence (HR = 1.48, 95% CI = 1.21–1.82, $p < 0.001$) and age above 65 years was associated with decrease in relative incidence of recurrence (HR = 0.75, 95% CI = 0.61–0.92, $p = 0.007$) (Table 3). In the cause-specific hazard model, age above 65 years (HR = 0.79, 95% CI = 0.64–0.98, $p = 0.028$) was associated with decrease in cause-specific hazard of recurrence, while diabetes (HR = 1.45, 95% CI = 1.18–1.78, $p < 0.001$) and chronic kidney disease (HR = 1.29, 95% CI = 1.01–1.66, $p = 0.045$) increased the cause-specific hazard of recurrence (Table 3).

Cumulative incidence function was also plotted for variables significant in the cause-specific hazard model (Fig. 2). One-year ischemic stroke recurrence in patients aged less than 65 years was higher than older patients (5.8% [95% CI = 4.8%–6.6%] versus 4.7% [95% CI = 4.1%–5.2%], $p = 0.028$, Fig. 2A). One-year ischemic stroke recurrence was also higher in diabetic patients (6.5% [95% CI = 5.6%–7.5%] versus 4.3% [95% CI = 3.7%–4.8%] in non-diabetics, $p < 0.0001$, Fig. 2B) and in patients with chronic kidney disease (6.2% [95% CI = 5.0%–7.5%] versus 4.7% [95% CI = 4.2%–5.3%] in patients without chronic kidney disease, $p < 0.0001$, Fig. 2C).

3.4. All-cause mortality

Among the study cohort, patients who were lost to follow-up within one-year and patients from the year 2018 were excluded from trend analysis of all-cause mortality. Thus, 7563 patients were included in the all-cause mortality trends analysis. Out of 7563 patients, 1216 (16.1%) patients died within a year of the index stroke. When stratified by stroke recurrence, one-year all-cause mortality was not statistically different in patients with and without recurrence (16.9% vs 15.1%, $p = 0.269$). One-year all-cause mortality decreased significantly in interval C (14.8%) when compared to interval B (17.3%, $p < 0.032$) but not compared to interval A (17.0%, $p = 0.141$). The annual rates of ischemic stroke recurrence till year 2017 is given in Supplemental Fig. 3. The Cochrane-Armitage test for trend showed decreasing trend for one-year all-cause mortality ($Z = 1.7351$, $p = 0.0041$).

The patients who died within one-year of stroke were significantly older, 47.5% were men and had significantly higher rate of comorbidities like Atrial fibrillation/flutter, myocardial infarction, heart failure, chronic lung diseases, rheumatic diseases, chronic kidney disease, peripheral vascular disease and history neoplasm, ischemic/hemorrhagic stroke before index date (Table 2). They also had higher NIHSS and underwent mechanical thrombectomy at higher rate.

All 8561 patients were included in survival analysis by Kaplan-Meier estimator and Cox proportional hazards model. Based on Kaplan-Meier estimator, all-cause mortality was estimated to be 6.8% (95% CI: 6.3–7.4), 9.7% (95% CI: 9.1–10.3) and 16% (95% CI: 15.2–16.7) at 30 days, 90 days, and one year, respectively (Supplemental Fig. 4B). When stratified by five-year intervals, all-cause mortality decreased in interval C compared to interval B (Log-rank test: $p = 0.02$) but was not

Table 2
Comparison of demographics, comorbidities, NIHSS and acute stroke care between the patient groups with and without stroke outcomes.

Variable	One-year ischemic stroke recurrence (in 5444 patients)			All-cause mortality at 1 year (in 7563 patients)		
	Without	With	*p*-Value	Alive	Deceased	*p*-Value
Number of patients, n	5101	343		6347	1216	
Age at index ischemic stroke in years, mean (SD)	68.7 (13.0)	69.3 (14.2)	0.412	68.6 (13.9)	76.4 (12.0)	<0.001
Age at index ischemic stroke in years, median [IQR]	70 [59.7, 79.5]	70.7 [60.3, 80.8]	0.348	70.0 [59.6, 79.6]	79.5 [69.4, 86.6]	<0.001
Age categories			0.557			<0.001
≤ 55 years, n (%)	809 (15.9)	54 (15.7)		1020 (16.1)	67 (5.5)	
55.1–65 years, n (%)	1067 (20.9)	73 (21.3)		1337 (21.1)	153 (12.6)	
65.1–75 years, n (%)	1351 (26.5)	83 (24.2)		1651 (26.0)	252 (20.7)	
75.1–85 years, n (%)	1291 (25.3)	84 (24.5)		1599 (25.2)	376 (30.9)	
>85 years, n (%)	583 (11.4)	49 (14.3)		740 (11.7)	368 (30.3)	
Men, n (%)	2656 (52.1)	169 (49.3)	0.343	3348 (52.7)	577 (47.5)	0.001
National Institutes of Health Stroke Scale (NIHSS)[a], median [IQR]	3 [2, 6]	3 [2, 6]	0.815	3 [2, 6]	6 [3, 15]	<0.001
Atrial fibrillation, n (%)	997 (19.5)	65 (19.0)	0.843	1204 (19.0)	393 (32.3)	<0.001
Atrial flutter, n (%)	125 (2.5)	7 (2.0)	0.767	145 (2.3)	58 (4.8)	<0.001
Atrial fibrillation or flutter, n (%)	1016 (19.9)	67 (19.5)	0.918	1228 (19.3)	407 (33.5)	<0.001
Hypertension, n (%)	3880 (76.1)	270 (78.7)	0.293	4753 (74.9)	922 (75.8)	0.512
Myocardial infarction, n (%)	533 (10.4)	51 (14.9)	0.013	654 (10.3)	213 (17.5)	<0.001
Diabetes, n (%)	1628 (31.9)	142 (41.4)	<0.001	2009 (31.7)	419 (34.5)	0.059
Dyslipidemia, n (%)	3330 (65.3)	228 (66.5)	0.696	3985 (62.8)	700 (57.6)	0.001
Heart failure, n (%)	564 (11.1)	50 (14.6)	0.057	692 (10.9)	310 (25.5)	<0.001
Hypercoagulable states, n (%)	73 (1.4)	5 (1.5)	1	80 (1.3)	21 (1.7)	0.245
Chronic liver disease, n (%)	162 (3.2)	11 (3.2)	1	186 (2.9)	35 (2.9)	0.995
Chronic lung diseases, n (%)	1101 (21.6)	78 (22.7)	0.663	1280 (20.2)	310 (25.5)	<0.001
Rheumatic diseases, n (%)	205 (4.0)	16 (4.7)	0.656	230 (3.6)	69 (5.7)	0.001
Chronic kidney disease, n (%)	831 (16.3)	83 (24.2)	<0.001	987 (15.6)	363 (29.9)	<0.001
History of neoplasm, n (%)	773 (15.2)	51 (14.9)	0.948	867 (13.7)	313 (25.7)	<0.001
Peripheral vascular diseases, n (%)	826 (16.2)	66 (19.2)	0.161	964 (15.2)	245 (20.1)	<0.001
History of ischemic stroke, n (%)	431 (8.4)	44 (12.8)	0.007	533 (8.4)	159 (13.1)	<0.001
History of hemorrhagic stroke, n (%)	249 (4.9)	20 (5.8)	0.511	326 (5.1)	132 (10.9)	<0.001
Mechanical thrombectomy	55 (1.1)	3 (0.9)	0.933	66 (1.0)	36 (3.0)	<0.001
Intravenous thrombolysis	304 (6.0)	13 (3.8)	0.123	377 (5.9)	72 (5.9)	1.000

[a] Available for 1059 patients without one-year recurrence and 94 patients with one-year recurrence, 1435 patients alive at one year, and 233 patients deceased within one year.

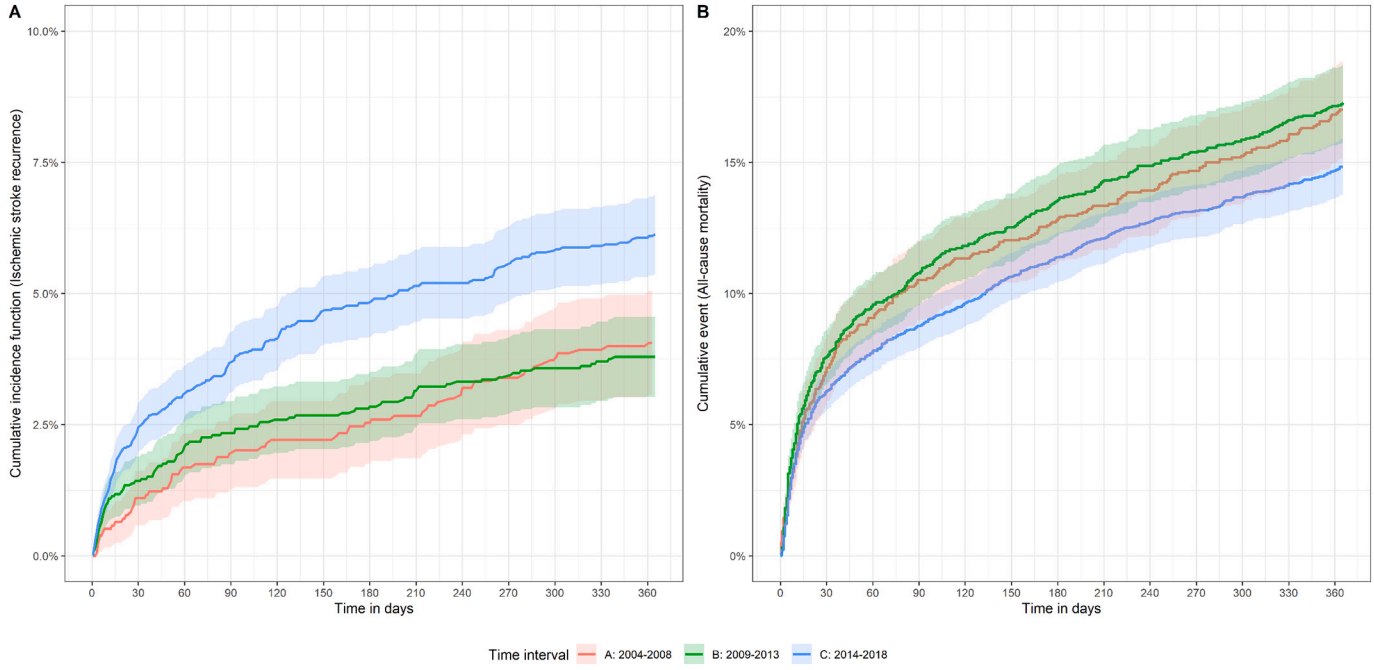

Fig. 1. A Cumulative incidence function of ischemic stroke recurrence till one year stratified by five-year intervals (competing risk: all-cause mortality not shown). B Cumulative event of all-cause mortality till one year based on Kaplan-Meier estimator and stratified by five-year intervals.

significantly decreased compared to interval A (Log-rank test: $p = 0.12$; Fig. 1B).

In the Cox proportional hazards model, age more than 65 years (HR: 2.02, 95% CI: 1.74–2.35, $p < 0.001$), atrial fibrillation or flutter (HR: 1.33, 95% CI: 1.17–1.5, $p < 0.001$), heart failure (HR: 1.64, 95% CI: 1.42–1.9, $p < 0.001$) and history of ischemic stroke before index date (HR:1.28, 95% CI: 1.08–1.52) were associated with higher one-year all-cause mortality (Table 4).

Table 3
Hazard ratios (and 95% Confidence Intervals) from Subdistribution hazard model and cause-specific hazard model for one-year ischemic stroke recurrence.

Variable	Subdistribution Hazard Model			Cause-specific Hazard Model		
	Hazard Ratio	95% Confidence Interval	*p* Value	Hazard Ratio	95% Confidence Interval	*p*Value
Men (vs. Women)	0.9	0.74–1.1	0.296	0.9	0.74–1.1	0.303
Age > 65 years	0.75	0.61–0.92	0.007	0.79	0.64–0.98	0.028
Myocardial Infarction	1.21	0.9–1.61	0.206	1.27	0.95–1.7	0.114
Diabetes	1.48	1.21–1.82	< 0.001	1.45	1.18–1.78	< 0.001
Heart failure	0.89	0.66–1.21	0.469	0.97	0.72–1.31	0.839
Chronic kidney disease	1.25	0.97–1.61	0.081	1.29	1.01–1.66	0.045

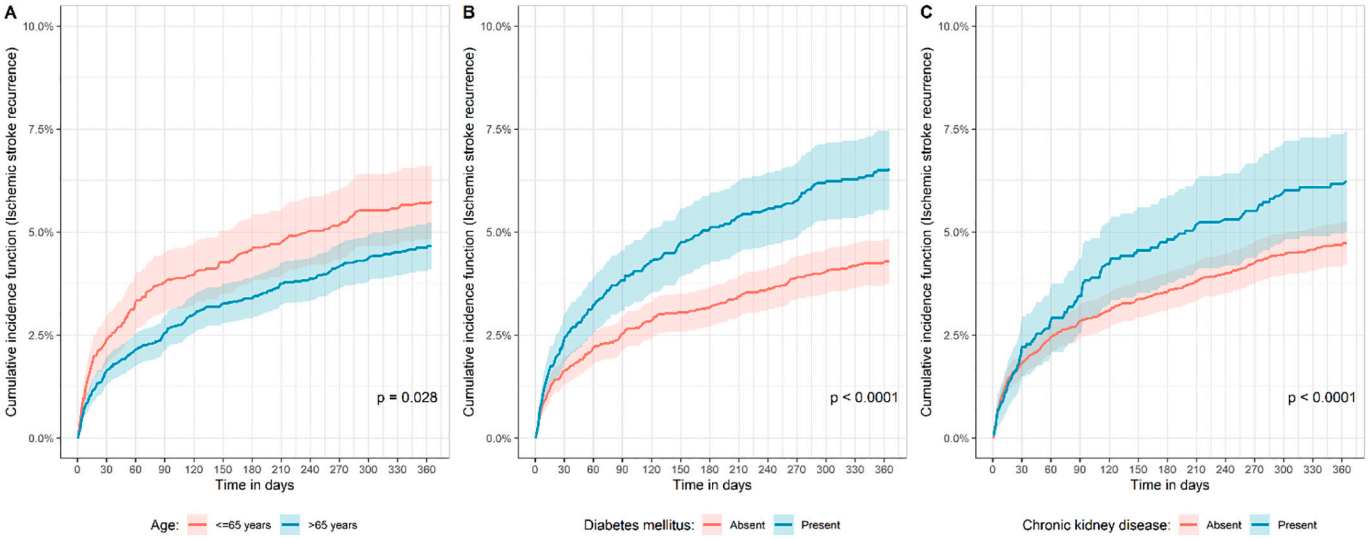

Fig. 2. Cumulative incidence function for ischemic stroke recurrence till one year (competing risk of mortality not shown) and stratified by:
A. Age more than 65 years at index date.
B. Diabetes.
C. Chronic kidney disease.

Table 4
Hazard ratios (and 95% Confidence Intervals) from stratified cox proportional hazards model for one-year all-cause mortality in ischemic stroke patients.

Variable	Hazard Ratio	95% Confidence Interval	p Value
Men (vs. Women)	0.91	0.82–1.02	0.117
Age > 65 years	2.02	1.74–2.35	< 0.001
Atrial fibrillation/flutter	1.33	1.17–1.5	< 0.001
Heart failure	1.64	1.42–1.9	< 0.001
Chronic lung diseases	1.07	0.93–1.22	0.344
Rheumatic diseases	1.26	0.99–1.61	0.056
History of ischemic stroke before index date	1.28	1.08–1.52	0.004

Kaplan-Meier survival curves were plotted for variables that were significant in the Cox proportional hazard model (Fig. 3). Survival probability at one-year for patients older than 65 years was significantly lower than younger patients (80.2% versus 91.6%, $p < 0.0001$, Fig. 3A). Similarly, one-year survival probability was lower in stroke patients with atrial fibrillation/flutter (75.1% versus 86.5%, $p < 0.0001$, Fig. 3B), heart failure (68.7% versus 86.4%, $p < 0.0001$, Fig. 3C) and prior ischemic stroke (78.4% versus 84.6%, $p < 0.0001$, Fig. 3D).

3.5. NIHSS and stroke outcomes

NIHSS was available for only 2016 patients included in the study. Separate survival models were employed to examine the effect on NIHSS on stroke recurrence and mortality. In both the Fine-Gray sub-distribution hazard model and cause-specific hazard model, NIHSS was not associated with one-year stroke recurrence (Supplemental Table 5). NIHSS did predict one-year mortality (HR: 1.07, 95% CI: 1.06–1.09, $p < 0.001$; Supplemental Table 6) in the Cox proportional hazards model.

4. Discussion

This study demonstrates an increasing trend in one-year stroke recurrence over a period of 15 years despite a significant decrease in one-year mortality over the same period. The observed decrease in mortality is consistent with other studies in Europe and the United States [21–23]. The mortality decline after 2013 parallels increased availability and utilization of endovascular stent thrombectomy [21,24–27]. Geisinger has considerably increased its mechanical thrombectomy capacity since 2014; 151 (3.4%) patients in this study were treated with thrombectomy between 2014 and 2018, and 24 (0.6%) before 2014. Many other reasons including the expansion of telestroke and the development of the *Get With The Guidelines (GWTG)-Stroke* program might have caused the decline in the one-year mortality in Geisinger population and across the nation [28–30].

Previous studies from urban populations have shown a general decline in stroke mortality and recurrence over the years [22,36–39]. Higher stroke mortality has been seen in rural areas compared to urban areas and appears to be due to higher stroke incidence in rural areas rather than case fatality [3]. Other rural-urban differences contributing to higher incidence in rural areas are more prevalent risk factors like diabetes and hyperlipidemia [4]. People in rural areas are less likely to

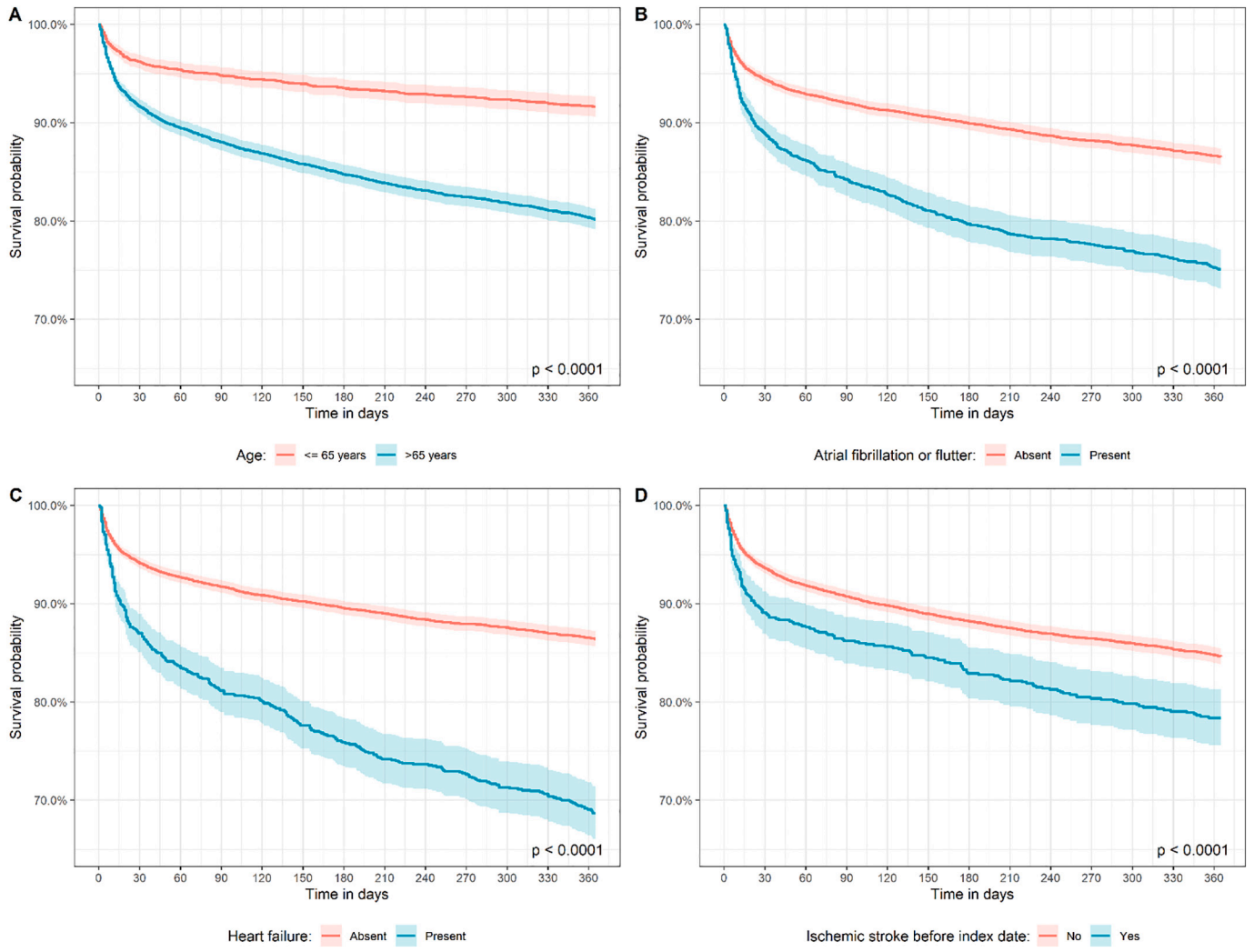

Fig. 3. Kaplan-Meier survival curves for all-cause mortality till one year stratified by:
A. Age more than 65 years at index date.
B. Atrial fibrillation/flutter.
C. Heart failure.
D. History of ischemic stroke before the index date.

be screened for diabetes and less likely to achieve diabetes control [4].

The one-year stroke recurrence rate is reported to be 5% to 15% in different studies [31–35]. One-year stroke recurrence using cumulative incidence function in this study was estimated to be 5% which is lower than given by Kaplan-Meier estimator (5.7% for this study) as Kaplan-Meier estimator does not take competing risks into account and thus overestimates the risk. Contrary to most studies where the rate of one-year recurrence declined [33,40,41], the recurrence rate in this study increased over the past fifteen years. The rise in stroke recurrence in a rural population as shown by this study is also similar to results from a study in rural China [42]. This disparity in the recurrent stroke trend between urban and rural populations should be further studied. In addition to the increased prevalence of risk factors in the recurrence group, the decline in stroke mortality leads to an increase in the number of stroke survivors, thus leading to a potential increase in the prevalence of recurrent stroke among survivors.

4.1. Stroke risk factors and predictors of poor outcomes

A recent meta-analysis showed that hypertension, diabetes, atrial fibrillation, and coronary heart disease are predictors of stroke recurrence [43]. In this study, diabetes was found to be a significant factor in both subdistribution hazard model and cause-specific hazard model. Another significant predictor was chronic kidney disease. Age more than 65 years was found to be associated with lower recurrence in the cause-specific hazard model. Young adults with stroke have different risk factors and etiologies than older patients and may have different rates of stroke recurrence. Epidemiologic data regarding stroke recurrence among younger patients are limited. In addition, several factors including older age [44], hypertension [45], diabetes [46,47], and current smoking [45] are associated with stroke death. Appelros et al. showed that old age, atrial fibrillation, stroke severity, and dementia were predictors of poor outcomes including death within one-year after stroke [48]. These observations are similar to the findings in this study. Chronic kidney disease was also confirmed to be an independent predictor of poor outcome.

Other studies indicated a global increase in vascular risk factors over the past years [49–52]. A study on 6032 patients over a 20-year window (1980–2000) in Minneapolis [38] reported an increasing trend in atrial fibrillation, hypertension, diabetes, and ischemic heart disease among stroke patients. The rates of hypertension, diabetes, current smoking, and myocardial infarction are the most prevalent risk factors reported by prospective studies in ischemic stroke population such as Reasons for Geographic and Racial Differences in Stroke (REGARDS) [53] and

Northern Manhattan Stroke Study (NOMASS) [54]. Although we did not study the effect of predictors on the trends in this study, a significant increase in the rate of risk factors prevailed in the recurrence and one-year mortality cohorts. Additionally, the vascular risk factors may vary based on geographic population and the trend might be higher in rural areas as compared to the urban counterparts [23]. Also, an increasing percentage of individuals older than 65 years (~25%) in rural areas [55] may be associated with a higher proportion of comorbidities in this population. With significant increase in stroke risk factors and stroke recurrence over the years, the focus needs to be on primary and secondary prevention.

An increased administration of medications such as statins, anti-platelet, and anticoagulants was observed in this study, which is similar to other studies [52,56,57]. However, there was negligible change in trends of antihypertensives despite an increasing diagnostic rate of hypertension in the population. There was also a discrepancy between the rate of atrial fibrillation/flutter (21.7%) at the time of index stroke, the documented diagnosis of atrial fibrillation/flutter prior to the stroke event (12.2%), and the medication history of anticoagulants (9.1%).

4.2. Strengths and limitations

The present study is one of the few reports that captures the trends of risk factors and outcomes in a large rural population-based cohort over a period of fifteen years in the United States. GNSIS represents one of the largest rural cohort of ischemic stroke patients across all ages. This study included patients from a specific area within a single health care system network and the results of this study might not be generalizable to the general population or other rural areas with different population demographics. The use of EHR and other data sources provided a comprehensive overview of patients' clinical data with deep phenotype and clinical evaluation as well as a large sample size. Furthermore, Geisinger has a stable patient population with a very low out-migration rate and rich longitudinal data. However, the use of these resources has its drawbacks, mainly centered around inherent noise due to the nature of the data, as well as biased patient selection. Patients were included in the GNSIS database based on strict criteria to ensure high specificity, thus cases of ischemic stroke not fulfilling these criteria may not represented in this database. Mortality presented in this study is all-cause mortality and not case-fatality rate and it can be influenced by improved management of other comorbidities contributing to death. We also looked at the overall risk factors causing an ischemic stroke, irrespective of ischemic stroke subtypes, socioeconomic determinants, or genetic predispositions [58,59]. Further research is needed to determine subtype-specific stroke risk factors and trends, taking into account non-clinical risk factors as well as genetic biomarkers.

5. Conclusion

Although stroke mortality has decreased, stroke recurrence and several vascular risk factors have significantly increased in this rural population over the past fifteen years. More effort is still needed to control stroke risk factors in high-risk and underserved subpopulations.

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Data availability statement

All relevant data are available in the article and/or supplemental file. Due to privacy and other restrictions, the primary data cannot be made openly available. Deidentified data may be available subject to data-sharing agreement with Geisinger Health System. Details about requesting access to the data are available from the corresponding author.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2021.117339.

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