

Sex disparity in long-term stroke recurrence and mortality in a rural population in the United States

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Abstract

Background: Several studies suggest women may be disproportionately affected by poorer stroke outcomes than men. This study aims to investigate whether women have a higher risk of all-cause mortality and recurrence after an ischemic stroke than men in a rural population in central Pennsylvania, United States.

Methods: We analyzed consecutive ischemic stroke patients captured in the Geisinger NeuroScience Ischemic Stroke research database from 2004 to 2019. Kaplan–Meier (KM) estimator curves stratified by gender and age were used to plot survival probabilities and Cox Proportional Hazards Ratios were used to analyze outcomes of all-cause mortality and the composite outcome of ischemic stroke recurrence or death. Fine–Gray Competing Risk models were used for the outcome of recurrent ischemic stroke, with death as the competing risk. Two models were generated; Model 1 was adjusted by data-driven associated health factors, and Model 2 was adjusted by traditional vascular risk factors.

Results: Among 8900 adult ischemic stroke patients [median age of 71.6 (interquartile range: 61.1–81.2) years and 48% women], women had a higher crude all-cause mortality. The KM curves demonstrated a 63.3% survival in women compared with a 65.7% survival in men ($p=0.003$) at 5 years; however, the survival difference was not present after controlling for covariates, including age, atrial fibrillation or flutter, myocardial infarction, diabetes mellitus, dyslipidemia, heart failure, chronic lung diseases, rheumatic disease, chronic kidney disease, neoplasm, peripheral vascular disease, past ischemic stroke, past hemorrhagic stroke, and depression. There was no adjusted or unadjusted sex difference in terms of recurrent ischemic stroke or composite outcome.

Conclusion: Sex was not an independent risk factor for all-cause mortality and ischemic stroke recurrence in the rural population in central Pennsylvania.

Keywords: EHR, ischemic stroke, recurrent stroke, risk factors, risk model, rural population, sex disparity, stroke mortality

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Introduction

Stroke is a significant cause of morbidity and mortality¹ and studies have suggested that women are being disproportionately affected by stroke^{2,3} and may have poorer stroke outcomes;⁴ however, variation exists in the literature.^{5–7} Women have a longer life expectancy than men and, therefore, likely have an increased lifetime risk of stroke.⁸ Women tend

to be older than men at the time of stroke^{5,8} and have a higher pre-stroke degree of disability or dependence in their daily activities, based on modified Rankin Score, which may contribute to worse outcomes.^{9,10} Some studies have suggested that women suffer more severe strokes overall compared with men based on stroke scale data.^{8,11,12} Increased likelihood of stroke recurrence in women may be

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due to differences in the treatment of index stroke or stroke risk factors. For example, daily aspirin has been shown to reduce stroke in women, more so than men; however, women are less likely to be prescribed aspirin.^{11,13–15}

A recent effort has been made to parse out ways in which healthcare providers can improve stroke outcomes for women, who may serve as a marginalized group in conventional stroke management algorithms. A higher crude mortality rate in women has been identified; however, after adjusting for age and other co-morbidities, the difference often disappears,^{4,12,16,17} which calls into question the true role of sex in stroke outcomes. A number of studies demonstrated that men and women have similar risk factors, diagnostic pathways, treatments, and outcomes,^{7,18} but geographical location⁶ and socioeconomic status^{16,19} may play a role in mediating the effects of sex on stroke outcome. Stroke outcomes in rural populations have been shown to be worse than in urban populations,²⁰ which could amplify the alleged sex disparity further. Rural populations seem to be disproportionately burdened by stroke risk factors, including hypertension and poorly controlled diabetes,²¹ nevertheless there is a relative paucity of data available on sex disparity in rural patients from the United States. The goal of this study was to determine whether a sex disparity exists, in terms of ischemic stroke recurrence and all-cause mortality, in a rural Pennsylvania population in the United States, while secondarily investigating whether there are any risk factors that disproportionately affect women.

Methods

This study was a retrospective analysis of data collected from September 2003 to May 2019 on ischemic stroke patients who presented to the Geisinger Health System. Geisinger is an integrated health system that includes 12 hospitals and several clinics located in central, south-central, and northeastern Pennsylvania. The study was reviewed and approved by the Geisinger Institutional Review Board to meet the “non-human subject research” category which uses de-identified information.

Data collection

This study utilized data extracted from the Geisinger NeuroScience Ischemic Stroke Database (Supplemental Material Appendix A

online). Patients with index and recurrent ischemic stroke were identified using the International Classification of Diseases (ICD) codes (Supplemental Material Table 1). Baseline characteristics and clinical data extracted were sex, systolic blood pressure (SBP), diastolic blood pressure, National Institute of Health Stroke Scale (NIHSS), family history of heart disease and stroke, atrial fibrillation (AF) or atrial flutter, hypertension (HTN), myocardial infarction (MI), diabetes mellitus (DM), dyslipidemia, heart failure (HF), hypercoagulable state, chronic liver disease, chronic lung disease, rheumatological disease, chronic kidney disease (CKD), neoplasm, peripheral vascular disease (PVD), history of ischemic stroke, depression and anxiety disorder, and acute stroke treatment [intravenous thrombolysis (IVT) and mechanical thrombectomy (MT)]. Patients who were over 18 years old were included in this study.

Outcome measures

Stroke (index and recurrent) was defined as patients who had (1) a discharge diagnosis of ischemic stroke based on ICD-9/ICD-10-CM codes (Supplemental Material Table 2), (2) a brain magnetic resonance imaging (MRI) during the same encounter and (3) an overnight stay in the hospital during the index event. Follow-up was restricted to 5 years and took place from the date of index ischemic stroke to the date of last recorded appointment for recurrence and composite outcome. For mortality, the patient’s status was based on hospital-level data complemented with Social Security death data. Three outcomes were examined in this study: ischemic stroke recurrence, all-cause mortality, and the composite outcome of ischemic stroke recurrence or all-cause mortality. Follow-up was limited to 5 years. For composite outcomes, patients who had both ischemic stroke recurrence and death, ‘time to event’ was taken from the date of the recurrence event.

Statistical analysis

Continuous variables were reported as mean \pm standard deviation or median with interquartile range (IQR). Categorical variables were reported as proportions. Group differences were assessed using Analysis of Variance or Student’s *t*-test for continuous variables and Chi-Square Test of Independence for non-continuous variables. Kaplan–Meier (KM) estimator was used to plot the survival free from

Table 1. Patient demographics and medical history at index stroke event.

Variable	Overall N = 8900	Women n = 4309	Men n = 4591	p
Age at index stroke, median (IQR)	71.6 (61.1, 81.2)	74.7 (63.8, 83.5)	68.9 (59.4, 78.6)	<0.001
Systolic blood pressure, mean (SD)	137 (23)	137 (24)	136 (22)	0.111
Diastolic blood pressure, mean (SD)	74 (13)	74 (13)	75 (13)	<0.001
NIHSS, median (IQR)	4 (2, 7)	4 (2, 7)	4 (2, 6)	0.018
Atrial fibrillation, n (%)	1881 (21.1)	989 (23.0)	892 (19.4)	<0.001
Atrial flutter, n (%)	235 (2.6)	97 (2.3)	138 (3.0)	0.031
Atrial fibrillation or flutter, n (%)	1932 (21.7)	1014 (23.5)	918 (20.0)	<0.001
Hypertension, n (%)	6709 (75.4)	3226 (74.9)	3483 (75.9)	0.285
Myocardial infarction, n (%)	1031 (11.6)	400 (9.3)	631 (13.7)	<0.001
Diabetes mellitus, n (%)	2898 (32.6)	1372 (31.8)	1526 (33.2)	0.166
Dyslipidemia, n (%)	5558 (62.4)	2658 (61.7)	2900 (63.2)	0.155
Heart failure, n (%)	1202 (13.5)	634 (14.7)	568 (12.4)	0.001
Hypercoagulable states, n (%)	117 (1.3)	63 (1.5)	54 (1.2)	0.276
Chronic liver disease, n (%)	275 (3.1)	139 (3.2)	136 (3.0)	0.511
Chronic lung diseases, n (%)	1916 (21.5)	960 (22.3)	956 (20.8)	0.100
Rheumatic diseases, n (%)	361 (4.1)	265 (6.1)	96 (2.1)	<0.001
Chronic kidney diseases, n (%)	1684 (18.9)	885 (20.5)	799 (17.4)	<0.001
Neoplasm, n (%)	1373 (15.4)	626 (14.5)	747 (16.3)	0.025
Peripheral vascular diseases, n (%)	1423 (16.0)	607 (14.1)	816 (17.8)	<0.001
Past ischemic stroke, n (%)	849 (9.5)	408 (9.5)	441 (9.6)	0.854
Past hemorrhagic stroke, n (%)	588 (6.6)	278 (6.5)	310 (6.8)	0.597
Depression, n (%)	1479 (16.6)	891 (20.7)	588 (12.8)	<0.001
Anxiety disorders, n (%)	1349 (15.2)	881 (20.4)	468 (10.2)	<0.001
Family history of heart disease, n (%)	3165 (35.6)	1612 (37.4)	1553 (33.8)	<0.001
Family history of stroke, n (%)	1203 (13.5)	633 (14.7)	570 (12.4)	0.002

IQR, interquartile range.

Overall and sex stratified demographic and medical history information is displayed. Differences between men and women are based on Student's t-test for continuous variables or Chi-Square Test of Independence for non-continuous variables. National Institutes of Health Stroke Scale (NIHSS) was available for 2148 patients (1019 female and 1129 male patients). Blood pressure reading available for 6136 patients (3081 female and 3055 male patients). All other variables were available for all 8900 patients.

Table 2. Patient demographics and medical history stratified by outcomes.

Variable	5-year mortality		5-year stroke recurrence		5-year composite outcome				
	Alive	Deceased	p	No recurrence	Recurrence	p	No composite outcome	Composite outcome	p
Number of patients	6334	2566		8248	652		5874	3026	
Male sex, n (%)	3321 (52.4)	1270 (49.5)	0.013	4274 (51.8)	317 (48.6)		3097 (52.7)	1494 (49.4)	0.003
Age at index stroke, median (IQR)	68.7 (58.8, 78.5)	78.6 (69.1, 85.1)	<0.001	71.6 (61.0, 81.3)	71.7 (61.6, 80.5)		68.5 (58.7, 78.5)	77.5 (67.3, 84.4)	<0.001
Systolic blood pressure, mean (SD)	137 (23)	136 (24)	0.016	136 (23)	139 (25)		137 (22)	136 (24)	0.228
Diastolic blood pressure, mean (SD)	76 (13)	72 (13)	<0.001	74 (13)	75 (13)		76 (13)	72 (13)	<0.001
NIHSS, median (IQR)	3 (2, 6)	5 (2, 12)	<0.001	4 (2, 7)	3 (2, 5)		3 (2, 6)	4 (2, 9)	<0.001
Atrial fibrillation, n (%)	1117 (17.6)	764 (29.8)	<0.001	1737 (21.1)	144 (22.1)		1038 (17.7)	843 (27.9)	<0.001
Atrial flutter, n (%)	131 (2.1)	104 (4.1)	<0.001	217 (2.6)	18 (2.8)		118 (2.0)	117 (3.9)	<0.001
Atrial fibrillation or flutter, n (%)	1140 (18.0)	792 (30.9)	<0.001	1785 (21.6)	147 (22.5)		1059 (18.0)	873 (28.8)	<0.001
Hypertension, n (%)	4748 (75.0)	1961 (76.4)	0.155	6191 (75.1)	518 (79.4)		4386 (74.7)	2323 (76.8)	0.031
Myocardial infarction, n (%)	621 (9.8)	410 (16.0)	<0.001	940 (11.4)	91 (14.0)		561 (9.6)	470 (15.5)	<0.001
Diabetes mellitus, n (%)	1963 (31.0)	935 (36.4)	<0.001	2628 (31.9)	270 (41.4)		1776 (30.2)	1122 (37.1)	<0.001
Dyslipidemia, n (%)	4051 (64.0)	1507 (58.7)	<0.001	5111 (62.0)	447 (68.6)		3737 (63.6)	1821 (60.2)	0.002
Heart failure, n (%)	5 (73 (9.0)	629 (24.5)	<0.001	1114 (13.5)	88 (13.5)		531 (9.0)	671 (22.2)	<0.001
Hypercoagulable states, n (%)	76 (1.2)	41 (1.6)	0.164	109 (1.3)	8 (1.2)		73 (1.2)	44 (1.5)	0.465
Chronic liver disease, n (%)	194 (3.1)	81 (3.2)	0.870	249 (3.0)	26 (4.0)		178 (3.0)	97 (3.2)	0.698
Chronic lung diseases, n (%)	1236 (19.5)	680 (26.5)	<0.001	1769 (21.4)	147 (22.5)		1141 (19.4)	775 (25.6)	<0.001
Rheumatic diseases, n (%)	228 (3.6)	133 (5.2)	0.001	327 (4.0)	34 (5.2)		209 (3.6)	152 (5.0)	0.001
Chronic kidney diseases, n (%)	953 (15.0)	731 (28.5)	<0.001	1555 (18.9)	129 (19.8)		886 (15.1)	798 (26.4)	<0.001
Neoplasms, n (%)	755 (11.9)	618 (24.1)	<0.001	1269 (15.4)	104 (16.0)		695 (11.8)	678 (22.4)	<0.001
Peripheral vascular diseases, n (%)	883 (13.9)	540 (21.0)	<0.001	1295 (15.7)	128 (19.6)		797 (13.6)	626 (20.7)	<0.001
Past ischemic stroke, n (%)	551 (8.7)	298 (11.6)	<0.001	782 (9.5)	67 (10.3)		506 (8.6)	343 (11.3)	<0.001
Past hemorrhagic stroke, n (%)	337 (5.3)	251 (9.8)	<0.001	548 (6.6)	40 (6.1)		313 (5.3)	275 (9.1)	<0.001
Depression, n (%)	1016 (16.0)	463 (18.0)	0.023	1352 (16.4)	127 (19.5)		926 (15.8)	553 (18.3)	0.003
Anxiety disorder, n (%)	960 (15.2)	389 (15.2)	1.000	1258 (15.3)	91 (14.0)		896 (15.3)	453 (15.0)	0.747
Family history of heart disease, n (%)	2342 (37.0)	823 (32.1)	<0.001	2886 (35.0)	279 (42.8)		2135 (36.3)	1030 (34.0)	0.033
Family history of stroke, n (%)	917 (14.5)	286 (11.1)	<0.001	1095 (13.3)	108 (16.6)		834 (14.2)	369 (12.2)	0.010

IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale. Outcome stratified (alive vs. deceased for all-cause mortality, recurrence vs. no recurrence, and composite outcome vs. no composite outcome) demographic and medical history information is displayed. Differences between outcomes are based on Analysis of Variance (ANOVA) or Student's t-test for continuous variables or Chi-Square Test of Independence for non-continuous variables. National Institutes of Health Stroke Scale (NIHSS) was available for 2148 patients (1019 female and 1129 male patients). Blood pressure reading available for 6136 patients (3081 female and 3055 male patients). All other variables were available for 8900 patients.

Table 3. Fine–Gray competing risk model for ischemic stroke recurrence.

	Unadjusted analysis		Model 1 _a		Model 2	
	Unadjusted HR	<i>p</i> [#]	Adjusted HR	<i>p</i>	Adjusted HR	<i>p</i>
Overall Male (female as reference)	0.893 [0.767–1.04]	0.145	0.866 [0.741–1.013]	0.071	0.857 [0.733–1.002]	0.053
Subgroup analysis ^{##} :						
Age group I Male (female as reference)	0.875 [0.638–1.2]	1.000	0.909 [0.656–1.261]	1.000	0.875 [0.636–1.204]	1.000
Age group II Male (female as reference)	0.853 [0.633–1.149]	1.000	0.869 [0.645–1.171]	1.000	0.847 [0.627–1.146]	1.000
Age group III Male (female as reference)	0.892 [0.669–1.188]	1.000	0.875 [0.648–1.18]	1.000	0.878 [0.649–1.188]	1.000
Age group IV Male (female as reference)	0.883 [0.632–1.234]	1.000	0.902 [0.641–1.269]	1.000	0.889 [0.63–1.255]	1.000

[#]*p* values were corrected with a Bonferroni correction for subgroup analysis (i.e. when more than one test of significance was applied to the sample).

^{##}.

Age group	Age in years	Number of patients
I	18.3–61.0	2218
II	61.1–71.5	2230
III	71.6–81.1	2221
IV	81.2 and above	2231

HR, hazard ratio

mortality or stroke recurrence and a log-rank test was used to assess the statistical significance of the difference in survival between female and male patients (Supplemental Material Table 3).

Cox proportional hazards models were used for outcomes of all-cause mortality and the composite outcome of recurrence or death. Fine–Gray competing risk model²² was used for the outcome of ischemic stroke recurrence, with death as a competing risk. Hazard ratios (HRs) referred to all-cause mortality-free survival probability, recurrence-free survival probability, and composite outcome-free survival probability, respectively. Models were prepared in two ways. Model 1 was a data-driven model where only variables with statistically significant *p* values (<0.05) when stratified by outcome were included. Model 1_a (for ischemic stroke recurrence) was adjusted for age, HTN, DM, dyslipidemia, PVD, and depression. Model 1_b (for all-cause mortality) was adjusted for

age, AF/atrial flutter, MI, DM, dyslipidemia, HF, chronic lung diseases, rheumatic disease, CKD, neoplasm, PVD, past ischemic stroke, past hemorrhagic stroke, and depression. Model 1_c (for composite outcome) was adjusted for age, AF/atrial flutter, HTN, MI, DM, dyslipidemia, HF, chronic lung diseases, rheumatic disease, CKD, neoplasm, PVD, past ischemic stroke, past hemorrhagic stroke, and depression. Model 2, a common associated factors model, based on current literature,^{16,23,24} was adjusted for age, HTN, AF/atrial flutter, DM, MI, HF, PVD, past ischemic stroke, and past hemorrhagic stroke.

Subgroup analysis was conducted for each age stratum based on age quartiles. A *p*-value of 0.05 was set for tests of significance which involved the entire cohort and a *p*-value of 0.0125, based on Bonferroni correction, was set for subgroup analysis. All analyses were done in R/RStudio (R v.4.0.2, RStudio v.1.3.959).^{25,26}

Results

Patient population and clinical data

A total of 8900 adult ischemic stroke patients were included. Overall sex-stratified (Table 1) and outcome stratified (Table 2) baseline characteristics, comorbidities, and associated health factors were reported. Women constituted 48% of the patients ($n=4309$). The median age of index stroke was 74.7 years (IQR=63.8–83.5) in women *versus* 68.9 years (IQR=59.4–78.6) in men ($p<0.001$). The median follow-up time to event or censoring was 639 (IQR=118–1618) days for both ischemic stroke recurrence and composite outcome, and 1047 (IQR=363–1826) days for all-cause mortality. Median time to event was 208 (IQR=34–623) days for ischemic stroke recurrence, 306 (IQR=36–850) days for all-cause mortality and 252 (IQR=31–780) days for composite outcome. Overall, 214 patients received MT, 50.4% of whom were women, and 583 patients received IVT at index stroke, 53% of whom were women. The rate of MT and IVT use was not statistically different between men and women.

Associated factors and comorbidities stratified by age is summarized in Table 1 and stratified by outcome is summarized in Table 2. Women had a higher incidence of AF ($p<0.001$), rheumatic disease ($p<0.001$), CKD ($p<0.001$), depression ($p<0.001$), and anxiety ($p<0.001$). Women were also more likely to report a positive family history of stroke ($p=0.002$). Men had MI ($p<0.001$), neoplasm ($p=0.025$), and PVD ($p<0.001$) more often than women. HTN, SBP, diabetes, hypercoagulability, and a personal history of ischemic and hemorrhagic strokes did not differ significantly between men and women. After a median follow-up of 2.9 years, 3321 patients remained alive and 47.6% were female ($p=0.013$). The population who died had an older median age at index stroke ($p<0.001$). NIHSS score ($p<0.001$), AF ($p<0.001$), atrial flutter ($p<0.001$), MI ($p<0.001$), DM ($p<0.001$), HF ($p<0.001$), chronic lung disease ($p<0.001$), rheumatic disease ($p=0.001$), CKD ($p<0.001$), neoplasm ($p<0.001$), PVD ($p<0.001$), past ischemic stroke ($p<0.001$), past hemorrhagic stroke ($p<0.001$), and depression ($p=0.023$) were all more common in patients who died. Gender and age at index stroke did not differ significantly between those who experienced recurrent ischemic stroke and those who did not. HTN ($p=0.014$), DM ($p<0.001$), dyslipidemia ($p=0.001$), PVD ($p=0.01$), depression ($p=0.047$),

family history of heart disease ($p<0.001$), and family history of stroke ($p=0.021$) were more common in patients who experienced ischemic stroke recurrence. After a median follow-up of 1.8 years 3026 patients experienced the composite outcome of ischemic stroke recurrence or death and 50.6% of them were female, whereas 5874 patients did not experience the composite outcome and 47.3% were female ($p=0.003$).

Stroke outcomes

Ischemic stroke recurrence. There were 652 (7.3%) patients who experienced ischemic stroke recurrence within 5 years and no sex predominance was observed in adjusted and unadjusted analyses. Neither Model 1_a (adjusted for age, HTN, DM, dyslipidemia, PVD, and depression) or Model 2 (adjusted for age, HTN, AF, atrial flutter, DM, MI, HF, PVD, past ischemic stroke, and past hemorrhagic stroke) yielded statistically significant findings. The results of the subgroup analysis by age quartiles were also not significant (Table 3). Sex stratified KM curves did not demonstrate a significant difference in stroke recurrence, indicating that there was no sex-based difference in vulnerability to stroke recurrence over 5 years [Figure 1(A)]. Age group stratified KM curves also demonstrated no significant sex difference [Figure 2(A)]. Women had an 86.9% [95% confidence interval (CI) 85.5–88.3] ischemic stroke recurrence-free survival probability at 5 years compared with men with 88.6% (95% CI 87.4–89.9) survival probability and this difference was not statistically significant ($p=0.092$).

All-cause mortality. There were 2566 deaths (28.8%) in this population within 5 years of the index date. Overall unadjusted HR for all-cause mortality indicated that women were more vulnerable to death than men (HR for men, with women as reference = 0.890, CI = 0.823–0.961, $p=0.003$) within 5 years. However, adjustment by covariates yielded no statistically significant findings. Neither Model 1_b (adjusted for age, AF, atrial flutter, MI, DM, dyslipidemia, HF, chronic lung diseases, rheumatic disease, CKD, neoplasm, PVD, past ischemic stroke, past hemorrhagic stroke, and depression) or Model 2 demonstrated a sex difference (Table 4). Sex stratified KM curves showed a statistically significant difference between men and women in terms of all-cause mortality, whereby women had a lower probability of survival free from all-cause

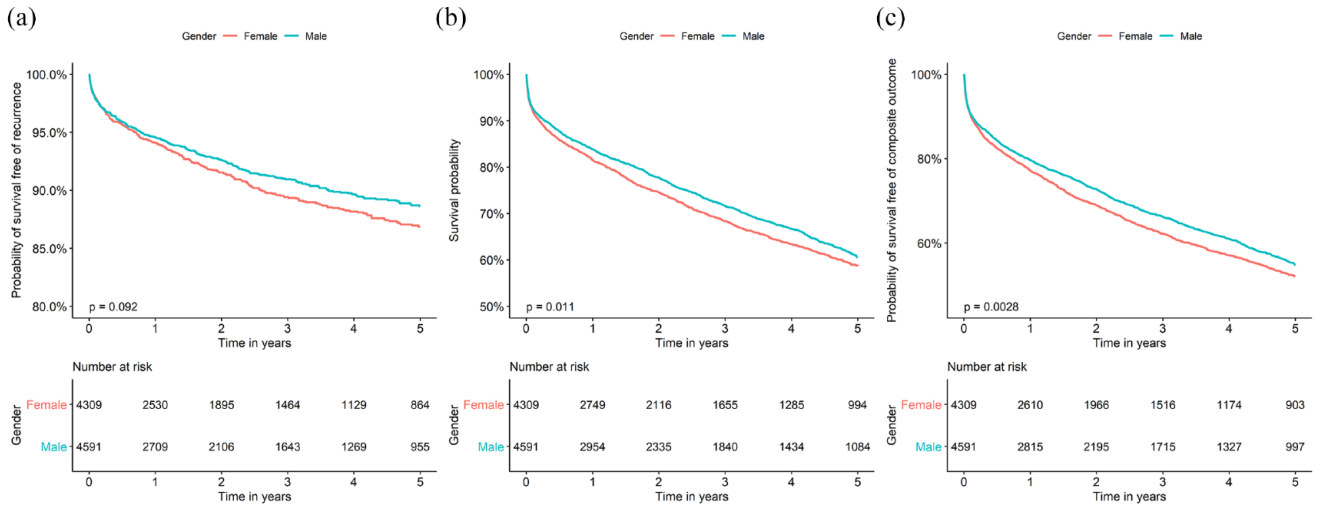


Figure 1. Kaplan–Meier survival curves stratified by sex: (A) 5-year ischemic stroke recurrence, (B) 5-year all-cause mortality, (C) 5-year composite outcome of recurrence or mortality.

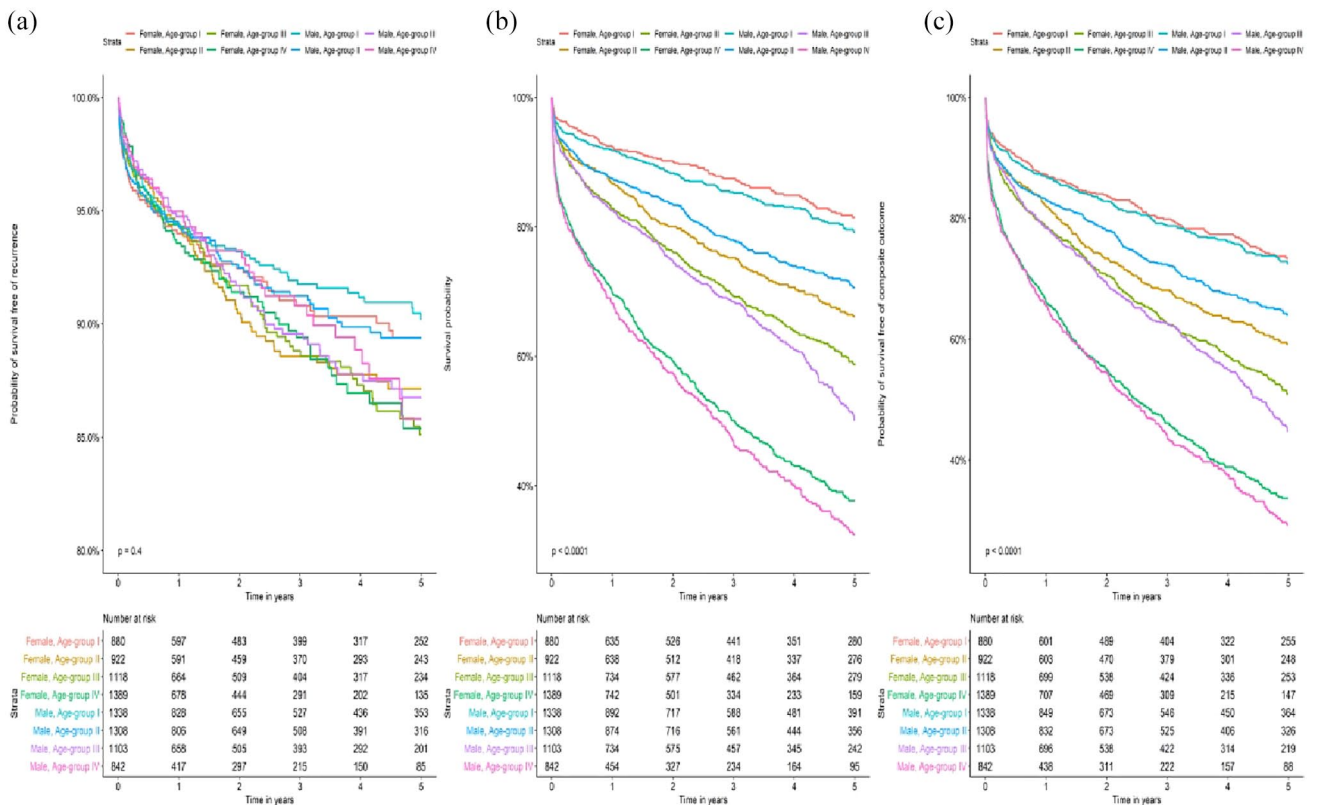


Figure 2. Kaplan–Meier survival curves stratified by sex and age group: (A) 5-year ischemic stroke recurrence, (B) 5-year all-cause mortality, (C) 5-year composite outcome of recurrence or mortality.

mortality by 5 years. There was a 63.3% survival in women (95% CI: 61.7–65.0%), compared with a 65.7% survival in men (95% CI: 64.1–67%.4,

$p = 0.011$) [Figure 1(B)]. KM curves stratified by age group demonstrated no sex difference in terms of vulnerability to mortality [Figure 2(B)].

Table 4. Cox proportional hazard ratio model for all-cause mortality.

	Unadjusted analysis		Model 1 _b		Model 2	
	Unadjusted HR	<i>p</i>	Adjusted HR	<i>p</i>	Adjusted HR	<i>p</i>
Overall Male (female as reference)	0.890 (0.823–0.961)	0.003	1.05 (0.971–1.144)	0.209	1.06 (0.983–1.153)	0.125
Subgroup analysis:						
Age group I Male (female as reference)	1.079 (0.855–1.363)	1.000	1.14 (0.89–1.448)	1.000	1.09 (0.859–1.377)	1.000
Age group II Male (female as reference)	0.830 (0.697–0.99)	0.152	0.862 (0.718–1.035)	0.444	0.825 (0.69–0.985)	0.136
Age group III[#] Male (female as reference)	1.166 (1.008–1.349)	0.156	1.10 (0.946–1.277)	0.876	1.13 (0.972–1.306)	0.448
Age group IV Male (female as reference)	1.149 (1.016–1.301)	0.108	1.15 (1.01–1.306)	0.140	1.14 (1.005–1.29)	0.168
[#] Sex was deemed to be violating the proportional hazards assumption for all-cause mortality and composite outcome in age group III. HR, hazard ratio						

Table 5. Cox proportional hazard ratio model for composite outcome.

	Unadjusted analysis		Model 1 _c		Model 2	
	Unadjusted HR	<i>p</i>	Adjusted HR	<i>p</i>	Adjusted HR	<i>p</i>
Overall Male (female as reference)	0.897 (0.836–0.964)	0.003	1.003 (0.929–1.083)	0.939	1.011 (0.939–1.088)	0.779
Subgroup analysis:						
Age group I Male (female as reference)	1.050 (0.866–1.273)	1.000	1.100 (0.899–1.348)	1.000	1.049 (0.862–1.277)	1.000
Age group II Male (female as reference)	0.866 (0.74–1.013)	0.288	0.871 (0.74–1.026)	0.396	0.848 (0.723–0.994)	0.168
Age group III Male (female as reference)	1.105 (0.966–1.264)	0.588	1.049 (0.913–1.205)	1.000	1.065 (0.929–1.22)	1.000
Age group IV Male (female as reference)	1.064 (0.944–1.2)	1.000	1.061 (0.936–1.202)	1.000	1.048 (0.929–1.183)	1.000
HR, hazard ratio						

Composite outcome. There were 3026 (34.0%) composite outcomes of recurrence or death within the 5 year study period. Overall unadjusted HR for the composite outcome suggested that women were more vulnerable to the composite outcome than men (HR for men, with women as reference = 0.897, 95% CI 0.836–0.964, $p=0.003$). However, both Model 1_c (adjusted for age, AF/atrial flutter, HTN, MI, DM, dyslipidemia, HF, chronic lung diseases,

rheumatic disease, CKD, neoplasm, PVD, past ischemic stroke, past hemorrhagic stroke, and depression) and Model 2 did not yield any significant sex differences (Table 5). Sex stratified KM curves were significant for the composite outcome [Figure 1(C)], suggesting that women were more vulnerable to developing recurrence or death by 5 years. Women had a lower probability of survival free from composite outcome with a 52.2%

survival (95% CI 50.3–54.1) *versus* men with a 54.9% survival (95% CI 53.1–56.8, $p=0.003$). Further stratification by age groups demonstrated no sex difference [Figure 2(C)].

Discussion

Our study results indicate that women may have higher crude mortality after stroke; however, sex is not an independent risk factor for all-cause mortality in the rural area of Pennsylvania. Ischemic stroke recurrence and the composite outcome of stroke recurrence or death also did not demonstrate evidence of a sex disparity. There are a number of associated factors that occurred more frequently in women in this population, including older age at index stroke, AF, atrial flutter, HF, rheumatic disease, CKD, depression, anxiety, family history of heart disease, and family history of stroke. On the other hand, MI, neoplasm, and PVD are more common in men. Interestingly some commonly known risk factors for stroke, including HTN, DM, dyslipidemia, hypercoagulability, and past personal history of hemorrhagic or ischemic stroke,^{16,23,24} were not significantly different between men and women in this cohort. When examining associated health factors stratified by outcome, there were more women in the cohorts who died and who experienced the composite outcome compared with those who survived and did not experience the composite outcome, respectively. However, there was no sex difference in the cohort who experienced ischemic stroke recurrence compared with those who did not. The crude mortality difference we observed may be attributed to age difference,^{4,5,18} whereby women live longer than men overall and are older at their index stroke, or it may be related to one of the other variables we controlled for in the analysis.

When analyzing populations that include older adults there is a significant risk of death from any cause. In our population, where the median age at index event is 71.6 years, the risk of having a recurrent stroke is constantly competing with the risk of death from another cause. While Cox proportional hazard regression remains a sound methodology for assessing all-cause mortality, the use of this test for stroke recurrence runs the risk of overestimating the probability of a single outcome.²⁷ In an effort to overcome this limitation we used a Fine–Gray competing risk model^{22,28} for assessing stroke recurrence, which demonstrated no sex disparity in this regard.

Thakkar *et al.* and Zhu *et al.* provide compelling pre-clinical research on the protective effects of estrogen and progesterone and suggest hormone level changes after menopause could lead to poorer stroke outcomes in women with ischemic stroke.^{29,30} Change in lipid profiles, increased body weight and abdominal girth, and an increase in cardiovascular risk factors^{31,32} are associated with menopause and could lead to an increase in the risk of atherosclerosis,³³ which may develop slowly during the decade following the menopause. Age category subgroup analysis is an important methodology to employ when researching sex disparity in stroke because the perimenopausal age group undergoes a unique loss of protective estrogen, likely putting them at higher risk of stroke.^{31,34} A number of studies categorized their populations based on 10-year age groups.^{5,19} The latter approach could introduce bias by overestimating sex disparity in the oldest age group, where there may be more female strokes than male strokes, given that women have both a longer life span and an older age at index stroke.⁸ To overcome this potential bias we performed a data driven subgroup analysis using age quartiles. However, the lack of difference overall and within age subgroups in our study calls into question the role that hormonal changes play in terms of stroke risk. One might logically hypothesize that women would undergo a stark increase in stroke incidence after losing protective levels of estrogen. However, in our population sex is not an independent predictor of stroke recurrence or mortality probability, even in the perimenopausal age groups.

Much of the current literature focuses on worse functional outcomes in women and post-stroke disability.^{5,6,35} Our study on the other hand focuses on mortality and recurrence of ischemic stroke. There is significant variation in the literature on this subject^{3,4,6,16} and sex-specific stroke recurrence data in rural American populations is sparse. Dhamoon and colleagues found unadjusted mortality was higher in women; however, after adjustment for age, income, vascular risk factors, and Charleston Comorbidities Index scores women had a lower mortality risk than men.¹⁶ Similarly, our unadjusted HR showed women were more likely to have all-cause mortality, but after adjustment by age and risk factors the finding was not significant. Our results support the findings of Dhamoon *et al.*, which suggest that observed mortality differences are not independently due to sex. Dhamoon and colleagues also examined stroke

readmission as a proxy for stroke recurrence and found no difference between sexes.¹⁶ Similarly, we found no overall difference in recurrence with death as a competing risk. However, Dhmoon *et al.* looked specifically at women with diabetes, and while we assessed the prevalence of diabetes as a known risk factor for stroke, not all patients studied in our cohort had diabetes, making our findings difficult to directly compare.¹⁶

A review of the literature undertaken by Cordonnier *et al.* highlighted that AF was more common in women and that sex is a risk factor for poor stroke outcomes, possibly mediated by AF.³ Pancholy *et al.* and Emdin *et al.* echoed these findings^{36,37} and it has been hypothesized that women may be more severely affected by AF than men.¹¹ Our findings confirmed that AF was more prevalent in women; however, our lack of robust sex differences suggests that while AF occurs more frequently in women, being female does not predict mortality.

The difference in diagnostic and therapeutic modalities has been a hypothesized cause of sex disparity in stroke outcomes and data from the Michigan Stroke Registry demonstrated that women under 75 years old had a lower chance of receiving IVT,¹⁷ which could be responsible for worse outcomes; nonetheless our data and data from Kapral and colleagues¹⁸ alike did not show any sex differences in treatment modalities (MT or IVT).

This study had several strengths and limitations. The electronic health record (EHR) data used in model development was longitudinally rich and we were able to capture a large number of variables. However, that also leads to some of the limitations of the study. Although we had a large sample size, our population may not be representative of the rural population in the entire US. There is an inherent noise associated with the use of EHR; there was a lack of information regarding stroke severity captured for the majority of the patients. We also did not have information about stroke subtypes. Our phenotype definition to extract patients with stroke using information from EHR was strict, leading to 100% specificity on a randomly selected sample, which also means that our criteria likely missed some of the cases (for instance, if the patient had some contraindication for MRI). Nevertheless, MRI is part of our stroke order-set and is performed for every stroke patient unless the patient refuses or has a contraindication (e.g. non-compatible pacemaker, etc.). We also did not

include transient ischemic attacks since it is associated with significant misdiagnosis.³⁸ The database also did not capture diagnostic methods or information on post-stroke disabilities, which limited the scope of our findings.

These findings call into question the previously identified role that sex plays in predicting stroke outcomes. That being said, our population was rural, predominantly White, and had many comorbidities and is not generalizable. Further efforts to understand why a sex difference is present in some cohorts but was not present in this population are needed before definitive therapeutic and clinical implications can be deduced. Sex differences might exist with regard to disability after stroke in this population and this is an important area of future research. It will also become increasingly important to reach a consensus on what the most accurate and acceptable manner of analysis is in this field of research. Many different methods of analysis have been employed, making it difficult to make population comparisons and assess the validity of individual findings. Ensuring the capacity for coherent comparison and the generation of robust meta-analysis is a clear next step in this field of work.

Conclusion

This retrospective study aimed to identify any possible sex disparity in terms of ischemic stroke recurrence and all-cause mortality for up to 5 years after the index stroke in a population comprising mainly White Americans living in rural Pennsylvania. Females had a higher crude all-cause mortality; however, no difference existed after adjustment for age and risk factors. No sex difference was observed in terms of ischemic stroke recurrence or composite outcome (recurrence or death). Sex is therefore not an independent risk factor for poor outcomes in this population.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

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