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Sex Differences in Outcomes Over the First Year After Ischemic Stroke

A Population-Based Longitudinal Study

Chen Chen,[1,*] Madeline Kwicklis,[1] Lewis B. Morgenstern,[1,2] and Lynda D. Lisabeth[1,2,*]

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Correspondence
Dr. Chen
chensph@umich.edu
or Dr. Lisabeth
llisabet@umich.edu

Abstract

Background and Objectives

Given the growing number of US stroke survivors, especially female survivors, understanding contemporary trajectories of stroke outcomes by sex is crucial. Yet, such data are rare. We estimated sex-specific changes in poststroke functional, neurologic, quality of life, and cognitive outcomes.

Methods

This cohort study included first-ever ischemic strokes (ISs) ascertained from the Brain Attack Surveillance in Corpus Christi Project (south Texas, 2014–2019). Data were from medical records (e.g., age, sex) and interviews (baseline, 3, 6, and 12 months after stroke), including functional (activities of daily living/instrumental activities of daily living score [ADL/IADL]), neurologic (NIH Stroke Scale), quality of life (abbreviated Stroke-specific Quality of Life scale), and cognitive (Modified Mini-Mental State Examination [3MSE]) outcomes. Multivariable adjusted linear mixed effects models including interactions between sex and time were used to estimate sex differences at each time point and sex-specific changes in outcomes.

Results

Among the 1,046 IS (mean age 66, 47.6% female survivors), female survivors had higher adjusted mean ADL/IADL scores than male survivors at 3, 6, and 12 months, despite a decrease in ADL/IADL scores from 3 to 12 months only among female survivors (adjusted mean difference in ADL/IADL scores −0.08, 95% CI −0.14 to −0.03). While no significant sex differences were observed for other outcomes, both sexes experienced an improvement in neurologic outcome, and an improvement in cognition was only found among male survivors (adjusted mean difference in 3MSE scores 0.97, 95% CI 0.09–1.85). Improvements were primarily driven by recoveries from 3 to 6 months.

Discussion

Female survivors had worse functional outcome but not other outcomes than male survivors up to 12 months after stroke. Although outcomes generally continued improving after 3 months poststroke for both sexes, the recovery pattern differed by sex. These results suggest that early and continued assessments of functional outcome after stroke may be needed, particularly for female survivors to reduce the sex differences, and that future interventions designed to improve outcomes in the chronic phase of stroke should consider the sex-specific recovery patterns. The generalizability may be limited by our single community study population, and results should be replicated in other populations.

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Supplementary Material

*These authors contributed equally to this work as co-corresponding authors.

[1]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor; and [2]Stroke Program, University of Michigan Medical School, Ann Arbor.

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Glossary

3MSE = Modified Mini-Mental State Examination; **ADL** = activities of daily living; **BASIC** = Brain Attack Surveillance in Corpus Christi; **IADL** = instrumental activities of daily living; **IP** = inverse probability; **IS** = ischemic stroke; **IV-tPA** = IV tissue plasminogen activator; **MA** = Mexican American; **mRS** = modified Rankin scale; **NHW** = non-Hispanic White; **NIHSS** = NIH Stroke Scale; **SSQOL** = Stroke-specific Quality of Life scale.

Introduction

There are an estimated 7 million stroke survivors in the United States,[1] with around one-third of them living with physical, cognitive, and emotional disfunction, severely affecting on their quality of life.[2] With the aging of the US population, the number of stroke survivors is growing, with 60% projected to be female survivors by 2050.[3] Therefore, understanding sex differences in poststroke outcomes is crucial for assessing the need for sex-specific stroke management and postacute care.

Many studies have examined sex differences in short-term patient-reported outcomes after stroke,[4-8] including functional, neurologic, quality of life, and cognitive outcomes. These outcomes were usually assessed at 1 time point after stroke, predominantly at 3 months poststroke. While evidence on sex differences in quality of life and cognition after stroke in the short term is mixed,[4-7] prior studies have consistently shown worse functional outcome among female stroke survivors.[4]

Existing research has also suggested that delayed stroke recovery is not uncommon past 3 months,[9,10] especially for severely affected patients who may require a longer time to improve. Female patients are known to have more severe strokes[3]; however, few longitudinal studies with multiple time points to assess outcomes after stroke have investigated sex differences in longer-term recovery. Contemporary data on longitudinal changes in sex differences in multiple stroke outcomes may provide insights for the necessity of sex-specific interventions for rehabilitation and recovery.

Using data on 4 patient-reported outcomes (physical function, neurologic function, quality of life, and cognition) assessed at 3, 6, and 12 months after first-ever ischemic stroke (IS) from a population-based study, we aimed to more comprehensively capture sex differences and sex-specific changes in stroke outcomes over time. We also aimed to examine whether sex differences in stroke recovery vary by age and initial stroke severity given prior evidence on sex differences in age at stroke onset and initial stroke severity and the differential recovery pattern by these factors.

Methods

Study Setting and Participants

Data for the current study came from the Brain Attack Surveillance in Corpus Christi (BASIC) Project, a population-based stroke study taking place in Nueces County, TX. Most of the eligible participants in BASIC is nonimmigrant Mexican American (MA) and non-Hispanic White (NHW) American.[11,12] Details of the BASIC Project have been described elsewhere.[11,12] Briefly, residents of the community aged 45 years or older who had a stroke are eligible for the BASIC Project. Using active and passive surveillance, BASIC captures all possible stroke cases in all 7 acute care hospitals in Nueces County. Fellowship-trained stroke neurologists validated all possible cases. Active surveillance captures stroke cases through daily screening of hospital admission logs and routine examination of medical wards and intensive care units. Passive surveillance identifies cases by searching hospital and emergency department discharge diagnoses codes based on International Classification of Diseases, Ninth and Tenth Revisions.

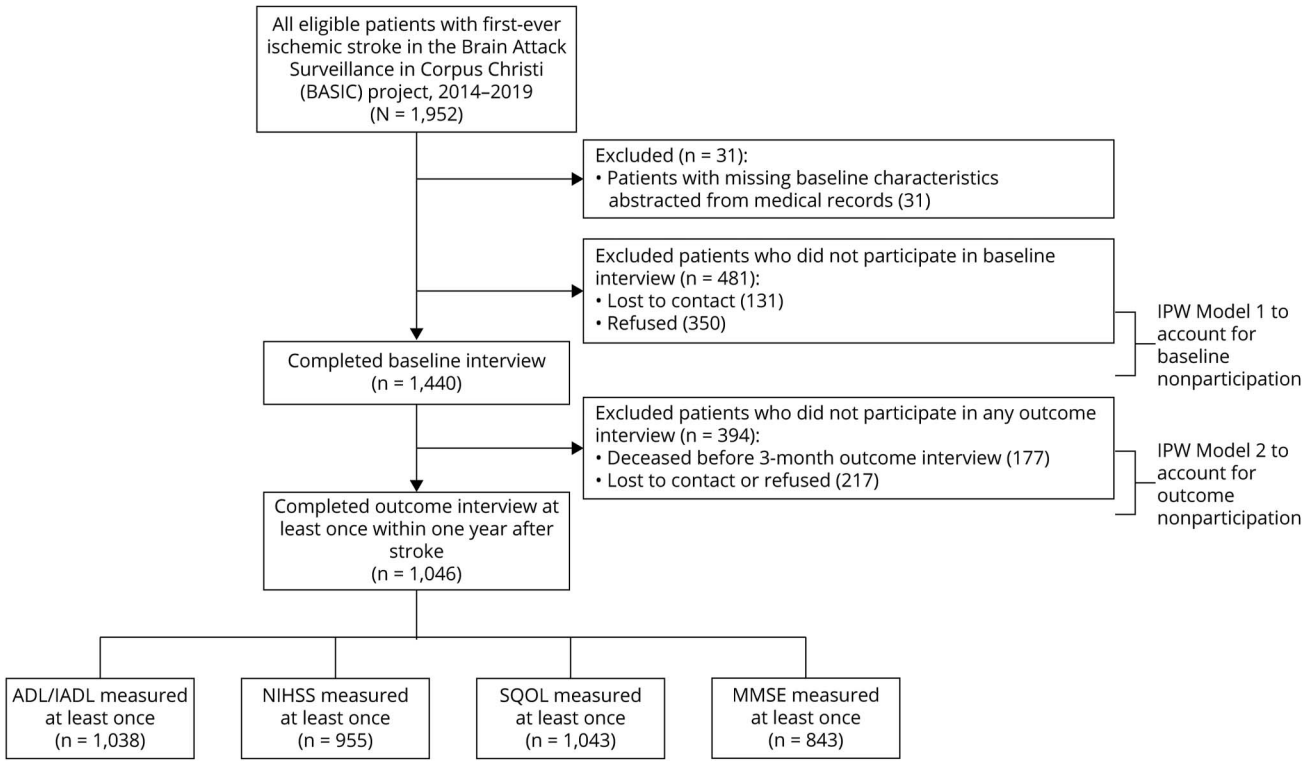
Patients with validated stroke are invited to participate in structured baseline interviews shortly after stroke onset (median of 7 days after stroke onset; interquartile range, 15 days). Proxy interviews are administered if patients are unable to communicate (female patients: 18.9%, male patients: 14.6%; $p = 0.06$). Most baseline interviews occur at hospitals. Those who participate in baseline interviews are contacted for outcome interviews at roughly 3, 6, and 12 months poststroke. Most of the outcome interviews occur at patients' homes. Both baseline and outcome interviews are performed in person whenever possible and in English or Spanish, depending on patient's preference. Telephone interviews are conducted, if necessary (<5% for both interviews).

The study population for the current research was first-ever IS patients ascertained between January 1, 2014, and December 31, 2019, in BASIC and who completed an outcome interview at least once during the 12 months of the follow-up period (Figure 1).

Outcome Measures

For the outcome interview at each time point after stroke, functional, neurologic, quality of life, and cognitive outcomes were assessed. Patient-reported or proxy-reported functional outcome was measured by difficulties with 7 activities of daily living (ADL) and 15 instrumental activities of daily living (IADL). Each activity is scored on a 4-point scale: (1) no difficulty, (2) some difficulty, (3) a lot of difficulty, and (4) can only do with help. ADLs and IADLs were averaged, and the resulting score ranged from 1 to 4 (higher scores worse).[12] Neurologic outcome was assessed by study coordinators using the NIH Stroke Scale (NIHSS, 0–42, higher scores worse).[12] Patient-reported or proxy-reported quality of life was

Figure 1 Study Flow Diagram, BASIC, 2014–2019



ADL = activities of daily living; BASIC = Brain Attack Surveillance in Corpus Christi; IADL = Instrumental Activities of Daily Living; IPW = inverse probability weighting; MMSE = Mini-Mental State Examination; SSQOL = Stroke-specific Quality of Life.

measured by the validated and abbreviated Stroke-specific Quality of Life scale (SSQOL, 1–5, higher scores better).[13] Cognitive outcome was assessed by the modified Mini-Mental State Examination (3MSE, 0–100, higher scores better), which was limited to patient interviews only. Use of proxies to assess patients' functional outcome and quality of life was stable over the follow-up period and did not differ by sex at any time point (3 months: female patients 16.0%, male patients 13.1%; $p = 0.21$; 6 months: female patients 15.2%, male patients 12.4%; $p = 0.26$; 12 months: female patients 15.2%, male patients 11.4%; $p = 0.14$).

Sex and Other Potential Confounders

Sex and other potential confounders were ascertained at baseline from interviews and medical records. Information from baseline interviews included self-reported race-ethnicity (MA, NHW American, and others including Black and Asian American), prestroke functional disability measured by the modified Rankin scale (mRS; no disability, slight or moderate disability, severe disability), prestroke cognitive function measured by the Informant Questionnaire of Cognitive Decline in the Elderly (normal cognition, cognitive impairment but no dementia, dementia), prestroke depression status measured by self-reported physician diagnosis and use of antidepressant medications (no depression, history of depression, current use of antidepressants), educational attainment (below high school, high school degree or equivalent, above high school), marital status (unmarried, married), and insurance status (uninsured, insured). Information on prestroke depression was collected only if the baseline interview was completed by the patient (i.e., not completed for proxy interviews).

Information from medical records included age, sex, initial stroke severity assessed by the NIHSS, thrombolytic treatment (IV tissue plasminogen activator [IV-tPA]), body mass index (categorized into normal weight, overweight, and obesity), and comorbidities (a composite score adding up the numbers of diseases a patient has among hypertension, diabetes, heart disease/myocardial infarction, atrial fibrillation, high cholesterol, cancer, Parkinson disease, Alzheimer disease/dementia, chronic obstructive pulmonary disorder, congestive heart failure, epilepsy, and end-stage renal disease).

Recurrent stroke status within 12 months of follow-up after first stroke was determined through the active and passive stroke surveillance methods detailed above. Mortality status within 12 months of follow-up after first stroke was ascertained from routine active surveillance of all in-hospital deaths and by matching BASIC participants to the Texas Department of State Health Services death certificate database.[14]

The percentage of missing covariate data was the highest for prestroke cognitive function (20%), followed by prestroke

depression status (16.3%) and less than 2.3% for other covariates (Table 1). Additional details for data collection and measurement of above confounders are in eMethods.

Statistical Analysis

Baseline characteristics of study participants overall and by sex were calculated and sex differences examined using $\chi 2$ tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.

We used linear mixed effects models with unstructured working covariance to account for within individual correlations for each outcome measurement. Note that for the neurologic outcome, NIHSS score was log-transformed given its non-normal distribution. To estimate sex differences and sex-specific changes in outcomes, we included time (a continuous variable denoting months after stroke when outcome interviews were completed), sex, and the interaction between time and sex as fixed effects in the model. To capture the potential nonlinear recovery of outcomes, we assessed the functional form of time using likelihood ratio tests (i.e., comparing models with quadratic functional forms of time with models with linear forms of time). Time was modeled in a quadratic form for functional, neurologic, and quality-of-life outcomes and in a linear form for cognitive outcome. Random effects included random intercepts and linear terms for random slopes. We calculated unadjusted sex differences in the mean of the outcomes at each outcome interview time point.

We adjusted for age at stroke onset, race-ethnicity, educational attainment, marital status, insurance status, log-transformed initial NIHSS score, comorbidity score, prestroke disability, prestroke depression, prestroke cognition, and recurrence status. To minimize residual confounding, the potential nonlinear relationships between continuous variables (age, initial NIHSS score, comorbidity score) and the outcomes were checked using likelihood ratio tests. Age was included in the models in its quadratic form for all 4 outcomes, and initial NIHSS score was included in its quadratic form for functional and quality of life outcomes. Using the fitted models, we calculated conditional means of each outcome at each time point for both sexes, with covariates set at average age (66.4 years), MA race-ethnicity, below high school education, uninsured, married, average log-transformed initial NIHSS (1.32, approximately 2.7 on original scale), no IV-tPA treatment, average number of comorbidities, obese, severe prestroke physical disability, prestroke dementia, prestroke depression, and no recurrent stroke. We also computed adjusted sex differences at each time point and the sex-specific changes in the mean of outcomes after stroke.

Because baseline and outcome participation may be influenced by differential survival by sex and factors associated with outcomes,[15] potential selection bias of the sex differences in longitudinal recovery may exist in our analytic sample. Therefore, we applied inverse probability (IP) weighting techniques to reflect the original patient population that was eligible for baseline interview.[16] The IP weights were calculated as the reciprocal of the product of the probabilities of completing baseline interviews and completing any outcome interview generated from logistic prediction models. Detailed methodology for creating the weights are documented in eMethods.

Assuming missing at random, we used multiple imputation by chained equations with fully conditional specification to fill in missing values of baseline characteristics and outcomes.[17,18] Variables in the imputation model were sex, age in quadratic form, race-ethnicity, educational attainment, marital status, insurance status, routine physician access ascertained from baseline interview, log-transformed initial NIHSS score in quadratic form, hypertension, high cholesterol, diabetes mellitus, atrial fibrillation, coronary artery disease, comorbidity score, current smoking status, alcohol consumption, body mass index, prestroke cognition, prestroke disability, prestroke depression, recurrence status, mortality status, IP weights, and longitudinally measured outcomes. To preserve the correlations between longitudinally measured outcomes, we used the Just-Another-Variable approach to impute the outcomes.[17] We created 30 imputed datasets, conducted the linear mixed models in each of the 30 imputed datasets, and combined the results using Rubin's rule.[18] More details of the multiple imputations are in the eMethods.

Stratified models by age (younger than 65 years and age 65 years or older) and initial stroke severity (initial NIHSS ≤5 and initial NIHSS >5) were also conducted to examine subgroup-specific sex differences and sex-specific recovery in stroke outcomes.

For sensitivity analyses that were conducted to assess the robustness of results, final models were run for the following conditions: (1) with ADL and IADL subscales as separate outcomes; (2) among those whose outcome interviews were completed by patients only; (3) without applying IP weighting; and (4) in the dataset where both covariates and outcomes were not imputed.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC), and all p values were 2-sided tests.

Standard Protocol Approvals, Registrations, and Patient Consents

BASIC was approved by the Institutional Review Boards at the University of Michigan and the 2 local hospital systems in Corpus Christi. All participants provided their written informed consent.

Data Availability

Given the restricted nature of the data, deidentified data will be available from the corresponding author upon reasonable request.

Table 1 Baseline Characteristics of the Study Population Overall and by Sex From the BASIC, 2014–2019

Characteristics[a]	All (N = 1,046)	Males (N = 548)	Females (N = 498)	*p* Value
Age, y	66.4 (11.8)	65.0 (10.9)	67.9 (12.7)	<0.001
Race-ethnicity				0.70
NHW American	358 (34.2)	194 (35.4)	164 (32.9)	
MA	604 (57.7)	311 (56.8)	293 (58.8)	
Others	84 (8.0)	43 (7.8)	41 (8.2)	
Education[b]				0.02
Above high school	369 (35.5)	203 (37.2)	166 (33.6)	
High school or equivalent	375 (36.1)	207 (38.0)	168 (34.0)	
Below high school	295 (28.4)	135 (24.8)	160 (32.4)	
Marital status				<0.001
Unmarried	546 (52.2)	230 (42.0)	316 (63.4)	
Married or living with someone	500 (47.8)	318 (58.0)	182 (36.6)	
Insured[b]	890 (85.2)	455 (83.2)	435 (87.3)	0.01
Routine physician access[b]	888 (85.1)	431 (78.9)	457 (92.0)	<0.001
Initial stroke severity	4.5 (5.5)	4.2 (5.7)	4.8 (5.3)	0.0004
IV-tPA treatment	167 (16.0)	85 (15.5)	82 (16.5)	0.67
Prestroke depression status[b]				<0.001
No history of depression	552 (63.0)	336 (71.8)	216 (52.9)	
History of depression	157 (17.9)	64 (13.7)	93 (22.8)	
On medication for depression at stroke onset	167 (19.1)	68 (14.5)	99 (24.3)	
Prestroke disability[b]				<0.001
No symptoms/disability	487 (47.7)	289 (53.9)	198 (40.7)	
Slight/moderate disability	444 (43.4)	217 (40.5)	227 (46.7)	
Moderately severe/severe disability	91 (8.9)	30 (5.6)	61 (12.6)	
Prestroke cognitive function[b]				0.005
Normal function	243 (29.0)	116 (26.1)	127 (32.4)	
Cognitive impairment no dementia	484 (57.8)	280 (62.9)	204 (52.0)	
Dementia	110 (13.1)	49 (11.0)	61 (15.6)	
Recurrence within 1 y after first stroke	56 (5.4)	37 (6.8)	19 (3.8)	0.03
Death within 1 y after stroke	61 (5.8)	37 (6.8)	24 (4.8)	0.18
Obesity status				0.005
Normal	221 (21.2)	110 (20.1)	111 (22.4)	
Overweight	363 (34.8)	220 (40.2)	143 (28.8)	
Obesity	459 (44.0)	217 (39.7)	242 (48.8)	
No. of comorbidity	3.8 (1.8)	3.8 (1.7)	3.8 (1.8)	0.4028

Abbreviations: BASIC = Brain Attack Surveillance in Corpus Christi; IV-tPA = IV tissue plasminogen activator; MA = Mexican American; NHW = non-Hispanic White.

[a] For continuous variables (age, stroke severity measured by the NIH Stroke Scale, number of comorbidities), mean and standard deviation were presented. For the remaining categorical variable, numbers (percentages) were used unless stated otherwise. Prestroke disability and cognitive function were measured by modified Rankin scale and the Informant Questionnaire on Cognitive Decline in the Elderly, respectively.

[b] Variables with missing data. The numbers of missing values are 7 (0.7%) for education, 1 (0.09%) for insurance status, 3 (0.3%) for routine physician access, 170 (16.3%) for prestroke depression status, 24 (2.3%) for prestroke disability status, 209 (20.0%) for prestroke cognitive function, and 3 (0.3%) for obesity status.

Results

Baseline Characteristics of Participants

Figure 1 shows that among 1,952 patients with first-ever IS identified between 2014 and 2019, a total of 1,440 (73.8%) completed the baseline interview. After excluding 394 patients who did not participate in any outcome interview within 12 months after stroke, a total of 1,046 (72.6%) participants who completed at least 1 follow-up interview remained in our analytical sample. Percentages of missing outcomes by follow-up time were presented in eTable 1.

Table 1 presents characteristics of patients overall and by sex in the final analytic sample before imputation (mean age 66.4 ± 11.8 years, 47.6% female patients, 57.7% MA). Compared with male patients, female patients were more likely to be older, have below high school education, be unmarried, have health insurance, have routine physician access, have a more severe stroke, have prestroke depression, moderately severe to severe prestroke disability, dementia, and be obese. Characteristics of patients by baseline interview participation status among eligible participants and by outcome interview participation status among those who participated in baseline interviews are shown in eTables 2 and 3. There were no sex differences in baseline interview participation ($p = 0.52$) and in any outcome interview participation ($p = 0.33$). Those who participated in baseline interview and who did not differed in characteristics including age, race-ethnicity, and comorbidities (eTable 2). Compared with those who did not participated in any outcome interview, those who participated in any outcome interview had similar characteristics including age, race-ethnicity, marital status, initial stroke severity, prestroke disability, and obesity (eTable 3).

Sex Differences in Outcomes Within the Year After Stroke

Table 2 shows the unadjusted mean scores for all 4 outcomes at each outcome interview time point by sex. Female patients had 0.35 (95% CI 0.24–0.47) higher mean ADL/IADL score, 0.29 (95% CI 0.01–0.57) higher mean NIHSS score, and 0.27 (95% CI −0.40 to −0.14) lower mean SSQOL score than male patients at 3 months after stroke (Table 2). These statistically significant sex differences persisted to 6 months and 12 months after stroke for ADL/IADL and SSQOL, but not for NIHSS. For 3MSE, although female patients had lower mean scores than male patients at all 3 time points, the sex differences were not statistically significant.

After adjusting for potential confounders, although the sex differences were attenuated for all outcomes, they were still significant at all 3 time points for ADL/IADL but not for the other outcomes at any time point (Figure 2). Female patients had 0.13 (95% CI 0.04–0.23), 0.10 (95% CI 0.00–0.19), and 0.09 (95% CI −0.02 to 0.19) higher adjusted mean ADL/IADL score than male patients at 3, 6, and 12 months after stroke, respectively, which translated into Cohen's standardized effect sizes of 0.14, 0.11, and 0.10 and were considered as small effect sizes. However, the adjusted means of ADL/IADL for both sexes were between 2 and 3 at all 3 time points (Figure 2), suggesting that patients experienced some (value of 2 on ADL/IADL score) to a lot (value of 3 on the ADL/IADL score) of difficulty in performing ADL/IADL tasks. Sex differences in 3MSE reversed with female patients having higher scores than male patients at all 3 time points.

The adjusted sex differences for all outcomes at each time point did not differ by age or initial stroke severity (eTable 4), except that significant sex differences in ADL/IADL were observed at all 3 time points among those with less severe stroke (initial NIHSS ≤5) but not among those with moderately severe or severe stroke (initial NIHSS >5).

Sex-Specific Changes in Outcomes Within the Year After Stroke

Figure 2 and Table 3 present the changes in the adjusted mean scores for all outcomes between the 3 time points by sex. In general, all outcomes continued improving after 3 months poststroke for both sexes. For ADL/IADL, adjusted mean scores for female patients decreased from 3.06 (95% CI 2.79–3.33) at 3 months to 2.98 (95% CI 2.71–3.25) at 12 months, driven by the decrease from 3 to 6 months (−0.12, 95% CI −0.16 to −0.08). Although no significant change was found for male patients from 3 to 12 months, male patients also had a 0.08 (95% CI −0.12 to −0.04) decrease in the mean score from 3 to 6 months. For NIHSS, adjusted mean scores decreased for both sexes from 3 to 12 months, with female patients experiencing a larger decrease (for female: −0.82, 95% CI −0.97 to −0.67; for males −0.22, 95% CI −0.49 to 0.02). These decreases were driven by the significant changes from 3 to 6 months. While the adjusted mean score did not change from 6 to 12 months for female patients, it increased 0.39 (95% CI 0.06–0.72) for male patients. For SSQOL, no significant changes were found for both sexes from 3 to 12 months, although female patients had a slight increase in the adjusted mean score from 2.20 (95% CI 1.88–2.53) at 3 months to 2.29 (95% CI 1.97–2.62) at 6 months. For 3MSE, while no significant change in the adjusted mean scores was found for female patients, male patients had a 0.32 (95% CI 0.03–0.62) increase in the score from 3 to 6 months and 0.65 (95% CI 0.06–1.24) increase from 6 to 12 months.

These sex-specific changes in each outcome did not differ by age or initial stroke severity (eTables 5 and 6), except for functional and cognitive outcomes. There was a 0.09 (95% CI 0.03–0.16) increase in the mean ADL/IADL score among females aged 65 or older from 6 to 12 months (eTable 5). Among those with less severe stroke at baseline, an increase in adjusted mean ADL/IADL scores among both sexes was also observed (eTable 6). For cognitive outcome, sex-specific changes over time were not statistically significant in both age groups, potentially because of the small sample sizes (eTable 5). Although increases in adjusted mean scores of 3MSE were observed during 3–12 months of follow-up among male patients with less severe stroke, no statistically significant

Table 2 Unadjusted Means of and Sex Differences in Outcomes by Time After Stroke in BASIC, 2014–2019

	N	Female patients Mean of outcome (95% CI)	Male patients Mean of outcome (95% CI)	Mean of sex differences (95% CI)	N	Female patients Mean of outcome (95% CI)	Male patients Mean of outcome (95% CI)	Mean of sex differences (95% CI)
	Functional outcome				Neurologic outcome			
3 mo	932	2.39 (2.31–2.48)	2.04 (1.96–2.12)	0.35 (0.24 to 0.47)	857	1.96 (1.78–2.17)	1.67 (1.51–1.84)	0.29 (0.01 to 0.57)
6 mo	793	2.28 (2.19–2.36)	1.96 (1.88–2.04)	0.32 (0.20 to 0.44)	711	1.45 (1.26–1.64)	1.34 (1.18–1.51)	0.11 (−0.16 to 0.37)
12 mo	732	2.31 (2.23–2.40)	2.00 (1.91–2.09)	0.31 (0.19 to 0.43)	634	1.49 (1.26–1.74)	1.55 (1.31–1.82)	−0.06 (−0.40 to 0.27)
	Quality of life				Cognitive outcome			
3 mo	947	3.22 (3.13–3.32)	3.50 (3.41–3.59)	−0.27 (−0.40 to −0.14)	755	85.12 (83.95–86.29)	86.42 (85.31–87.53)	−1.30 (−2.90 to 0.31)
6 mo	797	3.31 (3.21–3.41)	3.55 (3.45–3.64)	−0.24 (−0.37 to −0.10)	628	85.32 (84.17–86.47)	86.74 (85.66–87.82)	−1.42 (−2.99 to 0.15)
12 mo	734	3.28 (3.17–3.39)	3.49 (3.37–3.61)	−0.22 (−0.37 to −0.08)	569	85.71 (84.37–87.05)	87.38 (86.15–88.61)	−1.67 (−3.52 to 0.18)

Abbreviation: BASIC = Brain Attack Surveillance in Corpus Christi.
Functional outcome was measured by activities of daily living/instrumental activities of daily living score (higher score, worse outcome); neurologic outcome was measured by NIH Stroke Scale (higher score, worse outcome); quality of life was measured by 12-domain Stroke-specific Quality of Life scale (higher score, better outcome); cognitive outcome was measured by Modified Mini-Mental State Examination (higher score, better outcome).

changes were found among female patients regardless of initial stroke severity (eTable 6).

Sensitivity Analyses

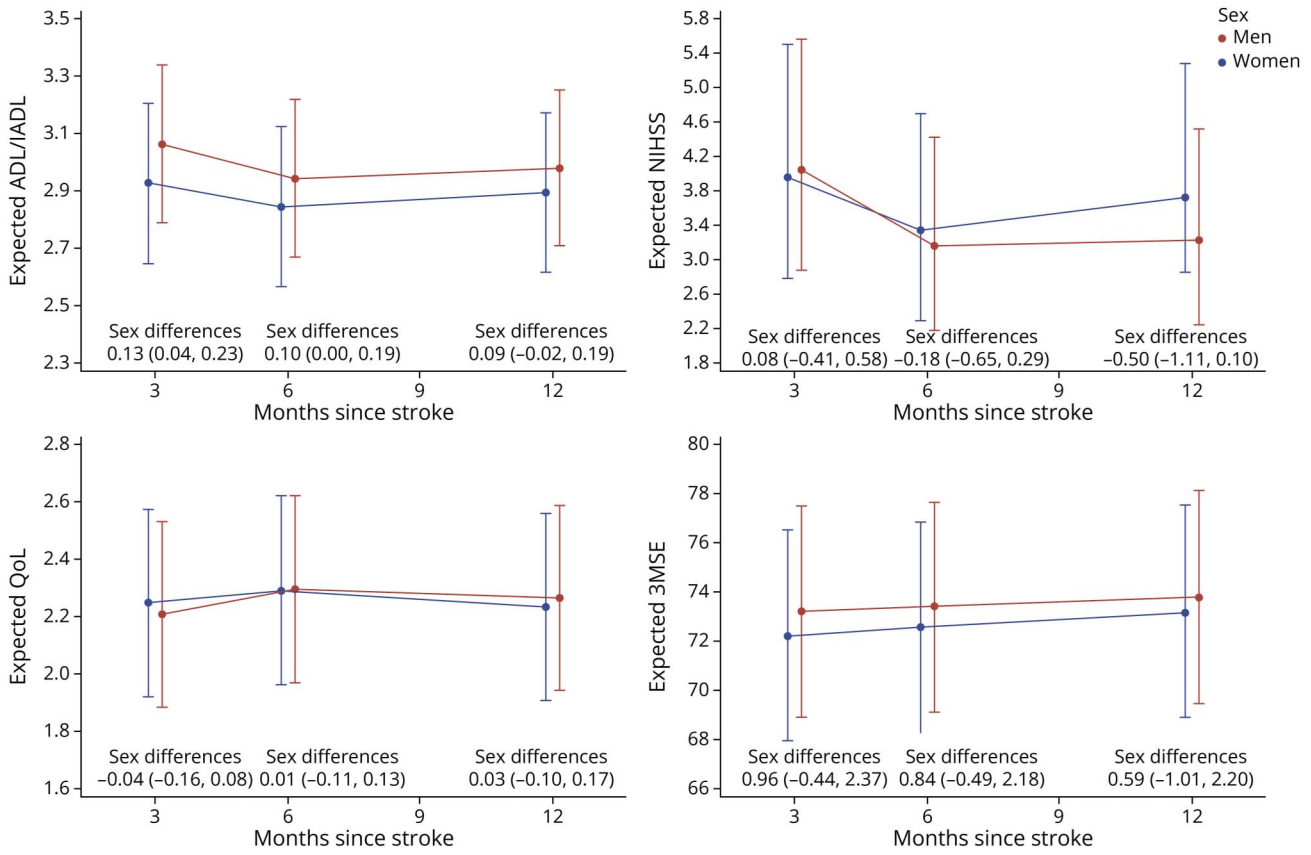
The sensitivity analysis considering ADL and IADL subscores as separate outcomes suggests that sex differences in functional outcome were mainly driven by sex differences in IADL (eTable 7). When restricting the analysis to the population whose interviews were completed by patients (eTables 8 and 9), while sex differences in outcomes were somewhat larger than those from the main analysis, sex-specific changes in outcomes were similar. Results were also similar to the main analysis when IP weighting was not applied (eTables 10 and 11) and when missing outcomes and covariates were not imputed (eTables 12 and 13), except that larger sex differences in cognitive outcome at all 3 time points were observed.

Discussion

In this population-based study with functional, neurologic, quality of life, and cognitive outcomes measured longitudinally at 3, 6, and 12 months after stroke, we found that female patients persistently had worse functional outcome than males despite that an overall recovery from 3 to 12 months was only observed among female patients. The adjusted sex differences were small on the absolute scale at all 3 time points, but both female patients and male patients continued experiencing some to a lot of difficulty in performing ADL/IADL tasks, suggesting remaining functional deficits and that early and continued assessments of functional outcome after stroke may be needed, particularly for female patients to reduce the sex differences. While no significant sex differences were observed for other outcomes, both sexes experienced an overall recovery in neurologic outcome and a recovery in cognition was only observed among males. These findings suggest that future interventions designed to improve outcomes in the chronic phase of stroke should consider the sex-specific recovery patterns to help both sexes achieve better and continuous improvements.

Our finding of a sex difference in functional outcome after multivariable adjustment at 3 months poststroke is consistent with prior research.[4] However, few studies have examined whether this sex difference persists over the year after stroke.[19-22] A study conducted in the Third China National Stroke Registry with 15,166 consecutively enrolled acute ischemic stroke patients from 2015 to 2018 reported significantly higher odds of unfavorable functional outcome (mRS >2) among female patients at 6 and 12 months after stroke only before but not after adjusting for potential confounders, including age, initial stroke severity, and prestroke function.[19] In our study, we found significantly worse functional outcome among female patients both before and after similar covariate adjustment. In addition, the sex differences were modified by initial stroke severity such that the differences were only observed among those with less severe stroke, consistent with prior findings in BASIC focusing on the outcome at 3 months.[23] Causes of the persistent sex differences are unclear, but our sensitivity analysis showed that this may be driven by the poorer IADL rather than ADL. Considering that we adjusted for demographics, prestroke physical, psychological, and cognitive function, and clinical factors which are known contributors to the sex difference, our finding suggests that future studies need to understand the role of modifiable poststroke factors, such as post-acute care and poststroke depression, which may be important intervention targets for improving functional outcome in the chronic phase of stroke in female patients.

Figure 2 Adjust Means of and Sex Differences in Outcomes by Time After Stroke in BASIC, 2014–2019



The adjusted means were calculated at the reference levels of average age, Mexican American persons, below high school education, uninsured, married, average log-transformed initial NIHSS, no IV-tPA treatment, average numbers of comorbidities, obese, prestroke modified Rankin scale ≥4, prestroke IQCODE ≥3.44, prestroke depression, alive during the 12-month follow-up, and no recurrent stroke. ADL = activities of daily living; BASIC = Brain Attack Surveillance in Corpus Christi; IADL = Instrumental Activities of Daily Living; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; IV-tPA = IV tissue plasminogen activator; NIHSS = NIH Stroke Scale.

We found significantly worse neurologic, quality of life, and cognitive outcomes among female patients at 3, 6, and 12 months only before but not after adjustment. Research in these outcomes focused on 6 months and 12 months is scarce and findings mixed for 3-month outcomes,[4-7,22,24,25] which could be due to differences in the study population, study design (registry-based vs population-based), measures used to assess stroke outcomes, and other methodologies including the analytical model and whether potential selection bias was addressed. In our study, we used IP weighting to account for participants who did not participate in any outcome interview because of death or loss to follow-up to minimize possible selection bias.

Our study contributes to the literature by reporting sex-specific changes in stroke outcomes over the year after stroke. A systematic review including 28 longitudinal studies evaluating changes in ADL from 3 months poststroke found a small but significant improvement in ADL from 3 to 12 months poststroke,[26] which mainly seemed to be driven by the improvement between 3 and 6 months.[26] However, no sex-specific changes were reported in these studies. Our results show that this pattern was only observed among female patients but not male patients for functional outcome and among both sexes for neurologic outcome. Furthermore, some studies have reported a deterioration in functional outcome between 3 and 12 months poststroke among stroke survivors aged 75 years or older who were female or moderately impaired,[27,28] but it is unclear when this decrease occurred. We found that functional outcome worsened among older female patients and among both sexes with less severe stroke from 6 to 12 months by a smaller magnitude than the improvement between 3 and 6 months. The reason for this deterioration was unclear and needs future investigation. It is possible that these individuals received shorter duration and/or less intense rehabilitations, impeding their continued recovery. Therefore, older female patients and patients with less severe strokes may need continued monitoring and interventions. For example, screening for and active treatment of musculoskeletal (e.g., osteoporosis or arthritis) disorders that are more prevalent in females may be particularly important for their functional recovery in the chronic phase of stroke.[4,29] In addition, given our observed sex differences in functional outcome were mainly driven by pulling a large object,

Table 3 Adjusted Sex-specific Changes in Means of Outcomes Within 1 Year After Stroke in BASIC, 2014–2019[a]

	Female patients Mean difference (95% CI)[b]	Male patients Mean difference (95% CI)[b]	Female patients Mean difference (95% CI)[b]	Male patients Mean difference (95% CI)[b]
	Functional outcome		Neurologic outcome	
12 vs 3 mo	−0.08 (−0.14 to −0.03)	−0.03 (−0.10 to 0.03)	−0.82 (−0.97 to −0.67)	−0.22 (−0.49 to 0.02)
6 vs 3 mo	−0.12 (−0.16 to −0.08)	−0.08 (−0.12 to −0.04)	−0.88 (−1.09 to −0.67)	−0.62 (−0.89 to −0.35)
12 vs 6 mo	0.04 (−0.01 to 0.09)	0.05 (−0.02 to 0.12)	0.07 (−0.29 to 0.43)	0.39 (0.06 to 0.72)
	Quality of life		Cognitive outcome	
12 vs 3 mo	0.06 (−0.02 to 0.13)	−0.02 (−0.11 to 0.07)	0.60 (−0.32 to 1.52)	0.97 (0.09 to 1.85)
6 vs 3 mo	0.09 (0.03 to 0.15)	0.04 (−0.02 to 0.10)	0.20 (−0.11 to 0.51)	0.32 (0.03 to 0.62)
12 vs 6 mo	−0.03 (−0.10 to 0.04)	−0.06 (−0.15 to 0.04)	0.40 (−0.21 to 1.01)	0.65 (0.06 to 1.24)

Abbreviations: BASIC = Brain Attack Surveillance in Corpus Christi; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; IV-tPA = IV tissue plasminogen activator; NIHSS = NIH Stroke Scale.
[a] Functional outcome was measured by activities of daily living/instrumental activities of daily living score (higher score, worse outcome); neurologic outcome was measured by NIHSS (higher score, worse outcome); quality of life was measured by abbreviated Stroke-specific Quality of Life scale (higher score, better outcome); cognitive outcome was measured by Modified Mini-Mental State Examination (higher score, better outcome).
[b] Adjusted for sex, race/ethnicity, education, insurance status, marital status, initial NIHSS, IV-tPA use, comorbidity index (including hypertension, diabetes etc), obesity, prestroke disability (measured by modified Rankin scale), and prestroke cognition (measured by IQCODE). The adjusted means were calculated at the reference levels of average age, Mexican American persons, below high school education, uninsured, married, average log-transformed initial NIHSS, no IV-tPA treatment, average numbers of comorbidities, obese, prestroke modified Rankin scale ≥4, prestroke IQCODE ≥3.44, prestroke depression, alive during the 12-month follow-up, and no recurrent stroke.

bending, carrying heavy weights, straightening up from bending, cooking, doing heavy housework, and shopping (data not shown), future interventions may consider designing sex-specific musculoskeletal strengthening activities, especially those improving upper limb functional recovery. Finally, female patients may be exposed to greater socioeconomic disadvantage and more vulnerable to loneliness and social isolation,[4,30,31] and therefore, particular attention may be needed to assess their social risk at discharge and connect them to community resources in a timely manner.

Longitudinal changes in quality of life among stroke survivors within 12 months of follow-up have been inconsistent across studies,[32-38] with some reporting an improvement,[32-34] others not finding a change,[35,36] and some others reporting a decline.[37,38] A few studies have reported an improvement in global cognitive function from 3 to 12 months among stroke survivors.[39-42] These studies have been limited by small sample sizes, only 2 follow-ups, selected samples of hospitalized patients, and a lack of investigation of sex-specific recoveries. Our population-based study overcame these limitations and found an improvement in quality of life among females from 3 to 6 months, along with the improvements in functional and neurologic outcomes during this period. However, we also found that cognitive outcome was stable among female patients over the several assessments. Male patients experienced a continuous improvement in cognitive function up to 12 months along with their improvement in functional and neurologic outcomes from 3 to 6 months, but their quality of life remained stable over several assessments. Our findings suggest the importance of improving poststroke cognitive outcome among female patients, in addition to improving their functional ability to complete activities of daily living. In addition, more attention is needed for maximizing quality of life among male patients after stroke.

Our study has several strengths. Our data collection on multiple outcomes at multiple time points after stroke allowed us systematically evaluate sex differences and sex-specific changes in multiple stroke outcomes over the first year after stroke. It has been suggested both physical and cognitive impairments after stroke should be routinely evaluated and reassessed in the clinical care of patients with stroke because of their independent prognostic implications and the dynamic nature of recovery.[43,44] We are also able to adjust for important confounders, including social factors, stroke treatment, initial stroke severity, and prestroke functional disability, depression, and cognition.

Several limitations exist. First, we do not have data on the use of rehabilitative services and therefore are unable to assess its impact on our results. In a pilot study of BASIC, 25% of the patients were discharged to inpatient rehabilitation facilities, 12.5% to skilled nursing facilities, and 5.5% to home health agencies.[45] Ongoing work in BASIC is examining the role of rehabilitation status in explaining ethnic and sex differences in poststroke outcomes. Second, our assumption of the outcome data missing at random may not hold, but previous studies have shown that sex differences in outcomes at 3 months poststroke were robust across a series of hypothesized associations between the missing value of the outcomes and the probability of missing.[6,23] Third, despite the important role of poststroke depression in outcome recoveries, we did not adjust for it because poststroke depression and other outcomes

were collected at the same time and reverse causation bias may arise with adjustment. In addition, poststroke depression status may not confound the sex differences in poststroke outcome trajectories as a prior study in BASIC found that sex differences in poststroke depression were fully explained by baseline sociodemographic, stroke, and prestroke characteristics.[5] Fourth, because our study population was mainly composed of nonimmigrant MA and NHW American from a single community in south Texas, the generalizability of our results may be limited when applied to other sexual, racial, ethnic, and immigrant minority populations. In addition, our cognitive outcome assessment was only conducted for patients, and therefore, we may not generalize our results to patients who require a proxy respondent.

Female patients had worse functional outcome than male patients up to 12 months after stroke, even after adjusting for sociodemographic factors, initial stroke severity, and prestroke functional disability status. Although no significant sex differences were found for other outcomes and all outcomes generally continued improving after 3 months poststroke for both sexes, the recovery pattern over the first year after stroke differed by sex. These results suggest that early and continued assessments of functional outcome after stroke is particularly needed for females to reduce the sex differences and that future interventions designed to improve outcomes in the chronic phase of stroke should consider the sex-specific recovery patterns.

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Author Contributions

C. Chen: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. M. Kwicklis: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. L.B. Morgenstern: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L.D. Lisabeth: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data.

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Disclosure

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