

Exploring sex differences for acute ischemic stroke clinical, imaging and thrombus characteristics in the INTERRSeCT study

Journal of Cerebral Blood Flow & Metabolism
2023, Vol. 43(10) 1803–1809
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DOI: 10.1177/0271678X231189908
journals.sagepub.com/home/jcbfm



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Abstract

Women, especially following menopause, are known to have worse outcomes following acute ischemic stroke. One primary postulated biological mechanism for worse outcomes in older women is a reduction in the vasculoprotective effects of estrogen. Using the INTERRseCT cohort, a multicentre international observational cohort studying recanalization in acute ischemic stroke, we explored the effects of sex, and modifying effects of age, on neuroradiological predictors of recanalization including robustness of leptomeningeal collaterals, thrombus burden and thrombus permeability. Ordinal regression analyses were used to examine the relationship between sex and each of the neuroradiological markers. Further, we explored both multiplicative and additive interactions between age and sex. All patients ($n = 575$) from INTERRseCT were included. Mean age was 70.2 years (SD: 13.1) and 48.5% were women. In the unadjusted model, female sex was associated with better collaterals (OR 1.37, 95% CIs: 1.01–1.85), however this relationship was not significant after adjusting for age and relevant comorbidities. There were no significant interactions between age and sex. In a large prospective international cohort, we found no association between sex and radiological predictors of recanalization including leptomeningeal collaterals, thrombus permeability and thrombus burden.

Keywords

Stroke, menopause, collaterals, thrombus, recanalization

Received 10 November 2022; Revised 21 June 2023; Accepted 24 June 2023

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Background

Multiple prospective studies have shown an association between sex and ischemic stroke severity, with females having worse outcomes than males.^{1–3} Stroke risk also increases markedly with age in women, doubling within the 10 years following menopause.⁴ The shift in risk profile and prognosis after stroke in post-menopausal women is thought to be due in part to the loss of the vasculoprotective effects of sex steroid hormones, particularly estrogen. Estrogen interacts with cerebral endothelium and thus may have an effect on collateral circulation. Additionally, estrogen suppresses endothelial plasminogen activator inhibitor and influences the levels of several clotting factors.⁵ Thus, there may be differences in clot burden and thrombus composition that may also affect likelihood of recanalization in premenopausal versus post-menopausal women.

In INTERRseCT, a multicentre international observational study studying recanalization in ischemic stroke, clot burden score and thrombus permeability were both independently associated with recanalization in both patients treated with thrombolysis and those treated conservatively.⁶ Robust collateral circulation is known to predict more favorable outcomes after stroke.⁶ In the interest of exploring potential biological factors impacting disparities in stroke outcome between men and women, we explored the effects of sex, and modifying effects of age, on these predictors of recanalization and more favourable outcome.

Methods

Study design

The details of the INTERRseCT protocol were published previously.⁶ The experimental protocol was approved by the Conjoint Health Research Ethics Board at the University of Calgary and conformed to the Declaration of Helsinki. All participants provided written informed consent for the study. Briefly, the study enrolled patients with acute ischemic stroke and intracranial occlusion on baseline CT angiogram (CTA).⁶ Eligibility criteria included patients presenting to an emergency department within 12 hours of last known well and older than 40 years. Patients with vertebrobasilar artery occlusion were excluded. The study included patients that did and did not receive intravenous (IV) thrombolysis.

Demographic data, including relevant past medical history, smoking status, medication use on admission, including exogenous hormones, were recorded. Patients underwent a baseline head and neck CTA. An imaging expert blinded to all clinical information read all images using OsiriX version 3.5. Extent of

intracranial thrombus burden was measured with the clot burden score. A complete occlusion of the ipsilateral anterior circulation vessels has a clot burden score of 0; no occlusion has a score of 10.^{6,7} Thrombus permeability was assessed using residual flow grades as follows: grade 0, no contrast permeation of thrombus; grade 1, contrast permeating diffusely through thrombus; grade 2, tiny hairline lumen or streak of well-defined contrast within the thrombus extending either through its entire length or part of thrombus.⁶ Collaterals (anterior cerebral-middle cerebral artery and posterior cerebral artery-middle cerebral artery) were scored from 0–10 using a previously published methodology, where a higher score indicates better collateral flow.⁶

Statistical analysis

This was a post-hoc analysis. As data on menopausal status was not collected, we used age of 50 years as a proxy for menopausal status. We selected age 50 years as a proxy based on the population-level Canadian Longitudinal Study on Aging, in which the median self-reported age of natural menopause was 51 (IQR 49–54),⁸ and a global meta-analysis citing the mean age of natural menopause as 48.8 (95% CI 48.3–49.2).^{8,9} We performed sensitivity analyses using additional cutoff values (55 years and 60 years) as proxies for menopause. Cut-points lower than age 50 were not explored due to the small number of female participants under age 50.

We used univariable and multivariable ordinal logistic regression to examine the relationship between sex and each of collateral status, thrombus permeability and clot burden scores, and looked for multiplicative and additive interactions between age and sex. Age was explored both as a continuous variable and with dichotomous age cut-points (≤ 50 , ≤ 55 and ≤ 60), serving as proxies for menopausal status. Variables were included in the multivariable model if they met a threshold of $p < 0.1$ in univariate analysis, or were forced into multivariable modeling if considered clinically relevant. We repeated our ordinal regression analyses, restricted to female patients, to examine relationships between dichotomous age cut-points and each of collateral status, thrombus permeability and clot burden. We further explored the effect of age and sex on our dependent variables in our logistic regression model by examining for multiplicative interactions with an age*sex term, and by using an additive interaction model. To explore additive interaction we created dummy variables for age (< 50 , 50–59, > 60 years) and sex (female and male). We compared clinical outcomes, specifically modified Rankin scale (mRS) and NIH Stroke Scale (NIHSS) scores at 90 days,

using the Mann-Whitney U test. All data analyses were conducted in SPSS Statistics (version 26.0, IBM Corp., Armonk, NY). Significance was set at $p < 0.05$. Given the hypothesis-generating nature of our study, no corrections were made for multiple comparisons.

Results

Our analyses included all patients ($n = 575$) from INTERRseCT. Women comprised nearly half (48.5%) of the cohort. Mean age was 70.2 years (SD: 13.1). Distribution of age by sex is summarized in Figure 1. Proportion of participants aged ≤ 50 , ≤ 55 and ≤ 60 years were 8.0% (8.6% of female patients), 15.0% (14.3% of females) and 21.2% (18.3% of females), respectively.

Overall, women were 6 years older than men ($p < 0.001$), with a higher proportion of hypertension (8% difference, $p = 0.035$), less coronary artery disease (7% difference, $p = 0.034$), less dyslipidemia (12% difference, $p = 0.003$), and fewer with a smoking history (25% difference, $p < 0.001$) compared to men (Table 1). Three women were taking an oral contraceptive agent at the time of their event, five were taking hormone replacement therapy, and one was taking a selective

estrogen receptor modulator (raloxifene). There was no difference in baseline antiplatelet or anticoagulant use between sexes. Baseline clinical characteristics are summarized in Table 1.

In unadjusted analysis, female sex was associated with better collaterals (OR 1.37, 95% CIs: 1.01–1.85, $p = 0.04$). However, this relationship was not significant after adjusting for age and relevant comorbidities. We found no association between sex and clot burden score, or thrombus permeability (Table 2). Our results did not change when exploring different age cut-points for female participants (Table 3).

There were no significant multiplicative or additive interactions between age and sex when we used dummy variables for age (i.e. < 50 , 50–59, > 60 years). In our multiplicative model, there were no significant age*sex interaction for collaterals (OR 0.88 [95% CI: 0.53–1.45]), thrombus permeability (OR 0.86 [95% CI: 0.44–1.65]) or clot burden (OR 0.93 [95% CI: 0.56–1.54]). The additive interactions from this model also did not find any significant effects of sex on the relationship between age and collaterals (OR 0.97 [95% CI: 0.24–3.85]), age and thrombus permeability (OR 0.56 [95% CI: 0.09–3.45]) or age and clot burden (OR 0.85 [95% CI: 0.21–3.45]). Similarly, there were no

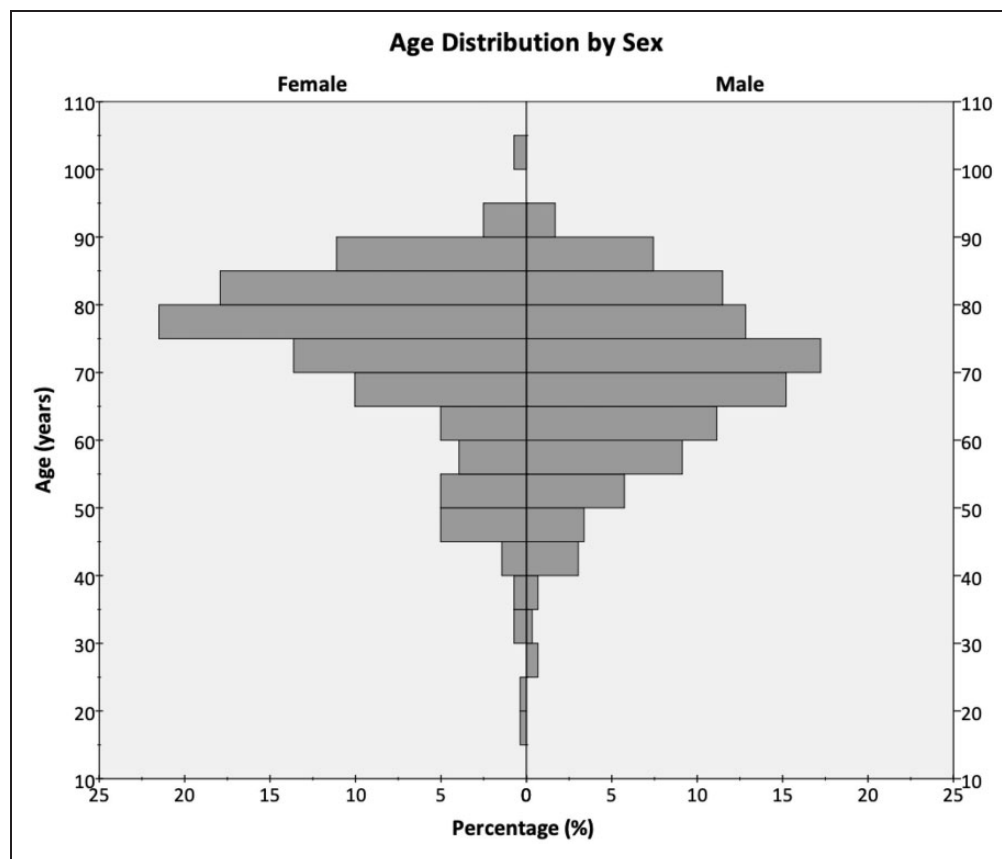


Figure 1. Distribution of age by sex in the INTERRseCT cohort.

Table 1. Baseline characteristics of male and female participants.

Baseline demographics	Male (n = 296)	Female (n = 279)	Significance (p)
Mean age (median, IQR)	70 (61, 78)	76 (65, 82)	<0.001*
Hypertension (n, %)	171 (58)	185 (66)	0.035*
Dyslipidemia (n, %)	114 (39)	75 (27)	0.003*
Ever Smoker (n, %)	168 (58)	65 (23)	<0.001*
Diabetes type 2 (n, %)	50 (20)	26 (9)	0.18
Atrial fibrillation (n, %)	89 (30)	88 (32)	0.702
Coronary artery disease (n, %)	71 (24)	47 (17)	0.034*
Congestive heart failure (n, %)	10 (3)	9 (3)	0.919
Malignancy (n, %)	11 (4)	14 (5)	0.444
Antiplatelet use (n, %)	112 (38)	89 (32)	0.136
Anticoagulant use (n, %)	35 (12)	40 (14)	0.371
Baseline NIHSS (median, IQR)	14 (8, 19)	15 (9, 19)	0.167

Asterisk (*) indicates significance at $p < 0.05$.

mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale.

Table 2. Unadjusted ordinal regression analysis exploring association between sex, age and comorbidities, and baseline radiological predictors of recanalization (collaterals, thrombus permeability and clot burden score).

Variable	Improved collaterals	Higher thrombus permeability	Lower clot burden
	OR (95% Cis)	OR (95% Cis)	OR (95% Cis)
Sex (female)	1.37 (1.01–1.85)*	0.83 (0.56–1.27)	1.03 (0.76–1.39)
Age (continuous)	1.00 (0.98–1.01)	0.99 (0.97–1.00)	1.00 (0.99–1.01)
Age ≤ 50 years	1.08 (0.62–1.88)	0.98 (0.46–2.08)	1.20 (0.68–2.09)
Age ≤ 55 years	1.06 (0.70–1.62)	1.14 (0.65–2.00)	1.09 (0.71–1.68)
Age ≤ 60 years	1.10 (0.76–1.59)	1.43 (0.89–2.30)	0.95 (0.66–1.37)
Hypertension	0.88 (0.64–1.21)	0.72 (0.48–1.09)	1.25 (0.92–1.71)
Dyslipidemia	0.78 (0.56–1.08)	1.24 (0.81–1.90)	1.25 (0.90–1.73)
Atrial fibrillation	0.59 (0.42–0.83)*	0.68 (0.42–1.08)	0.80 (0.58–1.10)
Diabetes	1.07 (0.67–1.70)	0.70 (0.37–1.31)	1.44 (0.92–2.25)
Smoking	0.83 (0.61–1.14)	1.13 (1.00–1.67)	0.83 (0.60–1.13)
Coronary Artery Disease	0.67 (0.45–0.98)*	1.09 (0.66–1.79)	0.86 (0.59–1.24)
Congestive Heart Failure	0.48 (0.20–1.17)	0.47 (0.11–2.08)	0.64 (0.28–1.48)
Cancer	0.94 (0.46–1.93)	1.85 (0.80–4.31)	0.90 (0.45–1.82)
Antiplatelet use	0.72 (0.52–0.99)*	0.69 (0.44–1.08)	0.79 (0.57–1.09)
Anticoagulant use	0.69 (0.44–1.01)	1.02 (0.56–1.86)	0.85 (0.55–1.31)

For collaterals, OR indicate likelihood of *improved* collateral flow. For thrombus permeability, OR indicates likelihood of *higher* permeability. For clot burden, OR indicates likelihood of *lower* clot burden. Asterisk (*) indicates significance at $p < 0.05$.

Table 3. Unadjusted ordinal regression models, restricted to female patients, exploring associations between dichotomous age cut-points and collaterals, thrombus permeability and clot burden score.

	Age		
	≤ 50 years OR (95% CIs)	≤ 55 years OR (95% CIs)	≤ 60 years OR (95% CIs)
Collaterals	1.15 (0.53–2.46)	1.04 (0.57–1.90)	0.92 (0.53–1.58)
Thrombus Permeability	0.67 (0.19–2.36)	1.45 (0.64–3.26)	1.55 (0.75–3.20)
Clot Burden Score	1.36 (0.61–3.06)	1.05 (0.57–1.92)	0.86 (0.50–1.47)

For collaterals, ORs indicate likelihood of *improved* collateral flow; for thrombus permeability, ORs indicate likelihood of *higher* permeability; for clot burden, ORs indicate likelihood of *lower* clot burden.

significant additive effects of age on the relationship between sex and collaterals (OR 1.03 [95% CI: 0.72–1.46]), sex and thrombus permeability (OR 0.93 [95% CI: 0.57–1.53]), or sex and clot burden (OR 1.01 [95% CI: 0.70–1.45]).

In unadjusted models, testing for the proportional odds assumption was satisfied (i.e. $p > 0.05$) for all variables except for hypertension and collaterals ($p = 0.018$), diabetes and collaterals ($p < 0.001$), and diabetes and clot burden ($p < 0.001$). In unadjusted ordinal regression models restricted to female patients, testing for the proportional odds assumption was satisfied (i.e. $p > 0.05$) for all variables.

Workflow-related factors, such as onset-to-CT and CT-to-thrombolysis did not significantly differ by sex. However, females were observed to have a 12-minute faster CT-to-groin-puncture time compared to males (Table 4). There were no differences by sex with respect to rates of either thrombolysis or endovascular therapy.

At 90 days post-stroke there were no significant differences between sexes for mRS or NIHSS outcomes. Median (IQR) 90-day mRS for males was 2 (1–4) and 2 (1–4) for females, $p = 0.1$. Median (IQR) 90-day NIHSS for males was 2 (0–8) and 2 (0–13) for females, $p = 0.69$. There were no significant age*sex interactions for either mRS or NIHSS outcomes.

Discussion

In an international cohort of acute ischemic stroke patients, we found no association between sex and radiographic prognostic markers of recanalization. In our unadjusted model, female sex was marginally associated with better collaterals, but this effect was confounded as it disappeared after including relevant co-variables in our adjusted model. We found no evidence to support the hypothesis that cerebrovascular collaterals or thrombus characteristics were modified by the effect of pre- versus post-menopausal age and, indirectly, found no suggestion that these factors may

contribute to sex differences in age-related post-stroke outcomes.

We observed no difference in collaterals between women of pre- and post-menopausal age with acute ischemic stroke. Based on evidence predominantly from rodent models, estrogen is thought to be protective in ischemic stroke via vasodilatory and anti-inflammatory mechanisms.^{10–14} Additionally, in a small study in healthy volunteers, premenopausal women demonstrated better cerebrovascular reactivity compared to post-menopausal women and age-matched men.¹⁵ Nonetheless, our findings are congruent with other clinical studies that have failed to find an association between sex and collateral status.^{16–19}

In our cohort, sex did not meaningfully contribute to radiographic variability in collaterals in ischemic stroke patients. We have previously found in this cohort that 45–53% of between-patient variability in leptomeningeal collaterals is explained by patient demographics, comorbidities, clinical and laboratory variables.²⁰ Genetic factors, including ApoE genotype, were not explored and may also contribute to between-patient variability in leptomeningeal collaterals, and may interact with sex in cerebrovascular regulation.²¹ Sex differences in gene expression provides a hypothesized mechanism for sexual dimorphism in microvascular function and responsive to ischemic events.²² Rodent models of cerebral blood flow have shown that sex differences in expression of mitochondrial proteins in both cerebral micro-vessels and large vessels lead to differences in mitochondrial-mediated dilation following ischemia.^{23,24} We suspect that any effect of sex on collaterals in our sample was attenuated when other confounding factors affecting collateral status were considered.

We also found no relationship between thrombus permeability or clot burden score and women of pre- and post- menopausal age. Estrogen is known to influence the clotting cascade, and exogenous estrogen is associated with increased risk of both venous and arterial thromboembolic events.²⁵ However, it is uncertain

Table 4. Workflow times and treatment strategy comparison between male and female participants.

	Male (n = 296)	Female (n = 279)	Significance (p)
Workflow times			
Onset-to-CT (minutes; median, IQR)	115 (72, 171)	114 (75, 196)	0.169
CT-to-thrombolysis (minutes; median, IQR)	24 (17, 32)	23 (18, 36)	0.383
CT-to-groin-puncture (minutes; median, IQR)	74 (52, 98)	62 (42, 80)	0.001*
Treatment			
Thrombolysis alone (n, %)	137 (46)	138 (49)	0.46
Thrombolysis + EVT (n, %)	24 (8)	24 (9)	
EVT alone (n, %)	100 (34)	95 (34)	
Conservative (n, %)	35 (12)	22 (8)	

Time is given in minutes. Asterisk (*) indicates significance at $p < 0.05$.

as to whether estrogen would mediate differences in the histopathology of an arterial thrombus, and whether these differences, if present, would be reflected radiographically. It is unclear whether our findings signify a true absence of a relationship between pre- versus post-menopausal age and these thrombus characteristics, or whether our data are underpowered to detect a relationship. Whether endogenous estrogen levels are associated with different thrombus characteristics warrants further study, as this information could inform future personalized strategies for reperfusion.

Previous studies in Canada and elsewhere have described longer treatment times for women than men with acute ischemic stroke, and lower rates of reperfusion therapy being administered to women.^{26–28} Contrary to these previously published data, in our cohort, rates of reperfusion therapy (both tPA and/or EVT) were similar between and sexes and there were no workflow-related differences by sex apart from a faster CT-to-groin puncture time in females. Further, despite the older age of females in our cohort, the 90-day mRS and NIHSS outcomes were similar to male patients, and there was no significant interaction effect between sex and age with regards to clinical outcomes at 90 days post stroke. It is reassuring that in this study cohort the workflow times, treatment cohorts and outcomes are similar, suggesting that women appear to be getting appropriate care for acute stroke and benefiting as much as men. These findings may be reflective of local patterns of practice at study sites, which were at academic hospitals. Alternatively, there could be biases inherent to the INTERSeCT cohort that attenuate sex differences that may be occurring in routine clinical practice, though this is less likely in the context of consecutive recruitment.

This study provides novel preliminary data exploring the relationship between sex and radiographic predictors of recanalization, and the potential modifying effects of age on this relationship. Our work was intended to be hypothesis-generating, and has several limitations. As expected, in keeping with the demographics of ischemic stroke we had a small number of female participants of pre-menopausal age. Our neutral results may therefore be due in part to Type II error. Similarly, small numbers prevent us from examining any potential mediating effect of exogenous hormone or estrogen receptor agonist use. Another limitation is the lack of primary data collected on menopausal status. By using age as a proxy for menopausal status, we may have misclassified pre- or post-menopausal women. Future work examining stroke-related outcomes should seek to prospectively collect data on menopausal status.

Conclusions

In an international cohort of acute ischemic stroke patients presenting with intracranial occlusions on CTA we found no association between sex and radiological predictors of thrombus recanalization. More work is warranted to better elucidate genetic, biologic and social contributions to sex and gender differences in stroke risk and prognosis after stroke.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This prospective cohort study was funded by an operating grant from the Canadian Institutes of Health Research.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Field receives in-kind study medication from Bayer Canada and has received honoraria for advisory board work for HLS Therapeutics and Roche Canada. She is supported by a Sauder/Heart and Stroke Professorship from the University of British Columbia, the Vancouver Coastal Health Research Institute, the Michael Smith Institute for Health Research, and the Heart and Stroke Foundation of Canada. Dr. Menon reported holding stock and a patent for systems of triage in acute stroke in Circle NVI. Dr. Dowlathshahi reported receiving a grant from Heart & Stroke Foundation of Canada and personal fees from Apopharma, BMS, and Bayer. Dr Goyal reported receiving research grants to the University of Calgary by Stryker and Cerenovus and receiving consulting fees from Stryker, Mentice, Medtronic and Microvention. Dr. Demchuk reported receiving honoraria from Medtronic and holding stock and a patent in Circle NVI, a startup stroke imaging software company. Dr Hill reports grants from Covidien (Medtronic LLC), grants from Alberta Innovates, grants from Heart & Stroke Foundation of Canada, grants from Canadian Institutes of Health Research (Canadian Stroke Prevention Intervention Network), grants from University of Calgary (Hotchkiss Brain Institute), grants from Boehringer Ingelheim Canada, grants from NoNO, Inc, and grants from Biogen. In addition, Dr Hill has a patent to US Patent office Number: 62/086,077 and is Stock owner in Pure Web Incorporated and CircleNVI. Dr. Hill is a director of the Canadian Federation of Neurological Sciences, a not-for-profit group, is a director of the Canadian Stroke Consortium, a not-for-profit group, is a director of Circle NeuroVascular, and has received public grant support to the University of Calgary from Alberta Innovates Health Solutions, Canadian Institutes of Health Research, Heart & Stroke Foundation of Canada and National Institutes of Neurological Disorders and Stroke. The other authors report no conflicts.


Authors' contributions

Dr. Rebchuk made a substantial contribution to data analysis, interpretation of data, and drafting the manuscript. Drs. Hill, Menon and Field made a substantial contribution to the concept and design, data acquisition, data analysis, interpretation of data, drafting and revising the manuscript. Drs. Goyal, Demchuck, Coutts, Asdaghi, Dowlatshahi, Holodinsky, Fainardi, Shankar, Najm, Rubiera, Khaw and Qiu contributed to study concept and design, data acquisition and revised the manuscript for important intellectual content. All authors approved the manuscript prior to publication.

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