Effect of Sex on Outcomes of Mechanical Thrombectomy in Basilar Artery Occlusion: A Multicentre Cohort Study

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Keywords
Sex · Acute ischaemic stroke · Thrombectomy · Basilar artery occlusion

Abstract

Introduction: Identifying differences in outcome of basilar artery occlusion (BAO) between males and females may be useful in aiding clinical management. Recent studies have demonstrated widespread underrepresentation of women in acute stroke clinical trials. This international multicentre study aimed to determine sex differences in outcome after mechanical thrombectomy (MT) for patients with acute BAO.

Methods: We performed a retrospective analysis of consecutive patients with BAO who had undergone MT in seven stroke centres across five countries (Singapore, Taiwan, United Kingdom, Sweden, and Germany), between 2015 and 2020. Primary outcome was a favourable functional outcome measured by a modified Ranking Scale (mRS) of 0–3 at 90 days. Secondary outcomes were mRS 0–3 upon discharge, Benjamin Y.Q. Tan and Isabel Siow have contributed equally.
mortality, symptomatic intracranial haemorrhage (sICH) and subarachnoid haemorrhage (SAH). **Results:** Among the 322 patients who underwent MT, 206 (64.0%) patients were male and 116 (36.0%) were female. Females were older than males (mean ± SD 70.9 ± 14.3 years vs. 65.6 ± 13.3 years; p = 0.001) and had higher rates of atrial fibrillation (38.9% vs. 24.2%; p = 0.012). Time from groin puncture to reperfusion was shorter in females than males (mean ± SD 57.2 ± 37.2 min vs. 71.1 ± 50.9 min; p = 0.021). Despite these differences, primary and secondary outcome measures were similar in females and males, with comparable rates of favourable 90-day mRS scores (mean ± SD 46 ± 39.7 vs. 71 ± 34.5; OR = 1.20; 95% confidence interval [CI] = 0.59–2.43; p = 0.611), favourable discharge mRS scores (mean ± SD 39 ± 31.6 vs. 43 ± 25.9; OR = 1.38; 95% CI = 0.69–2.78; p = 0.368) and in-hospital mortality (mean ± SD 30 ± 25.9 vs. 47 ± 22.8; OR = 1.15; 95% CI = 0.55–2.43; p = 0.710). Rates of complications such as sICH (mean ± SD 5 ± 4.3 vs. 9 ± 4.4; OR = 0.46; 95% CI = 0.08–2.66; p = 0.385) and SAH (mean ± SD 4 ± 3.4 vs. 5 ± 2.4; OR = 0.29; 95% CI = 0.03–3.09; p = 0.303) comparably low in both groups. **Conclusion:** Females achieved comparable functional outcomes compared with males after undergoing MT for BAO acute ischemic stroke.

**Introduction**

Basilar artery occlusion (BAO) acute ischaemic stroke (AIS) is a neurological emergency that has devastating rates of severe morbidity and mortality despite advances in acute stroke care [1, 2]. Occlusion of the basilar artery can disrupt supply to the central reticular activating system, resulting in hemiparesis, quadriplegic, or calaminous locked-in syndrome [3]. AIS outcomes appear to differ between females and males [4, 5], with previous studies suggesting worse clinical and functional outcomes for females [6, 7], even with successful recanalization [7–16].

Recent analyses have demonstrated widespread under-enrolment and hence misrepresentation of women in AIS clinical trials [17–19], potentially leading to biased conclusions for women in outcomes and stroke management. As such, studies have begun to increase recruitment of females to explore the effect of sex on AIS treatment outcomes, with some demonstrating similar outcomes across both sexes [10, 17–19]. However, most of these studies involved patients with anterior circulation strokes. Sex-related differences in outcomes after recanalization treatment in posterior circulation strokes have yet to be investigated in detail. Through an international collaboration conducted across comprehensive stroke centres, this study aimed to investigate the independent effect of sex on the outcomes of recanalization treatment in BAO.

**Methods**

**Ethics and Standard Protocol Approvals**

This study protocol was reviewed and approved by the National Health Group Domain Specific Review Board, approval number 2019/00252. Approval from the Ethical Standards Committee to conduct this study was received and the Ethics Board determined that participant consent was waived. No recognizable photographs, videos, or other information of persons were included in this article. This study did not involve experiments using human participants, experiments involving live vertebrates or higher invertebrates.

**Data Collection**

Data were collected from seven comprehensive stroke centres across five countries (Singapore, Taiwan, United Kingdom, Sweden, and Germany). Between January 2015 and December 2020, consecutive patients with BAO strokes who underwent mechanical thrombectomy (MT) up to 24 h from symptom onset or last known well were time included in this study. Baseline patient characteristics collected from each centre consisted of demographics and comorbid cardiovascular risk factors namely hypertension, hyperlipidaemia, diabetes mellitus, atrial fibrillation, previous ischaemic stroke, and smoking history.

Clinical variables included the National Institute of Health Stroke Scale (NIHSS) on admission, the mechanism of ischaemic stroke as defined by the trial of ORG 10172 in acute stroke treatment classification [20], time from stroke-onset to groin puncture, time from stroke-onset to reperfusion, and time from groin puncture to reperfusion. Data on the type of MT employed and number of attempts were collected when available.

Brain imaging including CT and/or MRI was repeated 22–36 h after MT and evaluated for intracranial haemorrhage (ICH), which was classified according to the European Co-operative Acute Stroke Study (ECASS). The extent of angiographic reperfusion was classified according to the modified Thrombolysis in Cerebral Infarction (mTICI) grading system. Functional outcomes were determined at discharge and at 90-days during a follow-up visit and categorized according to the modified Ranking Scale (mRS) [21].

The primary outcome measure was functional recovery at 90 days. Favourable functional outcome was defined as mRS ≤3 at 90 days [22]. Good functional outcome was defined as mRS ≤2. Secondary outcomes were successful reperfusion defined as mTICI ≥2b, in-hospital mortality, mRS score at discharge, and the presence of subarachnoid haemorrhage and symptomatic ICH after the procedure, defined as any haemorrhage accompanied by a deterioration of NIHSS score of 4 points or more.

**Treatment**

All patients were managed according to international guidelines for the management of BAO AIS [3]. In each institution, the specific endovascular therapeutic treatment was left to the discretion of the neurointerventionist and neurologist, including the decision to administer bridging intravenous recombinant tissue-type...
plasminogen activator (t-PA). MT techniques used included stent retrievers, thromboaspiration, or both. During the initial phase after the procedure, patients were monitored in either the intensive care unit or a high dependency unit.

Statistical Analysis
All statistical analysis was performed using SPSS Version 26 (SPSS Inc., Chicago, IL, USA). Numeric variables were first tested for normality with the Shapiro Wilk test. Student’s t-test was used for normally distributed data and a Mann-Whitney U test for non-normally distributed data. Categorical variables were compared using a Pearson χ² test, with computation of Wald and score confidence intervals (CI) for the incidence odds ratio. Multivariate logistic regression was used to assess for the effect of sex against the primary and secondary outcomes of the study. We first adjusted for age in Model I, followed by age and comorbidities, i.e., diabetes mellitus, hypertension, hyperlipidaemia, atrial fibrillation, and previous stroke in Model II, followed by age, comorbidities, bridging IVT, and time from stroke onset to groin puncture in Model III. The selection of variables for multivariate analyses was decided a priori based on previously known factors from the literature that determine functional outcome after MT. We performed a subgroup analysis of the data for the predetermined outcomes for the different stroke mechanisms, age, and sex of the patients.

Results

Baseline Characteristics
Between January 2015 and December 2020, there were 345 patients who suffered BAO stroke and underwent MT in the participating centres. Twenty-three patients were excluded as outcome measures were not documented. Thus, a total of 322 patients were included in the final analysis, of whom 206 (64.0%) were male while 116 (36.0%) were female. Females were older compared to males (70.9 ± 14.3 years vs. 65.6 ± 13.6 years; p = 0.001). Females showed higher rates of atrial fibrillation (38.9% vs. 24.2%; p = 0.012). There were no sex differences in the rest of the cardiovascular risk factors (Table 1). There were also no sex differences in NIHSS at admission and aetiology of BAO strokes (Table 1).

Comparison of Treatment between Males and Females
The mean time from groin puncture to reperfusion was longer in males compared to females (71.1 ± 50.9 min vs. 57.2 ± 37.2 min; p = 0.021). Conversely, time from
stroke-onset to groin puncture and time from stroke-onset to reperfusion was similar across both sexes. There were no sex differences in the type of MT device employed and number of attempts for MT (Fig. 1).

**Primary Outcome**

A total of 117 (36.3%) patients achieved favourable functional outcome at 90 days (mRS ≤3), without any significant difference between sexes, even after adjusting for age, comorbidities, IVT, and time from stroke-onset to groin puncture (mean ± SD females = 46 ± 39.7 vs. males = 71 ± 34.5; OR = 1.20; 95% CI = 0.59–2.43; p = 0.611) (Fig. 2). There were no sex differences in functional outcomes on discharge, on both univariate and multivariate analysis (mean ± SD females 39 ± 31.6 vs. males 43 ± 25.9; OR = 1.38; 95% CI = 0.69–2.78; p = 0.368). (Tables 2, 3).

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**Table 2.** Comparison of outcomes between males and females

| Outcome                        | Males (N = 206) | Females (N = 116) | Total (N = 322) | p value |
|--------------------------------|-----------------|-------------------|-----------------|---------|
| 90-day mRS, N (%)              |                 |                   |                 |         |
| 0–3 (good)                     | 71 (34.5)       | 46 (39.7)         | 117/322 (36.3)  | 0.353   |
| 4–6 (poor)                     | 135 (65.5)      | 70 (60.3)         | 205/322 (63.7)  |         |
| 90-day mRS, N (%)              |                 |                   |                 |         |
| 0–2 (good)                     | 56 (27.2)       | 35 (30.2)         | 91/322 (28.3)   | 0.568   |
| 3–6 (poor)                     | 150 (72.8)      | 81 (69.8)         | 231/322 (71.7)  |         |
| Discharge mRS, N (%)           |                 |                   |                 |         |
| 0–3 (good)                     | 43/166 (25.9)   | 39/95 (31.6)      | 73/261 (28.0)   | 0.326   |
| 4–6 (poor)                     | 123/166 (74.1)  | 65/95 (68.4)      | 188/261 (72.0)  |         |
| Discharge mRS, N (%)           |                 |                   |                 |         |
| 0–2 (good)                     | 34/166 (20.5)   | 21/95 (22.1)      | 55/261 (21.1)   | 0.757   |
| 3–6 (poor)                     | 132/166 (79.5)  | 74/95 (77.9)      | 206/261 (78.9)  |         |
| In-hospital mortality, N (%)   |                 |                   |                 |         |
| Survival                       | 159 (77.2)      | 86 (74.1)         | 245 (76.1)      | 0.538   |
| Death                          | 47 (22.8)       | 30 (25.9)         | 77 (23.9)       |         |
| mTICI posttreatment, N (%)     |                 |                   |                 |         |
| 0–2a (poor)                    | 28/203 (13.8)   | 17/114 (14.9)     | 45/317 (14.2)   | 0.784   |
| 2b–3 (good)                    | 175/203 (86.2)  | 97/114 (85.1)     | 272/317 (85.8)  |         |
| mTICI posttreatment, N (%)     |                 |                   |                 |         |
| 0–2b (poor)                    | 79/203 (38.9)   | 41/114 (36.0)     | 120/317 (37.9)  | 0.603   |
| 2c–3 (good)                    | 124/203 (61.1)  | 73/114 (64.0)     | 197/317 (62.1)  |         |
| SICH 24 h post-intervention, N (%) | 9 (4.4) | 5 (4.3) | 14 (4.3) | 0.980 |
| Subarachnoid haemorrhage, N (%) | 5 (2.4) | 4 (3.4) | 9 (2.8) | 0.594 |

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**Fig. 1.** Treatment intervals according to gender.
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Secondary Outcomes

There were no significant sex differences in rate of successful reperfusion (males: 86.2% vs. females: 85.1%, $p = 0.074$), in-hospital mortality (males: 22.8% vs. females: 25.9%, $p = 0.710$), symptomatic ICH (males: 4.4% vs. females: 4.3%, $p = 0.385$), subarachnoid haemorrhage (males: 2.4% vs. females: 3.4%, $p = 0.303$), even after adjusting for covariates (Tables 2, 3).

Discussion

Our study showed that there were no sex differences in outcomes and complications in individuals with BAO after MT. Few studies have evaluated the effect of sex on outcomes in AIS patients undergoing MT [8, 9, 11, 14]. To our knowledge, none have studied this specifically in BAO ischaemic stroke. It must be noted that the use of MT in

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Table 3. Comparison of outcomes between males and females

| Outcome                      | Unadjusted estimates OR (95% CI); $p$ value | Model 1 OR (95% CI); $p$ value | Model 2 OR (95% CI); $p$ value | Model 3 OR (95% CI); $p$ value |
|-----------------------------|-------------------------------------------|--------------------------------|--------------------------------|--------------------------------|
| 90-day mRS                  | 1.25 (0.78–2.00); 0.353                   | 1.41 (0.87–2.29); 0.165       | 1.60 (0.85–2.99); 0.145       | 1.20 (0.59–2.43); 0.611       |
| Discharge mRS               | 1.32 (0.76–2.30); 0.326                   | 1.45 (0.82–2.59); 0.206       | 1.65 (0.87–3.10); 0.124       | 1.38 (0.69–2.78); 0.368       |
| Mortality in hospital       | 1.18 (0.70–2.00); 0.539                   | 1.15 (0.70–1.96); 0.622       | 1.18 (0.62–2.28); 0.613       | 1.15 (0.55–2.43); 0.710       |
| mTICI post treatment        | 0.91 (0.48–1.75); 0.784                   | 0.91 (0.47–1.77); 0.788       | 0.49 (0.22–1.12); 0.092       | 0.41 (0.16–1.09); 0.074       |
| SICH 24 h post-intervention | 0.99 (0.32–3.02); 0.980                   | 1.04 (0.34–3.24); 0.943       | 0.52 (0.09–2.96); 0.463       | 0.46 (0.08–2.66); 0.385       |
| Subarachnoid haemorrhage    | 1.44 (0.38–5.46); 0.595                   | 1.33 (0.34–5.19); 0.686       | 0.49 (0.09–2.82); 0.425       | 0.29 (0.03–3.09); 0.303       |

Model 1: adjusted for age only. Model 2: adjusted for age and comorbidities (diabetes mellitus, hypertension, hyperlipidaemia, atrial fibrillation, previous stroke). Model 3: adjusted for age, comorbidities, bridging IVT, and time from groin puncture to reperfusion.
posterior circulation strokes remains a contentious topic especially after the Basilar Artery International Coopera-
tion Study [23] and Basilar Artery Occlusion Endovascu-
lar Intervention Versus Standard Medical Treatment [24]
trials failed to show superiority of endovascular therapy
over best medical therapy, and vice versa. Furthermore,
females are underrepresented in many large trials study-
ing management of AIS [4, 17, 18], leading to uncertainty
about their functional outcomes after intervention.

There is currently no consensus regarding whether
MT yields worse outcomes in males or females with AIS.
Most studies have shown that females with AIS achieve
poorer outcomes after MT [16, 25]. However, some re-
cent studies show that both males and females with ante-
rior circulation stroke achieve similar functional out-
comes [8, 15, 26] and others even show that males achieve
poorer outcomes after MT compared to females [27]. The
discrepancy in findings might have been due to an inclu-
sion of a disproportionately higher proportion of poste-
rior circulation strokes in the male subgroup in some
studies. Some factors leading to poorer outcomes in fe-
males include sex steroid hormone differences [28]. Sex
steroid hormones, particularly oestrogen, promote vaso-
dilation and blood flow. In postmenopausal females, the
serum levels of oestradiol decrease, leading to poorer an-
ti-inflammatory and vascular responses compared to age-
matched men [28]. Results from our study lend further
support to the stand that females achieve comparable out-
comes to males when treated for AIS with MT. Therefore,
it is suggestive that females with BAO ischaemic stroke
may also derive benefit from acute intervention [15, 26].

In this study cohort, females had higher rates of atrial
fibrillation and more advanced ages compared with males. This finding has been consistently demonstrated
in numerous previous studies [15, 26]. Despite this, fe-
males in this cohort still achieved comparable outcomes
in the short and long-term follow-up, with low rates of
complications. Notably, a higher proportion of women in
our study received IVT. This, combined with shorter
groin puncture to reperfusion time, could have improved
the outcomes of females and led to comparable results
between males and females.

Previous studies have also demonstrated longer door
to groin puncture time and lower rates of IVT in females
compared with males [26], possibly due to atypical symp-
toms of presentation which can be seen in women leading
to a delay in treatment [26]. In our study, there were no
differences in time from stroke onset to groin puncture
and reperfusion between males and females. However,
the duration from groin puncture to reperfusion was
shorter in females than in males. This could be attributed
to females having higher rates of atrial fibrillation in this
study, and embolized clots were less technically challeng-
ing to recanalize compared with intracranial atheroscle-
rotic disease resulting in large vessel occlusion [22].

A factor that might contribute to the difference in func-
tional outcomes between males and females after MT is the
extent and quality of collateral circulation supplying the
brainstem via the posterior communicating arteries. Col-
laterals provide alternative avenues of blood flow to pen-
umbra after a large vessel occlusion. It is hypothesised that
a more extensive network of collaterals would facilitate a
smaller infarct volume and thus better functional outcomes.
However, studies in both rodents and patient have not
shown a clear sex-based predilection towards poorer col-
laterals. Instead, the current literature yields conflicting re-
results, with some demonstrating comparable collateraliza-
tion in both sexes [29] and others demonstrating poorer
collateralization in males [30]. Another factor that might
contribute to differences in functional outcomes between
the two sexes is the location of BAO i.e., proximal, middle,
or distal segments, with distal segments possibly covering
the posterior communicating arteries [31]. Further work
can be done to explore these areas.

Our study has limitations that stem from its retrospec-
tive non-randomized nature. Heterogeneity of medical re-
cords and functional status of patients prior to their admis-
sion could have resulted in baseline differences in patients
included in the study. The non-randomized nature of this
study may have introduced selection bias as different cen-
tres may have different inclusion criteria for MT, and often,
treatment allocations were made at the discretion of the
treating stroke neurologist and neurointerventionist, whose
experiences would vary. However, despite this potential se-
lection bias, the baseline characteristics of the two sex
groups were relatively homogeneous. We did not collect
data on the posterior collateral status, the PC-ASPECTS
score nor the location of the occlusion within the basilar
artery (i.e., proximal, middle, or distal). Finally, there was
no control group thus we are unable to compare MT against
best medical treatment between the two different sexes.

**Conclusion**

In this evaluation of the impact of sex on outcome for
BAO AIS after MT, the outcomes were similar in terms of
functional status and mortality although females tended
to present at an older age with higher rates of atrial fibril-
lation.
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B. Y. T., I. S., K. S. L., and V. C. conceptualized and wrote the manuscript. I. S. performed all data analyses. N. O., A. G., C. L., P. B., E. L., O. S., I. M., J. F., P. P., A. K., M. A., S. Z., Q. W., A. M., V. M., T. A., V. G., F. A., T. -H. L., B. C., H. L. T., R. C. S., and V. S. were involved in data collection. L. L. L. Y. supervised the project. All the authors discussed and commented on the manuscript.

Statement of Ethics

The manuscript has not been submitted elsewhere nor published elsewhere in whole or in part, except as an abstract, and no such additional submission will be made before completion of the review process by cerebrovascular diseases. This study protocol was reviewed and approved by the National Health Group Domain Specific Review Board, approval number 2019/00252.

Conflict of Interest Statement

All the authors have no conflicts of interest to declare.

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