Sex differences in stroke mortality in Thailand: a National cohort study.

Abdel-Fattah, Abdel-Rahman; Pana, Tiberiu; Tiamkao, Somsak ; Sawanyawisuth, Kittisak ; Kasemsap, Narongrit; Mamas, Mamas A; Myint, Phyo Kyaw

Published in:
Annales de cardiologie

Publication date:
2022

Document Version
Peer reviewed version

Différences sexuelles dans la mortalité par accident vasculaire cérébral en Thaïlande: une étude de cohorte nationale

ABSTRAIT

Contexte

Plus de la moitié du fardeau mondial croissant de la mortalité par accident vasculaire cérébral est imputable au seul sous-continent est-asiatique. Les différences entre les sexes dans la mortalité par accident vasculaire cérébral dans la population asiatique n'ont pas encore été évaluées dans la littérature. Nous avons cherché à évaluer les différences entre les sexes dans la mortalité après un AVC dans une grande cohorte de patients thaïlandais.

Méthodes

Toutes les admissions d'AVC entre 2004 et 2015 ont été incluses à partir de la base de données de l'assurance-santé publique thaïlandaise. L'association entre le sexe et la mortalité a été évaluée à l'hôpital, à un mois, un an et cinq ans, à l'aide de regressions de Cox multivariées, séparément pour l'AVC ischémique (IS), l'AVC hémorragique (HS) et l'AVC de -type indéterminé (SUT), en ajustant les facteurs de confusion.

Résultats

608 890 patients ont été inclus: 370 527 patients avec IS(60,9%), 173 236 avec HS(28,5%) et 65 127 avec SUT(10,6%). Les femmes étaient plus âgées que les hommes dans les trois groupes et avaient une prévalence plus élevée de comorbidités. Les rapports de risque (RR) ajustés de la mortalité ont montré que les femmes avaient une mortalité post-IS plus élevée que les hommes (à l'hôpital: HR:1,20 ;IC à 95%:1,17-1,23 ; à un mois : HR:1,17; IC à 95%:1,15-1,20 ; un an : HR:1,10 ; IC à 95%:1,09-1,12 et cinq ans : HR 1,02 ;IC à 95%:1,01-1,03). Les femmes avaient également une mortalité plus élevée après HS (à l'hôpital : HR:1,02 ;IC à 95%:1,00-1,04 ; à un mois : HR:1,08 ;IC à 95%:1,06-1,10 ; à un an : HR:1,04;

IC à 95%:1,03-1,06 et à cinq ans : HR:1,09; IC à 95%:1,08-1,11) et SUT (à l'hôpital : HR:1,04 ; IC à 95%:1,03-1,06 ;un mois : HR:1,20; IC à 95%:1,14-1,27 ; un an : HR:1,14; IC à 95%:1,09-1,18 et cinq ans: HR:1,06; IC à 95%:1,03-1,10).

Conclusion

Comparativement aux hommes, les femmes étaient plus âgées au moment du diagnostic d'AVC et présentaient une charge plus élevée de facteurs de risque d'AVC. Les femmes avaient également une mortalité plus élevée après un AVC, quel que soit le type d'AVC ou la durée depuis le début de l'AVC. Après l'IS, la surmortalité par accident vasculaire cérébral chez les femmes était la plus élevée pendant la période d'hospitalisation, tandis que la surmortalité par accident vasculaire cérébral augmentait avec le temps chez les femmes atteintes d'HS. Aucune relation claire n'a été trouvée entre la durée depuis le début de l'AVC et la mortalité chez les patients qui ont subi un SUT.

Mots-clés: différence de sexe; AVC ischémique; AVC hémorragique; mortalité; Asie

Sex differences in stroke mortality in Thailand: a National cohort study

ABSTRACT

Background

Over half of the growing global stroke-mortality burden is accounted for by the East-Asian-subcontinent alone. Sex differences in stroke-mortality in the Asian population is yet to be assessed in the literature. We aimed to assess the sex-differences in mortality following stroke in a large cohort of Thai-patients.

Methods

All stroke admissions between 2004-2015 were included from the Thailand public-health-insurance-database. The association between sex and mortality was assessed in-hospital, at one-month, one-year and five-years, using multivariable Cox-regressions, separately for ischaemic-stroke(IS), haemorrhagic-stroke(HS) and stroke-of-undetermined-type(SUT), adjusting for confounders.

Results

608,890 patients were included: 370,527 patients with IS(60.9%), 173,236 with HS(28.5%) and 65,127 with SUT(10.6%). Women were older than men in all three groups and had higher prevalence of comorbidities. Adjusted hazard-ratios(HRs) of mortality showed women had higher mortality post-IS compared to men (in-hospital: HR:1.20; 95%CI:1.17-1.23; one-month: HR:1.17; 95%CI:1.15-1.20; one-year: HR:1.10; 95%CI:1.09-1.12 and five-years: HR:1.02; 95%CI:1.01-1.03). Women also had higher mortality after HS (in-hospital: HR:1.02; 95%CI:1.00-1.04; one-month: HR:1.08; 95%CI:1.06-1.10; one-year: HR:1.04;

95%CI:1.03-1.06 and five-years: HR:1.09; 95%CI:1.08-1.11), and SUT (in-hospital: HR:1.04; 95%CI:1.03-1.06; one-month: HR:1.20; 95%CI: 1.14-1.27; one-year: HR:1.14; 95%CI:1.09-1.18 and five-years: HR:1.06; 95%CI:1.03-1.10).

Conclusions

Compared to men, women were older at time of stroke-diagnosis and had higher burden of stroke risk-factors. Women also had higher mortality after stroke regardless of stroke-type or duration since stroke-onset. Post-IS, excess stroke-mortality in women was greatest during the in-hospital period, whereas excess stroke-mortality increased with time in women who had HS. No clear relationship was found between duration since stroke-onset and mortality in patients who had SUT.

Keywords: sex difference; ischemic stroke; hemorrhagic stroke; mortality; Asia

INTRODUCTION

Addressing the increasing global stroke mortality burden is an important public health concern.[1,2] Whether sex differences in stroke mortality exist has been subject to growing debate in the literature.[3] A large number of studies suggest that women are less likely to die after stroke compared to men despite having more severe strokes.[4-6] However, there is an apparent bias in the evidence-base as the large majority of studies are in Western populations. Therefore, the sex differences in mortality of stroke patients in Asia remain poorly understood. Marked differences in biology, risk factors, comorbidity profile, socioeconomic conditions, and access to healthcare in Asian populations would suggest that the relationship between sex and stroke mortality may be different to that of Caucasians.[6]

A literature review of 18 studies examining temporal and geographical trends of stroke in South Asia in 2014 highlighted the marked paucity of literature examining stroke in women in this region, with no studies assessing stroke mortality specifically.[35] Despite this, the 2014 review found that stroke had become the leading cause of death in South-Asian women over the age of 60 years. In addition, it concluded that 60% of stroke deaths occur in the East-Asian subcontinent alone.[35] Recognising these data is vital in order to stimulate appropriate changes to service provision and stroke care for women and address the overall increase in global burden of stroke mortality.[35]

We aimed to determine the sex differences in stroke subtype-specific mortality at various follow-up points, from in-hospital mortality to five-years post-discharge, in a population of hospitalised Thai patients admitted with ischaemic stroke (IS), haemorrhagic stroke (HS) or stroke of undetermined-type (SUT).

METHODS

The study population consisted of consecutively admitted stroke patients from the Thailand Universal Coverage (UC) Health Insurance Database between October 2004 and September 2015. Eligible patients were selected using the recorded primary diagnosis from the database, using International-Classification of Disease-tenth edition (ICD-10) codes I61 (intracerebral hemorrhage), I63 (cerebral infarction) and I64 (Stroke, not specified as haemorrhage or infarction).

Pre-existing co-morbidities, demographic and clinical data were extracted from insurance reimbursement forms using ICD-10 codes detailed in **Table 1**. Details regarding this health insurance database have been previously described.[11,12] In Thailand, stroke diagnosis is ascertained by clinicians based on the clinical and radiological features, including computed-tomography (CT) scan findings. The ICD codes (I61, I63 and I64) were assigned to patients admitted to public hospitals and who were covered by Universal Coverage Health Security Insurance Scheme admitted by a board-certified clinician based on the patient's pre-existing co-morbidities and clinical presentation.

Ethics

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee in Human Research, Khon Kaen University, Khon Kaen, Thailand.

Inclusion criteria

The inclusion criteria, outcomes of interest (mortality in-hospital, at one-month, one-year and five-years) and selection of study variables were determined *a priori*. The exclusion criteria were defined as follows: patients younger than 18 (n=1427) or older than 100 (n=43) and those missing post-discharge data (n=5419).

Statistical Analysis

All analyses were performed using STATA 14.2 SE (StataCorp 2015) for the entire cohort, and then separately for patients with IS, HS and SUT. Differences in baseline characteristics between women and men were compared using the Student's t-test for normally distributed continuous variables and the chi-squared test for categorical variables.

The mortality outcome was analysed in-hospital, at one-month, one-year and five-year time-points. Patients with missing post-discharge data were deemed lost to follow-up. For each of the time-points, both univariable and multivariable Cox-proportional hazards models and Kaplan-Meier survival plots were constructed. The variables adjusted for in the multivariable analysis were: age, hypertension (HTN), hyperlipidaemia (HL), ischaemic heart disease (IHD), atrial fibrillation (AF), congestive-cardiac-failure (CCF), peripheral-vascular-disease (PVD), diabetes mellitus (DM), chronic-kidney-disease (CKD), chronic-obstructive-pulmonary-disease (COPD), liver disease (LD), cancer and anaemia (**Table 3**). The confounders were chosen based on previous literature[7-10] and clinical relevance. The satisfaction of the proportional hazards assumption was verified for each Cox-model using log-minus-log plots of the survival function stratified by sex over time.

RESULTS

Descriptive Statistics

The study population consisted of 608, 890 consecutive stroke patients, from the Thailand Universal Coverage (UC) Health Insurance Database admitted between October 2004 and September 2015 (**Figure 1**). Details of patient characteristics on admission are detailed in **Table 1**. There were 370,527 (60.9%) patients who were diagnosed with IS, 173,236 patients with HS (28.5%) and 65, 127 patients with SUT (10.6%) on admission. Women accounted for 46.6% of patients in the IS cohort (n=172, 800), 41.3% in the HS cohort (n=69, 828) and 48.1% in the SUT cohort (n=31326). Further, women were older in all three groups; mean-age (SD): 67.1 (13.4) in comparison to 64.1 (12.9) in men, 64.2 (14.3) in comparison to 59.1 (13.9) in men and 66.4 (13.4) in comparison to 62.6 (13.5), respectively.

Comorbidities

Table 1 shows that in patients admitted following an IS, women had a higher prevalence of HTN, HL, IHD, AF, CCF, DM, cancer, and anaemia than men. However, women were found to have had a lower prevalence of CKD and COPD. In patients admitted following a HS or SUT, women had higher prevalence of HTN, HL, AF, DM, and anaemia, whereas, they had a lower prevalence of COPD.

Mortality analysis

Table 2 illustrates the adjusted-mortality results of the data analysis and **Figures 2-4** illustrate the Kaplan-Meier survival plots of unadjusted mortality data. Compared to men, women had higher mortality in-hospital, one-month, one-year, and five years after IS (HR: 1.20; 95%CI: 1.17-1.23, p<0.01; HR: 1.17; 95%CI: 1.15-1.20, p<0.01; HR: 1.10; 95%CI: 1.09-1.12, p<0.01; HR: 1.02; 95%CI: 1.01-1.03, p<0.01, respectively). Women also had a higher mortality after HS (HR: 1.02; 95%CI: 1.00-1.04, p<0.01; HR: 1.08; 95%CI: 1.06-1.10, p<0.01;

HR: 1.04; 95%CI: 1.03-1.06, p<0.01; HR: 1.09; 95%CI: 1.08-1.11, p<0.01, respectively). Similarly, in patients with SUT, women had higher mortality than men (HR: 1.04; 95% CI: 1.03-1.06, p<0.01; HR: 1.20; 95% CI: 1.14-1.27, p<0.01; HR: 1.14; 95% CI: 1.09-1.18, p<0.01; HR: 1.06; 95% CI: 1.03-1.10, p<0.01). The excess mortality in women after IS appeared to be highest in-hospital, whereas in HS the excess mortality appeared to increase with time after discharge. In the SUT group, the excess mortality in women was highest at one-month after discharge and lowest in hospital.

DISCUSSION

This study is the first to describe the sex differences in stroke mortality in the Thai population. Our results showed that women were older at time of stroke onset. Women also had a greater burden of risk factors for stroke than men. Most pertinently however are our mortality findings. Compared to men, women were found to experience 20% more deaths after IS in-hospital and approximately 10% more deaths after HS at five years. These differences in mortality risk in women appeared to be highest in-hospital after IS, whereas the excess mortality in women who had HS appeared to increase over the five-year follow-up period. Our data also showed that women experienced 20% more deaths after SUT at one-month and 14% at one-year, however no clear relationship between duration since SUT-onset and mortality was found.

Compared to studies examining sex differences in stroke mortality of Western populations, our data revealed opposing conclusions. Data from a large national cohort study of 29 549 patients between 2003-2005 from the Danish National Indicator Project (DNIP) (which included all acute strokes with a vascular aetiology), showed that women had a 21%

lower risk of mortality (adjusted mortality-rate-ratio[MRR]: 0.79; 95% CI 0.72-0.86) at 30-days.[28] In comparison, our study found that Thai women have a 17% greater risk of mortality at 30 days (HR: 1.17; 95% CI: 1.15-1.20, p<0.01) after IS and 8% greater risk after HS (HR: 1.08; 95% CI: 1.06-1.10, p<0.01). In another Danish community-based study of 999 patients, focussing on long-term follow-up, women had a 47% greater likelihood of survival at five-years (HR 1.47; 95% CI 1.23-1.76, p<0.01). In comparison, our study found a marginally greater likelihood of mortality at 5-years following IS and a larger difference following HS (IS: HR:1.02; 95% CI: 1.01-1.03, p<0.01 and HS: HR:1.09; 95% CI: 1.08-1.11, p<0.01, respectively).[8] Two large cohort studies in Sweden (n=20 761)[32] and Ontario (n=44 832)[33] also drew the same conclusions for sex differences in mortality after stroke as the Danish studies.

Several propositions have been made to explain the higher stroke mortality in Asian compared to Caucasian populations, and in particular Asian women compared to men. The overall demographic differences include a greater prevalence of HTN (p=0.002), DM (p=0.028) and HL, and specifically plasma LDL concentration (p=0.02).[21] Our data provides additional evidence that these comorbidities disproportionately affect Asian women compared to men (HT: 51.7% vs. 43.9%, p<0.001; DM 25.3% vs. 16.1%, p<0.001; 33.2% vs. 29.2%, p<0.001). In addition, the literature shows that the preponderance of IS subtype varies by region as the pattern of atherosclerotic disease is ethnicity-dependant.[19] One example of this is the higher burden of small-vessel disease and intracranial atherosclerosis in Chinese populations compared to Caucasians (69.1% vs. 38.5%, p=0.02).[19]

Alongside underlying differences in risk factor profile, a Chinese registry-based cohort study in 2019 revealed differences in access to healthcare and chronic-disease management

(for example access to anti-hypertensive medication), particularly for women living in more rural settings with lower incomes and lower educational attainment.[37] These disparities are addressable facets contributing to this sex difference, and provide a more plausible rationale beyond the over-simplification of aetiology due to biological differences alone.[35,36] Furthermore, the majority of the literature concludes that patients living in Asia have poorer access to healthcare and poorer social-care services (important as women who live longer than men, often in isolation or as widows) compared to the West.[26-27] There is also less emphasis on engagement with primary prevention measures, such as: diabetic monitoring, echocardiography and angiography.[28-29] Combined with a poorer pre-stroke functional status and less prompt stroke intervention in women compared to men[27], it appears plausible that women, and in particular Asian women, receive substandard stroke care that does not cater for their specific health requirements.

Previous studies in Caucasian populations have suggested that women have a lower mortality risk after stroke based on the 'Female Stroke Survival Advantage' hypothesis. This theory explains the sex difference by the neuroprotective properties of oestrogen and female gonadal hormones.[35,36] However, more recent literature in Asian women has suggested that the neuroprotective properties of female gonadal hormones is influenced by ethnicity, and that there is a naturally lower plasma oestrogen level in Asian women.[23,24] Similarly, a secondary analysis of data from the Women's Health Initiative (WHI) randomised-controlled-trials of 27 347 patients, investigating the role of hormone therapy on cardiovascular disease and stroke risk in post-menopausal women, found that oestrogen played no role in reducing the risk of stroke in women in the post-menopausal period.[37]

Strengths and Limitations

This large nationwide cohort study has a number of strengths. Our sample size includes over half-a-million patients from South-East Asia increasing the generalisability of our analysis to the wider Asian hemisphere. It is also the first study to focus exclusively on the sex differences in mortality of women compared to men in an Asian population. With such a large sample size, stratification of mortality by stroke-subtype was also made possible. Moreover, the large sample size facilitated the control of many confounding variables such as age, HTN, AF and several other comorbidities, leading to robust statistical analyses and valuable epidemiological findings. Nonetheless, there are some limitations of note. This study only included patients who were admitted and diagnosed with stroke in a hospital setting. Therefore, patients who died of stroke in the community were not included. This may be a more significant matter in Asian populations, such as Thailand, where poor access to healthcare is an inherent issue. Another notable limitation is that there was an obvious lack of treatment information both acutely and at discharge. Possible differential treatment between sexes may have contributed to the higher mortality rate in women. In addition, the absence of a stroke-severity scoring system (such as the National-Institute-of-Health-Stroke Scale [NIHSS]) has limited our ability to comment on potential sex differences in stroke severity which may have influenced mortality.

Recommendations

Public health panels, involving local community representatives, should assemble to consider ways to address the sex differences in mortality after stroke, particularly in Asian populations. Addressing modifiable risk factors including HTN, DM, HL and obesity in women is a key primary prevention strategy to tackle this disparity. In addition, integration of health and social care services is an important policy change which can improve healthcare access for

elderly patients and help engage the community with chronic disease services, including self-monitoring of blood sugar and hypertension clinics.

CONCLUSION

Compared to men, women were older at time of stroke-diagnosis and had higher burden of risk factors for stroke. Women also had higher mortality after stroke regardless of stroke-type or duration since stroke onset. Excess stroke mortality in women was greatest during the in-hospital period after IS, whereas excess mortality increased with time in women who had a HS. No clear relationship was found between duration since stroke-onset and mortality in patients who had SUT. More high-quality research into sex differences in stroke mortality in non-Western populations is essential to identify regions requiring population-tailored changes to the delivery of stroke care for women and to reduce the overall global burden of stroke-related morbidity and mortality.

ACKNOWLEDGEMENTS

AA: primary author, drafting manuscript

TAP: statistical analysis and supervision

ST: data acquisition of Thai data, data interpretation

KS: data acquisition of Thai data, data interpretation

NK: data acquisition of Thai data, data interpretation

MAM: supervision, critical revision

PKM: supervision, senior author critical revision

PKM is the guarantor.

REFERENCES

1. Johnson W, Onuma O, Owolabi M, et al. Stroke: a global response is needed. *Bull World Health Organ.* 2016;94(9):634–634A. doi:10.2471/BLT.16.181636.
2. Reeves M, Bushnell C, Howard G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol.* 2008;7(10):915-26. doi: 10.1016/S1474-4422(08)70193-5.
3. Petrea R, Beiser A, Seshadri S, et al. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. *Stroke*. 2009;40(4):1032-7. doi: 10.1161/STROKEAHA.108.542894.
4. Kapral M, Degani N, Hall R, et al. Gender differences in stroke care and outcomes in Ontario. *Womens Health Issues*. 2011;21(2):171-6. doi: 10.1016/j.whi.2010.10.002.
5. Thorvaldsen P, Kuulasmaa K, Rajakangas A, et al. Stroke trends in the WHO MONICA project. *Stroke.* 1997;28:500-506. doi: 10.1161/01.str.28.3.500.
6. Das S, Banerjee T, Biswas A, et al. A prospective community-based study of stroke in Kolkata, India. *Stroke.* 2007;38:906-910. doi: 10.1161/01.STR.0000258111.00319.58.
7. Tafreshi G, Raman R, Ernstrom K, et al. Gender differences in acute stroke treatment: the University of California San Diego experience. *Stroke.* 2010;41(8):1755-7. doi: 10.1161/STROKEAHA.110.584136.
8. Andersen M, Andersen K, Kammersgaard L, et al. Sex differences in stroke survival: 10-year follow-up of the Copenhagen stroke study cohort. *J Stroke Cerebrovasc Dis* 2005;14:215–220. doi: 10.1016/j.jstrokecerebrovasdis.2005.06.002.
9. James M, Cox M, Xian Y, et al. Sex and age interactions and differences in outcomes after intracerebral hemorrhage. *J Womens Health (Larchmt).* 2017;26(4):380-388. doi: 10.1089/jwh.2016.5849.

10. Wiszniewska M, Niewada M, Czlonkowska A, et al. Sex differences in risk factor distribution, severity, and outcome of ischemic stroke. *Acta Clin Croat.* 2011;50(1):21-28.
11. Wood A, Mannu G, Clark A, et al. Rheumatic mitral valve disease is associated with worse outcomes in stroke. *Stroke*. 2016;47:2695–701. doi: 10.1161/STROKEAHA.116.014512
12. Cumming K, Tiamkao S, Kongbunkiat K, et al. Impact of HIV on inpatient mortality and complications in stroke in Thailand: a national database study. *Epidemiol Infect* 2017;145:1285–91. doi:10.1017/S095026881600340X
13. Roy-O'Reilly M and McCullough L. Age and Sex Are Critical Factors in Ischemic Stroke Pathology. *Endocrinology.* 2018;159(8):3120-3131. doi: 10.1210/en.2018-00465.
14. Poorthuis M, Algra A, Algra A, et al. Female- and Male-Specific Risk Factors for Stroke: A Systematic Review and Meta-analysis. *JAMA Neurol*. 2017;74(1):75-81. doi: 10.1001/jamaneurol.2016.3482.
15. Ong C, Wong Y, Sung S, et al. Sex-related differences in the risk factors for in-hospital mortality and outcomes of ischemic stroke patients in rural areas of taiwan. *PLoS One.* 2017;12(9):e0185361. doi: 10.1371/journal.pone.0185361.
16. Stuart-Shor E, Wellenius G, DelloIacono D, et al. Gender differences in presenting and prodromal stroke symptoms. *Stroke.* 2009;40(4):1121–1126. doi:10.1161/STROKEAHA.108.543371.
17. Kapral M, Fang J, Hill M, et al. Sex differences in stroke care and outcomes: Results from the registry of the canadian stroke network. *Stroke*. 2005;36(4):809-814. doi: 10.1161/01.STR.0000157662.09551.e5.
18. Towfighi A, Tai W, Markovic D, et al. Sex-specific temporal trends in in-hospital mortality after stroke among middle-age individuals in the united states. *Stroke.* 2011;42(10):2740-2745. doi: 10.1161/STROKEAHA.110.612648.

19. Watase H, Shen M, Sui B, et al. Differences in atheroma between Caucasian and Asian subjects with anterior stroke: A vessel wall MRI study. *Stroke Vasc Neurol.* 2021;6(1):25-32. doi: 10.1136/svn-2020-000370.
20. Caplan L. Lacunar infarction and small vessel disease: pathology and pathophysiology. *J Stroke.* 2015;17(1):2-6. doi: 10.5853/jos.2015.17.1.2.
21. Gezmu T, Schneider D, Demissie K, et al. Risk factors for acute stroke among South Asians compared to other racial/ethnic groups. *PLoS One*. 2014;30;9(9):e108901. doi: 10.1371/journal.pone.0108901.
22. Mapoure Y, Eyambe N, Dzudie A, et al. Gender-related differences and short-term outcome of stroke: Results from a hospital-based registry in sub-saharan africa. *Neuroepidemiology.* 2017;49(3-4):179-188. doi: 10.1159/000484319.
23. Bushnell C, Chaturvedi S, Gage K, et al. Sex differences in stroke: Challenges and opportunities. *J Cereb Blood Flow Metab*. 2018 Dec;38(12):2179-2191. doi: 10.1177/0271678X18793324.
24. Visvanathan K and Yager J. Ethnic Variations in Estrogen and Its Metabolites: Sufficient to Explain Differences in Breast Cancer Incidence Rates? *J Natl Cancer Inst.* 2016;108(11):djw147. doi: 10.1093/jnci/djw147. Erratum in: *J Natl Cancer Inst*. 2016;108(9). pii: djw187. doi: 10.1093/jnci/djw187.
25. Tafreshi G, Raman R, Ernstrom K, et al. Gender differences in acute stroke treatment: the University of California San Diego experience. *Stroke.* 2010 Aug;41(8):1755-7. doi: 10.1161/STROKEAHA.110.584136.
26. Petrea R, Beiser A, Seshadri S, et al. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. *Stroke.* 2009;40(4):1032-7. doi: 10.1161/STROKEAHA.108.542894.

27. Di Carlo A, Lamassa M, Baldereschi M, et al. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in europe: Data from a multicenter multinational hospital-based registry. *Stroke.* 2003;34(5):1114-1119. doi: 10.1161/01.STR.0000068410.07397.D7.
28. Palnum K, Andersen G, Ingeman A, et al. Sex-related differences in quality of care and short-term mortality among patients with acute stroke in Denmark: a nationwide follow-up study. *Stroke.* 2009;40(4):1134-9. doi: 10.1161/STROKEAHA.108.543819.
29. Eriksson M, Åsberg S, Sunnerhagen K, et al. Sex Differences in Stroke Care and Outcome 2005-2018: Observations From the Swedish Stroke Register. *Stroke.* 2021;52(10):3233-3242. doi: 10.1161/STROKEAHA.120.033893.
30. Saklayen M. The Global Epidemic of the Metabolic Syndrome. *Curr Hypertens Rep.* 2018;20(2):12. doi: 10.1007/s11906-018-0812-z.
31. Vaartjes I, Reitsma J, Berger-van Sijl M, et al. Gender differences in mortality after hospital admission for stroke. *Cerebrovasc Dis*. 2009;28(6):564-571. doi: 10.1159/000247600.
32. Glader E, Stegmayr B, Norrving B, et al. Riks-Stroke Collaboration. Sex differences in management and outcome after stroke: a Swedish national perspective. *Stroke.* 2003;34(8):1970-5. doi: 10.1161/01.STR.0000083534.81284.C5.
33. Holroyd-Leduc J, Kapral M, Austin P, et al. Sex differences and similarities in the management and outcome of stroke patients. *Stroke.* 2000;31(8):1833-7. doi: 10.1161/01.str.31.8.1833.
34. Mehndiratta M, Khan M, Mehndiratta P, et al. Stroke in Asia: geographical variations and temporal trends. *J Neurol Neurosurg Psychiatry*. 2014;85(12):1308-12. doi: 10.1136/jnnp-2013-306992.

35. Olsen T, Dehlendorff C and Andersen K. Sex-related time-dependent variations in post-stroke survival--evidence of a female stroke survival advantage. *Neuroepidemiology.* 2007;29(3-4):218-25. doi: 10.1159/000112464

36. Olsen T and Andersen K. Female survival advantage relates to male inferiority rather than female superiority: A hypothesis based on the impact of age and stroke severity on 1-week to 1-year case fatality in 40,155 men and women. *Gend Med*. 2010;7(4):284-95. doi: 10.1016/j.genm.2010.08.001.

37. Gu H, Yang X, Rao Z, et al. China National Stroke Registries Investigators. Disparities in outcomes associated with rural-urban insurance status in China among inpatient women with stroke: a registry-based cohort study. *Ann Transl Med*. 2019;7(18):426. doi: 10.21037/atm.2019.08.125.