НЕЙРОХИРУРГИЯ
Russian Journal of Neurosurgery
4 ТОМ 27 Vol. 27 2025

DOI: https://doi.org/10.63769/1683-3295-2025-27-4-37-45

Complex network populational analysis of comorbidities in patients with ruptured cerebral aneurysms, taking into account sex differences

Contacts:
Yuriy Vladimirovich Kivelev
j.v.kivelev@gmail.com

Yu.V. Kivelev[1, 2], E.N. Bailiuk[3], A.L. Krivoshapkin[1, 4], V.Yu. Cherebillo[5]

[1]Neurosurgery Clinic, European Medical Center; 35 Schepkina St., Moscow 129090, Russia;
[2]Center of Postgraduate Education, A.P. Zilber Medical Institute, Petrozavodsk State University; 31 Krasnoarmeyskaya St., Petrozavodsk 185035, Russia;
[3]"Lakhta" Hospital of the "Mother and child" Group of Companies; Bld. 1, 100a Lakhtinskiy Ave., Saint Petersburg 197229, Russia;
[4]Peoples' Friendship University of Russia n. a. Patrice Lumumba; 6 Miklukho-Maklaya St., Moscow 117198, Russia;
[5]Department of Neurosurgery, I.P. Pavlov First Saint Petersburg State Medical University; 6–8 L'va Tolstogo St., Saint Petersburg 197022, Russia

Background. The population characteristics of comorbidities in patients with subarachnoid hemorrhage (SAH) are insufficiently underlined in the literature.
Aim. To test the method of complex network analysis (NA) in studying sex differences in comorbidities among patients with SAH at the population level.
Materials and methods. CN analysis was conducted on a population-based "big data" sample, including 628,831 patients. Statistical networks of comorbidities were created for 873 patients with SAH caused by cerebral aneurysms rupture of various localizations. Comorbidities were defined as any additional diagnoses presenting in patients with a ruptured cerebral aneurysm both before and after the SAH event. At the final stage of the CN analysis, all associations of comorbidities with the index diagnosis and with each other were examined for statistical significance.
Results. The CN analysis revealed 336 statistically significant associations between diagnostic codes. The number of comorbidities in women was 1.7 times higher than in men. In cases of vertebrobasilar aneurysms, the difference reached 10 times. Arterial hypertension was statistically correlated with the development of SAH only in women.
Conclusion. The CN method is applicable for analyzing clinical data at the population level. The analysis revealed that women with SAH have a higher number of comorbidities, particularly in cases of vertebrobasilar aneurysms. Interpretation of the results should consider the limitations and advantages of the method.

Keywords: cerebral aneurysm, subarachnoid hemorrhage, comorbidities, sex differences, complex network analysis

For citation: Kivelev Yu.V., Bailiuk E.N., Krivoshapkin A.L., Cherebillo V.Yu. Complex network populational analysis of comorbidities in patients with ruptured cerebral aneurysms, taking into account sex differences. Neyrokhirurgiya = Russian Journal of Neurosurgery 2025;27(4):37–45. DOI: https://doi.org/10.63769/1683-3295-2025-27-4-37-45

BACKGROUND

The theory of network analysis, developed at the intersection of research in the field of mathematics and theoretical physics, made it possible to create a methodological tool for use in medicine, particularly in neurovascular diseases [1].

One of the most dangerous types of neurovascular pathology is aneurysmal subarachnoid hemorrhage (SAH). This type of intracranial hemorrhage is characterized by high mortality rates, reaching 40 % within the first 30 days [2, 3], and a high degree of disability [4].

Cerebral aneurysms occur in 3 % of the population and are the cause of 5 % of all acute cerebrovascular accidents [2, 5–7]. According to the literature, cerebral aneurysms are more common in women, and the risk of SAH after 50 years old is 2.2 times higher in them comparing to men [8, 9].

In recent decades, there has been a downward trend in the incidence of aneurysmal SAH in almost all countries worldwide. According to a meta-analysis by N. Etminan et al., the global incidence of SAH decreased from 10.2 to 6.1 cases per 100,000 people per year from 1980 to 2010 [3]. When assessing regional characteristics, the authors noted

that during this period, the decline in the SAH incidence in Europe was 40.6 %, in Asia – 46.2 %, in the USA – 14.2 %, however, in Japan there was a sharp increase in this indicator by 59.1 %, and only in women.

It is important to note that, despite the global trend toward a decrease in the SAH occurence, the incidence of unruptured cerebral aneurysms, according to the literature, has increased in recent decades [10]. Thus, it can be said about an epidemiological paradox, the nature of which remains unclear. In this context, the adaptation of modern computer technologies to the statistical analysis of large samples may open new perspectives for analyzing and understanding the population characteristics of SAH incidence [11].

One of the methods for analyzing the big data is NA [1, 12, 13]. The NA method allows to identify the reliable statistical relationships between variables in very large and heterogeneous samples, as well as effectively exclude random coincidences in pool of data [13].

We previously demonstrated the potential of NA to assess the incidence of comorbidities associated with unruptured cerebral aneurysms at the population level [1]. Given the above-mentioned literature data on sex differences, the studying of the epidemiological characteristics of conditions associated with SAH may expand our understanding of this disease.

Aim – to test the NA method in studying the sex differences for comorbid diseases (CD) in patients with SAH at the population level.

MATERIALS AND METHODS

The design was a retrospective, population-based, longitudinal study. A big data set was compiled in consultation with the local research center from the outhwest Finland Health Region's patient registry, covering 870,000 people. All patients who had contact with healthcare facilities in the region between January 1, 2004, and July 31, 2019, were included in the registry from the regional healthcare facility digital data warehouse. Only data from patients with a diagnosis coded according to the International Classification of Diseases, 10th revision (ICD-10) were included in the subsequent analysis.

To standardize the codes, the diagnosis coding accuracy level at the initial stage of patient selection was set to XNN (X is the letter denoting the diagnosis class, NN is the first two digits of the category). The data were distributed by patient age groups (0–9, 10–19, 20–29 years, etc.) separately for men and women. The information on all diagnoses recorded in patients was stored in the corresponding age groups. For example, if a patient was diagnosed with diagnosis No. 1 at age 55 and diagnosis No. 2 at age 65, then according to our data separation system, one information signal (diagnosis No. 1) was included in the 50–59-year-old cohort, and both signals (diagnoses No. 1 and No. 2) were included in the 60–69-year-old cohort.

Due to this approach it is allowed for the broadest possible coverage of registered diagnoses for each individual patient across all age cohorts. This approach was suitable for 628,831 patients from the total sample. From the resulting data, 873 patients with SAH from aneurysms of various locations were then identified. SAH was established as the index diagnosis. The coding accuracy level at this stage was expanded to a three-digit category (e. g., I60.5). Any other diagnosis, registered both before and after SAH, was defined as concomitant.

To reveal the correlations between the index and associated diagnoses, the statistical method NA [1] was applied to the resulting sample. Networks of diagnosis codes were created, where the relationship between each given ICD-10 diagnosis code (node) and any other diagnosis code (node) in the population was designated as a link between nodes in the statistical network. The link between nodes itself denoted the presence of at least one patient from the entire sample (628,831 individuals) with both the given diagnosis and a randomly distributed diagnosis in the population.

To calculate the statistical weighting of relationships and determine the statistical significance (p-values), the method of M. Tumminello et al. [9] was used. Statistical validation of the network was performed using the false discovery rate (FDR) method. This method was used to validate all possible and obtained p-values for each relationship between diagnosis codes (Fig. 1). The current p-value threshold was increased in a linear sequence. Upon reaching a certain level (p >0.001), false positive relationships in the original network were identified for removal.

After statistical processing according to the above mentioned conditions, the so-called egonetworks of diagnoses were created, which represented the relationships of the index code of the diagnosis with other diagnoses, as well as the relationships of the latter with each other. Seven ICD-10 codes corresponding to aneurysmal SAH were used as index codes of diagnoses, including I60.0 (SAH from the carotid sinus and bifurcation), I60.1 (SAH from the middle cerebral artery (MCA)), I60.2 (SAH from the anterior communicating artery), I60.3 (SAH from the posterior communicating artery), I60.4 (SAH from the basilar artery), I60.5 (SAH from the vertebral artery), I60.6 (SAH from other intracranial arteries).

The division of diagnoses by the localization of intracranial arteries was due to the different epidemiological, pathophysiological and hemodynamic characteristics of cerebral aneurysms of different intracranial arteries.

RESULTS

A total of 336 connections between the CD codes were confirmed across all 7 specified codes (Table 1). Connections in the networks were unevenly distributed and depended on the location of the ruptured aneurysm. Thus, the largest number of CD codes, namely 97, were found for ruptured MCA aneurysms (code I60.1). The fewest CD diagnosis codes, namely 11, were found for ruptured vertebral artery aneurysms (code I60.5).

НЕЙРОХИРУРГИЯ
Russian Journal of Neurosurgery
4 ТОМ 27 Vol. 27 2025

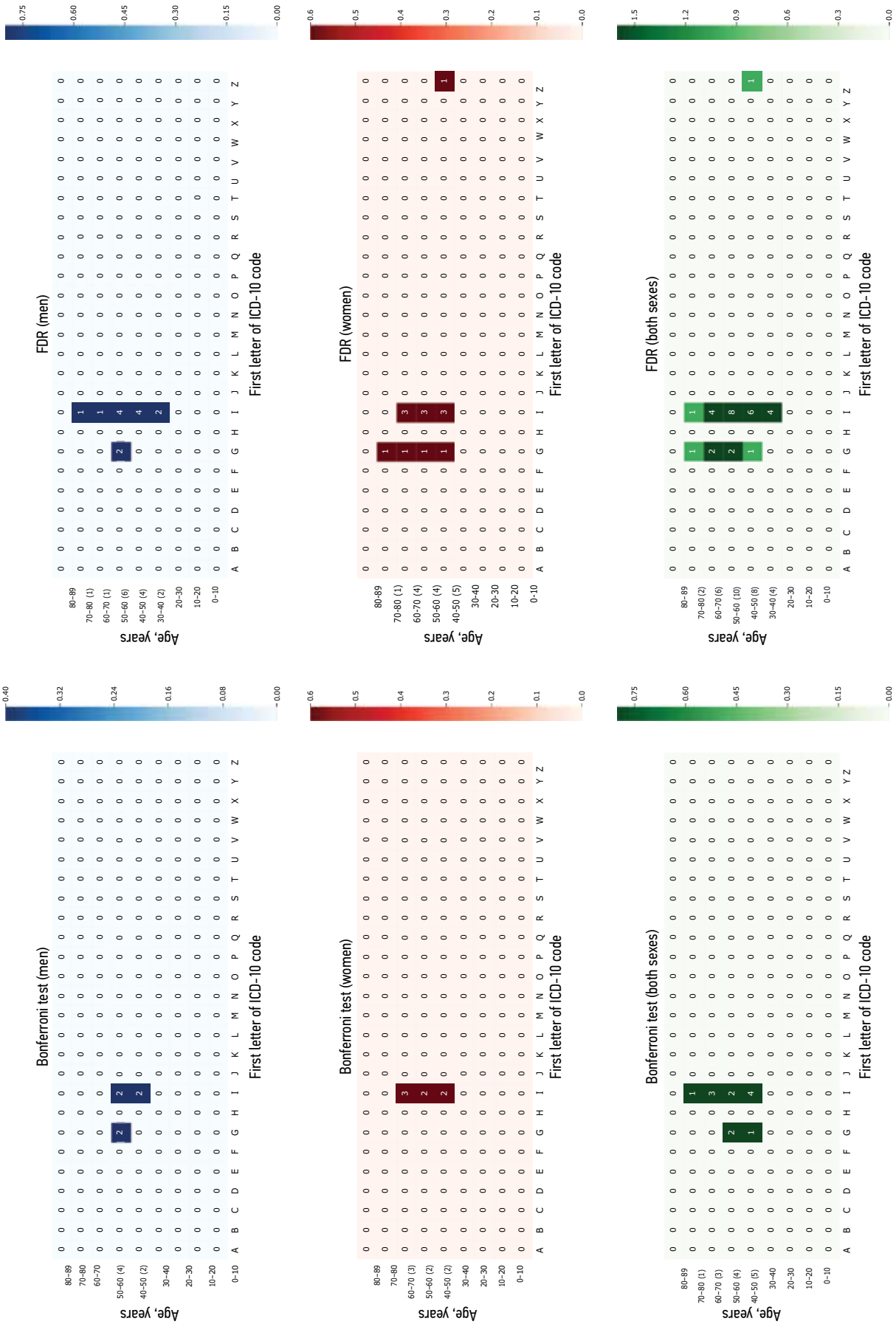

Fig. 1. *Heartmap of comorbidities in network of I60.6 diagnosis according to International Classification of Diseases 10th revision (ICD-10). FDR – false discovery rate*

Table 1. Comorbidities among subarachnoid hemorrhage patients with different aneurysm localization

ICD-10 code	Aneurysm localization	Men, *n*	Women, *n*	Total, *n*	Ratio (women/men)
I60.0	ICA	38	53	91	1.4
I60.1	MCA	36	61	97	1.7
I60.2	ACA	28	40	68	1.4
I60.3	PCA	4	12	16	3
I60.4	BA	5	20	25	4
I60.5	VA	1	10	11	10
I60.6	Other	14	14	28	1
Total		*126*	*210*	*336*	–

Note. *ICD-10 – International Classification of Diseases 10th revision; ICA – internal carotid artery; MCA – middle cerebral artery; ACA – anterior communicating artery; PCA – posterior cerebral artery; BA – basilar artery; VA – vertebral artery.*

Excluding diagnosis I60.6, where the number of CD codes was equal for men and women, for all other aneurysm locations, the number of CD codes in women exceeded that in men (median 1.7 times). For internal carotid artery (ICA) aneurysms, this figure was 1.4 times higher, for MCA aneurysms, 1.7 times higher, and for anterior communicating artery (ACoA) aneurysms, 1.4 times higher.

When the aneurysm was localized in the vertebrobasilar system, the difference increased, reaching a threefold excess for posterior cerebral artery (PCA) aneurysms, a fourfold excess for basilar artery 9BA) aneurysms, and a tenfold excess for vertebral artery (VA) aneurysms. The distribution of CD diagnoses and the level of detected and threshold *p*-values is presented in Table 2 using the given diagnosis I60.5 as an example.

The overwhelming majority of CD diagnosis codes across all aneurysm locations directly indicated a diagnosis of SAH (I60.0 – I60.9). Moreover, in some cases, a code indicating a ruptured aneurysm at one location was often statistically significant associated with a SAH code for an aneurysm at another location.

This obviously reflects a real-life clinical situation, where the location of a ruptured aneurysm is clarified after additional investigations and/or in cases of multiple aneurysms. Accordingly, the database may contain both diagnostic codes, which are subsequently considered in the NA.

In addition, the associations with the code I67.1 (unruptured cerebral aneurysms) were recorded, which also indicates the presence of multiple aneurysms in a patient who underwent SAH due to a ruptured aneurysm at a given location, and the remaining aneurysms were later coded using the appropriate code.

Diagnoses associated with the sequelae and complications of SAH included, among them I61.0 (intracerebral hemorrhage in the subcortical hemisphere), G94.2 (hydrocephalus), Z98.2 (presence of a device for drainage of cerebrospinal fluid), G00.9 (bacterial meningitis), G40.2 (localized (focal, partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures).

Arterial hypertension (AH) (I10) was detected only in women aged 40–69 years, most often with MCA aneurysms and BA aneurysms. No association between SAH and AH was observed in men.

DISCUSSION

In this study, we demonstrated the potential of NA to examine CD in patients with aneurysmal SAH at a population level. According to the results, the statistically validated set of CD diagnosis codes in this patient group primarily included conditions related either directly to SAH or to its sequelae.

Sex differences in the number of CDs have been revealed depending on the location of the ruptured aneurysm. In general, sex differences in patients with SAH have been described in sufficient detail in the literature [8, 9]. One possible reason for their presence is the decrease in estrogen levels during menopause, which may contribute to the formation and rupture of aneurysms [14, 15].

This is verified by the results of studies showing that women with late menarche and early menopause have an increased risk of SAH due to a reduced period of cumulative estrogen exposure throughout life [16]. Laboratory experiments have shown that the administration of basodoxifene (an estrogen receptor agonist) to ovariectomized rodents reduced the risk of SAH by 17 % compared to the control group [17].

The studies analyzing the role of isoflavones contained in dietary legumes (beans, peas, soybeans, etc.) and possessing pronounced estrogenic activity and affinity for the corresponding tissue receptors are also in the area of interest [18, 19]. When obtained from food, a phytoestrogen such as daidzein is digested by intestinal flora to form equol, which, after absorption, binds to estrogen β-receptors [20]. In an experimental study on animals, K. Yokosuka et al.

Table 2. Comorbidities in network of I60.5

Age, year	Sex	Comorbidity (ICD-10 code)	*p*	Threshold of *p*-value
40–49	Female	I69.0	5.52 e-08	7.07 e-06
40–49	Female	I60.7	5.71 e-07	8.63 e-06
50–59	Female	I60.9	3.02 e-10	5.28 e-06
50–59	Female	I69.0	3.20 e-10	5.30 e-06
60–69	Male	I60.4	2.30 e-10	6.31 e-06
60–69	Female	I69.0	3.68 e-07	9.78 e-06
60–69	Female	I60.9	4.67 e-07	1.00 e-05
60–69	Female	I61.5	1.17 e-06	1.09 e-05
60–69	Female	T85.0	2.04 e-06	1.15 e-05
60–69	Female	G94.2	1.54 e-08	7.50 e-06
70–79	Female	I60.9	6.23 e-09	7.03 e-06

Note. *ICD-10 – International Classification of Diseases 10th revision; I60.5 – subarachnoid hemorrhage from the vertebral artery; I69.0 – sequelae of nontraumatic subarachnoid hemorrhage; I60.7 – nontraumatic subarachnoid hemorrhage from unspecified intracranial artery; I60.9 – nontraumatic subarachnoid hemorrhage, unspecified; I60.4 – subarachnoid hemorrhage from basilar artery; I61.5 – nontraumatic intracerebral hemorrhage, intraventricular; T85.0 – mechanical complication of ventricular intracranial (communicating) shunt; G94.2 – hydrocephalus in other diseases classified elsewhere.*

found that daidzein and its metabolite equol reduce the risk of developing arterial aneurysms [21].

According to the trend which we identified for a higher number of diagnoses of vertebrobasilar systemic cerebrovascular accident in women, we suggest that the arteries in this location may be more sensitive to fluctuations in estrogen exposure. This assumption is based on published data on the presence of estrogen β-receptors in the pericytes of cerebral arteries, which, when exposed to estradiol, improve endothelial integrity [22].

To current, we have not found any studies in the available literature indicating specific patterns of estrogen β-receptor distribution in cerebral arteries. We believe it is reasonable to hypothesize that a genetically determined decrease in the concentration and/or inactivation of estrogen receptors in the walls of predominantly posterior circulation arteries in postmenopausal women may play a role, increasing the risk of SAH.

According to the literature, the role of genetic factors in sex differences in SAH is revealed primarily in the characteristics of inflammatory processes in the arterial wall [23, 24]. In a study devoted to the examine of the effect of aspirin on the behavior of cerebral aneurysms, a more pronounced decrease in the expression of the 15-PGDH (15-hydroxyprostaglandin dehydrogenase) gene and an increased content of inflammatory mediators (COX-2, CD-68, MMP-9, MCP-1, NF-κB) were recorded in women.

While the inflammatory process is one of the main mechanisms underlying the pathophysiological changes in the arterial wall and aneurysm formation, the discovery of sex-associated variations in the genetic regulation of the inflammatory response opens new perspectives for studying the mechanisms of this disease.

Compared with our previous analysis of unruptured cerebral aneurysms using the NA method [1], the resulting set of CD diagnosis codes for SAH is less diverse. In unruptured cerebral aneurysms, along with known vascular risk-associated pathologies such as hypertension, smoking, and atherosclerosis, we also found conditions such as chronic obstructive pulmonary disease in nonsmokers, depressive disorders, and chronic streptococcal infection [1].

No such statistically significant correlations were observed in the SAH analysis. Moreover, such a widely recognized risk factor as tobacco smoking was not associated with SAH in any of the subgroups in our analysis. This is most likely due to shortcomings in recording the diagnosis of tobacco smoking as a separate ICD code, and mention of smoking in text form was not included in the NA, as per the study design.

It should be emphasized that the smoking factor plays a significant role in studying sex differences in SAH. According to the literature, the growth of cerebral aneurysms and the risk of SAH increase in smokers by 3–4 times [25]. Moreover, in the study by J.S. Catapano et al. in the sample of 1014 patients with SAH, 69 % were women, but men were almost 10 % more likely to be smokers. The median age of women was 56.6 years, and the number of smokers among them was significantly lower than among men [8]. N. Etminan et al. in a study devoted to global trends in the incidence of SAH found that in women in Japan from 1980 to 2010, an increase in the incidence of SAH by almost 60 % was noted [3].

Although the percentage of smokers in Japan in this study was slightly higher than in other regions (26.1 % and 19.3 %, respectively), this could not explain such a significant increase in the incidence of SAH in women. Among other factors, the authors of this study also recorded a decrease in the incidence of SAH with a population-wide decrease in blood pressure [3].

In our study, arterial hypertension was statistically significant correlated with SAH in women over 50 years old. The absence of this association in men in our study contradicts clinical experience, and the reason for this result most likely is in the shortcomings of the NA method. According to the literature, arterial hypertension is a powerful risk factor for aneurysm rupture and the development of SAH [5]. In hypertension, hemodynamic stress affects arterial vessels, causing narrowing of their caliber and decreased elasticity of the arterial wall [26].

With prolonged exposure of arterial hypertension, the processes of autoregulation of cerebral arteries deteriorate [27]. It should be noted that both under arterial hypertension and in normal conditions, blood flow in the cerebral arteries may have sex differences. The ICA diameter is usually smaller in women, which creates a 50 % greater hemodynamic load on the bifurcation of the ICA than in men [6, 28]. Measurements of blood flow velocity in the cerebral arteries also show clear sex differences. Thus, in the study of J.R. Cebral et al., average values of blood flow velocity in the MCA were determined at 75 cm/s in women and 64 cm/s in men, in the ICA – 42 cm/s in women and 34 cm/s in men [29].

In the presence of arterial hypertension, with impaired autoregulation and changes in the caliber of the main cerebral arteries, the anatomical features may predispose women to more severe hemodynamic impairment and, at least indirectly, increase the risk of SAH. Combined with hormonal influences, these factors are associated with a predisposition to cerebral aneurysm rupture in women over 50, that was also confirmed by our study.

Our obtained data may have practical implications for clinical practice in neurosurgery, particularly within the framework of the modern concept of individualized treatment approaches. Given the identified sex differences in comorbid conditions, more careful monitoring of CD in women is recommended, particularly for vertebrobasilar aneurysms. Furthermore, further research into the role of estrogens and their receptors in aneurysm formation and rupture may serve as a basis for developing new preventive strategies and screening regimens for these populations.

The NA method has a number of limitations that must be considered when interpreting the results. This method is relatively sensitive to the quality of data entry in the registers. The accuracy and completeness of diagnosis coding, as well as systematic errors or gaps in the data in our study, could have directly impacted the identified associations. Furthermore, one significant drawback of the NA method is the low detection rate of false negative associations.

For example, despite known epidemiological data on the association between SAH and tobacco smoking, our analysis failed to detect such a link. This may be due to deficiencies in the coding of data in medical registries by clinicians and the method insufficient sensitivity to rare or infrequently recorded factors. It is important to emphasize that the NA method does not establish causal relationships, but only captures statistical correlations.

One of our study limitations is the regional feature of the sample. Despite the large dataset (628,831 patients), these data were obtained from a registry within a specific region, necessitating caution in generalizing the findings to other populations. The identified differences in the frequency of comorbid diagnoses by sex and aneurysm location require further confirmation using prospective studies.

CONCLUSION

Our study demonstrated the potential of the NA method for population-based analysis of SAH and other associated pathological conditions. Data from 628,831 patients revealed 873 cases of SAH from aneurysms of various locations, including 336 statistically significant associations with CD. The analysis revealed that women diagnosed with SAH are characterized by a higher incidence of CD, especially with vertebrobasilar aneurysms. Hemodynamic, endocrinological, and genetic differences between the sexes are considered as possible causes. The obtained data can be used for further research into the etiology and mechanisms of cerebral aneurysm development and rupture.

References

1. Kivelev J., Saarenpää I., Karlsson A. et al. Complex networks approach to study comorbidities in patients with unruptured intracranial aneurysms. Sci Rep 2024;14(1):9175. DOI: 10.1038/s41598-024-59919-2
2. Van Gijn J., Kerr R.S., Rinkel G.J. Subarachnoid haemorrhage. Lancet 2007;369(9558):306–18. DOI: 10.1016/S0140-6736(07)60153-6
3. Etminan N., Brown R.D. Jr., Beseoglu K. et al. The unruptured intracranial aneurysm treatment score: a multidisciplinary consensus. Neurology 2015;85(10):881–9. DOI: 10.1212/WNL.0000000000001891
4. Suarez J.I., Tarr R.W., Selman W.R. Aneurysmal subarachnoid hemorrhage. N Engl J Med 2006;354(4):387–96. DOI: 10.1056/NEJMra052732
5. Lawton M.T., Vates G.E. Subarachnoid hemorrhage. N Engl J Med 2017;377(3):257–66. DOI: 10.1056/NEJMcp1605827
6. Peng C., Zhao Y., Li F. et al., Aneurysmal subarachnoid hemorrhage and sex differences: analysis of epidemiology, outcomes, and risk factors. Neurocrit Care 2024;41(1):119–28. DOI: 10.1007/s12028-023-01929-5
7. Rinkel G.J., Djibuti M., Algra A., van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke 1998;29(1):251–6. DOI: 10.1161/01.str.29.1.251
8. Catapano J.S., Winkler E.A., Rudy R.F. et al. Sex differences in patients with and without high-risk factors associated with aneurysmal subarachnoid hemorrhage. Acta Neurochir (Wien) 2024;166(1):125. DOI: 10.1007/s00701-024-06021-1
9. Vlak M.H., Algra A., Brandenburg R., Rinkel G.J. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet Neurol 2011;10(7):626–36. DOI: 10.1016/S1474-4422(11)70109-0
10. Laukka D., Kivelev J., Rahi M. et al. Detection rates and trends of asymptomatic unruptured intracranial aneurysms from 2005 to 2019. Neurosurgery 2024;94(2):297–306. DOI: 10.1227/neu.0000000000002664
11. Kivelev J.V., Saarenpää I., Krivoshapkin A.L. Establishing of big data clinical dataset in brain vessel aneurysm research. Sibirski nauchnyi medicinskij jurnal = Sibirian Scientidic Medical Journal 2023;43(3):86–94. (In Russ.). DOI: 10.18699/SSMJ20230311
12. Barabási A.L. Network medicine – from obesity to the “diseasome”. New Engl J Med 2007;357(4):404–7. DOI: 10.1056/NEJMe078114
13. Tumminello M., Micciché S., Lillo F. et al., Statistically validated networks in bipartite complex systems. PloS One 2011;6(3):e17994. DOI: 10.1371/journal.pone.0017994
14. Tabuchi S. Relationship between postmenopausal estrogen deficiency and aneurysmal subarachnoid hemorrhage. Behav Neurol 2015;2015:720141. DOI: 10.1155/2015/720141
15. Tada Y., Wada K., Shimada K. et al., Estrogen protects against intracranial aneurysm rupture in ovariectomized mice. Hypertension 2014;63(6):1339–44. DOI: 10.1161/HYPERTENSIONAHA.114.03300
16. Algra A.M., Klijn C.J., Helmerhorst F.M. et al. Female risk factors for subarachnoid hemorrhage: a systematic review. Neurology 2012;79(12):1230–6. DOI: 10.1212/WNL.0b013e31826aace6
17. Maekawa H., Tada Y., Yagi K. et al., Bazedoxifene, a selective estrogen receptor modulator, reduces cerebral aneurysm rupture in Ovariectomized rats. J Neuroinflammation 2017;14(1):197. DOI: 10.1186/s12974-017-0966-7
18. Jackson R.L., Greiwe J.S., Schwen R.J. Emerging evidence of the health benefits of S-equol, an estrogen receptor β agonist. Nutr Rev 2011;69(8):432–48. DOI: 10.1111/j.1753-4887.2011.00400.x
19. Mayo B., Vázquez L., Flórez A.B. Equol: a bacterial metabolite from the daidzein isoflavone and its presumed beneficial health effects. Nutrients 2019;11(9):2231. DOI: 10.3390/nu11092231
20. Setchell K.D., Clerici C., Lephart E.D. et al. S-equol, a potent ligand for estrogen receptor beta, is the exclusive enantiomeric form of the soy isoflavone metabolite produced by human intestinal bacterial flora. Am J Clin Nutr 2005;81(5):1072–9. DOI: 10.1093/ajcn/81.5.1072
21. Yokosuka K., Rutledge C., Kamio Y. et al. Roles of phytoestrogen in the pathophysiology of intracranial aneurysm. Stroke 2021;52(8):2661–70. DOI: 10.1161/STROKEAHA.120.032042
22. Kurmann L., Okoniewski M., Dubey R.K. Estradiol inhibits human brain vascular pericyte migration activity: a functional and transcriptomic analysis. Cells 2021;10(9):2314. DOI: 10.3390/cells10092314
23. Hasan D.M., Mahaney K.B., Brown R.D. Jr. et al., Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. Stroke 2011;42(11):3156–62. DOI: 10.1161/STROKEAHA.111.619411
24. Chalouhi N., Starke R.M., Correa T. et al. Differential sex response to aspirin in decreasing aneurysm rupture in humans and mice. Hypertension 2016;68(2):411–7. DOI: 10.1161/HYPERTENSIONAHA.116.07515
25. Woo D., Khoury J., Haverbusch M.M. et al., Smoking and family history and risk of aneurysmal subarachnoid hemorrhage. Neurology 2009;72(1):69–72. DOI: 10.1212/01.wnl.0000338567.90260.46
26. Cipolla M.J., Liebeskind D.S., Chan S.L. The importance of comorbidities in ischemic stroke: Impact of hypertension on the cerebral circulation. J Cereb Blood Flow Metab 2018;38(12): 2129–49. DOI: 10.1177/0271678X18800589
27. Baumbach G.L., Faraci F.M., Heistad D.D. Effects of local reduction in pressure on endothelium-dependent responses of cerebral arterioles. Stroke 1994;25(7):1456–61; discussion 1461–2. DOI: 10.1161/01.str.25.7.1456
28. Lindekleiv H.M., Valen-Sendstad K., Morgan M.K. et al. Sex differences in intracranial arterial bifurcations. Gend Med 2010;7(2):149–55. DOI: 10.1016/j.genm.2010.03.003
29. Cebral J.R., Castro M.A., Putman C.M., Alperin N. Flow-area relationship in internal carotid and vertebral arteries. Physiol Meas 2008;29(5):585–94. DOI: 10.1088/0967-3334/29/5/005

Acknowledgements. The authors thank J. Piilo, R.N. Mantegna, A. Karlsson, P. Crisafulli, and F. Musciotto for creating and analyzing the database and conducting the network statistical analysis.

Authors' contributions
Yu.V. Kivelev: development of the research concept and design, data collection and processing, statistical data processing, writing and editing of the article; E.N. Bailiuk, A.L. Krivoshapkin, V.Yu. Cherebillo: editing of the article.

ORCID of authors
Yu.V. Kivelev: https://orcid.org/0000-0002-5499-9628
E.N. Bailiuk: https://orcid.org/0009-0001-7863-2089
A.L. Krivoshapkin: https://orcid.org/0000-0003-0789-8039
V.Yu. Cherebillo: https://orcid.org/0000-0001-6803-9954

Conflict of interest. The authors declare no conflict of interest.

Funding. The study was performed without external funding.

Compliance with patient rights and principles of bioethics. The study was retrospective.

Article submitted: 24.03.2025. **Accepted for publication:** 28.08.2025. **Published online:** 25.12.2025