



# Key Risk Factors for Intracerebral Hemorrhage According to Regional Population-Based Stroke Registry

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## Abstract

**Introduction.** Intracerebral hemorrhage (ICH) registry data allow assessing epidemiological parameters and risk factors in different age, gender, race, ethnicity, and other subgroups.

This study **aimed** to evaluate the prevalence of key risk factors in a group of Yakutsk residents with primary hypertensive ICH included in the regional population-based stroke registry from 2015 to 2017.

**Materials and methods.** This study of risk factors was conducted in patients with hypertensive ICH ( $n = 251$ ) from the regional population-based stroke registry, including 133 (53%) men and 118 (47%) women of Asian or Caucasian races. We performed statistical analysis of data.

**Results.** The analysis of risk factors showed that the prevalence of smoking and excessive alcohol consumption was higher in men with ICH compared with women ( $p < 0.001$ ). There were no statistically significant differences in the incidence of hypertension, history of myocardial infarction, dyslipidemia, or diabetes mellitus in patients with ICH in gender or ethnicity subgroups. Fibrillation and other heart diseases were more common in Caucasian patients than in Asian ( $p = 0.005$ ). ICH was associated with high levels of low-density lipoproteins and triglycerides with low levels of total cholesterol and high-density lipoproteins compared with healthy individuals.

**Conclusions.** We described gender and ethnic differences in the prevalence of risk factors in patients with hypertensive ICH.

**Keywords:** intracranial hemorrhage; risk factors

**Ethics approval.** The study was approved by the Ethics Committee of the Yakut Scientific Center for Complex Medical Problems (protocol No. 37, November 28, 2014).

**Source of funding.** The study was not supported by any external sources of funding.

**Conflict of interest.** The authors declare no apparent or potential conflicts of interest related to the publication of this article.

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**For citation:** Maksimova M.Yu., Chugunova S.A. Key risk factors for intracerebral hemorrhage according to regional population-based stroke registry. *Annals of Clinical and Experimental Neurology*. 2024;18(1):5–11. (In Russ.)

DOI: <https://doi.org/10.54101/ACEN.2024.1.1>

Received 14.12.2023 / Accepted 28.12.2023 / Published 25.03.2024

## Основные факторы риска внутричерепных кровоизлияний (по данным территориально-популяционного регистра инсульта)

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## Аннотация

**Введение.** Анализ данных регистра внутричерепных кровоизлияний (ВМК) предоставляет уникальную возможность изучения особенностей эпидемиологических показателей и факторов риска в зависимости от возрастных, гендерных, расово-этнических и других факторов.

**Цель исследования** – изучить распространённость основных факторов риска в группе пациентов с гипертензивными ВМК – резидентов г. Якутска, включённых в территориально-популяционный регистр инсульта за 2015–2017 гг.

**Материалы и методы.** Исследование факторов риска проведено у пациентов с гипертензивными ВМК ( $n = 251$ ), включённых в территориально-популяционный регистр инсульта, в том числе у 133 (53%) мужчин и 118 (47%) женщин, принадлежащих к азиатской и европеоидной расам. Выполнен статистический анализ данных.

**Результаты.** Анализ факторов риска показал, что при ВМК распространённость курения и чрезмерного потребления алкоголя была выше среди мужчин по сравнению с женщинами ( $p < 0,001$ ). Частота артериальной гипертензии, инфаркта миокарда в анамнезе, дислипидемии, сахарного диабета при ВМК не имела статистически значимых различий в зависимости от пола и этнической принадлежности. Фибрилляция предсердий и другие болезни сердца выявлялись чаще среди пациентов европеоидной расы по сравнению с пациентами азиатской расы ( $p = 0,005$ ). Развитие ВМК характеризовалось высокими показателями липопротеинов низкой плотности и триглицеридов, низкими показателями общего холестерина и липопротеинов высокой плотности по сравнению со здоровыми лицами.

**Заключение.** Установлены гендерные и этнические особенности в распространённости факторов риска среди пациентов с гипертензивными ВМК.

**Ключевые слова:** внутримозговые кровоизлияния; факторы риска

**Этическое утверждение.** Проведение исследования одобрено Этическим комитетом Якутского научного центра комплексных медицинских проблем (протокол № 37 от 28.11.2014).

**Источник финансирования.** Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

**Конфликт интересов.** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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**Для цитирования:** Максимова М.Ю., Чугунова С.А. Основные факторы риска внутримозговых кровоизлияний (по данным территориально-популяционного регистра инсульта). *Анналы клинической и экспериментальной неврологии*. 2024;18(1):5–11.

DOI: <https://doi.org/10.54101/ACEN.2024.1.1>

Поступила 14.12.2023 / Принята в печать 28.12.2023 / Опубликовано 25.03.2024

Received 14.12.2023 / Accepted 28.12.2023 / Published 25.03.2024

## Introduction

A concept for risk factors and areas for preventive activities for cerebrovascular disease was formed based on the results of epidemiological studies [1].

Hemorrhagic stroke (HS) is one of the most severe acute cerebrovascular accidents; most often, it complicates the course of hypertension and is associated with high case fatality rate (mortality rate is up to 50%) and severe disability [2]. According to a prospective population-based study (27,702 subjects without a history of stroke in the Swedish population), relative risk of developing massive cerebral hematomas in patients with high blood pressure exceeds the risk of developing ischemic stroke (IS) [3].

S.R. Martini et al. studied risk factors for intracerebral hemorrhage (ICH) in 597 patients and 1548 controls [4]. Hypertension, warfarin use, heredity (i.e. ICH in close family members), history of IS, no higher education,  $\epsilon 2$  or  $\epsilon 4$  alleles of the *APOE* gene were associated with the risk of developing ICH. A relationship was established between

non-lobar hematomas and hypertension with hypercholesterolemia, while lobar hematomas were associated with  $\epsilon 2$  or  $\epsilon 4$  alleles of the *APOE* gene.

The relationship between cholesterol levels and the development of HS is controversial [5]. Low cholesterol levels were reported to be associated with an increased risk of ICH [6]. However, several studies gave opposite results. For example, I. Suh et al. did not find any relationship between low cholesterol levels and the risk of developing ICH [7].

Distribution of IS risk factors in different ethnic groups was thoroughly studied using a regional population-based registry. However, few studies investigated ethnic aspects of risk factors for HS [8–11].

A recent study by C.F. Tsai et al. [8] to assess key risk factors for stroke among patients with HS or IS in the Chinese population was conducted using hospital registry data from 2006 to 2011. A total of 1373 patients with HS and 4953 patients with IS were assessed. The mean age of patients with HS was significantly lower than that of

patients with IS (61 years vs. 68 years;  $p < 0.001$ ) without significant age differences in gender groups. Hypertension (OR = 2.23; 95% CI 1.74–2.87) and alcohol abuse (OR = 1.44; 95% CI 1.16–1.77) had more significant associations with HS than with IS, while diabetes mellitus, atrial fibrillation, coronary artery disease, hyperlipidemia, smoking, and transient ischemic attacks were more frequent in patients with IS than in patients with HS. The authors concluded that hypertension and alcohol abuse in the Chinese population had a stronger association with the risk of HS compared with IS, especially in younger patients.

N.A. Khan et al. studied ICH prevalence in the Canadian population [12]. The proportion of ICH was the highest among representatives of East Asian ethnic groups (30% in the total structure of stroke), followed by patients from South Asia (17%) and the Caucasian population (15%) ( $p < 0.001$ ).

N.C. Smeeton et al. showed that the incidence of hypertension before hemorrhagic stroke was the highest in young black patients [9].

A study was conducted to evaluate the prevalence of risk factors in patients with stroke according to the regional population-based register in Yakutsk from 2002 to 2004. Hypertension was detected in 88.9% of patients, smoking in 43.1%, dyslipidemia in 39.5%, coronary artery disease in 38.6%, atrial fibrillation in 14.8%, myocardial infarction in 14.0%, diabetes mellitus in 11.9%, alcohol abuse in 4.5%, stress in 19.9%, and family history of stroke in 60.7%. In stroke patients from the non-indigenous Yakutian population, smoking, diabetes mellitus, and alcohol abuse were more common [13]. When comparing the frequencies of risk factors for stroke, the authors showed that diabetes mellitus and overweight were less common in the Yakutian population compared to the Moscow one: 7.7% and 21.9% ( $p = 0.005$ ), 49.5% and 72% ( $p = 0.004$ ), respectively. Key risk factors for IS in the Moscow and Yakutian populations included hypertension (84.5% and 74.0%), heart disease (75% and 65.4%), and smoking (43% and 42.3% respectively) [14].

Therefore, ICH registry data allowed assessing epidemiological parameters in different age, gender, race, ethnicity, economic, climate, geographical, and other subgroups.

This study aimed to evaluate the prevalence of key risk factors in a group of Yakutsk residents with primary hypertensive ICH included in the regional population-based stroke registry from 2015 to 2017.

## Materials and methods

This study of risk factors was conducted in 251 patients with primary hypertensive ICH from the regional popula-

tion-based stroke registry, including 133 (53%) men and 118 (47%) women of Asian or Caucasian races. Ethnicity was determined by patients' self-identification. Subjects were considered as the native ethnic population of Asian race if their ethnicity was indicated as Yakuts, Evenks, Evens, or Yukaghirs or as Caucasian if they indicated that they belonged to the Caucasian race.

Brain computed tomography (CT) was performed using 64-slice SOMATOM Definition AS scanner (Siemens), and magnetic resonance imaging (MRI) was performed using Magnetom Espree 1.5 T (Siemens).

The following risk factors for ICH were evaluated: hypertension, cigarette smoking, excessive alcohol consumption, atrial fibrillation, history of myocardial infarction, other heart disorders (i.e. stable coronary artery disease, valvular heart disease, and cardiomyopathies), dyslipidemia, and diabetes mellitus.

Patients who smoked at least 1 cigarette per day during at least 1 year were considered smokers. Excessive alcohol consumption was defined as systematic intake of more than 21 standard drinks per week (1 standard drink corresponds to 30 mL of distilled spirits) or more than 70 g of pure ethanol per day.

Atrial fibrillation according to ECG data was recorded in 28 patients without a history of cardiac arrhythmias.

Standard blood biochemistry parameters were measured using Konelab PRIME 30i (Thermo Fisher Scientific).

A case-control study was conducted to evaluate a possible relationship of blood lipid parameters and the risk of ICH.

*Inclusion criteria for the test group:* patients under the age of 60 years with acute ICH.

*Inclusion criteria for the control group:* healthy individuals under the age of 60 years without a history or clinical data of acute cerebrovascular accidents.

Statistical analysis was conducted using IBM SPSS Statistics v. 22 software package. Quantitative characteristics without normal distribution were described as median values (Me) with lower and upper quartiles [Q1; Q3]. Mann–Whitney U-test was used to compare samples with distribution other than normal. Descriptive statistics for categorical variables were presented as rates ( $n$ ) and percentages (%). A relationship between qualitative characteristics was assessed using contingency tables. Significance of differences was assessed using Pearson  $\chi^2$  test.  $\chi^2$  test with Yates' correction and Fisher's exact test were used when several expected frequencies in the tables were less than 10. The power of associations was evaluated using

odds ratios (ORs). ORs with 95% confidence intervals (CI) were presented; associations with CI that included 1 were not considered statistically significant.

## Results

Smoking and excessive alcohol consumption in patients with ICH were more common in men than in women ( $p < 0.001$ ;  $\chi^2 = 14.111$ ;  $df = 1$ ;  $OR = 3.048$ ; 95% CI 1.682–5.523). The incidence of hypertension, atrial fibrillation, history of myocardial infarction, dyslipidemia, and diabetes mellitus in patients with ICH did not have any statistically significant differences in gender subgroups (Table 1).

In patients with ICH, incidence of hypertension ( $p = 1.000$ ), tobacco smoking ( $p = 0.556$ ), history of myocardial infarction ( $p = 0.120$ ), dyslipidemia ( $p = 0.437$ ), and diabetes mellitus ( $p = 0.886$ ) did not have statistically significant differences in ethnic subgroups (Table 2). Asian patients less frequently had atrial fibrillation ( $p = 0.005$ ;  $\chi^2 = 7.858$ ;  $df = 1$ ;  $OR = 0.328$ ; 95% CI 0.146–0.735) and other heart diseases ( $p = 0.014$ ;  $\chi^2 = 6.089$ ;  $df = 1$ ;  $OR = 0.392$ ; 95% CI 0.185–0.831) compared with Caucasian patients.

In patients with ICH, total cholesterol and high-density lipoprotein (HDL) levels were significantly lower ( $4.98 \pm 1.26$  and  $5.21 \pm 0.98$  ( $p = 0.015$ ),  $1.18 \pm 0.44$  and  $1.52 \pm 0.48$  ( $p < 0.0001$ ), respectively), while triglyceride and low-density lipoprotein (LDL) levels were significantly higher than in healthy individ-

uals ( $1.35 \pm 0.86$  and  $1.04 \pm 0.59$  ( $p = 0.000001$ ),  $3.50 \pm 1.13$  vs.  $2.90 \pm 0.88$  ( $p < 0.0001$ ), respectively; Table 3). No differences in lipid parameters were seen in ethnic subgroups (Table 4).

## Discussion

Hypertensive ICH accounts for 10% of all stroke types [1, 15, 16]. ICH prevalence varies depending on geographic regions. Particularly high incidence of ICH was shown in Japan and Korea [15, 17].

Modifiable risk factors include smoking, excessive alcohol consumption, and lipid levels. Non-modifiable risk factors for ICH include older age and male gender [15, 17–19]. Over the past 30 years, the incidence of hypertensive ICH has decreased, while the incidence of ICH associated with anti-thrombotic agents has increased [20].

Our study showed that in patients with ICH, atrial fibrillation and other heart diseases (stable coronary artery disease, valvular heart disease, cardiomyopathies) were detected more often in Caucasian men than in Asian men. There were no significant differences in the incidence of hypertension, history of myocardial infarction, diabetes mellitus, or dyslipidemia in gender or ethnicity groups.

Risk factors for developing ICH that are of major concern include smoking and excessive alcohol consumption. Nicotine, the main toxic agent in cigarette smoke, which con-

**Table 1. Prevalence of risk factors in patients with ICH in different gender subgroups,  $n$  (%)**

Risk factor	Male ( $n = 133$ )	Female ( $n = 118$ )	$p$ ( $\chi^2$ ; $df$ )	OR (95% CI) for significant differences
Arterial hypertension	131 (98.5)	116 (98.3)	1.000**	–
Cigarette smoking	51 (38.3)	20 (16.9)	$< 0.0001^*$ (14.111; $df = 1$ )	3.048 (1.682–5.523)
Excessive alcohol consumption	51 (38.3)	20 (16.9)	$< 0.0001^*$ (14.111; $df = 1$ )	3.048 (1.682–5.523)
Atrial fibrillation	14 (10.5)	14 (11.9)	0.737* (0.113; $df = 1$ )	–
History of myocardial infarction	12 (9.02)	16 (13.6)	0.254* (1.298; $df = 1$ )	–
Other heart diseases	66 (49.6)	61 (51.7)	0.743 (0.107; $df = 1$ )	–
Dyslipidemia	56 (42.1)	56 (47.5)	0.395* (0.725; $df = 1$ )	–
Diabetes mellitus	9 (6.8)	12 (10.2)	0.331* (0.944; $df = 1$ )	–

**Note.** Here and in Table 2, other heart diseases include stable coronary artery disease, valvular heart disease, cardiomyopathies; \*Pearson  $\chi^2$  test; \*\*Fisher's exact test.

**Table 2. Prevalence of risk factors in patients with ICH by their ethnicity, *n* (%)**

Risk factor	Asian race ( <i>n</i> = 159)	Caucasian race ( <i>n</i> = 92)	<i>p</i> ( $\chi^2$ ; <i>df</i> )	OR (95% CI) for significant differences
Arterial hypertension	156 (98.1)	91 (98.9)	1.000**	–
Cigarette smoking	47 (29.6)	24 (26.1)	0.556* (0.346; <i>df</i> = 1)	–
Excessive alcohol consumption	47 (29.6)	24 (26.1)	0.556* (0.346; <i>df</i> = 1)	–
Atrial fibrillation	11 (6.9)	17 (18.5)	0.005* (7.858; <i>df</i> = 1)	0.328 (0.146–0.735)
History of myocardial infarction	14 (8.8)	14 (15.2)	0.120* (2.418; <i>df</i> = 1)	–
Other heart diseases	28 (41.8)	33 (64.7)	0.014* (6.089; <i>df</i> = 1)	0.392 (0.185–0.831)
Dyslipidemia	68 (42.8)	44 (47.8)	0.437* (0.604; <i>df</i> = 1)	–
Diabetes mellitus	13 (8.2)	8 (8.7)	0.886* (0.021; <i>df</i> = 1)	–

**Table 3. Lipid parameters in patients with ICH**

Parameter	Patients with ICH ( <i>n</i> = 251)	Healthy controls ( <i>n</i> = 537)	<i>p</i> *
Total cholesterol. mmol/liter	4.90 [4.05; 5.75]	5.15 [4.53; 5.77]	0.012
Low-density lipoproteins. mmol/liter	3.44 [2.74; 4.13]	2.82 [2.29; 3.43]	< 0.0001
Triglycerides. mmol/liter	1.13 [0.79; 1.68]	0.89 [0.64; 1.26]	0.001
High-density lipoproteins. mmol/liter	1.11 [0.92; 1.35]	1.44 [1.16; 1.72]	< 0.0001

Note. \*Mann–Whitney U-test.

**Table 4. Lipid parameters in patients with ICH by their ethnicity**

Parameter	Asian race ( <i>n</i> = 159)	Caucasian ( <i>n</i> = 92)	<i>p</i> *
Total cholesterol. mmol/liter	4.9 [4.1; 5.8]	5.0 [4.0; 6.2]	0.166
Low-density lipoproteins. mmol/liter	3.4 [2.8; 4.0]	3.7 [2.8; 4.7]	0.061
Triglycerides. mmol/liter	1.1 [0.8; 1.6]	1.2 [0.9; 1.7]	0.189
High-density lipoproteins. mmol/liter	1.1 [0.9; 1.4]	1.2 [0.4; 1.6]	0.240

Note. \*Mann–Whitney U-test.

tains over 9,000 different chemicals, increases the risk of cardiovascular and cerebrovascular disease [21]. Smoking and excessive alcohol consumption were shown to increase the risk of ICH across different populations [22]. ICH incidence is higher in men than in women [23, 24]. Compared with non-smokers, the risk ratio for ICH in men and women who smoke is 1.82 and 1.3, respectively [25]. In our study, smoking and excessive alcohol consumption were more common in male patients with ICH compared with female.

Data on the relationship between lipid parameters and the risk of cerebrovascular disease, including stroke, are contradictory [6, 26–28]. Multiple studies showed that hypercholesterolemia was associated with the risk of IS [6, 29], while the role of lipid parameters for the development of HS was not so obvious.

According to several studies, low TC levels were associated with ICH risk [6] and unfavorable outcome [5]. However, other studies showed that increased cholesterol and LDL levels and low HDL levels were associated with ICH risk [30].

Our study showed that patients with ICH had statistically significant decreases in TC and HDL and statistically significant increases in TG and LDL compared with healthy controls.

Our data are consistent with another study [30], which showed that increased TG levels were not associated with the risk of primary ICH, while increased LDL and TC levels and low HDL levels were associated with ICH. In addition, previous studies [6, 31, 32] showed that low TC levels were a predictor for ICH.

## Conclusion

The analysis of risk factors showed no statistically significant differences in the incidence of hypertension, history of myocardial infarction, diabetes mellitus, or dyslipidemia in patients with hypertensive ICH in gender or ethnicity subgroups. Atrial fibrillation and other heart diseases were more common in Caucasian patients compared with Asian. Smoking and excessive alcohol consumption were more common in men than in women. ICH was associated with high LDL and TG levels and low TC and HDL levels compared with healthy controls.

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