■ Original article

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Epileptic Disorders

Prevalence of various risk factors associated with new-onset epilepsy after the age of 50: a retrospective population-based study

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ABSTRACT

Objective. Population-based studies of epilepsy risk factors are rare. We aimed to evaluate the prevalence of various risk factors associated with new-onset epilepsy after the age of 50 years. We included all incident cases in North Macedonia between 2015 and 2018.

Methods. Study participants were ascertained from the national healthcare platform. We performed a retrospective analysis of Electronic Health Records of 2,367 patients (1,017 females and 1,350 males) whose epileptic seizures started after the age of 50 years. Patients were stratified into 10-year age groups.

Results. The most common risk factor for new-onset epilepsy in our cohort was stroke, which was associated with new-onset epilepsy in 20% of patients aged 50-59 years and almost 50% of patients aged 70-79 years. The second most frequent risk factor was neoplasm in patients aged 50-69 years and dementia in patients older than 70 years. The other pre-existing conditions included: metabolic disorders, traumatic brain injury, and postencephalitic and inflammatory diseases. Chronic alcoholism was the most common metabolic risk factor associated with new-onset epilepsy and accounted for 84% of cases in this subgroup. Only metabolic disorders were significantly more frequent in males than in females ($p<0.00001$). We did not identify any epilepsy risk factor in 967 patients (41%). Systemic vascular risk factors were frequent in our cohort: 1,574 patients had hypertension (66%) and 449 patients had diabetes (19%), and 339 had both conditions (14%).

Significance. We found that structural lesions were the most prevalent risk factor associated with new-onset epilepsy in middle-aged and elderly patients. Recognition of possibly modifiable factors associated with late-onset epilepsy could have a positive impact on reducing the risk of developing epilepsy.

Key words: epilepsy, risk factors, adults, elderly

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Epilepsy incidence is bimodally distributed with two peaks: in childhood and the elderly, but over time, it constantly tends to increase in the group over 50 years of age and decline in the young [1-3]. Large, population-based studies revealing the aetiology of epilepsy in adults and the elderly have been published a few decades ago [1, 4], while more recent hospital-based studies

have examined causes of epilepsy in a limited number of patients [5-8]. Nevertheless, change in health and modifiable risk factors in the overall population over a period of years might impact epilepsy risk and causes. Furthermore, the identification of epilepsy aetiology is methodology-driven, and modern technological advancements have improved the detection and verification of multiple underlying causes.

Consequently, there is a growing need for a comprehensive and current assessment of possible etiological factors for new-onset epilepsy in the late middle-aged and elderly.

We aimed to evaluate the prevalence of various risk factors associated with new-onset epilepsy after the age of 50 years. We included all incident cases in North Macedonia between 2015 and 2018.

Methods

Data source

Study participants were ascertained from the national healthcare platform (NHP). NHP is a countrywide central electronic system, established by the Macedonian Ministry of Health [9] The platform integrates all existing electronic information systems used in public and private health organizations (*i.e.*, data is held locally in autonomous systems, but some of these data are included in the central database). The unique Electronic Health Record (EHR) of each patient consists of six groups of key components: administrative components (patients' personal, demographic, employment, and insurance information); laboratory components; radiology components; pharmacy components (generation, transmission, and filling of medical prescriptions); physician report (from all three levels of healthcare) and documentation of hospitalizations [10]. From a data collection point of view, the system continuously creates new records and updates existing records [9]. Besides clinical use at the point of care, the EHR is a comprehensive data repository that can be used for clinical research. EHR can be accessed through a web portal and is available to all health care workers and institutions according to their access privileges. We had access to patients' diagnostic codes, demographics, number and time of doctors' visits, hospitalizations, diagnostic procedures (*e.g.*, EEG, CAT scan, MRI, etc.), and lists of medications.

Study cohort

We identified the initial patient population by following search criteria using the diagnostic code for epilepsy and prescription of antiseizure medication (ASM). We included ICD-10 codes G40.0-9, *i.e.*, G40.0: localization-related (focal) idiopathic epilepsy and epileptic syndromes with seizures of localized onset; G40.1 and G40.2: localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures; G40.3: generalized idiopathic epilepsy and epileptic syndromes; G40.40: other generalized epilepsy and epileptic syndromes, not intractable; G40.5: epileptic seizures related to external causes; G40.5: special epileptic syndromes; G40.6: grand mal seizures, unspecified (with or without petit mal); G40.7: petit mal, unspecified, without grand mal seizures; G40.8: other epilepsy; G40.9: epilepsy, unspecified; G40.8: other epilepsy and recurrent seizures; and G40.9: epilepsy, unspecified. Linking evidence of treatment with ASM was used to strengthen the diagnostic accuracy because, in our country, general practitioners cannot prescribe ASM without consulting a neurologist. Further analysis of the aforementioned initial patient cohort identified all patients aged 50 and older between January 1st, 2015 and December 31, 2018. From this population, patients with new-onset epilepsy were selected as those with a first diagnosis of epilepsy, *i.e.*, for each year from 2015 to 2018. We then searched for associated conditions cited as possible risk factors for new-onset epilepsy in prior studies [11-17]. Specifically, we included ICD-10 diagnostic codes for ischaemic stroke (IS), haemorrhagic stroke (HS), and sequelae of cerebrovascular disease; degenerative, inflammatory, infective, and parasitic central nervous system disorders; traumatic brain injury, primary brain tumours, and metastases; as well as metabolic disorders (chronic hepatic and renal failure and chronic alcoholism). Also, we evaluated systemic vascular risk factors, for which there is inconsistent evidence regarding their association with epilepsy (hypertension and diabetes) [11, 12, 18]. In addition to pre-existing diagnostic codes, we reviewed the number and type of diagnostic procedures (*e.g.*, laboratory tests, EEG, CAT scan, MRI, neuropsychological testing, *etc.*) as well as the list of medications. We did not review the medical records of identified subjects nor re-evaluate the diagnosis and classification made by treating physicians. In cases with remote stroke and ICD code of sequelae of cerebrovascular disease of unspecified nature, we strengthened the diagnostic accuracy by linking and evaluating prescribed antithrombotic and anticoagulant therapy. When patients had more than one coded possible etiological factor, we reviewed as follows: in patients with a structural lesion (*e.g.*, stroke) and metabolic dysfunction (*e.g.*, renal failure), the structural lesion was classified as an etiological risk factor; in patients with remote stroke and poststroke dementia, stroke was classified as an etiological risk factor for epilepsy, while dementia was considered as a co-occurrent condition; in patients with brain neoplasms and

concomitant cerebrovascular disease, neoplasms were identified as a risk factor for epilepsy.
The study subjects were stratified into 10-year groups as follows: 50-59 years, 60-69 years, 70-79 years, and ≥80 years.

Statistical analysis

The etiological factors were described as numbers and percentages (for the four different age groups). The categorical variables were compared using Chi-square with Bonferroni corrections, applied for multiple analyses.

Results

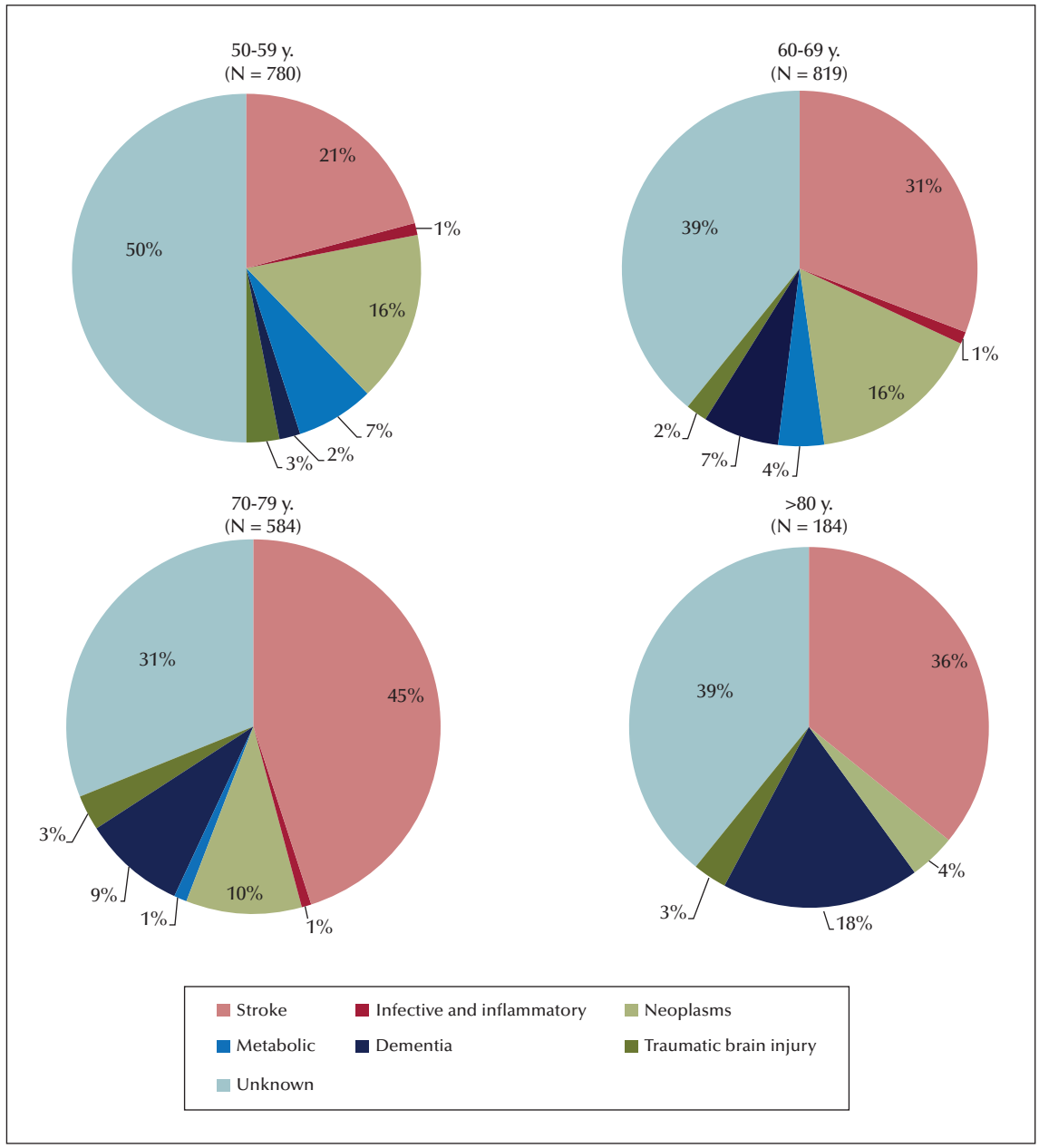
A total of 2,367 patients (1,017 females and 1,350 males) with new-onset epilepsy over the age of 50 years were identified from the database. We were able to ascertain risk factors for epilepsy in 1,400 patients (59%). *Table 1* exhibits the overall and gender-specific factors associated with epilepsy in our cohort. The risk factors, broken down into age groups, are presented in *figure 1*. They slightly varied across the age groups. Stroke was the most common risk factor and its prevalence gradually increased in subsequent age groups. It was associated with new-onset epilepsy in 20% of patients aged 50-59 years and almost 50% of cases aged 70-79 years. The second most frequent risk factor was neoplasm in patients aged 50-69 years and dementia in patients older than 70 years. Noteworthy, 45 patients with stroke and 18 patients with dementia also had chronic renal failure. In addition, 90 patients with stroke had vascular dementia (12%) and 53 patients with brain neoplasm had concomitant cerebrovascular disease (16%). Chronic alcoholism was the most frequent metabolic risk factor associated with new-onset epilepsy and accounted for 84% of cases in this subgroup. Only metabolic disorders were significantly more frequent in males than in females ($p<0.00001$). We could not identify any established risk factor associated with epilepsy in 967 patients (41%). Of note, all patients in this subgroup had screening laboratory tests, EEG, and CAT scans, but only 281 patients had MRI (29%). Remarkably, 22 patients suffered a stroke and 21 patients were diagnosed with dementia within three years of the first epilepsy-related code. Systemic vascular risk factors were frequent in our cohort: 1,574 patients had hypertension (66%) and 449 patients had diabetes (19%), and 339 had both conditions (14%). In the subgroup of patients with an unknown etiological factor for epilepsy, 611 patients had hypertension (63%), 151 patients had diabetes (16%) and 117 of them had both conditions (12%).

Discussion

To our knowledge, this is the largest study that has evaluated the prevalence of various risk factors associated with new-onset epilepsy in the middle-aged and elderly. The major strengths of our study are that it is population-based and it included all incident cases in North Macedonia over four years. The major weaknesses of our study are the retrospective design and the use of precoded data. Thus, the accuracy of the

▼ **Table 1.** Overall and gender-specific risk factors associated with new-onset epilepsy over the age of 50 years in the Macedonian population between 2015 and 2018.

Aetiology	Total *n*	Females *n* (%)	Males *n* (%)
Ischaemic stroke	551	211 (38)	340 (62)
Haemorrhagic stroke	196	82 (42)	114 (58)
Dementia	156	75 (48)	81 (52)
Neoplasm	320	132 (41)	188 (59)
Traumatic brain injury	59	12 (20)	47 (80)
Postencephalitic	16	8 (50)	8 (50)
Metabolic encephalopathy	95	12 (13)	83 (87)
Multiple sclerosis	7	5 (71)	2 (29)
Unknown	967	480 (50)	487 (50)
Total	**2367**	**1017**	**1350**



■ **Figure 1.** Prevalence of various risk factors associated with new-onset epilepsy after the age of 50 years stratified into 10-year age groups.

diagnosis of epilepsy was not confirmed by direct evaluation of the medical records by an epileptologist. However, given that all patients with epilepsy are treated by neurologists in our country, we may assume that the degree of misdiagnosis of epilepsy is insignificant. Nevertheless, ascertainment of risk factors associated with epilepsy may have been incomplete; for example, MRI was not performed on all participants and some silent strokes might have been overlooked. Furthermore, the identification of the causes and risk factors of epilepsy is not as simple as it might at first appear. The underlying mechanisms are complex and might involve genetic predisposition and multiple risk factors and associated conditions [13, 15, 19]. Indeed, we found additional risk factors in 10-15% of patients with stroke, neoplasm, and traumatic brain injury. Sometimes, the identification of causative factors is not straightforward and we

might have missed aetiologies that would become evident years after the diagnosis of epilepsy was made. Several patients in our cohort developed dementia within three years of the first epilepsy-related code, and it is possible that undiagnosed dementia preceded late-onset epilepsy. Finally, the population in North Macedonia is Caucasian and our findings may not be applicable to racially diverse populations, as some risk factors may differ based on race [11-12].

Consistent with the literature, we found that stroke was the most common risk factor associated with new-onset epilepsy in the middle-aged and the elderly [5-8, 20]. Hypertension and diabetes, which are frequent in those patients, might further influence and modulate post-stroke epileptogenesis [21]. Moreover, there might be an additive effect of cerebrovascular disease and poststroke dementia in the later development of epilepsy [11].

Neoplasm was the second most prevalent risk factor associated with epilepsy in the subgroup of patients younger than 70 years, in line with de Assis *et al*. [7]. The high proportion of tumour-associated epilepsy in this age group is due to the high incidence of brain neoplasms in adulthood and the elderly [22].

Dementia of all types, but especially Alzheimer's disease, is a common cause of seizures in older age [14]. Dementia was associated with 10–20% of late-onset cases after the age of 70 years in our cohort, similar to findings of de Assis *et al*. [7] and slightly higher than the 7% reported by Tanaka *et al*. [5].

Consistent with a study from Japan [5], traumatic brain injury accounted for 3% of epilepsy in our cohort. This is considerably lower than what was estimated in Russia (27% of cases with focal epilepsy) [23]. The discrepancy may be due to variation in the populations studied. Guekht *et al*. examined new-onset epilepsy in older teenagers and adults, whereas our study focused exclusively on the late-midlife and elderly population. The proportion of patients with epilepsy after brain injury might be also influenced by country-specific incidence and prevalence of brain trauma [24].

We found a higher proportion of metabolic risk factors in the middle-aged compared to the elderly (7% vs 1%). This is in contrast to the results from the Brazilian tertiary centre study, in which metabolic aetiology was highest in patients older than 75 years and accounted for 9.4% of new-onset cases [5]. Opposing results may be due to variances in underlying metabolic risk factors. Chronic renal and liver failure, hypoglycaemia, hyponatraemia, and hypoxia dominated in the Brazilian study, whilst chronic alcoholism accounted for the majority of cases in our cohort. The over-representation of alcoholism is a possible explanation for the significant difference between genders in our study, because the prevalence of alcohol use is much higher in men than women [25]. Alcohol has also been recognized as one of the commonest causes of seizures in young adults and several pathogenic mechanisms have been suggested, although none of them have been proven to be the unique causative pathway for epilepsy [26].

Infective aetiology accounted for only a minor proportion of new-onset epilepsy in our cohort. Geographical location is important in this instance because parasitic conditions, such as malaria, neurocysticercosis, and onchocerciasis, are among the common risk factors for epilepsy in different geographic regions [27-29].

Finally, we observed a high prevalence of hypertension and diabetes in our cohort. The evidence for the association between vascular risk factors and late-onset epilepsy is inconsistent. Hypertension was found to be an independent risk factor for developing epilepsy based on a case-control hospital-based study and in the recent prospective Atherosclerosis Risk in Communities (ARIC) study [18, 12]. On the contrary, according to the National Veterans Affairs database study, hypertension was not associated with greater odds of new-onset epilepsy after controlling for underlying variables of cerebrovascular disease and dementia [11]. Diabetes was associated with late-onset epilepsy with a significantly higher effect in black individuals than in white individuals based on the ARIC study [12].

Conclusion

In conclusion, in the largest sample to date of patients ≥50 years, we found that stroke, neoplasms, and metabolic disorders (chronic alcoholism) were the most prevalent risk factors associated with new-onset epilepsy in middle-aged patients. As in other studies, stroke, dementia, and neoplasm were the most common pre-existing conditions in elderly patients with new-onset epilepsy. Recognition of possibly modifiable factors associated with late-onset epilepsy is important for reducing the potential risk of developing epilepsy. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
None of the authors have any conflicts of interest to disclose.

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TEST YOURSELF

(1) Which of the following is the most frequent risk factor associated with new-onset epilepsy in patients >50 years?

A. Brain neoplasms
B. Stroke
C. Dementia
D. Metabolic disorders

(2) Which of the following is the second most prevalent risk factor associated with epilepsy in the subgroup of patients <70 years?

A. Dementia
B. Neoplasm
C. Traumatic brain injury
D. Alcoholism

(3) Post-infection and parasitic epilepsies are:

A. Most frequent cause of epilepsy in elderly worldwide
B. The most frequent cause of epilepsy in late middle-age worldwide
C. More frequent in some geographic regions than others
D. None of above

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.