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Comparing the risk of subsequent ischemic stroke and mortality in patients with epilepsy and patients with ischemic stroke

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ABSTRACT

Patients with stroke or epilepsy face an elevated risk of subsequent strokes. This nationwide retrospective cohort study analyzed data from Taiwan's National Health Insurance Research Database (2012–2020) to compare the risk of future ischemic stroke or transient ischemic attack (IS/TIA) among patients with epilepsy and those with prior IS/TIA. Patients were categorized into four groups: epilepsy with subsequent IS/TIA (E/S), epilepsy without IS/TIA (E), IS/TIA without epilepsy (S), and neither condition (C). Incidence rates and adjusted hazard ratios for IS/TIA and mortality were assessed across groups, which included 5,606, 11,212, 11,212, and 56,060 patients. The corresponding incidence rates of subsequent IS/TIA were 0.67, 0.03, 0.41, and 0.01 per 100 person-years in the E/S, E, S, and C groups, respectively. Compared to the S group, the E/S group had a higher adjusted hazard ratio for IS/TIA (aHR 1.68, 95% CI: 1.30–2.17), whereas the E group had a significantly lower adjusted hazard ratio (aHR 0.08, 95% CI: 0.04–0.14). Mortality risk was significantly elevated in both the E/S group (aHR 1.90, 95% CI: 1.75–2.05) and the E group (aHR 1.21, 95% CI: 1.12–1.30), compared to the S group. These findings suggest that epilepsy increases the risk of subsequent IS/TIA, though to a lesser extent than prior IS/TIA. They underscore the importance of condition-specific prevention strategies and the need for further research into the mechanisms linking epilepsy and stroke risk.

1. Introduction

Patients with epilepsy and those with a history of ischemic stroke or transient ischemic attack (IS/TIA) are both at an increased risk of experiencing subsequent IS/TIA [1,2]. The risk is particularly elevated immediately following the initial diagnosis of epilepsy or IS/TIA [1,3,4]. These shared epidemiological characteristics suggest a potential link between epilepsy and subclinical stroke [5]. However, it remains unclear whether the risk increase is comparable between epilepsy and prior IS/TIA, and whether their combined risks are additive or synergistic. This study aims to directly compare the risk of subsequent IS/TIA in patients with epilepsy to that in patients with a prior IS/TIA.

2. Materials and Methods

This nationwide retrospective cohort study utilized the National Health Insurance Research Database (NHIRD) in Taiwan, which covers 99.9 % of the Taiwanese population. The study was approved by the Institutional Review Board of National Cheng Kung University Hospital (IRB Approval No. B-ER-109–168).

We identified adult patients (≥ 18 years) with newly diagnosed epilepsy from 2012 to 2020 as the epilepsy cohort. Newly diagnosed epilepsy was defined by a first-time epilepsy diagnosis code (ICD-9: 345 or ICD-10: G40) confirmed by two medical visits, alongside a prescription for any antiseizure medication (ASM) (ATC code N03). Patients with a history of any stroke (ICD-9: 430–438, V12.54, 997.02; ICD-10: I60-I69, G46, R29, Z86, I97.81, I97.82) before their first epilepsy ICD diagnosis or first ASM prescription were excluded, as were individuals with unrecorded sex. The control cohort included adult patients (≥ 18 years) with no history of epilepsy, no ASM prescriptions, and no history of stroke before July 1st of each year, also excluding those with unrecorded sex.

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In the epilepsy cohort, patients who experienced subsequent IS/TIA (ICD-9: 433–435; ICD-10: I63, G45, G46) were classified as the E/S group, with their index date defined as the date of IS/TIA occurrence. Epileptic patients without IS/TIA were classified as the E group, with the index date set at the epilepsy diagnosis. From the control cohort, patients without epilepsy who had IS/TIA were classified as the S group (index date: IS/TIA diagnosis), while those without IS/TIA were categorized as the C group (index date: July 1st of the enrollment year). The selection of the E, S, and C groups, using the E/S group as a reference, was matched by index year (±2 years), age (±5 years), and sex at a ratio of 1:2:2:10.

To further clarify stroke risk and mortality associated with focal or generalized epilepsy, patients in the epilepsy cohort were classified into subgroups based on their ICD codes at the time of analysis if they exclusively had either focal epilepsy (ICD-9: 345.4, 345.5, 345.7; ICD-10: G40.0, G40.1, G40.2) or generalized epilepsy (ICD-9: 345.0, 345.1, 345.2, 345.3; ICD-10: G40.3, G40.A, G40.B, G40.4). These subgroups followed the same process as the overall cohort to form the E/S, E, S, and C groups while maintaining the same matching ratio.

The primary outcome was the rate of subsequent IS/TIA, identified using diagnostic codes from hospitalizations or emergency visits after the index date and validated by brain computed tomography (CT) or magnetic resonance imaging (MRI) codes. Secondary outcomes included IS/TIA and mortality rates at 0–2, 2–4, and 4–6 years post-index, as well as subgroup analyses of IS/TIA and mortality rates in the focal and generalized epilepsy subgroups. Incidence and hazard ratios (HRs) were analyzed for the four groups, with adjusted HRs (aHRs) controlling for age, sex, income, and comorbidities. Group comparisons of incidence rates used the chi-square test, with $p < 0.05$ considered statistically significant.

3. Results

We enrolled 63,724 patients in the epilepsy cohort and 549,652 in the control cohort. After matching, the E/S, E, S, and C groups consisted of 5,606, 11,212, 11,212, and 56,060 individuals, respectively (Supplementary Fig. 1). There were no significant differences in sex or age distribution among the groups. However, conventional stroke risk factors were more prevalent in patients with prior ischemic stroke (the E/S and S groups), whereas low-income, chronic kidney disease, migraine, malignancy, and mental disorders were more common in patients with epilepsy (the E/S and E groups) (Table 1).

The incidence rates of subsequent IS/TIA were 0.67, 0.03, 0.41, and 0.01 per 100 person-years in the E/S, E, S, and C groups, respectively (Table 2). Among these events, 64.7 % were validated using both MRI and CT, 10.9 % with MRI, and 24.4 % with CT only. Compared to the S group, the risk of subsequent IS/TIA was higher in the E/S group (aHR 1.68, 95 % confidence interval [CI] 1.30–2.17), lower in the E group (aHR 0.08, 95 % CI 0.04–0.14), and lowest in the C group (aHR 0.02, 95 % CI 0.01–0.04). Mortality rates were 8.27, 4.60, 3.03, and 0.65 per 100 person-years in the E/S, E, S, and C groups, respectively. Compared to the S group, mortality risk was significantly elevated in both the E/S group (aHR 1.90, 95 % CI: 1.75–2.05) and the E group (aHR 1.21, 95 % CI: 1.12–1.30).

Supplementary Table 1 and Supplementary Fig. 2 present the temporal analysis of incidence rates and the risk of subsequent IS/TIA and mortality after the index date. Compared to the S group, the risk of subsequent IS/TIA was higher in the E/S groups, particularly within the first two years post-index date (aHR 1.82, 95 % CI 1.34–2.47). This elevated risk gradually declined over time. In contrast, compared to the S group, the risk of IS/TIA remained lower in the E and C groups throughout the study period. Regarding the temporal analysis of mortality, the E/S group exhibited persistently elevated mortality rates compared to the S group over the follow-up period. On the other hand, compared to the S group, the mortality in the E group was comparable (aHR 0.88, 95 % CI 0.80–0.97) within the first two years post-index date, and elevated afterward, suggesting a lower long-term survival.

Table 1
Demographic data and comorbidity of patients. Conventional stroke risk factors were more common among patients in patients with a history of ischemic stroke (E/S and S groups), while low income, chronic kidney disease, migraine, malignancy, and mental disorders were more prevalent in patients with epilepsy (E/S and E groups). (E/S group, epileptic patients with subsequent ischemic stroke or transient ischemic attack; E group, epileptic patients without history of ischemic stroke or transient ischemic attack; S group, nonepileptic patients with history of ischemic stroke or transient ischemic attack; C group, nonepileptic patients without history of ischemic stroke or transient ischemic attack; SD, standard deviation; NTD: New Taiwan Dollars; CKD/ESRD, chronic kidney disease or end-stage renal disease).

	E/S group (N = 5606) n (%)	E group (N = 11212) n (%)	S group (N = 11212) n (%)	C group (N = 56060) n (%)	*p-value*
Age when index date (y/o, Mean ± SD)	59.4 ± 16.0	59.3 ± 15.9	59.4 ± 16.0	59.4 ± 16.0	0.834
Sex (Female)	2402 (42.85)	4804 (42.85)	4804 (42.85)	24,020 (42.85)	1.000
Low income (≤15,840 NTD)	1915 (34.16)	3528 (31.47)	2582 (23.03)	12,853 (22.93)	<0.001
Comorbidity					
Diabetes mellitus	1530 (27.29)	2102 (18.75)	2430 (21.67)	5633 (10.05)	<0.001
Hypertension	2555 (45.58)	3584 (31.97)	5051 (45.05)	10,948 (19.53)	<0.001
Hyperlipidemia	1136 (20.26)	1812 (16.16)	2983 (26.61)	6678 (11.91)	<0.001
Coronary heart disease	690 (12.31)	907 (8.09)	1128 (10.06)	2448 (4.37)	<0.001
Heart failure	280 (4.99)	300 (2.68)	361 (3.22)	451 (0.80)	<0.001
Atrial fibrillation	98 (1.75)	103 (0.92)	168 (1.50)	182 (0.32)	<0.001
CKD/ESRD	565 (10.08)	711 (6.34)	516 (4.60)	883 (1.58)	<0.001
Migraine	108 (1.93)	183 (1.63)	109 (0.97)	98 (0.17)	<0.001
Malignancy	632 (11.27)	1018 (9.08)	588 (5.24)	1608 (2.87)	<0.001
Mental disorder	2533 (45.18)	4041 (36.04)	1438 (12.83)	2893 (5.16)	<0.001

Supplementary Tables 2 and 3 present the incidence rates and risks of subsequent IS/TIA and mortality in patients with focal and generalized epilepsy, respectively. Compared to those with a prior stroke within each subgroup, both focal and generalized epilepsy patients had a lower risk of subsequent IS/TIA. However, only patients with generalized epilepsy exhibited significantly higher mortality, whereas those with focal epilepsy did not. The E/S group had the highest risk of subsequent IS/TIA and mortality compared to patients with a prior stroke.

4. Discussion

This study demonstrated that while patients with epilepsy have an increased risk of subsequent IS/TIA compared to healthy people, their risk is lower than that of patients with a prior IS/TIA event. Furthermore, the risk of subsequent IS/TIA was synergistic in patients with both epilepsy and a prior IS/TIA. Notably, this is the first study to directly compare the risk of subsequent IS/TIA between patients with epilepsy and those with a history of IS/TIA. The lower risk observed in epilepsy patients suggests that stroke prevention strategies for this group may need re-evaluation, rather than relying on general stroke secondary prevention guidelines. For example, the bleeding risk associated with antiplatelet therapy may not be justified by the relatively lower ischemic stroke risk in epilepsy patients. Future studies should assess the

Table 2
Risk of subsequent ischemic stroke or transient ischemic attack (IS/TIA) and mortality after index diagnosis. Compared to patients with prior IS/TIA (S group), patients with prior epilepsy followed by prior IS/TIA (E/S group) have an increased risk of subsequent IS/TIA, while patients with epilepsy (E group) have a lower risk of subsequent IS/TIA. On the other hand, epilepsy patients, with or without prior IS/TIA (E/S group and E group) have an increased mortality rate compared to patients with IS/TIA history (S group). (E/S group, epileptic patients with subsequent ischemic stroke or transient ischemic attack; E group, epileptic patients without a history of ischemic stroke or transient ischemic attack; S group, nonepileptic patients with a history of ischemic stroke or transient ischemic attack; C group, nonepileptic patients without a history of ischemic stroke or transient ischemic attack; HR, hazard ratio).

Group	IS / TIA rate per 100 person-years	Univariate model Crude HR (95 % CI)	p-value	Multivariable model Adjusted HR (95 % CI)	p-value
E/S group	0.67	1.55 (1.22–1.97)	<0.001	1.68 (1.30–2.17)	<0.001
E group	0.03	0.07 (0.04–0.12)	<0.001	0.08 (0.04–0.14)	<0.001
S group	0.41	Ref.		Ref.	
C group	0.01	0.02 (0.01–0.03)	<0.001	0.02 (0.01–0.04)	<0.001

Group	Death rate per 100 person-years	Univariate model Crude HR (95 % CI)	p-value	Multivariable model Adjusted HR (95 % CI)	p-value
E/S group	8.27	2.67 (2.48–2.88)	<0.001	1.90 (1.75–2.05)	<0.001
E group	4.60	1.50 (1.39–1.61)	<0.001	1.21 (1.12–1.30)	<0.001
S group	3.03	Ref.		Ref.	
C group	0.65	0.21 (0.20–0.23)	<0.001	0.25 (0.23–0.27)	<0.001

effectiveness, side effects, and cost-effectiveness of stroke prevention strategies before broader application in the epileptic cohort.

Considering the hypothetical correlation between late-onset epilepsy and subclinical stroke [5], this study provides supporting evidence. Our findings revealed a lower subsequent IS/TIA risk in epileptic patients compared to those with a history of IS/TIA, which aligns with the epidemiological characteristics of subclinical stroke. A previous systematic review reported a relative risk of 2.94 for stroke following a silent brain infarction, compared to the general population [6]. Moreover, the additive risk of subsequent IS/TIA in patients with both epilepsy and prior IS/TIA was comparable to the synergistic risk observed between white matter hyperintensity and prior ischemic stroke in a previous study [7]. We also observed a disparity in the mortality curves between patients with epilepsy and those with a prior history of IS/TIA. The higher long-term mortality rate in epilepsy patients compared to those with IS/TIA may reflect additional life-threatening conditions associated with epilepsy beyond IS/TIA. Furthermore, within subgroups, mortality was elevated in generalized but not focal epilepsy compared to patients with prior IS/TIA. In our view, the divergence in mortality curves and the risk of recurrent stroke are not contradictory but rather intuitively reflect distinct mechanisms and their associations with stroke, underscoring the need for comprehensive epilepsy care to mitigate mortality risks beyond stroke, particularly in generalized epilepsy.

This study has several limitations. First, the retrospective cohort design and reliance on a health insurance database restricted us from selecting controls from non-epileptic patients who sought medical care, rather than from a truly healthy population. As a result, these groups may have a higher risk of disease compared to the general healthy population. Second, due to the inherent limitations of the NHIRD, we were unable to quantify the severity or mechanisms of both prior IS/TIA and subsequent IS/TIA. Consequently, our study could not provide additional insights for mechanistic investigations into post-epileptic ischemic stroke. Third, despite adjusting for age, sex, income, and comorbidities, unmeasured confounders may still influence the outcomes. Factors such as lifestyle, medication adherence, and detailed clinical characteristics were not accounted for, potentially impacting the results. Fourth, the possibility of diagnostic coding errors cannot be excluded, particularly in the classification of focal and generalized epilepsy. Therefore, the results of the subgroup analysis should be interpreted with caution, and further validation studies are warranted to establish a solid conclusion.

5. Conclusion

In conclusion, while epilepsy increases the risk of subsequent IS/TIA, this risk is lower compared to that following a prior IS/TIA. Further research is needed to investigate the similarities in stroke risk between epilepsy and subclinical stroke, and to evaluate mechanism-based or cost-effective stroke prevention strategies specifically tailored to patients with epilepsy, rather than universally applying general stroke prevention strategies.

Data availability statement.

Data are available from the National Health Insurance Research Database (NHIRD) published by Taiwan National Health Insurance Bureau. Due to legal restrictions imposed by the government of Taiwan about the “Personal Information Protection Act”, data cannot be made publicly available. Requests for data can be sent as a formal proposal to the NHIRD (https://nhird.nhri.org.tw).

IRB Statement.

This research was approved by the Institutional Review Board of National Cheng Kung University Hospital (IRB Approval No. B-ER-109–168). Participant consent was waived under IRB approval.

Conflict of Interest/Ethical Publication Statement.

1. None of the authors has any conflict of interest to disclose.

2. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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CRediT authorship contribution statement

Lin Po-Yu: Conceptualization, Writing – original draft. **Sheng-Hsiang Lin:** Formal analysis, Data curation. **Sung Pi-Shan:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2025.100766.

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