Excess mortality and hospitalized morbidity in newly treated epilepsy patients

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ABSTRACT

Objective: To assess the burden of mortality and hospitalized morbidity in newly treated epilepsy patients.

Methods: We extracted relevant data of patients with newly treated epilepsy between September 16, 2005, and September 15, 2010, from the data repository covering all public hospitals in Hong Kong. Patients were followed up until September 15, 2011. Mortality and hospitalized morbidity were assessed, stratified by baseline comorbidities, number of antiepileptic drugs (AEDs) used, and treatment with enzyme-inducing AEDs (EIAEDs). Mortality was compared to the age- and sex-specific general population in Hong Kong.

Results: Of the 7,461 newly treated epilepsy patients (55% male; median age 60 years), 2,166 (29%) died during the study period. The standardized mortality ratio was 5.09 (95% confidence interval [CI] 4.88–5.31), and was higher among those with physical or psychiatric baseline comorbidity (5.46; 95% CI 5.22–5.71) than those without (3.28; 95% CI 2.87–3.73). Standardized hospitalization ratio was 6.76 (95% CI 6.70–6.82). Baseline physical comorbidity–free patients (n = 3,514) exhibited higher risk of developing stroke (standardized incidence ratio [SIR] 4.96; 95% CI 4.19–5.84) and ischemic heart disease (SIR 4.18; 95% CI 3.54–4.91), and male patients had elevated risk of developing cancer (SIR 2.30; 95% CI 1.75–2.97). Patients treated with EIAEDs had higher risk of being subsequently recorded with new physical comorbidities than those with non-EIAEDs (relative risk [RR] 1.48; 95% CI 1.19–1.85), especially for cerebrovascular disease (RR 1.78; 95% CI 1.14–2.77).

Conclusions: Newly treated epilepsy patients bear excess mortality and hospitalization risks. They have higher risk of developing stroke, ischemic heart disease, and cancer. Treatment with EIAEDs was associated with increased overall morbidity. *Neurology*® 2016;87:718–725

GLOSSARY

AED = antiepileptic drug; **CI** = confidence interval; **EIAED** = enzyme-inducing antiepileptic drug; **HA** = Hospital Authority; **ICD-9-CM** = *International Classification of Diseases-9-clinical modification*; **IQR** = interquartile range; **RR** = relative risk; **SHR** = standardized hospitalization rate; **SIR** = standardized incidence ratio; **SLR** = standardized length of stay ratio; **SLRA** = standardized length of stay ratio per admission; **SMR** = standardized mortality ratio.

People with epilepsy have higher mortality attributable to both seizure-related and unrelated causes.[1,2] Reported standardized mortality ratios (SMRs) among people with epilepsy have ranged from 1.6 to 4.1 in community-based studies, and as high as 15.9 in selected populations.[3] In addition, epilepsy is associated with a range of comorbidities.[3–6] For instance, compared to the general population, people with epilepsy bear twice the risk of psychiatric disorders and a 7-fold increased risk of cerebrovascular diseases.[6,7] Increasing evidence suggests that the latter might be attributed to acceleration of atherosclerosis due to exposure to antiepileptic drugs (AEDs) that induce cytochrome P450 enzymes (enzyme-inducing AEDs [EIAEDs]).[8,9] However, the potential effects of existing comorbidities or exposure to EIAEDs on mortality and morbidity remain poorly understood. There is scant study on new morbidities and hospitalization among patients with newly diagnosed epilepsy.

Supplemental data at Neurology.org

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The aim of this study was to quantify the burden of mortality and hospitalized morbidity among people with newly treated epilepsy in Hong Kong.

METHODS

Study population and definitions. Over 90% of the Hong Kong population receives public health care via a single tax-funded provider (Hospital Authority [HA]).[10] We extracted data from the HA electronic data repository, which integrates all medical records for patients attending any of the HA-managed public hospitals and clinics. The methods of data extraction and definition of eligible patients have been described in detail previously.[11] For the purposes of the present analysis, the study population comprised patients who were newly diagnosed with epilepsy and commenced AED therapy during hospitalization between September 16, 2005, and September 15, 2010. Included patients had no previous diagnosis or treatment of epilepsy. Epilepsy care in Hong Kong follows guidelines that comply with international guidelines.[12] In general, routine initiation of AED therapy after a first seizure is not recommended, unless there is a high risk of recurrence or the benefits of reducing the risk of a second seizure outweigh the risk of AED adverse effects.

Information on hospitalization and in-hospital death was collected from discharge summaries until September 15, 2011. According to the HA Statistical Reports published during the study period,[13,14] 80% of all deaths in Hong Kong occur in HA-managed institutions. Discharge diagnoses were coded by the managing medical team upon discharge according to the ICD-9-CM. An admission was considered not to be seizure-related if no corresponding ICD-9-CM codes (345 and 780.3) were recorded. Physical comorbidities were weighted according to Charlson Comorbidity Index[15] and based on the enhanced ICD-9-CM coding algorithm developed by Quan et al.[16] Psychiatric comorbidities were summarized by using a similar technique suggested by Fazel et al.[17]

To avoid confounding effects from other preexisting conditions, analysis of new comorbidities was concentrated on patients who did not have any recorded comorbidity at baseline. Analysis of the risk of developing new comorbidities and the type and number of AEDs exposed was further confined to comorbidities that were recorded at least 30 days after commencing the initial AED, adjusted for age and sex. AEDs were classified into those that induce cytochrome P450 enzymes and those that do not (table e-1 on the *Neurology*® Web site at Neurology.org).[18,19]

Statistical analyses. Mortality was assessed in the total study cohort and in the subgroups stratified by baseline comorbidity (present or absent), exposure to EIAED, and number of AEDs used. SMR was calculated by dividing the number of observed deaths in the study cohort by the expected number of deaths, with the latter estimated from applying published mortality rates (all deaths from 2006 to 2011) for the Hong Kong population[20] to the relevant person-years of follow-up for each age- and sex-specific stratum.

Similarly, standardized hospitalization rates (SHRs), standardized length of stay ratio (SLR), and SLR per admission (SLRA) were calculated using age- and sex-specific reference data for hospitalization rates, obtained from HA Statistical Reports for 2005–2011. Age- and sex-specific standardized incidence ratios (SIR) for stroke, ischemic heart disease and cancer in epilepsy patients without baseline comorbidities were compared with general population data that were also derived from HA's data repository.[21–23]

Byar approximation[24] was used to calculate the 95% confidence interval (CI) for standardized ratios. A generalized linear model with log-binomial regression was used to estimate the relative risks (RRs) of developing new comorbidities in the defined AED monotherapy subgroups, adjusted for age and sex. All statistical tests were performed by using STATA 12 (StataCorp, College Station, TX). A user-supplied STATA command by Stagg was used to calculate Charlson index of mortality.[25]

Standard protocol approvals, registrations, and patient consents. The study was approved by the joint research ethics committee of the Chinese University of Hong Kong and HA's New Territories East Cluster. Patient data were anonymized and deidentified prior to analysis.

RESULTS

Baseline characteristics. The total study population comprised 7,461 newly diagnosed and treated epilepsy patients (55% male) with a total follow-up of 21,348 person-years. The median age at onset was 60 years (interquartile range [IQR] 25–78) (table 1). The majority (69%) of patients were treated with a single AED throughout the study period, and 78% treated with at least one EIAED. Among the study population, 4,340 (58%) had one or more recorded physical (Charlson) or psychiatric comorbidity at baseline; 3,947 (53%) had physical comorbidity, 1,220 (16.4%) had psychiatric comorbidity, and 827 (11%) had both. Among the 3,947 patients who had baseline physical comorbidity, cerebrovascular disease was the most frequently recorded condition, being present in 3,069 (78%) patients (table e-2A). Among the 1,220 patients with baseline psychiatric comorbidity, 705 (58%) had organic psychosis (e.g., dementias, substance-induced mental disorders), 152 (12%) had depression or mood disorder, 63 (5%) had alcohol or drug dependence, and 445 (36%) had other psychiatric conditions (e.g., anxiety, intellectual disabilities) (table e-2B).

Mortality. Among the study population, 2,166 (29%) died during the study period. The observed numbers

Table 1 Characteristics of newly diagnosed and treated epilepsy inpatients in Hong Kong from September 16, 2005, to September 15, 2010, and followed up until September 15, 2011

	Study cohort	Patients without baseline Charlson Comorbidity Index and psychiatric comorbidity	Patients who died
No. patients	7,461	3,121	2,166
Male, n (%)	4,086 (55)	1,783 (57)	1,129 (52)
Median onset age, y (IQR)	60 (25–78)	26 (11–49)	78 (70–85)
Median follow-up time, mo (IQR)	33 (17–53)	45 (29–60)	8.7 (2.3–23)
Single AED used, n (%)	5,134 (69)	2,084 (67)	1,535 (71)
EIAED used, n (%)	5,826 (78)	2,033 (65)	1,983 (92)

Abbreviations: AED = antiepileptic drug; EIAED = enzyme-inducing antiepileptic drug; IQR = interquartile range.

of deaths were higher than expected across all age and sex strata when referenced to the general population of Hong Kong[20] (figure), especially among children aged 1–4 years (RR 42.3; 95% CI 21.1–75.7) and 5–9 years (RR 46.4; 95% CI 17.0–101) (table e-3A). SMR was 5.09 (95% CI 4.88–5.31) for the entire study cohort (table e-3A), being higher among those with physical or psychiatric baseline comorbidity (5.46; 95% CI 5.22–5.71) (table e-3C) than those without (3.28; 95% CI 2.87–3.73) (table e-3B). Patients with both physical and psychiatric baseline comorbidities had the highest SMR (6.47; 95% CI 5.89–7.10) (tables e-3, E and F).

Patients who were treated with multiple AEDs (n = 2,327) had higher SMR (5.98; 95% CI 5.53–6.47) than those who took only one (4.80; 95% CI 4.56–5.05). Among the patients who had been treated with only 1 AED, the overall SMRs were not different between those treated with EIAEDs (SMR 4.76; 95% CI 4.51–5.02) and those not treated with EIAEDs (SMR 5.13; 95% CI 4.38–5.96) (table 2).

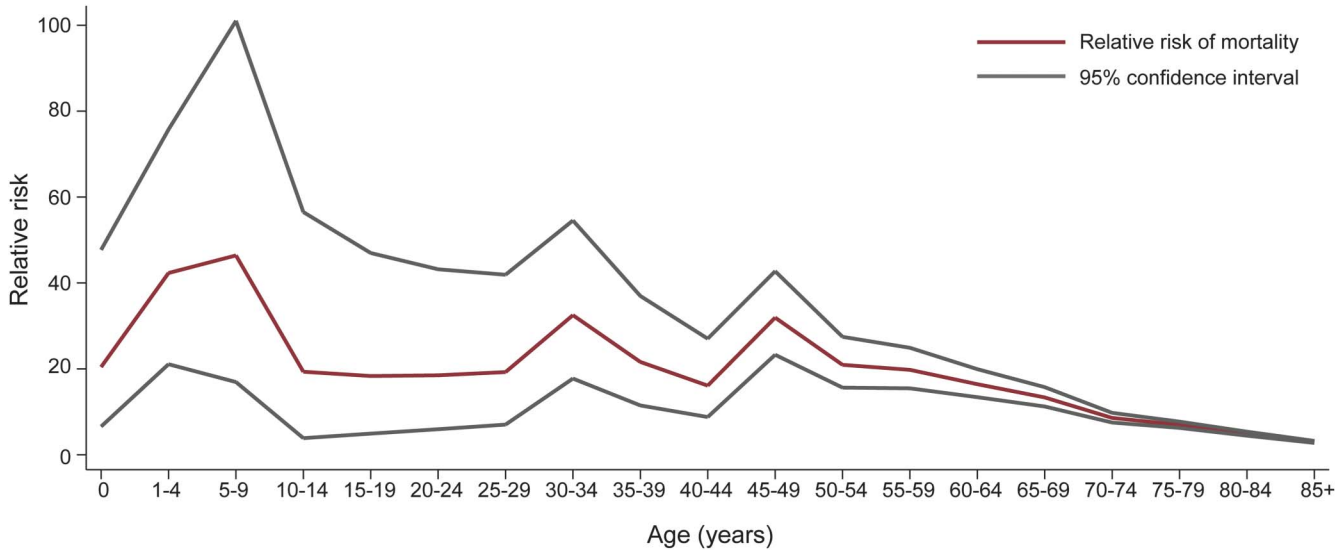
Morbidity. ***Hospitalization.*** During the study period, 6,184 patients had a total of 39,903 subsequent hospital admissions after commencing AED therapy. Most (63%) of these were non-seizure-related. The SHR of patients with newly treated epilepsy was 6.76 (95% CI 6.70–6.82) compared to the general population. Patients aged 15–44 years (RR 22.2; 95% CI 21.5–22.8) and 5–14 years (RR 25.1; 95% CI 23.9–26.4) had the highest risks. Among patients without baseline comorbidity, SHR was 7.31 (95% CI 7.20–7.42), with correspondingly longer total number of hospitalization days (table 3). However, the average length of stay per admission in the patients was similar to the general population (SLRA 1.22; 95% CI 0.54–2.36).

New comorbidities. Among patients who did not have any baseline psychiatric comorbidity (n = 6,241), 903 (14%) were subsequently recorded as having one or more new psychiatric conditions. Among these patients, 499 (55%) had been recorded with new organic psychiatric comorbidity, 120 (13%) depression and related mood disorder, 45 (5%) substance misuse or dependence, and 359 (40%) other type of psychiatric disorder. The new comorbidities were not mutually exclusive.

Among patients who did not have any recorded physical comorbidity at baseline (n = 3,514), 535 (15%) were subsequently admitted for at least one new comorbidity that is included in the Charlson Comorbidity Index (table e-4).

Cancers. During follow-up, 78 patients were diagnosed with new primary cancer (20 were of CNS origin and 58 were of other sites) after the diagnosis of epilepsy was made; 57 (73%) were after 30 days of commencing AED treatment. The SIR for cancer of all sites was 1.97 (95% CI 1.56–2.46) (table e-5A), being predominantly borne by men (SIR 2.30; 95% CI 1.75–2.97 vs women SIR 1.37; 95% CI 0.82–2.14). The incidence of cancer in all patients remained elevated after excluding cancers of CNS origin (SIR 1.48; 95% CI 1.12–1.91) (table e-5B). Again, higher risk was borne by men only (SIR 1.69; 95% CI 1.22–2.28 vs women SIR 1.09; 95% CI 0.61–1.80). The median times to hospitalization for cancer were 7.40 months (IQR 3.47–14.9) after the

Figure **Age-specific relative risks of mortality among epilepsy patients in Hong Kong**



Age-specific relative risks of mortality in newly diagnosed and treated epilepsy patients compared to the general population of Hong Kong.

Table 2 Standardized mortality ratios (SMRs) in patients treated with enzyme-inducing antiepileptic drugs (EIAEDs) and non-EIAEDs as monotherapy

	Follow-up time, person-years	Expected no. deaths	Observed no. deaths	SMR (95% CI)	p Value
All patients on monotherapy (n = 5,134)					
EIAED (n = 3,693)	9,727	287	1,367	4.76 (4.51–5.02)	<0.001
Non-EIAED (n = 1,441)	4,620	32.8	168	5.13 (4.38–5.96)	<0.001
No physical baseline comorbidity (n = 2,336)					
EIAED (n = 1,247)	4,524	50.2	138	2.75 (2.31–3.25)	<0.001
Non-EIAED (n = 1,089)	3,833	10.3	36.0	3.49 (2.45–4.83)	<0.001
With physical baseline comorbidity (n = 2,798)					
EIAED (n = 2,446)	5,202	237	1,229	5.19 (4.9–5.49)	<0.001
Non-EIAED (n = 352)	787	22	132	5.88 (4.92–6.97)	<0.001

Abbreviation: CI = confidence interval.

diagnosis of epilepsy for CNS cancers (30% more than 1 year) and 16.2 months (IQR 2.90–36.8) for non-CNS cancers.

Acute stroke. During follow-up, 109 patients were admitted for 156 new episodes of acute stroke, of which 96 (67%) were ischemic and 60 (33%) hemorrhagic. Compared to the general population aged 35 years and above for whom data have been reported,[22] the incidence of acute stroke was nearly 5 times higher among epilepsy patients (SIR 4.96; 95% CI 4.19–5.84). The rate was increased for both hemorrhagic (SIR 7.99; 95% CI 5.95–10.5) and ischemic stroke (SIR 4.11; 95% CI 3.32–5.03), and was highest among patients aged 35–44 years (table e-5C). The median time from first seizure onset to hospitalization for first acute stroke was 9.90 months (IQR 3.23–22.9) (11.9 months [IQR 4.57–26.5] for ischemic stroke and 9.47 months [IQR 2.17–19.5] for hemorrhagic stroke).

Ischemic heart disease. Population incidence has been reported for both acute and subacute forms of ischemic heart disease (ICD-9-CM diagnosis code 411 and all subcodes), angina pectoris (ICD-9-CM diagnosis code 413 and all subcodes), and other forms of chronic ischemic heart disease (ICD-9-CM diagnosis code 414 and all subcodes).[23] Employing the same classification method showed that 68 patients incurred 153 episodes of ischemic heart disease during subsequent admissions. Compared to the general population, epilepsy patients had elevated risk of developing ischemic heart disease (overall: SIR 4.18, 95% CI 3.54–4.91; female: SIR 6.25, 95% CI 4.89–7.87; male: SIR 3.21, 95% CI 2.54–4.00) (table e-5D).

Relationship between new physical comorbidities and type of AEDs used. Among baseline comorbidity-free patients, 407 had the first new comorbidity recorded at least 30 days after commencing AED treatment. The risk of developing comorbidity did not differ between patients who had been treated with only one AED (n = 300) and those with more than one AED (n = 107; RR 1.02; 95% CI 0.85–1.23). After adjusting for age and sex, patients who had been treated with one or more EIAEDs (n = 325) had significantly higher risk of developing new comorbidities compared to those treated with non-EIAEDs only (n = 82; RR 1.48; 95% CI 1.19–1.85). At the last admission within the study period, the cumulative Charlson Comorbidity Index scores were significantly higher in patients exposed to EIAEDs (mean 0.41; SD 1.25) than those who never used an EIAED (mean 0.11; SD 0.54; $p = 0.002$), after adjusting for age, sex, and whether multiple AEDs had been used.

Table 3 Standardized hospitalization and length of stay ratios of newly diagnosed and treated epilepsy patients

	Expected no.[a]	Observed no.	Standardized ratio (95% CI)	p Value
Study cohort (n = 7,461)				
Admission[b]	7,010	47,364	6.76 (6.70–6.82)	<0.001
Total LoS, d	49,046	405,382	8.27 (8.24–8.29)	<0.001
LoS per admission, d	7.00	8.56	1.22 (0.54–2.36)	0.65
Patients without baseline comorbidity (n = 3,514)				
Admission[b]	2,349	17,169	7.31 (7.20–7.42)	<0.001
Total LoS	14,344	130,933	9.13 (9.08–9.18)	<0.001
LoS per admission	6.11	7.63	1.25 (0.52–2.50)	0.64

Abbreviations: CI = confidence interval; LoS = length of stay.
[a] Calculated from average Hong Kong age- and sex-specific discharge rate and length of stay from 2005 to 2010.
[b] Includes index admission.

Examination of individual comorbidities included in the Charlson Comorbidity Index (table 4) showed that after adjusting for age and sex, treatment with EIAEDs (compared with non-EIAEDs) was associated with higher recorded incidence of cerebrovascular disease (RR 1.78; 95% CI 1.14–2.77) and mild liver disease (RR 2.43; 95% CI 1.32–4.48). These were also the most common new comorbidities recorded. Among the patients with cerebrovascular disease recorded after commencing AED treatment, 87% (156/177) were treated with EIAEDs. The association between treatment with EIAEDs and record of mild liver disease was limited to nonviral and nonalcoholic subtypes (RR 2.82; 95% CI 1.29–6.15). These include acute necrosis of liver, drug-induced hepatitis, toxic liver disease, and other unspecified liver diseases. Among the patients recorded to have mild liver disease, 88% (49/56) had been treated with at least one EIAED.

DISCUSSION Using whole population data, we found that newly diagnosed and treated epilepsy is associated with a substantial health burden in terms of both mortality and morbidity. The observed SMR in Hong Kong appeared higher than previous studies performed in predominantly Nordic populations (RR 2.87; 95% CI 2.16–3.81), and more comparable to those in developing countries.[1] Excess mortality conferred by epilepsy is relatively greater among younger patients, who are exposed to fewer competing mortality risks generally. As expected, patients with baseline comorbidities, whether physical or psychiatric, had higher mortality, as did patients taking multiple AEDs. The latter likely reflects the severity of the epilepsy, which is a predictor of greater mortality risk.[26]

Remarkably, newly treated epilepsy patients were nearly 7 times more likely to be hospitalized compared to the general population. Perhaps more importantly, the majority of the hospitalizations were attributed to non-seizure-related conditions. Specifically, patients without baseline physical comorbidity had higher risks of recorded cancer, cerebrovascular disease, and ischemic heart disease. These findings are consistent with results of a recent report from the community-based UK National

Table 4 Relative risk of being newly diagnosed with comorbidities in baseline comorbidity-free patients exposed to enzyme-inducing antiepileptic drugs (EIAEDs) (compared to non-EIAEDs only) or multiple antiepileptic drugs (AEDs) (compared to single AED), adjusted for age and sex

	Exposed to EIAED monotherapy			Exposed to multiple AEDs		
Comorbidity (total no. patients)	No.	RR (95% CI)	*p* Value	No.	RR (95% CI)	*p* Value
Cerebrovascular disease (n = 177)	156	1.78 (1.14–2.77)	0.011	51	1.14 (0.86–1.50)	0.36
Acute stroke (n = 77)	64	1.20 (0.66–2.20)	0.55	25	1.31 (0.83–2.46)	0.25
Mild liver disease (n = 85)	73	2.43 (1.32–4.48)	0.004	32	1.35 (0.88–2.07)	0.17
Exclude alcohol-related or viral hepatitis (n = 56)	49	2.82 (1.29–6.15)	0.009	22	1.40 (0.82–2.36)	0.22
Diabetes without complications (n = 73)	64	1.66 (0.83–3.32)	0.15	18	0.91 (0.54–1.52)	0.72
Chronic pulmonary disease (n = 59)	40	0.62 (0.37–1.05)	0.078	16	0.80 (0.49–1.45)	0.53
Cancer (n = 56)	49	2.11 (0.96–4.67)	0.064	18	1.14 (0.66–1.96)	0.64
Paraplegia and hemiplegia (n = 55)	43	1.72 (0.92–3.23)	0.09	22	1.38 (0.80–2.37)	0.24
Congestive heart failure (n = 44)	40	2.17 (0.78–6.01)	0.14	11	0.90 (0.46–1.76)	0.76
Dementia (n = 43)	39	1.77 (0.64–4.92)	0.27	15	1.55 (0.86–2.82)	0.15
Renal disease (n = 24)	19	0.84 (0.31–2.27)	0.74	7	1.04 (0.43–2.52)	0.93
Metastatic carcinoma (n = 22)	20	2.25 (0.51–9.86)	0.28	7	1.22 (0.50–2.98)	0.66
Myocardial infarct (n = 17)	14	0.88 (0.25–3.06)	0.84	7	1.94 (0.75–5.03)	0.17
Peptic ulcer disease (n = 16)	16	NA[a]		3	0.56 (0.16–1.97)	0.36
Peripheral vascular disease (n = 12)	11	1.91 (0.22–16.3)	0.56	4	1.46 (0.46–4.60)	0.52
Diabetes with complications (n = 10)	8	0.88 (0.17–4.47)	0.88	2	0.65 (0.13–3.29)	0.60
Moderate or severe liver disease (n = 6)	5	1.88 (0.19–18.4)	0.59	1	0.42 (0.05–3.79)	0.44
Connective tissue or rheumatic disease (n = 4)	4	NA[a]		1	0.77 (0.08–7.70)	0.83
AIDS/HIV (n = 1)	0	NA[b]		0	NA[b]	

Abbreviations: CI = confidence interval; NA = relative risk was not applicable due to zero frequency observed in certain event; RR = relative risk.
[a] All patients who newly developed the underlying condition were exposed to EIAED as monotherapy.
[b] Only one patient newly developed AIDS/HIV and was exposed to valproic acid monotherapy.

General Practice Study of Epilepsy, which identified noncerebral neoplasm and cardiovascular and cerebrovascular diseases as the most common causes of deaths in people with epilepsy.[27]

Whether epilepsy per se or its treatment confers increased risk of cancers is a subject of intense debate.[28] It is possible that the increased risk of cancer merely reflects surveillance bias (i.e., the diagnosis of epilepsy may have prompted medical examination that leads to the detection of occult cancer), which is most likely the case for CNS cancer.[29] Nonetheless, 30% of CNS cancers and more than half of non-CNS cancers were recorded more than 1 year after epilepsy was diagnosed. In another population-based study that utilized registers in Denmark and excluded people who developed cancer within a year of epilepsy diagnosis or initiation of AED therapy, use of AED increased the rates of most cancers little or not at all.[30] In contrast, epilepsy was associated with increased rates of CNS, mouth and throat, and respiratory tract cancers, independent of AED use. These findings raise the possibility of etiologic factors common to epilepsy and cancer.

Similar to the increased rate of cancer, it is possible that the recorded cerebrovascular disease already existed at the time of diagnosis of epilepsy.[31] However, acute stroke rate was also higher in epilepsy patients regardless of stroke subtypes, particularly in the younger age group, supporting recent observations that epilepsy might also predict subsequent stroke.[32–34] Newly treated epilepsy patients were also found to have higher risk of developing ischemic heart disease. These results are consistent with those reported from another Danish population study, showing that in patients without previous stroke, AED-treated epilepsy was associated with an increased risk of myocardial infarction, stroke, and cardiovascular death.[35]

One of the mechanisms postulated to increase the risk of both cerebrovascular and coronary diseases in epilepsy patients relates to the effects of EIAEDs on vascular risk factors, such as cholesterol metabolism.[18] This was explored in our study by comparing the incidence of new comorbidities between baseline comorbid-free patients newly treated with EIAEDs and with non-EIAEDs. Indeed, the former group had higher overall risk of developing new comorbidities and higher Charlson Comorbidity Index scores. This was mainly driven by the recorded diagnosis of cerebrovascular disease and mild liver disease, while no difference was observed for acute stroke or cardiovascular disease. EIAEDs are known to cause an increase of liver enzymes that is usually of no clinical significance. Since the association is well-recognized, we suspect that liver function test may be more frequently ordered by physicians in patients treated with EIAEDs, resulting in testing bias. The results of liver function test or confirmatory investigations (e.g., ultrasound or biopsy) were not available for analysis and it was unknown whether the test was performed equally in patients regardless of AED types.

A bidirectional relationship may exist between epilepsy and psychiatric disorders.[36] In our cohort, 1 in 6 patients with newly treated epilepsy had preexisting psychiatric disorders and 1 in 7 were subsequently diagnosed with de novo psychiatric conditions. These rates are comparable to population-based studies from Western countries,[17,36] although underrecognition cannot be ruled out owing to cultural factors. Data on the prevalence of mental disorders in the general population in Hong Kong is scant and future study is needed to evaluate whether epilepsy confers a higher risk.

Our study only included patients who were admitted to the public hospitals and commenced on AED therapy. Therefore, patients with newly diagnosed epilepsy who only sought private health care, did not require hospitalized care, or did not commence AED treatment were excluded, although their number is likely to be relatively small. Nonetheless, the exclusion of these patients might have led to bias towards including older patients with more severe epilepsy, contributing in part to the higher SMRs observed in our study compared to others.[26,37,38] Moreover, due to coding limitations, it is not possible to identify the etiology. Second, we used only in-hospital deaths to calculate SMRs, which might have led to underestimation, and counteracted any potential overestimation from including patients with more severe epilepsy. Third, because new comorbidities were identified during subsequent hospitalization, there was risk of underestimating mild, nonacute, and longer-term physical comorbidities, as well as psychiatric illnesses. Nonetheless, there was robustness in the diagnosis and recording of acute, severe conditions, such as acute stroke and myocardial infarction, as they generally require immediate hospital care. Finally, due to deidentification and anonymization of the dataset, it was not possible to analyze the direct cause of death from death certificates or medical records. Further study will be conducted to pursue the causes of death in this cohort.

Our study found that newly diagnosed and treated epilepsy patients bear a substantially higher burden of mortality and morbidity compared with the general population. They are more likely to develop cancer, cerebrovascular disease, and ischemic heart disease. Treatment with EIAEDs is associated with higher overall comorbidity burden. Further investigations

to understand the biological mechanisms underpinning these differences are needed.

AUTHOR CONTRIBUTIONS

Z. Chen conducted the statistical analysis, interpreted the analysis, and drafted the manuscript. Dr. Liew interpreted the analysis and drafted the manuscript. Dr. Kwan conceived and designed the study, obtained the data, interpreted the analysis, and drafted the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

Z. Chen reports no disclosures relevant to the manuscript. D. Liew has received research grants from the National Health and Medical Research Council of Australia, the Australian Research Council, and the National Heart Foundation of Australia. He/his institution has also received speaker or consultancy fees and/or research grants from Pfizer, AbbVie, Sanofi, AstraZeneca, GlaxoSmithKline, and Amgen. P. Kwan has received research grants from the National Health and Medical Research Council of Australia, the Australian Research Council, the US NIH, Hong Kong Research Grants Council, Innovation and Technology Fund, Health and Health Services Research Fund, and Health and Medical Research Fund. He/his institution also received speaker or consultancy fees and/or research grants from Eisai, GlaxoSmithKline, Johnson & Johnson, Pfizer, and UCB Pharma. Go to Neurology.org for full disclosures.

Received January 21, 2016. Accepted in final form May 9, 2016.

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