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## Research paper Evaluating clinical risk factors for suicide attempts in patients with epilepsy Tomor Harnod<sup>a,b</sup>, Cheng-Li Lin<sup>c,d</sup>, Chia-Hung Kao<sup>e,f,g,\*</sup>



<sup>a</sup> Department of Neurosurgery, Hualien Tzu Chi General Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan

<sup>b</sup> College of Medicine, Tzu Chi University, Hualien, Taiwan

<sup>c</sup> Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan

<sup>d</sup> College of Medicine, China Medical University, Taichung, Taiwan

e Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan

<sup>f</sup> Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan

<sup>8</sup> Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan

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#### ABSTRACT

*Objective:* We would like to exam whether epilepsy patients in Taiwan have a high risk of attempted and completed suicide.

*Methods*: In this study, we used a subset of the National Health Insurance Research Database (NHIRD) of Taiwan. Inpatients ( $\geq$  18 years) who received a new diagnosis of epilepsy between 2000 and 2011 were enrolled in the epilepsy cohort. The epilepsy and comparison cohorts included 68,543 patients and 2-fold controls respectively. We calculated the adjusted hazard ratio (aHR) for suicide attempts after adjustment for age, sex, monthly income, the urbanization level, occupation, and comorbidity.

*Results*: The epilepsy cohort had a 2.06-fold risk of suicide attempts (95% CI = 1.65-2.56) compared with the control cohort. The suicide attempt risk did not significantly differ between men and women and between patients with and without psychiatric comorbidity. The mortality risk after a suicide attempt was higher in the epilepsy cohort than in the comparison cohort (aHR = 1.66, 95% CI = 1.02-2.69).

*Conclusion:* Epilepsy is an independent and predisposing factor for suicide attempt. These results provide important information for clinicians and governments to prevent suicide in epilepsy patients in Asian countries.

#### 1. Introduction

Epilepsy, a common, chronic neurological disease, not only affects the quality of life of patients but also leads to premature death (Chang et al., 2012; Ridsdale, 2015; Fazel et al., 2013a). Among the multiple etiologies of premature death in patients with various types of epilepsies, suicidal deaths possibly account for up to 5% death of epilepsy patients (Bell et al., 2009). It remains controversial whether any type of epilepsy is independently associated with suicide attempts, (Fazel et al., 2013a; Christensen et al., 2007a; Cockerell et al., 1994) because the confounding effects of several psychiatric comorbidities are often observed in patients with epilepsy and may precede a suicide attempt. Moreover, most related studies have been conducted in Western countries in the past 2 decades (Ridsdale, 2015; Fazel et al., 2013a; Bell et al., 2009; Christensen et al., 2007a; Cockerell et al., 1994); it is difficult to apply the results of Western studies to developing countries in Asia because of the considerable socioeconomic and cultural differences between Western and Asian societies.

The poor socioeconomic status or low income of a patient is widely recognized to be associated with a high risk of various diseases preceding and causing epilepsy, with an increased risk of epilepsy, and with increased mortality rates in patients with epilepsy (Newton and Garcia 2012; Beghi and Hesdorffer, 2014). Moreover, sex, age, socioeconomic, and ethnic factors together play important roles in patients dying prematurely or attempting suicide (Tumbull et al. 2015; Martin et al., 2014). In Western countries, a patient might be highly intolerant to dependence or disability because of a chronic illness, and several studies have reported notably higher rates of suicidal ideation, suicide attempts, and completed suicides in patients with disabilities than in the general population (Bell et al., 2009; Christensen et al., 2007a; Tumbull et al., 2015; Martin et al., 2014). However, because of inter-ethnic and inter-cultural differences, Asians usually have higher

E-mail address: d10040@mail.cmuh.org.tw (C.-H. Kao).

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Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; NHIRD, National Health Insurance Research Database; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification

<sup>\*</sup> Correspondence to: Graduate Institute of Clinical Medicine Science and School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 404, Taiwan.

tolerance to impairment, dependence, or disability in daily life than do Europeans and Americans (Vázquez and Blanco, 2016; Chen et al., 2010; Greenfield and Suzuki).

Taiwan located in East Asia, exhibits the cultural mores of the Han people; Taiwan mores are similar to those people of China and Southeast Asian societies (Tu 1991; Ying and Han, 2008). Although the Taiwan government has established a health care system covering approximately 99% of the population for the past 2 decades (Database NHIR, 2017; Hu and Lin, 2017), we do not have actual data on the risk of suicide attempts in patients with epilepsy in Taiwan. Moreover, we would like to investigate the association between the possible clinical risk factors and suicide attempts in these patients and their mortality rate. The study findings might provide an opportunity to develop a more efficient prevention system with newly established risk factors for attempted suicide. We used a nationwide population-based database to determine whether risk factors for suicide attempts in epilepsy in Taiwan are similar to those in Western countries. We would like to exam whether patients with epilepsy in Taiwan have a high risk of attempted and completed suicide. Moreover, we tried to investigate the association between the possible clinical risk factors and suicide attempts in patients with epilepsy and their mortality rate.

#### 2. Methods

#### 2.1. Data source

Data in this retrospective study were retrieved from the National Health Insurance Research Database (NHIRD), which is maintained by the National Health Research Institutes of Taiwan. In this study, we used a subset of the NHIRD healthcare data including files of inpatient claims and the Registry of Beneficiaries. Diseases were recorded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

The NHIRD covers approximately 99% of 23.74 million residents of Taiwan because the compulsory health insurance is operated by a single-buyer, the government of Taiwan Database NHIR (2017). All insurance claims should be scrutinized by medical reimbursement specialists and peer review according to the standard diagnosed criteria. If these doctors or hospitals make wrong diagnoses or coding, they will be punished with a lot of penalties. Therefore, the validation of diagnoses using the ICD-9 codes in the NHIRD is highly reliable. The coding system and relative files have been successfully used for analysis in previous studies (Hu and Lin, 2017; Lin et al., 2017; Chiu et al., 2017).

#### 2.2. Ethics statement

The NHIRD encrypts patients' personal information to protect their privacy and provides researchers with anonymous identification numbers associated with relevant claims information, namely sex, birth date, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was exempted by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-CR2), specifically for informed consent requirement.

#### 2.3. Sampled participants

The epilepsy cohort included inpatients aged 18 years or more who were newly diagnosed with either idiopathic or symptomatic epilepsy (ICD-9-CM 345), from 2000 to 2011. The first diagnosis of epilepsy during this period was defined as the index date. We designed this study based on inpatient claims for the higher validity of enrolled data. Patients with a history of suicide attempts (ICD-9-CM E950–E959) before the index date or with incomplete age or sex information were excluded. For each epilepsy patient, two comparisons were randomly selected from the pool of participants without epilepsy and suicide attempts at the baseline, frequency-matched them with the patients by sex, age (at 5-year intervals), and the index year.

#### 2.4. Outcomes and comorbidities

All patients were followed until a new episode of suicide attempt (ICD-9-CM E950–E959) during the follow-up period. Each patient was monitored from the index date until a suicide attempt; withdrawal from the NHI program; death from other causes; or December 31, 2011. The patients with claims records for a history of schizophrenia (ICD-9-CM code 295), depression (ICD-9-CM codes 296.2, 296.3, 296.82, 300.4, and 311), alcohol-related illness (ICD-9-CM codes 291, 303, 305.00, 305.01, 305.02, 305.03, 571.0, 571.1, 571.3, 790.3, and V11.3), anxiety (ICD-9-CM code 300.00), mental disorders (ICD-9-CM codes 290–319), and insomnia (ICD-9-CM codes 307.4 and 780.5) identified prior to the endpoint were considered to have comorbidities that were further analyzed for adjustment.

#### 2.5. Statistical analysis

The distributions of sociodemographic status, comorbidities and follow-up period are presented as frequency (%) or mean ± standard deviation. The differences between categorical variables were analyzed using the chi-squared test, and those between continuous variables were estimated using Student's t-tests. We calculated the incidence density of suicide attempts (per 10,000 person-years) in the epilepsy and comparison cohorts. Univariable and multivariable Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) to determine the effects of epilepsy on the risk of suicide attempts. The variables with a p value < 0.05 in the univariable analysis were included in the multivariable analysis. Further analysis was performed to assess whether epilepsy was independently associated with the outcomes of different suicide methods. We considered death from other causes as a competing event for in the epilepsy cohort and estimated the subhazard ratios (SHRs) and 95% CIs by using the standard univariable and multivariable Cox proportional hazard regression models. Further data analysis was performed to evaluate the risk of mortality among patients with suicide attempts in the epilepsy cohort and compared with those in the comparison cohort.

All analyses were conducted using SAS software Version 9.4 (SAS Institute Inc., Cary, NC, USA), and 2-tailed P < 0.05 was considered statistically significant.

#### 3. Results

The epilepsy and comparison cohorts included 68,543 patients and 2-fold controls, respectively (Table 1). No statistical significance was observed in the distributions of sex and age between the epilepsy and comparison cohorts because of case-control matching. In both cohorts, most participants were men (62.9%), were older than 65 years (39.6%), and had income levels of 15,000-19,999 New Taiwan Dollar (NTD; approximately equivalent to 495-660 USD) per month (46.7% vs 44.9%). Compared with the controls, the patients had a higher tendency to live in the least urbanized areas (34.5% vs 26.1%) and to perform labor work (42.4% vs 37.4%). In the epilepsy cohort, the predominant comorbidity was mental disorders (26.4%), followed by alcohol-related illness (10.4%) and depression (8.34%) (Table 1). During the mean follow-up periods of 4.07 years in the epilepsy cohort and 5.58 years in the comparison cohort, 351 and 185 suicide attempts were noted in the epilepsy and comparison cohorts, respectively. Supplementary Fig. 1 showed that the cumulative incidences of suicide were significant higher for epilepsy cohort than for non-epilepsy cohort (log-rank test p < 0.001). After adjustment for age, monthly income, urbanization level, occupation category, and comorbidities, the

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