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Original Research Article

A meta-analysis of key risk factors for sudden unexpected death in epilepsy

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Abstract

Purpose: *To examine the risk factors (RFs), associated with Sudden Unexpected Death in Epilepsy (SUDEP), and the quantitative standards required to measure them*
Methods: *The literature on RFs associated with SUDEP was systematically reviewed up to August 2020 in databases, including PubMed, the Cochrane Database and Embase. Revised Newcastle-Ottawa Scale (NOS) was performed to determine the quality of each study in this meta-analysis (MA), with a score of ≥ 3, indicating good quality. Any controversies in data extraction and quality assessment were resolved through counsel or adjudication with a third researcher.*
Results: *An initial screening of the literature following the search strategy and manual inclusion yielded a total of 767 studies. After excluding duplicates as well as articles that did not match the topic, 112 studies remained. Twenty-nine studies were finally selected based on the inclusion and exclusion criteria. After a careful review of the full text, nine studies were included in the MA.*
Conclusion: *The five RFs for SUDEP included age at the onset of epilepsy ≤15 years, generalized-tonic-clonic seizure, seizure frequency ≥50 seizures/year, treatment with a combination of multiple antiepileptic drugs, and history of alcohol abuse.*

Keywords: *Sudden unexpected death in epilepsy (SUDEP), Risk factors, Meta-analysis, Antiepileptic drugs, Alcohol abuse, Seizure frequency*

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INTRODUCTION

Epilepsy (EP) is a group of symptoms with different clinical, electrophysiological, imaging and pathological patterns. Despite the great efforts of leaders in the field of epileptology and advanced knowledge of EP, in terms of clinical, genetic, imaging, and biological characteristics, no measurable objective criteria has been proposed to identify EP types and EP syndromes as a separate diagnostic entity [1]. The diagnosis of EP is therefore difficult because in practice, the electrical features may not be present during the interictal period, especially in adults, or if seizures are rare and patients without seizures occasionally develop interictal epileptiform discharges [2].

Most patients with EP behave normally during the absence of seizures, but often have life-

threatening episodes due to the sudden seizure. Public Health, England has published a report on neurological disease-related deaths in England from 2001-2014, highlighting an alarming trend, with EP-related deaths increasing by 70 % in recent years and growing steadily [3]. Increased mortality is associated with many factors, and sudden unexpected death in epilepsy (SUDEP) is the leading cause of death from chronic EP [4]. Data shows that the incidence of SUDEP ranged from 0.09 to 9.3 per 1,000 persons per year [5].

Essentially, the screening of SUDEP cases in EP cohorts and samples from the community is mostly retrospective, and this involves a data review from hospital and autopsy records. A population-based study in the United States showed 0.35 cases of EP per 1,000 persons per year, and the mortality rate was approximately 24 times that of other healthy populations [6]. Similar results were obtained in a national population study in Denmark [7]. A higher incidence of SUDEP has also been found in epileptic populations. SUDEP is a challenge for scientists, and there are several studies on its mechanisms and risk factors (RFs). However, at present, there is no quantitative standard to measure the RFs for SUDEP. Therefore, in this study, the RFs for SUDEP were reviewed, and a detailed meta-analysis (MA) was performed to provide guidance for the occurrence and prevention of SUDEP.

Sudden unexpected death in epilepsy refers to deaths in people with EP that are not caused by injury, drowning, or other known causes [8,9].

There are many studies on SUDEP RFs that are investigatively heterogeneous in terms of population and methodology. As a result, correlations found in single study can be hard to explain and are often contradictory. Many demographic factors are related to increased risk of SUDEP. Males tended to develop seizures before the age of 16. Duration of EP over 15 years was also identified as a significant RF [10,11].

The type and the frequency of seizures is also a significant RF for SUDEP [12]. A correlation was found amongst the number of convulsions, the number of antiepileptic drugs (AEDs), and the risk of SUDEP [10]. An animal experiment showed that convulsive seizures immediately reduce the complexity of cardiac rhythm regulation, as reflected by a decrease in ApEn. Recurrent episodes of seizures may cause long-term neurological abnormalities in the neurocardiac regulation, particularly parasympathetic nervous system, which limits the appropriate autonomic response. The acquired abnormalities may, in turn, predispose individuals to sudden death from cardiac arrhythmias and seizures [13]. Multiple AED may be effective for poor seizure control. After adjusting for confounding factors including seizure frequency, multidrug therapy was an important independent RF for SUDEP [13].

Epileptic patients with intellectual disability (ID) are known to have high rates of refractory EP and comorbidities. The adjusted odds ratio for ID was 4.6 (1.2-1.8), which is probably an important independent RF for SUDEP [14]. Generalized tonic-clonic seizure is one RF for SUDEP [15], and many studies have shown that patients with EP who have generalized tonic-clonic seizure (GTCS) are more likely to develop SUDEP. The findings of a national cohort study in Sweden indicate that any psychiatric comorbid condition may increase the risk of SUDEP. In women, the risk of SUDEP may be five times higher in people with psychiatric comorbidities than in people without psychiatric comorbidities. It was found that treatment with anxiolytics and antipsychotics increases the risk of SUDEP [16]. Evidence indicate that carbamazepine monotherapy may also increase the risk of SUDEP, which may due to the fact that CBZ inhibits parasympathetic and sympathetic function in newly diagnosed EP cases [17]. A previous study has found that alcohol is also a RF, and that patients with cardiac lesions are more likely to develop SUDEP, suggesting that triggers for SUDEP include long QT syndrome-related mutations [18].

In this study, a MA of the RFs was conducted to provide the basis for the prevention of sudden death in EP, thus reducing the possibility of sudden death in EP.

MATERIALS AND METHODS

Literature inclusion criteria

The literature meeting the following criteria was included: (1) patients with a diagnosis of SUDEP; (2) the literature was written in English; and (3) full-text was available.

Literature exclusion criteria

The following types of literature were excluded: (1) case reports, review articles, and animal studies; (2) incomplete data or unavailable full-text; (3) irrelevant topics; (4) studies without clear diagnostic method for SUDEP; (5) studies not written in English language.

Literature search

The databases such as PubMed, Embase and Cochrane databases were systematically reviewed. When searching the studies prior to August 2020, a combination of keywords was adopted with the formula "Sudden Unexpected Death in Epilepsy" (Mesh) OR "SUDEP" (Title/Abstract) AND "RFs" (Mesh OR Factor, Risk (Title/Abstract) OR "RF" (Title/Abstract) OR "Health Correlates" (Title/Abstract) OR "Correlates, Health" (Title/Abstract) OR "Risk Scores" (Title/Abstract) OR "Risk Score" (Title/Abstract) OR "Score, Risk" (Title/Abstract) OR "RF Scores" (Title /Abstract).

Data extraction

Data including titles, first author, date of publication, type of study, number of cases per group, and journal of publication, were extracted. Eleven RFs, i.e., gender, age at onset of EP, seizure type, seizure frequency, AED therapy, multidrug combination therapy, carbamazepine monotherapy, history of cardiac disease, previous psychiatric disorders, mental retardation, and history of alcohol abuse were analyzed in this MA. The revised NOS was applied to assess the methodological quality for each study. Studies were grouped as high risk of bias (<3 points) or low risk of bias (≥3 points). If there was any disagreement in data extraction and quality assessment, a third researcher was invited to join the discussion prior to arrival at the final decision.

Statistical analysis

Revman 5.3 software (London, UK) was applied for MA. Heterogeneity between studies was assessed by I2 values, with I2 values < 50 %, and ≥ 50 % suggested low and high heterogeneity of results, respectively. Since the random-effects model tends to provide a wider CI than the fixed-effect model and are preferable in the presence of heterogeneity among studies, random effects MA was used to summarize the studies if heterogeneity is greater than 50 %. When the *p*-value was less than 0.05, the study results were statistically significant; when the *p*-value was greater than 0.05, it was considered not statistically significant.

RESULTS

Basic information about the included literature

Figure 1 shows the detailed selection process. A preliminary literature search using the search strategy yielded 767 studies. After excluding duplicates as well as articles that did not conform to the subject, 112 studies were left. Finally, 29 studies were selected after inclusion and exclusion criteria screening. After a careful review of the full text, nine studies were included in the MA. The basic information of the nine included articles is shown in Table 1. Table 2 shows the results of MA of RFs associated with SUDEP.

Risk factors for SUDEP

Gender

Figure 2 reveals a forest plot for comparison of the incidence of SUDEP in the male group with the female group, showing no significant differences ($p = 0.57$), indicating that gender was not a RF.

Duration of disease

Figure 3 reveals a forest plot for comparison of the incidence of SUDEP in the group with age of onset of EP ≤ 15 years with age of onset >15 years. It was found that the difference in the incidence of EP was 4.72 times between groups ($p < 0.000001$), indicating that the duration of disease was a RF.

Table 1: Basic information on the included articles

First author	Year	Country	Research type	Controls /Cases	NOS score	Journal source
Opeskin [1]	1999	Australia	retrospective	44/44	8	Epilepsia
Nilsson [2]	1999	Sweden	retrospective	57/171	8	Lancet
Kloster [3]	1999	Canada	retrospective	42/37	8	J Neurol Neurosurg Psychiatry
Walczak [4]	2001	America	Prospective	20/80	8	Neurology
Opeskin [5]	2003	Australia	Prospective	50/50	9	Seizure
Beran [6]	2004	Australia	Prospective	21/21	7	Seizure
Hitiris [7]	2007	Scotland	retrospective	62/124	8	Epilepsy Behav
Vlooswijk [8]	2007	Netherlands	retrospective	29/104	8	Seizure
Sveinsson [9]	2020	Sweden	retrospective	255/1148	8	Neurology

Table 2: Results of meta-analysis of risk factors associated with sudden death in epilepsy

Risk factors	I2 value	Statistical methods	OR (95%CI)	Z value	*P*-value	Research literature
Gender	28 %	Fixed effect model	0.94(0.77,1.16)	0.57	0.57	[2] [3] [4] [5] [7] [8] [9]
Duration of epilepsy	32 %	Fixed effect model	4.72(3.08,7.25)	7.10	<0.0001	[2] [5] [7]
Seizure type	77 %	Random effect model	2.88(1.26,6.62)	2.5	0.01	[2] [4] [5] [7] [8] [9]
Seizure frequency	0 %	Fixed effect model	3.62(1.68,7.81)	3.29	0.001	[2] [4] [5]
Antiepileptic-drug treatment	0 %	Fixed effect model	1.27(0.93,1.73)	1.49	0.14	[1] [4] [5] [9]
Multidrug-joint treatment	73 %	Random effect model	1.90(1.10,3.28)	2.30	0.02	[2] [5] [6] [7] [9]
Kamamasine monotherapy	60 %	Random effect model	1.19(0.76,1.88)	0.77	0.44	[1] [2] [3] [5] [7] [9]
History of heart disease	38 %	Fixed effect model	0.57(0.25,1.26)	1.39	0.17	[2] [3]
Mental disorders	16 %	Fixed effect model	0.73(0.41,1.30)	1.09	0.28	[2] [4] [5]
Mentally disabled	81 %	Random effect model	2.39(0.53,10.8)	1.13	0.26	[2] [4] [5]
Alcohol abuse	77 %	Random effect model	2.03(1.39,2.98)	3.64	0.0003	[2] [5] [9]

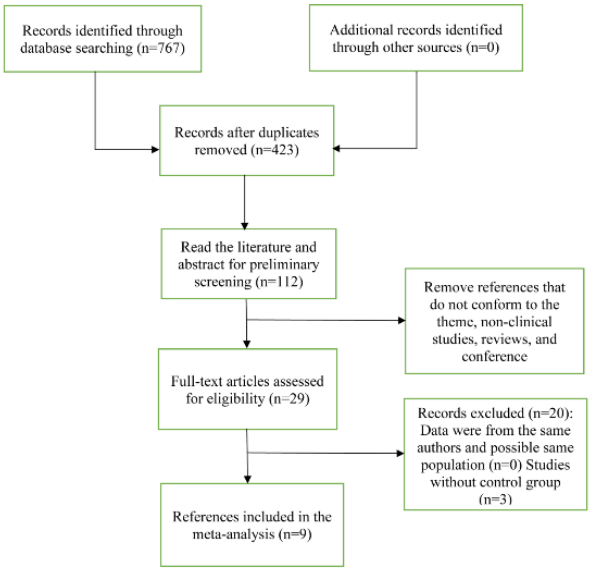

Figure 1: Detailed flow chart for selection of included literature

Seizure type

Figure 4 shows a forest plot for comparison of SUDEP in the GTCS group with the non-GTCS group, and a 2.88 times difference was found between two groups (p=0.01), indicating that GTCS episode was a RF.

Seizure frequency

Figure 5 is a forest plot for comparison of SUDEP between seizure frequency ≥ 50 seizures/year with seizure frequency <50 seizures/year. The incidence differed by 3.62 times between two groups (p=0.001), indicating that seizure frequency was a RF.

AED treatment

Figure 6 is a forest plot for the comparison of SUDEP in the AED group with the non-AED group, and the difference in the incidence of SUDEP was 1.27 times between two groups (p=0.14), indicating that AED treatment was not a RF.

Multidrug combination therapy

Figure 7 is a forest plot for the comparison of SUDEP in the multidrug combination group with the monotherapy group, and the difference in the incidence of SUDEP was 1.90 times between the two groups (p=0.02), indicating that multidrug combination therapy was a RF.

Carbamazepine monotherapy

Figure 8 is a forest plot for the comparison of SUDEP in the carbamazepine monotherapy group with the AED treatment groups, and the difference in the incidence of SUDEP was 1.19 times between the two groups (p=0.44), indicating that carbamazepine monotherapy was not a RF.

History of cardiac disease

Figure 9 shows a forest plot for the comparison of SUDEP in patients with EP with a history of previous cardiac disease and without a history of cardiac disease, and the difference in the incidence of SUDEP was 0.57 times between the two groups (p=0.17), indicating that a history of cardiac disease was not a RF.

History of psychotic disorder

Figure 10 shows a forest plot for the comparison of SUDEP in patients with and without previous psychotic disorders, and the difference in the incidence of SUDEP was 0.73 times between the two groups (p=0.28), indicating that a history of psychotic disorder was not a RF.

Intellectual disability

Figure 11 is a forest plot for the comparison of SUDEP in patients with and without ID, and the difference in the incidence of SUDEP was 2.39

times between the two groups (p=0.26), indicating that ID was not a RF.

History of alcoholism

Figure 12 is a forest plot for the comparison of SUDEP in patients with and without history of alcoholism, and the difference in the incidence of SUDEP was 1.14 times between two groups (p = 0.0003), indicating that a history of alcoholism was a RF.

Bias analysis results

The Figures 13-17 are funnel plots with >50% heterogeneity.

DISCUSSION

Sudden unexpected death in epilepsy is a major cause of death in epileptic patients, and the risk of death caused by SUDEP translates into a significant health burden. In terms of years of potential life lost, SUDEP is second only to stroke [19]. However, effective interventions for SUDEP are lacking. Therefore, RFs for sudden death in EP should be identified to improve the awareness and prevention of the disease [20].

In this MA, the incidence of SUDEP in age group ≤15 years was higher than that in the age group >15 years, indicating that the earlier onset was adverse to disease control.

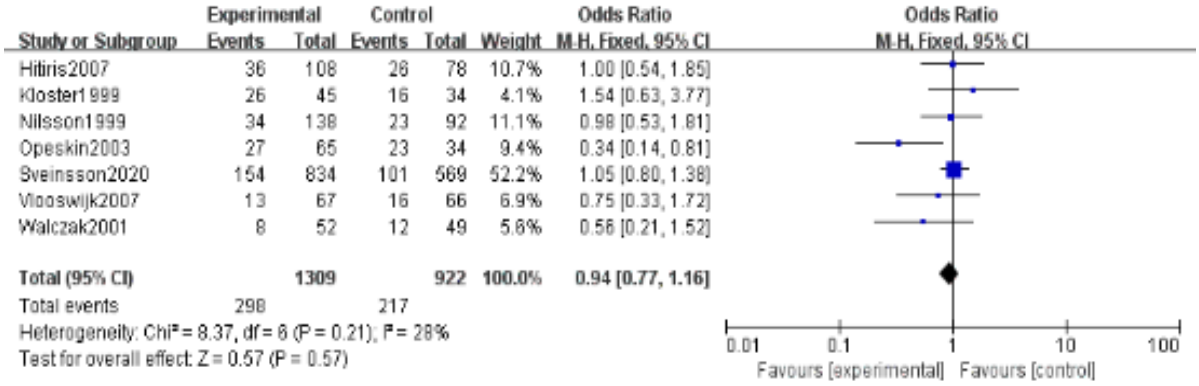

Figure 2: Incidence of SUDEP in the male group relative to the female group

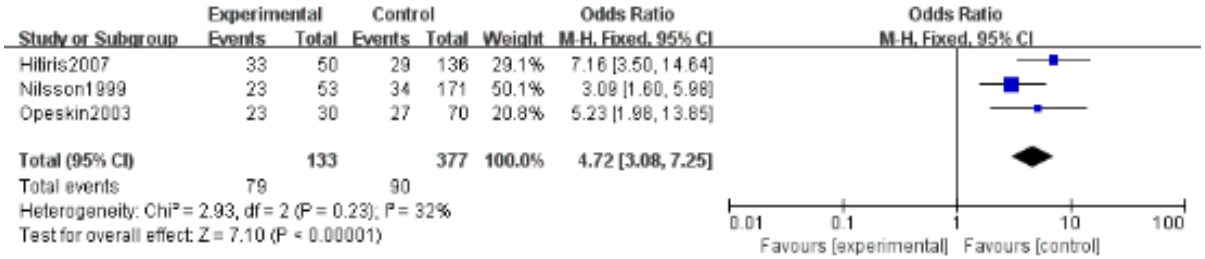

Figure 3: Incidence of SUDEP in at age of onset ≤ 15 years relative to age of onset >15 years

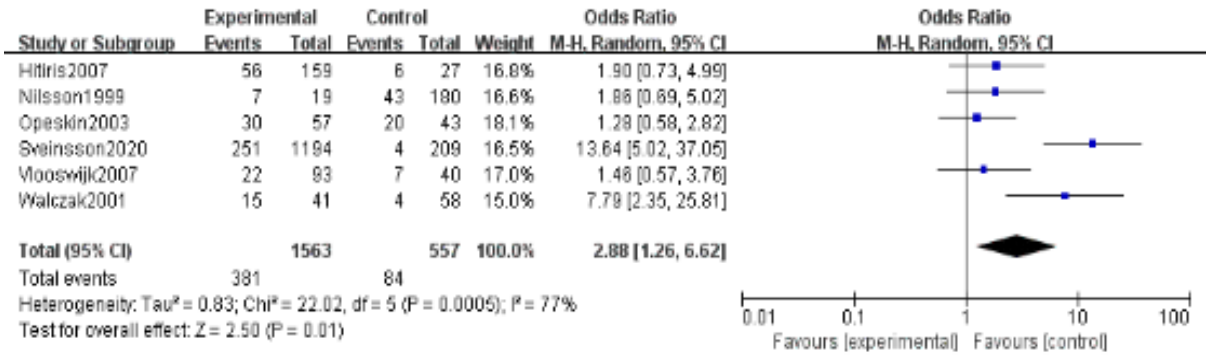

Figure 4: Incidence of SUDEP in the GTCS group relative with the non-GTCS group

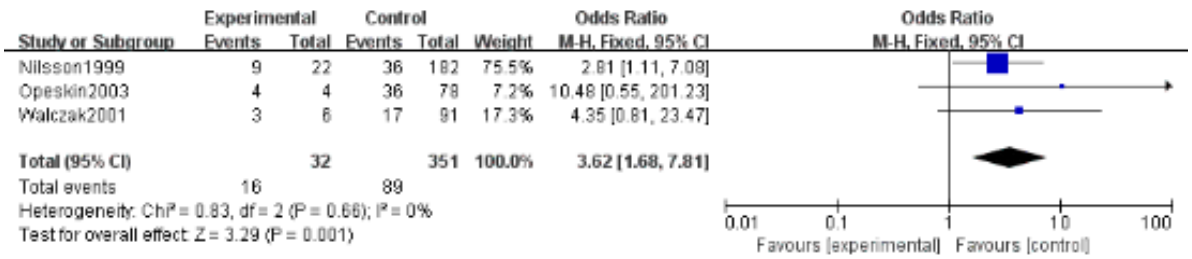

Figure 5: Incidence of SUDEP in seizure frequency ≥50 seizures/year relative with seizure frequency <50 seizures/year

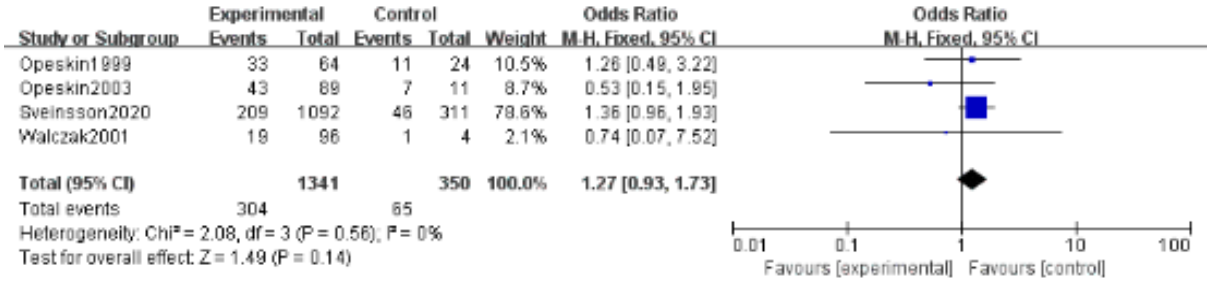

Figure 6: Incidence of SUDEP in the AED treatment group relative with the non-AED treatment group

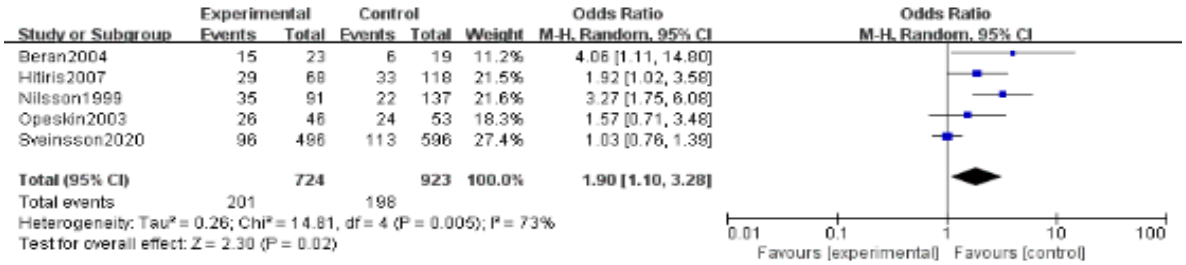

Figure 7: Incidence of SUDEP in the multidrug treatment group compared with the monotherapy group

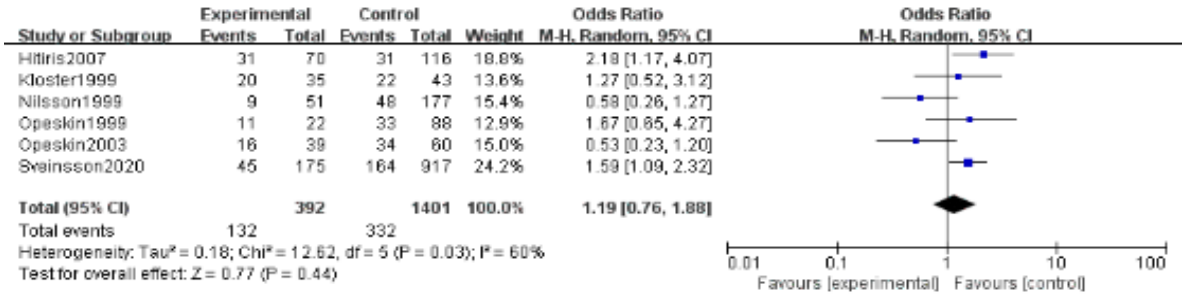

Figure 8: Incidence of SUDEP in the carbamazepine monotherapy group relative to the other AED treatment groups

Figure 9: Incidence of SUDEP in patients with a previous history of cardiac disease relative to those without a history of cardiac disease

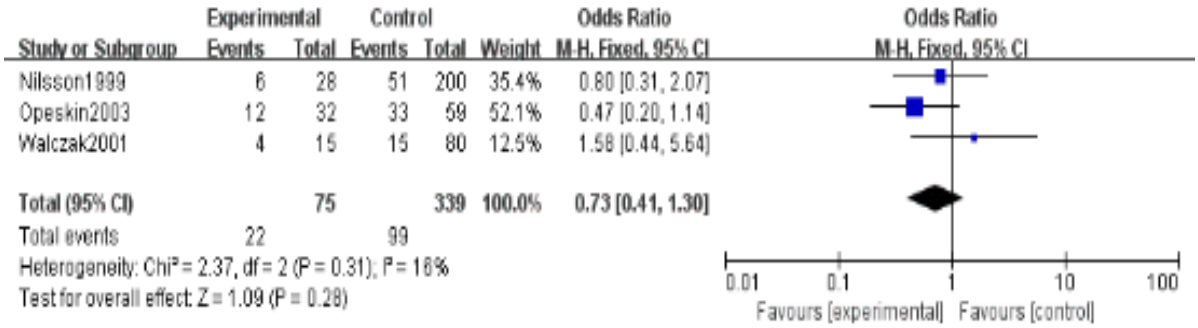

Figure 10: Incidence of SUDEP in patients with a history of psychiatric disorders relative to those without a history of psychiatric disorders

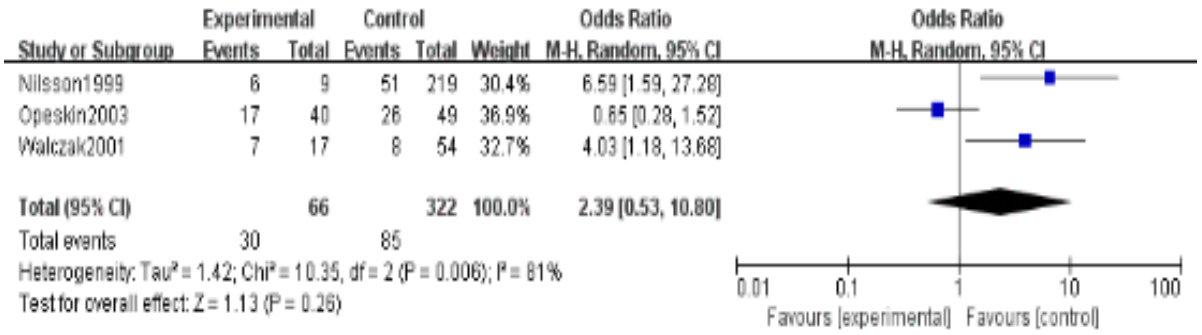

Figure 11: Incidence of SUDEP in patients with ID relative to those without ID

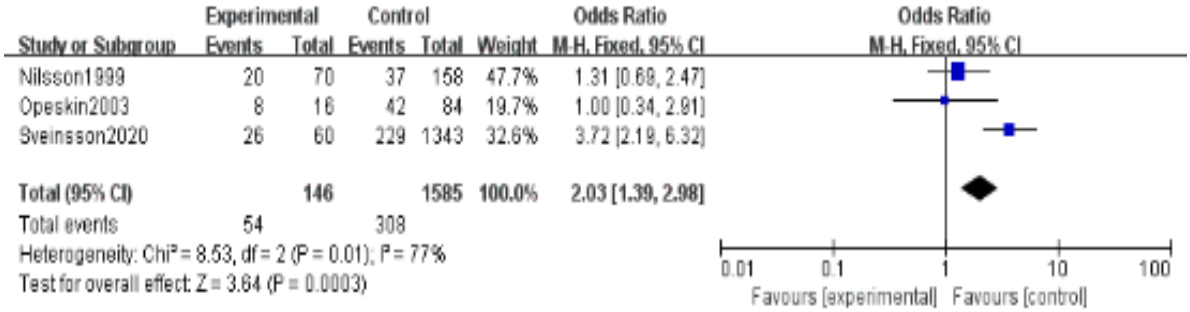

Figure 12: Incidence of SUDEP in patients with a history of alcohol abuse relative to those without a history of alcohol abuse

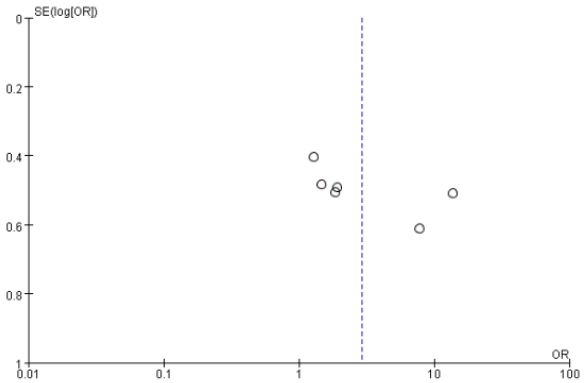

Figure 13: Funnel plot for comparison of the incidence of SUDEP between the GTCS group and the non-GTCS group

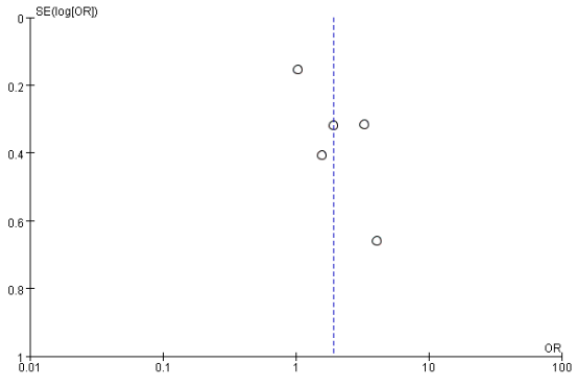

Figure 14: Funnel plot for comparison of the incidence of SUDEP between the multidrug combination therapy group and the monotherapy group

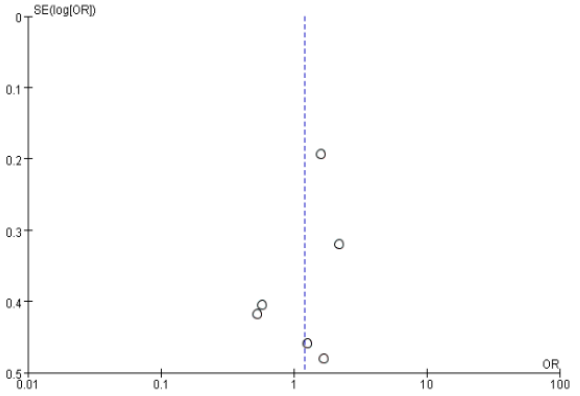

Figure 15: Funnel plot for comparison of the incidence of SUDEP in the carbamazepine monotherapy group with the incidence in the other AED treatment groups

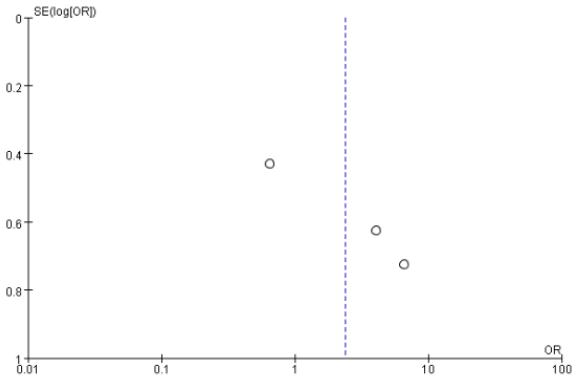

Figure 16: Funnel plot for comparison of the incidence of SUDEP between patients with epilepsy with intellectual impairment and those without intellectual impairment

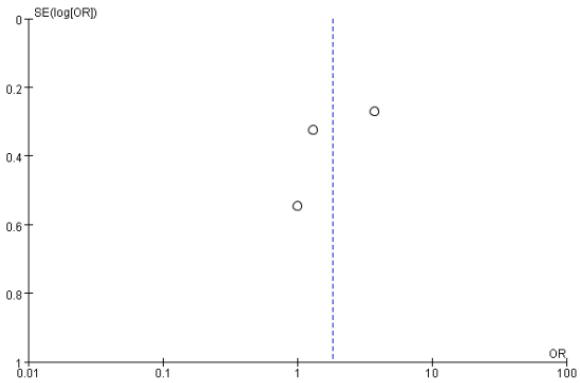

Figure 17: Funnel plot for comparison of the incidence of SUDEP between patients with epilepsy with a history of alcohol abuse and those without a history of alcohol abuse.

The underlying reason may be that the earlier onset of EP indicates a longer history of EP, which may impair autonomic function, thereby increasing the risk of sudden death [21].

Uncontrolled tonic-clonic seizures is the most determinate RF for SUDEP, but the mechanism remains unclear. A study suggested that a possible effects on cardiac function during seizures [22]. The present study observed a significant difference in SUDEP between GTCS group and non-GTCS group, which is similar to the results of other cohort studies. Therefore, it is recommended that GTCS seizures should be controlled aggressively with medications, so as to reduce the occurrence of SUDEP.

In this study, all patients with EP were divided into 2 groups, i.e., ≥ 50 seizures/year group and < 50 seizures/year group. The findings revealed that the incidence of SUDEP was markedly higher in the group of ≥ 50 seizures/year than in the group of < 50 seizure frequency/year. The mechanism may be that a seizure frequency of > 50 per year indicates a more severe epileptic condition, and reflects that the seizure control of patients with EP is not good. Hence, these patients should seek prompt medical attention and their AED regimen should be adjusted according to their condition.

Antiepileptic drugs are critical treatments for refractory EP. In clinical practice, a single drug is not effective in controlling epileptic seizures for most epileptic patients. Therefore, more than two AEDs are often required. However, treatment with multiple anti-epileptic drugs is accompanied by an increased risk of side effects. The present study showed that multiple antiepileptic drugs is one RF for the occurrence of SUDEP. This suggests that in clinical practice, multiple drug therapy should not be given in epileptic patients whose seizures can be controlled well with monotherapy [23].

Alcohol is one RF for sudden death in epileptic patients. This may be due to increased rate of seizures caused by alcohol withdrawal [24]. A marked difference was found in the incidence of SUDEP between patients with and without alcohol abuse, and the alcohol-abusing group showed increased the incidence of SUDEP compared with the non-alcohol-abusing group, indicating that alcohol abuse is a RF. Therefore, it is crucial that clinicians should ask patients about their history of alcohol consumption.

Leading experts and advocacy groups are calling for systematic strategies to reduce mortality. Although much progress has been made in the understanding and management of EP, there is a growing recognition that person-centered risk communication remains a neglected area [25]. Physicians play a crucial part in patient education, which encourages self-management

of EP and ensures that patients with EP are fully aware of the risks of EP. Only when accurate information about EP is clearly communicated can patients with EP make informed decisions to reduce the risk of death from EP [26].

However, there are still barriers in meaningful discussions about SUDEP with people with EP [27], lacking clear understanding of how to conduct organized and patient-centered conversations. This could be supported by a general patient information leaflet incorporating brief semi-structured risk assessments. This could be a catalyst for public discussion, and contributed to guiding treatment by identifying areas where the risk status could be changed, supporting clinicians' interventions, and better understanding of those RFs within the patient's control.

This MA also has some shortcomings. Risk factors for SUDEP in children were not considered. As with adults, children with EP have markedly increased risks of death when compared with the other age groups. Most premature deaths in children with EP are not related to seizures and are usually caused by respiratory disease comorbid with severe neurological disability, chronic EP and comorbidities. Some RFs were not included due to insufficient sample size.

CONCLUSION

Age at onset of EP ≤ 15 years, GTCS, seizure frequency ≥ 50 seizures/year, multiple antiepileptic drugs, and history of alcohol abuse were important RFs for SUDEP. Epileptic patients with these RFs should be focused on to prevent the occurrence of SUDEP. In clinical practice, both physicians and family members should pay attention to the onset of symptoms in epileptic patients and provide appropriate and timely treatment.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

REFERENCES

1. *Beghi E. The concept of the epilepsy syndrome: how useful is it in clinical practice? Epilepsia 2009; 50 Suppl 5: 4-10.*
2. *Wang Y, Wang H, Zhao P, Cheng J, Gong W, Zhang J. Asiatic acid exerts neuroprotective effect against hypoxic-ischemic brain injury in neonatal rats via inhibition of oxidative damage. Trop J Pharm Res 2021; 20(9):1903-1908 doi: 10.4314/tjpr.v20i9.17*
3. *Watkins L, Shankar R. Reducing the risk of sudden unexpected death in epilepsy (SUDEP). Curr Treat Options Neurol 2018; 20(10): 40.*
4. *Sander JW, Bell GS. Reducing mortality: an important aim of epilepsy management. J Neurol Neurosurg Psychiatry 2004; 75(3): 349-351.*
5. *Shorvon S, Tomson T. Sudden unexpected death in epilepsy. Lancet 2011; 378(9808): 2028-2038.*
6. *Ficker DM, So EL, Shen WK, Annegers JF, O'Brien PC, Cascino GD, Belau PG. Population-based study of the incidence of sudden unexplained death in epilepsy. Neurology 1998; 51(5): 1270-1274.*
7. *Holst AG, Winkel BG, Risgaard B, Nielsen JB, Rasmussen PV, Haunso S, Sabers A, Uldall P, Tfelt-Hansen J. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. Epilepsia 2013; 54(9): 1613-1620.*

8. Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. Epilepsia 1997; 38(11 Suppl): S6-S8.
9. Annegers JF. United States perspective on definitions and classifications. Epilepsia 1997; 38(11 Suppl): S9-S12.
10. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, Walczak TS, Beghi E, Brodie MJ, Hauser A. Combined analysis of risk factors for SUDEP. Epilepsia 2011; 52(6): 1150-1159.
11. Tomson T, Surges R, Delamont R, Haywood S, Hesdorffer DC. Who to target in sudden unexpected death in epilepsy prevention and how? Risk factors, biomarkers, and intervention study designs. Epilepsia 2016; 57 Suppl 1: 4-16.
12. DeGiorgio CM, Markovic D, Mazumder R, Moseley BD. Ranking the leading risk factors for sudden unexpected death in epilepsy. Front Neurol 2017; 8: 473.
13. Naritoku DK, Casebeer DJ, Darbin O. Effects of seizure repetition on postictal and interictal neurocardiac regulation in the rat. Epilepsia 2003; 44(7): 912-916.
14. Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case-control study. Lancet 1999; 353(9156): 888-893.
15. Walczak TS, Leppik IE, D'Amelio M, Rarick J, So E, Ahman P, Ruggles K, Cascino GD, Annegers JF, Hauser WA. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology 2001; 56(4): 519-525.
16. Tomson T, Walczak T, Sillanpaa M, Sander JW. Sudden unexpected death in epilepsy: a review of incidence and risk factors. Epilepsia 2005; 46 Suppl 11: 54-61.
17. Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: A nationwide population-based cohort study. Neurology 2017; 89(2): 170-177.
18. Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. Epilepsy Res 2003; 57(1): 69-75.
19. Hesdorffer DC, Tomson T. Sudden unexpected death in epilepsy. Potential role of antiepileptic drugs. Cns Drugs 2013; 27(2): 113-119.
20. Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. Epilepsia 2014; 55(10): 1479-1485.
21. Monte CP, Arends JB, Tan IY, Aldenkamp AP, Limburg M, de Krom MC. Sudden unexpected death in epilepsy patients: Risk factors. A systematic review. Seizure 2007; 16(1): 1-7.
22. Kerling F, Dutsch M, Linke R, Kuwert T, Stefan H, Hilz MJ. Relation between ictal asystole and cardiac sympathetic dysfunction shown by MIBG-SPECT. Acta Neurol Scand 2009; 120(2): 123-129.
23. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Pharmacologic treatment and SUDEP risk: A nationwide, population-based, case-control study. Neurology 2020; 95(18): e2509-e2518.
24. Nashef L, Rugg-Gunn F. Reducing the risk of SUDEP: From uncertainty to reality. Neurology 2020; 95(18): 807-808.
25. Shankar R, Newman C, Hanna J, Ashton J, Jory C, McLean B, Anderson T, Walker M, Cox D, Ewins L. Keeping patients with epilepsy safe: a surmountable challenge? BMJ Qual Improv Rep 2015; 4(1).
26. Shankar R, Donner EJ, McLean B, Nashef L, Tomson T. Sudden unexpected death in epilepsy (SUDEP): what every neurologist should know. Epileptic Disord 2017; 19(1): 1-9.
27. Waddell B, McColl K, Turner C, Norman A, Coker A, White K, Roberts R, Heath CA. Are we discussing SUDEP? A retrospective case note analysis. Seizure 2013; 22(1): 74-76.