Journal Club

Seizure-related biomarkers of sudden unexpected death in epilepsy (SUDEP) in drug-resistant focal epilepsy (REPO$_2$MSE): a prospective, multicentre case-control study

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The *Practical Neurology* Journal Club met again to discuss a recent epilepsy paper with potentially practical implications. This was a prospective French multicentre case-control study exploring clinical and paraclinical biomarkers of sudden unexpected death in epilepsy (SUDEP) in patients aged ≥15 years with focal-onset drug-resistant epilepsy [1] and published in *Lancet Neurology*.

We were struck by the ambition of the study question. SUDEP remains the most devastating but least predictable complications of epilepsy, yet despite decades of research, we still have only limited ability to identify those at greatest risk [2]. We agreed that this study had potential to inform clinical practice for all neurologists and the wider medical community.

We first reviewed the current evidence for SUDEP risk factors. Well-described associations include frequent generalised tonic-clonic seizures (GTCs), sleep-related (nocturnal) seizures, male sex, sleeping alone, and poor anti-seizure medication adherence [3-7], as discussed in current epilepsy management guidelines [8, 9].

The REPO$_2$MSE investigators aimed primarily to identify possible new SUDEP biomarkers, including clinical peri-ictal bradycardia (<50 bpm) or asystole (cardiac arrest for ≥3 sec), the occurrence of peri-ictal hypoxaemia (<80% SpO_2), and the localisation of the epileptogenic zone.

We were impressed by the cohort size of 1,074 patients recruited, totalling 6,828 patient years. We acknowledged the challenges of recruitment of a prospective cohort, using a national registry linkage, rigorous SUDEP adjudication and a blinded epileptogenic zone classification system [1]. However, important limitations informed our discussion. Notably,

only 18 SUDEP cases were identified (four definite and 14 probable), and the low event numbers limited how reliably biomarkers could be analysed using statistical models. We also noted that the study focused on a tertiary presurgical population, limiting the generalisability of findings to broader epilepsy populations.

Other members of the group identified technical measurement issues and potential biases. For instance, post-ictal hypoxaemia was not analysed in focal-to-bilateral tonic-clonic seizures (FBTCS) because of the potential for movement artefact, and no blood-based biomarkers were assessed [1]. Data were frequently missing; for example, there was no peri-ictal arterial oxygen saturation reported in 27% of cases, and the sleep apnoea questionnaire results had absent datapoints in 21%. We discussed that with relatively few events, filling in missing data (imputation) may make the results less reliable. Additionally, with few events the analysis method used can result in a model that overfits the data and reduces the generalisability to other patient groups [10]. Overall, as the authors acknowledge, the biomarkers analysed are better viewed as associated factors rather than as validated predictors.

The final multivariable model identified four factors significantly associated with SUDEP **(Table 1):** male sex, extratemporal epileptogenic zone, BMI ≥30, and predominantly sleep-related seizures [1]. Male sex and sleep-related seizures are already well described risk factors for SUDEP [3-7]. Indeed, all 18 SUDEP cases in this study were unwitnessed, highting the importance of sleeping alone as a major risk factor. One of our group noticed that the article used the term “nocturnal seizures” throughout. While this terminology is common, we discussed that “sleep-related seizures” may be more precise. The risk associated with these events is linked to the state of sleep itself rather than the time of day, and seizures can occur during daytime sleep as well as at night. The term “sleep-related” seizure may therefore better reflect the underlying risk and avoid ambiguity.

Being overweight/obese has been reported as a risk factor for SUDEP in two prospective cohort studies in China [11,12]. The mechanism for increased SUDEP risk in patients with obesity is unclear, but may include comorbid sleep apnoea, obesity-hypoventilation syndrome and/or cardiovascular disease [1,11,12]. The study’s most novel associated risk factor was extratemporal seizure onset, previously suggested by only one cross-sectional study [13]. We hypothesised whether an extratemporal epileptogenic zone might correlate with sleep-related seizures as a predominant feature of frontal lobe epilepsy [14]. The authors also discussed the role of the insula in central autonomic control, and the contribution of the frontocentral and opercular regions in motor control of the respiratory tract. Surprisingly, the frequency of FBTCS was not associated with SUDEP risk in this study, in contrast to previous studies [5,6]. The authors wondered if this discrepancy related to the difference in the observation period for FBTCS between this study (frequency at the time of inclusion in the study, with a median time of 3–6 years between inclusion and SUDEP) compared with previous work (frequency during the year before SUDEP) [5,6]. The other key biomarkers investigated in the study (peri-ictal bradycardia, asystole, and peri-ictal hypoxaemia) were not significantly associated with SUDEP.

One of our group noted that two of the SUDEP cases in the study occurred in patients who were reportedly seizure-free following epilepsy surgery. This prompted discussion as to whether these cases might reflect ongoing subclinical seizure activity or, alternatively, under-reporting of persistent seizures by patients. Previous studies have found that SUDEP remains a cause of death in post-surgical epilepsy cohorts, although incidence rates are substantially lower than in those who have not undergone surgery [15-17]. In one post-surgical cohort, seizures continuing at follow-up was identified as an independent risk factor for SUDEP; notably, this association was observed for both GTC and non–GTC seizures [15]. SUDEP has previously been reported in patients who were considered seizure-free following surgery [15].

We discussed the study's generalisability to clinical practice. This is a highly selected epilepsy population including drug-resistant focal epilepsy from presurgical tertiary centres within French healthcare infrastructure [1]. They found obesity, sleep-related seizure predominance and epilepsy originating from an extratemporal focus were risk factors and patients with these risk factors may warrant heightened counselling about their personal risk of SUDEP. These findings need to be validated in other patient cohorts.

Most of the world's population with epilepsy (80%) live in low- and middle-income countries, with limited access to comprehensive epilepsy services and specialist neurosurgical care [18]. Should further research confirm an association between an extratemporal seizure focus and SUDEP risk, this would have important implications for global health equity. Populations already bearing the greatest burden of epilepsy may have the least access to the investigations and treatments that could mitigate SUDEP risk, potentially widening existing disparities in epilepsy outcomes.

In summary, we admired the ambition of the study, which clearly required a substantial multi-centre collaboration and is highly commendable for advancing patient care. This study highlights the difficulty in prospective studies of SUDEP.

Risk factor	**Odds ratio (95% CI)**	**p value***
Male sex	12.6 (1.5-106.8)	0.02
Extratemporal epileptogenic zone	37.8 (3.2-446.2)	0.004
Predominantly sleep-related seizures	6.0 (1.2-28.7)	0.03
BMI ≥30	26.0 (2.0-339.6)	0.01

Table 1: The risk factors identified as having a statistically significant increased risk of SUDEP (Final non-penalised conditional logistic regression model. Adapted from [1]. *Two-tailed *p* values (Wald test)).

Competing interests

PS is co-editor of *Practical Neurology*; JC, LMW and EO'C are on its editorial board.

Contributorship

LMW was responsible for the initial conceptualisation of this book club review. JC prepared the original draft of the manuscript. All authors contributed to the review and editing of the article. All authors have read and approved the final manuscript for publication.

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References

1. Ryvlin P, Huot M, Valton L, Maillard L, Bartolomei F, Derambure P, Hirsch E, Michel V, Chassoux F, Petit J, Crespel A, Biraben A, Navarro V, Kahane P, De Toffol B, Thomas P, Rosenberg S, Bernini A, Charlois AL, Craciun L, Chorfa F, Ducouret P, Ferreira A, Leclercq M, Marty M, Mercedes Alvarez B, Sampaio M, Spahr A, Timestit-Kurland N, Touya M, Roy P, Rheims S; REPO2MSE study group. Seizure-related biomarkers of sudden unexpected death in epilepsy (SUDEP) in drug-resistant focal epilepsy (REPO2MSE): a prospective, multicentre case-control study. Lancet Neurol. 2026 Jan;25(1):50-60. doi: 10.1016/S1474-4422(25)00379-5. Epub 2025 Nov 21. PMID: 41285145.

2. Whitney R, Donner EJ. Risk Factors for Sudden Unexpected Death in Epilepsy (SUDEP) and Their Mitigation. Curr Treat Options Neurol. 2019 Feb 13;21(2):7. doi: 10.1007/s11940-019-0547-4. PMID: 30758730.
3. Sveinsson O, Andersson T, Carlsson S, Tomson T. Circumstances of SUDEP: A nationwide population-based case series. Epilepsia. 2018 May;59(5):1074-1082. doi: 10.1111/epi.14079. Epub 2018 Apr 17. PMID: 29663344.
4. Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, Boon P, Crespel A, Dworetzky BA, Høgenhaven H, Lerche H, Maillard L, Malter MP, Marchal C, Murthy JM, Nitsche M, Pataraia E, Rabben T, Rheims S, Sadzot B, Schulze-Bonhage A, Seyal M, So EL, Spitz M, Szucs A, Tan M, Tao JX, Tomson T. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol. 2013 Oct;12(10):966-77. doi: 10.1016/S1474-4422(13)70214-X. Epub 2013 Sep 4. PMID: 24012372.
5. Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, French JA, Gil-Nagel A, Hesdorffer DC, Smithson WH, Spitz MC, Walczak TS, Sander JW, Ryvlin P. Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2017 Apr 25;88(17):1674-1680. doi: 10.1212/WNL.0000000000003685. Erratum in: Neurology. 2019 Nov 26;93(22):982. doi: 10.1212/WNL.0000000000008565. Erratum in: Neurology. 2020 Mar 3;94(9):414. doi: 10.1212/WNL.0000000000008668. PMID: 28438841.
6. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: A nationwide population-based case-control study. Neurology. 2020 Jan 28;94(4):e419-e429. doi: 10.1212/WNL.0000000000008741. Epub 2019 Dec 12.

Erratum in: Neurology. 2020 Mar 10;94(10):459. doi: 10.1212/WNL.0000000000009154. PMID: 31831600; PMCID: PMC7079690.

7. Ochoa-Urrea M, Luo X, Vilella L, Lacuey N, Omidi SJ, Hupp NJ, Talavera B, Hampson JP, Rani MRS, Tao S, Li X, Miyake CY, Cui L, Hampson JS, Chaitanya G, Vakilna YS, Sainju RK, Friedman D, Nei M, Allen L, Scott CA, Oliveira J, Gehlbach B, Schuele SU, Ogren JA, Harper RM, Diehl B, Bateman LM, Richerson GB, Yamal JM, Zhang GQ, Devinsky O, Lhatoo SD. Risk markers for sudden unexpected death in epilepsy: an observational, prospective, multicentre cohort study. Lancet. 2025 Oct 4;406(10511):1497-1507. doi: 10.1016/S0140-6736(25)01636-8. Epub 2025 Sep 17. Erratum in: Lancet. 2025 Oct 4;406(10511):1472. doi: 10.1016/S0140-6736(25)01970-1. PMID: 40975113; PMCID: PMC12707170.
8. National Institute for Health and Care Excellence (NICE] Guidance. Epilepsies in children, young people and adults (NG 217). Published 27 April 2022, last updated 30 January 2025. Last accessed 4 March 2026.
9. Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults (SIGN 143). Published May 2015, last updated 2018. Last accessed 4 March 2026.
10. Pavlou M, Ambler G, Seaman S, De Iorio M, Omar RZ. Review and evaluation of penalised regression methods for risk prediction in low-dimensional data with few events. Stat Med. 2016 Mar 30;35(7):1159-77. doi: 10.1002/sim.6782. Epub 2015 Oct 29. PMID: 26514699; PMCID: PMC4982098.
11. Liu Q, Tan B, Zhang J, Jin Y, Lei P, Wang X, Li M, Qin Y, Zhang Q. Derivation and validation of a new prediction model for sudden unexpected death in epilepsy based on a longitudinal prospective population-based cohort. Epilepsy Behav. 2023

Oct;147:109446. doi: 10.1016/j.yebeh.2023.109446. Epub 2023 Sep 25. PMID: 37757716.

12. Li R, Zhao D, Hu B, Li N, Li J, Lin W. Incidence and risk factors of sudden unexpected death in epilepsy in rural Northeast China. Seizure 2025; 126: 99–105.
13. Almeida AG, Nunes ML, Palmini AL, Costa JC. Incidence of SUDEP in a cohort of patients with refractory epilepsy: the role of surgery and lesion localization. Arq Neuropsiquiatr. 2010 Dec;68(6):898-902. doi: 10.1590/s0004-282x2010000600013. PMID: 21243249.
14. Crespel A, Baldy-Moulinier M, Coubes P. The relationship between sleep and epilepsy in frontal and temporal lobe epilepsies: practical and physiopathologic considerations. Epilepsia. 1998 Feb;39(2):150-7. doi: 10.1111/j.1528-1157.1998.tb01352.x. PMID: 9577994.
15. Granthon C, Tranberg AE, Malmgren K, Strandberg MC, Kumlien E, Redfors P. Reduced long- term mortality after suc cessful resective epilepsy surgery: a population-based study. J Neurol Neurosurg Psychiatry. 2023;95(3):249–55.
16. Fiore G, de Tisi J, O'Keeffe A, Miserocchi A, McEvoy AW, Sander JW, Duncan JS. Long-term survival after adult epilepsy surgery: Mortality and predictors in a large cohort. Epilepsia. 2025 Nov;66(11):4198-4210. doi: 10.1111/epi.18564. Epub 2025 Jul 25. PMID: 40711417; PMCID: PMC12661268.
17. Rheims S, Sperling MR, Ryvlin P. Drug- resistant epilepsy and mortality—why and when do neuromodulation and epilepsy surgery reduce overall mortality. Epilepsia. 2022;63:3020–36.
18. Nico Enslin JM, Muh CR, Wang X, von Hertwig Fernandes de Olivera T, McKhann GM, Damisah E, Al-Otaibi F, Rydenhag B, Ali RP, Dorfer C, Englot DJ, Cukiert A; Epilepsy Surgery Education Taskforce of the International League Against Epilepsy.

Epilepsy surgery education and practice around the globe: An ILAE taskforce report. Epilepsia. 2025 Feb;66(2):319-327. doi: 10.1111/epi.18199. Epub 2024 Dec 5. PMID: 39636690; PMCID: PMC11827745.

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