



Seizing Off This Mortal Coil: A Matter of Epilepsy and Death

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Premature Mortality and Causes of Death Among People With Epilepsy: A Nationwide Population-Based Incident Cohort Study

Moon HJ, Lee H, Yoon D, Koo YS, Shin JY, Lee SY. *Neurology*. 2023;100(20): e2060-e2070. doi:10.1212/WNL.0000000000207212. PMID: 36948594; PMCID: PMC10186245

Background and objectives: People with epilepsy (PWE) are at risk of premature death with considerable variability according to the study population. We aimed to estimate the risk and causes of death in PWE according to age, disease severity, disease course, comorbidities, and socioeconomic status in Korea. **Methods:** We conducted a nationwide population-based retrospective cohort study using the National Health Insurance database linked with the national death register. Newly treated PWE from 2008 to 2016 who were identified by antiseizure medication (ASM) prescriptions and diagnostic codes for epilepsy/seizure were included and observed until 2017. We assessed all-cause and cause-specific crude mortality rates and standardized mortality ratios (SMRs). **Results:** Among 138,998 PWE, 20,095 deaths were identified, and the mean follow-up period was 4.79 years. The SMR was 2.25 in the overall group of PWE, with a higher value in the younger age group at diagnosis and a shorter time interval after diagnosis. The SMR in the monotherapy group was 1.56, while that in the group with 4 or more ASMs was 4.93. PWE without any comorbidities had an SMR of 1.61. PWE who were rural residents had a higher SMR than those who were urban residents (2.47 vs 2.03, respectively). The causes of death among PWE were cerebrovascular disease (18.9%, SMR 4.50), malignant neoplasms outside the CNS (15.7%, SMR 1.37), malignant neoplasms of the CNS (6.7%, SMR 46.95), pneumonia (6.0%, SMR 2.08), and external causes (7.2%, SMR 2.17), including suicide (2.6%, SMR 2.07). Epilepsy itself and status epilepticus accounted for 1.9% of the overall death. The excess mortality associated with pneumonia and external causes was persistently high, whereas the excess mortality associated with malignancy and cerebrovascular diseases tended to decrease with increasing time since diagnosis. **Discussion:** This study showed excess mortality in PWE, even in those without comorbidities and those receiving monotherapy. Regional disparities and sustained risks of deaths from external causes over 10 years imply potential points of intervention. In addition to active control of seizures, education about injury prevention, monitoring for suicidal ideation, and efforts to improve accessibility to epilepsy care are all required to reduce mortality.

Commentary

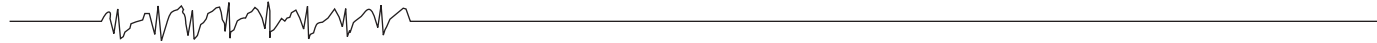
First highlighted by G Mackenzie Bacon and his contemporaries in the 1800s, the phenomenon of premature mortality in people with epilepsy (PWE) has since gained significant attention.¹ Over a century later, in the 1970s, sudden unexpected death in epilepsy (SUDEP) was formally recognized as a distinct entity.² With a growing interest in SUDEP and elevated all-cause mortality in PWE, the past 50 years have seen noteworthy advancements in our understanding of these phenomena. The etiology of premature mortality in PWE is multifaceted and has been attributed both to epilepsy itself and external factors.³⁻⁵ Research has shown that mortality rates vary depending on the study population and differ among low-and-middle-income (LMIC) and high-income countries (HIC).^{3,4} While some Asian countries have explored

the risk and causes of mortality in PWE,^{3,6} others, like Korea, have scarce literature on these.

To answer the aforementioned questions, Moon et al conducted a population-based study using Korean nation-wide health care database.⁷ Authors included 138,998 newly treated PWE between 2008 and 2016 to investigate all-cause and cause-specific mortality and standardized mortality ratios (SMR). Epilepsy diagnosis was based on >2 visits with epilepsy/seizure diagnostic code and use of anti-seizure medication (ASM) for >180 days. Causes of mortality were categorized using ICD-10 codes. Mortality was assessed based on comorbidities, ASMs, status epilepticus (SE), and hospitalizations during follow-up and stratified according to economic status and residential area.



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Of 138,998 PWE, 20,095 deceased, indicating a 2.25-fold higher mortality risk in PWE than the general population. In contrast to most previous studies,^{3,4} SMR was greater in women than men. Standardized mortality ratio was highest in children <4 years and decreased with age. Standardized mortality ratio was highest in the year following diagnosis. The most common etiologies of death were cerebrovascular disease, non-central nervous system (non-CNS) malignant tumors, external causes, malignant CNS tumors, and pneumonia, respectively.

The study's robustness is rooted in its comprehensive analysis of the entire Korean population using national data to increase generalizability and assess mortality risks stratified on age, disease duration/severity, comorbidities, economic standing, residential location, and etiology.⁷ A significant contribution of the study is the analysis of cause-specific mortality risk by age and disease progression in PWE. Furthermore, by including only newly treated PWE, the authors assessed the entire period from epilepsy diagnosis to demise.

In the realm of untimely death in PWE, an important question arises: Do geographical coordinates and riches hold significance? A systematic review by ILAE task force demonstrated higher premature mortality in LMIC than HIC.³ Similarly, the current study identified higher SMR in medical aid group compared to the highest-income group in Korea. Authors also found regional disparities with higher mortality in rural areas. The mortality gap between different regions and income levels within Korea and between LMIC³ and HIC⁴ is attributed to variability in fundamental public health care, medical resources, access to epilepsy care, and preventable external causes, all of which directly impact mortality in PWE.^{3,7} These also identify potential intervention opportunities to prevent mortality.

Does age also matter? Indeed, the smallest ones have the biggest risk of premature death in epilepsy.⁸⁻¹¹ Higher mortality in children than adults has been reported⁸⁻¹¹ in both HIC and LMIC.^{3,4} Moseley et al showed the highest risk in those <12 months old.¹² Four separate population-based studies by Berg et al, Nickels-et-al, Camfield et-al, and Sillanpää and Shinnar showed that elevated mortality in childhood epilepsy was most commonly associated with underlying conditions, their complications, symptomatic etiology, neurocognitive impairment, and disorders contributing to neurological deficits.⁸⁻¹¹ Pooled analysis from these 4 cohorts showed that while children with complicated epilepsy had higher mortality, most premature mortality was not epilepsy related.¹³ The current study supports the existing evidence of higher mortality in pediatrics. It also underscores a particularly vulnerable group, especially in LMIC, that warrants further investigation.

External causes of premature mortality also deserve special attention because they are potentially preventable. In this study, they contributed to 7% of overall mortality with twofold increased mortality in PWE. Surprisingly, mortality from accidents, drowning, and falls were lower than previously reported.³ Distinctive from previous studies,³ suicide (2.6%, SMR = 2.07) was the most common external cause of death.

Without a doubt, the high overall suicide rate in Korea is a likely contributor but a multitude of other factors also merit particular focus. These include mood disorders, lack of employment opportunities, stigma related to epilepsy, and quality of life in PWE. Further studies are needed to understand trends in mortality from external causes, especially suicide, in PWE in LMIC, their contributing factors, and prevention strategies.

Similar to previous studies,³ authors found an inversely proportional relationship between SMR and time since epilepsy diagnosis. The highest mortality rates shortly after diagnosis inevitably draw one's focus to the most notable shortcoming of the study. Namely, the inclusion criteria that mandated >180 days of ASM use, thereby excluding those who died before this period. This probably led to underestimation of mortality by excluding epilepsy etiologies with poor prognoses, such as CNS tumors, malignant strokes, and new-onset refractory SE (NORSE).


Another pitfall of the study is that diagnosis was based on ICD codes, which may not be accurate. Known predictors of mortality in PWE³ (seizure frequency, etiology) and treatment adherence were not explored. And while authors effectively showcased regional and economic disparities within Korea, they faced challenges in comparing their exclusively newly treated PWE cohort with previous prevalence-focused Asian studies.⁶

Finally, no discussion on mortality in PWE is complete without addressing epilepsy as a culprit itself. This is especially relevant for this study because death from epilepsy and SE is higher in LMIC than HIC.^{3,4} Interestingly, Moon et al found that epilepsy and SE (SMR = 7.05) accounted for 1.4% and 0.5% of deaths, respectively, compared to previous reports of 14.8% to 39.3%.³ However, as previously noted, authors excluded PWE on ASMs <180 days, thereby inadvertently excluding those at the highest mortality risk early-on, such as critically ill PWE and NORSE.

This leads to yet another question: Is disease severity another factor at play? A population-based study found lack of remission to be the only predictor of premature mortality.¹⁰ In this study, disease severity was assessed based on ASM number, hospitalizations, and SE. Standardized mortality ratio was lowest in PWE on monotherapy. Among PWE with >2 hospitalizations, SMR was proportional to the number of hospitalizations. While these factors were explored independently, their cumulative impact on mortality was not assessed. More comprehensive ways or a scoring system to define disease severity are needed in future studies.


Despite its limitations, the present study demonstrates that the magnified risk of mortality in PWE varies widely depending on several factors and highlights regional disparities in mortality and high suicide rates in PWE in Korea. National action plans involving improved access to epilepsy health care, early screening and close monitoring for suicidal ideation, management of mood disorders, education about epilepsy to reduce stigma, timely management, and injury prevention highlight some areas of targeted intervention that can reduce mortality in PWE in Korea and other LMIC. These findings also call for urgent public health initiatives to reduce mortality

in PWE from preventable causes globally. After all, it is a matter of epilepsy and death . . .

Ifrah Zawar, MD 

Epilepsy Division, Department of Neurology,
School of Medicine, University of Virginia

ORCID iD

Ifrah Zawar  <https://orcid.org/0000-0002-6103-4250>

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References

- O'Donoghue MF, Sander JWAS. A historical perspective on the mortality associated with chronic epilepsy. *Acta Neurol Scand.* 1997;96(3):138-141. doi:10.1111/J.1600-0404.1997.TB00255.X
- Earnest MP, Thomas GE, Eden RA, Hossack KF. The sudden unexplained death syndrome in epilepsy: demographic, clinical, and postmortem features. *Epilepsia.* 1992;33(2):310-316. doi:10.1111/J.1528-1157.1992.TB02321.X
- Levira F, Thurman DJ, Sander JW, et al. Premature mortality of epilepsy in low- and middle-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia.* 2017;58(1):6-16. doi:10.1111/EPL.13603
- Thurman DJ, Logroscino G, Beghi E, et al. The burden of premature mortality of epilepsy in high-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia.* 2017;58(1):17-26. doi:10.1111/epi.13604
- Zawar I, Quigg M, Manning C, Kapur J. Seizures in dementia are associated with worse clinical outcomes, higher mortality and shorter lifespans (P3-1.001). *Neurology.* 2023;100(17 Supplement 2):1774. doi:10.1212/WNL.0000000000202113
- Trinka E, Kwan P, Lee BI, Dash A. Epilepsy in Asia: disease burden, management barriers, and challenges. *Epilepsia.* 2019;60(S1):7-21. doi:10.1111/EPL.14458
- Moon HJ, Lee H, Yoon D, Koo YS, Shin JY, Lee SY. Premature mortality and causes of death among people with epilepsy a nationwide population-based incident cohort study. *Neurology.* 2023;100(20):E2060-E2070. doi:10.1212/WNL.0000000000207212
- Camfield CS, Camfield PR, Veugelers PJ. Death in children with epilepsy: a population-based study. *Lancet.* 2002;359(9321):1891-1895. doi:10.1016/S0140-6736(02)08779-2
- Berg AT, Shinnar S, Testa FM, Levy SR, Smith SN, Beckerman B. Mortality in childhood-onset epilepsy. *Arch Pediatr Adolesc Med.* 2004;158(12):1147-1152. doi:10.1001/archpedi.158.12.1147
- Sillanpää M, Shinnar S. Long-term mortality in childhood-onset epilepsy. *N Engl J Med.* 2010;363(26):2522-2529. doi:10.1056/NEJMoa0911610
- Nickels KC, Grossardt BR, Wirrell EC. Epilepsy-related mortality is low in children: a 30-year population-based study in Olmsted County, MN. *Epilepsia.* 2012;53(12):2164-2171. doi:10.1111/j.1528-1167.2012.03661.x
- Moseley BD, Wirrell EC, Wong-Kisiel LC, Nickels K. Early onset epilepsy is associated with increased mortality: a population-based study. *Epilepsy Res.* 2013;105(3):410-414. doi:10.1016/j.eplepsyres.2013.03.002
- Berg AT, Nickels K, Wirrell EC, et al. Mortality risks in new-onset childhood epilepsy. *Pediatrics.* 2013;132(1):124-131. doi:10.1542/peds.2012-3998