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Change in Mortality of Generalized Convulsive Status Epilepticus in High-Income Countries Over Time
A Systematic Review and Meta-analysis

Aidan Neligan, MSc, PhD, MRCP; Alastair John Noyce, MSc, PhD, MRCP; Tushar Divakar Gosavi, MD, MRCP; Simon D. Shorvon, MA, MD, FRCP; Sebastian Köhler, MSc, PhD; Matthew C. Walker, MC, MA, PhD, FRCP

IMPORTANCE Status epilepticus (SE) is associated with significant morbidity and mortality. Since the late 1990s, a more aggressive management of prolonged convulsive seizures lasting longer than 5 minutes has been advocated.

OBJECTIVE To determine if convulsive SE mortality has decreased during a time of increasing advocacy for out-of-hospital treatment and escalating and earlier treatment protocols for prolonged seizures and SE.

DATA SOURCE This systemic review and meta-analysis on studies focused on the mortality of convulsive status epilepticus was conducted by searching MEDLINE, Embase, PsychINFO, CINAHL Plus, and the Cochrane Database of Systematic Reviews between January 1, 1990, and June 30, 2017.

STUDY SELECTION Studies were excluded if they had fewer than 30 participants (<20 for refractory SE), were limited to SE of single specific etiology or an evaluation of a single treatment modality, or were studies of nonconvulsive SE.

DATA EXTRACTION AND SYNTHESIS Data were abstracted and their quality was assessed via a modified Newcastle-Ottawa scale independently by 2 reviewers (A.N. and T.D.G.) using the Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines. Data were pooled using a random-effects model.

MAIN OUTCOMES AND MEASURES The main outcome measure was in-hospital mortality or 30-day case fatality expressed as proportional mortality.

RESULTS Sixty-one studies were included in the analysis. The pooled mortality ratios were 15.9% (95% CI, 12.7-19.2) for adult studies, 13.0% (95% CI, 7.2-19.0) for all-age population studies, 3.6% (95% CI, 2.0%-5.2%) for pediatric studies, and 17.3% (95% CI, 9.8-24.7) for refractory SE studies, with very high between-study heterogeneity. We found no evidence of a change in prognosis over time nor by the definition of SE used.

CONCLUSIONS AND RELEVANCE The mortality of convulsive SE is higher in adults than in children and there was no evidence for improved survival over time. Although there are many explanations for these findings, they can be explained by aetiology of SE being the major determinant of mortality. However, there are potential confounders, including differences in case ascertainment and study heterogeneity. This meta-analysis highlights the need for strict international guidelines for the study of this condition.

Editorial

Supplemental content

Author Affiliations: Homerton University Hospital NHS Foundation Trust, Homerton Row, London, England (Neligan); University College London Queen Square Institute of Neurology, Queen Square, London, England (Neligan, Noyce, Shorvon, Walker); Preventive Neurology Unit, Wolfson Institute of Preventative Medicine, Queen Mary University of London, London, England (Neligan, Noyce); National Neuroscience Institute, Singapore (Gosavi); Singapore General Hospital, Singapore (Gosavi); Maastricht University Medical Centre, School for Mental Health and Neuroscience, Alzheimer Centre Limburg, Maastricht, the Netherlands (Köhler).

Corresponding Author: Aidan Neligan, MSc, PhD, MRCP, Homerton University Hospital National Health Service Foundation Trust, Homerton Row, London E9 6SR, England (a.neligan@ucl.ac.uk).

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Status epilepticus (SE) is a prolonged seizure state (convulsive or nonconvulsive) and can be a serious consequence of epilepsy or can occur de novo in almost half of cases.[1,2] Despite the introduction of more aggressive protocols for treating SE, mortality is still substantial, particularly in adults and in those who do not respond to first-line therapy. The interpretation of epidemiological studies of SE has been hampered by variable definitions of when a prolonged seizure becomes SE.[3-5]

In 1999, Lowenstein and colleagues proposed an "operational definition" of SE: "Generalized, convulsive status epilepticus in adults and older children (>5 years old) refers to 5-minutes of (a) continuous seizures or (b) two or more discrete seizures between which there is incomplete recovery of consciousness."[6] They also proposed a mechanistic definition that "Generalised, convulsive status epilepticus refers to a condition in which there is a failure of the 'normal' factors that serve to terminate a typical generalized tonic-clonic seizure"[6] but did not specify a duration in this definition. The goal of the operational definition was to encourage treatment intervention at 5 minutes and not 30 minutes to prevent intractability and neuronal damage.[7] Indeed, this dichotomy of the point at which emergency intervention should be initiated and the point after which neuronal damage is likely to occur is maintained in the International League Against Epilepsy's recent positional article on the definition of SE.[8] However, whether introducing this operational definition (and hence earlier treatment) has resulted in better prognosis is, to our knowledge, unknown.

The aim of this systematic review and meta-analysis was to determine secular trends in the mortality rate of convulsive SE during the past decades and in different populations, study designs, and in refractory SE, primarily to address whether there has been a change in the mortality of SE given the change in definition. A secondary aim was to give pooled mortality estimates by study design and SE subtype (established SE, refractory SE [RSE]) in addition to an overall assessment of the SE literature. We hypothesized that the operational definition of generalized convulsive SE (GCSE) proposed in 1999 led to a shift to earlier and more aggressive treatment of SE.

Key Points

Question Has the mortality associated with convulsive status epilepticus (SE) changed over time?

Findings This systematic review and meta-analysis of 61 SE studies conducted between 1990 and 2017 did not demonstrate definitive evidence of improved SE prognosis over time.

Meaning Changes in definition and treatment approaches in high-income countries have not been significantly associated with the mortality of convulsive status epilepticus.

Methods

This study adhered to the Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines.[9] For inclusion, the period of observation of the study had to commence after January 1, 1990, and be completed by June 30, 2017. Studies for which the period of observation commenced before January 1, 1990 (eg, 1989-1991), were excluded. A starting point of January 1, 1990, was chosen, as the early 1990s were the time during which SE was starting to be treated in a systematic manner and the first national and international treatment algorithms for managing SE were published.[10] The primary focus of this study was the mortality of GCSE, which is the most recognizable and advanced form of SE for which earlier and more aggressive treatment has been advocated.

Consequently, for inclusion, a limit was set of at least 30 patients with GCSE or 20 patients with generalized convulsive refractory SE (RSE). An exception to this rule was made for incident population-based studies. These figures were chosen because it was believed that smaller figures may underestimate or overestimate the associated mortality and, in the case of RSE, risk an overrepresentation of cases of nonconvulsive SE. Most studies present the mortality of all subtypes of SE together, but where possible, mortality from GCSE was extracted and presented alone. Mortality from other SE subtypes (eg, complex partial SE and nonconvulsive SE) was not analyzed, but rather overall SE mortality (to which GCSE is believed the major contributor). Similarly, studies in which the primary focus was the prognosis of patients with nonconvulsive SE or studies where this predominated (including RSE studies) were excluded. Refractory SE studies with SE secondary to hypoxic ischemic encephalopathy were excluded.

Studies in which the efficacy of 1 treatment modality was evaluated (eg, levetiracetam or therapeutic coma) were excluded, as these studies tend to be selective in the choice of the patients who are included (eg, nonconsecutive patients or more refractory cases for which other treatment modalities have already been trialed) and are therefore not representative of the population of people with SE. Studies limited to SE due to a specific etiology (inflammatory, poststroke) were excluded. Similarly, studies limited to cases of de novo SE occurring in the absence of preexisting epilepsy were also excluded. No specific etiology was excluded; in particular, the decision whether to include SE following hypoxic-ischemic encephalopathy was left to the discretion of the individual study's authors, although this was increasingly excluded as an etiology in later studies.

It is well recognized that many factors determine the prognosis of SE, but one of the major factors is the duration of GCSE,[2] particularly the delay in initiating treatment, albeit the association between duration and prognosis weakens the longer the SE persists.[11] Consequently, in an effort to try to minimize the variation in access to health care facilities, this review was limited to studies performed in high-income countries as designated by the World Bank (2017). The study was not registered with the PROSPERO (or other comparable) database, although we did verify that no similar study was registered before undertaking this study.

Data Extraction and Quality Assessment

We searched MEDLINE, Embase, PsychINFO, CINAHL Plus, and the Cochrane Database of Systematic Reviews databases be-

tween January 1990 and June 2017. The guidelines outlined in the Cochrane Reviewers' Handbook were followed to create a comprehensive search strategy. Medical subheading terms were used and expanded when appropriate to optimize the search strategy, using the terms *Status AND epilepticus*; *generali#ed AND Convulsive*; *Status Epilepticus*; *Grand AND Mal AND Status AND Epilepticus*; *Status AND Epilepticus AND Generali#ed*; or *Status AND Epilepticus AND Generali#ed AND Convulsive* and *Mortality OR Fatality OR Death OR Prognosis OR Outcome*, with limits of publication year (1990-2017) and human studies. In addition, the reference lists of all selected articles were perused to identify any articles missed. The literature search was carried out independently by 2 authors (A.N. and T.D.G.) and any point of disagreement was discussed and arbitrated with the third reviewer (M.C.W.). Quality aspects were assessed by a modified version of the Newcastle-Ottawa Scale.[12]

Statistical Analysis

Proportional mortalities (P) were used (Standard Error = Square Root [P(1-P)/N]). Only studies in which a *P* could be calculated were included in the meta-analysis. Given the expectation of high study heterogeneity, we used a random-effects model to estimate pooled mortality figures. Statistical heterogeneity was assessed using the I^2 statistic (I^2 > 50% corresponding to high heterogeneity and I^2 > 75% to very high heterogeneity). We pooled data from studies in 3 periods (1990-2000, 2001-2010, and 2010-present [1999-2000, 2001-2005, and 2006-present for pediatric studies]) and assessed the evidence for the change in mortality across time bands using meta-regressions and linear regressions (using study midpoints) in the adult and pediatric studies. We then undertook further subanalyses to assess the association of age (eg, pediatric, adult, and all ages), study design (purpose-built cohort studies and studies incorporating routine clinical record data large data), the SE definition used, study location (North America, Europe, and elsewhere), and the study setting (intensive care unit [ICU]/non-ICU) using a meta-regression to assess the changes in P. Small study effects were assessed using a funnel plot and the Egger test. Estimates were then adjusted using the "trim-and-fill" method when appropriate. All analyses were performed using Stata, version 13.1 (StataCorp) and statistical significance was set at P < .05.

Results

Using our search strategy, 6120 potential references were identified, of which 5738 (93.8%) were excluded based on review of the title or abstract. This was further reduced by removing duplicates to 166 potential articles. Thereafter, the full text was accessed (when available) (eFigure 1 in the Supplement). Ultimately, 61 articles were included in the final review (eFigure 1 in the Supplement). The studies were drawn from 17 countries and approximately two-thirds of the studies were retrospective (eTable 1 in the Supplement).

There was 1 study covering 1990 to 1995, 9 studies largely covering 1996 to 2000, 8 studies largely covering 2001 to 2005, 16 studies covering 2006 to 2010, 12 studies covering 2011 to 2017, and the remainder covered several periods (eFigure 2 in the Supplement). There were 12 studies covering all age groups (eTable 2 in the Supplement), 11 pediatric studies (with a variable age range of 0-21 years) (eTable 3 in the Supplement), and 30 adult studies (age range, 12-97 years), with 1 study confined to those 65 years or older (eTable 4 in the Supplement).

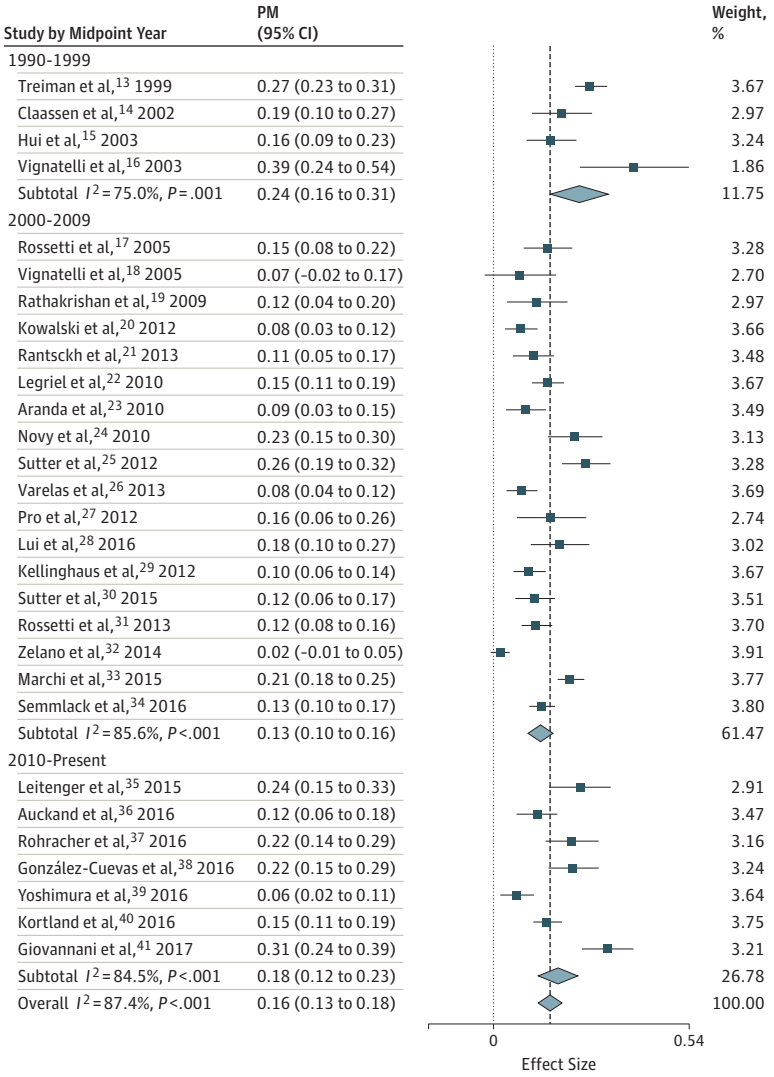
Seven studies, including 2 pediatric studies, focused on prognosis in RSE (all were published between 2013-2017), with 1 study focusing exclusively on suprarefractory SE (eTable 5 in the Supplement). All of the studies that exclusively focused on RSE defined it as a failure of seizure cessation following administration of 2 antiepileptic drugs. In contrast, there were numerous definitions of RSE that were used in the other studies or RSE was not defined.

There was considerable variation in the definition of SE used: a continuous seizure longer than 30 minutes (25 studies), longer than 5 minutes (23 studies), or longer than 10 minutes (5 studies), with the remainder using the *International Classification of Diseases, Ninth Revision* or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* classifications. There was similar heterogeneity in the definition of RSE, although all studies for which RSE was the primary end point used the same definition.

Adult Studies

There were 30 adult studies (excluding large data studies) with an estimated pooled proportional mortality of 15.6% (95% CI, 12.8-18.4) with substantial heterogeneity between studies (I^2 = 87.4%) (**Figure 1**[13-41]). Excluding studies judged to be low quality did not significantly change this or in any subsequent analysis (15.9%; 95% CI, 12.7%-19.2%; I^2 = 89.0%). Overall, there was evidence of a small-study effect using the Egger meta-regression model (4.18; 95% CI, 1.49-6.86; P < .01). Applying the trim-and-fill method reduced the pooled mortality to 10.3% (95% CI, 7.2%-13.4%). Studies performed before 2000 had a higher pooled mortality (24.0%; 95% CI, 16%-31%; I^2 = 75.0%) compared with studies performed between 2000 and 2010 (13.0%, 95% CI 10%-16%; I^2 = 85.6%) and after 2010 (18.0%; 95% CI, 12%-23%; I^2 = 84.5%). The corresponding funnel plots (eFigures 3-5 in the Supplement) indicated possible bias due to a small-study effect. The quantitative assessment conducted using the Egger test supported a small-study effect in the 2001 to 2010 period (4.29; 95% CI, 0.53-8.04; P = .03), but there was no significant small-study effect in the 1990 to 2000 period (−1.45; 95% CI, −11.38 to 8.29; P = .67) and a trend for the 2011 to 2017 period (6.40; 95% CI, 0.63-13.44; P = .07). Comparing the pooled mortality of the earliest period (1990-1999) with the later periods by means of a meta-regression demonstrated weak evidence of a change in mortality in the second period (2000-2010; −0.75; 95% CI, −0.16 to 0.01; P = .07) but not with the later period (after 2010; −0.30; 95% CI, −0.12 to 0.06; P = .51). A meta-regression (R^2 = 10.7%; P = .12) (eFigure 6 in the Supplement) and linear regression analysis using study midpoints did not demonstrate any significant change in mortality over time (R^2 = 0.022; P = .44) (**Figure 2**).

Figure 1. Forest Plot of Status Epilepticus Proportional Mortality in Adult Studies by Study Midpoint Year



Weights are drawn from a random-effects analysis. PM indicates proportional mortality.

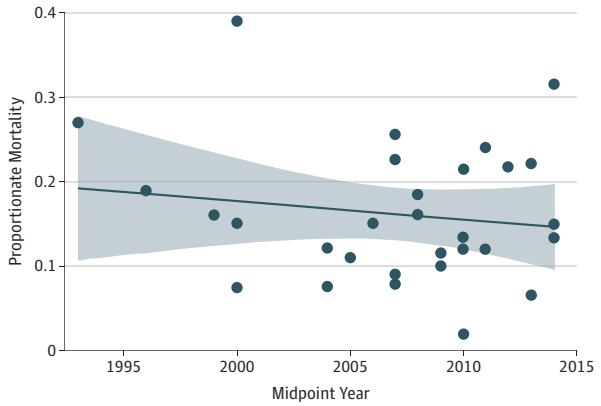
Pediatric Studies

There were 7 pediatric studies (excluding 3 studies with no reported mortality and 1 routine data study) giving an estimated pooled proportional mortality of 3.6% (95% CI, 2.0-5.2) with high heterogeneity between studies (I^2 = 72.2%) (**Figure 3**[42-48]). Excluding studies judged to be low quality did not significantly change the overall mortality in this, or any subsequent, analysis (pooled mortality, 4.4%; 95% CI, 1.1%-7.6%; I^2 = 81.5%). There was 1 study using the Kid's Inpatient Database in the United States in 4 separate years (1997, 2000, 2003, and 2006 with the data pooled) with 12 365 cases of GCSE (representing 0.083% of all hospital admissions) in children aged 0 to 20 years identified. Overall mortality (case fatality rate) was 0.95%, which is significantly lower than the pooled estimate.[49] Studies performed before 2000 had a worse prognosis apart from 1 study[46] that was a retrospective study from a single pediatric ICU between 1999 and 2006, judged to be moderate-quality, which was a significant outlier as evidenced by the funnel plot (eFigure 7 in the Supplement). There was evidence of a small-study effect using the Egger test (2.69; 95% CI, 0.48-4.89; P = .03) with a downward projection of mortality (2.1%; 95% CI, 0.4%-3.8%) using the trim-and-fill method. Comparing 3 periods (1990-1999, 2000-2005, and 2006-2017) revealed similar pooled mortality for the first 2 periods (4.9%; 95% CI, 2.5%-7.0%; I^2 = 42.9% and 5.8%; 95% CI, 0.0%-11.8%; I^2 = 80.3%, respectively) but a lower mortality for the last period (1.7%; 95% CI, 0.6%-2.9%; I^2 = 51.7%). Comparing the pooled mortality in the earliest period with the later periods (2000-2005) and (2006-2017) using a meta-regression did not demonstrate a significant difference in mortality (0.001; 95% CI, −0.06 to 0.07; P = .96 [2000-2005]; −0.03; 95% CI, −0.09 to 0.02; P = .17 [2006-2017]). The meta-regression analysis did not demonstrate evidence of a significant change in mortality over time (R^2 = 10.99%; P = .21) (eFigure 8 in the Supplement).

All-Age Population Studies

There were 6 studies identified where people of all ages were included, most of which were population-based studies. The

Figure 2. Linear Regression Analysis of Status Epilepticus Proportional Mortality in Adults Over Time



The shaded area indicates the 95% confidence intervals for status epilepticus proportional mortality. The blue line indicates the projected change in status epilepticus proportional mortality over time.

overall estimated mortality was 13.1% (95% CI, 7.2%-19.0%) with very high heterogeneity (I^2 = 79.6%) (**Figure 4**[50-55]). One study, a retrospective, moderate-quality, single-center study from Spain conducted between 1992 and 1998 of 57 people with SE and a reported mortality of 37%, represented a significant outlier[50] (eFigure 9 in the Supplement). There was no evidence of change in mortality over time using a meta-regression (−0.04; 95% CI, −0.33 to 0.25; *P* = .73). There was some evidence of a small-study effect (Egger test; 4.59; 95% CI, −0.20 to 9.38; *P* = .06), with a downward estimation of mortality of 8.5% (95% CI, 1.7%-15.3%) using the trim-and-fill method.

Routinely Collected Data Studies

Seven large routinely collected data studies, 6 (85.7%) covering all age groups and 1 (14.3%) of just adults (>16 years), were identified, with data derived from national inpatient/discharge databases or national mortality data. One study[56] covered four 5-year periods (1990-1994, 1995-1999, 2000-2004, and 2005-2009) and these periods were included separately in the analysis. Two studies[57,58] gave whole-population mortality data and so did not give *P* figures and were therefore not included in the meta-analysis. In one of these studies that used 2 national databases in the United States, population-standardized hospital admissions for SE increased by 56% from 8.86 in 1999 to 13.86 in 2010 (incident rate ratio [IRR], 1.013; 95% CI, 1.012-1.013) while the corresponding SE-associated mortality increased by only 5.6% (1.79 in 1999 to 1.86 in 2010 [IRR, 1.004; 95% CI, 1.002-1.006]), suggesting a fall in the individual mortality rate.[57] In a study using national mortality data, SE-associated mortality decreased by 32% between 2001 and 2013 in England and Wales,[58] but, to our knowledge, the corresponding number of admissions for SE over this period is not known.

Using the remaining 5 studies, the pooled SE mortality was 7.9% (95% CI, 6.7%-9.0%) with very high study heterogeneity (I^2 = 99.6%) (**Figure 5**[56,59-62]). The Egger test did not indicate a small-study effect (−14.28; 95% CI, −43.62 to 15.07; *P* = .28) (eFigure 10 in the Supplement).

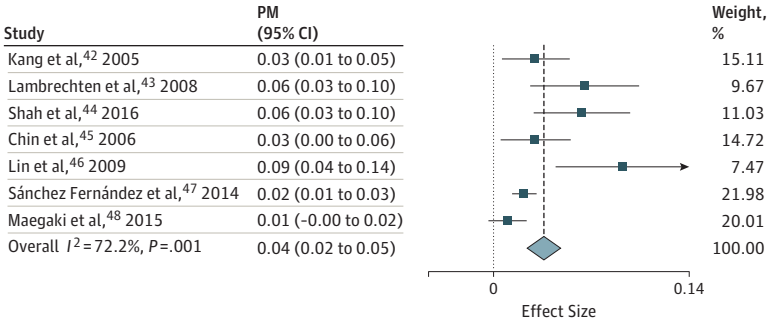
Refractory SE

In 5 studies[63-67] confined to adults with RSE (requiring anesthetic agents for seizure cessation), the pooled mortality was higher at 17.0% (95% CI, 10.0%-25.0%), with very high heterogeneity (I^2 = 92.4) (eFigure 11 in the Supplement). Excluding 1 study judged to be low quality (confined to cases of suprarefractory SE) did not significantly change the mortality (20%; 95% CI, 8.1%-31.9%; I^2 = 94.1%). In addition, there were 2 pediatric studies of RSE, one covering 2008 to 2009 with an overall mortality of 4.0%[68] and the other from 2011 to 2016 with an overall mortality of 4.7%.[69] There was no significant evidence of a small-study effect from the Egger test results (5.39; 95% CI, −2.38 to 13.16; *P* = .11; eFigure 12 in the Supplement). Notably, the RSE cases probably included a higher proportion with nonconvulsive SE and so cannot be directly compared with the convulsive SE data.

Association of Study Location, SE Definition, Age, and Study Setting

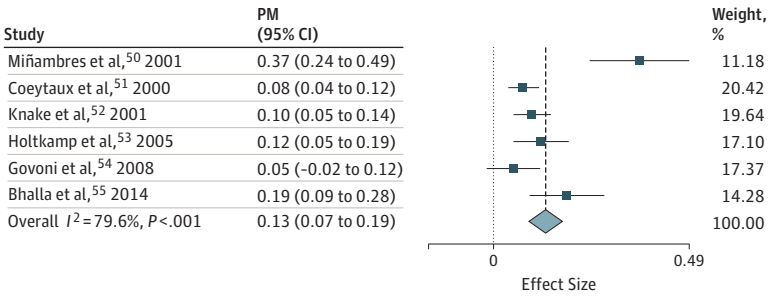
Subdividing high-income countries into 3 regions (North America, Europe, and Asia/Oceania) and using a meta-regression analysis that included all studies, we found no difference in SE prognosis among the 3 regions in the adult (North America vs Europe, 0.02; 95% CI, −0.05 to 0.09; *P* = .57; North America vs Asia/Oceania, −0.01; 95% CI, −0.11 to 0.08; *P* = .76; overall *P* = .63), pediatric (North America vs Europe, 0.02; 95% CI, −0.12 to 0.09; *P* = .68; North America vs Asia/Oceania, −0.01; 95% CI, −0.08 to 0.07; *P* = .75; overall *P* = .89), and the all-age groups (North America vs Europe, 0.04; 95% CI, −0.02 to 0.11; *P* = .19; North America vs Asia/Oceania, −0.02; 95% CI, −0.10 to 0.06; *P* = .67; overall *P* = .15). Similarly, we compared studies by the definition of SE used (SE as a prolonged seizure of >30 minutes vs any other period) and observed no difference in mortality in the adult (<5 minutes, 15.2%; 95% CI, 12.1-17.9 vs >30 minutes, 16.8%; 95% CI, 10.1-23.5; *P* = .64), pediatric (<5 minutes, 3.9%; 95% CI, 0.00-0.08 vs >30 minutes, 3.9%; 95% CI, 0.02-0.06; *P* = .97), and all-age groups (43 studies) (<5 minutes, 14.1%; 95% CI, 10.5-17.6 vs >30 minutes, 12.3%; 95% CI, 8.8-15.7; *P* = .55) groups. Similarly, there was no difference in mortality in retrospective compared with prospective studies in all age groups. Splitting each age group into non-ICU and ICU cohorts did not demonstrate a significant difference in SE mortality in the adult (non-ICU, 15.0%; 95% CI, 12.1-17.9 vs ICU, 16.8%; 95% CI, 10.1-23.5; *P* = .64), pediatric (non-ICU, 3.0%; 95% CI, 1.6-4.3 vs 1 ICU study, 9.2%; *P* = .11) and all-age groups (non-ICU, 12.3%; 95% CI, 9.8-17.6 vs ICU, 15.6%; 95% CI, 10.1-21.1; *P* = .32). There was no evidence of change in P over time using a meta-regression in the all-age group (1990-1999 vs 2000-2009, −0.03; 95% CI, −0.09 to 0.03; *P* = .35; 1990-1999 vs 2010-2017, 0.04; 95% CI, −0.04 to 0.12; *P* = .34; overall *P* = .16). However, there was clear evidence of a difference in SE-associated mortality with age when comparing adult with pediatric (adult vs pediatric, 0.11; 95% CI, 0.05-0.17; *P* < .001) and all-age (population) studies (adult vs all-age, 0.09; 95% CI, 0.01-0.17; *P* = .04). Finally, we per-

Figure 3. Forest Plot of Status Epilepticus Proportional Mortality for Pediatric Studies



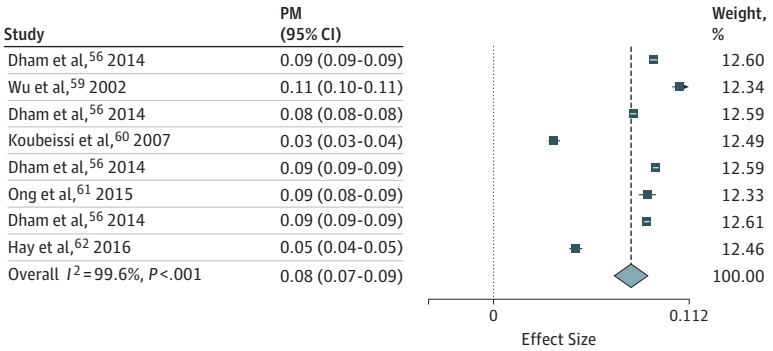
Weights are drawn from a random-effects analysis.

Figure 4. Forest Plot of Status Epilepticus Proportional Mortality for All-age Studies



Weights are drawn from a random-effects analysis.

Figure 5. Forest Plot of Status Epilepticus Proportional Mortality in Routinely Collected Data Studies



Weights are drawn from a random-effects analysis.

formed a multivariate meta-regression combining all variables (country, definition of SE, time [study midpoint], methods, study setting, and age group [all-age group]) separately in the adult, pediatric, and all-age groups, with no significant reduction in heterogeneity demonstrated (I^2 > 75%).

Discussion

The primary aim of this study was to study mortality trends in SE over time, comparing pooled mortality to determine if there was evidence of a decrease in SE mortality particularly since the 1990s. It was our hypothesis that earlier and more aggressive treatment of prolonged seizures lasting more than 5 minutes (as first proposed in the operational definition of SE in 1999) would lead to evidence of improved prognosis of SE with reduced mortality rates.

From the 61 studies included in this systematic review, there is no strong evidence that this is true. However, in pediatric cohorts, the larger and later studies have lower SE mortality rates (0%-3%) (eTable 3 in the Supplement), and in adult populations, there was some evidence of a decrease in mortality in studies conducted between 2000 and 2010 compared with before 2000. It is possible that the high degree of heterogeneity evident in the studies is obscuring a more modest improvement in SE rates over time. To try to minimize the heterogeneity inherent in the studies, we separated studies by age (with clear evidence of a difference in prognosis) and study design (eg, large data, population studies, and studies of RSE), yet a high degree of heterogeneity remained. In the meta-

regression analysis, we found no evidence that the prognosis of SE varied by individual factors separately or combined in a multivariate multiregression model (with a persistently elevated I^2), either in all studies combined or in the adult and pediatric studies individually.

The failure to demonstrate a consistent difference in SE mortality was independent of the definition of SE used. However, this is a roundabout way of trying to answer the more pertinent question, which is whether the period during which treatment was initiated for convulsive SE has changed over time. Unfortunately, seizure duration and the timing of treatment initiation is not typically reliably recorded in most studies, making this more relevant analysis impossible. Using an SE definition of a prolonged convulsive seizure longer than 5 minutes does not reliably imply that treatment is being initiated earlier. The recently published SENSE study, a prospective observational study of SE over 4 years in 3 European countries, suggests that treatment protocols are not followed in many patients. The mean latency to treatment in GCSE was 30 minutes, with only 221 of 457 GCSE cases (48.4%) having treatment initiated in 30 minutes or less.[70]

This could partly explain our failure to demonstrate unequivocal evidence of lower mortality rates over time. A further explanation is the strong association that etiology has with prognosis, which has been emphasized in studies in adults[71] and children.[72] It is also likely that case ascertainment and case definition changed over time. Retrospective studies from ICUs, particularly the more recent dedicated neuro-ICUs, will include more severe SE cases with poorer prognosis, and such studies will not be representative of the total SE population. Moreover, it is possible that the fact that SE mortality has not changed may be a reflection of the advent of specialist neuro-ICUs and advances in critical care management, which has resulted in more critically ill patients with multiple comorbidities surviving longer and subsequently developing SE. This bias would particularly apply to RSE.

Our study also indicated a small-study effect in which the smaller studies had larger mortality rates. While using national hospital databases is a powerful tool to examine population trends in incidence and mortality providing very large sample sizes, this will be offset by the loss of control over case ascertainment. In contrast, cross-sectional studies, in which the case ascertainment can be rigorously verified, have sample sizes that are much smaller.

Limitations

The primary limitations of this study are self-evident, namely the appropriateness of using a meta-analysis for assessing mortality trends over time and the marked heterogeneity of the studies themselves, which is particularly evident in the pediatric studies in which the upper age limit varied from 12 to 20 years. In addition, there were few studies conducted before 2000, with most performed after 2010. Moreover, there are almost no data in any of the studies about the time taken to initiate therapy after the onset of SE. This would be critical information in assessing whether the change in definition of SE had led to the earlier initiation of treatment.

The failure to demonstrate clear evidence of improved prognosis may partly be because of the poor quality of reporting, evidence of marked heterogeneity between studies, a lack of high-quality studies in the field, and too many small studies with an overestimation of mortality in SE.[73] This requires attention and we recommend the creation of guidelines for further epidemiological studies of SE, much in line with the previous epilepsy epidemiology taskforce guideline.[74] In particular, we recommend large-scale collaborative research; the standardization of definitions (SE, RSE), age parameters, and statistical methods; improvement and standardization of study designs; and the creation of an agreed scale for assessing quality and bias in SE cohort studies, for which preexisting scales, such as the Ottawa-Newcastle scale,[12] are poorly suited for SE studies (hence the use of a modified scale in this study).

Conclusions

This study indicates that a drive to change practice in the treatment of SE in high-income countries over the last 30 years has not had a demonstrable association with mortality, which remains high. There are many potential factors as to why this is true. Further research into the causes and treatment of SE-associated mortality is needed.

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Author Contributions: Dr Neligan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Neligan, Walker.
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