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SYSTEMATIC REVIEW

Treatment Outcomes of Newly Diagnosed Epilepsy: A Systematic Review and Meta-analysis

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Abstract

Background and Objectives Understanding the multi-faceted treatment outcomes of newly diagnosed epilepsy is critical for developing rational therapeutic strategies. A meta-analysis was conducted to derive pooled estimates of a range of seizure outcomes in children and adults with newly diagnosed epilepsy commenced on antiseizure medication treatment, and to identify factors associated with different outcomes.

Methods PubMed/EMBASE were screened for eligible articles between 1 January, 1995 and 1 May, 2021 to include unselected cohort studies with a ≥ 12-month follow-up of seizure outcomes. Proportions of patients seizure free at different follow-up timepoints and their characteristics at the study population level were extracted. The patients were group-wise aggregated using a random-effects model. Primary outcomes were proportions of patients with cumulative 1-year seizure freedom (C1YSF), and 1-year and 5-year terminal seizure freedom (T1YSF and T5YSF). Secondary outcomes included the proportions of patients with early sustained seizure freedom, drug-resistant epilepsy and seizure-free off antiseizure medication at the last follow-up (off antiseizure medications). A separate random-effects meta-analysis was performed for nine predictors of importance.

Results In total, 39 cohorts (total $n = 21{,}139$) met eligibility criteria. They included 15 predominantly adult cohorts ($n = 12{,}024$), 19 children ($n = 6569$), and 5 of mixed-age groups ($n = 2546$). The pooled C1YSF was 79% (95% confidence interval [CI] 74–83). T1YSF was 68% (95% CI 63–72) and T5YSF was 69% (95% CI 62–75). Children had higher C1YSF (85% vs 68%, $p < 0.001$) and T1YSF than adult cohorts (74% vs 61%, $p = 0.007$). For secondary outcomes, 33% (95% CI 27–39) of patients achieved early sustained seizure freedom, 17% (95% CI 13–21) developed drug resistance, and 39% (95% CI 30–50) were off antiseizure medications at the last follow-up. Studies with a longer follow-up duration correlated with higher C1YSF ($p < 0.001$) and being off antiseizure medications ($p = 0.045$). Outcomes were not associated with study design (prospective vs retrospective), cohort size, publication year, or the earliest date of recruitment. Predictors of importance in newly diagnosed epilepsy include etiology, epilepsy type, abnormal diagnostics (neuroimaging, examination, and electroencephalogram findings), number of seizure types, and pre-treatment seizure burden.

Conclusions Seizure freedom is achieved with currently available antiseizure medications in most patients with newly diagnosed epilepsy, yet this is often not immediate, may not be sustainable, and has not improved over recent decades. Symptomatic etiology, abnormal neuro-diagnostics, and increased pre-treatment seizure burden and seizure types are important predictors for unfavorable outcomes in newly diagnosed epilepsy. The study findings may be used as a quantitative benchmark on the efficacy of future antiseizure medication therapy for this patient population.

Extended author information available on the last page of the article

Key Points

Most patients with newly diagnosed epilepsy commenced on antiseizure medication(s) will achieve at least 1 year of seizure freedom at some point during the treatment period.

However, less than 70% of patients are seizure free for 1 and 5 years at the last follow-up, indicating a fluctuating course. Thirty-three percent of patients achieved early sustained seizure freedom, 17% developed drug resistance, and 39% were seizure free off antiseizure medications at the last follow-up.

Dispersion of seizure freedom rates indicated significant between-study heterogeneity of study cohorts with prediction intervals approximating 40–90% for 1- and 5-year terminal seizure freedom. Childhood-onset epilepsy shows better prognosis than adult-onset epilepsy in terms of cumulative and terminal 1-year seizure freedom.

Studies recruiting higher female proportions correlated with early sustained seizure freedom and being seizure free off antiseizure medications, while a longer follow-up duration was correlated with higher proportions of cumulative 1-year seizure free and seizure free off antiseizure medications.

Prognostic variables most relevant in newly diagnosed epilepsy include etiology, epilepsy type classification, number of seizure types, pre-treatment seizure burden, epileptiform electroencephalogram, abnormal neuroimaging, and abnormal neurologic exam. Febrile seizures and family history were not predictive of treatment outcomes in this meta-analysis.

1 Introduction

Epilepsy is amongst the most common, serious chronic neurological disorders worldwide with an estimated incidence of 68 per 100,000 persons per year [1]. Epilepsy can commence at any stage of life, and understanding the prognosis of newly diagnosed epilepsy in the real-world setting is critical for patient counseling and formulating rational therapeutic strategies [2].

A number of longitudinal observational studies have reported that 60–70% of patients with newly diagnosed epilepsy become seizure free for at least 12 months upon commencement of antiseizure medications (ASMs), suggesting a relatively good prognosis at a population level [3–6]. However, given that most patients require long-term, if not lifelong treatment, no single measure of seizure freedom is adequate to fully describe the disease course in an individual [7–9]. Therefore, a range of treatment outcome measures are needed to understand the disease course. Moreover, given their "real-world" nature, observational studies vary widely in the characteristics of the patient populations and parameters of seizure outcomes used. For example, studies of children [9, 10] have tended to report higher seizure-free rates compared with adult populations [3, 11]. Further, there is recent evidence that despite the availability of more than 15 new ASMs in the past 30 years [12], seizure outcomes have not changed over time [3], but this has not been systematically studied.

To achieve a more comprehensive understanding of the seizure outcomes in children and adults with newly diagnosed epilepsy, we undertook a systematic review and meta-analysis of longitudinal observational studies published over the past 3 decades. The primary aim was to extract and aggregate commonly reported measures of seizure freedom (cumulative and 'terminal' seizure freedom) across the general epilepsy population, and to analyze factors influencing outcomes. We also analyzed other clinically relevant outcome measures, including early sustained seizure freedom, pharmacoresistance, and seizure freedom off ASM treatment. Given that the response to treatment influences direct costs associated with epilepsy care [13], the findings will also be useful for policy makers in planning the utilization of healthcare resources.

2 Methods

2.1 Search Strategy and Eligibility

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist in conducting the meta-analysis. The study is registered on PROSPERO (CRD42017073299). We searched publications in PubMed and EMBASE with keywords of seizure, epilepsy, newly diagnosed, anticonvulsants, remission, and prognosis (see the Electronic Supplementary Material [ESM] for detailed search methodology). We included full-length articles published between 1 January, 1995 and 1 May, 2021, some of which commenced recruitment as early as 1959. The study period was selected to encompass the expansion of modern ASMs from the 1990s to give a representation of the pharmacologic outcomes in the recent era. Each publication identified was initially screened by the primary reviewer (MJ), followed by a second independent review by one of the three secondary reviewers (HH, SH, and SO), using

the pre-defined eligibility criteria. Any discrepancies were resolved by the senior author (PK).

We performed the screening in two phases. In the first phase, we screened the titles and abstract. The full text was reviewed when the titles and abstracts did not provide adequate information. Inclusion criteria for phase 1 screening were retrospective or prospective observational or randomized controlled studies that included populations of newly diagnosed epilepsy, regardless of epilepsy type, syndrome, etiology, who were treatment naïve and who had been followed for at least 12 months from enrollment, randomization, or start of treatment. Exclusion criteria were studies that included patients (a) without epilepsy; (b) already treated with ASM treatment on recruitment; (c) with pre-specified epilepsy syndromes, types, or etiologies (e.g., exclusive cohorts of patients with juvenile myoclonic epilepsy or traumatic brain injury); (d) predominantly with a first seizure (or did not report separate outcomes for patients with a first seizure and newly diagnosed epilepsy); (e) with status epilepticus; or (f) with exclusively neonatal or infantile onset of epilepsy. The latter was to avoid bias of outcomes in patients with developmental and epileptic encephalopathies, which are associated with high rates of drug resistance and adverse neurodevelopmental outcomes. We also excluded studies with fewer than 50 patients at the end of the follow-up for seizure freedom analysis. Studies that reported a follow-up less than 12 months or did not clearly define a follow-up duration were excluded. Abstracts, conference, or review articles were excluded.

We performed a second phase of screening with a full-text review to exclude studies restricted by pre-specified epilepsy syndromes or etiologies. Studies were also excluded if there was discrepancy of seizure freedom/outcome definitions, if they included analysis of the first ASM only, randomized controlled trials, and studies of infantile-onset epilepsy. However, we included comparative monotherapy studies if they did not designate the initial ASM treatment failure as a primary outcome failure and permitted ongoing treatment changes (e.g., the SANAD studies) [4, 5].

2.2 Definitions

2.2.1 Outcome Measures

The primary outcomes were proportions of patients achieving seizure freedom at any time during the follow-up (cumulative 1-year seizure freedom, C1YSF), and who were seizure free for at least 1 year (T1YSF) or 5 years (T5YSF) at the last follow-up ('terminal' seizure freedom). Short-term studies that reported at least 1- or 2-year periods of cumulative seizure freedom during the follow-up were combined to derive C1YSF. Similarly, studies providing 1- or 2-year terminal seizure freedom outcome were combined for the analysis of T1YSF.

Secondary outcome measures were proportions of patients (a) with early sustained seizure freedom, defined in most studies as immediate seizure freedom upon commencement of the first ASM sustained up to the last follow-up without relapse; (b) who were seizure free and off ASMs at the last follow-up; and (c) who developed drug-resistant epilepsy during the follow-up, defined according to the consensus definition of the International League Against Epilepsy (ILAE) as the failure of two or more tolerated ASMs that have been appropriately chosen and used [14].

2.2.2 Cohort Size

We defined the evaluation cohort as the total number of patients available for analysis of the specific outcome measure. This excluded in most studies patients with missing data, incomplete seizure reporting, and a lack of follow-up. Some studies excluded patients with poor drug adherence. Most prospective studies, except a few, had discrepancy between the inclusion number of the original cohort and numbers at the final follow-up owing to the common reasons of attrition described above for longitudinal cohort studies. Retrospective studies included patients with a pre-defined minimum follow-up period as the inclusion criteria in most cases. A few studies had reported multiple seizure freedom endpoints and the proportion available for the time period of interest was taken into account. For instance, C1YSF for the Kuopio University Hospital dataset [15] was analyzed on the evaluation cohort of 456 patients but 132 patients were available for a T5YSF analysis.

2.2.3 Age Subgroups

Cohorts were grouped into adult, children, or mixed-age groups according to the predominant age at onset of epilepsy of the patients included. Age at diagnosis was used where age at onset was not provided. The majority of the studies included exclusively adults or children with five studies being mixed. For the purpose of this meta-analysis, four additional studies were categorized as children [16–19] and four others as adults [3, 5, 20, 21] based on the predominant age group being children or adults (more than two thirds of the cohort). Two studies provided separate outcome data in children and adults [22, 23].

2.3 Predictor Analysis

Although multiple measures of seizure freedom were extractable from cohorts, target outcomes and relevant raw data presented differed amongst authors. Outcomes for prognostication in individual studies utilized different seizure

measures, stages of treatment remission, and patterns of seizure fluctuations. Similarly, categorization of predictor variables differed amongst the studies according to the outcome opted by the author for the prognostic analysis. Given the above, we carefully selected studies and predictors that would be suitable for pooling, allowing some variation in seizure freedom measures and predictor categorization. Pooled effect sizes using a random-effects meta-analysis for nine prognostic relevant variables in relation to grouped favorable or unfavorable outcomes are provided. These include etiology, pre-treatment seizures, number of seizure types, febrile seizures, family history, neuroimaging, abnormal epileptiform electroencephalogram (EEG), neurologic examination, and epilepsy-type classification. All these represented recurrent predictors assessed in the literature.

2.4 Data Extraction and Quality Rating Scale

Two reviewers (MJ and HH) extracted the data and critically appraised each study. Given the lack of a control group and a specific exposure, we used the National Heart, Lung, and Blood Institute quality assessment tool for case series studies (see ESM for detail) and added details on confounders, which may introduce the risk of bias in the outcomes of interest. We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) guideline to determine the overall certainty of evidence for the three primary outcomes across different studies.

2.5 Statistical Analysis

We used a random-effects meta-analysis with the DerSimonian and Laird method for the outcome analysis. A subgroup analysis was performed for three age groups (children, adult, and mixed age) using the predominant age group at epilepsy onset as a categorical variable. For the subgroup analysis, we assumed the variation between groups was different. The 95% prediction intervals (PIs) were calculated to indicate that future studies would likely fall within that range. We derived I-square statistics (I^2) to assess the variability in effect estimates that was due to heterogeneity rather than chance. The I^2 index can be interpreted as insignificant for 0–40%, moderate for 30–60%, substantial for 50–90%, and considerable for 75–100% [24]. We performed a meta-regression to further explore the sources of heterogeneity using study-level variables. We provide R^2 values to assess the proportion of the observed variability in the observed effect size that could be explained by age group, female proportion, follow-up duration, study design (retrospective vs prospective design), year of publication, and the earliest date of recruitment, and assessed their effects on the outcomes. We applied a funnel plot visual analysis and Egger's test to evaluate the small study effect and publication bias for pooled seizure outcomes with Freeman–Tukey double arcsine transformation. The statistical significance level was set at $p = 0.05$. All statistical analyses and forest plot visualizations were performed using Stata version 16 (StataCorp., College Station, Texas, US), with user-written packages 'metaprop' for the meta-analysis of proportions [25].

3 Results

Figure 1 shows the PRISMA flow diagram of study inclusion. After removing duplicates, 6911 articles were screened for titles and abstracts. After the first phase of screening, 98 articles remained for further analysis. Fifty-six articles were excluded during the second phase of screening (full text) because of ambiguities in initial inclusion criteria, exclusion of certain epilepsy syndromes, discrepancy of seizure freedom/outcome definitions, analysis of the outcome on first ASM only, duplicate cohorts, or cohorts comprising predominantly infants. Finally, a total of 42 articles corresponding to 39 cohorts were included for data extraction and meta-analysis. In broad age groups, these included 15 predominantly adult groups ($n = 12{,}024$), 19 children groups ($n = 6569$), and 5 cohorts of mixed-age groups ($n = 2546$), respectively. Two cohorts of the mixed-age group provided separate outcome data for adults and children. Table 1 summarizes the characteristics of the cohorts included. All studies utilized one or more epileptologist or neurologist to confirm the diagnosis of epilepsy in line with the prevalent ILAE diagnostic criteria during the study period (ESM). This required two unprovoked seizures in the traditional classification with some later studies allowing one unprovoked seizure with supporting clinical, EEG, imaging, or neurodevelopmental risk factors for recurrence [26]. Studies included for drug resistance were based on authors' categorization of ongoing seizure control based on the 2010 ILAE consensus definition [14].

3.1 Primary Outcome Measures

3.1.1 Cumulative 1-Year Seizure Freedom (C1YSF)

Twenty-two studies ($n = 24$ cohorts) were included in the pooled analysis of C1YSF, comprising ten adult cohorts (total evaluation $n = 6920$), 11 children groups (total evaluation $n = 3518$), and 3 of mixed-age groups (total evaluation $n = 2053$). The duration of the follow-up ranged from a mean or median of 1–50 years. The overall C1YSF was 79% (95% confidence interval [CI] 74–83; 95% PI 52–96) (Fig. 2). There was considerable heterogeneity across the studies ($I^2 = 97\%$, $p < 0.001$) (Fig. 2). Overall, higher cumulative seizure freedom proportions were noted in cohorts of children (85%; 95% CI 79–89) compared with adults (68%;

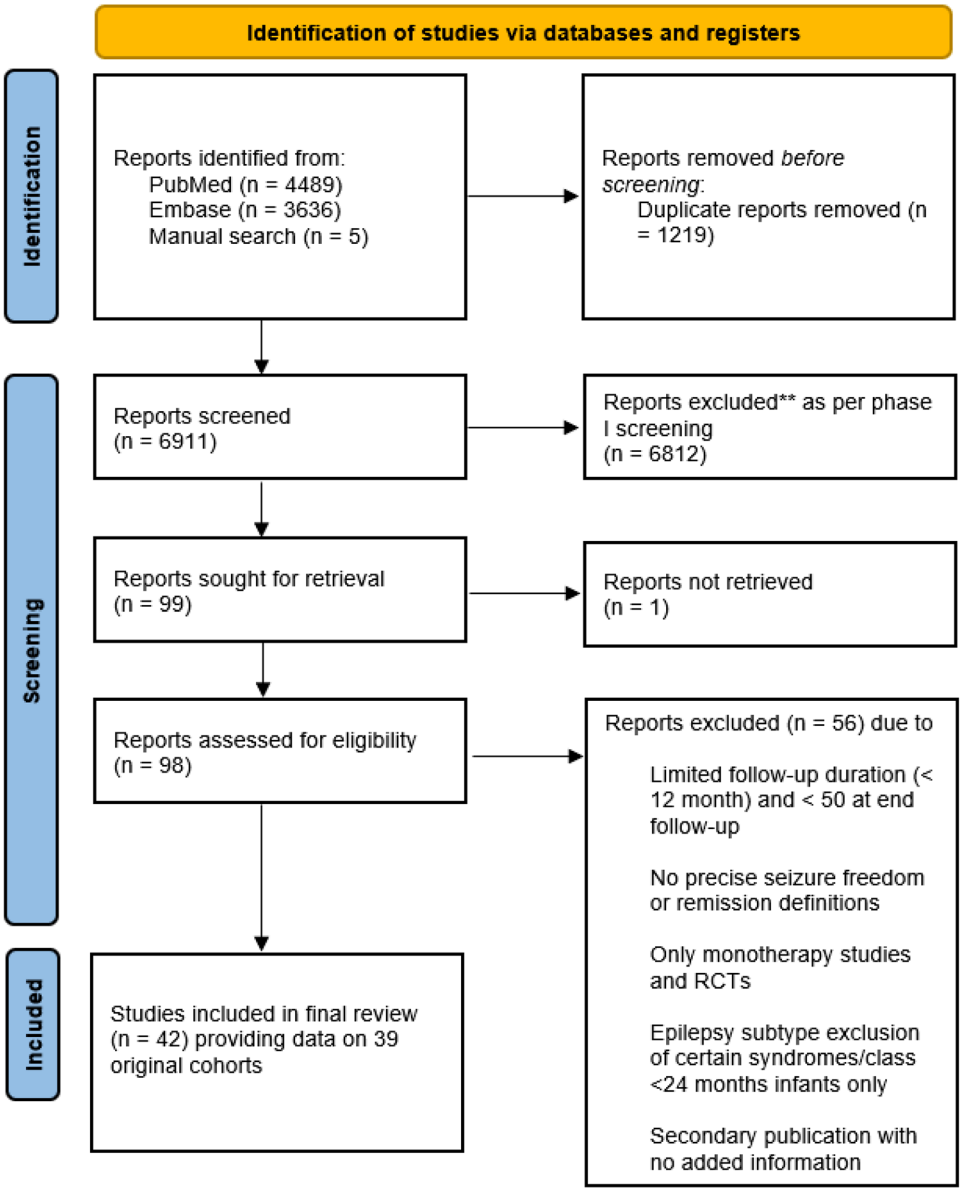

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. **Major exclusion criteria, reports unrelated to studies of epilepsy; cohorts that included already commenced or non-naïve patients before enrollment or when the majority of the cohort was represented by that, restricted epilepsy syndromes; types or etiologies (e.g., exclusive juvenile myoclonic epilepsy cohort or traumatic brain injury or only exclusively focal or generalized epilepsy cohorts); studies that included predominantly first-seizure patients or which did not separate outcomes of first seizure versus epilepsy diagnosed; status epilepticus studies, abstract, conference studies or review articles; premature or neonatal-onset epilepsy. *RCTs* randomized controlled trials

95% CI 65–72). The three cohorts with mixed-age groups showed overall C1YSF of 87% (95% CI 76–95). There was a significant between-group difference in heterogeneity ($p < 0.001$).

Meta-regression with the age group of epilepsy onset as a categorical variable showed a significant difference between children and adult cohorts ($p < 0.001$, $R^2 = 54\%$). A longer follow-up duration was also associated with a higher percentage of C1YSF ($p < 0.001$, $R^2 = 46\%$). In a two-covariate meta-regression model, both follow-up duration and age group were significant factors underlying heterogeneity (combined $R^2 = 68\%$). There was no other moderator of significance when tested including study design, year of publication, or sex proportions. Earliest year of recruitment was not significant when adjusted for follow-up date or age group or both.

3.1.2 At Least 1-Year Terminal Seizure Freedom (T1YSF)

A total of 27 studies ($n = 27$ cohorts) were included for the T1YSF analysis. These included 10 cohorts of adults (evaluation $n = 4183$), 13 children groups (evaluation $n = 4319$), and 4 mixed-age groups (evaluation $n = 1787$). The mean duration of follow-up ranged from 1 to 34 years. The pooled proportion of patients in terminal seizure freedom across all the studies was 68% (95% CI 63–72, 95% PI 42–89) (Fig. 3). Similar to C1YSF, the pediatric cohorts showed a higher pooled T1YSF (74%; 95% CI 68–79) compared with the adult cohorts (61%; 95% CI 52–69), with adults also having a wider dispersion (95% PI 28–89), while the T1YSF in the mixed-age cohorts was 67% (95% CI 58–76). The test of heterogeneity between subgroups was significant (p

Table 1 Characteristics of the cohorts included

First author (year of publication)	Country	Age (years)	Female (%)	Follow-up duration (years)	Study design	Recruitment cohort (*n*)	Outcomes evaluated (patient number included for evaluation)	Seizure rates[a]
Adult or predominantly adult cohorts								
Besocke (2013) [45]	Argentina	Median 78 (IQR 72–83)	66	Median 1.25 (IQR 1–2)	R	122	C1YSF (122), T1YSF (122), DRE (122)	56% T1YSF
Del Felice (2010) [21]	Italy	Mean 31.5 (< 15 = 37; > 15 = 315)	49	Mean 6.89, median 6.25	R	352	C1YSF (352), T1YSF (352), ESSF (352)	38% T1YSF
Caprara (2020) [52]	Brazil	Mean 16.6 (SD 8.9)	45	Mean 9.8	P	349	T1YSF (302), ESSF (302), DRE (302)	71% T1YSF
Chen (2018) [3]	Scotland	Median 19 (range 9–93)	46	Median 11 (IQR 7–16)	P	2082	T1YSF (1795)	64% T1YSF
Huang (2016) [53]	China	Mean 31.5 (range 14–70)	37	Mean 2	P	340	T1YSF (298), Off-ASM (298)	62% T1YSF
Bruun (2016) [15]	Finland	Range 65–94	48	Up to 5 year (55% at least 2 years)	R	529	T1YSF (293), T5YSF (132), ESSF (293)	80% T5YSF
Gidey (2019) [54]	Ethiopia	Mean 27.4 (SD 11.2)	40	Median 3.6 (range 2–7)	R	639	T1YSF (404), C1YSF (404), ESSF (404)	38% T1YSF
Yao (2019) [20]	China	≤ 16 = 82; > 16 = 205	49	Mean 5.76 (SD 1.24)	P	287	C1YSF (287)	72% C1YSF
Lindsten (2001) [55]	Sweden	Median 52 (range 17–83)	NA	Mean 7.5 (range < 1−12)	P	107	C1YSF (89)	62% C1YSF
Marson (focal) (2007) [5]	UK	Mean 38.3 (SD 18.3)	40	Mean 3.28 (all at least 12 months)	P	1721	C1YSF (1644)	65% C1YSF
Obiako (2014) [50]	Nigeria	Mean 19 (SD 15) (< 18 = 14; > 18 = 220)	32	2-year completers	P	234	C1YSF (207)	71% C1YSF
Badawy (2010) [56]	Australia	Mean 31.5 (range 14–70)	58	1-year completers	P	106	T1YSF (99)	70% T1YSF
Petrovski (2010) [57]	Australia	Mean 38.15	30	1-year completers	P	170	T1YSF (99)	67% T1YSF
Powell[b] (2019) [23]	UK	87% adults. Children: mean 8.5 (SD 4), adults: mean 45.9 (SD 20.4)	48	Mean 4.3 (adults), 4.5 (children)	R	4388	C1YSF (3730)	76% C1YSF
Sharma (2021) [6]	Australia	Median 39 (range 14–88)	38	Median 4.3 (IQR 2.4–7.9)	P	598	C1YSF (380), T1YSF (380)	56% T1YSF
Children or predominantly children cohorts								
Aaberg (2018) [58]	Norway	Median 3	46	Median 6 (range 1–13)	P	606	T1YSF (600), DRE (600)	59% T1YSF
Modi (2014) [49]	USA	Mean 7.2 (SD 3)	39	4-year completers	P	125	T1YSF (99)	79% T1YSF
Ashmawi (2016) [16]	Egypt	Mean 14.7 (SD 11.3)	44	Mean 7.8 (range 4–20)	R	287	C1YSF (287), T1YSF (287), ESSF (287)	77% T1YSF
Berg (2015) [9]	USA	Mean 5.8 (SD 4)	48	Mean 15.3, median 17 (IQR 13.5–18.7)	P	613	C1YSF (516), T1YSF (516), T5YSF (516), ESSF (516), Off-ASM (516), DRE (516)	72% T5YSF
Camfield (1996) [39]	Canada	Mean 6.79, median 6.4 (range 0.1–16.25)	48	Mean 7.09 (range 0.25–15.6)	R	479	T1YSF (479), Off-ASM (479)	69% T1YSF

Table 1 (continued)

First author (year of publication)	Country	Age (years)	Female (%)	Follow-up duration (years)	Study design	Recruitment cohort (*n*)	Outcomes evaluated (patient number included for evaluation)	Seizure rates[a]
Shackleton (2003) [17]	The Netherlands	Mean 15 (SD 11) (< 19 = 70%)	48	Mean 34	R	333	T1YSF (228), T5YSF (228), Off-ASM (228)	64% T1YSF
Hauser (1996) [31]	Austria	Range 0–15	45	Mean 5.3	R	281	C1YSF (281), T1YSF (281), Off-ASM (281)	85% T1YSF
Simard-Tremblay (2009) [51]	Canada	Mean 14 (SD 1.4)	46	Mean 3.1 (SD 1.1)	R	65	T1YSF (65), Off-ASM (65)	82% T1YSF
Geerts (2010 and 2012) [10, 42]	The Netherlands	Mean 5.5, median 5.1 (range 0–15.5)	53	Mean 14.8 (range 11.6–17.5)	P	494	C1YSF (453), T1YSF (413), T5YSF (413), ESSF (413), Off-ASM (413), DRE (413)	71% T5YSF
Ramoz-Lizana (2012) [59]	Spain	Mean 4.9 (SD 3.8) age at diagnosis	46	Mean 7.5 (range 2–14)	P	520	T1YSF (508), ESSF (508), DRE (508)	69% T1YSF
Nickels (2012) [60]	USA	Mean 6.9 (0.1–17)	47	Median 7.87 (range 0.04–29.49)	R	467	T1YSF (467), Off-ASM (467)	67% T1YSF
Brorson (2019) [28]	Sweden	Mean 6.1	52	Mean 50	P	129	T5YSF (94), Off-ASM (94)	83% T5YSF
Huang (2014) [53]	China	Mean 5.1 (SD 3.2)	21	Mean 6.6 (range 3–19)	P	668	C1YSF (649)	82% C1YSF
Oskoui (2005) [48]	Canada	Mean 7.6 (SD 3.7)	50	Mean 4.58 (SD 2.5)	R	196	T1YSF (196)	
Sillanpaa (2008 and 2009)	Finland	Range 0−15	48	Mean 40 (range 11–47)	P	150	C1YSF (144), T5YSF (144) Off-ASM (144)	68% T5YSF
Su (2013) [19]	China	Median 12 (range 1–65)	46	Median 3 (range 2–14)	P	228	C1YSF (171)	78% C1YSF
Wakamoto (2000) [30]	Japan	< 1 = 12, 1–4 = 34, 5–9 = 63, 10–14 = 42, 15–16 = 4	50	Mean 18.9 (range, 6–37.5)	P	167	T5YSF (148), Off-ASM (148)	63% T5YSF
Zhang (2013) [18]	China	Median 13 (range 1-65)	48	Median 5 (range 2–10)	P	212	C1YSF (180), T1YSF (180), ESSF (180), ILAE-DRE (180)	60% T1YSF
Jiang (2017) [27]	China	Median 11 (IQR 7–17)	42	Median 6 (IQR 5.3–7.6)	R	549	C1YSF (336), T5YSF (336), Off-ASM (336)	49% T5YSF
Cohorts of mixed-age groups								
Beghi (2019) [43] (2021) [37]	Italy	Median 16.8 (IQR 10–31)	48	Median 16 (range 10–57)	R	1006	C1YSF (1006), T1YSF (1006), ESSF (1006), Off-ASM (1006)	72% T1YSF
Bell (2016) [8]	UK	Median 23.5 (13.9–55.6)	51	Median 23.6	P	370	C1YSF (354), T1YSF (354), T5YSF (318), ESSF (354), Off-ASM (178)	73% T5YSF
Shen (2016) [22][c]	China	Range 17–85 for adults and range 2–16 for children	50	Median 3.58 (range 2.2–6.7)	P	250	C1YSF (223), T1YSF (223), ESSF (223), DRE (223):	57% T1YSF

Table 1 (continued)

First author (year of publication)	Country	Age (years)	Female (%)	Follow-up duration (years)	Study design	Recruitment cohort (*n*)	Outcomes evaluated (patient number included for evaluation)	Seizure rates[a]
Xia (2017) [44]	China	Mean 17 (range 2–55) (≤ 16 = 115, > 16 = 89)	39	4.8 (range 3–6.5)	P	204	T1YSF (204)	58% T1YSF
Marson (generalized) (2007) [4]	UK	Mean 17.8 (SD 12.5)	45	Mean 3.37	P	716	C1YSF (693)	76% C1YSF

C1YSF cumulative 1-year seizure freedom, *DRE* drug-resistant epilepsy as per ILAE 2010 definition, *ESSF* early sustained seizure freedom, *IQR* interquartile range, *NA* not available, *Off-ASM* off antiseizure medication at last follow-up and seizure free, *P* prospective, *R* retrospective, *SD* standard deviation, *T1YSF* terminal 1 year seizure freedom, *T5YSF* terminal 5-year seizure freedom

[a]Seizure-free outcome available in the study or lowest of the available primary outcome measures

[b]Powell (2019), adult predominant cohort with C1YSF data (Fig. 2) extractable for adults and children

[c]Shen (2016), mixed-aged group cohort with C1YSF data (Fig. 2) extractable for adults and children

= 0.035), which remained so after excluding the studies of mixed-age groups. The overall heterogeneity for all studies was $I^2 = 96\%$ ($p < 0.001$).

Subgroup categories were significant in a single covariate (age-group) meta-regression model ($p = 0.027$, $R^2 = 12\%$). There was no significant association with all other moderator variables tested including publication year, earliest year of recruitment, cohort size, sex proportion, study design, and cohort size.

3.1.3 5-Year Terminal Seizure Freedom (T5YSF)

Only nine cohorts ($n = 2329$, 132 adults, 1879 children, 318 mixed age) were eligible for inclusion in this longer term analysis, seven of which comprised pediatric cohorts. The mean or median follow-up duration ranged from 6 years [27] to 50 years [28], and exceeded 10 years in seven studies [8–10, 17, 28–30]. The pooled T5YSF proportion was 69% (95% CI 62–75; 95% PI 43–89) with considerable heterogeneity across the studies $I^2 = 91\%$ ($p < 0.001$) (Fig. 4). One study included patients with adult-onset epilepsy of a relatively small sample size with a >5-year follow-up ($n = 132$) and reported a T5YSF of 80% (95% CI 72–86) [15], compared with 66% (95% CI 58–74, 95% PI 37–90) in the seven studies of childhood-onset epilepsy. The single study with mixed children and adults reported a T5YSF of 73% (95% CI 67–77). Meta-regression was not performed because there were fewer than ten studies in this outcome group.

3.2 Secondary Outcome Measures

3.2.1 Early Sustained Seizure Freedom

Twelve cohorts (five children, four adults, and three mixed age; total $n = 4838$) reported early sustained seizure freedom, which showed a pooled proportion of 33% (95% CI 27–39; 95% PI 13–58) (Fig. 5). The heterogeneity test between groups was insignificant ($p = 0.60$) and overall heterogeneity of studies was $I^2 = 95\%$ ($p < 0.001$). All studies defined early sustained seizure freedom as seizure freedom attained within 1 year of commencing ASM treatment, except one [16] that allowed up to 2 years from diagnosis (Table S1A in the ESM). Excluding this study did not alter the pooled estimate. Cohorts with a higher female proportion showed a higher proportion of patients with this outcome ($p = 0.001$) in the regression model. Meta-regression on individual moderators (follow-up duration, age groups, study design, publication year) showed no significant associations.

3.2.2 Seizure Free Off ASM Treatment at the Last Follow-Up

Fourteen studies (11 children, 1 adult, and 2 mixed-age group; total $n = 4653$) reported the proportion of patients

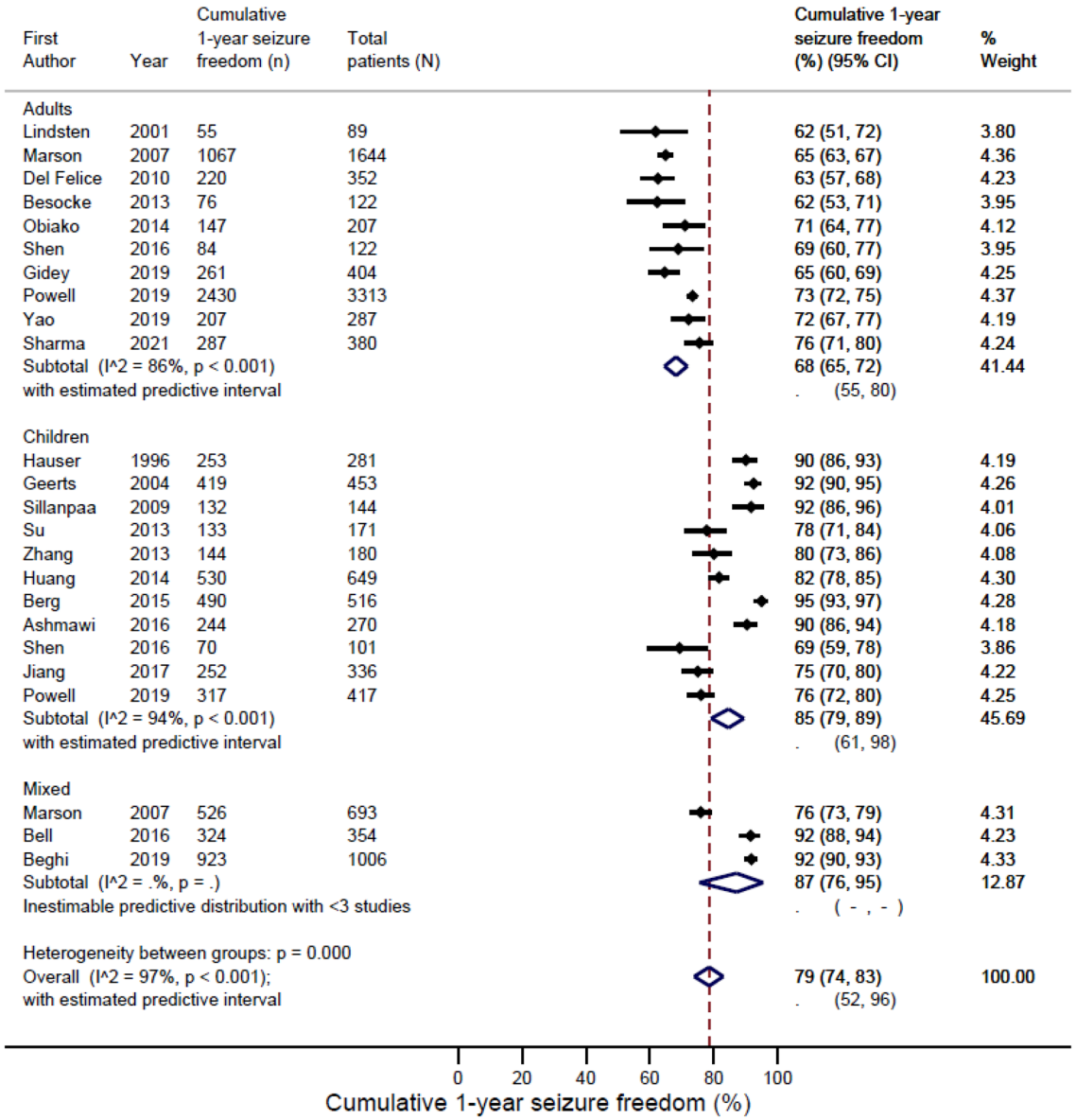

Fig. 2 Proportions of patients with cumulative 1-year seizure freedom. *CI* confidence interval

who were seizure free and off ASM treatment at the last follow-up (Table S1B in the ESM). The overall proportion of patients (> 1 or 5 years) off ASM and seizure free was 39% (95% CI 30–50) (Fig. 6). The I^2 was 98% across all studies and the 95% PI was wide (6–81). Eight of these studies (seven children and one adult) also reported T5YSF ($n = 1375/2057$ evaluated patients) with a substantial majority at the end of follow-up being off ASM ($n = 956$, 46%) [Table S1B of the ESM]. A higher percent of patients off ASMs was observed in cohorts with a higher proportion of female individuals ($p = 0.002$), and with a longer follow-up duration ($p = 0.045$, $R^2 = 9\%$). Other moderators tested, including publication date and study design, were not significant.

3.2.3 Drug-Resistant Epilepsy

Eight studies ($n = 2864$) reported the proportion of patients developing drug-resistant epilepsy according to the ILAE definition. Five of the cohorts were pediatric cohorts, two were adult cohorts, and one was a mixed cohort (Table S1C in the ESM). The mean or median follow-up duration for this subset of studies ranged between 1.5 and 15.3 years. The pooled proportion was 17% (95%

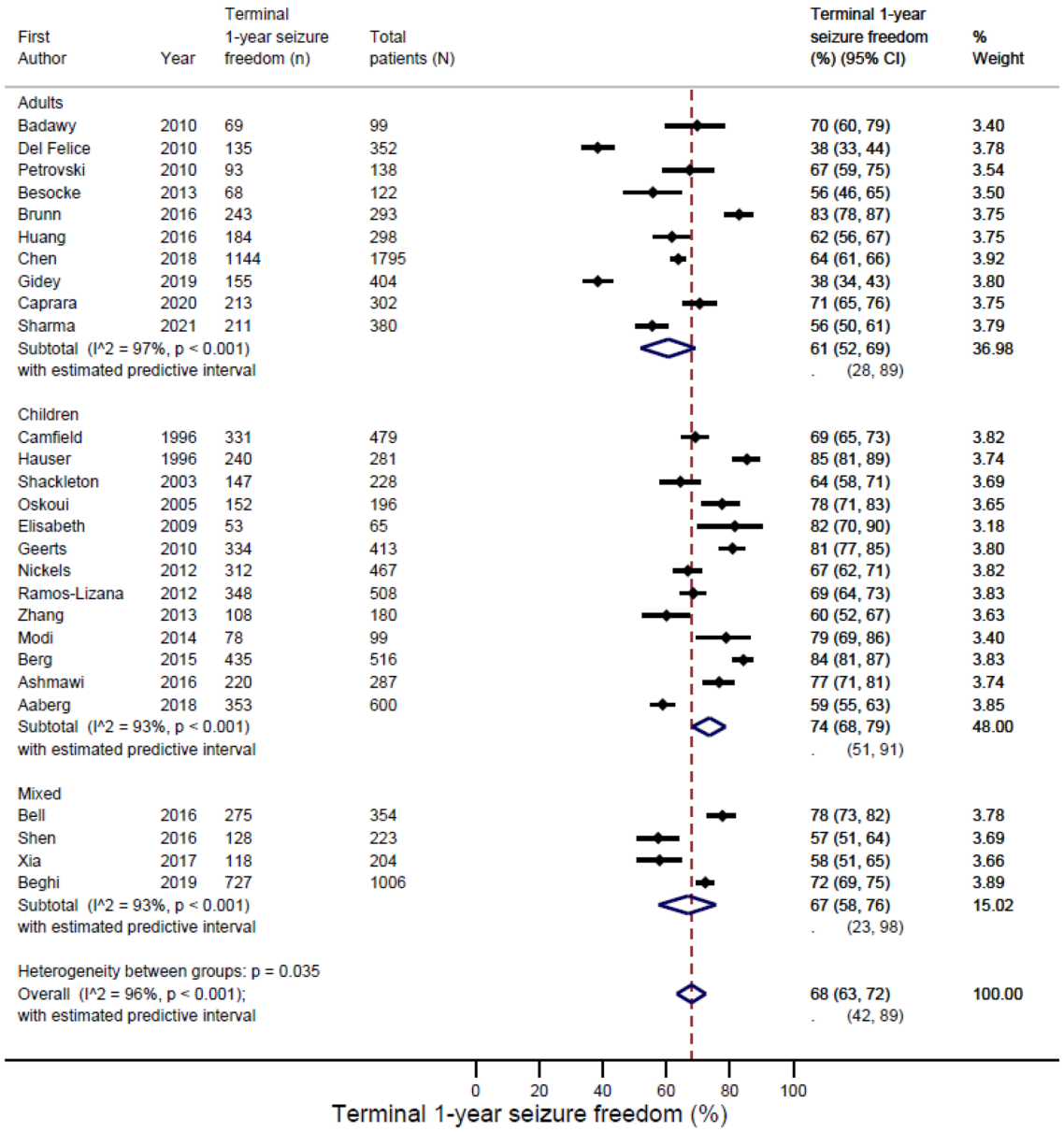

Fig. 3 Proportions of patients with 1-year terminal seizure freedom. *CI* confidence interval

CI 13–21; 95% PI 4–35) at the end of the follow-up (Fig. 7). A moderator analysis was not performed because of the limited studies included.

3.3 Predictor Pooling

A separate random-effect meta-analysis and forest plots were carried out for common selected predictors (ESM). Several predictors identified in previous individual observational studies were validated in this systematic review. In terms of etiology, idiopathic epilepsy had a better prognosis than symptomatic epilepsy (log odds ratio [OR] 0.65 95% CI 0.31–0.98, $p < 0.001$) but no differences were noted when evaluated against cryptogenic epilepsy (log OR 0.14, $p = 0.24$). Patients with cryptogenic epilepsy showed better outcomes compared with patients with symptomatic epilepsy (log OR 0.61, 95% CI 0.24–0.98, $p < 0.01$). Relatedly, normal imaging ($n = 10$ studies) was predictive of favorable outcomes (log OR 0.79 95% CI 0.43–1.15, $p < 0.001$) and an abnormal neurologic exam ($n = 8$) was predictive of unfavorable outcomes (log OR − 0.87, 95% CI − 1.58 to − 0.16, $p = 0.02$). Generalized epilepsy type treatment outcomes were favorable compared with focal epilepsy (log OR 0.81, 95% CI 0.66–0.96, $p < 0.001$). Patients with only one seizure type ($n = 6$) in contrast to more than one seizure type were more likely to have better seizure freedom outcomes (log OR 1.25, 95% CI 0.81–1.69, $p < 0.001$). Pre-treatment

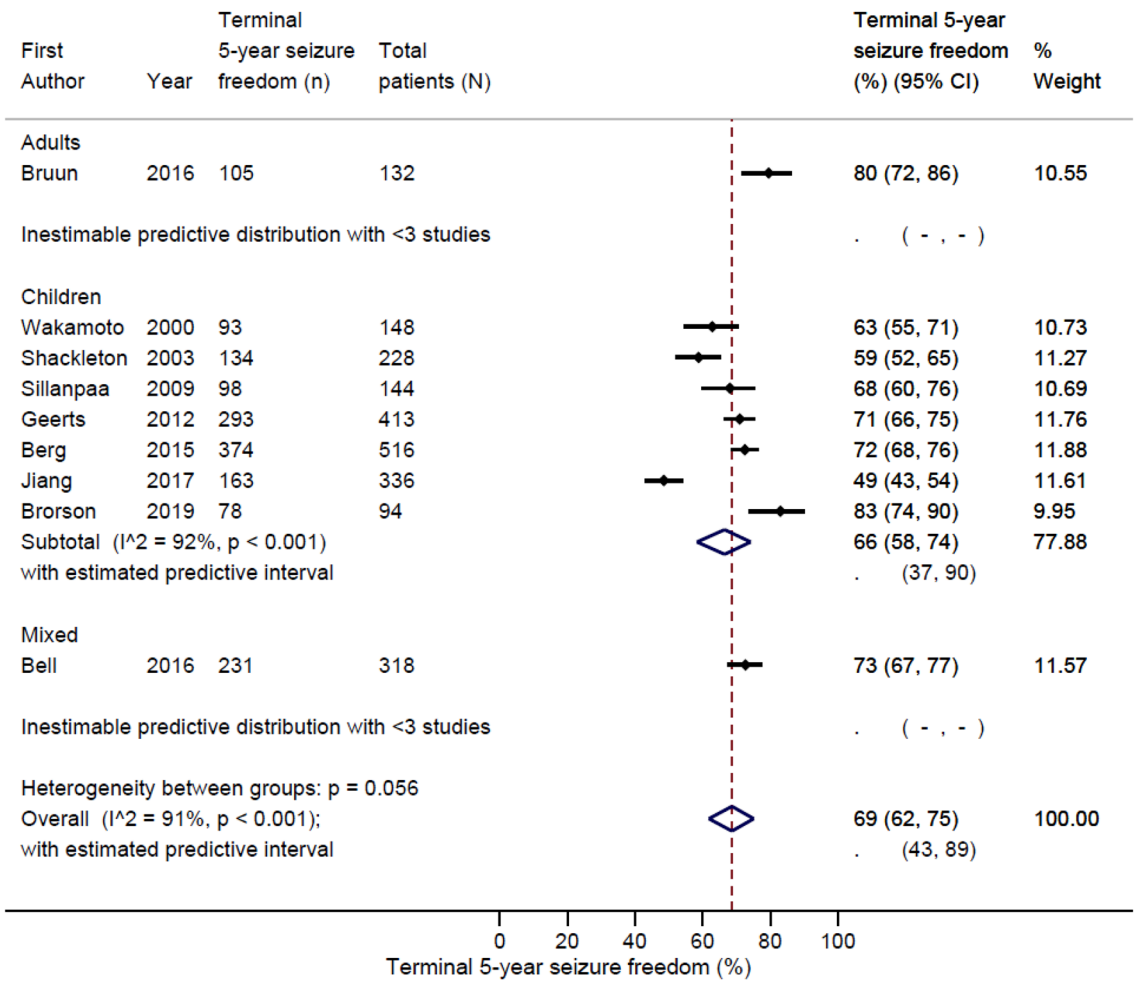

Fig. 4 Proportions of patients with 5-year terminal seizure freedom. *CI* confidence interval

seizure burden ($n = 10$) showed favorable outcomes in patients with fewer seizures prior to treatment (log OR 0.89, 95% CI 0.67–1.10, $p < 0.001$). An epileptiform abnormal EEG ($n = 11$) at diagnosis or enrollment was a negative predictor for successful outcomes (log OR − 0.59, 95% CI − 0.95 to − 0.23, $p < 0.001$). Febrile seizure history ($n = 9$ studies, log OR 0.06, 95% CI − 0.16 to 0.29, $p = 0.58$) and a personal family history of epilepsy ($n = 14$) were not predictors for successful outcomes (log OR − 0.05, 95% CI − 0.32 to 0.21, $p = 0.70$).

3.4 Study Quality and Publication Bias

Critical appraisal using the National Heart, Lung, and Blood Institute quality assessment tool by two raters (MJ and HH) found most studies to have adequate quality and a low risk of bias for the purposes of estimation of the summary effect for the primary outcomes (ESM). The Egger's test for small-study effects for the three primary outcome measures (C1YSF, T1YSF, and T5YSF) showed no evidence of publication bias ($p < 0.24$, $p < 0.50$, and $p < 0.25$, respectively). Funnel plots also showed a low risk of publication bias for the primary outcome measures (Fig. S2 in the ESM). Confidence intervals of seizure freedom outcomes assessed showed adequate precision (C1YSF 95% CI 74–83, T1YSF 95% CI 63–72, T5YSF 95% CI 62–75). For the three primary outcomes, evidence of certainty was deemed to be moderate to high with confidence that the true effect lies close to that of the estimate of the pooled effect size.

4 Discussion

This meta-analysis provides pooled estimates of a range of seizure outcome measures in newly diagnosed epilepsy reported across studies involving over 20,000 recruited children and adults. Separately, nine common predictors were assessed. GRADE-based implementation shows at least a moderate level of confidence for the estimates. Almost all

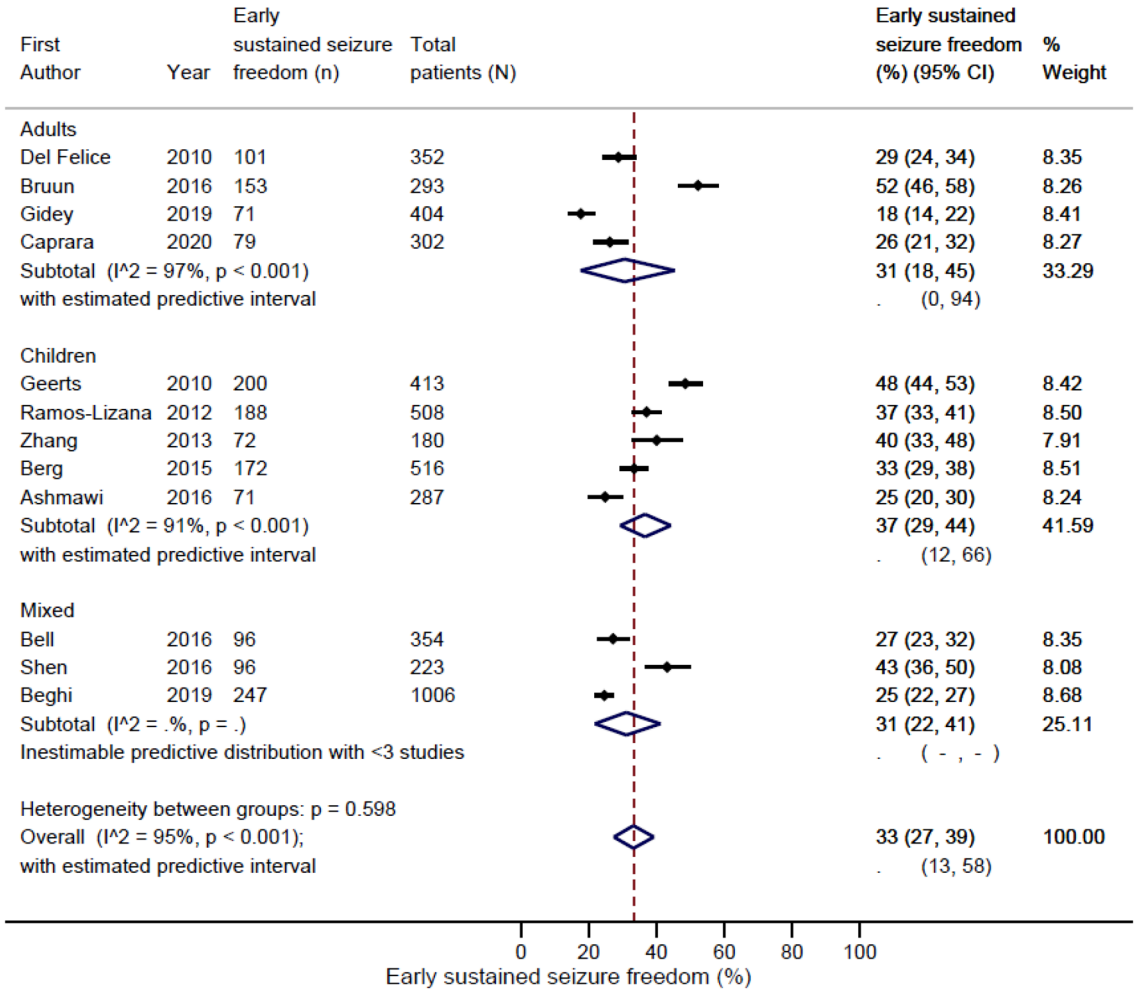

Fig. 5 Proportions of patients with early sustained seizure freedom. *CI* confidence interval

the studies showed that 80–90% of patients became seizure free for at least 1 year during the course of treatment, but less than 70% were seizure free at the last follow-up. A recent study that employed Markov modeling showed that while seizure freedom was likely to persist once achieved irrespective of the regimen, this effect fell with the use of subsequent ASM regimens [2]. Collectively, these findings reinforce the contemporary understanding of an overall good prognosis for newly diagnosed and treated epilepsy, and that only a minority of patients experience persistent uncontrolled seizures. However, the lower terminal than cumulative seizure-free rate suggests that the seizures may relapse over time, which is more likely to occur if remission is not achieved on the initial ASM regimen. This is further supported by the finding of a meta-regression that a longer follow-up duration was associated with a higher C1YSF.

The meta-regression also showed that the age of the cohorts was another source of heterogeneity in seizure freedom measures in our meta-analysis. A subgroup analysis confirmed that childhood-onset epilepsy generally has a better prognosis than adult-onset epilepsy, both in terms of 1-year cumulative and terminal seizure freedom proportion, respectively. Notable examples include the Connecticut study [9], which showed that 95% of children achieved 1-year cumulative seizure freedom over a mean follow-up duration of 15 years, while four additional studies of children also demonstrated cumulative 1-year seizure freedom of ≥ 90% [10, 16, 31, 32]. In comparison, adult-onset epilepsy showed a lower 1-year cumulative seizure freedom of 72%. The difference likely arises from childhood epilepsies that are typically self-limited such as benign epilepsy with centro-temporal spikes, childhood absence epilepsy, and other infantile epilepsies with excellent prognosis. Genetic generalized epilepsy, a common epilepsy type with a favorable prognosis [3], also presents with a higher incidence in childhood [33].

Analysis of secondary outcomes showed that approximately one third of patients achieved early sustained

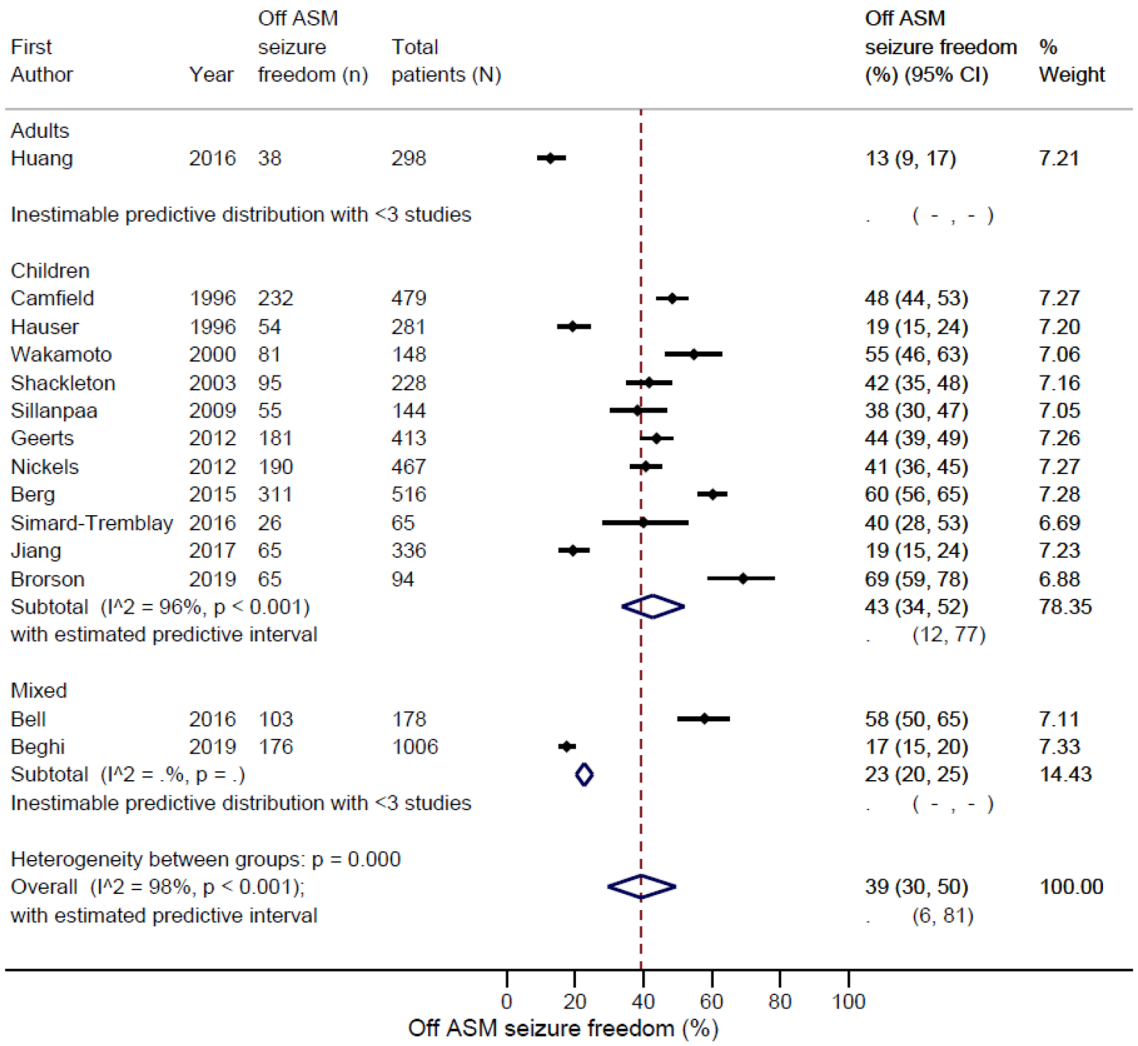

Fig. 6 Proportions of patients seizure free and off antiseizure medication (ASM) at the last follow-up. *CI* confidence interval

seizure freedom, which may be considered the most favorable treatment outcome in newly diagnosed epilepsy. This pattern of response has been described in childhood cohorts as 'smooth-sailing epilepsy' [9, 34], and is also recognized in adult cohorts [7]. Most of these patients achieved sustained seizure freedom on the first ASM prescribed. In the Glasgow cohort of adults with newly diagnosed epilepsy (n = 1065), 29% were seizure free at 1 year while taking the first ASM [35]. In the SANAD study series, 25–31% were seizure free while taking the first ASM at 1 year of treatment in the per-protocol analysis [4, 5, 36]. Nonetheless, our meta-analysis found that 80% of patients were able to achieve at least 1-year seizure freedom during the follow-up with subsequent regimens. This is a reflection of a current 'trial-and-error' approach of choosing ASMs and implies that some patients might have become seizure free sooner if they were given the 'right' drug at the outset [35]. A more reliable method to predict response is needed so that the most effective drug can be selected for an individual patient at the time of treatment initiation, potentially by using machine learning approaches [3].

Successful withdrawal of ASM treatment after achieving seizure freedom represents another favorable outcome of treated epilepsy. Being seizure free and off ASM treatment at the last follow-up was observed in 39% of patients in the studies included. Not surprisingly, this was observed in a higher proportion in patient cohorts with a longer follow-up duration. Studies with higher proportions of female patients were also noted to have higher proportions of ASM withdrawal. The reason for this is unclear, as only two studies provided the proportions of ASM withdrawal among male and female patients separately, showing no significant difference between the two sexes [37, 38]. Only three studies

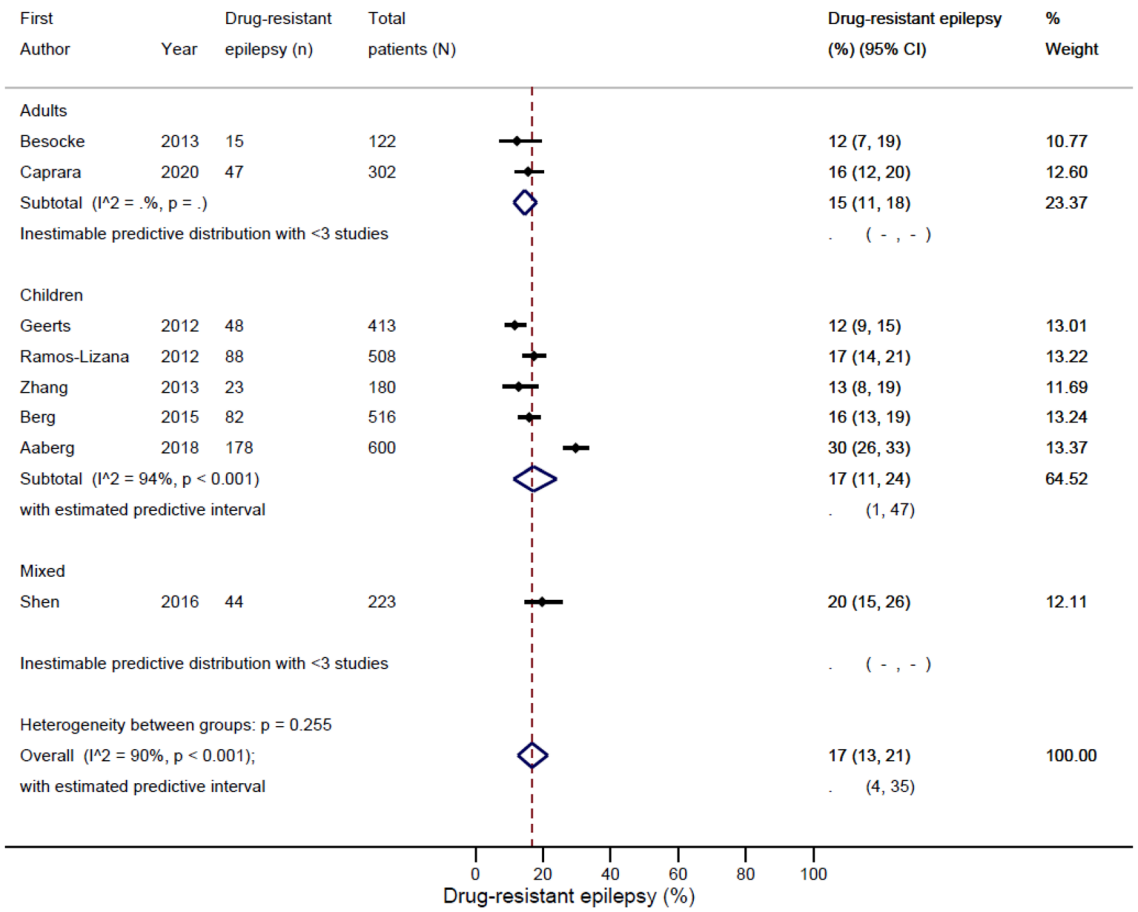

Fig. 7 Proportions of patients with drug-resistant epilepsy. *CI* confidence interval

provided clear and explicit durations of follow-up after ASM withdrawal, including two of childhood-onset epilepsy [9, 39] and one mixed cohort [37], making it difficult to determine whether the ASM withdrawal was 'successful'. One of these studies showed that 60.3% of the cohort had not been taking ASMs for 5 years at the last follow-up, thus providing a very optimistic prognosis of childhood epilepsy. However, another study showed 50% of patients relapse within 10 years after a ASM discontinuation trial with predictors including being adult, having abnormal neuroimaging, and symptomatic/cryptogenic etiology [37]. The probability of remission was 76% after relapse at 12 months. The decision of ASM withdrawal varies widely in clinical practice. In a survey of 186 respondents who had been seizure free for at least 5 years, only a third had discussed ASM withdrawal with their treating physicians [40].

At the other end of the spectrum of treatment outcomes is drug resistance, which was observed in 17% of patients in the seven studies included ($n = 2864$) that employed the ILAE consensus definition [14]. This is similar to the pooled estimate of 17% (95% CI 12–23) reported in a systematic review of the incidence of drug-resistant epilepsy that included 13 newly diagnosed cohorts and used varied definitions of intractability/remission [41]. The wide 95% PI and discrepancy with terminal seizure freedom likely arose because of indeterminate patients with fluctuating seizure control who may not have had an adequate or optimal trial of two tolerated drugs before the end of the follow-up. Although limited studies were reviewed in our meta-analysis, outcomes were not associated with the publication year or the earliest date of cohort recruitment. This is consistent with findings from the recent analysis from the Glasgow cohort that showed a similar probability of seizure freedom between patients who commenced treatment from 1982 to 2012 despite the increasing use of the newer ASMs over this time period [3].

We also explored separately prognostic variables of interest. In addition to the established favorable prognosis of idiopathic etiology over symptomatic etiology, recurring themes of prognostic factors influencing outcomes were noted amongst the studies in either a univariate or multivariate analysis. Epilepsy type (focal over generalized) [3, 16, 27, 42, 43], abnormal neuroimaging [44], and neurologic exam abnormality and epileptiform EEG [45,

46] were all negative predictors of outcomes after pooling. A high number of pre-treatment seizures [3, 20–22, 29, 44] and multiple seizure types [18, 20, 22, 47, 48] were also associated with negative remission outcome. Febrile seizures and family history were not noted to be predictors in our study.

This meta-analysis has limitations. First, studies of newly diagnosed epilepsy were excluded if they exclusively and selectively included only one or a limited epilepsy type, syndrome, or etiology. This was done as the objective of the study was to analyze specific outcomes as reported in the literature of observational studies in a broad heterogeneous group of newly diagnosed epilepsy for several pragmatic reasons. Including etiology, syndrome, or type-specific studies published would be impractical requiring multiple systematic searches, whilst selecting only a few selected etiologies or subgroups (for e.g., juvenile myoclonic epilepsy or autoimmune encephalitis-specific studies) would bias the pooled results towards those studies. It is important however to note that this meta-analysis does not ignore but rather incorporates all the many etiologies commonly seen in newly diagnosed epilepsy and provides data important in the early counseling process in community or hospital centers seeing such diverse patients. Second, the search strategy was designed to focus on studies that reported the primary outcomes in terms of cumulative and terminal seizure freedom. Therefore, the pooled estimates of the secondary outcomes might not be comprehensive. Third, given the variety of study settings, clinical practice, and patient characteristics, between-study heterogeneity was inevitably and expectedly present. This was reflected in the quantitative measure of I^2 as well as more intuitively by the PIs that showed a wide dispersion of effect sizes approximating 40–90% for the primary outcome measures of T1YSF and T5YSF and 50–95% for C1YSF. Statistical analysis of heterogeneity for each of the six outcomes was however limited to standardizable variables extractable owing to authors reporting predictor categorization in varied manners and according to a single preferred target outcome. We performed a separate random-effects meta-analysis for important predictors acknowledging some methodological assumptions and permitted outcome variables to be grouped into favorable or unfavorable. The results validate and demonstrate the association of several predictors identified in major observational studies with treatment-related outcomes in newly diagnosed patients. Fourth, response to any treatment is affected by adherence, which tends to be inconsistently reported in observational studies. Some studies did not report ASM adherence while others excluded patients with poor drug adherence. A few studies examined adherence as a prognostic factor [49–51], showing poor adherence as a negative marker of seizure freedom. Most studies were performed in high-income countries, with few in developing countries where the etiologies of epilepsy and clinical practice may differ substantially. Therefore, our findings may not be generalizable across the global epilepsy population.

Finally, although seizure-based outcomes remain of considerable importance, several domains in epilepsy care such as quality of life, cognitive function, mental health, and adverse events also remain of core importance to patients and carers. Treatment outcomes of these domains were not studied in this systematic review.

5 Conclusions

This systematic review of studies published in the past three decades showed, through assessment of a variety of seizure outcome measures, that seizure freedom is achieved with currently available ASMs in most patients with newly diagnosed epilepsy. It also validates several important predictors important for clinical practice on a meta-analysis level. Findings from this analysis may be used as a quantitative benchmark on the efficacy of future ASM therapy for this patient population. Future research should aim to increase the proportion of patients with early and sustained seizure freedom by choosing the 'right drug' at the first trial, develop novel therapies to overcome pharmacoresistance, and design disease-modifying treatments targeting specific disease mechanisms.

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Declarations

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Conflicts of Interest/Competing Interests MJ and HH are supported by the Monash University RTP Stipend scholarship. PP is supported by the National Health and Medical Research Council (APP1163708), the Epilepsy Foundation, The University of Melbourne, Monash University, Brain Australia, the Weary Dunlop Medical Research Foundation, and the Norman Beischer Medical Research Foundation and has received speaker honoraria or consultancy fees to his institution from Chiesi, Eisai, LivaNova, Novartis, Sun Pharma, Supernus, and UCB Pharma, outside the submitted work. He is an Associate Editor for Epilepsia Open. TJO is supported by an NHMRC Investigator Grant (APP1176426) and his institution has received research grants, speaker honoraria, or consultancy fees from Chiesi, Eisai, UCB Pharma, Zynerba Pharmaceuticals, ES Pharmaceuticals, Supernus, and LivaNova, outside the submitted work. ZC is supported by an Early Career Fellowship from the National Health and Medical Research Council of Australia (GNT1156444), and he/his institution has re-

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Ethics Approval No ethical approval was required for this study. All data were study-level characteristics and outcomes for a meta-analysis. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material All data extracted have been made available in the online supplementary material. Further cohort data information can be obtained through request to the corresponding author.

Code Availability Not applicable.

Authors' Contributions MJ was the first author involved in the design, systematic search protocol, conceptualization, screening, data extraction, quality rating, statistical contribution, and authoring of the manuscript. HH was involved in the screening, data extraction, quality rating, and editing of the manuscript. SO, LV, and SH were involved in the screening and editing of the manuscript. A-AB was involved in the design, quality rating, and editing of the manuscript. ZC was involved in the design, statistical analysis, and editing of the manuscript. PP and TO were involved in the editing of the manuscript. PK was the senior author in the conceptualizing, design, statistical contribution, and editing of the manuscript.

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