Alare *et al.*
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REVIEW

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Drug resistance predictive utility of age of onset and cortical imaging abnormalities in epilepsy: a systematic review and meta-analysis

Kehinde Alare[1,2*], Bridget Ogungbemi[1], Ayomide Fagbenro[1], Busayo Adetunji[1,2], Oladoja Owonikoko[1], Taiwo Omoniyo[1,2], Habiblah Jagunmolu[1,2], Ayomide Kayode[1,2] and Samson Afolabi[1,2]

Abstract

Background Drug resistance has been a global burden in the management of epilepsy. It is desirable if this could be predicted earlier in the course of management to give time for alternative and a more definitive mode of management, such as epilepsy surgeries.

Methods We conducted a systematic review and meta-analysis to investigate the relationship between elevated age at the onset of the first seizure or cortical imaging abnormalities and the development of drug resistance in epilepsy. We performed a systematic search in PubMed, EMBASE, and SCOPUS databases for studies investigating the predictive utility of age of onset or cortical imaging abnormalities on drug resistance.

Results Odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CIs) were extracted and analyzed by the RevMan 5.4 software. Meta-analysis was done across 12 studies involving 5315 patients. Age of onset of seizures younger than 5 years was found to be associated with the development of drug resistance (OR: 0.685, 95% CI 0.410–0.960), also cortical imaging abnormalities were found to be associated with the development of drug resistance.

Conclusion Children with early onset seizures could better from neurosurgical management than pharmacological management as the early age of onset was associated with drug resistance and cortical abnormalities on neuroimaging could be an indication for neurosurgical management of epilepsies.

Introduction

Epilepsy is one of the most well-known neurological chronic disorders, having an estimated prevalence of 0.5–1%. Presently, treatment choices for epilepsy are predominantly based on the presenting symptoms. Seizure control is achieved in most patients after the administration of initial two antiseizure medications. Consequently, patients who cannot achieve proper control of seizure after that are characterized as pharmacoresistant, refractory, or intractable [1]. However, despite the availability of more than 20 antiseizure medications (ASMs), about

*Correspondence:
Kehinde Alare
alarekehindepaul@gmail.com
[1] Department of Medicine, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria
[2] Ladoke Akintola University Medical Journal Club, College of Health Sciences, Ladoke Akintola University of Technology, P.M.B 4000, ILORIN Road, Ogbomoso, Oyo State, Nigeria

one-third of epilepsies remain drug-resistant [2]; the effects of this on the patients are adverse effects of the drugs the patients are being exposed to despite not offering therapeutic advantage on the progression of their disease states and also on the cost in purchasing those drugs. There is a need for an effective prognostic tool that would facilitate earlier and easier identification of patients who will be refractory to medication to be considered for neurosurgery.

The age of onset is the age of the patient when they notice the first symptoms of epilepsy [3]. In recent years, age of onset has been used in prognosticating some neurological conditions such as cancer, stroke, subarachnoid haemorrhage, gliomas, amyotrophic lateral sclerosis (ALS), acute neurological emergencies, and brain metastasis [4–10]. Also, cortical structural abnormalities such as sclerosis, cortical thinning, and other imagining abnormalities of the cerebral cortex especially those involving the temporal lobe have been reported in patients with refractory epilepsy [11, 12]. However, the association between age of onset or cortical structural abnormalities and clinical prognosis in the management of epilepsy and determination of refractory epilepsy has not been established. Hence, we will be carrying out a meta-analysis to analyze existing evidence and evaluate the relationship between age of onset, cortical structural abnormalities, and the development of refractory in epilepsy. If a meta-analysis is not possible then we will follow the SWiM guidelines [13].

Study aims

- To assess the independent relationship between the age of onset of the first seizure and the development of drug resistance.
- To assess the independent relationship between cortical abnormalities found on imaging and the development of drug resistance.
- To aid patient selection for neurosurgical management of epilepsies.
- To reduce the burden of drug resistance in epilepsy.

Methods

The protocol was conducted using Arksey and O'Malley's framework [14] and involved the five stages: (i) identify the research question, (ii) identify relevant studies, (iii) select studies, (iv) chart the data, and (v) collate, summarize and report the result.

Literature search

We performed a comprehensive literature search using the PubMed, SCOPUS, and EMBASE databases from inception till June 9, 2022. We searched the abstracts/titles/ keywords on these databases as follows: ((Age of onset) OR (Age at Inception)) AND ((Cortical Sclerosis) OR (Lobar Sclerosis) OR (Temporal Sclerosis) OR (Cortical Thinning) OR (Abnormal Cortical Imaging)) AND ((Pharmacoresistant Epil*) OR (Refractory Epil*) OR (Intractable Epil*) OR (Untreatable Epil*) OR (Uncontrollable Epil*))NOT ((Brain Tumor) OR (Stroke)). The Prisma flow diagram was generated using PRISMA2020 reported in Fig. 1 below [15].

Inclusion/exclusion criteria

We apply the standard PICO (Population, Intervention, Comparator, and Outcome) protocol with:

(a) P (population)—patients with epilepsy.
(b) I (intervention)—development of drug resistance epilepsy.
(c) C (comparator)—we searched for studies comparing patients with refractory and non-refractory epilepsy.
(d) O (Outcome)—an association between age of onset or cortical imaging abnormalities and DRE.

A study was included if it met the following criteria: (1) included patients with any type of seizure that has never undergone surgery; (2) evaluates the relationship between refractory as an outcome and age of onset; (3) evaluates the relationship between refractory as an outcome and cortical imaging abnormalities and (4) English language and full text available. Exclusion criteria were (1) review articles, expert opinions, letters, conference abstracts, case reports, or editorials; or (2) non-human subjects; (3) epilepsy secondary to surgery or (4) age of onset or cortical sclerosis used for diagnostic purposes and/or assessment of disease severity only.

Study selection

Duplicates were excluded in Mendeley (Elsevier, London, UK). The abstracts were screened independently by eight of the authors using Rayyan software. The abstracts were divided into four groups, and each group of abstracts was reviewed by a pair of authors, with a third author (KA) adjudicating any discrepancies. Full texts of potentially relevant studies were assessed (KA).

Data extraction

Data extraction was conducted independently by eight of the authors using a predesigned standardized data extraction proforma. The eligible full texts were divided into three groups, and data extraction from each group of full texts was performed by a pair of authors, with a third author adjudicating any discrepancies. The data extracted were title, author, year of publication, study design, study

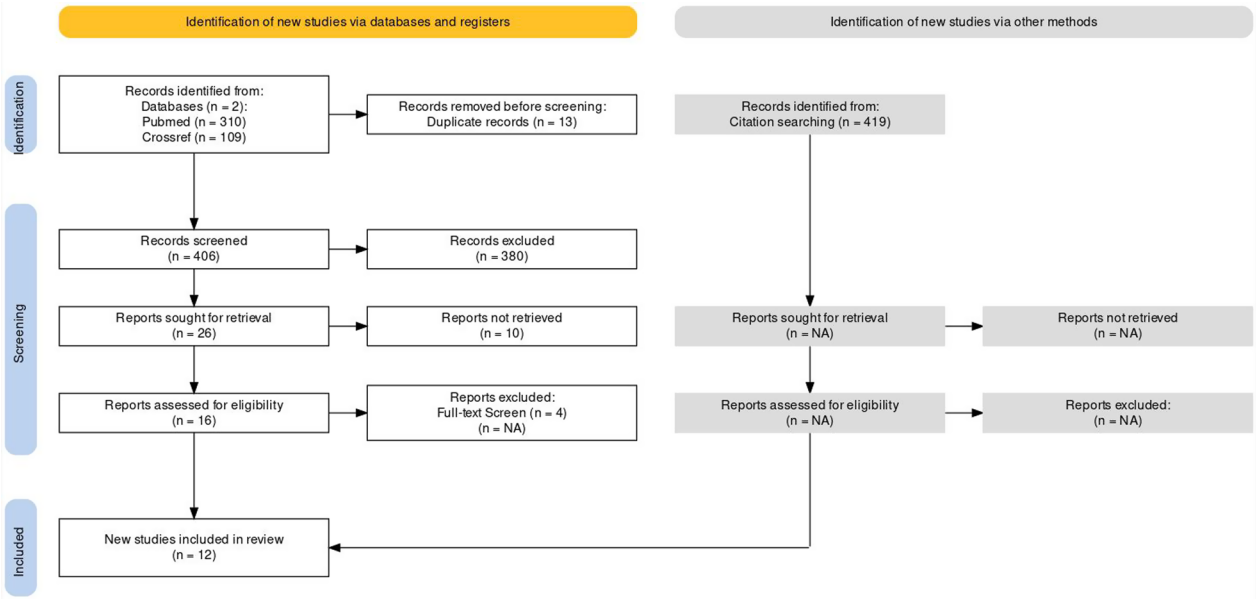

Fig. 1 PRISMA chart [15]

population (sample size, gender, age, average age of onset value, types of seizure, cortical involvement, part of cerebral cortex involved, treatment received, geographical location), inclusion criteria, exclusion criteria, exclusion of patients with post-surgical epilepsy, length of follow-up, the incidence of event/ non-event, event ratio (with 95% confidence interval), days of presentation from the initial onset of symptoms. Multivariate data were preferred to univariate data if both were provided. However, univariate data were acceptable if no multivariate results were presented.

Statistical analysis and data synthesis

For the studies that did not report event ratio or AUC, but provided individual patient data, we conducted multiple logistic regression analyses while adjusting for the variables controlled by the authors of those studies. Logistic regression analysis was conducted on IBM SPSS Statistics 27 (Windows).

We conducted meta-analyses using the Review Manager (RevMan) software (Version 5.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). Where meta-analysis was possible, for each outcome measure, extracted OR/HR and corresponding 95% confidence interval (CI) were pooled using the generic inverse-variance methods to evaluate the association between early age of onset and/or cortical imaging abnormalities with drug resistance in epilepsy. We evaluated heterogeneity among the studies using the Cochrane Q-statistic and I^2 statistic tests. A random-effects model was used to account for study heterogeneity. To identify and minimize heterogeneity, we conducted subgroup analyses of the studies that investigated similar outcome measures in patients with similar spine conditions/procedures.

For some outcome measures, only a few articles reported event ratio, hence conducting meta-analyses was not possible for these outcomes. Thus, a narrative synthesis using the SWiM reporting guideline was conducted for each outcome measure [15]. Based on difference measures between outcome event and non-event groups (event ratio, mean/median difference, p-values), we summarized the direction of the effect of age of onset and cortical imaging abnormalities on the outcome (development of drug resistance) and synthesized forest and funnel plots using Jamovi Software (Version 2.4) [16].

The Newcastle–Ottawa Scale (NOS) was used to evaluate the risk of bias in the included studies [17]. The risk of bias assessment was conducted independently by eight of the authors. The eligible full texts were divided into three groups, and the risk of bias assessment was performed by three authors, with a fourth author (KA) adjudicating any discrepancies. Studies with NOS scores of 0–3, 4–5, 6–7, and 8–9 were considered unsatisfactory, satisfactory, good quality and very good quality, respectively. We conducted sensitivity analysis by repeating our primary analysis after excluding the studies considered unsatisfactory or satisfactory (NOS scores: 0–5).

Results

Study selection

The search generated 419 results. A total of 13 duplicates were removed using Mendeley (Elsevier, London, UK), resulting in 406 unique studies. Following the abstract/title screening, 12 articles were found to meet our selection criteria. On full-text screening, four studies were excluded for not striking the relationship between age of onset or cortical imaging abnormalities with drug resistance. The full summary of findings of all included articles is provided in Additional file 1. In total, 12 studies consisting of 5315 patients were included. The characteristics of the included studies are shown in the table below (Table 1).

Description of included studies

Three studies were conducted in the United States of America [20, 23, 24]. There were two studies from Italy [21, 26], two from India [22, 29], two from Turkey [25, 28], one from China [18] one from Egypt [19], and one from Spain [26]. This review includes eight case–control studies [18–21, 25, 26, 28, 29], and four prospective cohort studies [22–24, 27].

All 12 studies evaluated the association between the age of onset and development of drug resistance [18–29],

Table 1 Characteristics of studies

Author	Year	Country	Study design	Medical condition	Types of seizures	Sample size	Mean age/ median age in years	Male-to-female ratio(M/F)
Chen [18]	2021	China	Retrospective case–control	Epilepsy	–	141	Mean (± SD) 33.49 (± 1.42)	89/52
Taghreed I [19]	2018	Egypt	Retrospective case–control	Refractory epilepsy	Partial seizure, generalized seizure, multiple seizure	186 93 case 93 control	Mean (± SD) 5.7 (± 3.0) refractory group 5.4 (± 2.9) responsive group	118/68
Jeong [20]	2017	USA and Belgium	Retrospective case–control	Epilepsy and tuberous sclerosis complex	Infantile seizure, focal seizure, others	1546	Median (IQR) 16 (9.6 – 25.5)	803/743
Gasparin Sara [21]	2013	Italy	Retrospective case–control	Cryptogenic focal epilepsy	–	186	Median (IQR) 25 (9–99)	105/81
Rawat [22]	2018	India	Prospective cohort	Epilepsy	–	1056	Median (IQR) 20 (5–67)	665/391
Berg [23]	2011	USA	Prospective cohort	Epilepsy	–	613	–	–
Berg [24]	2014	USA	Prospective cohort	Epilepsy	–	599	–	307/292
Karaoglu [25]	2021	Turkey	Retrospective case–control	Epilepsy	–	458	Mean (± SD) 7.37 (± 4.72)	248/210
Lattanzi [26]	2021	Italy	Retrospective case–control	Post-stroke epilepsy	Focal onset, focal to bilateral tonic–clonic, generalized, unknown	159	–	104/55
Ramos-Lizana [27]	2009	Spain	Prospective cohort	Epilepsy	Partial, generalized	343	Mean (± SD) 4.8 (± 3.8)	191/152
Ayca [28]	2019	Turkey	Retrospective case–control	Epilepsy	Generalized tonic–clonic, myoclonic	241	Mean (± SD) 7.00 (± 4.36) Intractable group 7.00 (± 4.36) Control group	130/111
Tripathi [29]	2011	India	Retrospective case–control	Intractable epilepsy and well-controlled epilepsy	Generalized, partial, myoclonic, other/ mixed	400 200 intractable 200 control	–	Case 142/58 Control 128/72

SD standard deviation, *IQR* interquartile range, *USA* United States of America

while five studies also evaluated the association between cortical imaging abnormalities and with development of drug resistance [18, 25, 27–29].

Association between age of onset and drug resistance

The 12 studies [18–29] involving 5315 patients investigated the association between age of onset and development of drug resistance in epilepsy patients. Four studies show a significant association between the age of onset of seizure lesser or equal to 1 year of age and the development of drug resistance [19, 20, 27, 28], a study reported the association between age of onset lesser or equal to 2 years and the development of drug resistance [23], another study stated a significant association between age of onset lesser than 5 years and development of drug resistance [22], also another reported that age of onset of seizure lesser than 14 years is associated with drug resistance [29], a study done in stroke patients with epilepsy reported that early age of onset of seizure in these patients was associated with the development of drug resistance [26], another study reported that early age of onset of seizure is generally associated with the development of drug resistance [25], while no association was found in two studies [18, 21]. Table 2 shows the findings of the studies.

After pooling the event ratios, we found that early age of onset (especially age of onset between 0 and 5 years) is significantly associated with development drug resistance (OR: 0.685, 95% CI 0.410–0.960), shown in Table 3. There was substantial between-study heterogeneity ($\tau^2 = 0.069$; $I^2 = 99.55\%$; $p < 0.001$) shown in Table 4. The forest plot and funnel plot are shown in Fig. 2A, B below.

Association between cortical imaging abnormalities and drug resistance

Five studies [18, 25, 27–29] involving 1,733 patients with a mean follow-up across the studies was 4.41 ± 2.32 years, investigated the association between cortical imaging abnormalities and the development of drug resistance in epilepsy patients. All five studies reported a significant association between cortical imaging abnormalities and the development of drug resistance [18, 25, 27–29], however multivariate analysis of one of the studies reveals no association [27] shown in Table 5. The forest and funnel plots are shown in Fig. 2C, D below. OR Odds Ratio, HR Hazard Ratio

Discussion

In this systematic review and meta-analysis, we evaluated the predictive utility of age of onset and/or cortical imaging abnormalities on drug resistance in epileptic patients. We found out that the early age of onset of seizures younger than five years especially in infants predicts later development of drug resistance in epilepsy. This finding is similar to other research, that focuses on cognitive performance, and a systematic review done among tuberous sclerosis patients with epilepsy [30–34]. While we did not find any significant relationship between the age of onset older than five years and the development of pharmacoresistant epilepsy, however, a study shows that the age of onset of seizure up to 9 years has a negative relationship with pharmacoresponsive epilepsy [35]. Younger age of onset of seizures is clinically associated with drug resistance [19, 20, 22–29]. Four of the studies set the threshold of the age of onset to 1 year [19, 20, 27, 28], a study set it at 2 years [24], another at 5 years [22], and another at 14 years [29], while other studies did not set a specific threshold.

Also, we found that the presence of abnormalities in cortical imaging can be used in predicting the development of drug resistance in epilepsy. This was in tandem with another study that reported neuroimaging abnormalities as an important risk factor for the development of drug resistance epilepsy [1], another also reported a similar finding [36]. Imaging abnormalities reported include epileptogenic structural lesions and other nonspecific lesions [29]; this is an independent indicator of drug resistance in epilepsy.

Drug resistance is defined in most included studies following the International League Against Epilepsy (ILAE). Villanueva and colleagues emphasized the unmet needs of patients with drug-resistant epilepsy and stated that predicting patients that will develop drug resistance will go a long way in meeting such needs [37]. This is a novel systematic review and meta-analysis that looks into a way of predicting drug resistance in epilepsy using the age of onset and neuroimaging abnormalities as two independent variables, to detect those that will develop resistance to antiepileptic drugs (AEDs) early and offer them other forms of therapy, especially neurosurgery.

Limitations

This review should be interpreted with consideration of certain limitations. Firstly, although most of the included studies had a low risk of bias, most of the studies were retrospective and single-centered, and due to the small number of studies per outcome measure, we were unable to formally assess the presence and effect of publication bias. Secondly, some relevant studies not written in the English language may be missed during the process of literature search. Also, being not specific with the cortical imaging abnormalities could affect our analysis but this may not be significant if a generalized association is found and since will be reporting the abnormalities included. There is a need to design more international prospective multicentre clinical trials to investigate the

Table 2 Effect of age of onset

Publication	Average age of onset	Length of follow-up	Age of onset threshold	No patients with/without an event	Event ratio (95% CI)	Inference
Taghred [19]	–	12 months	< 1 year > 1 year	Age of onset < 1 year: 70/40 > 1 year:23/53	OR: 4.0 $p < 0.001$	Age of onset lesser than 1 year is associated with an increased risk of drug resistance
Jeong [20]	Median (IQR): 5 (3–7.2) months	–	< 1 year > 1 year	650/896	OR 1.9 (1.4–2.5) $p < 0.001$	Age of onset of less than 1 year increases the risk of drug resistance
Rawat [22]	Median(IQR): 15 (0–56) months	12 months	5 years	581/475	OR 2.02 (1.31–3.13) $p = 0.0016$	Age of Onset younger than 5 years is associated with increased risk for drug resistance or recurrence
Chen [18]	Mean (SD) 22.18 (± 1.38)years	4–9 years	–	41/100	2.508 (0.270, 23.316) $p = 0.419$	Age of onset is not associated with drug resistance
Berg [23]	–	≥ 10 years < 10 years	2–5 years	205/311	–	–
Berg [24]	The group followed < 10 years: 7.0 (4.2) Group followed ≥ 10 years: 5.5 (4.1)	≥ 10 years < 10 years	–	347/266	Age of onset < 2 Hazard ratio: 1.000 Age of onset 2–5 Hazard ratio: 0.72 (0.48, 1.11) Age of onset 5–10 Hazard ratio: 0.78 (0.52, 1.18) Age of onset 10 + Hazard Ratio: 0.50 (0.30, 0.82)	Age of onset of less than 2 years increases the likelihood of drug resistance
Karaoglu [25]	Mean Drug-resistant: 1.85 years Drug receptive: 4.92 years	Median 46 months (range: 28–126 months)	–	177/281	$p < 0.001$ Univariate analysis	There is an association between the Early age of Onset and the development of drug-resistant epilepsy
Senem [28]	Range, intractable group: 0–1 Control group: 1–5	4 years	> 1 year < 1 year	61/180	Odd ratio Age < 1: 9.43 (3.66–24.30) 1–4 years: 1.79 (0.65–4.89) 5 and above: 1.04 (0.11–9.91) $p = 0.001$	Age of onset of less than one year was found to be associated with an increased risk for intractable seizure
Lattanzi [26]	Mean (± SD) Overall = 56.7 (± 14.9)years Refractory group = 52.1 (± 15.3) years Responsive group = 57.8 (± 14.7) years	Median (range) 5 (3–9) years	–	29/130	Multivariate OR = 0.97 $p = 0.044$	There is an association between younger age of stroke onset and the development of drug resistance post-stroke epilepsy
Ramos-Lizana [27]	4.8 years (± 3.8 SD) Mean used	Mean (± SD) (range) 76.2 (± 35.2 SD) month (24–139)	> 1 year	30/313	Univariate HR = 4.9 $p = 0.000$ Multivariate HR = 2.6 $p = 0.051$	Age of onset lesser than 1 year was found to be associated with refractory epilepsy with univariate analysis and almost associated with multivariate analysis

Table 2 (continued)

Publication	Average age of onset	Length of follow-up	Age of onset threshold	No patients with/without an event	Event ratio (95% CI)	Inference
Tripathi [29]	Mean(± SD): Case = 5.18 (± 7.62) Control = 5.62 (± 9.18)	–	< 14 years > 14 years	200/200	Multivariate analysis Age of onset < 14 OR = 3.09 + $p < 0.005$	There is an association between an age of onset of less than 14 years and the development of intractable epilepsy
Sara [21]	Mean ± SD 31 ± 21	Mean 9.4 years SD (4.2) Median 8.1 years range (5.0–23.1)	17 year	143/43	–	Age of onset does not predict drug resistance

OR odd ratio, *HR* hazard ratio

Table 3 Mixed-effects model ($k = 10$) of age of onset

	Estimate	SE	*Z*	*p*	CI lower bound	CI upper bound
Intercept	0.6849	0.1405	4.88	< 0.001	0.410	0.960
Moderator	−0.0430	0.0341	−1.26	0.207	−0.110	0.024

Tau^2 estimator: maximum-likelihood

Table 4 Heterogeneity statistics of age of onset

Tau	Tau^2	I^2	H^2	R^2	df	Q	*p*
0.253	0.0639 (SE = 0.0292)	99.55%	220.133	13.98%	9.000	3622.119	< 0.001

Table 5 Effect of cortical imaging abnormalities

Publication	Length of follow-up	Types of cortical imaging abnormalities	Numbers of patients with/without event	Event ratio 95% CI	Inference
Chen [18]	4–9 years	–	8/41	OR 6.838 (1.518,30.809) $p = 0.012$	Imaging abnormalities are associated with drug resistance
Karaoglu [25]	Median 46 months range (28–126 months)	–	Drug resistance 134/177 Drug receptive 108/281	OR 1.9 (0.71–5.05) $p = 0.0000$ multivariate	There is an association between MRI abnormalities and the development of drug-resistant epilepsy
Senem [28]	4 years	–	49/192	OR: 37.55 (16.41–85.94) $p = 0.000$	Abnormal imaging suggesting Cortical involvement was found to be associated with the development of intractable seizure
Ramos-Lizana [27]	Mean (± SD) (range) 76.2(± 35.2 SD) month (24–139)	–	30/313	Univariate analysis: HR = 5.0 + $p = 0.000$ Multivariate analysis: HR = 2.3 + $p = 0.693$	Multivariate analysis shows there is no relationship between abnormal cortical lesions and refractory epilepsy while univariate does
Tripathi [29]	–	Case: Known epileptogenic structural lesions (133) None (26) Nonspecific (41) Control: Known epileptogenic structural lesions(15) None (63) Nonspecific (122)	200/200	Univariate OR = 20.46 + $p < 0.05$ Multivariate OR = 20.47 + $p < 0.005$	There is an association between findings of cortical structural lesions on brain imaging and development of refractory epilepsy

OR Odds Ratio, *HR* Hazard Ratio

drug resistance predictive utilities of the age of onset and/or cortical imaging abnormalities in epilepsy and a possible risk assessment score could be created using other possible predictive factors.

Conclusion

In summary, our review suggests that the age of seizure onset of less than 5 years predicts drug resistance, especially the onset of seizure in children younger than 1 year of age. These children could better benefit from

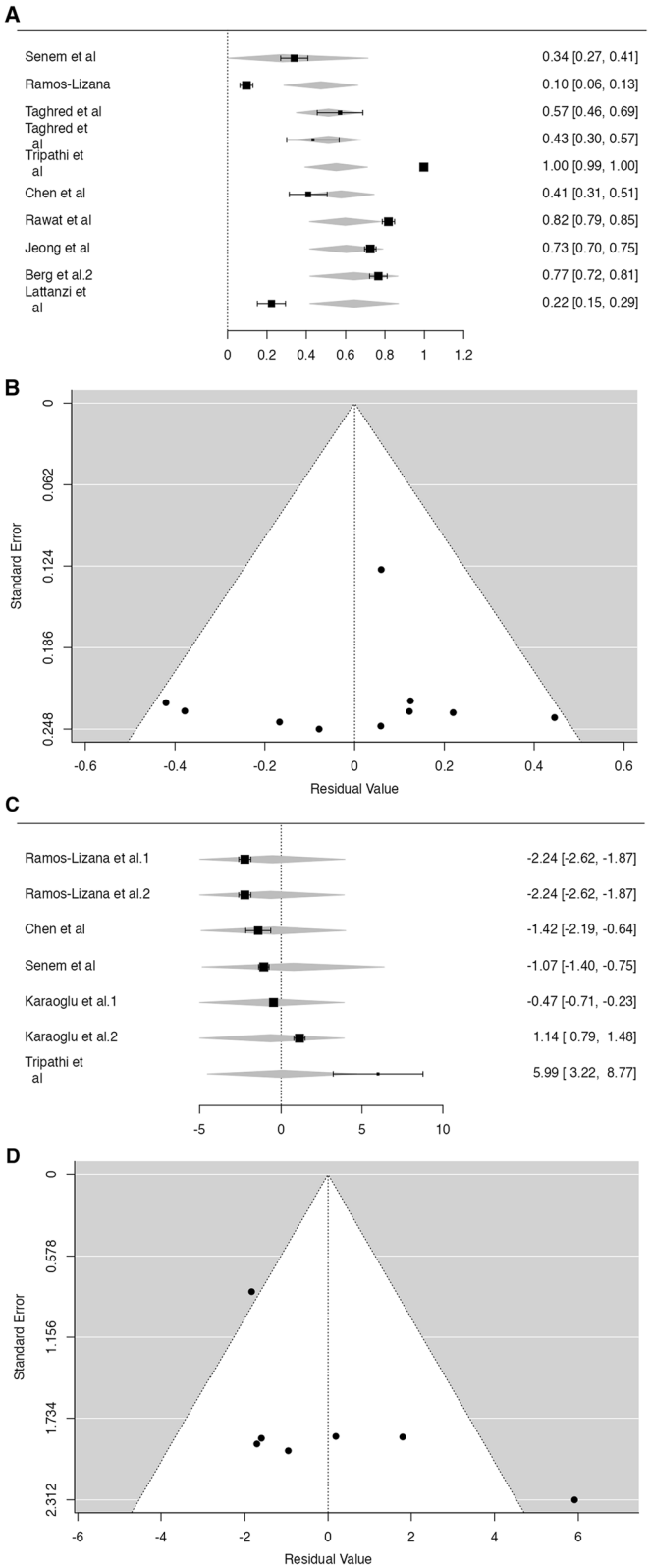

Fig. 2 **A** Forest plot of age of onset and drug resistance. **B** Funnel plot of age of onset and drug resistance. **C** Forest plot of cortical imaging abnormalities and drug resistance. **D** Funnel plot of cortical imaging abnormalities and drug resistance

neurosurgical management. The new onset of seizure in young adults or the elderly responds well to medical management. While the presence of any structural abnormalities on neuroimaging predicts drug resistance, a trial drug can be done in these patients while surgical management should be planned if not responsive. This will help in reducing the global burden of drug-resistant epilepsy.

Abbreviations

AEDs	Antiepileptic drugs
ASMs	Antiseizure medications
SD	Standard deviation
IQR	Interquartile range
USA	United States of America
NOS	Newcastle–Ottawa Scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41983-023-00786-5.

Additional file 1. Details of Data Extracted from included articles.

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Author contributions
KA contributed to the study's conception and design. Abstract/title screening, data extraction, and risk of bias assessment were performed by all the authors. Data analysis was performed by KA and all authors contributed to the interpretation of the results. The first draft of the paper was written by all authors, and all authors commented on the subsequent versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
Extracted data from the studies included in this review are presented in Additional file 1.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent to publication
Not applicable.

Informed consent
Not applicable for this systematic review.

Competing interests
The authors declare that they have no competing interests.

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