Systematic Review and Meta-Analysis

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# Risk factors for drug-resistant epilepsy

## A systematic review and meta-analysis

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**Abstract**

**Background:** Drug resistant epilepsy (DRE) is very common among children and adults and studies had found some related risk factors for DRE, while the results were not consistent. The aim of this study was to identify risk factors for drug-resistant epilepsy.

**Methods:** Three electronic databases (Medline, Embase and Cochrane library) were searched to identify studies with a cohort design reporting on epidemiologic evidence regarding risk factors for DRE.

**Results:** The pooled prevalence of DRE in newly diagnosed epilepsy patients was 25% (95% CI 17–32%). Abnormal electroencephalography (EEG) (both slow wave and epileptiform discharges) (RR 2.80; 95% CI 1.95–4.0), status epilepticus (SE) (RR 11.60; 95% CI 7.39–18.22), symptomatic etiology (RR 3.36; 95% CI 2.53–4.46), multiple seizure types (RR 3.66; 95% CI 2.37–5.64) and febrile seizures (RR 3.43; 95% CI 1.95–6.02) were identified as strong risk factors for DRE. In addition, firm conclusions cannot be drawn for poor short-term outcomes of therapy, neurodevelopment delay and high initial seizure frequency for the heterogeneity of study results. The predictive effect of focus onset seizure was not stable after removing one study and switching the effect model. Age of onset was not risk factors for DRE.

**Conclusions:** The current meta-analysis identified potential risk factors for DRE. The results may contribute to better prevention strategies and treatments for DRE.

**Abbreviations:** DRE = drug-resistant epilepsy, EEG = electroencephalogram, MTLE = mesial temporal lobe epilepsy, CI = confidence interval, RR = relative risk, AED = anti-epileptic drug, CNS = central nervous system, ILAE = International League against Epilepsy, MTLEHS = mesial temporal lobe epilepsy with hippocampal sclerosis.

**Keywords:** drug-resistant epilepsy, predictors, risk factors

## 1. Introduction

Epilepsy is one of the most common serious neurological disorders, and it is characterized by recurrent spontaneous seizures. Its prevalence ranges from 0.5% to 1% of the population in developed countries and even higher in developing countries.[1] According to the new International League against Epilepsy (ILAE) classification of epilepsy,[2] seizures are classified into focal onset, generalized onset, and unknown onset. In addition, the types of epilepsy include the well-established generalized epilepsy, focal epilepsy and a new category of combined generalized and focal epilepsy. This classification is helpful in choosing the appropriate anti-epileptic drugs (AED). Regardless of the etiology, suffering from recurrent seizures exposes patients to a variety of physical, psychological and social morbidities.[3] Thus, these consequences can be avoided to a large extent by the complete control of seizures.[4] Eliminating seizures is the ultimate goal of antiepileptic treatment. Therefore, most of the patients diagnosed with epilepsy are very likely to achieve good control of seizures with AED therapy,[5,6] unfortunately, a fraction of them are still suffering from seizures despite taking a range of AEDs in adequate doses either singly or in combination, and their seizures are also more frequently associated with intractability.

In fact, the definition of drug resistance has varied in different periods. In general, the existing definitions of drug-resistant epilepsy have focused on the numbers of failures in designing drugs, endpoint (e.g., seizure freedom or tolerable seizure frequency), and time consumed to achieve this endpoint.[7] Previous studies of remission have not directly addressed the development of intractability. Nearly 7% to 20% children have drug-resistant epilepsy.[8–10] Meanwhile, 30% to 40% of adult patients remain refractory to pharmacological treatment.[11–13]

In clinical practice, drug resistance can be identified only after the failure of several AEDs. It is hard to predict at diagnosis who will have the risk of developing intractable epilepsy, except for some epilepsy syndromes, such as West syndrome, Lennox–Gastaut syndrome and so on.[7] Many studies have addressed the predictors associated with medical refractoriness both in children and adults. The related risk factors for drug resistance are as follows: younger onset age, abnormal EEG findings and neurological deficits or mental retardation at the time of diagnosis, symptomatic etiology, high-frequency seizures, and

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non-response to the first AED.[10,14,15] However, due to differences in study design, demographics, definitions of DRE and follow-up duration, risk factors for predicting DRE remain unclear, and thus this clinical practice has been prevented.

Here a quantitative review of the available literature covering all seizure and epilepsy types was performed to assess the overall prevalence of DRE among newly diagnosed epilepsy patients and identify the factors better predicting drug resistance.

## 2. Materials and methods

Ethical approval was not necessary for the present study due to no patient involvement. The study was conducted in accordance with PRISMA (preferred reporting items for systematic reviews and meta-analyses)[16] and the MOOSE (meta-analysis of observational studies in epidemiology protocol) guideline.[17] The protocol used in this study was based on the Cochrane Review Methods (www.cochrane-handbook.org).

### 2.1. Search strategy

Both Medline (1976 to Dec 10, 2018), Embase (1982 to Dec 10, 2018) and Cochrane Library databases (1987 to Dec 10, 2018) for relevant studies with no language restriction using a predefined search method were searched. The keywords used in the search were "drug-resistant epilepsy/seizure, intractable epilepsy/seizure, refractory epilepsy/seizure, pharmacoresistant epilepsy/seizure, medical-intractable epilepsy/seizure, medication resistant epilepsy, drug refractory epilepsy" and "risk factors, predictive factors, predictors, outcome, prognosis and newly diagnosed epilepsy" (Table S1).

### 2.2. Inclusion criteria and definition of DRE

The inclusion criteria for the meta-analysis were as follows:

1. a focus on patients newly diagnosed with epilepsy who had never received antiepileptic drugs,
2. intractability, refractoriness, or drug-resistance of epilepsy as an outcome, and had the clear definition of DRE,
3. the objective of determining the predictive factors out of a larger number of candidate predictors,
4. assessment of independent predictive factors using a multivariable analysis and
5. the study must be a retrospective or prospective cohort study and have included all types of seizures and epilepsy.

Articles with insufficient data or irrelevant outcome, studies with a sample size of less than 50 patients and less than 1-year follow-up duration, and single case reports were excluded. There were no restrictions on the time of publication. Two authors independently evaluated the retrieved studies according to the selection criteria and manually reviewed the reference lists of retrieved articles to identify additional relevant studies. Discrepancies were resolved by discussion until consensus was reached.

According to the definition proposed by the ILAE,[14] DRE was defined as the failure of 2 well-tolerated, and appropriately chosen and used AED schedules, whether as mono-therapy or in combination, to achieve a sustained seizure freedom for either one year or for a period equal to 3 times of the pre-intervention inter-seizure time, whichever was longer. While earlier studies used the different definition of DRE, the responding definition of the included studies in this meta-analysis was listed in Table 1. The responding risk factors were different and we would present how the prognostic factors appear in each subgroup according to the definition of DRE.

### 2.3. Data extraction and quality assessment

Two reviewers (WXP and WHJ) independently extracted data using a standardized data abstraction form from eligible articles and assessed the risk-of-bias of the selected studies to ensure the reliability of the collected data. Any disagreement between the 2 investigators was resolved by discussion with the help of a third investigator (LL). If there were unavailable data or uncertain information in any of the included studies, the authors would be contacted.

A 9-star system based on the Newcastle-Ottawa Scale (NOS) was used to assess study quality.[18]

The extracted data include first author, publication year, country, study design, statistical method, population demographics, the definition of DRE, identified risk factors and information and [prevalence of DRE in patients with epilepsy, hazard ratio, risk ratio, odds ratio, and raw data to calculate the relative risk (RR)] to evaluate the DRE risk factors [e.g., gender, age of onset, the initial seizure frequency, etiology of epilepsy, seizure type, epilepsy type, developmental delay at diagnosis, perinatal complication, prior febrile seizures, history of SE at diagnosis, family history, abnormal imaging, EEG and short-term outcome of therapy].

### 2.4. Statistical analysis

The overall prevalence of DRE in epilepsy patients was assessed, and the RR for each risk factor for DRE was calculated. To assess the between-study heterogeneity, we calculated the Cochrane Q statistic. The $I^2$ statistic was used to quantify the magnitude of heterogeneity.[19] In the absence of statistically significant heterogeneity ($P_{hetero} > .1$, $I^2 < 50\%$), the pooled estimate and 95% confidence intervals (CIs) were calculated with a fixed-effects model.

A subgroup analysis was conducted based on the number of AEDs in the definition of DRE, that is, at least 3 AEDs vs at least 2 AEDs. Another subgroup analysis with different seizure free times was also conducted. Sensitivity analyses, in addition to the switching between fixed- and random-effects models, were conducted as follows: assessing the influence of a single study on the pooled estimate by eliminating 1 study each time. Potential publication biases were roughly assessed by visual inspection of funnel plots and further identified by Egger linear regression test. A $P$ value $< .05$ was considered statistically significant.

STATA version 12.0 (Stata Corp, College Station, TX) was used for the statistical analyses. A $P$ value $< .05$ was considered statistically significant.

## 3. Results

### 3.1. Literature search and selection

The process of the literature search and selection was depicted in the flow diagram (Fig. 1). A total of 8397 citations were initially retrieved. Among them, 8327 studies were removed by reviewing the title or abstract, leaving 70 studies to be reviewed by the full-text article. Of the 70 studies, 54 were eliminated for not meeting the inclusion criteria. For those 4 studies among the same populations, we selected the longest follow-up periods or the

**Table 1**

**Characteristics and quality assessment of included studies in the meta-analysis.**

| Study | Design | Country year | Type of analysis | N (include) | Follow-up | Gender (% male) | Age (yr) (range/ mean) | Predictive factors | N (%) DRE | Definition of DRE |
|---|---|---|---|---|---|---|---|---|---|---|
| Aaberg. K. M. 2018 (Aaberg et al 2018) | Prospective Population-based | Norway 1999-2009 | Log-binomial Regression analyse | 600 | >1 year 1–13 years | Not given | 3–13 years old | 1. having an identified cause 2. ≥3 seizure types 3. EEG: epileptic activity 4. neurologic or developmental difficulties | 178 (30%) | Seizures within the last year of follow-up despite adequate trials of at least 2 AEDs |
| Berg, A. 2001 (Berg et al 2001) | Prospective | US 1993-1997 | Cox proportional Hazards regression | 599 | Median 5 years | 53% | 0-15 years old | 1. symptomatic or cryptogenic generalized syndrome 2. Log seizure frequency 3. focal slowing 4. SE | 60 (10%) | intractability defined as failure, for lack of seizure control, of more than 2 first-line AED with an average of more than 1 seizure per month for 18 months and more than 3 consecutive months seizure-free during that interval |
| Boonluksiri, P. 2015 (Boonluksiri et al 2015) | Retrospective | Thailand 1998-2012 | Multivariant logistic regression | 308 | 6 months-15 years | 54.2% | <15 years old | 1. age onset <5 years old 2. abnormal initial EEG 3. prior neurological deficits | 129 (42%) | failure of adequate trial of 2 tolerated and appropriately chosen and used AED schedules whether as monotherapy or combination to achieve sustained seizure freedom |
| Geerts, A. T. 2010 (Geerts et al 2010b) | Prospective | Netherlands 1988-1992 | Binary log regression | 413 | Median 14.8 yr years | 47% | One month-16 years old | 1. non-idiopathic aetiology 2. no 3-month remission during the first 6 months of follow up 4. intractability in the first 5 years | 35 (8.5%) | No remission exceeding 3 months during a 1-year period of observation despite adequate treatment during that year and the years before. Adequate treatment was the optimal use of at least 2 AEDs, either alone or in combination |
| Hiritis, N. 2007 (Hitiris et al 2007) | Prospective | UK 1982-2001 | Multivariant logistic regression | 780 | 2.5–21 years | 52% | Media 31 years (9–93 years old) | 1. family history of epilepsy 2. febrile seizures 3. traumatic brain injury 4. recreational drug use 5. psychiatric comorbidity 6.≥10 pretreatment seizures | 318 (41%) | Response to treatment was defined as achieving seizure freedom for at least the last 12 months of follow-up. The remaining patients were labelled as having refractory epilepsy |
| Huang, L 2014 (Huang et al 2014) | Prospective | Shanghai China 1992-2006 | Multivariant logistic regression | 649 | Median 6.6 yr 3–19 years | 79% | <12 year | 1. neurodevelopment delay 2. symptomatic aetiology 3. partial seizure 4. more than 10 seizures before diagnosis | 119 (18%) | DRE was defined as failure, due to lack of seizure control, of more than 2 AEDs at maximum tolerated doses, with an average of more than 1 seizure per month for 24 months and no more than 3 consecutive months of seizure freedom during this interval |
| Ko, T. S. 1999 (Ko and Holmes 1999) | Retrospective | Boston | Multivariant logistic regression | 183 | At least 2 years | 51.4% | <18 years old | 1. diffuse slowing and focal spike wave | Not given | Continued seizures despite adequate trials of 3 or more AEDs, used either alone or in combination therapy |
| Kwong, K. L. 2003 (Kwong et al 2003) | Prospective | Hong Kong China <1997 | Multivariant logistic regression | 255 | At least 2 years | Not given | <15 years old | 1.abnormal neurodevelopment status 2. daily seizures before therapy 3. >3 breakthrough seizures in the second 6 months after treatment 4. Febrile seizure | 44 (14.2%) | have uncontrolled seizures that occurred with an average frequency of at least one seizure per month over an observational period of 2 years or more, despite treatment with at least 3 different AEDs, administered singly or in combination |
| Oskoui, M.2005 (Oskoui et al 2005) | Retrospective | Canada 1991-2000 | Multivariant logistic regression | 196 | 55±30 months (24–163 months) | 50% | 2–17 years old | 1. more than one seizure type 2. mental retardation 3. seizure recurrence in the 6- | 12 (6.9%) | seizures recurring at least monthly for more than a year associated with failure of at least 3 antiepileptic drugs at the time of final assessment |

(*continued*)

**Table 1**

**(continued).**

| Study | Design | Country year | Type of analysis | N (include) | Follow-up | Gender (% male) | Age (yr) (range/ mean) | Predictive factors | N (%) DRE | Definition of DRE |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | to 12-month interval after initiating therapy | | |
| Zhang, Y. 2013 (Zhang et al 2013) | Prospective | China 2000-2010 | Multivariant logistic regression | 180 | Median 5 years (2–10 years) | 52.2% | Medium 19 years old (6–71 years old) | 1. multiple seizure types 2. changes in seizure type during treatment | 23 (12.8%) | failure of 2 well-tolerated, and appropriately chosen and used AED schedules, whether as monotherapy or in combination, to achieve a sustained seizure freedom for either one year or for a period equal to 3 times of the pre-intervention interseizure time, whichever was longer |
| Ramos-Lizana, J. 2009 (Ramos-Lizana et al 2009) | Prospective | Spain 1994-2004 | Cox proportional Hazards regression | 343 | Mean 76.2 months (24–239 months) | 56% | <14 years old | 1. >1 seizure during the first 6 months after diagnosis | 30 (8.7%) | refractory epilepsy: failure of >2 drugs plus >1 seizure/month for 18 months |
| Saygi, S. 2014 (Saygi et al 2014) | Retrospective | Turkey 2000-2008 | Multivariant logistic regression | 241 | 2.6±1.4 year for control 3.1±1.6 year for DRE | 58.1% | One month-18 years old | 1. symptomatic aetiology 2. high (daily) initial seizure frequency | 28 (11.6%) | Inadequate seizure control despite therapy with at least 3 AEDs at maximally tolerated doses for 1–2 years |
| Seker Yilmaz, B. 2013 (Seker Yilmaz et al 2013) | Retrospective Population-based | Turkey | Multivariant logistic regression | 408 | At least 2 years | Not given | Children Not clarified | 1. previous history of SE 2. abnormal EEG results 3. multiple seizures in one day | 200 (49%) | continued seizures in children despite adequate therapy with 2 or more antiepileptic drugs for more than 18 months |
| Sillanpaa, M. 1993 (Sillanpaa 1993) | Prospective Population-based | Finland 1961-1964 | Multivariant logistic regression | 178 | 23–39 years | Not given | ≤15 years old 3.1±1.6 | 1. poor short-term outcome of AED 2. occurrence of SE 3. high initial seizure frequency 4.remote symptomatic aetiology | 40 (22.5%) | Annual seizures for at least the last 10 years with no more than 1 year of accidental seizure freedom |
| Wirrell, E. 2012 (Wirrell et al 2012) | Retrospective Population-based | Olmsted country 1980-2009 | Multivariant logistic regression | 127 | Median 78 months | 51.2% | ≤36 months | 1. age ≤12 months at diagnosis 2. developmental delay at initial diagnosis 3.neuro-imaging abnormality 4. focal slowing on initial EEG | 44 (35%) | either (1) seizures greater than every 6 months at final follow-up and failure of 2 or more AEDs for lack of efficacy, or (2) having undergone epilepsy surgery after failure of 2 or more AEDs |
| Yildiz, E. 2018 (Yildiz et al 2018) | Retrospective | Turkey | Multivariant logistic regression | 229 | At least 2 years (25–130 months) | 48% | 1–24 months | 1. developmental delay at onset 2. EEG pattern of multifocal epileptiform discharges 3. history of SE | 140 (61%) | failure of 2 or more AEDs with seizure frequency of more than one every 6 months in the year immediately before final follow-up |

AED = antiepileptic drug, SE = status epilepticus, EEG = electroencephalogram, yr = year.

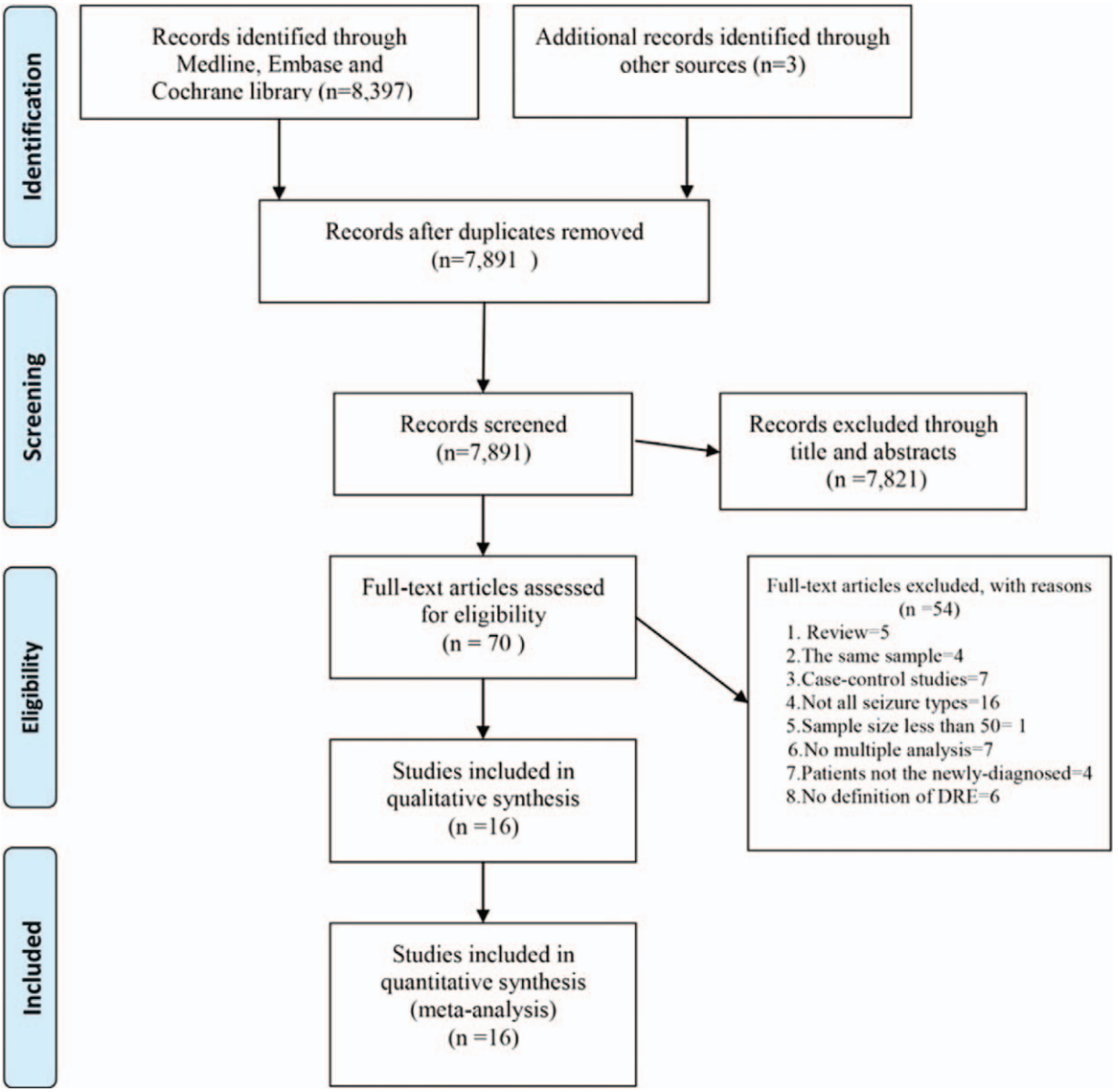


**Figure 1.** Flowchart of the literature search performed. DRE = drug resistant epilepsy.

biggest sample size. Eventually, 16 studies were included in the final meta-analysis.

### 3.2. Study characteristics and quality

The general characteristics and details of the included studies published between 1993 and 2018 are summarized in Table 1. The outcome "intractability" was defined by 2 or 3 antiepileptic drugs (AEDs), seizure frequency, and seizure-free periods. Four studies were conducted in Asian countries, with 3 from China[20–22] and 1 from Thailand.[23] Four cohort studies were population-based,[24–27] whereas all other cohorts were hospital-based. The sample size among the studies varied from 127 to 780, with a total of 5689 participants, duration of follow-up from at least 1 year up to 39 years, and the proportion of intractable cases 6.9% to 61%. DRE was developed in 1400 cases (24.6%). Fourteen cohorts included only children (the youngest was 1 month), 2 cohorts were patients of all ages, and no study was just for adults. The 16 studies included 9 prospective analyses[20–22,25–30] and 7 retrospective analyses.[23,24,31–35]

The NOS scores of the included studies are summarized in Table S2, http://links.lww.com/MD/D136, and they ranged from 5 to 9 with a mean of 7.25.

### 3.3. Pooled prevalence of DRE in newly diagnosed epilepsy patients

The included studies reported the prevalence of DRE in epilepsy patients ranging from 6.9% to 61%, with a high level of heterogeneity between the 15 studies ($P_{hetero} = .01$, $I^2 = 98.3\%$), as one study did not supply the prevalence of DRE.[32] According to the random-effects model, the pooled prevalence of DRE in epilepsy patients was 25% (95% CI 17–32%) (Fig. 2A). DRE was assessed using the definition of 2 AEDs in 10 studies, and the

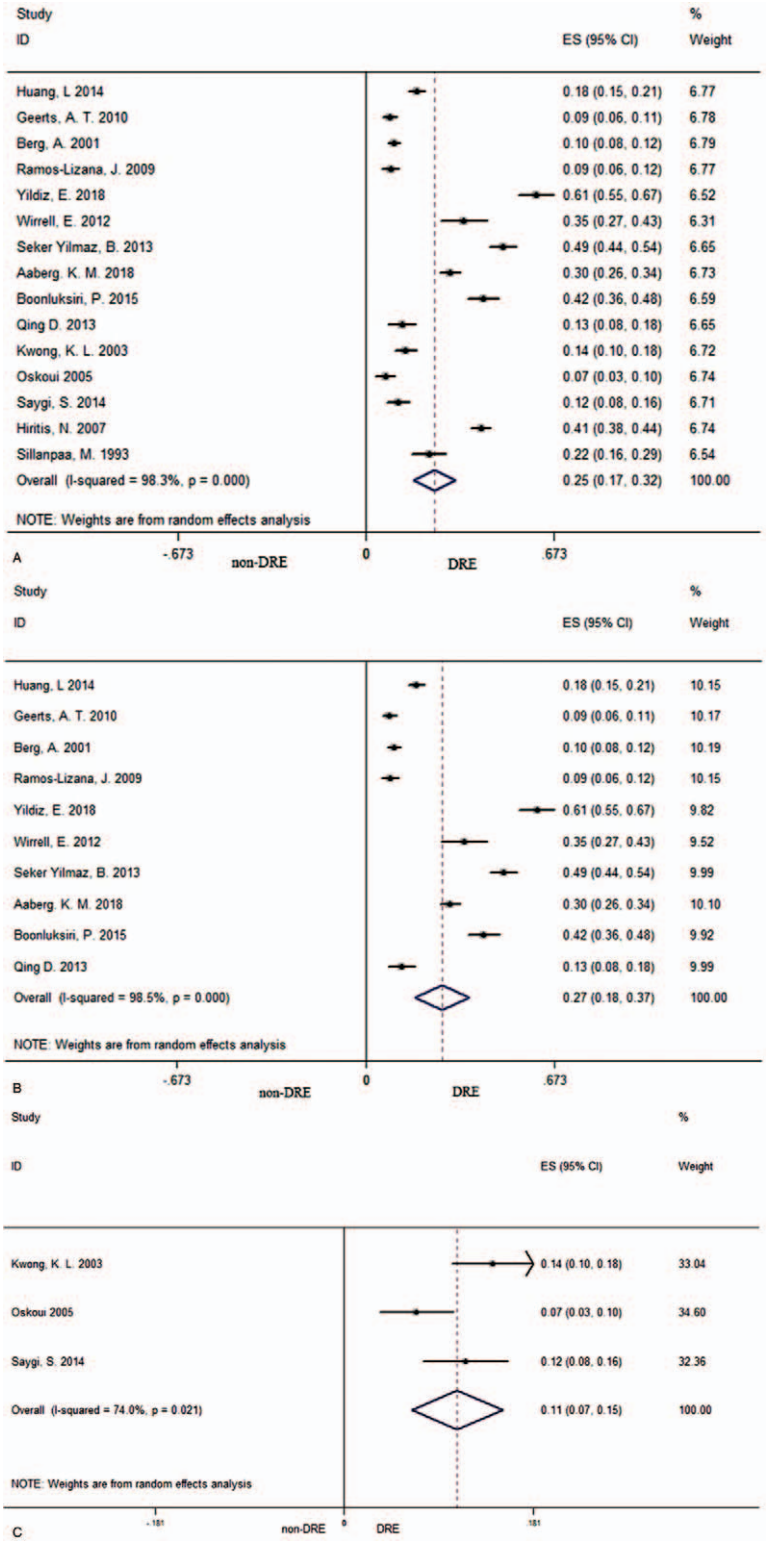


**Figure 2.** A. The pooled prevalence of DRE regardless of the number of AEDs. DRE = drug resistant epilepsy, AED = antiepileptic drug. B. The pooled prevalence of DRE by 2 AEDs. DRE = drug resistant epilepsy, AED = antiepileptic drug. C. The pooled prevalence of DRE by 3 AEDs. DRE = drug resistant epilepsy, AED = antiepileptic drug.

**Table 2**

**Pooled analyses of risk factors for drug-resistant epilepsy.**

| Risk factors | No. of studies | $I^2$ (%) | $P_{hetero}$ | *P* value | Fixed RR (95% CI) | Random RR (95% CI) |
|---|---|---|---|---|---|---|
| Age of onset | 2 | 88.9 | .000 | .187 | 0.91 (0.81–1.04) | 1.90 (0.73–4.91) |
| Symptomatic aetiology | 7 | 8.4 | .364 | .000 | 3.36 (2.53–4.46) | 3.36 (2.53–4.46) |
| EEG abnormality | 7 | 0.0 | .959 | .000 | 2.80 (1.95–4.0) | 2.80 (1.95–4.0) |
| Slowing on initial EEG | 3 | 0.0 | .627 | .000 | 2.65 (1.55–4.52) | 2.65 (1.55–4.52) |
| Epileptic activity | 4 | 0.0 | .917 | .000 | 2.92 (1.80–4.74) | 2.92 (1.80–4.74) |
| Status epilepticus | 4 | 0.0 | .436 | .000 | 11.60 (7.39–18.22) | 11.60 (7.39–18.22) |
| Focus onset seizures | 3 | 0.0 | .394 | .394 | 2.24 (1.63–3.08) | 2.24 (1.63–3.08) |
| Neurodevelopment delay | 6 | 81.8 | .000 | .000 | 3.99 (2.82–5.64) | 6.05 (2.51–14.58) |
| High initial seizure frequency | 7 | 90.3 | .000 | .000 | 1.76 (1.57–1.98) | 3.73 (2.13–6.53) |
| Daily seizure frequency | 3 | 93.5 | .000 | .046 | 3.15 (2.15–4.63) | 6.402 (1.03–39.61) |
| >10 seizures | 4 | 87.4 | .000 | .000 | 1.66 (1.47–1.88) | 2.85 (1.61–5.04) |
| Multiple seizure type | 3 | 0.0 | .719 | .000 | 3.66 (2.37–5.64) | 3.66 (2.37–5.64) |
| Febrile seizures | 3 | 0.0 | .820 | .000 | 3.43 (1.95–6.02) | 3.43 (1.95–6.02) |
| Poor short-term outcome of therapy | 4 | 70 | .018 | .000 | 8.20 (4.57–14.72) | 10.14 (3.28–31.41) |

EEG = electroencephalogram.

heterogeneity across the studies was high ($P_{hetero}$ = .00, $I^2$ = 98.5%). Using a random-effects model, the pooled prevalence of DRE in epilepsy patients was 27% (95% CI 18–37%) (Fig. 2B). The other 3 papers defined DRE by 3 AEDs, and heterogeneity across the studies was still high ($P_{hetero}$ = .021, $I^2$ = 74%), Using a random-effects model, the pooled prevalence of DRE in epilepsy patients was 11% (95% CI 7–15%) (Fig. 2C). However, 2 studies did not state the number of AEDs for the definition of DRE.[26,30]

### 3.4. Risk factors for DRE

The RR and 95% CI for DRE of each predictive factor and the heterogeneity of the eligible studies are shown in Table 2 and Fig. 3.

Abnormal EEG (both slow wave and epileptiform discharges) (RR 2.80; 95% CI 1.95–4.0), status epilepticus (RR 11.60; 95% CI 7.39–18.22), focus onset seizure (RR 3.63; 95% CI 1.71–7.74), symptomatic etiology (RR 3.36; 95% CI 2.53–4.46), multiple seizure types (RR 3.66; 95% CI 2.37–5.64) and febrile seizures (RR 3.43; 95% CI 1.95–6.02) were identified as strong risk factors for DRE. When we analyzed EEG slow wave and epileptiform discharges separately, they were also risk factors for DRE (slow wave: RR 2.65; 95% CI 1.55–4.52; epileptiform discharges: RR 2.92; 95% CI 1.80–4.75). In addition, the predictive value of poor short-term outcomes of therapy (RR 10.14; 95% CI 3.28–31.41), neurodevelopment delay (RR 6.05; 95% CI 2.51–14.58), and high initial seizure frequency (RR 3.73; 95% CI 2.13–6.53) was not firm where heterogeneity of them was high. In contrast, age of onset (RR 1.90; 95% CI 0.73–4.91) did not predict the incidence of DRE.

### 3.5. Subgroup analysis

Substantial heterogeneity of the effect estimates between studies was observed for poor short-term outcomes of therapy, neurodevelopment delay, and high initial seizure frequency. Subgroup analysis of "high initial seizure frequency", 3 studies defined it as daily seizures (RR 6.40; 95% CI 1.03–39.61, *P* = .000), while 4 studies referred to seizures more frequent than 10 times (RR 2.85; 95% CI 1.61–5.04, *P* = .000), and they were still had high heterogeneity.

When only combining results from studies defined DRE with at least 2 AEDs, the pooled estimate for neurodevelopment delay still had heterogeneity ($P_{hetero}$ = .000, $I^2$ = 81.3%), but it was statistically significant from both fixed- (RR = 3.52, 95% CI 2.46–5.05, *P* = .001) and random-effects models (RR = 4.93, 95% CI 1.99–12.19, *P* = .002). For high initial seizure frequency, there was no heterogeneity ($P_{hetero}$ = .233, $I^2$ = 29.9%), and the pooled estimate was statistically significant using both fixed- and random-effects models (RR = 4.43, 95% CI 2.88–6.81, *P* = .000; RR = 4.65, 95% CI 2.70–8.01, *P* = .000, respectively). For poor short-term outcomes of therapy, there was no heterogeneity ($P_{hetero}$ = .700, $I^2$ = 0%), and the pooled estimate was statistically significant using both fixed- and random-effects models (both: RR = 4.21, 95% CI 2.03–8.73, *P* = .000). While combining results from studies defined DRE with at least 3 or other number of AEDs, there was only 1 study for neurodevelopment delay. For high initial seizure frequency, the pooled estimate was statistically significant using both fixed- and random-effects models (RR = 1.64, 95% CI 1.45–1.85, *P* = .000; RR = 3.02, 95% CI 1.47–6.20, *P* = .003, respectively) with high heterogeneity ($P_{hetero}$ = .000, $I^2$ = 93.8%). For poor short-term outcomes of therapy, and the pooled estimate was statistically significant using both fixed- and random-effects models (both: RR = 27.35, 95% CI 10.26–72.87, *P* = .000) without heterogeneity ($P_{hetero}$ = .357, $I^2$ = 0%), (Table 3).

In the subgroup analysis of seizure-free time, a significant difference was seen in studies defined DRE with 1 year seizure free time using both fixed- and random-effects models for neurodevelopment delay (RR = 4.51, 95% CI 2.89–7.05, *P* = .000; RR = 6.48, 95% CI 1.91–21.96, *P* = .003, respectively) and poor short-term outcomes of therapy (RR = 9.52, 95% CI 4.58–19.79, *P* = .000; RR = 10.06, 95% CI 2.28–44.43, *P* = .002, respectively), compared to studies defined DRE with more than one year seizure free time, but both had significant heterogeneity ($P_{hetero}$ = .000, $I^2$ = 83.4%; $P_{hetero}$ = .043, $I^2$ = 75.5%, respectively). In contrast, for high initial seizure frequency, a significant different was seen in studies defined DRE with more than 1 year seizure free time with high heterogeneity from both fixed- and random-effects models ($P_{hetero}$ = .012, $I^2$ = 65.7%; RR = 2.75, 95% CI 2.19–3.47, *P* = .001; RR = 3.24, 95% CI 2.05–5.14, *P* = .000, respectively) (Table 4).

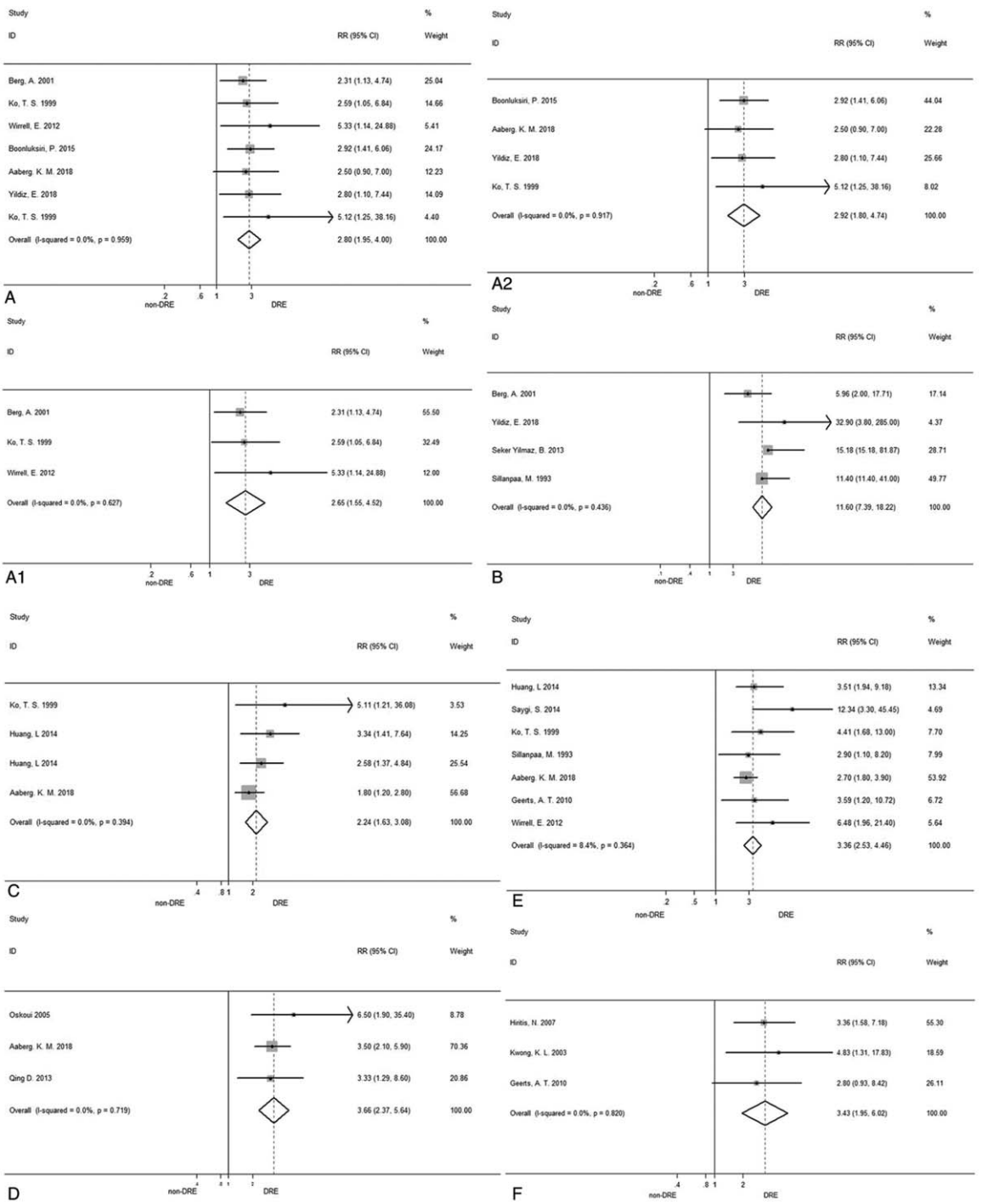


**Figure 3.** A. Pooled results of EEG abnormality for DRE, EEG = electroencephalogram. A-1. Pooled results of EEG slow wave for DRE, EEG = electroencephalogram. A-2. Pooled results of EEG epileptiform discharges for DRE, EEG = electroencephalogram. B. Pooled results of SE for DRE, SE = status epilepticus. C. Pooled results of focus onset seizure for DRE. D. Pooled results of multiple seizure type for DRE. E. Pooled results of symptomatic aetiology for DRE. F. Pooled results of febrile seizures for DRE. G. Pooled results of poor short-term outcome of therapy for DRE. H. Pooled results of neurodevelopment delay for DRE. I. Pooled results of high initial seizure frequency for DRE. I-1. Pooled results of daily seizures for DRE. I-2. Pooled results of seizures more frequent than 10 times for DRE. L. Pooled results of age of onset for DRE. DRE = drug resistant epilepsy.

### *3.6. Sensitivity analysis*

The variation and range of the pooled RRs after switching effect model from the meta-analysis were listed in Table 2.

The variation and range of the pooled RRs after removing a single study from the meta-analysis and repeating the process multiple times are listed in Table S3, http://links.lww.com/MD/D136, and no change in the result for symptomatic etiology, EEG abnormality, status epilepticus, multiple seizure type, and febrile seizures. For focus onset seizure, its significant changed after removing 1 study and switching the effect model. Thus, the

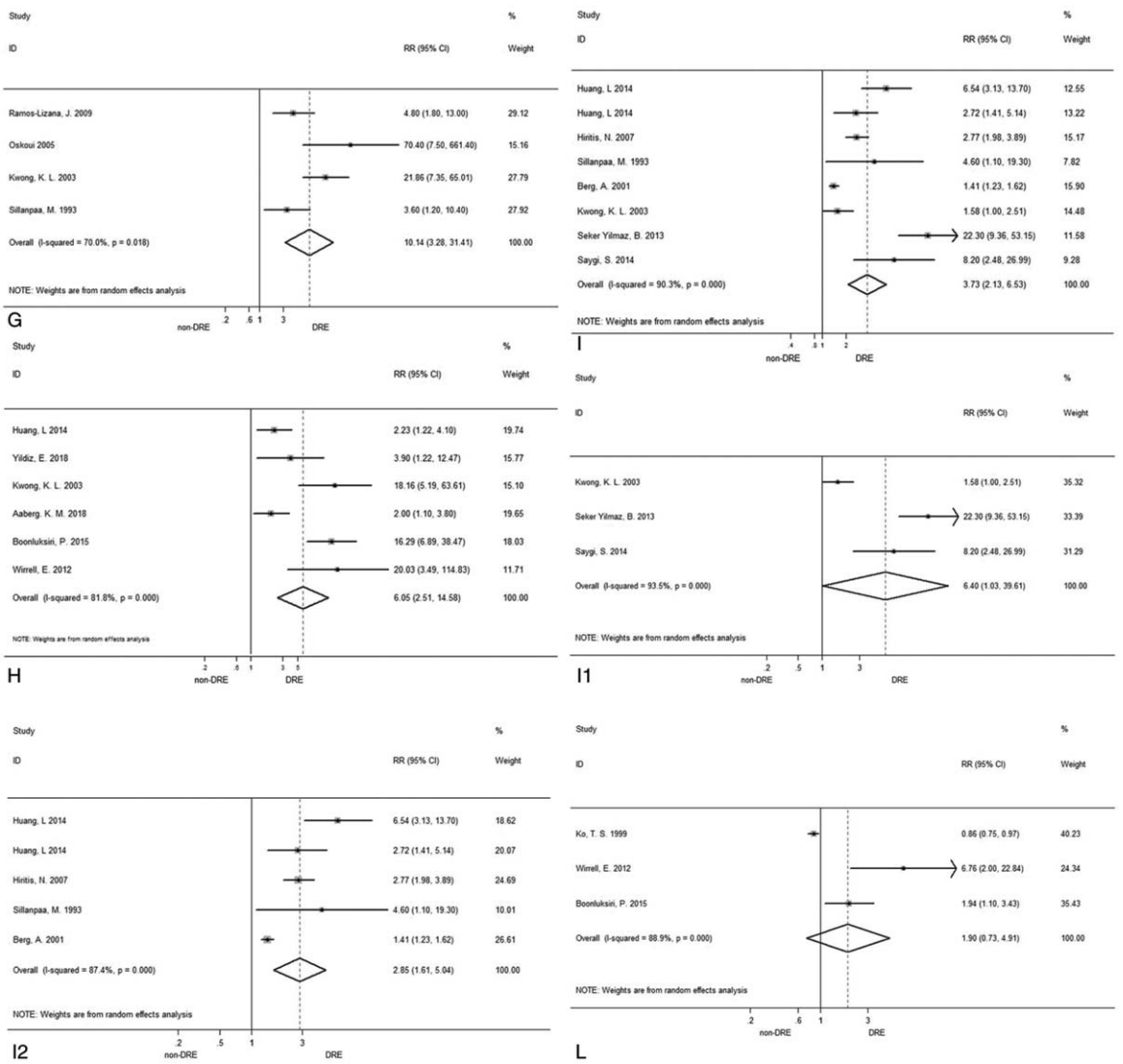


**Figure 3.** (Continued).

predictive effect of focus onset seizure was not stable and we should be cautious. The pooled RRs of high initial seizure frequency, neurodevelopment delay and poor short-term outcomes of therapy had significance, while there still existed high heterogeneity not matter which studies was removed.

### 3.7. Publication bias

Publication bias was assessed by visual inspection of the funnel plots, and no distinct asymmetry was found (Fig. 4). The Egger linear regression test indicated that those defined by both 2 and 3 AEDs or 2 AEDs ($P = .789$, and .659, respectively) had no

**Table 3**

**Overall and subgroup analysis by number of AEDs in the definition of DRE.**

| Subgroup | Risk factors | No. of studies | $P_{hetero}$ | $I^2$ (%) | Fixed RR (95% CI) | Random RR (95% CI) |
|---|---|---|---|---|---|---|
| Overall | neurodevelopment delay | 6 | .000 | 81.8 | 3.99 (2.82–5.64) | 6.05 (2.51–14.58) |
| | high initial seizure frequency | 7 | .000 | 90.3 | 1.76 (1.57–1.98) | 3.73 (2.13–6.53) |
| | poor short-term outcomes of therapy | 4 | .018 | 70 | 8.20 (4.57–14.72) | 10.14 (3.28–31.41) |
| 2 AEDs | neurodevelopment delay | 5 | .000 | 81.3 | 3.52 (2.46–5.05) | 4.93 (1.99–12.19) |
| | high initial seizure frequency | 3 | .233 | 29.9 | 4.43 (2.88–6.81) | 4.65 (2.70–8.01) |
| | poor short-term outcomes of therapy | 2 | .700 | 0 | 4.21 (2.03–8.73) | 4.21 (2.03–8.73) |
| 3 and other number AEDs | neurodevelopment delay | 1 | – | – | – | – |
| | high initial seizure frequency | 4 | .000 | 93.8 | 1.64 (1.45–1.85) | 3.02 (1.47–6.20) |
| | poor short-term outcomes of therapy | 2 | .357 | 0 | 27.35 (10.26–72.87) | 27.35 (10.26–72.87) |

AED = antiepileptic drugs, DRE = drug resistant epilepsy.

**Table 4**

**Overall and subgroup analysis by seizure free time in the definition of DRE.**

| Subgroup | Risk factors | No. of studies | $P_{hetero}$ | $I^2$ (%) | Fixed RR (95% CI) | Random RR (95% CI) |
|---|---|---|---|---|---|---|
| Overall | neurodevelopment delay | 6 | .000 | 81.8 | 3.99 (2.82–5.64) | 6.05 (2.51–14.58) |
| | high initial seizure frequency | 7 | .000 | 90.3 | 1.76 (1.57–1.98) | 3.73 (2.13–6.53) |
| | poor short-term outcomes of therapy | 4 | .018 | 70 | 8.20 (4.57–14.72) | 10.14 (3.28–31.41) |
| 1 year | neurodevelopment delay | 4 | .000 | 83.4 | 4.51 (2.89–7.05) | 6.48 (1.91–21.96) |
| | high initial seizure frequency | 2 | .000 | 97.4 | 1.51 (1.32–1.73) | 5.42 (0.36–80.99) |
| | poor short-term outcomes of therapy | 2 | .043 | 75.5 | 9.52 (4.58–19.79) | 10.06 (2.28–44.43) |
| More than 1 year | neurodevelopment delay | 2 | .003 | 88.5 | 3.32 (1.92–5.72) | 5.91 (0.76–45.88) |
| | high initial seizure frequency | 5 | .012 | 65.7 | 2.75 (2.19–3.47) | 3.24 (2.05–5.14) |
| | poor short-term outcomes of therapy | 2 | .019 | 81.8 | 6.31 (2.38–16.68) | 13.45 (0.74–243.22) |

AED = antiepileptic drugs, DRE = drug resistant epilepsy.

publication bias for overall prevalence of DRE. Publication bias for DRE as defined by 3 AEDs or risk factors of DRE was not assessed due to the small number of included studies (far less than 10).

## 4. Discussion

The prevalence and predictors of DRE had been reported in some papers, and some of them were confirmed by our review. We found that approximately 25% of newly diagnosed epilepsy patients had a risk to be intractable regardless of children or adults based on the 15 included studies (as one did not offer the prevalence of DRE).[32] The new definition of DRE was termed by 2 AEDs according to the 2010 ILAE commission, so the related prevalence would be 27% from our result. Two studies did not tell us the exact number of AEDs used for DRE.[26,30] Only 3 studies defined DRE with 3 AEDs, and their pooled prevalence was 11%, which was lower. According to this therapeutic principle, patients will take longer time to become drug-resistant in the studies defined DRE with 3 AEDs and the incidence of DRE is also lower than those defined DRE with 2 AEDs during the same follow-up periods. Some studies in our meta-analysis reported a higher prevalence of DRE as a result of younger sample age and longer follow-up time. A community-based study in southern France estimated that up to 22.5% of patients with epilepsy had drug-resistant epilepsy,[36] which was similar to our review.

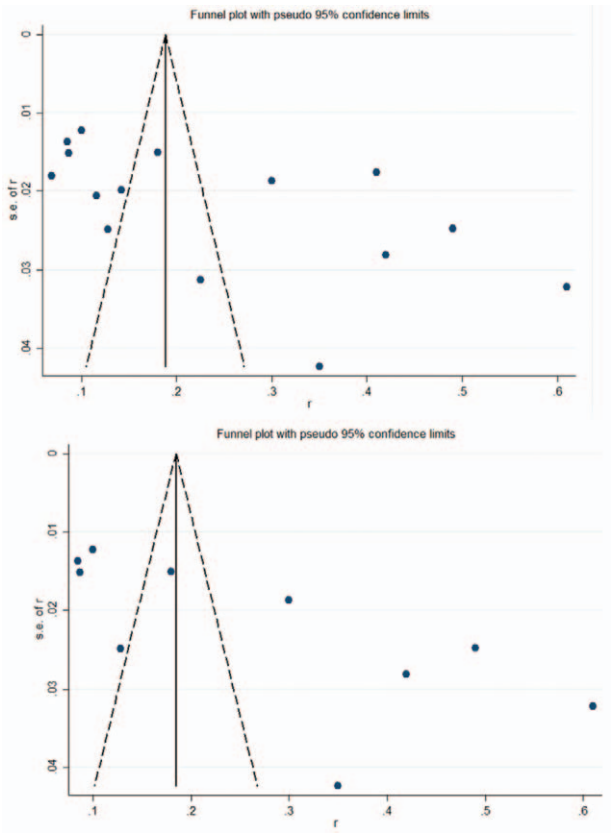


**Figure 4.** A. Publication bias test of overall prevalence of DRE. DRE = drug-resistant epilepsy. B. Publication bias test of overall prevalence of DRE defined by 2 AEDs. DRE = drug-resistant epilepsy, AED = antiepileptic drug.

With little heterogeneity between studies, abnormal EEG (both slow wave and epileptiform discharges), status epilepticus, febrile seizures, symptomatic etiology, and multiple seizure types were identified as strong risk factors for DRE. While there was substantial heterogeneity between studies in poor short-term outcomes of therapy, neurodevelopment delay, and high initial seizure frequency, using subgroup analysis, we found that the heterogeneity came from the drug numbers and seizure free time of DRE definition and these results were not stable, so they might not be used for predictors for refractoriness. Otherwise, the sensitive analysis found that the predictive value of focus onset seizure was not stable.

The current meta-analysis provides quantitative estimates of the magnitude of association between risk factors and DRE. Most of included literatures in our meta-analysis were conducted before 2017 and the classification of seizure or epilepsy types was based on old criteria,[37,38] while the ILAE published the new classification in 2017, which will be the foundation of studies and clinical treatment in future.[2] Due to the discrepancy of the classification criteria, some partial or generalized seizures would be classified as unknown onset seizure type and doctors also interview these patients. Thus, our meta-analysis included studies covering all kinds of seizure or epilepsy types and found risk factors to predict drug-resistance that could be widely used. In addition, this meta-analysis also contained studies of children and adults, we aimed to find predictors consistently among all age patients, but just 2 researches focused on all ages and this may be led to heterogeneity. However, study on all age patients conducted by Hiritis[30] found that febrile seizure was a risk factor for DRE and the pooled RR had significance with little heterogeneity, so was study by Zhang[22] for multiple seizure type. As a result, including these 2 studies on all age epilepsy

patients was not the source of heterogeneity and the results were stable.

Symptomatic etiology was found to be significantly associated with an increased risk of DRE. The changed structure and function of the central nervous system (CNS) led to hyper-excitability as the main cause of epilepsy.[39] Brain lesions resulted in neuronal death and reactive gliosis. One of the mechanisms of DRE is the "transporter hypothesis", and the structural abnormalities damage the capillary endothelial cells that constitute the blood-brain barrier, leading to the over-expression of efflux transports and drug resistance.[40]

In our meta-analysis, multiple seizure types and status epilepticus predicted intractability. These results were consistent for both adults and children. It is possible that the SE resulted from less inhibition and hyper-excitability, and as SE lasted longer, GABAergic function declined and excitatory input continued, contributing to neuronal death.[41] Wen et al reported that status epilepticus duration ≥24 hours was an independent predictor of DRE after convulsive status epilepticus.[42]

In many patients, febrile seizures lead to mesial temporal lobe epilepsy (MTLE)[43,44] and prolonged febrile seizures during infancy have been associated with severe damage to the temporomesial structures.[45] Most commonly, MTLE is associated with hippocampal changes, including diminished size and hardening neuron loss and lesions of the hippocampus.[46–48] Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLEHS) is typically a serious epilepsy syndrome and the most common drug-resistant epilepsy.[49]

The current meta-analysis found that the predictive effect of poor short-term outcome of drug therapy and high frequency of initial seizure was not firm. However, studied found that seizure recurrence in the first or second six months after initial AED therapy, increased the probability of achieving pharmcoresistance. Although most patients responded to AED treatment early, seizure would be controlled in initial 6 months after AED treatment.[50] According to the concept of "seizures beget seizures",[51] failure to control epileptic seizures would lead to more seizures and may become refractory seizures. This reminded us that the 2 indicators had the potency to predict the development of DRE which need more clinical trial to verify this phenomenon.

However, studies have defined and classified these factors differently, which makes it difficult to draw conclusions. For example, for a high initial seizure frequency, 3 studies used daily seizure as the predictor and indicated that it was related to refractoriness. In addition, the pooled results by analyzing 3 studies were consistent with single studies.[21,26,28] Nevertheless, 4 authors defined more than 10 seizures as a high initial seizure frequency, and their pooled results also contributed to the development of drug resistance.[20,24,30,31] Repeated seizures have been shown to produce neuronal loss and mossy fiber sprouting in the hippocampus, which in turn can reinforce their production, forming excitatory recurrent circuits.[52,53] Seven studies clearly showed that EEG abnormality was a predictor for intractability,[23,25,28,32,33,35] and 3 of them clarified that the EEG abnormality was a slow wave and 4 of that were epileptiform discharges. Both a slow wave and epileptiform discharges were risk factors for DRE.

This review has several limitations. The first major limitation is that the number of prior studies on adults was too small, and the definitions of DRE were different which caused high heterogeneity of this meta-analysis. The second is that for some variables researchers cited various definitions and lacked standard criteria. The third is that our pooled results for some variables were based on just 2 or 3 studies, and the results needed further verification.

Nevertheless, our meta-analysis still has some strengths. First, we clarify the risk factors for DRE from multiple candidate clinical indicators and quantified them. Second, the studies included in our meta-analysis covered all seizure types of children and adults and could be used for all age patients and was not influenced by the new classification criteria, and the samples were all new-onset epilepsy patients and never be treated with AEDs, therefore the results were not influenced by medication. Third, subgroup and sensitivity analyses were also conducted to ensure the robustness of the conclusions. Our meta-analysis confirmed some variables, and they could serve as candidates for subsequent studies, which provides a platform for vast heterogeneous data in studies exploring the risk factors of DRE under a common roof and provides some important insights.

Although there were many studies on the risk factors of intractable epilepsy for many years and a lot of factors were included, while the definitions of risk factors are different in each study, and the significance risk factors are also different. This meta-analysis found relatively consistent risk factors by summarizing previous studies. Recently, there have been many articles on disease prediction, all of which make prediction models based on the disease risk factors proposed in previous studies. Therefore, our article summarizes the literature factors related to refractory epilepsy, which can also provide a certain foundation for the establishment of refractory epilepsy prediction models in the later stage.

## 5. Conclusions

Our meta-analysis found that the prevalence of DRE was approximately 27% when defined by 2 AEDs according to the new definition in 2010, and the related risk factors were abnormal EEG (both slow wave and epileptiform discharges), status epilepticus, symptomatic etiology, febrile seizures, and multiple seizure types, while poor short-term outcome of therapy, neurodevelopment delay, and high initial seizure frequency were not firm risk factors for DRE because of high heterogeneity, and the predictive effect of focus onset seizure was not stable. Based on these risk factors, in clinical practice it would be helpful for doctors to predict the clinical course of an epilepsy patient within a short period after diagnosis and early identification of children at risk of intractable epilepsy is important both for parents' counseling and for physicians' consideration of alternative treatments. Some factors were only reported in 2 or 3 studies, and their power might lack stability. As most of the included studies were on childhood epilepsy and large-scale adults, multicenter studies including all ages of patients are warranted in the future.

## Author contributions

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**Supervision:** Ling Liu.
**Visualization:** Ling Liu.
**Writing – original draft:** Xueping Wang, Lina Zhu.
**Writing – review & editing:** Xueping Wang, Ling Liu.

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