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Predictors of seizure reduction outcome after vagus nerve stimulation in drug-resistant epilepsy

Hai-jiao Wang, Ge Tan, Li-na Zhu, Deng Chen, Da Xu, Shan-shan Chu, Ling Liu*

Department of Neurology, West China Hospital, Sichuan University, Wai Nan Guo Xue Lane 37 #, Chengdu 610041, Sichuan, China

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ABSTRACT

Purpose: To evaluate the predictors of seizure reduction outcome after vagus nerve stimulation (VNS) in patients with drug-resistant epilepsy (DRE).

Methods: A meta-analysis was performed using relevant research from databases such as PubMed, Embase, Cochrane Online Library, and Clinicaltrials.gov. Studies were selected according to predefined inclusion and exclusion criteria. The quality of studies was evaluated by using the Newcastle-Ottawa Scale (NOS) scale. All data was pooled by STATA 12.0 software for meta-analysis.

Results: The review considered 1281 articles, and 16 articles with NOS score ≥6 were included in the analysis. The meta-analysis showed that at 6 m, 1, 2, 3, 4, 6 and 12 years after implantation, 33.99, 43.42, 46.50, 63.31, 52.71, 54.64, 70.37 and 82.90% of patients exhibited > 50% reduction of seizure frequency after VNS. The duration of epilepsy showed a significant difference between the good responders and poor responders ($p = 0.038$), whereas age at VNS implantation ($p = 0.305$), age at seizure onset ($p = 0.530$), seizure type ($p = 0.11$), etiology ($p = 0.187$), and history of previous epilepsy surgery ($p = 0.075$) were not predictors of seizure reduction outcome after VNS. Several features about the electroencephalogram (EEG) feature and heart rhythm complexity (HRV) have not been analyzed by a sufficient number of studies.

Conclusions: DRE patients with shorter duration of epilepsy may be better candidates for VNS rather than those who are younger at onset and implantation. Several EEG or HRV features may have predictive value but more research is needed.

1. Introduction

About 30–40% of epilepsy patients whose seizures cannot be controlled with two well-tolerated, appropriately chosen, and used antiepileptic drugs (AEDs) are considered to have drug-resistant epilepsy (DRE) [1]. Even with adequate access to surgical treatment and further AEDs trials, 61.1% of patients with DRE have ongoing seizures [2]. Vagus nerve stimulation (VNS) was approved by the Food and Drug Administration (FDA) as adjunct therapy to reduce the frequency of seizures in adults with DRE [3]. VNS is an alternative therapeutic option for patients with DRE who are not suitable for conventional craniotomy surgery or who have experienced failed cranial surgery [4], and it is an effective treatment for many seizure types and epilepsy syndromes with a predictable and benign side-effect profile that supports its role as the most commonly prescribed device to treat DRE [5].

The efficacy of VNS varies substantially due to clinical factors, including epilepsy type, etiology, antiepileptic drug use, and severity of the epilepsy, and usually does not result in complete cessation of seizures [6]. It is still difficult to predict which patients will respond to VNS treatment, and to what extent [7]. Therefore, we performed a meta-analysis to review the literature systematically and evaluate the predictors of seizure reduction outcome after VNS in patients with DRE.

Abbreviations: VNS, vagus nerve stimulation; DRE, drug-resistant epilepsy; AEDs, antiepileptic drugs; FDA, Food and Drug Administration; NOS, Newcastle-Ottawa Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SMD, standardized mean difference; WMD, weighted mean difference; CI, confidence intervals; (M-H), Mantel-Haenszel; RR, relative risk; RD, rate difference; OR, odds ratio; EEG, electroencephalogram; HRV, heart rhythm complexity; IEDs, interictal epileptiform discharges; pdBSI, low pairwise–derived Brain Symmetry Index; MSE, multiscale entropy

* Corresponding author.
E-mail addresses: 844675111@qq.com (H.-j. Wang), tanhaoshua@163.com (G. Tan), Angelinazhuzhu@163.com (L.-n. Zhu), jerry.k.d@163.com (D. Chen), 498688793@qq.com (D. Xu), 1697705783@qq.com (S.-s. Chu), zjllxx1968@163.com (L. Liu).

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2. Methods

2.1. Data sources and search

We searched the online databases of PubMed, Embase, Cochrane Online Library, and Clinicaltrials.gov (https://clinicaltrials.gov/), using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) principles [8]. The last search was performed on September 8, 2018. Search terms included epilepsy, vagus nerve stimulation, and response or predict. Two reviewers independently reviewed the titles and abstracts for any potentially relevant article. Published trials without corresponding articles were also evaluated according to the information available online.

2.2. Study selection

The two reviewers independently assessed the eligibility of potentially relevant studies according to the predesigned inclusion criteria. Disputes about relevance were resolved by consensus among the investigators.

2.2.1. Inclusion criteria

1 Study design was limited to randomized, double-blind, placebo-controlled trials, and cohort studies.
2 Population: Study subjects needed a clinical diagnosis of drug-resistant epilepsy and ineligibility for epilepsy surgery.
3 Interventions: We included studies in which all patients of the study underwent VNS device implantation.
4 Outcomes: According to the patient's response to VNS, patients with 50% or greater decrease in seizure frequency were defined as good responders to VNS therapy, whereas those with < 50% decrease were defined as poor responders.

2.2.2. Exclusion criteria

1 Animal studies, reviews, and case reports were all excluded from our analysis.
2 Studies with fewer than 30 patients were excluded.
3 The study was excluded if it did not mention a clear outcome.
4 The study did not provide data characteristics of the patients.

2.3. Data extraction

The two reviewers extracted relevant information from the identified abstracts, using a data extraction form that included (1) general information: the first author and year of publication; (2) study characteristics: number of subjects, sex ratio (female/male), mean subject age, percent of responders, and follow-up; (3) patient characteristics in two groups, including a group with good responders and a group with poor responders; age at VNS implantation; age at seizure onset; epilepsy duration; seizure type; etiology; history of pre-surgery; EEG, and so on. If those were reported from the studies at multiple time points, we extracted data from the latest time point in the study protocol.

2.4. Evaluation of evidence

Two independent evaluators assessed the quality of the literature, using the quality evaluation criteria of the Newcastle-Ottawa Scale (NOS) from three aspects: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of studies. The total score was 9; a score ≥6 indicated high-quality literature, and < 6 indicated low-quality literature (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

2.5. Data analysis

All statistical analyses were performed using Stata 12.0. For all continuous variables, we calculated the standardized mean difference (SMD) as statistical value with 95% confidence intervals (CI). For counting variables we used the Mantel-Haenszel ((M-H)) model to calculate the relative risk (RR) and if the data contained zero, the statistic value selected the rate difference (RD). The test level α of the effect was set to 0.05. The inverse-variance method was used for meta-analysis. Statistical heterogeneity was evaluated by the χ^2 test. The fixed-effects model was used for comparisons with $I^2 < 50\%$, and the random-effects model was applied for comparisons with $I^2 \geq 50\%$ [9]. Sensitivity analysis was used to evaluate the stability of the meta-analysis results through the interconversion between the fixed-effects model and the random-effects model, and exchange of statistical values to recalculate 95% CI, such as RD and RR, were converted to odds ratio (OR) and SMD transformed to weighted mean difference (WMD). If the converted results were consistent, the results of the meta-analysis were stable; otherwise, they were unstable. The Egger's test was used to test the potential publication bias of the included literature, with $P > 0.050$ as the absence of publication bias.

3. Result

3.1. Study selection

A total of 1281 articles were enrolled from the preliminary literature search: 406 papers from PubMed, 841 from EMBASE, four from Cochrane Online Library, and 30 from clinicaltrials.gov. From this initial screening, we excluded studies without data about the difference between the good responders and poor responders. Finally, 150 articles were identified as relevant after reading the titles and abstracts, and after reading the full text, 16 studies were selected for inclusion in our meta-analysis. A flow diagram of the article-screening process is shown in Fig. 1.

3.2. Characteristics of the included studies

We included 16 studies [7,10–24] in this meta-analysis. The population of several studies was pediatric patients with drug-resistant epilepsy [19–22]. Kossoff et al. [21] analyzed patients for the predictor of the outcome with > 90% seizure reduction after VNS. Qiabi et al. [24] researched the predictor for seizure-free after VNS in follow-up. Among the included studies, there was no randomized controlled trial, and most were retrospective studies. Follow up was for at least one year. Study and patient characteristics of all included studies are shown in Table 1.

3.3. Statistical analysis

Among the studies 53.53% (568/1061) of patients with DRE achieved > 50% reduction of seizure frequency after VNS. At 6 m, 1, 2, 3, 4, 6 and 12 years after implantation, 33.99, 43.42, 46.50, 63.31, 52.71, 54.64, 70.37 and 82.90% of patients exhibited > 50% reduction of seizure frequency after VNS. In the 14 trials [7,10–12,14–22,24], including a total of 906 participants, analysis age at VNS implantation as a predictor for VNS outcome within each group, we found no significant difference between the good responders and poor responders ($p = 0.305$, SMD = –0.075, 95% CI: –0.220 to 0.069; heterogeneity test: $Chi^2 = 12.20$, $p = 0.526$, $I^2 = 0\%$, Fig. 2).

We analyzed age at seizure onset within each group in six studies [15,16,18–20,24], including 416 patients; we found no significant difference between the good responders and poor responders ($p = 0.530$, SMD = 0.075, 95% CI: –0.159 to 0.310, heterogeneity test: $Chi^2 = 7.44$, $p = 0.190$, $I^2 = 32.8\%$, Fig. 3).

Seven trials [11,16,18,19,21,22] included a total of 504

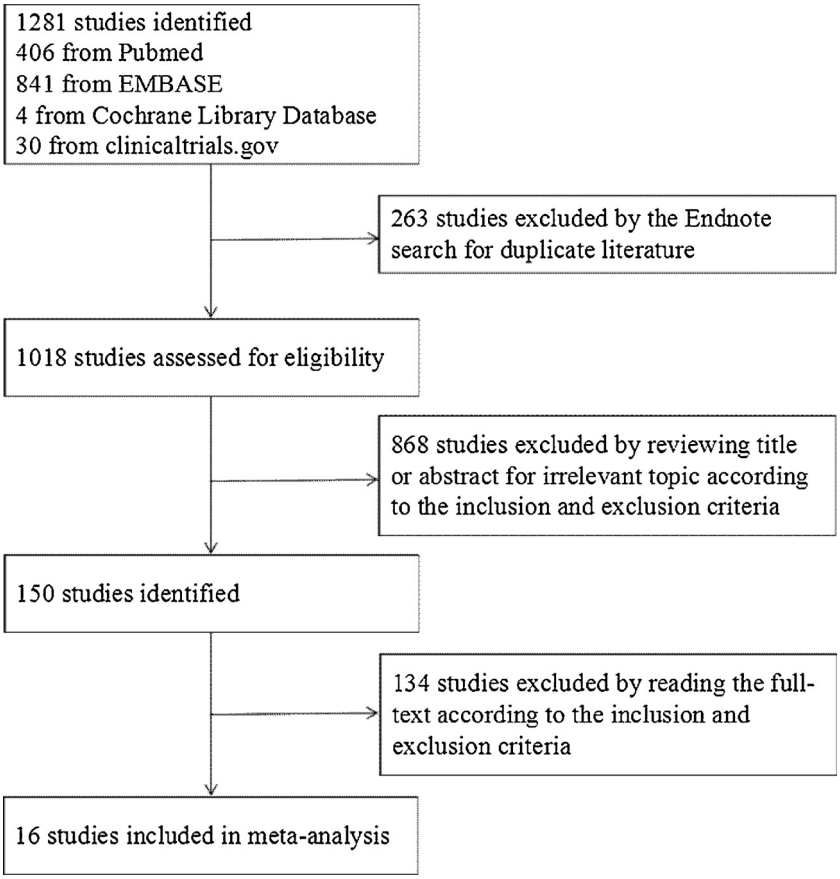

Fig. 1. Flow diagram of literature search and selection.

participants. When we analyzed duration of epilepsy within each group, we found a significant difference between the good responders and poor responders (p = 0.038, SMD = –0.218, 95% CI: –0.423 to –0.012; heterogeneity test: Chi^2 = 5.16, p = 0.523, I^2 = 0%, Fig. 4).

Four trials [13,15,20,22] included a total of 546 participants. We found no significant difference between the good responders and poor responders in seizure type (p = 0.113, RR = 0.784, 95% CI: 0.580–1.059; heterogeneity test: Chi^2 = 1.76, p = 0.624, I^2 = 0%, Fig. 5).

However, the data about etiology contained zero, so we selected the statistical values of RD to calculate it and found no significant difference between the good responders and poor responders in etiology in nine studies [7,10,14,16,18,20,22–24], including 697 patients (p = 0.187, RD = 0.063, 95% CI: –0.031 to 0.157; heterogeneity test: Chi^2 = 11.37, p = 0.182, I^2 = 29.6%, Fig. 6).

Five trials [15,16,18,20,24] included a total of 380 participants. When we analyzed the history of surgery for epilepsy within each group, we found no significant difference between the good responders

Table 1
Characteristics of the included studies.

Study	Year	N	F/M	Age (year)[b]	Seizure type	% responder	Follow-up (year) [b]	NOS (score)
Liu	2018	63	42/21	5-60	DRE	53.97	1	8
Chrastina	2018	103	56/47	> 18	DRE	53.40	1	7
Fujimoto	2017	56	20/36	24(3-56)	DRE	73.21	> 2	6
Hilderink	2017	39	24/15	> 18	–	25.64	1.67(0.67-2)	6
Liu	2017	32	11/21	19 ± 9	DRE	53.13	1	7
María	2016	85	36/49	33 (25-37)	DRE	54.12	1.5	8
Kim	2016	58	17/41	10.9 ± 4.6	DRE	50	8.4 ± 3.9	8
Ching	2013	100	39/61	44.21 ± 12.46	DRE	51	12	7
Menascu	2013	36	NA	36.4 ± 21.6	DRE	38.89	1.5	6
Burakgazi	2011	46	23/23	45.35 ± 12.73	DRE	70.37	5.20(4.78)	6
Qiabi	2011	34	20/14	29.9(16-57)	DRE	47.06	> 1	7
Ghaemi	2010	144	77/67	23.7 ± 13.4	DRE	61.81	1	8
Kabir	2009	69	24/45	10.69(3-16)	DRE	55.07	3.81(2.46)	7
Kossoff	2007	30	18/12	9.5 (4-24)	DRE[a]	70	1(0.04-8)	8
Herdt	2006	138	71/67	30(4-59)	DRE	59.42	> 1	8
Janszky	2004	47	25/22	22.7 ± 11.6	DRE	12.77[c]	> 1	8

F/M, female/male; NA, not available; DRE, drug-resistant epilepsy; NOS, Newcastle-Ottawa Scale.
[a] Children with DRE was treated with VNS and ketogenic diet.
[b] The data is presented as mean ± standard deviation or the range.
[c] It is the rate of seizure-free in the patients.

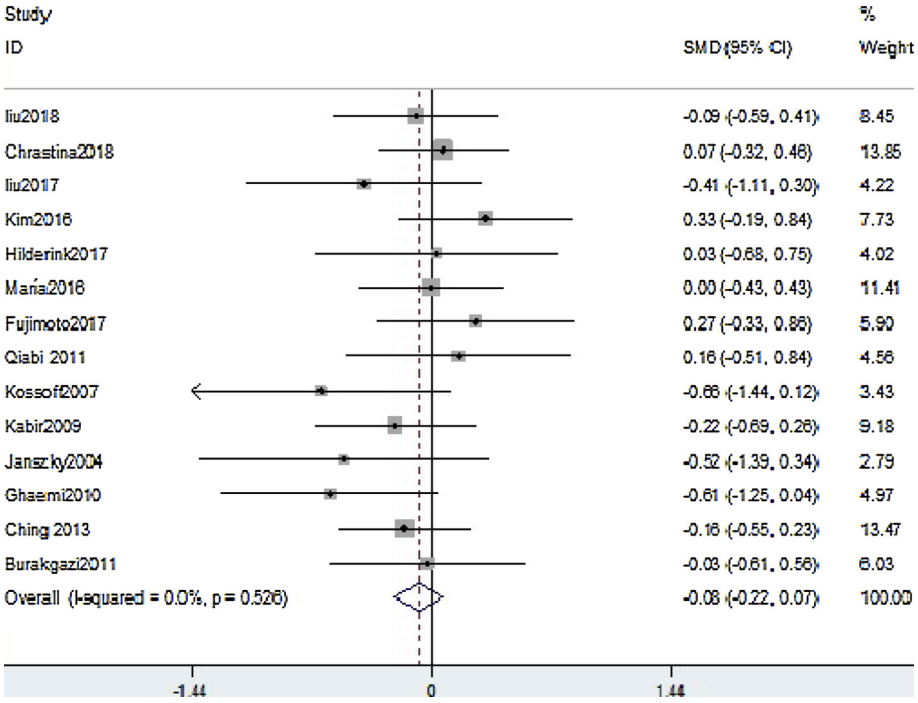

Fig. 2. Age at the implantation of VNS between the responders and non-responders.

and poor responders (p = 0.075, RR = 0.634, 95% CI: 0.384–1.047; heterogeneity test: $Chi^2 = 4.57$, p = 0.334, $I^2 = 12.5\%$, Fig. 7).

Several features about the electroencephalogram (EEG) feature and the heart rhythm complexity (HRV) have been reported, but that specific features have not been analyzed by a sufficient number of studies to allow us to include them in this meta-analysis. Hilderink et al. [17] showed that the low pairwise–derived Brain Symmetry Index (pdBSI) could predict good responders to VNS treatment for patients with epilepsy. Kim et al. [20] found that only focal or multifocal epileptiform discharges on interictal EEG were significantly associated with a good response to VNS therapy. Janszky et al. [18] suggested that absence of bilateral interictal epileptiform discharges (IEDs) was independently associated with a good outcome from VNS. Similarly, Ghaemi et al. [16] thought unilateral IEDs were independent predictors of good response to VNS in the long-term follow-up.

Liu et al. [7] analyzed preoperative heart rhythm complexity (HRV) by traditional linear methods and heart rhythm complexity analyses with multiscale entropy (MSE) to predict VNS outcomes in patients with DRE.

3.4. Sensitivity analysis

We conducted a two-part sensitivity test on our results. We converted the fixed-effects model to the random-effects model and exchanged statistical values from RR or SMD or RD to OR or WMD, and there were no significant changes in any of the results, as shown in Table 2.

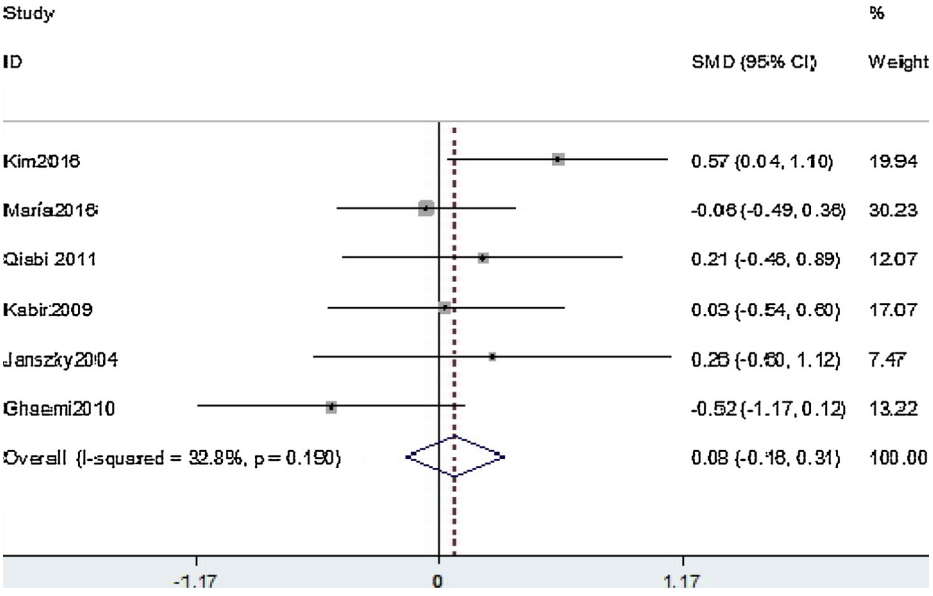

Fig. 3. Age at onset of seizure between the responders and non-responders.

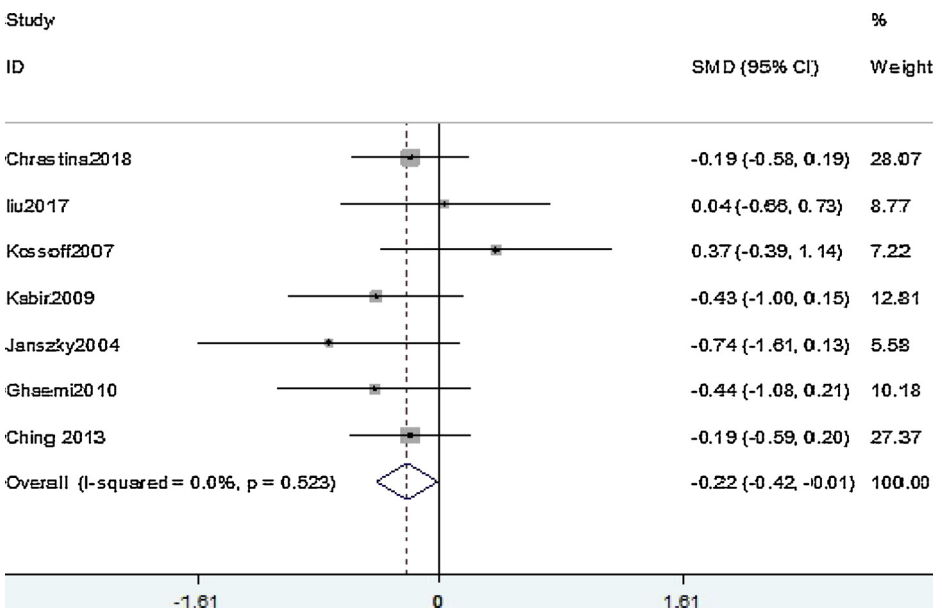

Fig. 4. Duration of epilepsy on the outcome of VNS between the responders and non-responders.

3.5. Publication bias

There was no publication bias ($P > 0.05$) in the studies contained in this meta-analysis about the predictors of the response to VNS treatment for patients with DRE through the Egger's test; thus, the influence of publication bias on the results could be ignored.

4. Discussion

In recent years, VNS has been a therapy of efficacy and safety to attain seizure control in patients with DRE [2–4]. The present study showed that 53.53% patient with DRE could achieve > 50% reduction of seizure frequency after VNS and this is consistent with the response rate found in most current studies. A large clinical study found that 60.1% of individuals were responders at last follow-up [25].

However, it is still not possible to predict which patients will respond to VNS treatment. Our meta-analysis showed that the age at implantation and age at seizure onset have no significant association with a good outcome from VNS, whereas shorter duration of epilepsy may lead to a good response to VNS for patients with DRE. That is inconsistent with the prior meta-analyses which showed that seizure freedom was predicted by age of epilepsy onset > 12 years and generalized seizure type, nonlesional epilepsy. We thought that the results of this study is more convincing because the present review is restricted to trials which is different from some prior reviews. Several studies considered that longer duration of epilepsy did not predict worse seizure reduction outcome after VNS [12,26], but Colicchio et al. [27] and Arya et al. [28] showed that a short duration of epilepsy before VNS implantation was a strong factor associated with good outcome. That can perhaps be explained by the working mechanism of VNS. Although the exact working mechanism of VNS is not known yet, several researches have indicated profound changes in brain blood flow, brain neurotransmitter metabolism, and electro-physiological parameters. It can be hypothesized that VNS, after some time, clearly induces long-lasting changes in the neuronal network involved in epilepsy and that the earlier this is done, the better the outcome [26].

Generally speaking, previous studies thought that young age at VNS implantation and age at seizure onset were associated with the good

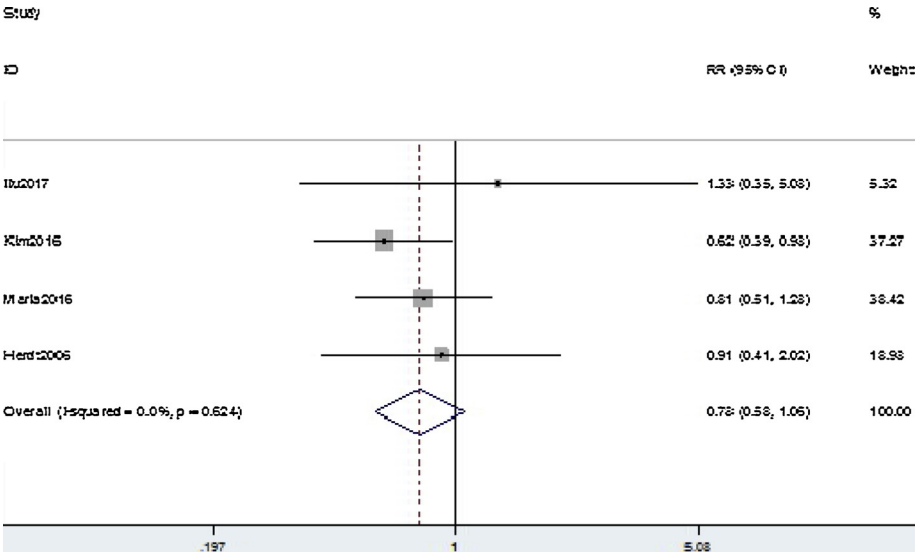

Fig. 5. Seizure type on the outcome of VNS between the responders and non-responders.

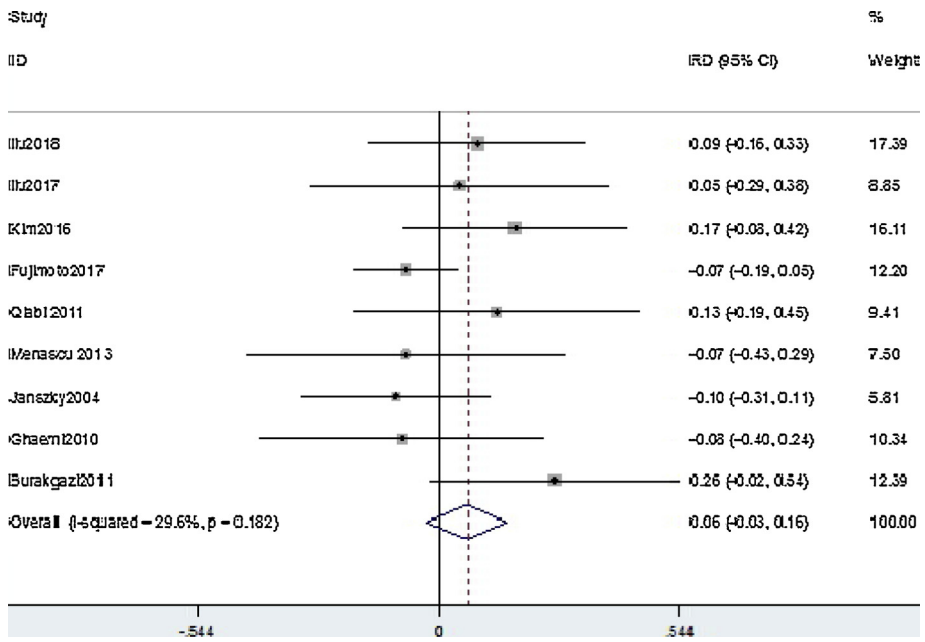

Fig. 6. Etiology on the outcome of VNS between the responders and non-responders.

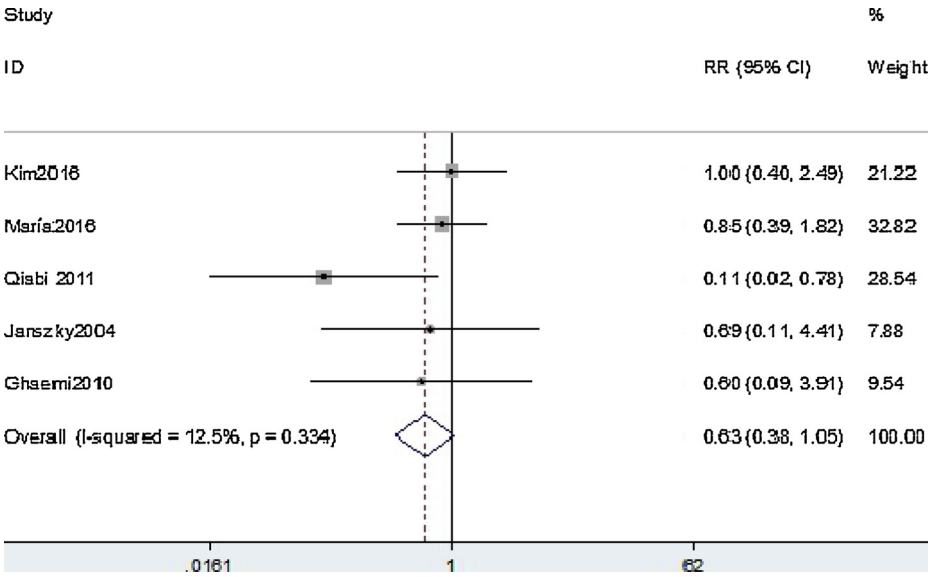

Fig. 7. History of Pre- surgery on the outcome of VNS between the responders and non-responders.

responder rate, as well as short duration of epilepsy [14,27,29–31], but Soleman et al. thought age at implantation did not influence the responder rate [32], which agrees with our study. Those different results may be caused by the small samples of patients of those studies; thus, through systematically evaluating the literature, our study suggested that DRE patients with shorter duration of epilepsy may be better candidates for VNS and they are easier to help attain seizure reduction, rather than those who are younger at onset and implantation. The age

Table 2
Sensitivity analysis of interconversion between fixed effects model and random effects model, and exchange of statistical values.

Item	Switching model			Exchange of statistic value		
	WMD or *RR* value	*WMD* or *RR* 95%CI	*P* value	*SMD* or *OR* value	*SMD* or *OR* 95%CI	*P* value
Age at VNS implantation	−0.075	−0.220~0.069	0.305	−0.737	−1.804~0.330	0.176
Age at seizure onset	0.077	−0.217~0.371	0.607	0.183	−0.753~1.118	0.702
Epilepsy duration	−0.218	−0.423~−0.012	0.024	−1.673	−3.120~−0.225	0.024
Seizure type	0.754	0.562~1.013	0.060	0.659	0.395~1.101	0.111
Etiology	0.024[a]	−0.075~0.123[a]	0.636	1.376	0.882~2.149	0.160
History of pre-surgery	0.717	0.401~1.281	0.261	0.562	0.302~1.045	0.069

[a] The statistic value is RD.

at implantation and onset may affect the outcome of VNS through the duration of epilepsy.

The present study failed to find a significant association between the etiology and good response for VNS. Englot et al. suggested that nonlesional patients would be good responders for VNS [25,33], as did the study of Arya et al. [28]. However, Landi et al. thought that structural epilepsies responded best when compared to genetic epilepsies or those with unknown etiology [29]. The research by Chrastina et al. found no significant predictor of VNS outcome in potential outcome predictors, such as age, MRI, or seizure type in a 10–17 year follow-up [34]. It is important that patients with symptomatic epilepsy were more likely to be candidates for resection, which results in fewer patients with symptomatic epilepsy undergoing VNS surgery, and that may lead to some bias. This study did not pay attention to the possibility of a specific etiology as a predictor for VNS outcome in DRE patients. Englot et al. showed that patients with posttraumatic epilepsy or tuberous sclerosis achieved a significantly better outcome after VNS [33].

This meta-analysis showed that a history of previous epilepsy surgery had no significant connection with the response to VNS, which was similar to the finding by Elliott [35], suggesting that failed cranial epilepsy surgeries did not affect the response to VNS therapy. Conversely, previous studies [36,37] thought the patients with corpus callosotomy had good response to VNS.

The specific features about EEG and HRV have not been analyzed by a sufficient number of studies to allow us to include them in this meta-analysis. But we still found that unilateral IEDs were perhaps predictors of good response to VNS, which agrees with Arcos et al. [38], who considered that a temporal lobe discharge on the video-EEG was an indicator of an early response. Besides IEDs, the other EEG features, also reported as effective predictors for good response to VNS, included positive polarity of slow cortical potential (SCP) shifts on scalp EEG [39], the increase in P300 amplitude [40], lower global synchronization levels in delta and alpha frequency bands [41], ictal synchronization of brain activities measured with scalp EEG [42], and decreased connectivity with SEEG signals [43]. Conversely, Barbella et al. [44] found no changes in epileptiform activity or in its localization in responders or non-responders, so more studies are needed that focus on the relation between EEG and the outcome of VNS in the future.

In the included studies, Liu et al. [7] suggested that preoperative HRV was useful to predict unresponsiveness to VNS treatment, and his other study [22] considered that VNS-induced effects on heart rate complexity may be associated with the therapeutic response to VNS in patients with DRE. That agreed with the results by Persson et al. [45], which indicated that patients with a poor outcome from surgery had a more significant impairment of sympathetic and parasympathetic cardiac control through measurements of preoperative heart rate variability, but the small sample number limited the reliability of the results.

Our findings may have been influenced by some potential confounding factors. First, the number of patients in the included articles in this study was a little small. More large, randomized, double-blind, placebo-controlled trials with good design are needed to demonstrate the role of predictors in VNS outcomes. Second, it was a pity that this study could not do a meta-analysis about EEG or HRV of the response to VNS because of the small quantity of study data. In the future, more research should focus on EEG or HRV for VNS outcome by patients with DRE. Third, the length of follow-up was not exactly the same across studies. In the included studies, the longest follow-up period was 12 years. The varied durations may have influenced the current results.

5. Conclusion

This meta-analysis provides evidence for the preoperative evaluation of VNS, that DRE patients with shorter duration of epilepsy may be better candidates for VNS and they are easier to help attain seizure reduction, rather than those who are younger at onset and implantation. Patients with DRE should consider VNS if they have had a shorter duration of epilepsy. Nonlesional epilepsy is not a significant predictor of VNS outcome. Patients with DRE regardless of etiology can be considered VNS candidates. Several EEG or HRV features such as unilateral IEDs may have predictive value but more research is needed to confirm their validity.

Declarations of interest

The authors report no conflicts of interest. 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.

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