



Association between Removal of High-Frequency Oscillations and the Effect of Epilepsy Surgery: A Meta-Analysis

Zhichuang Qu^{1,2,*} Juan Luo^{1,2,*} Xin Chen² Yuanyuan Zhang^{2,3} Sixun Yu² Haifeng Shu^{1,2,3}

¹Department of Neurosurgery, Affiliated Hospital of Southwest Medical University, Luzhou, China

²Department of Neurosurgery, The PLA Western Theater Command General Hospital, Chengdu, China

³Southwest Jiaotong University, Chengdu, China

Address for correspondence Haifeng Shu, Tianhui Road 270#, Rongdu Avenue, Jinniu District, Sichuan Province, China (e-mail: shuhaifeng@swjtu.edu.cn).

J Neurol Surg A Cent Eur Neurosurg 2024;85:294–301.

Abstract

Background High-frequency oscillations (HFOs) are spontaneous electroencephalographic (EEG) events that occur within the frequency range of 80 to 500 Hz and consist of at least four distinct oscillations that stand out from the background activity. They can be further classified into “ripples” (80–250 Hz) and “fast ripples” (FR; 250–500 Hz) based on different frequency bands. Studies have indicated that HFOs may serve as important markers for identifying epileptogenic regions and networks in patients with refractory epilepsy. Furthermore, a higher extent of removal of brain regions generating HFOs could potentially lead to improved prognosis. However, the clinical application criteria for HFOs remain controversial, and the results from different research groups exhibit inconsistencies. Given this controversy, the aim of this study was to conduct a meta-analysis to explore the utility of HFOs in predicting postoperative seizure outcomes by examining the prognosis of refractory epilepsy patients with varying ratios of HFO removal.

Methods Prospective and retrospective studies that analyzed HFOs and postoperative seizure outcomes in epilepsy patients who underwent resective surgery were included in the meta-analysis. The patients in these studies were grouped based on the ratio of HFOs removed, resulting in four groups: completely removed FR (C-FR), completely removed ripples (C-Ripples), mostly removed FR (P-FR), and partial ripples removal (P-Ripples). The prognosis of patients within each group was compared to investigate the correlation between the ratio of HFO removal and patient prognosis.

Results A total of nine studies were included in the meta-analysis. The prognosis of patients in the C-FR group was significantly better than that of patients with incomplete FR removal (odds ratio [OR] = 6.62; 95% confidence interval [CI]: 3.10–14.15; $p < 0.00001$). Similarly, patients in the C-Ripples group had a more favorable prognosis

Keywords

- ▶ high-frequency oscillations
- ▶ intractable epilepsy
- ▶ intracranial electrography
- ▶ epilepsy prognosis
- ▶ electrocorticogram

* These authors contributed equally to this work and should be regarded as co-first authors.

received
July 5, 2023
accepted
September 11, 2023
article published online
January 22, 2024

DOI <https://doi.org/10.1055/a-2202-9344>.
ISSN 2193-6315.

© 2024. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

compared with those with incomplete ripples removal (OR = 4.45; 95% CI: 1.33–14.89; $p = 0.02$). Patients in the P-FR group had better prognosis than those with a majority of FR remaining untouched (OR = 6.23; 95% CI: 2.04–19.06; $p = 0.001$). In the P-Ripples group, the prognosis of patients with a majority of ripples removed was superior to that of patients with a majority of ripples remaining untouched (OR = 8.14; 95% CI: 2.62–25.33; $p = 0.0003$).

Conclusions There is a positive correlation between the greater removal of brain regions generating HFOs and more favorable postoperative seizure outcomes. However, further investigations, particularly through clinical trials, are necessary to justify the clinical application of HFOs in guiding epilepsy surgery.

Introduction

The aim of an epilepsy surgery is to resect the brain tissue responsible for seizure generation, known as the epileptogenic zone (EZ). Prior to surgery, the brain tissue undergoes evaluation to identify the seizure onset zone (SOZ), which refers to the cortical region that initiates seizures. Accurate identification of the EZ holds the potential to improve patient prognosis.

In recent years, high-frequency oscillations (HFOs) have emerged as a promising marker for epileptogenicity. HFOs can be categorized into two frequency ranges: “ripples” (80–250 Hz) and “fast ripples” (FR; 250–500 Hz).¹ HFOs have demonstrated superior effectiveness in specifically identifying the SOZ compared with spikes.^{2–5} Previous studies have consistently shown a strong association between HFOs and the SOZ,^{6–8} surpassing that of interictal epileptiform discharges.⁹ Significant disparities in HFOs rates and amplitudes have been observed between the SOZ and non-SOZ regions in various brain lobes.^{10,11} Hence, HFOs play a crucial role in the detection and delineation of epileptic regions.

Several studies have established a close relationship between HFOs and surgical outcomes. Complete removal of HFO-producing brain regions has been linked to favorable postoperative outcomes,^{12–14} while incomplete removal correlated with epileptic recurrence.^{4,15–18}

However, no significant distinction has been found in the delineation of the SOZ using HFOs instead of spikes.^{19,20} Gloss et al’s meta-analysis of two prospective studies did not yield a significant improvement in postoperative seizure outcomes with the use of HFOs.²¹ Similarly, Höller et al reported minor differences in their meta-analysis of HFOs pertaining to epilepsy outcomes.²² Therefore, the reliability of HFOs as a biomarker for epileptic tissue remains a subject of ongoing debate.

HFOs can be monitored using scalp electroencephalogram (EEG), electrocorticogram (ECOG), and stereoelectroencephalography (SEEG). Scalp EEG is prone to artifacts and errors due to slight movements of the monitored individual, making EZ delineation challenging. ECOG, consisting of a grid or strip electrode that covers the brain cortex, offers denser contacts and fewer artifacts compared with scalp EEG.

SEEG, on the other hand, allows for monitoring of electrical activities in deep brain structures over a wider range. It provides detailed recordings of the origin and transmission of epileptic discharges, facilitating a better understanding of the transmission network of the cerebral cortex and accurate EZ delineation.^{23–25} In patients in whom noninvasive methods fail to satisfactorily identify epileptic tissue, intracranial electroencephalography (iEEG) monitoring serves as the gold standard for EZ delineation.^{26–28}

We conducted a meta-analysis to evaluate the association between postoperative efficacy and HFOs monitored using ECOG and SEEG.

Methods

Inclusion Criteria

The inclusion criteria were the following: prospective or retrospective studies investigating surgical outcomes in patients with intractable epilepsy using iEEG monitoring and studies providing information on the proportion of HFO resection and patient prognosis. Studies were excluded if they involved duplicate patient records or were not written in English.

Study Search

Two independent reviewers conducted a comprehensive search of PubMed and Cochrane databases up to January 2023, using the following retrieval strategy:

- PubMed: ((high frequency oscillations) OR (fast oscillations) OR (ripples)) AND ((epilepsy) OR (seizure)) AND ((surgery) OR (operation)).
- Cochrane: (high frequency oscillations) OR (fast oscillations) OR (ripples) AND (epilepsy) OR (seizure) AND (surgery) OR (operation).

Data Extraction

The following information was extracted by the author: type of iEEG used (ECOG or SEEG), patient characteristics including mean age at the time of surgery, sample size, sex ratio, mean follow-up time, and recorded outcomes. Additionally, details regarding the type of HFOs (ripples or FR), analysis of HFOs (visual or automatic), and the proportion of HFOs removed were collected.

Quality Assessment

The quality of the included studies was evaluated by two reviewers using Cochrane's risk of bias tool.²⁹ In cases of disagreement, a third author was consulted to reach a resolution. The following aspects were assessed for risk of bias, categorized as low, high, or unclear: age at surgery, iEEG methodology, detection and thresholding of HFOs, sample size, representation of females, follow-up duration, and recorded outcomes.

Data Classification and Analyses

The patients from the included studies were categorized into four groups based on the extent of HFOS removal: completely removed FR (C-FR), completely removed ripples (C-Ripples), mostly removed FR (P-FR), and mostly removed ripples (P-Ripples). A meta-analysis was conducted to investigate the relationship between seizure outcomes and the proportion of removed HFOs. However, some studies in the P-Ripples and P-FR groups did not provide specific criteria for determining the majority of HFOs removed.

To define the majority of HFOs removed, we applied the equation listed below.¹³ The criteria were as follows: if the value of RatioChanns (ev) was ≥ 0 and ≤ 1 , it was classified as the majority of HFOs removed; otherwise, it was classified as the majority of HFOs untouched.

$$\text{RatioChanns(ev)} = \frac{\# \text{ChannRem(ev)} - \# \text{ChannNonRem(ev)}}{\# \text{ChannRem(ev)} + \# \text{ChannNonRem(ev)}}$$

Here, ev represented HFOs (FR or ripples), ChannRem represented the channels of events that had been removed, ChannNonRem represented the channels of events that had not been removed, and RatioChanns(ev) represented the difference between the number of removed channels (ev) and the number of unremoved channels (ev), divided by the total number of channels (ev). The value of RatioChanns(ev) fell between 1 and -1. A value between 0 and 1 (including 0) indicated that the majority of events were removed, while a value between -1 and 0 (excluding 0) indicated that the majority of events were untouched.

Statistical Analyses

Review Manager 5.4 software was used to analyze the collected data. Patients without either ripples or FR were excluded from their respective studies. The assumption of heterogeneity was assessed using the chi-square-based Q test. A *p* value of ≥ 0.10 indicated a lack of heterogeneity among the studies. The fixed-effects model was used to calculate the odds ratio (OR) and 95% confidence interval (CI).

Results

Study Screening Results

A total of 216 records were retrieved from PubMed and 8 records were obtained from the Cochrane Library, all of which met the inclusion criteria. After reviewing the titles and abstracts, 20 studies were selected for further evaluation (►Fig. 1). However, only 10 studies provided the necessary

data upon full-text review. It should be noted that one study by Hussain et al³⁰ was excluded due to patient overlap with their previous study,³¹ which we already included. Consequently, a total of nine studies were included in this meta-analysis.

Quality Assessment

The Cochrane risk of bias assessment^{32,33} revealed that none of the included studies reported random allocation, allocation concealment, or implementation of blinding methods.

Clinical Characteristics

Most of the included studies provided demographic information, such as the age and gender of the patients (see ►Table 1). Four studies exclusively involved minors.^{31,34} One study did not specify the follow-up time,³⁴ while another study reported a small number of patients lost to follow-up.³⁵ Additionally, one study did not mention the criteria for prognostic assessment,³⁵ but defined seizure freedom at each follow-up visit as the absence of breakthrough seizures since the last clinical visit. For our analysis, we defined seizure freedom based on Engel I or International League Against Epilepsy I (ILAE I) classification. A study conducted by Fedele et al³⁶ evaluated the efficacy of C-FR and ripples, providing data on the removed HFOs for each patient. Hence, we were able to classify their patients into the P-Ripples or P-FR group.

Group Classification Based on Removed Ratio

The distribution of studies among the groups was as follows: 8 studies in the C-FR group, 5 studies in the C-Ripples group, 5 studies in the majority removed FR group, and 5 studies in the majority removed ripples group.

Completely Removed FR and Prognosis

►Fig. 2 illustrates the meta-analysis results regarding the relationship between C-FR and patient prognosis. The fixed-effects model was utilized, and the heterogeneity test indicated no significant heterogeneity ($I^2 = 0\%$; $p = 0.68$). The estimated model yielded a significant result, indicating that patients in the C-FR group had a significantly higher prognosis compared with those with incomplete removal (OR = 6.62; 95% CI: 3.10–14.15; $p \leq 0.00001$).

The funnel plot, displayed in ►Fig. 3, exhibits symmetrical distribution of points along the center line and both sides, suggesting no noticeable publication bias among the included studies.

Completely Removed Ripples and Prognosis

►Fig. 4 presents the meta-analysis results concerning the association between C-Ripples and patient prognosis in the C-Ripples group. The fixed-effects model was employed, and the heterogeneity test indicated no significant heterogeneity ($I^2 = 0\%$; $p = 0.59$). In the C-Ripples group, the estimated model yielded a significant result (OR = 4.45; 95% CI: 1.33–14.89; $p = 0.02$). Patients with C-Ripples demonstrated a significantly better prognosis compared with those with incomplete removal.

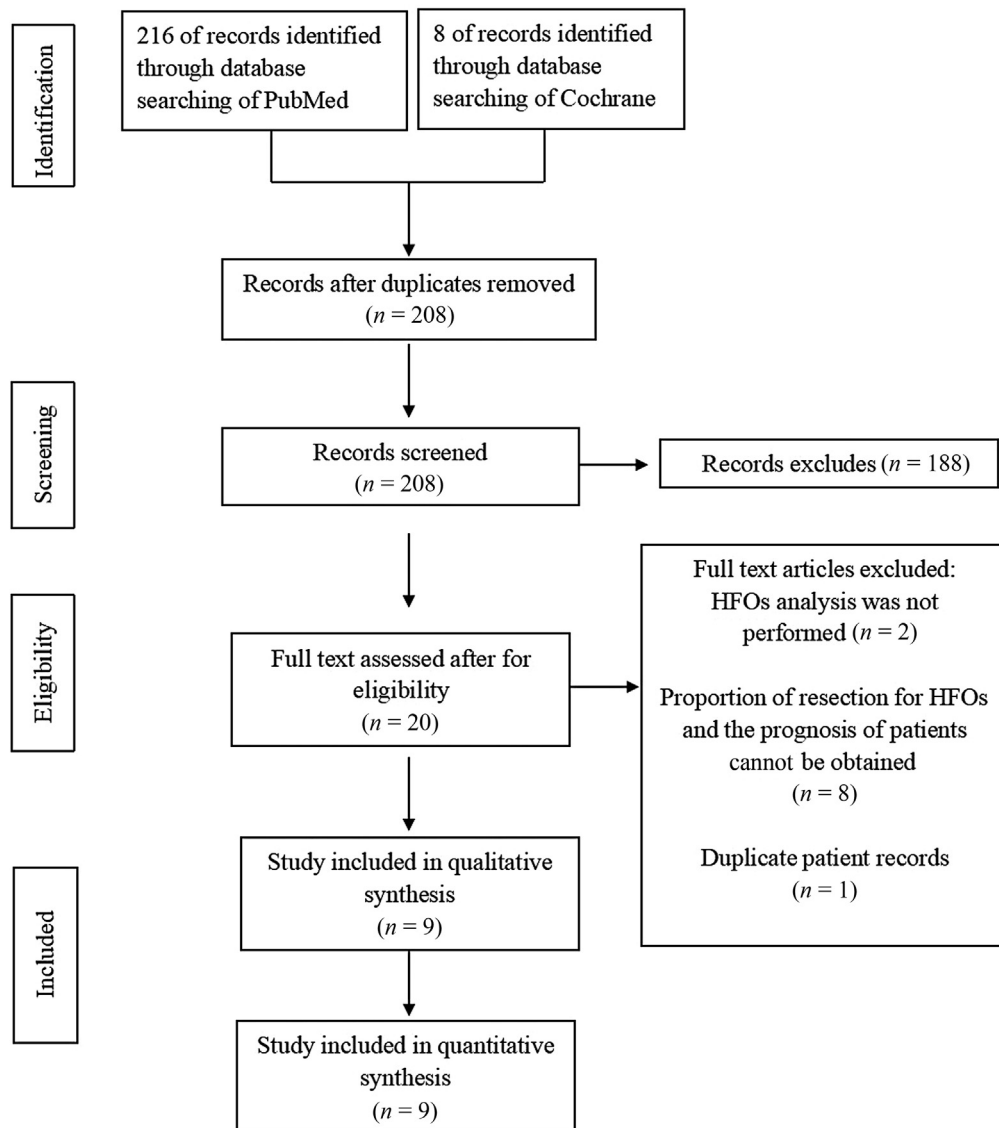


Fig. 1 Flow diagram of study selection. HFOs, high-frequency oscillations.

Majority of FR Removed and Prognosis

Data regarding the majority of FR removed was obtained from five studies. Since Fedele et al³⁶ did not specify the criteria for the majority removed FR, we applied the equation listed earlier¹³ to define the majority removed FR. ►Fig. 5 presents the meta-analysis results regarding the relationship between the majority of FR removed and patient prognosis in the P-FR group.

The fixed-effects model was utilized, and the heterogeneity test indicated no significant heterogeneity ($I^2 = 0\%$; $p = 0.68$). The estimated model yielded a significant result, indicating that patients with the majority of FR removed had a significantly higher prognosis compared with those with the majority of FR untouched (OR = 6.23; 95% CI: 2.04–19.06; $p = 0.001$).

Majority of Ripples Removed and Prognosis

Similar to the previous analysis, data on the majority of ripples removed were obtained from the aforementioned study. The same method was applied to the data from Fedele

et al³⁶ to define the criteria for the majority of ripples removed. ►Fig. 6 depicts the meta-analysis results for the majority of ripples removed and patient prognosis in the P-Ripples group. The fixed-effects model was used, and the heterogeneity test indicated no significant heterogeneity ($I^2 = 0\%$; $p = 0.67$). The estimated model yielded a significant result, showing that patients with the majority of ripples removed had a significantly better prognosis compared with those with the majority of ripples untouched (OR = 8.14; 95% CI: 2.62–25.33; $p = 0.0003$). The seizure-free ratio was higher in the majority of ripples removed groups than in the majority of ripples untouched groups.

Discussion

This study included a total of nine studies involving 228 patients, which were categorized into four groups based on the removal of HFOs: C-FR, C-Ripples, P-FR, and P-Ripples.

Table 1 Basic information of the included research literature

Study	Age at surgery (y)	iEEG	Detection	Threshold	HFOs	Sample	Female	Follow-up	Outcome
Akiyama et al ⁴¹	10.68 ± 5.0	SEEG/ ECoG	Auto	Bootstrapping	R/FR	28	–	≥2 y	LIAE
Fujiwara, 2012	–	ECoG	Auto	1/min	FR	41	–	≥12 mo	–
van Klink, 2014	18.43 ± 10.39	ECoG	Auto	1/min	R/FR	14	7	≥12 mo	Engel
Okanishi et al ⁴⁰	9.35 ± 5.26	ECoG	Auto	Bootstrapping	R/FR	10	4	≥19 mo	Engel
Fujiwara et al ³⁴	5.96 ± 4.43	ECoG	–	–	R/FR	14	7	–	LIAE
Hussain et al ³¹	8.93 ± 5.34	ECoG	Visually	–	FR	30	15	52.84 ± 26.29 mo	–
Fedele et al ³⁶	32.1 ± 11.5	SEEG/ ECoG	Auto	95%	R/FR	20	6	25.1 ± 12.5 mo	ILAE
Jacobs et al ³⁹	23.2 ± 17.2	SEEG/ ECoG	Visually/ auto	–	R/FR	52	34	≥12 mo	Engel
Nariai et al ³⁵	13.1 ± 5.4	SEEG/ ECoG	Visually	–	FR	19	10	–	–

Abbreviations: ECoG, electrocorticogram; FR, fast ripples; HFO, high-frequency oscillation; iEEG, intracranial electroencephalography; ILAE, International League Against Epilepsy; R, ripples; SEEG, stereoelectroencephalography.

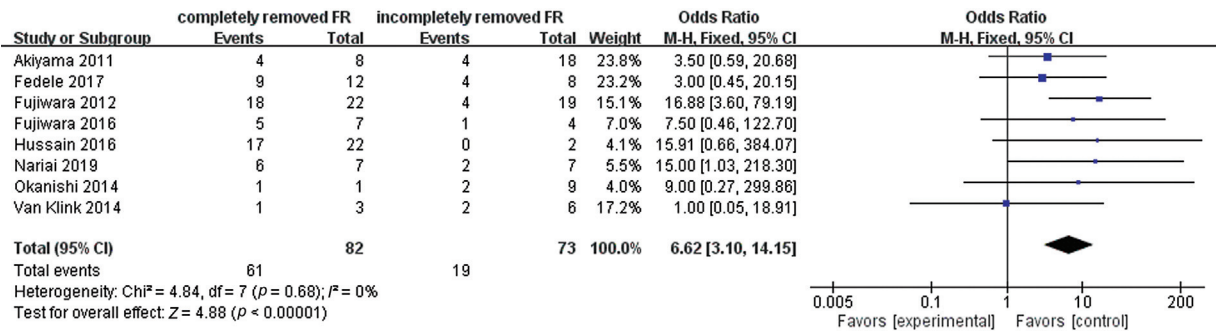


Fig. 2 Completely removed fast ripples (FR) and outcome. In seven studies, the confidence intervals (CIs) overlap with 0, indicating no clear difference in outcome between patients based on these seven studies alone. However, the pooled meta-analysis demonstrates a significant positive difference that does not overlap with 0. Therefore, it can be concluded that patients with completely removed FR have a better prognosis compared with those with incompletely removed FR (odds ratio [OR] = 6.62; 95% confidence interval [CI]: 3.10–14.15; $p < 0.00001$).

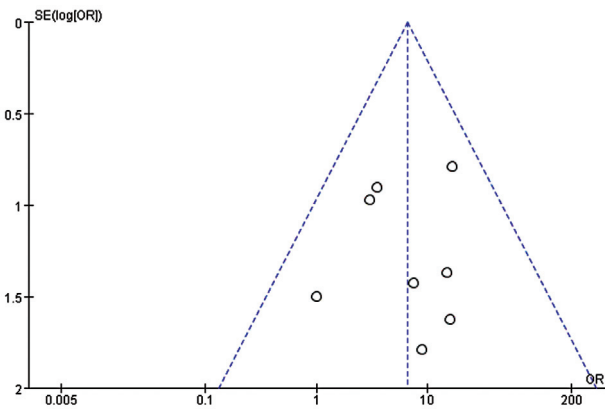


Fig. 3 Funnel plot. OR, odds ratio; SE, standard error.

The estimated model for all groups revealed that removing a larger region of HFOs could significantly enhance patient prognosis.

Prospective Studies

Currently, there is no standardized method for HFO detection, and interrater reliability remains a major challenge.^{37,38} Notably, a previous meta-analysis by Gloss et al²¹ that included two prospective studies reported no evidence supporting the use of HFOs to improve the efficacy of epileptic surgery. However, these findings are inconsistent with previous studies, likely due to variations in evaluation criteria and analysis methods for HFOs. In a recent prospective multicenter study by Jacobs et al,³⁹ which was one of the studies included in our analysis, complete removal of HFOs

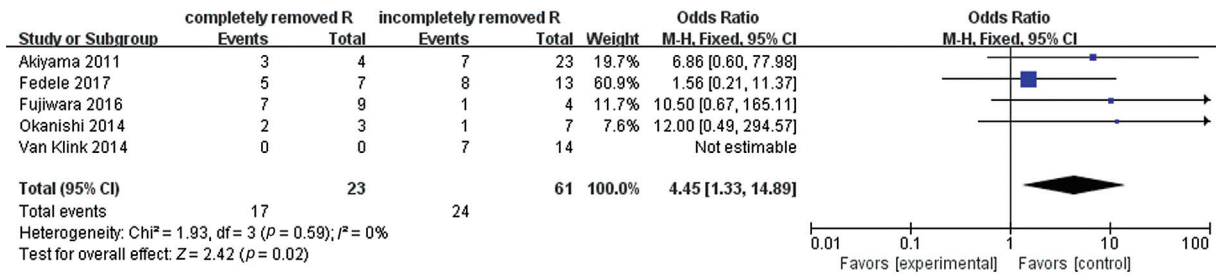


Fig. 4 Completely removed ripples and outcome. In four studies, the confidence intervals (CIs) overlap with 0, suggesting no clear difference in outcome between patients based on these four studies individually. However, the pooled meta-analysis reveals a positive difference without overlap with 0, indicating that the prognosis of patients with completely removed ripples is better than that of patients with incompletely removed ripples (odds ratio [OR] = 4.45; 95% CI: 1.33–14.89; $p = 0.02$).

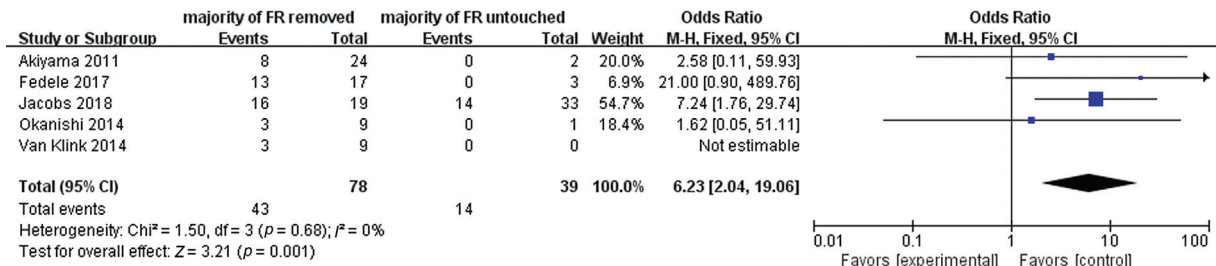


Fig. 5 Majority of fast ripples (FR) removed and outcome. In three studies, the confidence intervals (CIs) overlap with 0, indicating no clear difference in outcome between patients based on these three studies alone. Nevertheless, the pooled meta-analysis demonstrates a significant positive difference that does not overlap with 0. Thus, it can be concluded that the prognosis of patients with the majority of FR removed is better than that of patients with the majority of FR untouched (odds ratio [OR] = 6.23; 95% CI: 2.04–19.06; $p = 0.001$).

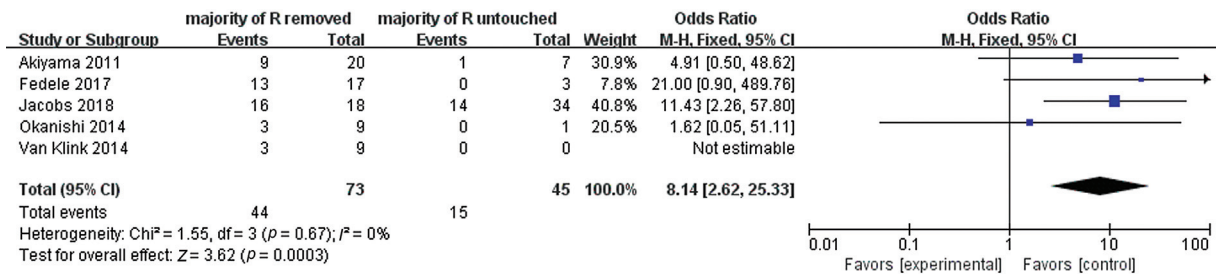


Fig. 6 Majority of ripples removed and outcome. In three studies, the confidence intervals (CIs) overlap with 0, suggesting no clear difference in outcome between patients based on these three studies individually. However, the pooled meta-analysis reveals a positive difference without overlap with 0, indicating that the prognosis of patients with the majority of ripples removed is better than that of patients with the majority of ripples untouched (odds ratio [OR] = 8.14; 95% CI: 2.62–25.33; $p = 0.0003$).

did not demonstrate a significant association with the efficacy of epileptic surgery. Nevertheless, their data from a single center suggested that completely removing HFOs was more likely to improve patient outcomes, consistent with their previous studies. The consistent positive results from this single-center study may be attributed to Jacobs et al.³⁹ using uniform criteria for recording and analyzing HFOs. Therefore, conducting prospective studies using consistent methods could yield more reliable and significant results.

A study by Nariai et al.³⁵ also included in our analysis, was the first prospective study to provide evidence linking complete

removal of visually recognized FR in ECoG with postoperative prognosis in epilepsy patients, supporting the findings of our meta-analysis. However, it is worth mentioning that similar prospective studies have included a limited number of cases, which reduces the credibility of their results. This limitation mainly stems from the high technical requirements and economic costs associated with these studies. Therefore, in the future, conducting more prospective studies with consistent criteria, either through a multicenter collaboration or systematic evaluations, would be beneficial in reducing heterogeneity among studies.

Heterogeneity

Studies by Okanishi et al⁴⁰ and Fujiwara et al³⁴ focused on minors with multiple tuberous sclerosis, while Akiyama et al⁴¹ and Hussain et al³¹ also exclusively included minors. Subgroup analysis of these four studies could be conducted if necessary to explore the relationship between HFOs and surgical efficacy in patients with multiple tuberous sclerosis complex or intractable epilepsy among minors. In a prospective multicenter study by Jacobs et al,³⁹ artificial visual recognition of HFOs was employed to test the effectiveness of automatic HFO detection. However, visual recognition is subjective, and the reliability of automatic HFO detection remains a subject of debate. Therefore, further studies are warranted to investigate this aspect.

Automated Detection

In recent years, many researchers have shifted toward the use of newly developed automatic detection methods instead of visual detection. Höller et al²² discovered that automatic detection outperforms visual detection. Moreover, when it comes to detecting HFOs in the operating room immediately after resection, automatic detection becomes essential. However, it should be noted that many detectors require offline processing of recorded signals to apply automatic or semiautomatic artifact elimination stages for the removal of events incorrectly classified as HFOs. Therefore, the development of automatic detection has become increasingly significant.

To comprehend the superiority of automatic detection over visual detection, researchers are increasingly emphasizing the need to compare the relationship between HFO removal and outcomes to verify the efficiency of the detectors in reverse. Previous studies have not established a clear relationship between the two. However, Burelo et al¹⁸ proposed a detector based on a spiking neural network (SNN) and spectral analysis to explore this relationship, offering the possibility of real-time detection of HFOs during epilepsy surgery.

Predicting Individual Outcome

Although the analysis at the group level revealed a correlation between the removal of HFO-generating tissue and seizure freedom, it should be noted that accurate prediction of patient outcomes based on HFO removal is limited to a subset of patients.^{13,14} In contrast to population-level results, it has been observed that HFOs are not consistently effective in identifying seizures at an individual patient level, as they exhibit similarities to spikes.¹⁹ This discrepancy may arise due to the challenge of differentiating physiological HFOs from pathological HFOs. There is significant frequency overlap between these two types of HFOs,^{42–45} and relying solely on frequency and amplitude analysis is inadequate for distinguishing between them.^{46,47} Therefore, achieving a better distinction between physiological and pathological HFOs may enhance the ability to predict the prognosis of individual patients.

Postoperative residual HFOs also hold importance in predicting the prognosis of individual patients. Many researchers have emphasized the significance of using residual HFOs to predict epilepsy outcomes. They have found that residual HFOs

observed in ECoG recordings may provide more reliable predictions of seizure outcomes compared with preoperative HFOs.^{4,48}

Conclusion

Our study reveals a significant correlation between the removal of HFOs and achieving seizure freedom. Specifically, the removal of a larger region containing HFOs is associated with favorable postoperative seizure outcomes. This meta-analysis highlights the crucial role of HFOs in identifying the EZ and guiding surgical strategies. However, to validate these findings, it is imperative to conduct prospective multicenter studies with standardized protocols and methods. Furthermore, additional research is needed to investigate the impact of residual HFOs on seizure outcomes. The efficacy of residual HFOs relies on the development of more advanced techniques for automatic intraoperative detection of HFOs. Hence, the future advancement of automatic intraoperative detectors holds great importance in this regard.

Funding

This work was supported by a joint key project (grant number: 2019LH01); Department of Science and Technology of Sichuan Province (grant number: 22CXRC0178); Medical Innovation Project (grant number: 21WQ040); Southwest Jiaotong University Medical and Industrial Combination Training Special Project (grant number: 2682021ZTPY024); Hospital Management Project of Western General Hospital (grant numbers 2021-XZYG-B22); and Hospital Management Project of Western Command General Hospital (grant numbers 2021-XZYG-B21).

Conflict of Interest

None declared.

References

- 1 Bragin A, Engel J Jr, Wilson CL, Fried I, Buzsáki G. High-frequency oscillations in human brain. *Hippocampus* 1999;9(02):137–142
- 2 Jacobs J, Levan P, Châtilion CE, Olivier A, Dubeau F, Gotman J. High frequency oscillations in intracranial EEGs mark epileptogenicity rather than lesion type. *Brain* 2009;132(Pt 4):1022–1037
- 3 Zijlmans M, Jiruska P, Zelmman R, Leijten FS, Jefferys JG, Gotman J. High-frequency oscillations as a new biomarker in epilepsy. *Ann Neurol* 2012;71(02):169–178
- 4 van 't Klooster MA, van Klink NEC, Zweiphenning WJEM, et al. Tailoring epilepsy surgery with fast ripples in the intraoperative electrocorticogram. *Ann Neurol* 2017;81(05):664–676
- 5 van Klink NEC, Zweiphenning WJEM, Ferrier CH, et al. Can we use intraoperative high-frequency oscillations to guide tumor-related epilepsy surgery? *Epilepsia* 2021;62(04):997–1004
- 6 Liu S, Gurses C, Sha Z, et al. Stereotyped high-frequency oscillations discriminate seizure onset zones and critical functional cortex in focal epilepsy. *Brain* 2018;141(03):713–730
- 7 Zijlmans M, Jacobs J, Kahn YU, Zelmman R, Dubeau F, Gotman J. Ictal and interictal high frequency oscillations in patients with focal epilepsy. *Clin Neurophysiol* 2011;122(04):664–671
- 8 Urrestarazu E, Jirsch JD, LeVan P, et al. High-frequency intracerebral EEG activity (100–500 Hz) following interictal spikes. *Epilepsia* 2006;47(09):1465–1476

- 9 Ren L, Kuciewicz MT, Cimbálik J, et al. Gamma oscillations precede interictal epileptiform spikes in the seizure onset zone. *Neurology* 2015;84(06):602–608
- 10 Guragain H, Cimbálik J, Stead M, et al. Spatial variation in high-frequency oscillation rates and amplitudes in intracranial EEG. *Neurology* 2018;90(08):e639–e646
- 11 Schönberger J, Huber C, Lachner-Piza D, et al. Interictal fast ripples are associated with the seizure-generating lesion in patients with dual pathology. *Front Neurol* 2020;11:573975
- 12 Wu JY, Sankar R, Lerner JT, Matsumoto JH, Vinters HV, Mathern GW. Removing interictal fast ripples on electrocorticography linked with seizure freedom in children. *Neurology* 2010;75(19):1686–1694
- 13 Jacobs J, Zijlmans M, Zelmann R, et al. High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. *Ann Neurol* 2010;67(02):209–220
- 14 Haegelen C, Perucca P, Châtillon CE, et al. High-frequency oscillations, extent of surgical resection, and surgical outcome in drug-resistant focal epilepsy. *Epilepsia* 2013;54(05):848–857
- 15 Boran E, Ramantani G, Krayenbühl N, et al. High-density ECoG improves the detection of high frequency oscillations that predict seizure outcome. *Clin Neurophysiol* 2019;130(10):1882–1888
- 16 Fedele T, Ramantani G, Burnos S, et al. Prediction of seizure outcome improved by fast ripples detected in low-noise intraoperative corticogram. *Clin Neurophysiol* 2017;128(07):1220–1226
- 17 Weiss SA, Berry B, Chervoneva I, et al. Visually validated semi-automatic high-frequency oscillation detection aides the delineation of epileptogenic regions during intra-operative electrocorticography. *Clin Neurophysiol* 2018;129(10):2089–2098
- 18 Burelo K, Sharifshazileh M, Krayenbühl N, Ramantani G, Indiveri G, Sarnthein J. A spiking neural network (SNN) for detecting high frequency oscillations (HFOs) in the intraoperative ECoG. *Sci Rep* 2021;11(01):6719
- 19 Roehri N, Pizzo F, Lagarde S, et al. High-frequency oscillations are not better biomarkers of epileptogenic tissues than spikes. *Ann Neurol* 2018;83(01):84–97
- 20 Roehri N, Bartolomei F. Are high-frequency oscillations better biomarkers of the epileptogenic zone than spikes? *Curr Opin Neurol* 2019;32(02):213–219
- 21 Gloss D, Nevitt SJ, Staba R. The role of high-frequency oscillations in epilepsy surgery planning. *Cochrane Database Syst Rev* 2017;10(10):CD010235
- 22 Höller Y, Kutil R, Klaffenböck L, et al. High-frequency oscillations in epilepsy and surgical outcome. A meta-analysis. *Front Hum Neurosci* 2015;9:574
- 23 Mo JJ, Hu WH, Zhang C, et al. Value of stereo-electroencephalogram in reoperation of patients with pharmacoresistant epilepsy: a single center, retrospective study. *Br J Neurosurg* 2018;32(06):663–670
- 24 Ollivier I, Behr C, Cebula H, et al. Efficacy and safety in frameless robot-assisted stereo-electroencephalography (SEEG) for drug-resistant epilepsy. *Neurochirurgie* 2017;63(04):286–290
- 25 Goldstein HE, Youngerman BE, Shao B, et al. Safety and efficacy of stereoelectroencephalography in pediatric focal epilepsy: a single-center experience. *J Neurosurg Pediatr* 2018;22(04):444–452
- 26 Bruder JC, Schmelzeisen C, Lachner-Piza D, Reinacher P, Schulze-Bonhage A, Jacobs J. Physiological ripples associated with sleep spindles can be identified in patients with refractory epilepsy beyond mesio-temporal structures. *Front Neurol* 2021;12:612293
- 27 Rosenow F, Lüders H. Presurgical evaluation of epilepsy. *Brain* 2001;124(Pt 9):1683–1700
- 28 Blount JP, Cormier J, Kim H, Kankirawatana P, Riley KO, Knowlton RC. Advances in intracranial monitoring. *Neurosurg Focus* 2008;25(03):E18
- 29 Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928
- 30 Hussain SA, Mathern GW, Hung P, Weng J, Sankar R, Wu JY. Intraoperative fast ripples independently predict postsurgical epilepsy outcome: comparison with other electrocorticographic phenomena. *Epilepsy Res* 2017;135:79–86
- 31 Hussain SA, Mathern GW, Sankar R, Wu JY. Prospective and “live” fast ripple detection and localization in the operating room: impact on epilepsy surgery outcomes in children. *Epilepsy Res* 2016;127:344–351
- 32 Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001;323(7304):101–105
- 33 Tridante A, De Martino L, De Luca D. Porcine vs bovine surfactant therapy for preterm neonates with RDS: systematic review with biological plausibility and pragmatic meta-analysis of respiratory outcomes. *Respir Res* 2019;20(01):28
- 34 Fujiwara H, Leach JL, Greiner HM, et al. Resection of ictal high frequency oscillations is associated with favorable surgical outcome in pediatric drug resistant epilepsy secondary to tuberous sclerosis complex. *Epilepsy Res* 2016;126:90–97
- 35 Nariai H, Hussain SA, Bernardo D, et al. Prospective observational study: fast ripple localization delineates the epileptogenic zone. *Clin Neurophysiol* 2019;130(11):2144–2152
- 36 Fedele T, Burnos S, Boran E, et al. Resection of high frequency oscillations predicts seizure outcome in the individual patient. *Sci Rep* 2017;7(01):13836
- 37 Frauscher B, Bartolomei F, Kobayashi K, et al. High-frequency oscillations: the state of clinical research. *Epilepsia* 2017;58(08):1316–1329
- 38 Spring AM, Pittman DJ, Aghakhani Y, et al. Interrater reliability of visually evaluated high frequency oscillations. *Clin Neurophysiol* 2017;128(03):433–441
- 39 Jacobs J, Wu JY, Perucca P, et al. Removing high-frequency oscillations: a prospective multicenter study on seizure outcome. *Neurology* 2018;91(11):e1040–e1052
- 40 Okanishi T, Akiyama T, Tanaka S, et al. Interictal high frequency oscillations correlating with seizure outcome in patients with widespread epileptic networks in tuberous sclerosis complex. *Epilepsia* 2014;55(10):1602–1610
- 41 Akiyama T, McCoy B, Go CY, et al. Focal resection of fast ripples on extraoperative intracranial EEG improves seizure outcome in pediatric epilepsy. *Epilepsia* 2011;52(10):1802–1811
- 42 Engel J Jr, Bragin A, Staba R, Mody I. High-frequency oscillations: what is normal and what is not? *Epilepsia* 2009;50(04):598–604
- 43 Matsumoto A, Brinkmann BH, Matthew Stead S, et al. Pathological and physiological high-frequency oscillations in focal human epilepsy. *J Neurophysiol* 2013;110(08):1958–1964
- 44 Pail M, Cimbálik J, Roman R, et al. High frequency oscillations in epileptic and non-epileptic human hippocampus during a cognitive task. *Sci Rep* 2020;10(01):18147
- 45 Brázdil M, Cimbálik J, Roman R, et al. Impact of cognitive stimulation on ripples within human epileptic and non-epileptic hippocampus. *BMC Neurosci* 2015;16:47
- 46 Pail M, Řehulka P, Cimbálik J, Doležalová I, Chrástina J, Brázdil M. Frequency-independent characteristics of high-frequency oscillations in epileptic and non-epileptic regions. *Clin Neurophysiol* 2017;128(01):106–114
- 47 Nagasawa T, Juhász C, Rothermel R, Hoechstetter K, Sood S, Asano E. Spontaneous and visually driven high-frequency oscillations in the occipital cortex: intracranial recording in epileptic patients. *Hum Brain Mapp* 2012;33(03):569–583
- 48 van 't Klooster MA, van Klink NE, Leijten FS, et al. Residual fast ripples in the intraoperative corticogram predict epilepsy surgery outcome. *Neurology* 2015;85(02):120–128