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A Preliminary Study on Multivariate Prediction of Seizure Outcome after Epilepsy Surgery

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Abstract

Surgical outcomes of epilepsy surgery vary across patients, and clinicians need to estimate possible outcomes before surgery. The aim of this study was to identify predictors of seizure outcome one year after surgery for patients with drug-resistant epilepsy. Twenty-three patients with Temporal Lobe Epilepsy (TLE) who underwent surgery were included in the study. Their demographical information, seizure history, findings of EEG and neuroimaging tests (mainly Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS), intracranial EEG (icEEG) findings, seizure outcome and pathological findings were reviewed. Bivariate analyses were performed to examine the univariate association of each variable with the outcome, and exclude the most insignificant ones. The remaining data were randomly assigned to the training and test sets, and three multivariate analysis approaches (Logistic Regression (LR), Linear Discriminant Analysis (LDA) and Artificial Neural Network (ANN)) were performed repetitively. Model performance was compared using Receiver-Operating Characteristic (ROC) analysis. Resampling the data to the training and test sets resulted in large variations in the classification accuracies of each multivariate approach. The ROC results indicated that the medium classification performances were moderate. Important outcome predictors identified included EEG lateralization score, icEEG lateralization score, and the presence of Hippocampal Sclerosis (HS). The results suggested that multivariate models could predict seizure outcome after TLE surgery with moderate accuracy. Further studies are needed to improve prediction accuracy and identify reliable predictors of seizure outcome.

Introduction

Epilepsy surgery opens the possibility of complete seizure control and brings the hope of seizure-free outcome for patients with drug-resistant epilepsy. Over decades, epilepsy surgery has improved gradually and approached 60% to 90% seizure-free outcome in patients with Temporal Lobe Epilepsy (TLE) and 40% to 60% in Extra Temporal Lobe Epilepsy (ETLE) [1]. However, surgical outcomes vary across patients, and clinicians need to weigh the risks of this procedure and estimate possible outcomes before surgery. Therefore, identification of prognostic factors for surgical outcome is important for outcome research, which may reduce the uncertainties in surgical candidates.

A number of clinical and demographic factors have been found associated with or unrelated to postsurgical seizure outcome. For example, factors such as lesional epilepsy, abnormal MRI, partial seizures, and complete resection were found to be positively associated with seizure outcome, and factors such as nonlesional epilepsy, poorly defined and localized epileptic focus, generalized seizures, and incomplete resection are negatively associated with outcome, while factors such as age at surgery and side of surgery are unrelated to seizure outcome for TLE and lesional ETLE [2].

However, prognostic factors identified vary across patient groups and studies. For a specific group of patients who underwent epilepsy surgery at a local epilepsy center, it is still unclear which factor in the presurgical or pathological findings is associated with postsurgical seizure outcome. In addition, previous studies showed that combining multiple prognostic factors in multivariate models to predict postoperative seizure outcome achieved moderate accuracy, e.g., Receiver Operating Characteristic (ROC) area of 0.63 [3]-0.74 [4]. Then, the question is: How accurate such outcome prediction is in a local patient population? Further, due to difficulties in data collection, patient data of small sample size are sometimes acquired and when the subject sample is small, how to obtain stable results?

In this study, we investigated the associations of the presurgical and pathological findings with seizure outcome one year after surgery in patients with drug-resistant Temporal Lobe Epilepsy (TLE) and identified factors that might indicate seizure outcome. Due to the relatively small sample size, multiple statistical analyses and bootstrap resampling were used to reduce bias.

Methods

Subjects

24 consecutive patients with drug-resistant epilepsy were admitted to the Department of Functional Neurology and Neurosurgery, Beijing Haidian Hospital during 2010 (July)-2012 (April) and were assessed for presurgical evaluation. 23 of them (8 females, 15 males, mean age at surgery: 26.9 ± 10.5 years) underwent surgery and were included in this study. The patients were diagnosed as TLE and underwent presurgical evaluation. Surgical outcomes were evaluated with Engel classification during patients 'post-operative revisits and the patients' follow up lasted for 1.5~3 years. This study was approved by the Institutional Review Board (IRB) at the Capital Medical University.

Surgery consisted of temporal lobe resection including amygdala hippocampectomy (15/23, 65.2%), and temporal lobe resection

together with tailored lesionectomy in the extra-temporal lobe (e.g., the frontal lobe) (8/23, 34.8%).

Data collection

The patients' demographical information, seizure history, the findings of presurgical EEG and imaging tests (mainly including Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS), Intracranial EEG (icEEG) findings, seizure outcome and pathological findings were reviewed [2].

The findings of imaging modalities were combined as imaging lateralization score for each patient, and the findings of EEG and/or icEEG were combined as EEG and/or icEEG lateralization scores. The lateralization scores of EEG, imaging and/or icEEG were determined as follows: For EEG, if there were clear correct lateralization findings in the ictal and/or interictal EEG data (concordant with intraoperative icEEG findings or the surgical site), then the EEG lateralization score was 1; if correct lateralization findings were uncertain, then 0.5; if there were non-lateralizing finding or wrong findings, then 0. For imaging (e.g., MRI), if there were clear correct lateralization findings, then the lateralization score for that imaging modality was 1; if the correct lateralization findings were uncertain, then 0.5; and if there were no findings or wrong findings (on abnormalities), then 0. The imaging lateralization score combined the lateralization scores of all presurgical imaging tests of every patient. For icEEG, if icEEG correctly lateralized the seizure focus, then the icEEG lateralization score was 1; if icEEG generated uncertain lateralization findings consistent with the surgical site, then 0.5; if icEEG had non-localizing finding or wrong findings or icEEG was not used, then 0.

Postoperative outcome

Seizure outcome was assessed based on clinical follow-up (on average 1 year after surgery) and classified into two categories [seizure free (Engel class I) vs. non-seizure-free (Engel class II-IV)] according to Engel classification.

Statistical analysis

Seven presurgical and/or pathological finding variables [age at surgery, gender, seizure duration, EEG lateralization score, imaging lateralization score, icEEG lateralization score and the presence of Hippocampal Sclerosis (HS)] were assessed. Due to the relatively small sample size (n=23), multiple statistical analysis approaches and bootstrap resampling were applied to the data to reduce related bias.

The chi-square test, *t*-test and bivariate Logistic Regression (LR) were performed as bivariate analyses to examine univariate association of each variable with the outcome. Resampling technique bootstrap (1000 samples) was used to estimate significance of the variables in bivariate LR. The most insignificant variables were excluded.

The remaining data were randomly assigned to the training and test sets, and three multivariate analyses [including LR, Linear Discriminant Analysis (LDA) and Artificial Neural Network (ANN)] were performed repetitively on the remaining data. In LR analysis, forward stepwise and backward stepwise selection approaches were used to develop models, and the variables in three LR models (with 3, 4 and 5 variables respectively) were assessed with bootstrap resampling. In ANN analysis, a portion of training data were reassigned to the testing set to help keep the network on track and avoid overtraining, i.e., chasing spurious patterns that appear in the training data by random variation [5].

Due to the variations in classification results, the model with

medium performance in each multivariate analysis method was selected. Outcome predictors were identified, and classification accuracies of the models were compared with ROC analysis. Bootstrap (1000 samples) was used in LR and LDA to estimate standard errors, confidence intervals and variable significance. All statistical analyses were performed with SPSS version 21 [5].

Results

Bivariate analyses

The results of chi-square test, *t*-test and bivariate logistic regression are shown in Table 1, which indicated that EEG lateralization score and icEEG lateralization score were significantly ($p<0.05$) associated with the outcome (and the presence of HS was 1-tailed significant at $p<0.1$), while age at surgery and gender were the least significant variables (associated with the outcome). Based on these results, the two most insignificant variables (age at surgery and gender) were excluded from further analyses (Table 1).

Multivariate analyses

The remaining 5 variables were used as dependent variables or input nodes in the multivariate analyses (LR, LDA and ANN). Among the models in the LR analysis, the Hosmer and Lemeshow test indicated a good model fit (*p*-values great than 0.05) for the three LR models (Table 2). Table 2 also shows that LR analysis found that

	Chi-square (*p*-value)	t-test (*p*-value)	Bivariate logistic regression			
			Sig. (*p*-value)	Sig.* (*p*-value)	Odds Ratio	95% CI.
Age at surgery (year)	0.497	0.574	0.556	0.513	0.974	0.893-1.063
Gender	0.472	0.495	0.388	0.476	0.500	0.074-3.359
Seizure duration (year)	0.250	0.221	0.214	0.199	1.076	0.958-1.095
EEG	**0.043**	**0.032**	**0.043**	**0.016**	0.119	0.015-0.932
Imaging	0.245	0.381	0.323	0.316	0.346	0.042-2.833
icEEG	0.074	**0.048**	0.058	**0.040**	7.308	0.932-57.280
HS (yes/no)	0.172	0.145	0.196	0.096	4.667	0.451-48.257

Sig.: Significance, p<0.05 in bold and gray background, p<0.1 in gray background; Sig.*: Significance generated by bootstrap resampling; CI: Confidence Interval of odds ratio; EEG: Correct lateralization of EEG compared with the surgical site; Imaging: Correct lateralization of imaging including MRI and MRS; icEEG: Correct lateralization of icEEG; HS (Hippocampus Sclerosis): The presence of HS in the surgical site based on pathological findings.

Table 1: Univariate associations of each variable with seizure outcome .

	Model 1		Model 2		Model 3	
H&L Sig.	0.18		0.22		0.16	
	Odds Ratio (95% CI)	*p*-value	Odds Ratio (95% CI)	*p*-value	Odds Ratio (95% CI)	*p*-value
Seizure duration	1.19 (0.97,1.47)	**0.04**	1.17 (0.96,1.43)	**0.04**	1.19 (0.95,1.49)	0.01
EEG	0.06 (0.00,0.90)	**0.01**	0.13 (0.01,3.54)	0.09	0.18 (0.01,5.28)	0.13
Imaging					0.17 (0.00, 6.95)	0.08
icEEG			3.25 (0.17,62.57)	0.23	6.02 (0.22,164.73)	0.08
HS	14.42 (0.52, 401.00)	**0.03**	13.45 (0.59,305.00)	**0.03**	0.04 (0.55,1012.03)	**0.02**

H&L Sig.: Hosmer and Lemeshow test significance; *p*-value: Bootstrap *p*-value; CI: Confidence interval

(A) Logistic regression models with bootstrap resampling

	Wilks' Lambda	Sig.	Structure Matrix	Standardized Coefficient	Bootstrap*		
					S.E.	95% CI	
						Lower	Lower
Seizure duration	.930	0.221	0.318	.616	.665	-1.080	1.448
EEG	.800	**0.032**	-0.577	-.433	.825	-1.390	1.611
Imaging	.956	0.339	-0.247	-.234	.581	-1.019	1.204
icEEG	.827	**0.048**	0.528	.486	.638	-.585	1.992
HS	.919	0.188	0.343	.698	.720	-1.114	1.666

*Based on 999 bootstrap samples; CI: Confidence Interval; The model explained 100% of the total variance indicating the efficacy of its discriminant function; Wilks' lambda value of the model was 0.572, and the significance of Wilks' lambda associated chi-square test was 0.066 indicating that the discriminant function did better than chance (1-tailed, p<0.10) at separating the data into the two outcome groups.
(B) Linear discriminant analysis with bootstrap resampling

Table 2: Multivariate models including predictors of seizure outcome.

Method	Order of importance				
LR*	EEG	HS	Seizure Duration	icEEG	Imaging
LDA	EEG	icEEG	HS	Seizure Duration	Imaging
ANN	EEG	HS	icEEG	Seizure Duration	Imaging

LR: Logistic Regression; LDA: Linear Discriminant Analysis; ANN: Artificial Neural Network; EEG: EEG lateralization score; Imaging: Imaging lateralization score; IcEEG: icEEG lateralization score; HS: Hippocampal Sclerosis

Table 3: The importance of predictors in multivariate analyses.

EEG lateralization score, the presence of HS and seizure duration were the most significant predictors, while LDA analysis revealed that EEG lateralization score, icEEG lateralization score and the presence of HS were more significant than the other predictors. The signs of the logistic model coefficients indicated that EEG lateralization score, the presence of HS and imaging lateralization score were positive predictors, while icEEG lateralization score and seizure duration were negative ones. The order of importance of the outcome predictors identified varied across the three multivariate analysis methods (Table 3), and the common important predictors across multivariate methods were EEG lateralization score, icEEG lateralization score, and the presence of HS.

Resampling the data to the training and test sets resulted in large variations in the classification accuracies (33% -95%). Example ROC curves of LR, LDA and ANN are shown in Figure 1. The ROC results indicated that the areas under the curve for the three multivariate analysis methods with medium performance were: 0.825 for LR, 0.858 for LDA, and 0.875 for ANN (Figure 2), and there were no significant differences between the three, revealing moderate classification performance of these multivariate models.

Discussion

In this study, associations of seven presurgical and/or pathological factors with seizure outcome one year after surgery in a local patient population were examined and outcome predictors were identified.

Classification of lateralization characteristics for presurgical variables

The quality of input data is crucial to the result of multivariate analysis. The process of classifying the lateralization characteristics of presurgical EEG, imaging and/or icEEG and determining the lateralization scores for each patient (as presurgical variables) is difficult and fuzzy in nature. It is especially hard to classify the characteristics of interical and ictal spikes of EEG and to determine individual EEG lateralization score. As a result, Baxendale et al. chose the requirement

of icEEG as a proxy for non-lateralizing EEG [6]; while Armon et al. used the percentage of EEG activity arising from the site of resection as the EEG localization variable, which combined the EEG and/or icEEG data based on: (1) invasive seizure localization (i.e., icEEG localization); (2) scalp seizure localization; and (3) interictal localization [4].

In this study, the rules that used to determine individual EEG, imaging and/or icEEG lateralization scores were simple and straightforward, but they may be oversimplified and the scores obtained via these rules might not be precise enough to accurately reflect the true lateralization value of each modality for every patient. To reflect the true lateralization value of presurgical tests, further studies with fuzzy logic are needed to improve the classification of the lateralization characteristics of presurgical EEG, imaging and/or icEEG.

Bivariate vs. multivariate analyses

Bivariate analyses (chi-square test, *t*-test and bivariate LR) examine the univariate association of each potential predictor with the outcome, while multivariate analyses (LR, LDA and ANN) assess the multivariate association of the potential predictors with the outcome. The significance obtained from bivariate analyses often changes in the multivariate analyses. In general, multivariate analysis overcomes the limitations of bivariate analysis by correcting its often over-optimistic significance results via assessing the incremental contribution of each predictor while controlling the others [4]. In this study, the bootstrap significances of EEG and icEEG lateralization scores (p=0.016 or 0.040) obtained from bivariate LR analysis (Table 1) were reduced and the two variables became less significant in two multivariate LR models in Table 2 (e.g., p=0.09 or 0.13 for EEG, p=0.23 or 0.08 for icEEG lateralization score), while the bootstrap significance for the presence of HS (p=0.096) obtained from bivariate LR analysis (Table 1) increased slightly in the multivariate LR analyses (e.g., p=0.03 or 0.02, Table 2). The reason for this increase was unclear.

Although SPSS did not give bootstrap significance for each variable in the LDA model, it provided much information on these variables via LDA. Wilks' lambda is a measure of a variable's potential and smaller values indicate the variable is better at discriminating between groups [5]. Significance value less than 0.10 indicates the variable contributes to the LDA model and since the significance values of EEG lateralization score and icEEG lateralization score both were less than 0.05, the two variables contributed to the model in outcome prediction.

However, correlation analysis revealed that EEG lateralization score and icEEG lateralization score were significantly correlated (R=-0.633, p<0.05) and the collinearity between the two variables in the correlation matrix may cause the discrepancy between the order of importance of the variables reflected by the standardized coefficients and that by the structure matrix. The structure matrix unaffected by collinearity indicates the correlation of each predictor variable with the discriminant function [5], it reflected the true importance of the variables and the importance of seizure duration and HS in the standardized coefficients was inflated by the collinearity between variables. Thus, EEG lateralization score best discriminated between seizure free and non-seizure free outcomes in this dataset, followed by icEEG lateralization score, which is consistent with the results of bivariate analyses (Chi-square, *t*-test and bivariate LR). Similarly, the importance of seizure duration and HS in the results of LR analysis (Table 2A) may be inflated as well in the LR models 2 and 3 due to the collinearity between variables. Thus, EEG lateralization score remains the best outcome predictor via LR analysis in this dataset, which is consistent with the findings of other multivariate studies that EEG or icEEG lateralization was a significant outcome predictor [4,6-8].
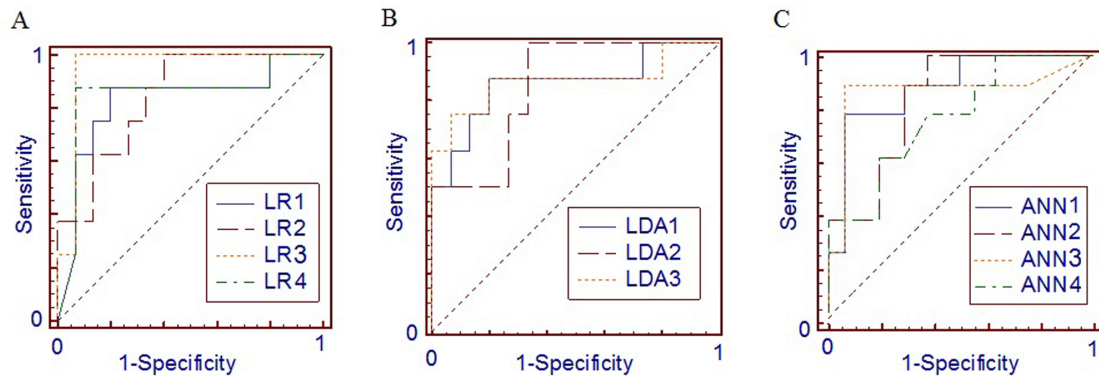
Figure 1: Example ROC curves of multivariate analyses

(A) Example ROC curves of LR: The areas of LR1, LR2, LR3, LR4 were: 0.825, 0.842, 0.950, 0.850; and 95% Confidence Intervals (CI) were: 0.611-0.950, 0.630-0.959, 0.771-0.998, 0.640-0.963 respectively;

(B) Example ROC curves of LDA: The areas of LDA1, LDA2 and LDA3 were: 0.858, 0.850, 0.867; and 95% CI were: 0.650-0.967, 0.640-0.963, 0.661-0.971 respectively;

(C) Example ROC curves of ANN: The areas of ANN1, ANN2, ANN3 and ANN4 were: 0.875, 0.842, 0.850, 0.771; and 95% CI were: 0.671-0.975, 0.630-0.959, 0.640-0.963, 0.550-0.918 respectively
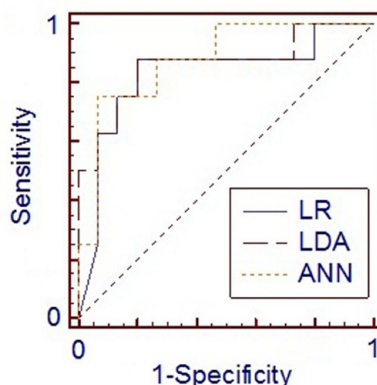

Figure 2: ROC curves of three multivariate analyses (with medium performance).
The area under the curve was 0.825 for LR; 0.858 for LDA; and 0.875 for ANN. The confidence intervals were 0.611-0.950 for LR; 0.650-0.967 for LDA; and 0.671-0.975 for ANN.

LR, LDA and ANN

With variable interactions, LR can be viewed as a generalized linear model (like linear model LDA); while without interactions, it may be viewed as a special case of a generalized nonlinear model like ANN [9]. An advantage of LR and ANN is that few assumptions are made, while LDA has a number of assumptions on the predictors (e.g., normal distribution). Further, ANN might achieve better prediction with fewer restrictions on the structure of the predictive model than LR [9]. An obvious advantage of ANN is that the structure of the model (e.g., a hidden layer) is less dependent on the data (e.g., in the training or test set) which makes it possible to obtain better classification and prediction, while the structure of a LR or LDA model is largely dependent on the data. On the other hand, ANN is like a black box—its model and results are hard to be interpreted, while the predictive models and results of LR and LDA are interpretable.

In this study, the data fitted the LR and ANN models well. With ANN, it is easy to prevent too extreme predictions such as overtraining, which is not straightforward in LR (or LDA). For LDA, although some of the predictor variables (e.g., the categorical variable the presence of HS) did not satisfy the assumptions of the LDA model, the model characteristics (such as Wilks' lambda and its associated chi-square test) indicated the efficacy of the LDA discriminant function (it did better than chance at separating the data into the two outcome groups, Table 2B). In addition, although the medium classification performances were moderate and there were no statistical differences between the three multivariate analysis approaches (LR, LDA, and ANN) in this dataset, ANN still had the potential to obtain better classification and prediction.

In recent years, newer classifiers such as Support Vector Machine (SVM) have been applied to the detection and classification of abnormalities on neuroimaging in epilepsy and other brain disorders and high classification accuracy (>=90%) has been achieved [10-12]. The promising classifier SVM may be applied to this and other related dataset(s) to improve classification and prediction in the future.

The predictive value of presurgical neuroimaging

In this study, the low significance of the imaging lateralization score obtained from multivariate analyses made it a less important predictor compared with other predictors in this dataset (Table 3). Since the imaging lateralization score was a combination of mainly the MRI and MRS data (the PET/SPECT data was available for only 2 patients and was ignored), the predictive value of neuroimaging was examined individually for MRI and MRS. LR analysis found that both MRI and MRS were insignificant, which led to the insignificance of the combined imaging lateralization score in the dataset. The insignificance of MRI and MRS may be due to the low resolution of the MRI scanner used to acquire the neuroimaging data of this study and the lack of experience of the radiologists who inspected the MRI and MRS of these patients [13].

Nevertheless, a number of studies have identified MRI lateralization or imaging abnormalities such as HS/MTS (Mesial Temporal Sclerosis) on MRI as a significant outcome predictor [3,4,8,14-16]. Systematic reviews and meta-analyses have found that abnormal MRI and/or the presence of HS (or other lesions) on MRI (or histopathology) is one of the most common predictors of seizure-free outcome after TLE surgery [17-21]. In addition, Lerner et al., Cossu et al., Widdess-Walsh et al. and Jeha et al. (2007) [22-25] have shown that complete resection of

the abnormality detected by preoperative MRI is the most important predictor of a favorable postoperative outcome. Further, Kuzniecky et al., Eberhardt et al., Stefan et al. [26-28] have demonstrated that bilateral MRS metabolite alterations in TLE with HS have a predictive value for surgical outcome. Thus, further studies are needed to examine the true predictive value of neuroimaging in this and other related dataset(s).

Limitations

Major limitations of this study are two-fold: First, the sample size (n=23) is small, which limits the number of variables examined in the multivariate models and thus "limits the ability to apply multivariate analysis and validation techniques" [4]. Errors and bias in the statistical estimation may be easily introduced into multivariate analyses due to small sample size [9,29,30] and result in unstable results (e.g., classification accuracies: 33%-95%). Although multiple statistical analysis approaches and bootstrap resampling (1000 samples) were applied to the data to reduce such bias, bias might still exist in the multivariate models obtained in this dataset. Further studies with large samples are needed in future studies [31,32].

Second, upon obtaining the classification accuracy (represented by the area of ROC), this study did not adjust over-optimistic prediction of the multivariate models, i.e., the classification accuracies obtained by the study over-optimistically estimated the classification and prediction performance of the multivariate models [9]. Bootstrap techniques are often used to adjust over-optimistic prediction of multivariate analysis. After such adjustment, the classification accuracy (ROC area) will decrease to some extent and reach a more realistic estimate of the usefulness of the multivariate models [3,4]. Two examples of prediction performance with adjustment of over-optimistic prediction were ROC area of 0.63 in 484 TLE patients [3], and ROC area of 0.74 in 116 TLE and extra-temporal-lobe epilepsy patients [4]. Both of them indicated moderate classification accuracies in seizure outcome prediction.

Conclusions

This research investigated the associations of presurgical and pathological findings with seizure outcome one year after surgery in patients with drug-resistant TLE, and identified three important prognostic factors: EEG lateralization, icEEG lateralization, and the presence of HS. The results of this study suggested that multivariate analyses could predict seizure outcome after TLE surgery with moderate accuracy. Further studies are needed to improve prediction accuracy and identify reliable predictors of seizure outcome.

Acknowledgements

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