Efficacy of Repetitive Transcranial Magnetic Stimulation on Neurophysiological Outcomes in Patients with Acute Stroke: A Systematic Review and Meta-analysis

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Abstract [**Objectives**] To evaluate the effects of repetitive transcranial magnetic stimulation (rTMS) on neurophysiological outcomes in patients with acute stroke. [**Methods**] A systematic literature search was conducted across PubMed, EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL databases up to March 1, 2025. Randomized controlled trials (RCTs) and clinical controlled trials (CCTs) involving adult patients (≥18 years) with acute ischemic stroke (within 2 weeks of onset) who received rTMS intervention were included. Data on motor evoked potential (MEP) amplitude, resting motor threshold (RMT), and central motor conduction time (CMCT) were extracted. The quality of the studies was assessed using the Cochrane risk of bias tool. Statistical analyses were performed using Stata 18.0, with standardized mean differences (*SMDs*) and 95% confidence intervals (*CIs*) calculated. Heterogeneity was evaluated using the I^2 statistic. [**Results**] Eight studies involving 932 identified records met the inclusion criteria. Meta-analysis revealed that rTMS significantly increased MEP amplitude (Hedges' $g = 0.77$, 95% CI: 0.52 – 1.02, $P < 0.01$) and reduced RMT (Hedges' $g = -1.13$, 95% CI: -1.63 to -0.62, $P < 0.01$) in the lesioned hemisphere, indicating enhanced corticospinal excitability. No significant effects were observed on MEP amplitude or RMT in the unaffected hemisphere. Additionally, rTMS did not significantly alter CMCT in either hemisphere. Heterogeneity was low to moderate for most outcomes, and no significant publication bias was detected. [**Conclusions**] rTMS is a safe and effective intervention for improving corticospinal excitability and motor recovery in patients with acute stroke. Both high-frequency stimulation of the ipsilesional hemisphere and low-frequency stimulation of the contralesional hemisphere have demonstrated beneficial effects, supporting the interhemispheric inhibition model. Future large-scale, multi-center RCTs are needed to optimize rTMS parameters and establish standardized treatment protocols for acute stroke rehabilitation.

Key words Repetitive transcranial magnetic stimulation (rTMS), Acute stroke, Motor recovery, Meta-analysis, Neurophysiology

1 Introduction

Stroke, a prevalent neurological disorder, is characterized by its high mortality and morbidity rates[1]. Motor dysfunction constitutes the most common neurological deficit in stroke patients, with approximately 80% of survivors suffering from upper limb impairment. Such motor dysfunctions severely undermine patients' ability to engage in activities of daily living and their participation in social life[2]. A wealth of neuroimaging studies has corroborated a close correlation between motor function recovery, cortical remodeling, and synaptic plasticity. Transcranial magnetic stimulation (TMS) is a non-invasive, safe, and effective neurorehabilitation technique that modulates cortical excitability via rapidly changing magnetic fields. It is commonly employed in the treatment of stroke patients to facilitate functional remodeling[3]. At present, the efficacy of repetitive transcranial magnetic stimulation (rTMS) in the treatment of hemiplegia subsequent to chronic stroke has been fully validated[4].

While TMS exhibits considerable potential and distinct advantages as an independent therapeutic intervention for ameliorating post-stroke motor dysfunction, its application in the acute phase (within 2 weeks of onset) remains relatively limited compared to its use in the subacute and chronic phases[5]. Previous meta-analysis focusing on early-stage stroke patients often failed to accurately distinguish between acute and subacute patients, frequently combining these two groups for analytical purposes[6]. Consequently, conducting additional meta-analysis specifically focused on clinical trials involving patients with acute stroke (within 2 weeks of onset) is of significant necessity and practical importance. To the best of the researchers' knowledge, this study represents the first literature to explore the application of rTMS in the treatment of motor dysfunction in patients with acute stroke (within 2 weeks of onset). In the present study, a rigorous screening process and meta-analysis were conducted on recently published literature concerning patients with acute stroke (within 2 weeks of onset), accompanied by a quality assessment. The objective was to systematically review the impacts of rTMS on motor function, activities of daily living, and neurophysiological indicators in patients with acute stroke, thereby providing high-quality evidence-based medical support for the recovery of motor function in this patient cohort.

2 Methods

2.1 Literature search Comprehensive literature searches were performed across multiple databases, including PubMed, EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL (EBSCOhost), with the search period concluding on March 1, 2025. A customized search strategy was formulated for each database, as detailed below. Stroke-related search terms included Stroke[Mesh], "cerebrovascular accident"[Ti/Ab], "cerebrovascular disorder"[Ti/Ab],

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"ischemic stroke"[Ti/Ab], "cerebrovascular apoplexy"[Ti/Ab], "apoplexy"[Ti/Ab], "cerebral infarction"[Ti/Ab], "brain infarction" [Ti/Ab], "brain ischemia" [Ti/Ab], ("stroke" [Mesh] OR "stroke"[Ti/Ab]) AND ("cerebrum"[Mesh] OR "cerebrum" [Ti/Ab] OR "cerebral" [Ti/Ab] OR "brain" [Mesh] OR "brain" [Ti/Ab]). rTMS-related search terms encompassed "Repetitive transcranial magnetic stimulation" [Ti/Ab], "rTMS"[Ti/Ab], "Magnetic Stimulations, Transcranial" [Ti/Ab], "Stimulation, Transcranial Magnetic" [Ti/Ab], "Stimulations, Transcranial Magnetic"[Ti/Ab], "Transcranial Magnetic Stimulations"[Ti/Ab], "Transcranial Magnetic Stimulation, Repetitive"[Ti/Ab], "theta-burst stimulation"[Ti/Ab], "theta burst stimulation"[Ti/Ab], "iTBS"[Ti/Ab], "cTBS" [Ti/Ab].

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria. Study design: only studies adopting a randomized controlled trial (RCT) or clinical controlled trial (CCT) design were included to ensure the rigor and validity of the research methodology. Study population: adult patients aged ≥ 18 years were included, and all were in the acute phase or early subacute phase of ischemic stroke (within 2 weeks of onset). Intervention measures: studies were required to provide a detailed account of the rTMS intervention protocol, including the stimulation site, frequency, and intensity, to enable a clear comprehension of the treatment method and its potential effects. Control group: the control group could receive sham rTMS stimulation, conventional treatment, or sham rehabilitation without rTMS. This design facilitated the effective isolation and evaluation of the specific therapeutic effects of rTMS. Outcome indicators: motor evoked potential (MEP) amplitude, resting motor threshold (RMT), and central motor conduction time (CMCT).

2.2.2 Data extraction. Initially, the lead researcher developed a data extraction form. In cases where the specific values of the outcome indicators were not explicitly presented in the text or tables of the published literature, the researchers contacted the corresponding authors of the articles via email to obtain accurate data. Two researchers independently extracted data from the figures and tables in the literature using WebPlotDigitizer software (Version 4.3) to ensure the scientific validity and accuracy of data acquisition[7]. When a study reported the median, standard error, or interquartile range, these data were converted into the mean and standard deviation (SD) to maintain consistency and comparability across different studies.

2.3 Quality assessment In accordance with the requirements specified in the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement, two researchers independently evaluated the methodological rigor of each RCT using the Cochrane risk of bias assessment tool.

2.4 Statistical methods Stata 18.0 software (College Station, Texas, USA) was utilized for statistical analysis in this study. For continuous outcome variables, the standardized mean difference (*SMD*) was employed as the primary effect measure, with the 95% confidence interval (*CI*) serving as the summary statistic. The I^2 statistic was adopted to rigorously assess the heterogeneity among studies, and the choice of analysis model was based on the results of the I^2 statistic: if $I^2 > 50\%$, significant heterogeneity was considered present, and a random-effects model was used to calculate the relevant parameters; if $I^2 \leq 50\%$, heterogeneity was deemed insignificant, and a fixed-effects model was employed for the analysis. When the number of included studies was ≥3, a funnel plot was used to assess publication bias. Contour-enhanced funnel plots, which display the effect size of each study against its standard error, were constructed to evaluate publication bias based on the reporting of the primary outcome indicators. Additionally, Egger's test was conducted to assess asymmetry in the funnel plot. If $P < 0.1$, significant publication bias was considered to exist. A two-tailed test was applied to determine statistical significance, with the significance level set at $\alpha = 0.05$.

3 Results and analysis

3.1 Search results A total of 932 studies were identified through database searches, and 203 studies remained after duplicates were removed. In accordance with the aforementioned inclusion and exclusion criteria, following full-text screening and the searching of reference lists to identify additional relevant studies, a total of 8 studies[8-15] were ultimately selected for qualitative analysis.

3.2 Risk of bias assessment A summary of the risk of bias for the included RCTs and CCTs is presented in Fig. 1. Overall, all studies performed well in the domains of incomplete outcome data and selective reporting, with a low risk of bias in both domains. However, the risk of bias in other domains was unclear for all studies. With regard to random sequence generation, all studies adopted appropriate randomization methods, resulting in a low risk of bias. In terms of allocation concealment, 6 studies had a low risk of bias, while 2 studies had an unclear risk. Concerning the blinding of participants and personnel, 4 studies had a low risk of bias, and 4 studies had an unclear risk. For the blinding of outcome assessment, all studies exhibited a low risk of bias.

3.3 Effect of rTMS on MEP amplitude in patients with acute stroke MEP refers to the electrical response generated by stimulating the motor cortex, which is capable of reflecting the functional integrity of the corticospinal tract and motor pathways. The MEP amplitude is an important indicator for evaluating corticospinal excitability, with larger amplitudes typically indicating better motor function. The results of the meta-analysis (Fig. 2) revealed that after rTMS treatment, the MEP amplitude in the lesioned hemisphere of patients was significantly increased, demonstrating a positive therapeutic effect (Hedges' $g = 0.77$, 95% *CI*: 0.52-1.02, $P < 0.01$). This indicates that rTMS promoted the recovery of patients' motor function by enhancing corticospinal excitability in the affected side. No significant heterogeneity was ob-

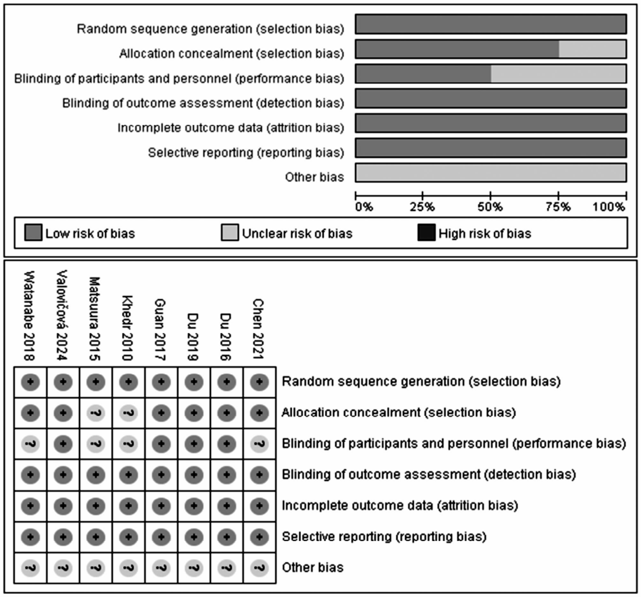

Fig. 1　Risk of bias in the included studies

served among the studies ($I^2 = 30.76\%$, $P = 0.18$). In contrast, rTMS exerted no significant effect on the MEP amplitude in the unaffected hemisphere. The meta-analysis results showed that there was no significant change in the MEP amplitude of the unaffected hemisphere (Hedges' $g = -0.22$, 95% CI: -0.62 – 0.18, $P = 0.29$), indicating that rTMS did not alter the corticospinal excitability of the unaffected side. Moderate heterogeneity was observed among the studies ($I^2 = 72.45\%$, $P < 0.01$), suggesting variability in the results across different studies. Potential publication bias was evaluated using a funnel plot, which showed no obvious asymmetry. Additionally, Egger's test also confirmed the absence of publication bias in the lesioned hemisphere ($P = 0.698$).

3.4　Effect of rTMS on RMT in patients with acute stroke

RMT is defined as the minimum intensity of TMS required to elicit a motor response in the muscle. It serves as a key indicator for evaluating corticospinal excitability. A lower RMT value indicates higher cortical excitability and, concurrently, better motor function. The results of the meta-analysis (Fig. 3) indicated that rTMS significantly reduced the RMT in the lesioned hemisphere of patients, suggesting improvements in the patients' cortical excitability and motor function, with a significant therapeutic effect (Hedges' $g = -1.13$, 95% CI: -1.63 to -0.62, $P < 0.01$). This implies that rTMS promoted the recovery of motor function in the affected side. However, significant heterogeneity was observed among the studies ($I^2 = 79.01\%$, $P < 0.01$), indicating substantial variations in the therapeutic effects across different studies. In the unaffected hemisphere, rTMS had no significant impact on the RMT (Hedges' $g = 0.26$, 95% CI: -0.14 – 0.66, $P = 0.20$), indicating that rTMS did not change the corticospinal excitability of the unaffected side. Moderate heterogeneity was observed among the studies, but the P value was 0.20, indicating that this heterogeneity did not reach a statistically significant level ($I^2 = 68.37\%$, $P = 0.20$).

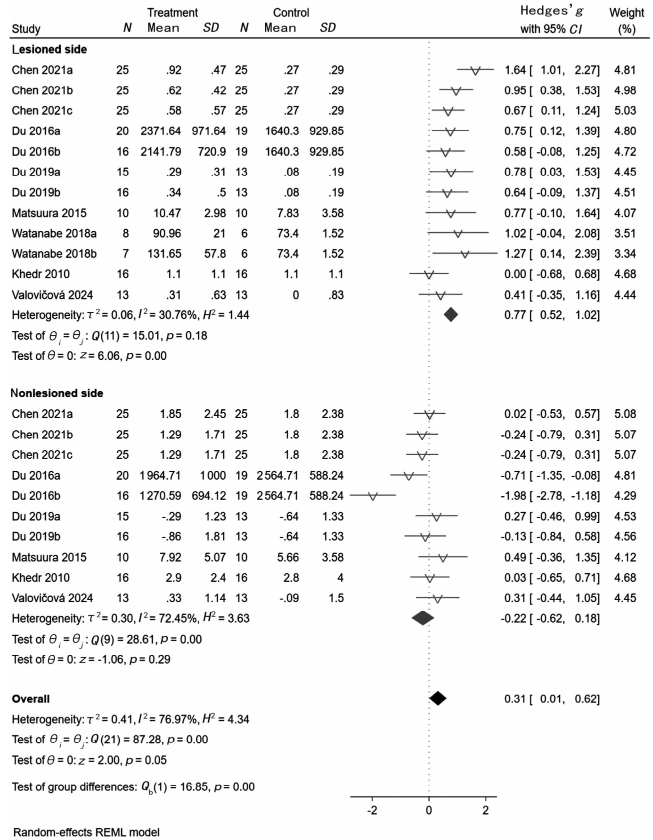

Fig. 2　Overall impact of rTMS on MEP amplitude in the early stage of stroke

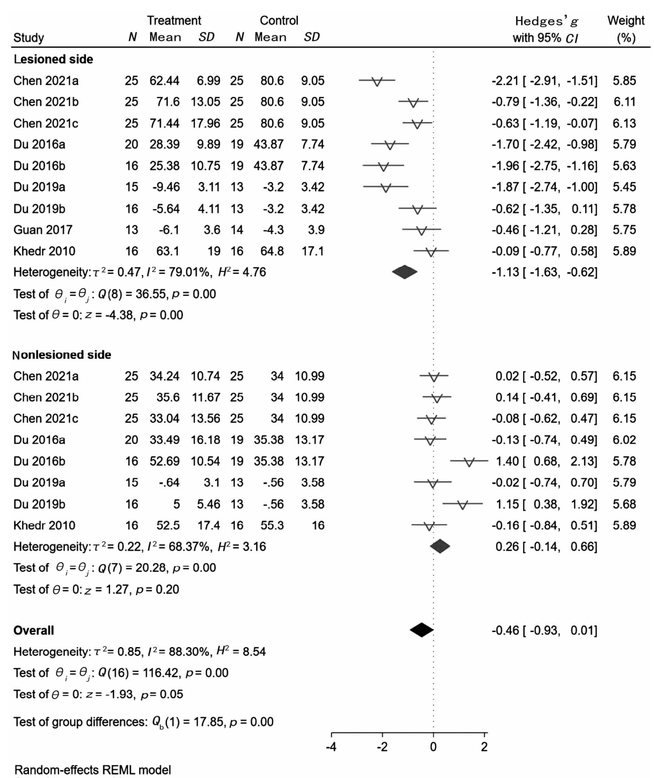

Fig. 3　Overall impact of rTMS on RMT in the early stage of stroke

3.5 Effect of rTMS on CMCT in patients with acute stroke

CMCT is used to measure the time required for motor signals to transmit from the motor cortex to the muscles. A prolonged CMCT usually indicates damage to the motor pathways and suggests a slow recovery of motor function. The results of the meta-analysis (Fig. 4) demonstrated that rTMS had no significant effect on the CMCT in either the lesioned hemisphere (Hedges' $g = -0.41$, 95% *CI*: $-0.85-0.02$, $P=0.06$) or the unaffected hemisphere (Hedges' $g = -0.19$, 95% *CI*: $-0.44-0.07$, $P=0.15$) of the patients. These findings suggest that rTMS did not improve the motor conduction function in either hemisphere.

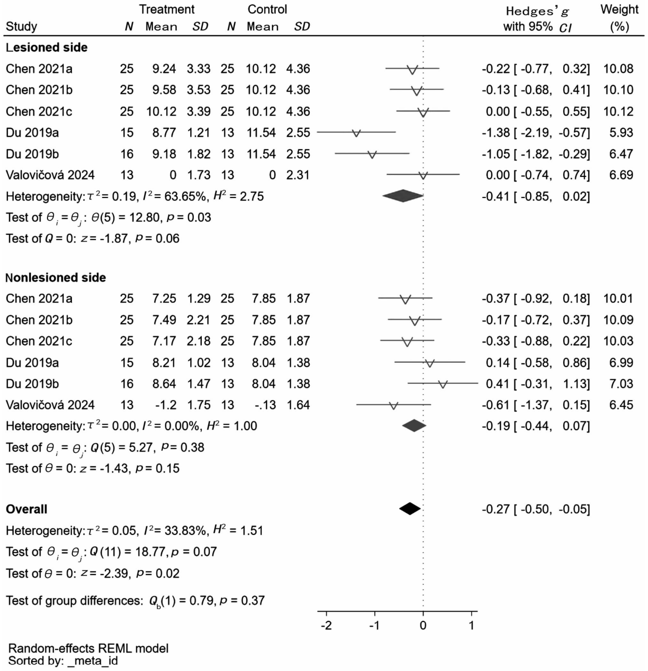

Fig. 4 Overall impact of rTMS on CMCT in the early stage of stroke

4 Discussion

The present systematic review and meta-analysis evaluated 8 rigorous RCTs. The results indicated that rTMS was significantly more effective than the control interventions in improving neurophysiological indicators, specifically MEP amplitude and RMT in the lesioned hemisphere, with no obvious adverse reactions observed. These findings not only align with the conclusions of previous meta-analysis on subacute and chronic stroke but also extend the application of rTMS to patients with acute stroke[16].

The *Evidence-Based Guidelines for the Therapeutic Application of Repetitive Transcranial Magnetic Stimulation*, issued by the International Federation of Clinical Neurophysiology, reviewed relevant literature from 2014 to 2018[17]. For motor dysfunction following subacute stroke, the guidelines recommend the use of low-frequency rTMS (LF-rTMS) targeting the contralateral primary motor cortex (M1 area) (Level A evidence: proven efficacy) and high-frequency rTMS (HF-rTMS) targeting the ipsilesional M1 area (Level B evidence: probable efficacy); for chronic stroke, the use of LF-rTMS targeting the contralateral M1 area is recommended (Level C evidence: possible efficacy)[18-19]. However, the guidelines failed to provide clear recommendations regarding rTMS treatment for acute stroke, which is consistent with the conclusions of several recent systematic reviews and meta-analysis. The results of this meta-analysis demonstrated that in comparison to sham stimulation, rTMS treatment offered significant benefits to patients with acute stroke. The application of TMS during the acute phase exerted a positive impact on neurophysiological indicators[20]. A large body of research emphasizes that stroke rehabilitation should begin during the acute phase rather than be delayed until the chronic phase. The acute phase of stroke is regarded as a critical window for treatment; interventions implemented during this phase are more effective in achieving neuroprotection and neural repair, enhancing synaptic plasticity, and thereby promoting the recovery of motor function, which is crucial for achieving favorable rehabilitation outcomes[19,21].

In the process of stroke recovery, the interhemispheric inhibition model constitutes a crucial concept. This model posits that the neuronal excitability of the two brain hemispheres mutually inhibits each other to maintain a state of interhemispheric balance[21]. Stroke disrupts this balance by reducing the excitability of the affected hemisphere, leading to excessive activation of the unaffected hemisphere[22]. This "excessive activation" of the unaffected hemisphere may exert abnormally strong interhemispheric inhibitory effects on the affected hemisphere, thereby impairing the motor ability of the affected limb and hindering its functional recovery[23]. Based on this mechanism, two main principles underlie the use of rTMS for the treatment of post-stroke motor dysfunction: first, enhancing the excitability of the ipsilesional M1 area through high-frequency stimulation; and second, inhibiting the excitability of the contralateral M1 area through low-frequency stimulation, thereby restoring interhemispheric balance[24]. Interhemispheric inhibition is a common phenomenon observed in patients with subacute and chronic stroke[25]. However, there is currently no clear conclusion regarding whether this phenomenon occurs in patients with acute stroke. Nevertheless, among the 8 studies included in this meta-analysis, some studies employed high-frequency stimulation of the ipsilesional M1 area, while others used low-frequency stimulation of the contralateral M1 area. Both approaches achieved favorable therapeutic effects. A study conducted by Du *et al.*[9] utilized task-based functional magnetic resonance imaging (fMRI) data and cortical excitability measurements, finding that applying high-frequency rTMS to the ipsilesional M1 area enhanced neural activity in this region, while applying low-frequency rTMS to the contralateral M1 area reduced the excessive activation in the contralateral motor area. Notably, during the post-intervention period and the 3-month follow-up assessment, the researchers observed a significant correlation between the activity of the ipsilesional motor cortex and the patients' motor function. Utilizing resting-state fMRI, Guo *et al.*[26] also found that both high-frequency rTMS stimulation of the ipsilesional M1 area and low-frequency rTMS stimulation of the contralateral M1 area significantly enhanced the functional connectivity within the motor network of the affected hemisphere. This integration of the damaged M1 area into the motor network structure facilitated improved motor function recovery in patients. These findings provide neuroimaging evidence supporting the application of rTMS in patients with acute stroke-related hemiplegia, based on the interhemispheric inhibition theory. In terms of the duration of therapeutic effects, a study by Du *et al.* [15] found that initiating TMS intervention during the acute phase of stroke could maintain the therapeutic effects for more than 3 months. Additionally, a study by Guan *et al.* [10] demonstrated that these therapeutic effects could persist for up to 12 months even after the cessation of treatment. This long-lasting therapeutic effect is not only beneficial for patient rehabilitation but can also reduce government healthcare expenditures to a certain extent. In terms of safety, no obvious adverse reactions were observed in any of the RCTs included in this study. This indicates that rTMS may serve as an effective neurorehabilitation method for the treatment of patients with hemiplegia following acute stroke, with a relatively low risk of adverse reactions. However, this conclusion still requires further validation through studies with larger sample sizes.

5 Conclusions

Although the present study has certain limitations, the results confirm that rTMS is a safe and effective treatment method during the acute phase of stroke. Preliminary evidence suggests that high-frequency stimulation of the affected hemisphere, with the stimulation intensity set at or below the motor threshold, may yield better therapeutic effects for patients. However, to determine the optimal parameters for rTMS treatment and to develop practical treatment protocols, it is necessary to conduct larger-scale clinical trials using unified methodologies. Future research should prioritize multi-center, large-sample, standardized neuronavigation double-blind RCTs, with increased emphasis on detecting molecular biomarkers and actively exploring the application of individualized precision localization techniques. These efforts are of great significance for establishing effective rTMS intervention strategies to address motor dysfunction following acute stroke.

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