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High-Frequency Repetitive Transcranial Magnetic Stimulation and Its Effects on Symptoms, Cognition and Subjective Experiences in Chronic Schizophrenia: A Sham-Controlled Study

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ABSTRACT

Introduction: Our object is to examine the effects of high-frequency repetitive transcranial magnetic stimulation (rTMS) on the symptoms, cognitive functions and subjective experiences in patients with chronic schizophrenia and to enhance the overall understanding of the TMS method.

Methods: Thirty three patients who had chronic schizophrenia were included in the study. Seventeen patients received rTMS and 16 received sham. The Positive and Negative Syndrome Scale, Repeatable Battery for the Assessment of Neuropsychological Status Scale, Insight and Treatment Attitudes Questionnaire and a self-experience checklist developed by the researchers to evaluate post-TMS experiences were applied to all patients.

Results: There were no statistical differences between the groups with regard to symptoms, cognitive functions and insight. However rTMS group reported overall better treatment experience and more positive subjective experiences.

Conclusion: rTMS treatment did not cause any improvement in symptoms, cognitive functions and insight but provided a better self-experience, which might improve treatment compliance.

Keywords: Cognitive functions, negative symptoms, positive symptoms, repetitive transcranial magnetic stimulation, schizophrenia

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INTRODUCTION

Schizophrenia has positive, negative and cognitive symptoms. At present, antipsychotic drug treatment only has an observable effect on 50%–80% of the positive symptoms, while its efficacy regarding the negative symptoms and cognitive function requires additional verification (1). As such, additional clinical treatment approaches are necessary.

Transcranial magnetic stimulation (TMS) is based on the technical principle of electromagnetic conversion, which applies stimulation using a strong pulsed magnetic field that is created in vitro. This generates an induction current on the nerve tissue in a specific part of the brain. Therefore, it is an electrical stimulation method. Repetitive TMS (rTMS) has demonstrated efficacy in the treatment of posttraumatic stress disorder, substance use disorders, mild cognitive impairment, Alzheimer's disease and other psychiatric and neurological conditions (2). It is thought to induce longer lasting effects if applied repeatedly (3,4), and it has been studied in relation to schizophrenia in terms of the treatment of auditory hallucinations, negative symptoms and cognitive deficits, with mixed results (5). However, less attention has been paid to the patient's self-experience, which includes activities related to thoughts, emotions, will, diet, sleep quality, neurocognitive function and physical feelings. Focusing on the patient's self-experience can improve their compliance, thereby improving the treatment efficacy. The aim of this paper is to evaluate the effect of rTMS on the negative, positive and general symptoms and the cognitive functions in patients with schizophrenia and to gain an understanding of the subjective self-experiences of patients with schizophrenia during rTMS treatment. The authors hypothesised that rTMS will improve the symptoms and cognitive functions and that the patients treated with rTMS will have different subjective experiences than those treated with a sham method.

Highlights

- **Repetitive TMS did not cause any improvement in symptoms, cognitions and insight.**
- **Repetitive TMS treatment provided a good self-experience.**
- **Repetitive TMS treatment might help treatment compliance.**

METHODS

Participants

The authors recruited patients who were admitted to Hebei General Hospital for Veterans who met the following criteria: 1) aged 18–65 years; 2) met the diagnostic criteria of the International Classification of

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Diseases Edition 10 (ICD-10) for schizophrenia; 3) had a disease duration of 5 years; 4) were in a stable condition; 5) their medication remained unchanged during treatment; 6) had no history of epilepsy (including history of antiepileptic drug use); 7) had no brain trauma or surgery history; and 8) had accepted the treatment voluntarily and provided signed informed consent for inclusion in the study. The exclusion criteria were as follows: 1) having contraindications for rTMS intervention; 2) had other neuropsychiatric disorders (based on the medical history and symptoms); 3) had received electroconvulsive treatment a month preceding the start of the study; 4) had exhibited an impulse for violence and engaged in destructive and self-harming behaviour; and 5) experienced delusions about electricity.

The participants underwent treatment following a routine examination. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Hebei General Hospital for Veterans. Written informed consent was obtained from all participants.

Fifty patients were enrolled from 1 March 2019 to 31 January 2020. All the patients were male since they were recruited from a veterans' hospital. In the study group, 17 patients were included and seven were excluded, five of whom left in the first week due to adverse events and two of whom were discharged during subsequent treatment. In the control group, 16 patients were included and 10 were excluded, seven of whom left in the first week due to adverse events and three of whom were discharged. There were no statistically significant differences in age, education level, and duration of schizophrenia between the two groups. In terms of drug treatment, clozapine was the primary drug used by the participants. No statistical dose difference was observed between the two groups (study group: 276.79±109.40 mg; control group, 309.09±87.52 mg; t=–0.798; p=0.433). Other drugs included aripiprazole, quetiapine, olanzapine and risperidone, but these were administered less frequently. Sociodemographic and clinical characteristics of rTMS and the control groups are depicted in Table 1.

Design

Patients who were eligible for admission were divided into a control group and a treatment group based on the date of hospitalisation. A double-blind approach was adopted. The participants were unaware of whether real/pseudo stimulation was applied, and the evaluators did not know the grouping specifics. All the enrolled cases were tested for stimulation thresholds in the bilateral prefrontal cortex. The TMS treatment device was a Magstim RAPID^2 neuromagnetic stimulator (Magstim) with an '8'-type coil.

The study group was administered real stimulation. The treatment parameters were as follows: frequency range=20 Hz, 90% motion threshold, 3 s of stimulation, a 57 s interval, and 15 min of stimulation for each side, five times per week for a total of 20 times. For the control group, a 60% motion threshold was set, while the remaining parameters were consistent with the study group but with no stimulating energy output. The therapeutic instrument model, appearance, operation process and sounds during treatment were the same for both groups.

Tools

Self-Experience Checklist for Post-Transcranial Magnetic Stimulation Treatment

In the present study, 'self-experience' refers to an evaluation of the changes in a patient's self-perception before and after TMS treatment. A self-experience checklist was developed by the researchers. It included questions related to thoughts, emotion, will, diet, sleep quality, neurocognitive function and physical feelings, while the specific inclusions were sleep quality, diet, memory, attention, speech, responsiveness, hallucinations, thoughts, mood, initiative, delusions, physical feelings and other feelings. The questionnaire included open-ended questions on these topics, and the patients could describe their personal experiences. In the case where it was difficult to provide a description, numbers could be selected for each entry in the questionnaire to indicate the degree of experienced change. A senior attending physician asked the questions one by one.

The checklist list was not a scale and was only used as an inquiry outline. It could not encompass all the noted changes; rather, it supplemented the inquiry and, importantly, tracked valuable clues within the provided answers. Suggestive questions and closed questions were not allowed, and the authors emphasised the importance of guiding the participants to compare the changes specific to their experience before and after treatment.

Positive and Negative Syndrome Scale (PANSS)

Chinese version of PANSS was used to assess the severity of symptoms in patients with schizophrenia (6,7). The scale evaluation was completed by an attending physician.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The Chinese version of RBANS (8,9) was used for evaluating the cognitive function level of the patients with schizophrenia. The RBANS scale included 12 test items that evaluated five sets of neuromental states (five factors): immediate memory (vocabulary learning and story review); visuospatial structure (graphic depiction and line positioning); language (picture-naming and semantic fluency); attention (digital breadth and symbolic numbers) and delayed memory (vocabulary recall, vocabulary cognition, story recall and graphic recall). The test was applied by a psychologist.

Table 1. Comparison of age, education level and clinical features between rTMS and control groups

	rTMS group (n=17)	Control group (n=16)	t/x²	p
Age (years)	46±8.37	49±8.00	-1.293	0.206
Education (years)	10.65±1.50	9.75±1.73	1.594	0.121
Duration of schizophrenia (years)	25.65±7.24	28.44±8.36	-1.027	0.312
Dose of Clozapine (mg)	276.79±109.40	309.09±87.52	–0.798	0.433
Number of patients using Clozapine	13	11	0.248	0.619
Number of patients using Aripiprazole	2	2	0.004	0.949
Number of patients using Quetiapine	1	0	-	-
Number of patients using Olanzapine	0	1	-	-
Number of patients using Risperidone	1	2	0.424	0.515

rTMS: Repetitive transcranial magnetic stimulation

Insight and Treatment Attitudes Questionnaire (ITAQ)

Chinese version of ITAQ (10,11) was used to evaluate patients' understanding of the disease and their attitude towards treatment. A higher score indicated that the patient had better self-knowledge. The internal consistency was 0.82 and the re-measuring reliability was 0.93/0.869. The scale was administered by an attending physician.

Statistics

The data statistical evaluation and analysis were conducted using IBM Statistical Package for Social Sciences (SPSS) program version 21.0 Statistics software. If the continuous variable conformed to the normal distribution, mean ± standard deviation was used to describe it. Covariance analysis was performed with PANSS, RBANS and ITAQ scores as dependent variables, treatment methods as main effects, and pre-treatment values as covariates. If the continuous variable did not conform to the normal distribution, the median (quartile interval) was used to describe it, and a nonparametric test was used to compare the differences between the two groups. The categorical variables were described by the number of cases (rate). A chi-squared test or Fisher's exact probability method was used to compare the differences between the two groups. A bilateral p-value of <0.05 was used as the standard of statistical significance.

RESULTS

The results of covariance analysis showed that different treatment methods had no effect on PANSS score. There was no significant difference in positive symptoms, negative symptoms, general psychopathology and PANSS total score between the two groups. The PANSS score before treatment had a positive effect on the PANSS score after treatment, the higher the score before treatment, the higher the score after treatment (Table 2 and Figure 1).

rTMS treatment had no effect on RBANS score. There was no difference in immediate memory, visual spatial structure, speech function, attention or delayed memory between the two groups. The RBANS score before treatment had a positive effect on the RBANS score after treatment, the higher the score before treatment, the higher the score after treatment (Table 3).

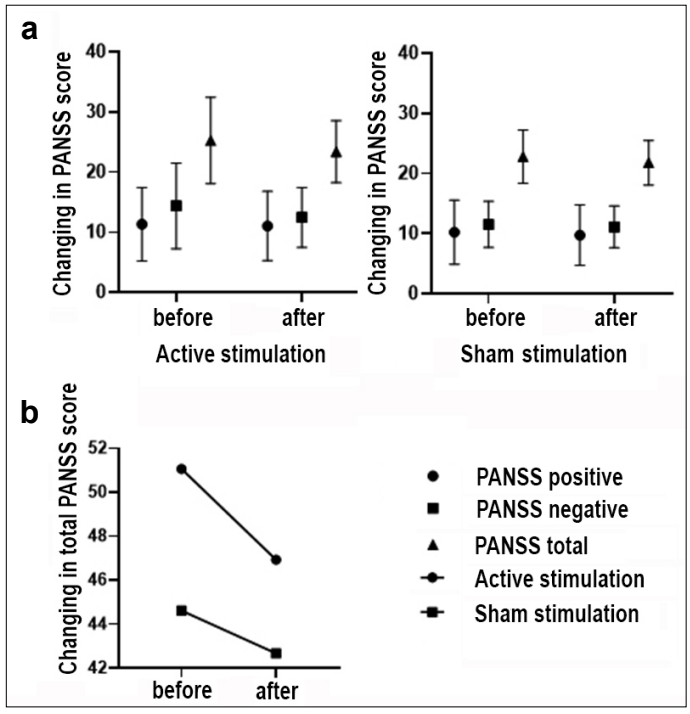

Figure 1. Change of clinical rating scores following active and sham stimulation. Positive and Negative Syndrome Scale (PANSS) subscales in the sham and actively stimulated groups **(a).** PANSS rating scale in the sham and actively treated groups **(b).**

The two groups were compared in terms of 10 items of ITAQ (sleep quality, thoughts, response, memory, attention, emotions, mood, initiative, diet, headache and other feelings). There was a statistically significant difference in terms of physical feelings between the two groups of patients (p=0.039). Given the small number of cases in each group, no comparison was made in terms of quantity. The overall treatment experience was better in the study group than in the control group (Table 4).

The proportion of adverse events following rTMS between the study and control groups was 13:9, and was not statistically significant (*p*=0.218) (Table 5).

Table 2. Comparison of the PANSS score before and after the treatment between the two groups

		rTMS group (n=17)	Control group (n=16)	t^a	P^a	t^b	P^b
Positive symptoms	Before the treatment	11.35±6.10	10.25±5.33	0.856	0.274	2.316	0.037
	After the treatment	11.06±5.77	9.75±5.04				
Negative symptoms	Before the treatment	14.41±7.12	11.56±3.83	0.537	0.714	2.736	0.018
	After the treatment	12.47±4.98	11.12±3.48				
General psychopathology	Before the treatment	25.29±7.18	22.81±4.43	0.811	0.173	3.272	0.005
	After the treatment	23.41±5.16	21.81±3.72				
PANSS score	Before the treatment	51.06±18.51	44.62±10.36	0.632	0.327	4.971	<0.001
	After the treatment	46.94±14.64	42.68±9.33				

PANSS: Positive and Negative Syndrome Scale; rTMS: Repetitive transcranial magnetic stimulation; a: statistical values and P values for treatment methods. b: statistical values and P values for pre-treatment values.

Table 3. Comparison of the RBANS score before and after the treatment between the two groups

		rTMS group (n=17)	Control group (n=16)	t^a	P^a	t^b	P^b
Immediate memory	Before the treatment	63.17±9.21	65.15±10.33	0.375	0.585	3.726	0.004
	After the treatment	67.72±11.72	66.01±12.60				
Visual spatial structure	Before the treatment	79.42±11.43	77.91±10.43	0.624	0.546	1.736	0.074
	After the treatment	76.32±11.48	75.36±14.20				
Speech function	Before the treatment	82.27±13.29	84.15±10.94	0.384	0.504	4.733	<0.001
	After the treatment	83.55±11.74	81.85±11.77				
Attention	Before the treatment	77.42±12.62	78.94±12.66	0.434	0.593	2.111	0.041
	After the treatment	84.28±9.24	84.93±10.93				
Delayed memory	Before the treatment	75.0/ ±16.68	73.97±17.42	0.683	0.737	3.625	0.007
	After the treatment	73.71±16.74	72.04±13.21				

RBANS: the Repeatable Battery for the Assessment of Neuropsychological Status; rTMS: Repetitive transcranial magnetic stimulation; a: statistical values and P values for treatment methods. b: statistical values and P values for pre-treatment values.

DISCUSSION

In this study, the difference in PANSS scores before and after rTMS treatment was not statistically significant. The symptoms did not improve or worsen in either of the groups. The degree of self-experience before and after treatment was inconsistent with the PANSS score changes. This may have been due to the low sensitivity of the PANSS, which could not meet the evaluation needs of the rTMS participants, and as such, did not apply to this study. A more suitable evaluation tool should be selected, or alternatively, a new tool must be developed to improve the sensitivity for evaluating the minor changes that are experienced by participants. Furthermore, 'self-experience' reflects the subjective descriptions that are provided by the participant, and, as such, lacks objective evidence. Future studies could include event-related potentials, functional brain imaging, brain white-matter fibre imaging and brain positron emission tomography data to verify the treatment results of rTMS from multiple perspectives. The present study had a small sample size, and the participants were all male; therefore, future studies should be more diverse (12,13).

The study group reported better self-experience than the control group. This was focused on their sleep quality, thoughts and physical feelings and patients in rTMS group reported they had clearer minds and experienced better sleep quality. The interview responses regarding these results revealed that some of the participants experienced continuous involuntarily thoughts or disorderly content and repeatedly thought of something or what was happening around them. Some of the participants noted that even when they were lying down, their minds were busy which made it difficult to fall asleep and affected their sleep quality. Following rTMS treatment, the subjects reported falling asleep faster, and that their sleep quality improved. They also reported a reduction in dream activity. The improvement in sleep quality among the patients may be related to the rTMS reducing their tension (14). However, a comparison between the two groups indicated no statistically significant differences in sleep improvement. Furthermore, it was found that the disordered mind of the participants affected their sleep quality.

The rTMS method represents a potential clinical tool that could ameliorate cognitive symptoms, especially in specific patient subtypes (15). Physical feelings can be divided into two types: benign and non-benign (adverse events). In this study, the discomfort that occurred during the experiment and was not secondary to the disease itself was defined as non-benign feelings (adverse event). This included feelings originating from the rTMS treatment or through self-suggestion but did not include the discomfort that occurred before the experiment. The discomfort that existed before the experiment and disappeared during the experiment, as well as the increased comfort during the experiment, were labelled benign feelings. This included factors such as TMS efficacy, reduced drug response, symptom relief and self-suggestion, but did not include the comfort that could be derived from other factors. This feeling was actively narrated by the patient or brought out by the researcher using non-suggestive language. The study group had better results compared to the control group regarding benign feelings, and the difference was statistically significant. There was no statistical difference relating to non-benign feelings between the two groups.

Different frequency-based rTMS methods have different effects on the nerve cells in the brain. Low-frequency rTMS has an inhibitory effect, while contrastingly, it also induces a high frequency of elevated feelings of excitement. The self-feeling in the study group was, on the whole, better compared to the control group, which was likely due to the 20-Hz stimulation that was applied to the dorsolateral cortex to activate the brain nerve cells, regulate the nerve-cell synaptic plasticity and optimise the structure of the brain's neural network. This needs to be explored in future research. The treatment experience reflected the therapeutic effect and suggested that patients with chronic schizophrenia still require individually tailored treatments.

Although the available evidence for randomized controlled trials evaluating the efficacy of rTMS on cognitive deficits in patients with schizophrenia (SCZ) and bipolar disorder (BD) remains controversial, overall, they indicate that rTMS is a potential clinical tool (15). Further research in this context is required. This study's results revealed no statistical difference across five specific factors before and after treatment (immediate memory, visuospatial structure, speech function, attention and delayed memory). However, the attention factor exhibited a

Table 4. Self-experience after rTMS treatment

	Factors	rTMS group (n=17)	Control group (n=16)
1	Sleeping (10:5)	Easy to fall asleep, sleep steadfast, not easily waking up, extended sleep time, less dreams, sleep quality improvement.	Falling asleep fast, extended sleep time, deep sleep, less dreams.
2	Thinking (12:8)	In the past, I could not control myself; there was a kind of oppression, difficult to stop. There was a sense of hesitation about going out.	My mind was clear now and before.
		Mind clarity increased, the old impulsive idea to smash the glass has now disappeared.	A little bit more ability and will to express than before, can understand what others say, the expression ability improved.
		Random thinking disappeared, logical thinking ability enhanced, clearer thinking than before.	Feeling the brain slightly became clear, little change.
		Clear mind, no longer passive thinking about some things, than before, can be more complete expression of their thoughts. Able to express their thoughts more completely comparing to before.	Before cannot describe the situation clearly, now mind is conscious, thinking more things than before, a little confused, now no longer overthinking, able to control. Love to express.
		The brain was no longer confused, become sober, organized. The number of words used increased	The brain feels clearer (not specifically). The number of words used increased.
		The brain was highly clear, the past mind has no logic, the speech was reversed, indifferent. Opinions towards problem have changed (not clear).	Confused thinking reduced, thinking of some people they knew, cannot control, less, did not disappear.
		Thinking reduced, no longer chaos, can be controlled by their own. In the past, thinking tended to be mixed, some nature of coercion, forced to think. Word number has increased.	Professor no longer teach themselves through space. Got smarter.
		The brain is clearer than before, thinking half as much, and can't remember it clearly, but felt like being pinched.	
		In the past, confused listening to others, still thinking when others do not talk, now occurs less. Better expression ability, able to express what you want to say.	
		Before repeatedly thinking about a question and then take an action, now reduced, the words increase, consciously love to talk , can express what you want to say.	
		Think less, unorganized nonsense lessen, feeling the brain cannot work.	
		Thinking less, mind is no longer so messy, mind is clear, not disappeared, but less influence on their own.	
3	The reaction was accelerated (4:1)	The reaction was accelerated	Fast; not as functional as before, better as earlier, slow, silly.
	The reaction has slowed down (0:1)		
4	Memory enhancement (2:2)	Enhanced.	Enhanced; now forget things, memory abilities decline
	Memory decline (1:2)	Memory abilities decline	
5	Attention concentration (2:2)	Concentrated	concentrated
	Attention is not focused (0:1)	More focused	not focused
6	Positive mood (6:4)	Low mood somewhat improved, irritability reduced; mood has improved	Used to be a little unhappy, now happy every day The mood has improved Emotion is like a lost brain; more stable than before
		No longer want to die. Emotional mood	
	Negative mood (0:1)	Patient, better temper and stable.	
		No longer want to commit suicide, the trouble feels less	
7	Initiative (4:3)	Before a little lazy, now the initiative has increased	The initiative has increased
		A little will to do things and help others	Actively making friends
		Some people proactively want to do things. Actively speaking more	
8	Diet (2:0)	Intake increased	Eating is better than before
		Eating is better than before	Intake increased
9	Headache (1:0)	Disappeared	
10	Physical feelings (7:1)	Head was uncomfortable, not clear, and became comfortable after the treatment.	Used to feel like having a big head, but now it feels smaller.
		More than ten years of dizziness has improved, the feeling of emptiness in mind disappeared.	
		Not used to sit still, but now can sit firmly on a chair (before sitting on the ground).	
		Consciously let the body loose, in the past tense, cannot sit still	
		The brain was uncomfortable. A rest worked well	
		The dizziness disappeared	
		Feeling comfortable after the treatment	

Table 5. Comparison of adverse events after rTMS

Group	rTMS group (n=17)	Control group (n=16)
Symptoms	Pain in the stimulating area, headaches, dizziness, scalp numbness, hidden pain in the back of the head with beating feeling, head beating feeling, needle ligation feeling, electrical stimulation feeling, neuralgia, tension and excitement, repetitive action, masturbation	Knock feeling, whole body numbness, head numbness, nose hemp, tooth root hemp, brain hair, temples hurt, waist and back pain, half-side facial muscle tension, electrical stimulation feeling

rTMS: repetitive transcranial magnetic stimulation.

tendency towards improvement following the treatment. If the treatment parameters were changed and the treatment time prolonged, a different treatment effect could have been observed. Self-knowledge reflects the patient's awareness of their condition. Restoring the self-knowledge of patients with schizophrenia is important for the maintenance of the treatment and the prevention of recurrence. However, doing so represents one of the difficulties of achieving a clinical level of complete self-knowledge. This study's results did not indicate effectiveness in this regard and, accordingly, comprehensive treatment programmes are required.

The number of cases that were ultimately excluded from the study accounted for 34% of those that were initially selected. Two types of stimulation were applied during rTMS treatment –sound and local stimulation– which was aimed at reaching the deep tissue through the skin. Compared to real stimulation, pseudo stimulation has no actual energy output. There was no difference in the appearance of the instrument model, display operating interface, stimulation coil, operation process and percussion sound emitted during treatment between the real stimulation and the pseudo stimulation. In addition, a localised area of skin also experienced the feeling of stimulation during the pseudo stimulation, which may have been the cause of a similar number of cases being excluded from each of the two groups.

Clozapine was being used by 82.3% of the study group participants. Changes in electroencephalogram results and seizures were among the adverse reactions to this drug. Both TMS and clozapine has the potential to induce seizures. In this study, the researchers employed 20-Hz pulse patterns, as well as 900 bilateral stimulation strings, while the participants were treated 20 times, and no seizures were recorded. Antipsychotic-induced epilepsy is related to the dosage of clozapine. The average dose of clozapine in the study group was 300 mg/day, suggesting that a moderate dose is safe and that the patients who had taken antipsychotics for a long period of time might have developed a better tolerance to these medications.

Self-experience has a subjective nature and is prone to errors in evaluation, but it is crucial for patients with schizophrenia. Treatment incorporating rTMS can yield positive results for patients' self-experience, which involves sleep quality, thoughts and physical feelings. A good experience in this regard might be beneficial for the treatment of schizophrenia, can improve treatment compliance and could serve as a reference for the treatment of other diseases.

This study involves certain limitations. First, this was a single-centre study, and the majority of the patients participating in the study were male veterans, which may have led to some bias in the results. Second, the sample size was insufficient, and future researches with larger sample sizes are needed.

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Hebei General Hospital for Veterans.

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- LL, LS; Design- DX, XW; Supervision- XW; Resource- (-); Materials- DX, XW; Data Collection and/or Processing- DX, XW, YW, QW, XW; Analysis and/or Interpretation- YW, QW, XW; Literature Search- (-); Writing- LL, LS; Critical Reviews- LL, LS, DX, XW, YW, QW, XW.

*These authors contributed equally to this study

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