

# Transcranial Magnetic Stimulation as a Therapy for Migraine: An Overview of Systematic Reviews

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**Introduction:** This overview of systematic reviews (SRs) systematically collected, evaluated, and combined the evidence for migraine treatment with transcranial magnetic stimulation (TMS).

**Methods:** We conducted a systematic literature search in various databases, such as PubMed, The Cochrane Library, Web of Science, Embase, the China National Knowledge Infrastructure, Wanfang, VIP, and China Biomedical Literature. Two reviewers independently assessed the methodological quality, risk of bias, reporting quality, and strength of evidence of the included studies using AMSTAR-2, ROBIS, the PRISMA checklist, and the GRADE system.

**Results:** We performed an overview of 7 relevant SRs, of which 4 were of moderate quality and 3 were of low quality according to AMSTAR 2. All SRs had low risk of bias in Phase 1 (Assessing relevance), Domain 1 (Study eligibility criteria), and Domain 4 (Synthesis and findings) as evaluated by ROBIS. In Domain 2 (Identification and selection of studies), 4 SRs (57.1%) had low risk of bias, while in Domain 3 (data collection and study appraisal) and Risk of Bias in the Review Phase 3, 4 SRs (57.1%) had low risk of bias. The PRISMA reporting standards were generally comprehensive, but some limitations were observed in the assessments, pooled results, evidence reliability, registration and protocols, and funding sources. The GRADE levels ranged from moderate to low, with 10 outcomes of moderate quality and 6 outcomes of low quality. The main reason for the low quality of evidence was the small sample size and high heterogeneity of the available studies.

**Conclusion:** TMS may improve migraine severity and frequency, but the evidence is limited due to methodological flaws and heterogeneity. Future studies should standardize use, assess side effects, and compare with other treatments.

**Keywords:** transcranial magnetic stimulation, migraine, evidence, overview, systematic reviews

## Introduction

Migraine is a common neurological disorder characterized by recurrent moderate to severe headaches and is often accompanied by other symptoms, such as nausea, vomiting, and sensitivity to light and sound.<sup>1</sup> Such symptoms affect approximately 12% of general population and are more prevalent in females than males.<sup>2,3</sup> The pathophysiology of migraine is complex, with cortical spreading depression (CSD) as a key event leading to central and peripheral sensitization.<sup>4</sup> CSD involves a depolarization wave followed by a slower neural inhibition wave, which typically develops in the occipital cortex and spreads to other cortical areas at a speed of 3–6 mm/minute.<sup>5</sup> TMS is a technique that uses brief magnetic pulses on the scalp to stimulate the brain tissue below.<sup>6</sup> This technique is non-invasive, meaning it does not require surgery or implants. A variation of TMS, called rTMS, delivers repeated pulses that can change the activity and adaptability of the brain area being stimulated.<sup>7</sup> TMS and rTMS may affect CSD by altering the balance of excitation and inhibition in the brain's cortex. The most common side effects of TMS and rTMS are mild headache, scalp discomfort, and temporary hearing impairment.<sup>8,9</sup>

In recent years, neuroregulation devices, such as transcranial magnetic stimulation (TMS) has gained wide recognition as an option for treating migraines.<sup>10–12</sup> In order to suppress or alleviate migraine symptoms, TMS has been

developed to target CSD through disrupting the propagation of electrical activity during migraine attacks via magnetic field stimulation of specific areas of the brain.<sup>13</sup> Considering its role in inhibiting CSD, there is growing interest in using TMS to treat migraines.<sup>14–17</sup> This overview of SRs/MAs is, to the best of our knowledge, the first one to systematically collect, appraise, and synthesize the evidence on the efficacy and safety of TMS for migraine treatment, while addressing the methodological quality and heterogeneity of the included SRs/MAs.

Several SRs and MAs have been conducted to assess the effectiveness and safety of TMS for migraine management.<sup>18–24</sup> However, not all SRs can provide reliable evidence, and low-quality evidence can mislead clinical decision-making. Therefore, an overview that summarizes the current evidence on the efficacy and safety of TMS for migraine treatment is needed. Moreover, this overview can serve as a user-friendly tool for healthcare professionals and patients with migraine by presenting the results of SRs/MAs in a unified format and minimizing information redundancy. The results of this overview can inform clinical decision-making and guideline development for the use of TMS in migraine management, as well as identify knowledge gaps and research priorities for future studies.

Methods

Registration and Protocol

The methodology of this study followed the Cochrane manual.<sup>25</sup> The PROSPERO database had this protocol listed as registered (CRD42021287635).

Inclusion and Exclusion Criteria

The inclusion criteria for the SRs/MAs were as follows: (1) SRs/MAs that synthesized the evidence from RCTs on TMS treatment for migraine prevention, regardless of the type, site, frequency, or intensity of TMS stimulation; (2) Migraine of any type that met the diagnostic criteria in the included RCTs; (3) TMS as an intervention of interest for migraine treatment, with a control group consisting of placebo or conventional medication; and (4) Clinical outcomes that measured headache intensity, headache frequency, clinical effectiveness, and adverse events.

The exclusion criteria were as follows: (1) Reviews including non-RCTs; (2) Reviews involving patients with Tension headache; (3) Reviews that were not efficacy evaluations; and (4) Studies without complete data, such as conference abstracts, letters or comments.

Search Methods for Identification of Reviews

From the inception of each database to February 28, 2023, searches were conducted on various databases including The China National Knowledge Infrastructure (CNKI), Wanfang, VIP, China Biomedical Literature (CBM), PubMed, the Cochrane Library, Web of Science and Embase. Systematic reviews related to the subject were also retrieved in order to locate more relevant studies. Specific search strategies were modified in different databases. Table 1 displays the Medicine database search strategy employed in this study.

Table 1 Search Strategy for the Medicine Database

Query	Search Term
#1	Migraine Disorders [Mesh]
#2	Migraine [Title/Abstract] OR Migraine*[Title/Abstract] OR Status Migrainosus*[Title/Abstract] OR Sick Headache* [Title/Abstract]
#3	#1 OR #2
#4	Transcranial Magnetic Stimulation [Mesh]
#5	Transcranial Magnetic Stimulation* [Title/Abstract] OR TMS[Title/Abstract]
#6	#4 OR #5
#7	Meta-Analysis as Topic [Mesh]
#8	Meta-analysis [Title/Abstract] OR Systematic review [Title/Abstract] OR Meta-analyses [Title/Abstract] OR Meta analysis [Title/Abstract] OR Metaanalysis [Title/Abstract]
#9	#7 OR #8
#10	#3 AND #6 AND #9

## Evaluation of Eligibility and Data Extraction

Two authors conducted literature review and independently extracted data. The retrieved literature was imported into Endnote X9 after eliminating duplicates. Titles and abstracts of the literature were read to determine whether the studies those met the inclusion criteria. For final inclusion, full texts of the selected literature were carefully read and analyzed. Information such as author name, publication year, country, enrolled trials, sample size, quality assessment techniques used, interventions and comparisons made in each study along with primary outcomes and data synthesis techniques employed were extracted from all the included studies.

## Quality Assessment

The Assessment of Multiple Systematic Reviews 2 (AMSTAR2) tool,<sup>26</sup> the Risk of Bias in Systematic Reviews (ROBIS),<sup>27</sup> the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist,<sup>28</sup> and the Grading of Recommendations Assessment, Development and Evaluation (GRADE)<sup>29</sup> system were independently applied by the two authors to evaluate methodological quality, Risk of bias, reporting quality, and evidence quality. Seven of the 16 items in AMSTAR-2 were considered to be key items (2, 4, 7, 9, 11, 13, and 15). ROBIS includes 3 phases with Phase 2 containing 4 domains. Each of the 27 items in PRISMA is given a rating of “not reported”, “completely reported”, or “partially reported”. The GRADE system evaluates evidence quality from five aspects: limitations, imprecision, indirectness, inconsistency, and publication bias for SRs/MAs results.

## Graphical Representation of Overlap for OVERviews

We used Excel spreadsheets to extract the studies contained in each summary to explore literature overlap and conduct evaluations. The Graphical Overview of Evidence (GROOVE)<sup>30</sup> is an easy-to-use tool and its calculation of evidence matrix and corrected covered area (CCA) may be one of the most comprehensive methods for measuring overlap. GROOVE uses statistical methods to calculate CCA coverage area and provides an overall interpretation of overlap assessment, which is considered slight if CCA <5%, moderate if it is between 5% and <10%, high if it is between 10% and <15%, and very high if CCA is 15% or higher.<sup>30</sup>

## Results

### Results on Literature Selection

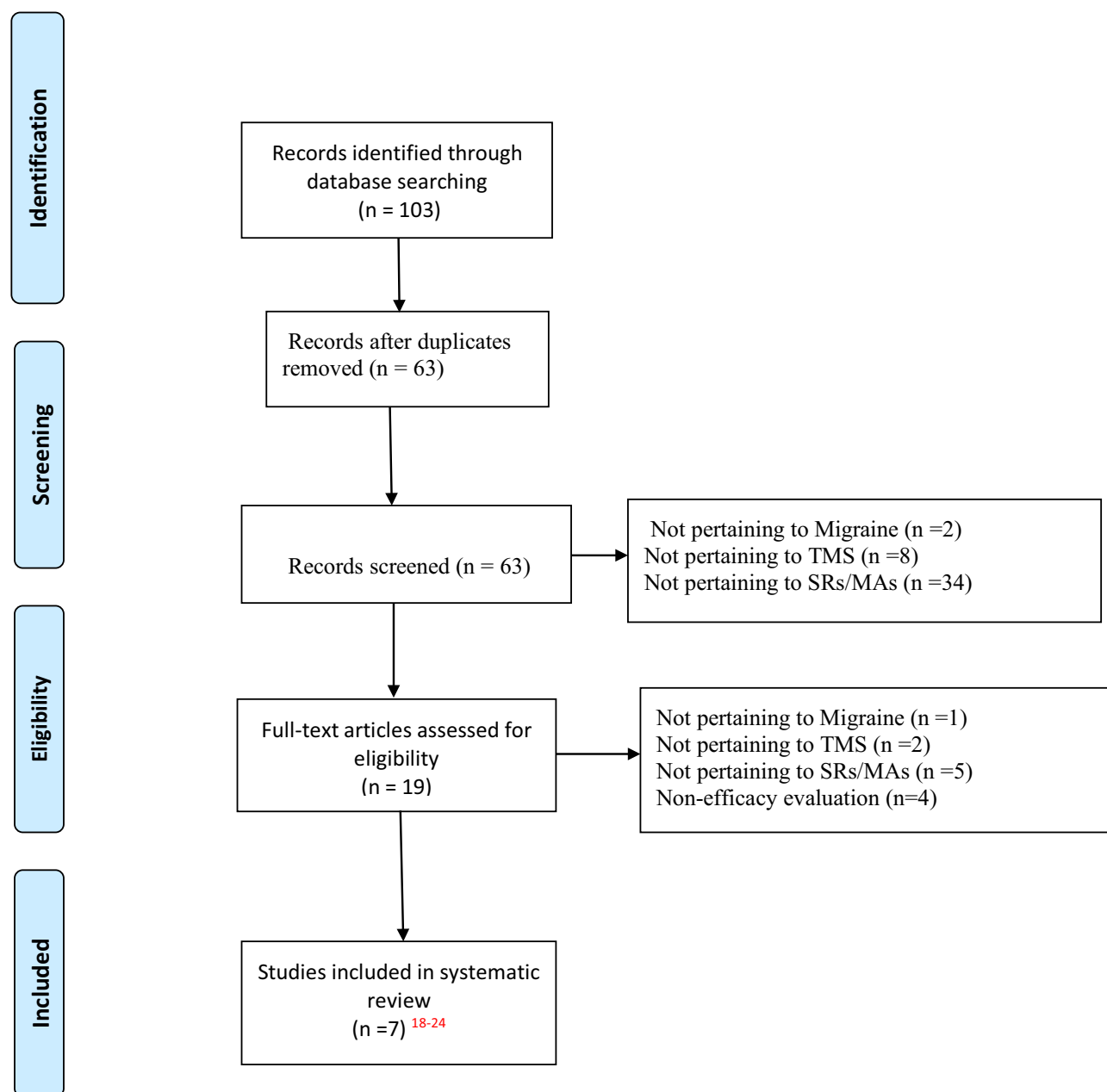
A total of 103 literature papers were found, of which 84 were excluded after reviewing their abstracts and titles. The remaining studies were carefully read in full, and 12 of them were subsequently excluded. Finally, 7 studies were considered as meeting our inclusion criteria.<sup>18–24</sup> A flow chart of literature selection is shown in [Figure 1](#).

### Characteristics of the Included Studies

This overview includes research published from 2016 to 2022. In all the SRs/MAs, the search scope was limited to RCT design. The SRs/MAs contained 3 to 9 RCTs, and the sample sizes ranged from 39 to 452. Regarding the nationality of the first author, 5 articles were published by Chinese authors, 1 article was published by a Finnish author, and 1 article was published by a Malaysian author. The interventions varied slightly. Six articles used rTMS technology, while 1 article used TMS (not specifically classified). For the control group, all the literature was compared using sham stimulation. When evaluating original literature quality, 5 articles used Cochrane bias risk standards, 1 article used PEDro method, and another article used an unknown method. For specific details please refer to [Table 2](#).

### Methodological Quality of the Included SRs

[Table 3](#) displays the results of evaluating methodological quality using the AMSTAR 2 tool. Among the 7 SRs, 4 were rated as moderate quality<sup>19,21–23</sup> and 3 were rated as low quality<sup>18,20,24</sup>. It was worth noting that items 2 and 7 received poor ratings. All the SRs included PICO components and 4<sup>19,21–23</sup> reported study protocols in advance. However, none of them provided a comprehensive list of excluded studies with exclusion reasons. Additionally, 1 SR<sup>24</sup> did not report funding source for the included studies.



**Figure 1** Flow-chart of study selection.

## Risk of Bias of the Included SRs

According to ROBIS, all systematic reviews (100%) were assessed as low risk in Phase 1 (assessment of relevance), Domain 1 (eligibility criteria), and Domain 4 (synthesis and findings) as shown in Table 4. For Domain 2, 4 systematic reviews (57.1%), which focus on the identification and selection of studies, were classified as low risk. Similarly, 4 systematic reviews (57.1%), which focus on data gathering and study evaluation, were rated as low risk for Domain 3. Finally, four systematic reviews (57.1%) were considered as low risk (Table 4) and belonged to the Phase 3 (Risk of bias in the review).

## Reporting Quality of the Included SRs

The reports included in the study met satisfactory standards for all 27 items on the PRISMA checklist. Only 3 studies met all the requirements for every item. Most of the included studies adequately reported on most items, with over a half

**Table 2** Characteristics of the Included Reviews

Studies	Country	Trials (Subjects)	Experimental Intervention	Control Intervention	Quality Assessment	Meta-Analyses	Results Summary
Lan, 2017 <sup>18</sup>	China	5 (313)	Single-pulse TMS	Placebo/ botulinum toxin-A injection	Cochrane criteria	Yes	TMS is effective for migraines, and using an 8-shaped coil to stimulate the left motor cortex and increase frequency may be more effective.
Zhong, 2022 <sup>19</sup>	China	8 (378)	rTMS	Placebo	Cochrane criteria	Yes	rTMS is an effective approach for reducing migraine re-attack when the DLPFC is stimulated.
Feng, 2019 <sup>20</sup>	China	4 (39)	rTMS	Placebo	PEDro	Yes	rTMS can effectively alleviate migraine pain by stimulating DLPFC, but it is not recommended for acute migraines.
Saltychev, 2022 <sup>21</sup>	Finland	8 (329)	rTMS	Placebo	Cochrane criteria	Yes	rTMS may have a positive effect on the severity and frequency of pain in chronic migraines compared to sham stimulation, with an average reduction of 8 days per month in pain frequency.
Safiai, 2022 <sup>22</sup>	Malaysia	5 (128)	HF-rTMS	Placebo	Cochrane criteria	Yes	HF-rTMS of the DLPFC appears to be beneficial in reducing acute drug intake and migraine disability. It also demonstrates good safety and tolerability, making it a potential method for effective migraine prevention.
Shirahige, 2016 <sup>23</sup>	China	9 (452)	rTMS	Placebo	Cochrane criteria	Yes	rTMS technology in migraine treatment is still in the experimental stage.
Jiang, 2016 <sup>24</sup>	China	3 (133)	HF-rTMS	Placebo	Not available	Yes	Current evidence shows that HF-rTMS is effective in preventing chronic migraine with few adverse effects.

**Table 3** Quality Assessment of the Included Reviews by the AMSTAR-2 Tool

Author, Year	AMSTAR-2																Quality
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	
Lan, 2017 <sup>18</sup>	Y	PY	Y	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Zhong, 2022 <sup>19</sup>	Y	Y	Y	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Feng, 2019 <sup>20</sup>	Y	PY	Y	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Saltychev, 2022 <sup>21</sup>	Y	Y	Y	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Safiai, 2022 <sup>22</sup>	Y	Y	Y	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Shirahige, 2016 <sup>23</sup>	Y	Y	Y	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Jiang, 2016 <sup>24</sup>	Y	PY	Y	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	N	Low

**Abbreviations:** Y, yes; N, no; PY, partially yes.

achieving a completion rate of 100%. However, some specific details were more challenging to achieve. For instance, only 4 studies completed review protocols and provided registration information and numbers (item 24a). Additionally, item 20d (synthesis of results) had a lower completion rate at 57.1% when compared to retrieval completion rates. Some other items, such as items 15, 22 and 25 did not reach a completion rate of 100% (Table 5).

**Table 4** Results of Risk of Bias in Systematic Reviews (ROBIS)

Review	Phase 1	Phase 2				Phase 3
	Assessing Relevance	Domain 1. Study Eligibility Criteria	Domain 2. Identification and Selection of Studies	Domain 3. Data Collection and Study Appraisal	Domain 4. Synthesis and Findings	Risk of Bias in the Review
Lan, 2017 <sup>18</sup>	A	A	B	C	A	B
Zhong, 2022 <sup>19</sup>	A	A	A	A	A	A
Feng, 2019 <sup>20</sup>	A	A	B	A	A	B
Saltychev, 2022 <sup>21</sup>	A	A	A	A	A	A
Safai, 2022 <sup>22</sup>	A	A	A	A	A	A
Shirahige, 2016 <sup>23</sup>	A	A	A	C	A	A
Jiang, 2016 <sup>24</sup>	A	A	B	B	A	B

Notes: A = low risk, B = high risk, C = unclear risk.

## Results of the Evidence Quality Assessment

Table 6 summarizes the quality of evidence in the research results using the GRADE system. Out of 16 outcome indicators, none were rated as high-quality confidence, while 10 (62.5%) were rated as moderate-quality confidence and the remaining 6 (37.5%) were rated as low-quality confidence. The primary reasons for downgrading the quality of evidence were small sample sizes and a high level of consistency among the existing studies.

**Table 5** Results of the Reporting Quality

Section/Topic	Items	Lan, 2017 <sup>18</sup>	Zhong, 2022 <sup>19</sup>	Feng, 2019 <sup>20</sup>	Saltychev, 2022 <sup>21</sup>	Safai, 2022 <sup>22</sup>	Shirahige, 2016 <sup>23</sup>	Jiang, 2016 <sup>24</sup>	Compliance (%)
Title	1	Y	Y	Y	Y	Y	Y	Y	100%
Abstract	2	Y	Y	Y	Y	Y	Y	Y	100%
Introduction	3	Y	Y	Y	Y	Y	Y	Y	100%
Methods	4	Y	Y	Y	Y	Y	Y	Y	100%
	5	Y	Y	Y	Y	Y	Y	Y	100%
	6	Y	Y	Y	Y	Y	Y	Y	100%
	7	Y	Y	Y	Y	Y	Y	Y	100%
	8	Y	Y	Y	Y	Y	Y	Y	100%
	9	Y	Y	Y	Y	Y	Y	Y	100%
	10a	Y	Y	Y	Y	Y	Y	Y	100%
	10b	Y	Y	Y	Y	Y	Y	Y	100%
	11	Y	Y	Y	Y	Y	Y	Y	100%
	12	Y	Y	Y	Y	Y	Y	Y	100%
	13a	Y	Y	Y	Y	Y	Y	Y	100%
	13b	Y	Y	Y	Y	Y	Y	Y	100%
	13c	Y	Y	Y	Y	Y	Y	Y	100%
	13d	Y	Y	Y	Y	Y	Y	Y	100%
	13e	Y	Y	Y	Y	Y	Y	Y	100%
	13f	Y	Y	Y	Y	Y	Y	Y	100%
	14	Y	Y	Y	Y	Y	Y	Y	100%
	15	Y	Y	Y	Y	Y	N	N	71.4%

(Continued)

Table 5 (Continued).

Section/ Topic	Items	Lan, 2017 <sup>18</sup>	Zhong, 2022 <sup>19</sup>	Feng, 2019 <sup>20</sup>	Saltychev, 2022 <sup>21</sup>	Safai, 2022 <sup>22</sup>	Shirahige, 2016 <sup>23</sup>	Jiang, 2016 <sup>24</sup>	Compliance (%)
Results	16a	Y	Y	Y	Y	Y	Y	Y	100%
	16b	Y	Y	Y	Y	Y	Y	Y	100%
	17	Y	Y	Y	Y	Y	Y	Y	100%
	18	Y	Y	Y	Y	Y	Y	Y	100%
	19	Y	Y	Y	Y	Y	Y	Y	100%
	20a	Y	Y	Y	Y	Y	Y	Y	100%
	20b	Y	Y	Y	Y	Y	Y	Y	100%
	20c	Y	Y	Y	Y	Y	Y	Y	100%
	20d	N	Y	Y	Y	Y	N	N	57.1%
	21	Y	Y	Y	Y	Y	Y	Y	100%
Discussion	22	Y	Y	Y	Y	Y	N	N	71.4%
	23a	Y	Y	Y	Y	Y	Y	Y	100%
	23b	Y	Y	Y	Y	Y	Y	Y	100%
	23c	Y	Y	Y	Y	Y	Y	Y	100%
	23d	Y	Y	Y	Y	Y	Y	Y	100%
Other information	24a	N	Y	N	Y	Y	Y	N	57.1%
	24b	Y	Y	Y	Y	Y	Y	Y	100%
	24c	Y	Y	Y	Y	Y	Y	Y	100%
	25	Y	Y	Y	Y	Y	Y	N	85.7%
	26	Y	Y	Y	Y	Y	Y	Y	100%
	27	Y	Y	Y	Y	Y	Y	Y	100%

Abbreviations: Y, yes; N, no.

## Overlap Between the Included Reviews

The OVERviews visuals highlighted potential overlaps between each pair of SR/MA in addition to computing the overall CCA. With a total of 21 nodes and considerable overlap throughout the contained comments, we discovered that 7 showed slightly overlapping, 1 showed moderately overlapping, 2 showed highly overlapping, and 11 showed heavily overlapping. For more detailed information please refer to [Figure 2](#).

## Efficacy and Safety of Interventions

One SRs<sup>18</sup> evaluated the acute relief effect of TMS compared to sham stimulation on migraine patients (OR 2.28 (1.15, 4.52)), while there was no significant improvement in chronic migraine (OR2.93 (0.71, 12.15)). Five SRs<sup>19–23</sup> assessed pain intensity with TMS compared to sham stimulation, with 2 showing significant improvement (SMD-1.139 (−2.207, −0.071); MD-13.56 (−21.80, −5.32)) and 3 showed no significant improvement (SMD-0.26 (−0.77, 0.24), MD 0.43 (−0.40, 1.27), SMD −0.29 (−1.14, 0.87)). 3 SRs<sup>19,23,24</sup> evaluated the frequency of migraine attacks with TMS compared to sham stimulation, and two showed a significant improvement (SMD −1.13 (−1.69, −0.58); MD7.55 (6.88, 8.21)). One SRs showed no significant improvement (SMD −0.14 (−1.681.40)). There were 2 studies<sup>21,22</sup> reporting shorter headache days, specifically, 1 indicated that compared to sham stimulation, TMS can reduce headache days (MD-8.09 (−11.40, −4.79)), while another indicated no difference (MD0.10 (−4.13, 4.32)). One SR<sup>22</sup> reported changes in medication intake and HIT-6 score after TMS treatment, which demonstrated that TMS reduced medication intake for migraine patients (MD9.78 (1.60, 17.96)) and HIT-6 scores (MD8 (4.37, 11.63)). One SRs<sup>23</sup> reported adverse reactions of TMS compared to sham stimulation, which showed that TMS did not induce headaches (OR2.21 (0.29, 16.93)) or cause sleep disturbances (OR0.93 (0.20, 4.26)).

## Discussion

According to the philosophy of evidence-based medicine, evidence derived from SRs is considered to have the highest level of credibility.<sup>31,32</sup> Many SRs have been carried out recently to assess the efficacy and safety of TMS in treating

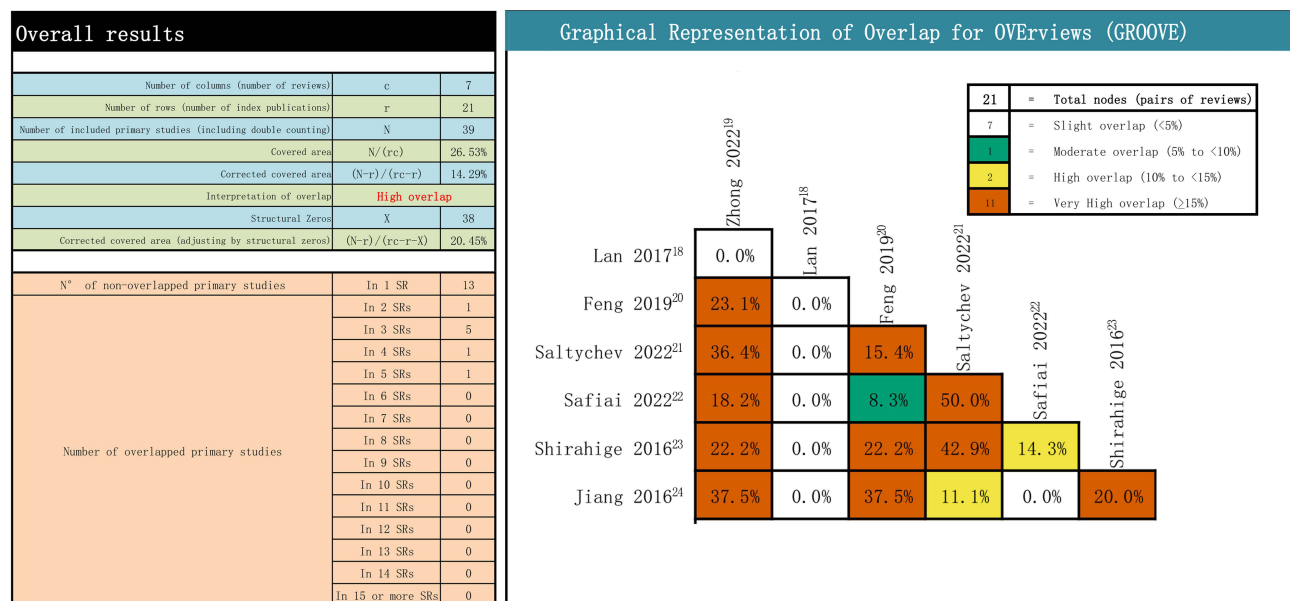
**Table 6** Results of Evidence Quality

Review	Outcomes	Certainty Assessment							No of Patients		Relative Effect (95% CI)	Quality
		No of Trails	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Experimental	Control		
Lan, 2017 <sup>18</sup>	Effect on chronic migraine	5	Rct	No	No	Serious <sup>b</sup>	No	No	140	137	OR2.93 (0.71, 12.15)	Moderate
	Effect on migraine with aura	4	Rct	No	No	Serious <sup>b</sup>	Serious <sup>c</sup>	No	74	75	OR 2.28 (1.15, 4.52)	Low
Zhong, 2022 <sup>19</sup>	Pain intensity	5	Rct	No	No	Serious <sup>b</sup>	Serious <sup>c</sup>	No	133	119	SMD -0.26 (-0.77, 0.24)	Low
	Frequency of migraine attacks	8	Rct	No	No	Serious <sup>b</sup>	No	No	199	208	SMD -1.13 (-1.69, -0.58)	Moderate
Feng, 2019 <sup>20</sup>	Pain intensity	3	Rct	No	No	No	Serious <sup>c</sup>	No	21	19	SMD-1.139 (-2.207,-0.071)	Moderate
Saltychev, 2022 <sup>21</sup>	Reduction of headache days	8	Rct	No	No	Serious <sup>b</sup>	No	No	166	173	MD -8.09 (-11.40,-4.79)	Moderate
	Pain intensity	6	Rct	No	No	Serious <sup>b</sup>	Serious <sup>c</sup>	No	136	121	MD-13.56 (-21.80,-5.32)	Low
Safiai, 2022 <sup>22</sup>	Reduction of headache days	4	Rct	No	No	Serious <sup>b</sup>	Serious <sup>c</sup>	No	62	55	MD0.10 (-4.13, 4.32)	Low
	Pain intensity	3	Rct	No	No	No	Serious <sup>c</sup>	No	60	56	MD0.43 (-0.40, 1.27)	Moderate
	Reductions in medication intake	3	Rct	No	No	Serious <sup>b</sup>	Serious <sup>c</sup>	No	61	53	MD9.78 (1.60, 17.96)	Moderate
	Reduction of HIT-6	2	Rct	No	No	No	Serious <sup>c</sup>	No	48	41	MD8 (4.37, 11.63)	Moderate
Shirahige, 2016 <sup>23</sup>	Frequency of migraine attacks	3	Rct	No	No	Serious <sup>b</sup>	Serious <sup>c</sup>	No	27	25	SMD -0.14 (-1.68, 1.40)	Low
	Pain intensity	3	Rct	No	No	Serious <sup>b</sup>	Serious <sup>c</sup>	No	27	25	SMD -0.29 (-1.14, 0.87)	Low
	Adverse effects (headache)	4	Rct	No	No	No	Serious <sup>c</sup>	No	111	109	OR2.21 (0.29, 16.93)	Moderate
	Adverse effects (sleepiness)	4	Rct	No	No	No	Serious <sup>c</sup>	No	111	109	OR0.93 (0.20, 4.26)	Moderate
Jiang, 2016 <sup>24</sup>	Frequency of migraine attacks	3	Rct	No	No	No	Serious <sup>c</sup>	No	66	67	MD7.55 (6.88, 8.21)	Moderate

**Notes:** <sup>b</sup>The confidence interval overlaps less, the heterogeneity test P was very small, and the I2 was larger; <sup>c</sup>The Confidence interval was not narrow enough, or the sample size is too small.

**Abbreviations:** Rct, randomized controlled trial; OR, odds ratio; SMD, standardized mean difference; MD, mean difference.





**Figure 2** Overlapping of the included reviews.

migraines.<sup>18–24</sup> However, the PRISMA statement has recommended by only a few SRs, and GRADE could evaluate their quality of evidence. Therefore, it is preferable to have a thorough understanding of these SRs rather than using a large number of low-quality SRs with dubious conclusions or meta-analyses.<sup>33</sup> Additionally, an overview can provide valuable insight for enhancing and guiding future high-quality SRs.<sup>34</sup> By evaluating the data from 7 SRs, our review investigated the use of TMS for migraines and proposed 3 key conclusions.

Firstly, due to the uncertainty of the results, caution should be taken when recommending TMS as an alternative treatment for migraines. The included SRs evaluated the effectiveness of TMS in improving pain intensity, reducing migraine frequency and decreasing headache days, however, all these evaluations were greatly underestimated by AMSTAR 2 methodological quality standards, especially items 2 and 7. Some were rated as high risk during ROBIS stage 2, which covers key review processes that may introduce bias into SR process transparency as an important domain to introduce SR bias. Therefore, it is necessary to confirm the effectiveness of TMS in improving pain intensity, frequency of migraine attacks, and reduction of headache days with high-quality methodology without risk biases. Such evidence came from one systemic review,<sup>23</sup> which demonstrates that TMS can reduce medication intake and migraine attacks patients with migraines. However, the GRADE level evidence quality was low due to the limited sample size, heterogeneity, and sample size. Promoting the use of TMS among patients with migraines is not recommended due to limited sample sizes and related safety indicators. Further large-scale clinical trials are needed to draw more convincing conclusions.

Secondly, there was sample opportunity within systematic review (SR) processes to address risks associated with bias, methodology, and reporting quality. Methodological flaws limit the validity of SRs, while the possibility of bias in SRs could affect the validity of the data. Improper reporting in SRs may omit to mention adverse reactions or inflate the impact of interventions, thereby reducing their design value. Our examination of 7 SRs using AMSTAR 2 revealed common deficiencies such as a lack of pre-published protocols or explanations for study design choices and exclusion of some SRs and funding sources. Based on the PRISMA results, all the 7 included SRs had varying degrees of reporting deficiencies, particularly in protocol and registration, synthesis results, certainty assessment, evidence reliability and funding. Future systematic reviews should adhere to both AMSTAR 2 and PRISMA guidelines. During stage two (identification and selection of studies) and stage three (reviewing risks associated with bias), ROBIS identified some low-risk assessments and result quality varied depending on GRADE results.

Thirdly, we extracted and analyzed every original RCT for TMS therapy of migraines in SRs/MAs using the GROOVE tool. Overall, there was a relatively high overlap between the included SRs/MAs. A majority of the overlaps (>5%) occurred among the studies, as shown in the overlapping distribution area in Figure 2. Therefore, current published systematic reviews had similar results that can explain why there were 3 SRs on TMS treatment for migraines in 2022. Further systematic review research is not necessary unless new double-blind and multicenter RCTs emerge.

## Implications for Future Study

Reviewers should adhere to the guidelines of AMSTAR 2, ROBIS, and PRISMA when conducting SRs. In particular, during the transparent process, research plans should be registered or published in PROSPERO (<http://www.crd.york.ac.uk/prospero>) or Cochrane beforehand, and gray literature should be considered. At the same time, conflicts of interest or funding sources should be stated, along with a list of eliminated studies and the reasons for elimination. To improve the quality of original research evidence on TMS treatment for migraine with aura, it is recommended to increase sample size. If significant heterogeneity exists, subgroup analysis or meta-regression analysis is needed for further improving evidence quality.

The AMSTAR 2 tool is widely used for assessing the quality of systematic reviews (SRs)<sup>26</sup> but does not assess the possibility of bias in SRs. To address this gap, the ROBIS tool was developed specifically for conducting overviews. The ROBIS instrument contains 3 stages, the second of which consists of 4 domains, each with signaling questions and a determination of the domain's bias risk.<sup>27</sup> Even though some aspects in AMSTAR 2 and ROBIS may be similar, these tools have diverse functions that work well together to give a more complete picture. The 7 SRs have several shortcomings, yet TMS could still reduce the severity and frequency of migraine patients' headache. Future research should pay more attention to standardizing TMS operations, such as localization, current intensity, operation frequency and time. In addition, we do not have enough evidence to show that TMS would produce adverse reactions, therefore further investigation is needed to determine its safety. It is worth noting that TMS has advantages such as non-invasiveness, repeatability and personalized treatment methods.

## Limitations

Our review has several limitations. Firstly, we might have overlooked a few studies in other languages as we only included SRs written in English and Mandarin. Secondly, the sample size of SRs that included RCTs was relatively small. Due to the GRADE level was in the moderate to low range, no definite conclusions can be made.

## Conclusion

TMS may have a beneficial effect on the severity and frequency of migraine episodes and has a good safety profile, but the evidence is limited and inconclusive due to the methodological flaws and heterogeneity of the existing studies. Some of the major limitations include small sample size, lack of blinding, heterogeneity of intervention parameters, variability of outcome measures, and risk of bias and publication bias in the included studies. Therefore, future studies should address these issues by carefully selecting patients, standardizing the use of TMS and rTMS, assessing side effects, and comparing with other treatments. This would provide more reliable and consistent evidence for the efficacy and safety of TMS in migraine management, as well as inform clinical decision-making and guideline development.

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## Disclosure

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