ISSN 2308-3840 (online)

World Journal of *Meta-Analysis*

Quarterly Volume 13 Number 1 March 18, 2025

Published by Baishideng Publishing Group Inc

WJMA

World Journal of Meta-Analysis

Contents

Quarterly Volume 13 Number 1 March 18, 2025

SYSTEMATIC REVIEWS

META-ANALYSIS

SCIENTOMETRICS

World Journal of Meta-Analysis

Quarterly Volume 13 Number 1 March 18, 2025

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Meta-Analysis*, Raymond Pranata, MD, Associate Chief Physician, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin General Hospital, Kota Bandung, Jawa Barat 40161, Indonesia. raymond_pranata@hotmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Meta-Analysis* (*WJMA*, *World J Meta-Anal*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality meta-analysis and systematic review articles and communicate their research findings online.

WJMA mainly publishes articles reporting research results and findings obtained through meta-analysis and systematic review in a wide range of areas, including medicine, pharmacy, preventive medicine, stomatology, nursing, medical imaging, and laboratory medicine.

INDEXING/ABSTRACTING

The *WJMA* is now abstracted and indexed in Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Meta-Analysis

ISSN
ISSN 2308-3840 (online)

LAUNCH DATE
May 26, 2013

FREQUENCY
Quarterly

EDITORS-IN-CHIEF
Jing Sun

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2308-3840/editorialboard.htm

PUBLICATION DATE
March 18, 2025

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2025 March 18; 13(1): 98933

DOI: 10.13105/wjma.v13.i1.98933

ISSN 2308-3840 (online)

SYSTEMATIC REVIEWS

Role of transcranial magnetic stimulation in the management of trichotillomania: A systematic review

Sujita Kumar Kar, Babli Kumari, Rini Joseph, Surobhi Chatterjee, Mohita Joshi, Aditya Agrawal

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A, Grade B, Grade D

Novelty: Grade A, Grade A, Grade B

Creativity or Innovation: Grade A, Grade B, Grade C

Scientific Significance: Grade A, Grade A, Grade B

P-Reviewer: Abzalova V; Miao CH; Zhao SQ

Received: July 9, 2024

Revised: October 16, 2024

Accepted: December 12, 2024

Published online: March 18, 2025

Processing time: 247 Days and 16.2 Hours

Sujita Kumar Kar, Babli Kumari, Mohita Joshi, Department of Psychiatry, King George's Medical University, Lucknow 226003, Uttar Pradesh, India

Rini Joseph, Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bengaluru 560029, Karnataka, India

Surobhi Chatterjee, Department of Psychiatry, All India Institute of Medical Sciences, Mangalagiri 522503, Andhra Pradesh, India

Aditya Agrawal, Department of Psychiatry, Dr. Ram Manohar Lohiya Institute of Medical Sciences, Lucknow 226010, Uttar Pradesh, India

Corresponding author: Sujita Kumar Kar, MD, Additional Professor, Department of Psychiatry, King George's Medical University, Shahmina Road, Lucknow 226003, Uttar Pradesh, India. drsujita@gmail.com

Abstract

BACKGROUND

Trichotillomania is a challenging to treat psychiatric disorder, with limited evidence for pharmacotherapy. Treatment typically involves medication, cognitive behavioral therapy, and behavioral interventions. Recently, transcranial magnetic stimulation (TMS) has emerged as a potential treatment strategy.

AIM

To assess the role of TMS in treating trichotillomania.

METHODS

A systematic search using specific terms was done in PubMed and Scopus databases for articles published until May 17, 2024, related to trichotillomania and TMS. The search included randomized controlled trials, open-label studies, case series, case reports, and retrospective chart reviews, following the Preferred Items for Systematic Reviews and Meta-Analysis guideline.

RESULTS

We identified 32 articles (6 in PubMed and 26 in Scopus). After removing duplicates and articles that did not meet the selection criteria, we conducted a final analysis of four articles. These included one retrospective study, two case series, and one case study, with a total of 22 patients diagnosed with trichotillomania enrolled across all four studies. The brain areas targeted were the supplementary

motor area (SMA), pre-SMA, and left dorsolateral prefrontal cortex. The studies reported an improvement in the severity of symptoms of trichotillomania in the majority of patients with negligible side effects. Nevertheless, it is important to note that the existing studies are mostly of low to moderate quality.

CONCLUSION
Early evidence suggests repetitive TMS and accelerated continuous theta burst stimulation can help treat trichotillomania adjunctively to other treatments.

Key Words: Neuromodulation; Transcranial magnetic stimulation; Theta burst stimulation; Trichotillomania; Systematic review

Core Tip: Transcranial magnetic stimulation (TMS) can be a viable treatment option in the management of trichotillomania. The brain areas targeted are supplementary motor area (SMA), pre-SMA, and left dorsolateral prefrontal cortex. TMS is well tolerated with negligible side effects. Maintenance TMS treatment facilitates sustained improvement of symptoms of trichotillomania.

Citation: Kar SK, Kumari B, Joseph R, Chatterjee S, Joshi M, Agrawal A. Role of transcranial magnetic stimulation in the management of trichotillomania: A systematic review. *World J Meta-Anal* 2025; 13(1): 98933
URL: https://www.wjgnet.com/2308-3840/full/v13/i1/98933.htm
DOI: https://dx.doi.org/10.13105/wjma.v13.i1.98933

INTRODUCTION

Trichotillomania is characterized by recurrent hair-pulling and is associated with significant distress[1,2]. A recent meta-analysis involving 30 studies, including 38526 individuals estimated the prevalence of trichotillomania to be 1.14%[2]. When individuals with hair-pulling behaviors are considered, prevalence goes close to 9%[2]. These figures indicate that the prevalence of these disorders is higher than the prevalence of schizophrenia or bipolar affective disorder alone. Trichotillomania and related disorders have a significant health impact and produce enormous psychological distress, which results in impairment of socio-occupational functioning and social embarrassment[3]. Patients with trichotillomania experience extreme shame and guilt[3].

The common age of onset of trichotillomania is the second decade of life (mean age 17.7 years), and 80% of the patients with trichotillomania have comorbid psychiatric illnesses[1]. The common psychiatric comorbidities associated with trichotillomania include anxiety disorders, obsessive-compulsive disorder (OCD), depression, post-traumatic stress disorder, and attention deficit hyperactivity disorder (ADHD)[1]. Several neurobiological changes have been identified in the brains of patients with trichotillomania. Chamberlain *et al*[4] found that patients with trichotillomania have increased cortical thickness in the region of the right inferior frontal gyrus, in contrast to impulsive-compulsive disorders like OCD, ADHD, and gambling disorders (where there is thinning of the cortex). In another neuroimaging study, it is found that during the activities of reward anticipation, there is hyperactivation of the bilateral inferior frontal gyrus in patients with body-focused repetitive disorders like trichotillomania and skin picking disorder[5]. A diffuse tensor imaging study revealed a significant reduction in fractional anisotropy of the anterior cingulate cortex, pre-supplementary motor area (SMA) and temporal cortex[6]. This abnormality of the white matter might be responsible for affective dysregulation, and dysregulation in the formation of motor habit[6]. A recent neuroimaging study found the involvement of inferior temporal gyrus and ventral visual pathways in trichotillomania[7]. Additionally, there is involvement of brain structures like parahippocampal gyrus, fusiform gyrus, cerebellum, as well as inferior parietal lobule during the above-mentioned task [5]. Evidence supports about several shared unique neural mechanisms in the pathogenesis of trichotillomania and OCD [8].

Comorbidities are common with trichotillomania. The common psychiatric comorbidities associated with trichotillomania are: (1) Anxiety disorders; (2) depression; (3) OCD; (4) ADHD; (5) panic disorder; (6) post-traumatic stress disorder; (7) substance use disorder; and (8) eating disorders[3]. Skin picking disorder is also commonly found to be comorbid with trichotillomania[3].

To date, there is no treatment that has been approved by the US Food and Drug Administration for the treatment of trichotillomania[9-11]. Various pharmacological and psychological/behavioral interventions are conventionally used in the treatment of trichotillomania. However, the mainstay of treatment remains psychotherapy and behavior therapy like habit reversal therapy[12,13]. Among the pharmacological treatment, serotonergic agents and tricyclic antidepressants such as clomipramine are commonly used in the management of trichotillomania, although N-acetyl cysteine, lamotrigine, olanzapine, naltrexone, and inositol are also used with some efficacy[12,14]. However, a recent Cochrane systematic review reported inconclusive evidence concerning the roles of different psychotropic agents in the treatment of trichotillomania and the existing studies are mostly of poor quality[15]. Despite trials of pharmacotherapy and psychotherapy, the treatment of trichotillomania remains challenging as many patients do not respond well to these therapies. Therefore,

Table 1 Characteristics of the included studies

Ref.	Title of the article	Journal name	Country	Type of study	Level of evidence
Chaudhary *et al* [18], 2024	Accelerated Continuous Theta Burst Stimulation in the Treatment of Trichotillomania: A Comprehensive Case Study From Acute Intervention to Maintenance Phase	*The Journal of ECT*	India	Case report	IV
Di Ponzio *et al* [19], 2023	rTMS investigation of resistant Obsessive-Compulsive Related Disorders: Efficacy of targeting the reward system	*Frontiers in Psychiatry*	Italy	Retrospective study	III
Aydin *et al*[17], 2020	Repetitive Transcranial Magnetic Stimulation for Treatment of Trichotillomania: Case Series	*Clinical Psychopharmacology and Neuroscience*	Turkey	Case series	IV
Kar *et al*[21], 2020	Successful treatment of trichotillomania with repetitive transcranial magnetic stimulation: A report of two cases with review of literature	*Asian Journal of Psychiatry*	India	Case series	IV

researchers explored other possible treatment avenues for trichotillomania. As trichotillomania is an OCD spectrum disorder and shares a lot of neurobiological similarities with OCD, possibly the targets of neuromodulation in OCD may also be useful in the management of trichotillomania.

Neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS)[16], transcranial direct current stimulation (tDCS), and electroconvulsive therapy (ECT) have been used in the management of trichotillomania in the recent decade[17-21]. The existing evidence is mostly limited to case studies. Neuromodulation treatment is a rapidly evolving field and evidence regarding the safety and efficacy of the above-mentioned neuromodulation techniques are well-established in various psychiatric disorders. However, a limited number of studies have discussed the scope and relevance of neuromodulation techniques in trichotillomania. Of the existing studies that discuss about the relevance of neuromodulation in trichotillomania, most have used TMS. TMS uses repetitively generated magnetic stimuli that modulate the neuronal activity of a focal group of neurons in the superficial cortical region (at the site of placement of the TMS coil). The underlying cortical neuronal activity following TMS application depends on the nature of TMS stimuli. High-frequency (> 5Hz) rTMS, and intermittent theta burst stimulation (a form of patterned TMS) produces underlying cortical stimulation whereas, low-frequency rTMS and continuous theta burst stimulation produces underlying cortical inhibition[22-25]. No systematic review has explored the relevance of TMS in the management of trichotillomania. This is the first systematic review that attempted to analyze the role of TMS in the management of trichotillomania.

MATERIALS AND METHODS

Methodology

A systematic search was done by using the search terms: (trichotillomania) AND ((TMS) OR (rTMS) OR (transcranial magnetic stimulation) OR ((transcranial magnetic stimulation))). The databases searched are PubMed and Scopus. All articles published from inception up to May 17, 2024 were included. To be included in this systematic review, the article had to be either a randomized controlled trial (RCT), open-label study, case series, case report, or retrospective chart review. The articles were extracted to RAYYAN software and screened by two investigators (Joshi M and Agrawal A) keeping the blinding on. Subsequently, a third investigator (Kar SK) evaluated the extracted articles, and through mutual discussion final selection of the articles was made. An additional search was done from the prominent journals focusing on neuromodulation (*Brain Stimulation*, *The Journal of ECT*, and *Neuromodulation*: *Technology at the Neural Interface*). Extraction of data in a given format was done by an independent investigator (Kumari B). The risk of bias assessment was done by using the Joanna Briggs Institute (JBI) critical appraisal tools[26] by two blinded investigators (Joseph R and Chatterjee S) independently and was finally sorted through mutual discussion. As this systematic review included one retrospective cohort study, two case series and one case report, the risk of bias assessment was done by applying specific tools for critical appraisal.

RESULTS

We found 32 hits (6 in PubMed and 26 in Scopus). Six duplicate articles were removed after the initial screening and subsequent screening of the title and abstract resulted in the exclusion of 21 more articles (Figure 1). Articles were excluded for multiple reasons (which were not mutually exclusive). Major reasons for exclusion were: wrong publication type (n = 21), wrong study design (n = 15), wrong outcomes (n = 14), wrong population (n = 11), and wrong intervention type (n = 4). A total of five articles were initially included; however, one[27] more article was excluded after a detailed evaluation of the whole article (as the article discussed biological markers, neuroimaging changes, and pathophysiological models in OCD and related disorders). The final analysis was done on four selected articles, which included one retrospective study, two case series and one case study (Table 1)[17-19,21]. A total of 22 patients diagnosed with trichotil-

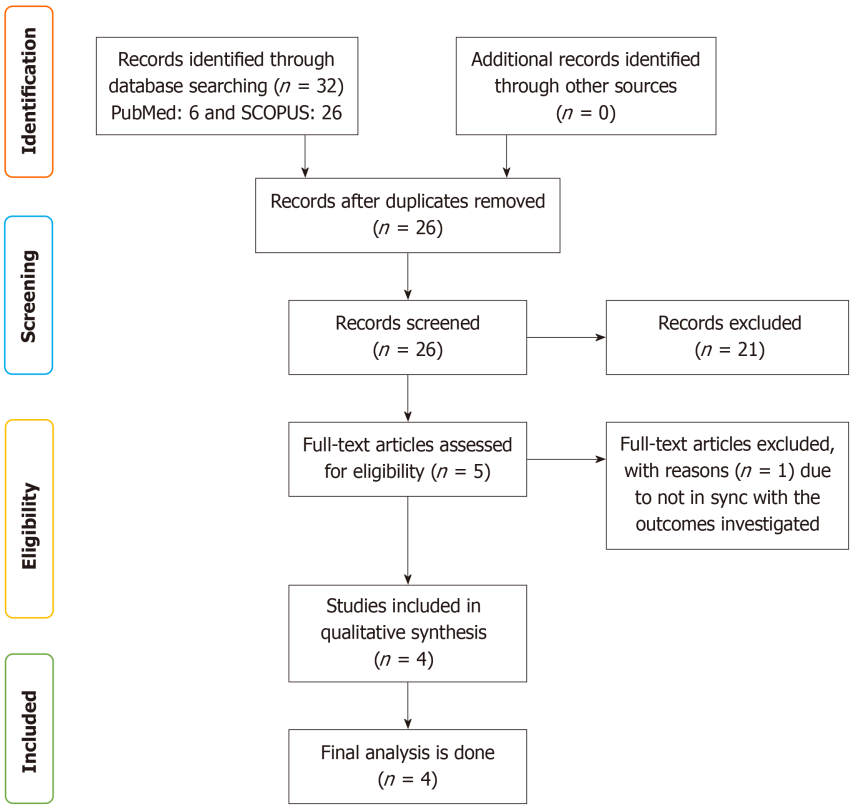


Figure 1 Preferred Items for Systematic Reviews and Meta-Analysis flow diagram describing the studies.

lomania were enrolled in these four studies (Table 2)[17-19,21]. In all the cases, TMS was being used as an add-on treatment modality to ongoing pharmacotherapy with or without psychotherapy. The brain areas targeted in managing trichotillomania were the SMA, pre-SMA, and left dorsolateral prefrontal cortex. Out of the four included studies, one study used accelerated continuous theta burst stimulation, one used high-frequency rTMS, and the other two used low-frequency rTMS (Table 3)[17-19,21]. On risk of bias assessment, only one study scored a JBI quality score of ≥ 70% [28], hence was of good quality and the other three were of moderate to low quality (Table 4, 5 and 6)[17-19,21].

DISCUSSION

Neuromodulation, like TMS, is a less-studied treatment modality to manage trichotillomania. To date, only four published articles discussed the efficacy/effectiveness of TMS in trichotillomania, of which three were case reports/series. Con-sidering the publications available in PubMed and Scopus until the week 3 of May 2024, the first reports of the use of TMS in management of trichotillomania were published in March 2020, by Kar *et al*[21] in the *Asian Journal of Psychiatry*. In November, 2020 another case series was published by Aydin *et al*[17], on five females with trichotillomania. The first observational study (retrospective database review) involving 41 patients, of whom, 14 had trichotillomania, and the rest had hoarding disorder or skin picking disorder, was published in 2022 by Di Ponzio *et al*[19]. A case study that used theta burst stimulation in an accelerated fashion for the first time in the management of trichotillomania was published in March 2024[18]. A total of 22 patients with trichotillomania received TMS treatment, of which only two were males (as part of the study of Di Ponzio *et al*[19]) and the remaining 20 were females[17,18,21]. Although some evidence suggests no gender difference in the prevalence of trichotillomania[1], most studies reported that females had a higher prevalence of trichotillomania than males had (odds ratio = 2.23), which involved hair-pulling with noticeable hair loss [2].

SMA and pre-SMA are commonly targeted in the management of trichotillomania[17,18,21]. Another study that used tDCS in the management of trichotillomania also targeted SMA as the target of neuromodulation[16]. As SMA and pre-SMA are commonly targeted in the management of OCD[29,30] and there is commonality in the neurobiology and phenomenology of OCD and trichotillomania[8,31,32], this probably tempts researchers to target these areas for focal neuromodulation. An inhibitory protocol is exclusively used for the management of trichotillomania targeting SMA and pre-SMA[16-18,21] as hyperactivity of these areas is consistently reported in OCD and related repetitive behavioral disorders.

The studies reported improvement in the severity of symptoms of trichotillomania in most patients with negligible side effects[17-19,21]. One study also considered maintenance accelerated continuous theta burst stimulation in the management of trichotillomania, with improvement of symptoms[18].

Table 2 Characteristics of participants

Ref.	Sample size	Psychiatric morbidities	Concurrent treatment		Past treatment		Outcome scale	Results	Side effects	Conclusion
			Psychotropics (mg/d)	Psychotherapy	Psychotropics (mg/d)	Psychotherapy				
Chaudhary *et al* [18], 2024	1	Not mentioned	Fluoxetine 80 mg, Aripiprazole 2 mg	Not mentioned	Yes (details not mentioned)	Not mentioned	YBOCS, MGH-HPS, and CGI-I	56% and 80% reduction in YBOCS and MGH-HPS scores, respectively. CGI-I scores improved from moderately worse to moderately efficacious. After 6 sessions of maintenance acTBS over 6 weeks, improvement was sustained	NR	First case report for acute and maintenance acTBS which was well tolerated and effects sustained
Di Ponzio *et al*[19], 2023	14	7 major depressive disorder, 2 ADHD, 4 GAD, 1 bipolar disorder	Selective serotonin reuptake inhibitors: Fluoxetine equivalent of 30 mg	None	Yes (details not mentioned)	Cortical bone trajectory	MGH-HPS and SDQ	Mean percentage of improvement was 58.2% in MGH-HPS and 17.1% in SDQ. No significant reduction after 1 month follow-up. Linear regression analysis indicated no age effect between pre- and post-intervention. Worsening of MGH-HPS scores was at follow-up in older age group	NR	Positive outcomes suggest implic-ations for reward circuits, which are usually used for addictions. This is consistent with the emerging view that obsessive-compulsive and related disorders are behavioral addictions. Worsening of MGH-HPS scores at follow-up in the older age group indicates reduced plasticity in elderly
Aydin *et al*[17], 2020	5	Case 1 ADHD; Case 2 none; Case 3 none; Case 4 GAD; Case 5 bipolar type II, obsessive-compulsive disorder, alcohol abuse, specific phobia	Case 1 Methyl-phenidate 36 mg; Case 2 no psycho-tropics; Case 3 Fluoxetine 80 mg; Case 4 Fluoxetine 20 mg; Case 5 Sertraline 100 mg, Aripiprazole 5 mg, Quetiapine 150 mg	None in all cases	Case 1 Fluoxetine 20 mg; Case 2 Escitalopram 20 mg; Case 3 Fluoxetine 80 mg, N-acetyl cystine 1200 mg; Case 4 no; Case 5 no	Yes in case 1 and case 3	MGH-HPS, Beck's anxiety inventory, Beck's depression inventory	Three patients had substantial benefit (100%, 75%, and 70% improvement in MGH-HSP), one patient had 33% improvement. The last patient experienced a mild increase in the severity	Transient flashes in eye for 2-3 session in one case	Repetitive transcranial magnetic stimulation was effective in 3 of 5 patients. One was a partial responder, and the other nonresponder might have been due to multiple comorbidities that

										acted as confounding factors
Kar *et al*[21], 2020	2	Not mentioned	Case 1 Escitalopram 30 mg; Case 2 Sertraline 200 mg	Habit reversal therapy	Not mentioned	Not mentioned	MGH-HPS	Reduction of 66.6% and 73.6% in both cases, respectively. Case 1 sustained benefits for 6 weeks, while case 2 was maintained well for 2 months then experienced worsening which improved with psychotherapy for 6 months	NR	Reduction in symptom severity and therapy was well tolerated

ADHD: Attention deficit hyperactivity disorder; acTBS: Accelerated continuous theta burst stimulation; CGI-I: Clinical global impression improvement; GAD: Generalized anxiety disorder; MGH-HPS: Massachusetts General Hospital Hair Pulling Scale; NR: None reported; SDQ: Symptoms of depression questionnaire; YBOCS: Yale-Brown Obsessive-Compulsive Scale.

Table 3 Parameters of protocols used

Ref.	Type of TMS intervention	Target area	Frequency (Hz)	Resting motor threshold (%)	Total no. of pulses	No. of sessions per day	Total no. of sessions	Duration of treatment (week)	Maintenance TMS
Chaudhary *et al* [18], 2024	Accelerated continuous theta burst stimulation	SMA	Not mentioned	Not mentioned	900	2 (15 min apart)	20	Not mentioned	Yes (6 > 6 weeks)
Di Ponzio *et al*[19], 2023	High frequency rTMS	Left dorsolateral prefrontal cortex	15	100	2400	1	24	4	No
Aydin *et al*[17], 2020	LF rTMS	Pre-SMA	1	100	1200	1	15	3	No
Kar *et al*[21], 2020	LF rTMS	SMA	1	Not mentioned	1200	1	20	4	No

LF: Low frequency; rTMS: Repetitive transcranial magnetic stimulation; SMA: Supplementary motor area; TMS: Transcranial magnetic stimulation.

The existing evidence is mostly limited to case reports/series or retrospective studies on a small sample. There was no RCT on TMS in trichotillomania. The existing studies were mostly of low to moderate quality. Hence, there is a need for extensive research, particularly RCTs, to substantiate the evidence for TMS treatment of trichotillomania.

A major limitation of this systematic review was the small number of studies and the heterogeneity among the studies in terms of the protocols used, sites targeted, number of sessions used, and the presence of comorbidity. Further research is required for better understanding about the efficacy and safety of TMS in trichotillomania.

Table 4 Risk of bias assessment of cohort study on Joanna Briggs Institute critical appraisal tool

Ref.	Were the two groups similar and recruited from the same population	Were the exposures measured similarly to assign people to both exposed and unexposed groups	Was the exposure measured in a valid and reliable way	Were confounding factors identified	Were strategies to deal with confounding factors stated	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)	Were the outcomes measured in a valid and reliable way	Was the follow up time reported and sufficient to be long enough for outcomes to occur	Was follow up complete, and if not, were the reasons to loss to follow up described and explored	Were strategies to address incomplete follow up utilized	Was appropriate statistical analysis used	Score
Di Ponzio *et al* [19], 2023	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	Yes	73%

Table 5 Risk of bias assessment of case series on Joanna Briggs Institute critical appraisal tool

Ref.	Were there clear criteria for inclusion in the case series	Was the condition measured in a standard, reliable way for all participants included in the case series	Were valid methods used for identification of the condition for all participants included in the case series	Did the case series have consecutive inclusion of participants	Did the case series have complete inclusion of participants	Was there clear reporting of the demographics of the participants in the study	Was there clear reporting of clinical information of the participants	Were the outcomes or follow up results of cases clearly reported	Was there clear reporting of the presenting site(s)/clinic(s) demographic information	Was statistical analysis appropriate	Score
Kar *et al*[21], 2020	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear	NA	30%
Aydin *et al* [17], 2020	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear	NA	40%

CONCLUSION

Trichotillomania is a difficult-to-treat mental illness, with limited evidence for pharmacotherapy. Preliminary evidence supports the beneficial role of rTMS and accelerated continuous theta burst stimulation in managing trichotillomania as an add-on treatment modality. There is a need for further research and more clinical trials in larger groups of patients with trichotillomania to establish the evidence.

Table 6 Risk of bias assessment of case reports on Joanna Briggs Institute critical appraisal tool

Ref.	Were patient's demographic characteristics clearly described	Was patient's history clearly described and presented as a timeline	Was current clinical condition of the patient on presentation clearly described	Were diagnostic tests or assessment methods and results clearly described	Was interventions or treatment procedure clearly described	Was post-intervention clinical condition clearly described	Were adverse events or unanticipated events identified and described	Does the case report provide takeaway lessons	Score
Chaudhary *et al*[18], 2024	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	63%

FOOTNOTES

Author contributions: Kar SK was responsible for conceptualization; Kar SK and Kumari B were responsible for manuscript writing; Kar SK, Joshi M, and Agrawal A were responsible for the literature search; Kumari B was responsible for tabulation and data extraction; Joseph R and Chatterjee S were responsible for risk of bias assessment; Kar SK, Kumari B, Joseph R, Chatterjee S, Joshi M, and Agrawal A were responsible for revision and editing of the manuscript; all of the authors read and approved the final version of the manuscript to be published.

Conflict-of-interest statement: All authors declare no conflict of interest in publishing the manuscript.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: India

ORCID number: Sujita Kumar Kar 0000-0003-1107-3021.

S-Editor: Luo ML
L-Editor: Kerr C
P-Editor: Zhao YQ

REFERENCES

1 **Grant JE**, Dougherty DD, Chamberlain SR. Prevalence, gender correlates, and co-morbidity of trichotillomania. *Psychiatry Res* 2020; **288**: 112948 [PMID: 32334275 DOI: 10.1016/j.psychres.2020.112948]
2 **Thomson HA**, Farhat LC, Olfson E, Levine JLS, Bloch MH. Prevalence and gender distribution of trichotillomania: A systematic review and

meta-analysis. *J Psychiatr Res* 2022; **153**: 73-81 [PMID: 35802953 DOI: 10.1016/j.jpsychires.2022.06.058]

3 **Mackay CE**. Trichotillomania: a perspective synthesised from neuroscience and lived experience. *BMJ Ment Health* 2023; **26**: e300795 [PMID: 37734751 DOI: 10.1136/bmjment-2023-300795]

4 **Chamberlain SR**, Harries M, Redden SA, Keuthen NJ, Stein DJ, Lochner C, Grant JE. Cortical thickness abnormalities in trichotillomania: international multi-site analysis. *Brain Imaging Behav* 2018; **12**: 823-828 [PMID: 28664230 DOI: 10.1007/s11682-017-9746-3]

5 **Grant JE**, Peris TS, Ricketts EJ, Bethlehem RAI, Chamberlain SR, O'Neill J, Scharf JM, Dougherty DD, Deckersbach T, Woods DW, Piacentini J, Keuthen NJ. Reward processing in trichotillomania and skin picking disorder. *Brain Imaging Behav* 2022; **16**: 547-556 [PMID: 34410609 DOI: 10.1007/s11682-021-00533-5]

6 **Chamberlain SR**, Hampshire A, Menzies LA, Garyfallidis E, Grant JE, Odlaug BL, Craig K, Fineberg N, Sahakian BJ. Reduced brain white matter integrity in trichotillomania: a diffusion tensor imaging study. *Arch Gen Psychiatry* 2010; **67**: 965-971 [PMID: 20819990 DOI: 10.1001/archgenpsychiatry.2010.109]

7 **Roos A**, Fouche JP, Stein DJ, Lochner C. Structural brain network connectivity in trichotillomania (hair-pulling disorder). *Brain Imaging Behav* 2023; **17**: 395-402 [PMID: 37059898 DOI: 10.1007/s11682-023-00767-5]

8 **Peris TS**, Salgari G, Perez J, Jurgiel J, Vreeland A, O'Neill J, Chang S, Piacentini J, Loo SK. Shared and unique neural mechanisms underlying pediatric trichotillomania and obsessive compulsive disorder. *Psychiatry Res* 2021; **298**: 113653 [PMID: 33621723 DOI: 10.1016/j.psychres.2020.113653]

9 **Baczynski C**, Sharma V. Pharmacotherapy for trichotillomania in adults. *Expert Opin Pharmacother* 2020; **21**: 1455-1466 [PMID: 32633577 DOI: 10.1080/14656566.2020.1761324]

10 **Johnson J**, El-Alfy AT. Review of available studies of the neurobiology and pharmacotherapeutic management of trichotillomania. *J Adv Res* 2016; **7**: 169-184 [PMID: 26966559 DOI: 10.1016/j.jare.2015.05.001]

11 **Richmond LM**. Trichotillomania Etiology Differs Among Patients, Calls for Range of Treatments. *Psychiatr News* 2024; **59**: 8 [DOI: 10.1176/appi.pn.2024.08.8.30]

12 **Farhat LC**, Olfson E, Nasir M, Levine JLS, Li F, Miguel EC, Bloch MH. Pharmacological and behavioral treatment for trichotillomania: An updated systematic review with meta-analysis. *Depress Anxiety* 2020; **37**: 715-727 [PMID: 32390221 DOI: 10.1002/da.23028]

13 **Jafferany M**, Mkhoyan R, Stamu-O'Brien C, Carniciu S. Nonpharmacological treatment approach in trichotillomania (hair-pulling disorder). *Dermatol Ther* 2020; **33**: e13622 [PMID: 32430952 DOI: 10.1111/dth.13622]

14 **Sani G**, Gualtieri I, Paolini M, Bonanni L, Spinazzola E, Maggiora M, Pinzone V, Brugnoli R, Angeletti G, Girardi P, Rapinesi C, Kotzalidis GD. Drug Treatment of Trichotillomania (Hair-Pulling Disorder), Excoriation (Skin-picking) Disorder, and Nail-biting (Onychophagia). *Curr Neuropharmacol* 2019; **17**: 775-786 [PMID: 30892151 DOI: 10.2174/1570159X17666190320164223]

15 **Hoffman J**, Williams T, Rothbart R, Ipser JC, Fineberg N, Chamberlain SR, Stein DJ. Pharmacotherapy for trichotillomania. *Cochrane Database Syst Rev* 2021; **9**: CD007662 [PMID: 34582562 DOI: 10.1002/14651858.CD007662.pub3]

16 **Alizadehgoradel J**, Pouresmali A, Taherifard M. Safety and Efficacy of an Intensified and Repeated Transcranial Direct Current Stimulation Targeting Supplementary Motor Area and Dorsolateral Prefrontal Cortex in Trichotillomania (Hair Pulling Disorder): A Case Report. *Clin Psychopharmacol Neurosci* 2024; **22**: 188-193 [PMID: 38247425 DOI: 10.9758/cpn.23.1082]

17 **Aydın EP**, Kenar JG, Tutan A, Akil Özer Ö, Oğuz Karamustafalıoğlu K. Repetitive Transcranial Magnetic Stimulation for Treatment of Trichotillomania: Case Series. *Clin Psychopharmacol Neurosci* 2020; **18**: 631-635 [PMID: 33124597 DOI: 10.9758/cpn.2020.18.4.631]

18 **Chaudhary P**, Kar SK. Accelerated Continuous Theta Burst Stimulation in the Treatment of Trichotillomania: A Comprehensive Case Study From Acute Intervention to Maintenance Phase. *J ECT* 2024; **40**: e35-e36 [PMID: 38522080 DOI: 10.1097/YCT.0000000000001010]

19 **Di Ponzio M**, Makris N, Tenerini C, Grassi E, Ragone S, Pallanti S. rTMS investigation of resistant Obsessive-Compulsive Related Disorders: Efficacy of targeting the reward system. *Front Psychiatry* 2022; **13**: 1035469 [PMID: 36819945 DOI: 10.3389/fpsyt.2022.1035469]

20 **Fontenelle LF**, Dos Santos-Ribeiro S, Kalaf J, Yücel M. Electroconvulsive therapy for trichotillomania in a bipolar patient. *Bull Menninger Clin* 2019; **83**: 97-104 [PMID: 30888852 DOI: 10.1521/bumc.2019.83.1.97]

21 **Kar SK**, Dixit S, Agarwal V, Tripathi A. Successful treatment of trichotillomania with repetitive transcranial magnetic stimulation: A report of two cases with review of literature. *Asian J Psychiatr* 2020; **49**: 101987 [PMID: 32135483 DOI: 10.1016/j.ajp.2020.101987]

22 **Chervyakov AV**, Chernyavsky AY, Sinitsyn DO, Piradov MA. Possible Mechanisms Underlying the Therapeutic Effects of Transcranial Magnetic Stimulation. *Front Hum Neurosci* 2015; **9**: 303 [PMID: 26136672 DOI: 10.3389/fnhum.2015.00303]

23 **Kar SK**. Predictors of Response to Repetitive Transcranial Magnetic Stimulation in Depression: A Review of Recent Updates. *Clin Psychopharmacol Neurosci* 2019; **17**: 25-33 [PMID: 30690937 DOI: 10.9758/cpn.2019.17.1.25]

24 **Peng Z**, Zhou C, Xue S, Bai J, Yu S, Li X, Wang H, Tan Q. Mechanism of Repetitive Transcranial Magnetic Stimulation for Depression. *Shanghai Arch Psychiatry* 2018; **30**: 84-92 [PMID: 29736128 DOI: 10.11919/j.issn.1002-0829.217047]

25 **Siebner HR**, Funke K, Aberra AS, Antal A, Bestmann S, Chen R, Classen J, Davare M, Di Lazzaro V, Fox PT, Hallett M, Karabanov AN, Kesselheim J, Beck MM, Koch G, Liebetanz D, Meunier S, Miniussi C, Paulus W, Peterchev AV, Popa T, Ridding MC, Thielscher A, Ziemann U, Rothwell JC, Ugawa Y. Transcranial magnetic stimulation of the brain: What is stimulated? - A consensus and critical position paper. *Clin Neurophysiol* 2022; **140**: 59-97 [PMID: 35738037 DOI: 10.1016/j.clinph.2022.04.022]

26 **Munn Z**, Barker TH, Moola S, Tufanaru C, Stern C, McArthur A, Stephenson M, Aromataris E. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. *JBI Evid Synth* 2020; **18**: 2127-2133 [PMID: 33038125 DOI: 10.11124/JBISRIR-D-19-00099]

27 **Price RB**, Gillan CM, Hanlon C, Ferrarelli F, Kim T, Karim HT, Renard M, Kaskie R, Degutis M, Wears A, Vienneau EP, Peterchev AV, Brown V, Siegle GJ, Wallace ML, Ahmari SE. Effect of Experimental Manipulation of the Orbitofrontal Cortex on Short-Term Markers of Compulsive Behavior: A Theta Burst Stimulation Study. *Am J Psychiatry* 2021; **178**: 459-468 [PMID: 33726523 DOI: 10.1176/appi.ajp.2020.20060821]

28 **George PP**, DeCastro Molina JA, Heng BH. The methodological quality of systematic reviews comparing intravitreal bevacizumab and alternates for neovascular age related macular degeneration: A systematic review of reviews. *Indian J Ophthalmol* 2014; **62**: 761-767 [PMID: 25116765 DOI: 10.4103/0301-4738.138615]

29 **Lefaucheur JP**, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, Cotelli M, De Ridder D, Ferrucci R, Langguth B, Marangolo P, Mylius V, Nitsche MA, Padberg F, Palm U, Poulet E, Priori A, Rossi S, Schecklmann M, Vanneste S, Ziemann U, Garcia-Larrea L, Paulus W. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol* 2017; **128**: 56-92 [PMID: 27866120 DOI: 10.1016/j.clinph.2016.10.087]

30 **Lefaucheur JP**, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, Filipović SR, Grefkes C, Hasan A, Hummel FC, Jääskeläinen

SK, Langguth B, Leocani L, Londero A, Nardone R, Nguyen JP, Nyffeler T, Oliveira-Maia AJ, Oliviero A, Padberg F, Palm U, Paulus W, Poulet E, Quartarone A, Rachid F, Rektorová I, Rossi S, Sahlsten H, Schecklmann M, Szekely D, Ziemann U. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clin Neurophysiol* 2020; **131**: 474-528 [PMID: 31901449 DOI: 10.1016/j.clinph.2019.11.002]

31 **Chamberlain SR**, Fineberg NA, Blackwell AD, Clark L, Robbins TW, Sahakian BJ. A neuropsychological comparison of obsessive-compulsive disorder and trichotillomania. *Neuropsychologia* 2007; **45**: 654-662 [PMID: 17005210 DOI: 10.1016/j.neuropsychologia.2006.07.016]

32 **Shephard E**, Batistuzzo MC, Hoexter MQ, Stern ER, Zuccolo PF, Ogawa CY, Silva RM, Brunoni AR, Costa DL, Doretto V, Saraiva L, Cappi C, Shavitt RG, Simpson HB, van den Heuvel OA, Miguel EC. Neurocircuit models of obsessive-compulsive disorder: limitations and future directions for research. *Braz J Psychiatry* 2022; **44**: 187-200 [PMID: 35617698 DOI: 10.1590/1516-4446-2020-1709]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2025 March 18; 13(1): 100176

DOI: 10.13105/wjma.v13.i1.100176

ISSN 2308-3840 (online)

SYSTEMATIC REVIEWS

Systematic review comparing the efficacy and safety of covered and uncovered self-expanding metal stents in benign airway stenosis

Luke Han, Ern Wei Peck, Elizabeth Teo, Kay Choong See

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade C

Scientific Significance: Grade B

P-Reviewer: Fahim FK

Received: August 9, 2024

Revised: January 11, 2025

Accepted: January 21, 2025

Published online: March 18, 2025

Processing time: 217 Days and 2 Hours

Luke Han, Ern Wei Peck, Elizabeth Teo, Yong Loo Li School of Medicine, National University of Singapore, Singapore 117597, Singapore

Kay Choong See, Division of Respiratory and Critical Care Medicine, Department of Medicine, National University Hospital, Singapore 119228, Singapore

Corresponding author: Kay Choong See, Associate Professor, Division of Respiratory and Critical Care Medicine, Department of Medicine, National University Hospital, Level 10, NUHS Tower Block, 1E Kent Ridge Road, Singapore 119228, Singapore.
kaychoongsee@nus.edu.sg

Abstract

BACKGROUND

Current United States Food and Drug Administration (FDA) guidelines established since 2005 recommend the usage of silicone stents over metal stents due to the risk of complications associated with the older generation of uncovered stents. Yet, with the advancement of technology, novel innovations of self-expanding metal stents (SEMS) have revolutionized the treatment of benign airway stenosis (BAS), where the insertion of SEMS is known to be easier than silicone stents.

AIM

To compare the efficacy and safety of covered SEMS against uncovered SEMS, and thereafter propose more direct trials comparing covered SEMS against silicone stents for consideration of revision of current FDA guidelines.

METHODS

A comprehensive literature review of MEDLINE and EMBASE was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Of 3002 articles, 64 publications met the eligibility criteria with a total of 900 patients (468 covered SEMS, 432 uncovered SEMS). The collected data were analyzed using Statistical Package for the Social Sciences version 11.5.

RESULTS

Covered SEMS showed a higher success rate of insertion (98.6% *vs* 88.2%) and lower complication rates of infection (1.3% *vs* 13.2%), restenosis (1.5% *vs* 10.6%), stent fracture (2.6% *vs* 7.4%), bleeding (0% *vs* 5.8%), and pneumothorax (0% *vs* 2.8%) compared to uncovered SEMS. However, covered SEMS compared to uncovered SEMS showed higher complication rates of stent migration (12.4% *vs* 6.9%) and granulation tissue formation (26.5% *vs* 20.1%).

CONCLUSION
Our study suggests that covered SEMS are an effective, safe, and viable option in the treatment of BAS. Thus, further consideration regarding the utilization of covered SEMS over other forms of stent types is appropriate.

Key Words: Benign; Airway; Stenosis; Stent; Outcomes

Core Tip: Covered self-expanding metal stents (SEMS) are viable alternatives to uncovered SEMS and silicone stents, with higher stenting success rates and less complication risks. This is a systematic review evaluating the safety and efficacy of SEMS in benign airway stenosis treatment. Our results challenge the existing guidelines that favor silicone stents and point to contemporary covered SEMS as a viable alternative in view of its increased insertion success and lower complication rates, compared to uncovered SEMS.

Citation: Han L, Peck EW, Teo E, See KC. Systematic review comparing the efficacy and safety of covered and uncovered self-expanding metal stents in benign airway stenosis. *World J Meta-Anal* 2025; 13(1): 100176
URL: https://www.wjgnet.com/2308-3840/full/v13/i1/100176.htm
DOI: https://dx.doi.org/10.13105/wjma.v13.i1.100176

INTRODUCTION

Benign airway stenosis (BAS) causes significant morbidity and mortality. Patients with tracheal stenosis present clinically with dyspnea, stridor, or wheezing with symptoms persisting for several years[1]. Causes of BAS can be broadly divided into mechanical causes and inflammatory diseases. A large proportion of mechanical causes include those of iatrogenic etiology such as post-tracheostomy tracheal stenosis and post-intubation tracheal stenosis. Other mechanical causes involve extramural compression due to trauma, aneurysm, and goiter. Inflammatory causes include tuberculosis of the lung, tracheobronchomalacia, granulomatosis with polyangiitis, sarcoidosis, amyloidosis, and relapsing polychondritis [2].

Airway stenting of benign tracheal stenosis is an effective approach that has been employed widely in clinical practice [3]. Silicone stents have been available since the mid-1980s and have traditionally been the mainstay treatment for BAS. In the 1980s, modified vascular metal stents (Gianturco) were used in airways, however this was eventually disfavored due to the unacceptable complication rates with over 30% of cases experiencing migration and/or rupture of the metallic mesh[4]. Subsequently in the 1990s, the introduction of self-expanding metal stents (SEMS) proved better clinical effectiveness and lower complication rates[5]. SEMS can be broadly categorized into two groups of covered and uncovered.

Among respiratory interventionists, there has been controversy regarding the advantages of SEMS *vs* silicone stents. Proponents of SEMS cite several advantages they have over silicon stents: (1) Their deployment *via* flexible bronchoscopy, which requires only topical airway anesthesia and moderate sedation compared to the use of rigid bronchoscopy needed in silicone stents[6-8]; (2) How SEMS have excellent adherence properties to the airway wall therefore decreasing risk of migration; and (3) The radio-opaque properties of SEMS, thereby being easily appreciated on radiography scans. However, others cite protocols and guidelines like the 2005 United States Food and Drug Administration (FDA) public health notification which favor the use of silicone stents over uncovered SEMS, due to the adverse complications faced during the insertion and removal of uncovered metal stents[9].

With the accumulation of almost two decades of evidence on newer covered SEMS since the conception of the FDA notification, this guideline requires reviewing as evident by the multiple advantages SEMS offer compared to silicone stents. There remains currently no literature on the comparison of SEMS and silicone stenting in the context of BAS.

Therefore, this paper provides a systematic review comparing the efficacy and safety of covered SEMS against uncovered SEMS, and thereafter proposes more direct trials comparing covered SEMS against silicone stents for consideration of revision of current FDA guidelines should there be resounding evidence for the use of covered SEMS in BAS.

MATERIALS AND METHODS

Study identification

The literature search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The search terms of "Metal", "Stent", "Benign airway obstruction", "Stenosis", "Airway", "Trachea", "Tracheol", "Bronchus", "Bronchial", "Self-expanding metal stents", "Self Expandable Metallic Stents", "Montgomery T tube", "Dumon stent", "Polyflex stent", "SEMS" were searched on Medline and EMBASE. Additionally, bibliographies of included citations were hand searched. The protocol for this study was registered in PROSPERO (No. CRD42022333088).

Study eligibility

The search was conducted on publications from database inception until December 31, 2021. A systematic review of literature was conducted for all existing cohort studies, case series, and case reports containing data on efficacy and safety of metal stent usage. Studies involving malignant airway diseases, non-pulmonary stenting, bronchoscopy procedures without the use of stents and pediatric patients (less than 16 years of age) were excluded. The search was limited to English and human studies. Systematic reviews, review articles, editorials, letters, and studies with no results were also excluded.

Outcomes of interest

The primary outcome of this study was to evaluate the efficacy and safety of SEMS in the treatment of BAS. The assessment of efficacy was based on the success of the procedure defined by declared correct placement of stents at the desired location to relieve airway stenosis with subsequent clinical, radiological, or functional improvement. A procedure was deemed effective if it reported success or postoperative improvements in any of these three domains.

Separately, the assessment of safety was evaluated throughout the course of treatment–stent insertion, stent-induced complications, stent removal, and stent-related death. The definitions of key terms summarizing the primary outcomes of efficacy and safety are shown in Table 1.

Data extraction and synthesis

Relevant studies were identified by two independent authors through title and abstract screening. Further selection for inclusion was based on the full text according to PRISMA guidelines, summarized in Figure 1. Then data were extracted independently by the authors. Data from individual articles included study design, types of stents (covered and uncovered), stent brand, demographic presentation of patients, stent insertion indication, number of successful stent insertions, stent induced complications, stent removal indication, number of successful stent removals, and number of deaths caused by stent intervention. A summary of stent indications and complications can be found in Supplementary Table 1[6,10-73]. Any discrepancies related to data extraction and synthesis were resolved by the senior author after further discussion.

Study quality

The Joanna Briggs Institute (JBI) Critical Appraisal tool is a validated tool used to assess the methodological quality of studies and to determine the extent of possible bias in terms of its design, conduct and analysis. For this study, the appraisal tools for cohort studies, case reports, and case series were utilized. The JBI critical appraisal tables can be found in Supplementary Table 2[10,28], Supplementary Table 3[6,11,13-16,18-23,25,26,29,31-34,36,37,39-41,43-45,47,49-52,54-58,60,62,63,65-69,71,73-79] and Supplementary Table 4[12,17,24,27,30,35,38,42,46,48,53,58,59,61,64,70,80-82].

Statistical analyses

The collected data were analyzed using Statistical Package for the Social Sciences version 11.5 (SPSS Inc., Chicago, IL, United States). Patient characteristics were described using proportions, means, and standard deviations. Comparison of proportions was done using Fisher's Exact Test.

RESULTS

From a pool of 3002 studies, 64 publications describing 900 patients cases met the inclusion criteria for final analysis in this systematic review. Of the 900 cases, 468 involved the utilization of covered SEMS, while the other 432 cases were on uncovered SEMS.

Of the 1082 stents inserted in 900 patients, we saw a promising rate of 93.6% (1013/1082) of metal stents successfully inserted. The 98.6% (511/518) of covered SEMS were successfully inserted, which was significantly better compared to the 88.2% (462/524) of uncovered SEMS ($P < 0.001$).

Overall, 95.2% (435/457) of metal stents were successfully removed. The 95.0% (305/321) of covered SEMS and 93.8% (90/96) of uncovered SEMS were successfully removed. This difference however was not statistically significant ($P = 0.607$).

A range of complications in SEMS were observed, most common being infection, restenosis, stent fracture, bleeding, pneumothorax, stent migration, and granulation tissue formation. For infection, restenosis, stent fracture, bleeding, and pneumothorax, patients with covered SEMS showed statistically significantly lower complication rates. The 1.3% (6/468) of patients with covered SEMS developed infection compared to 13.2% (57/432) of patients with uncovered SEMS ($P < 0.001$). The 1.5% (7/468) of patients with covered SEMS developed restenosis compared to 10.6% (46/432) of patients with uncovered SEMS ($P < 0.001$). The 2.6% (12/468) of patients with covered SEMS developed stent fracture compared to 7.4% (32/432) of patients with uncovered SEMS ($P = 0.001$). No (0/468) patient with covered SEMS developed bleeding or pneumothorax, compared to 5.8% (25/432) ($P < 0.001$) and 2.8% (12/432) ($P < 0.001$) respectively of patients with uncovered SEMS.

By contrast, for stent migration and granulation tissue formation, the results reflected a significantly higher complication rate in patients with covered SEMS compared to uncovered SEMS (12.4%, 58/468 to 6.9%, 30/432; and 26.5%, 124/468 to 20.1%, 87/432 respectively). Other complications such as halitosis, laryngeal oedema, tracheobronchial obstruction, bronchomalacia, dyspnea, and a change in stent configuration were more likely in patients with covered

Table 1 Definition of key terms

TS	TS was defined as the number of successful insertion procedures of a balloon catheter through a stenosis followed by appropriate positioning of the stent across the diseased segment and increase in tracheal diameter of the stenotic segment
CS	CS was defined as the number of patients with improved clinical symptoms pertaining to the tracheal pathology post-stent insertion
RS	RS was defined as the number of patients with a lack of abnormal pathological findings on chest X-ray investigation post-stent insertion
FS	FS was defined as the number of patients with an improved FEV1/forced vital capacity ratio or FEV1 post-stent insertion as compared to pre-stent insertion
Successful insertions[1]	Successful insertion of airway stent was defined as the number of insertion procedures where the stent was placed at the desired location to relieve airway stenosis
Unsuccessful insertions	Unsuccessful insertion of airway stent was defined as the number of insertion procedures where the stent could not be placed at the desired location to relieve airway stenosis
Removal success	Successful removal was defined as the number of removal procedures where airway stents were removed from tracheal lumen without immediate deterioration of patient's clinical symptoms or restenosis of airway
Unsuccessful removal	Unsuccessful removal of airway stent was defined as the number of removal procedures where the stent could not be removed and remained lodged in the patient's airway
Complications	Complications were defined as the number of a particular adverse stent-related clinical event occurring after insertion
Uncovered SEMS	Uncovered SEMS were defined as SEMS without any polymer coverage over the body of the stent
Covered SEMS	Covered SEMS were defined as SEMS covered with a complete polymer coverage across the entire body of the stent
Metal stent death	Metal stent death was defined as the number of patients whose death was directly caused by the insertion or removal of a SEMS

[1]Successful insertions defined as achieving either technical (technical success), clinical (clinical success), radiological (radiological success), or functional (functional success) success.

CS: Clinical success; FEV1: Forced expiratory volume in one second; FS: Functional success; RS: Radiological success; SEMS: Self-expanding metal stents; TS: Technical success.

SEMS (10.3%, 48/468) compared to patients with uncovered SEMS (3.5%, 15/432).

Stent-related death was rarely reported: 0% for covered SEMS *vs* 0.2% (1/432) for uncovered SEMS, the difference being found to be not statistically significant ($P = 0.480$). A summary of the results can be found in Table 2.

DISCUSSION

Determining the type of airway stents to employ in the treatment of BAS is a crucial decision with consideration of both patient and disease factors. Understanding the efficacy and safety of each airway stent is of paramount importance. An ideal stent should be easy to insert and remove, effective in relieving airway stenosis, and have minimal complications–it should not fracture, migrate nor pose any life-threatening risks to a patient[83]. The results of this systematic review argue for the use of covered SEMS over uncovered SEMS due to its higher rate of success in both stent insertions, and the lower prevalence of complications such as infection, restenosis, stent fracture, bleeding, and pneumothorax. Additionally, stent-related death was not reported for covered SEMS.

Comparison between SEMS and silicone stents

Despite SEMS being traditionally regarded as inferior to silicone stenting in BAS, an argument on the contrary can be made. SEMS have a thinner wall thickness compared to silicone stents and their ability to wrap the inner surface of the airway lumen provides an added benefit and advantage in the effective relief of airway stenosis. It is noteworthy that SEMS also overcome several intrinsic limitations of silicone stents such as customization for wider lumen sizes which is otherwise not possible in a fixed silicone stent[84]. Another practical advantage of SEMS is its ease of insertion *via* flexible bronchoscopy under topical anesthesia[85]. This bypasses the need for general anesthesia used in the insertion of silicone stents *via* rigid bronchoscopy which poses significant risks of cardiovascular and respiratory complications especially in patients with multiple comorbid medical conditions[86].

This paper acknowledges prior literature as reviewed by Rodriguez *et al*[87] in 2000 which highlights the difficulty of removal and high incidence of complications such as stent fracture associated with the use of uncovered SEMS in BAS, which amongst many, have supported the 2005 FDA discommendation of the use of uncovered SEMS in BAS.

However, it is important to acknowledge and recognize technological advancement and improvement of covered SEMS since the 2005 FDA advisory. Notably, this has led to a reduction in the stent fracture rate amongst covered SEMS to a level comparable to that of silicone stents[9]. An example of a recent study on such covered SEMS is one published by Salguero *et al*[88] on the safety of covered metal stents in airway diseases. Although it covers both malignant and benign

Table 2 Comparison between covered-self-expanding metal stents and uncovered- self-expanding metal stents, *n* (%)

	All patients with SEMS (*n* = 900)	Patients with covered SEMS (*n* = 468)	Patients with uncovered SEMS (*n* = 432)	*P* value (fisher's exact test)[7]
Successful insertions	1013 (93.6)[1]	511 (98.6)[2]	462 (88.2)[3]	< 0.001
Successful removals	435 (95.2)[4]	305 (95.0)[5]	90 (93.8)[6]	0.607
Stent-related deaths	1 (0.1)	0 (0.0)	1 (0.2)	0.480
Complication rate				
Stent migration	88 (9.8)	58 (12.4)	30 (6.9)	0.007
Granulation tissue formation	211 (23.0)	124 (26.5)	87 (20.1)	0.027
Infection	63 (7.0)	6 (1.3)	57 (13.2)	< 0.001
Restenosis	53 (5.9)	7 (1.5)	46 (10.6)	< 0.001
Stent fracture	44 (4.9)	12 (2.6)	32 (7.4)	0.001
Bleeding	25 (2.8)	0 (0.0)	25 (5.8)	< 0.001
Pneumothorax	12 (1.3)	0 (0.0)	12 (2.8)	< 0.001
Mucus plugging	11 (1.2)	7 (1.5)	4 (0.9)	0.550
Others[8]	63 (7.0)	48 (10.3)	15 (3.5)	< 0.001

[1]Total of 1082 metal stent insertions among patients (*n* = 900) with either covered or uncovered self-expanding metal stents (SEMS).
[2]Total of 518 insertions among patients (*n* = 468) with covered stents.
[3]Total of 524 insertions among patients (*n* = 432) with uncovered stents.
[4]Total of 457 metal stent removals among patients (*n* = 900) with either covered or uncovered SEMS.
[5]Total of 321 removals among patients (*n* = 468) with covered stents.
[6]Total of 96 removals among patients (*n* = 432) with uncovered stents.
[7]*P*-value showing Fisher's exact test comparison between covered and uncovered stent insertions.
[8]Other complications include-halitosis, laryngeal oedema, bronchial obstruction, bronchomalacia, dyspnoea and a change in stent configuration.
SEMS: Self-expanding metal stents.

airway pathologies, the paper concluded that in an era of contemporary stents and surveillance bronchoscopies, covered metal stents is a safe and applicable option, with multiple pragmatic advantages. Hence, it is evident that the practice of metal stenting is widely adopted internationally, and this study challenges the traditional and obsolete association of metal stents with high complication rates in airway diseases.

Complication rate of granulation tissue formation

The results of this paper show significantly lower complications rates of covered SEMS compared to uncovered SEMS in the domains of infection, restenosis, stent fracture, bleeding, pneumothorax, and other miscellaneous complications. However, we acknowledge the increased risks of granulation tissue formation and stent migration.

A study conducted by Xiong *et al*[72] in 2019 supports the findings of our study where there was a statistically significant increased complication rate of minor granulation of covered SEMS (22/59, 37.29%) compared to uncovered SEMS (8/72, 11.11%) in BAS, while major granulation (requiring stent replacement) complication rate was likewise higher although not statistically significant.

By contrast, a study by Li *et al*[89] in 2021 comparing covered SEMS with uncovered SEMS among 45 patients (36 covered SEMS, 9 uncovered SEMS), showed a significantly lower complication rate of granulation tissue formation in covered SEMS (15/36, 41%) compared to uncovered SEMS (9/9, 100%). This finding aligns with conventional pathophysiological understanding that granulation tissue regrowth is lower in covered SEMS compared to uncovered counterparts because they prevent the proliferation of tissue through stent interstices[90].

Evidently, there are differing data and reviews regarding complication rates of granulation tissue formation between covered and uncovered SEMS. There are two plausible explanations for this discrepancy. First, the degree of granulation tissue formation is not always quantified or defined as seen in Xiong *et al*'s review, and the extent of granulation tissue defined and assessed between studies could be inconsistent[72]. Second, the exact pathogenesis of granulation is multifactorial and still unclear. Multiple studies have surmised that the degree of granulation tissue hyperplasia is most likely due to an array of factors such as friction of the airway wall, pressure of stent on wall, site of stent implantation and the presence of ongoing airway infection, which confounds the evaluation of granulation tissue formation being definitively attributed to the type of SEMS[72,91]. Ultimately, this complication can be successfully managed and resolved using argon plasma coagulation[92], which can be performed without the use of a laser, reducing the chance of airway fire[93].

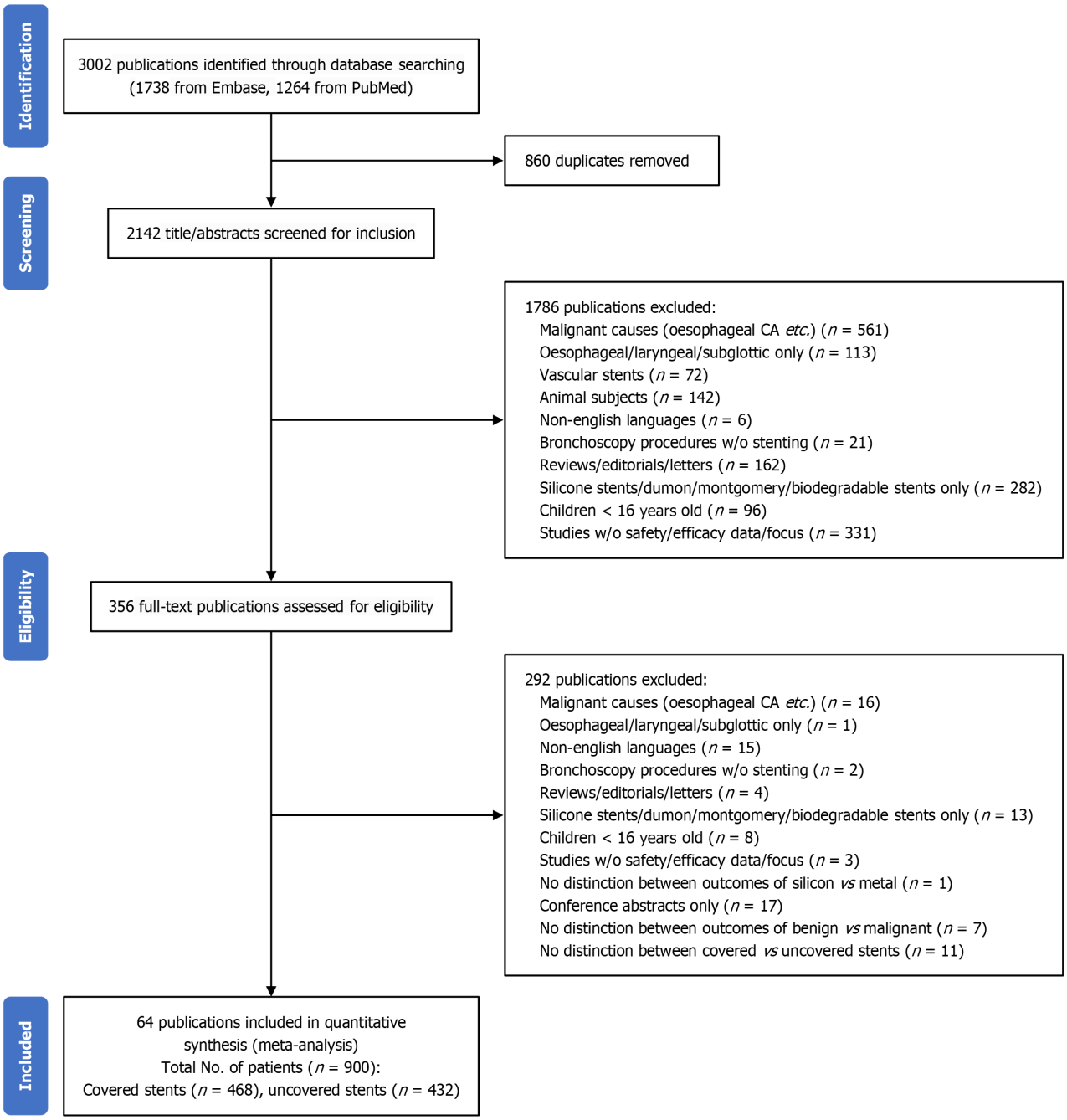


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart of study selection process for systematic review.

Complication rate of stent migration

As aforementioned, the complication rate of stent migration was significantly higher in covered SEMS compared to uncovered SEMS. This could be attributed to the allowance of stent ingrowth and epithelialization in uncovered SEMS which provides a lower risk of stent migration compared to covered SEMS.

Although there is a paucity of head-to-head comparative studies between covered SEMS and silicone stents in the existing literature, when comparison is made between covered SEMS and silicone stents, it is interesting to note that covered SEMS still provide a lower risk of stent migration compared to silicone stents (Table 3)[94-97]. According to a study published by Chen *et al*[94], based on a 7-year experience with silicone Dumon stents, covered SEMS appear to have a relatively low stent migration rate of 12.4% compared to silicone stents with stent migration rates ranging from 17.2% to 51.0%. A possible explanation for less frequent stent migration in metallic stents is the self-expanding nature of metal stents that promotes better wall adherence[68,80,98]. Additionally, it is noteworthy that only 69.0% of silicone stents were successfully inserted while 54.7% of them were successfully removed[99] which pales in comparison with the high success rate of insertion of covered SEMS as seen from this study, where covered SEMS had a relatively high success of stent insertion of 98.6%, and of stent removal of 95.0%.

Table 3 Comparison between covered self-expanding metal stents, uncovered self-expanding metal stents and silicone stents, *n* (%)

	Patients with covered SEMS (*n* = 468)	Patients with uncovered SEMS (*n* = 432)	Silicone stent study (No. 1) (*n* = 263)	Silicone stent study (No. 2) (*n* = 63)	Silicone stent study (No. 3) (*n* = 58)	Silicone stent study (No. 4) (*n* = 75)
Successful insertions	511 (98.6)[1]	462 (88.2)[2]	181 (69.0)	-	-	70 (93.3)
Successful removals	305 (95.0)[3]	90 (93.8)[4]	117 (54.7)	-	-	49 (65.0)
Stent-related deaths	0 (0.0)	1 (0.2)	2 (0.8)	-	-	-
Stent complication rate						
Stent migration	58 (12.4)	30 (6.9)	78 (18.6)[5]	62 (28.0)[5]	10 (17.2)	38 (51.0)
Granulation tissue formation	124 (26.5)	87 (20.1)	72 (17.2)[5]	-	-	-
Infection	6 (1.3)	57 (13.2)	-	-	14 (24.1)	-
Restenosis	7 (1.5)	46 (10.6)	24 (5.7)[5]	-	-	30 (40.0)
Stent fracture	12 (2.6)	32 (7.4)	-	-	1 (1.7)	-
Bleeding	0 (0.0)	25 (5.8)	-	-	-	1 (1.3)
Pneumothorax	0 (0.0)	12 (2.8)	-	-	-	5 (6.67)
Mucus plugging	7 (1.5)	4 (0.9)	-	131 (60.0)[5]	21 (36.2)	14 (19.0)
Others[6]	48 (10.3)	15 (3.5)	-	18 (8.0)[5]	6 (10.3)	-

[1]Total of 518 insertions among patients (*n* = 468) with covered stents.
[2]Total of 524 insertions among patients (*n* = 432) with uncovered stents.
[3]Total of 321 removals among patients (*n* = 468) with covered stents.
[4]Total of 96 removals among patients (*n* = 432) with uncovered stents.
[5]Total of number of stents involved (instead of number of patients) were used to calculate complication rates. The 419 stents were inserted in patients in the silicone stent study (No. 1), 220 stents were inserted in patients in the silicone stent study (No. 2).
[6]Other complications include-halitosis, laryngeal oedema, bronchial obstruction, bronchomalacia, dyspnea, and a change in stent configuration.

Limitations

Limitations of our study include the following. Firstly, although the total number of patients (*n* = 900) was substantial, there were 11 papers consisting of 204 patients that were excluded as these papers did not specify if covered or uncovered SEMS were used.

Second, due to the lack of comparative studies primarily comparing covered SEMS with silicone stents, evaluation regarding silicone stents could not be conducted in this systematic review. Therefore, further comparative studies with long-term follow up would be beneficial in directly addressing the advantages and disadvantages of SEMS against silicone stents.

Third, a main finding of the paper was the rate of restenosis whereby the data reflected a significant difference between covered and uncovered SEMS hence supporting that covered SEMS are of superior efficacy. It is noteworthy to consider factors which could confound this result such as experience and competence of the physician conducting the stent insertion, which are impossible to ascertain from the reports.

Lastly, given that the pooled data are from case reports, series and cohort studies with a diversity of patient population, in terms of ethnicity, age, and comorbidities, there is increased likelihood of heterogeneity within this study. Furthermore, we acknowledge that different airway pathologies are classically managed differently. For example, post-transplant stenosis/dehiscence are typically managed internationally with uncovered SEMS while benign tracheoesophageal fistulas are managed with fully covered SEMS due to the different and unique set of challenges each complex pathology poses. Given the aforementioned heterogeneity of the population of this study, this highlights the necessity for further subgroup analyses on this topic.

With these considerations, firm recommendations against FDA's advisory cannot be made solely based on the results of this study. However, it is evident that covered SEMS are likely superior to uncovered SEMS in view of significantly reduced complications and increased insertion and removal rates. Therefore, we propose and recommend for further direct trials and head-to-head comparative studies between covered SEMS and silicone stents. This would allow further subgroup analyses (*i.e.* post-transplant stenosis/dehiscence patients, benign tracheoesophageal fistula, tracheal/bronchial/Lobar stenosis, *etc.*) to be conducted and provide an avenue for more accurate representative data and definitive conclusion on the efficacy and safety of covered SEMS in BAS. We feel that these are necessary and urgently required to ascertain the relevance of the FDA guideline in the context of advanced medical technology, with improved

covered SEMS treatment in BAS.

CONCLUSION

To conclude, in our review of the efficacy and safety of SEMS, contemporary covered SEMS show higher success rates of stent insertion compared to uncovered SEMS making them a viable option for the treatment of BAS. Coupled with lower complication risks of infection, restenosis, stent fracture, bleeding, and pneumothorax the benefits of covered SEMS over uncovered SEMS warrant a re-evaluation of the 2005 FDA advisory against SEMS use in BAS[9].

FOOTNOTES

Author contributions: Han L and Peck EW contributed to the data collection; Teo E performed the data analysis; Han L, Peck EW, Teo E, and See KC contributed to the writing of this manuscript; All co-authors read and approved the manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: Singapore

ORCID number: Luke Han 0000-0001-5558-9498; Elizabeth Teo 0009-0006-4587-4483; Kay Choong See 0000-0003-2528-7282.

S-Editor: Luo ML
L-Editor: Filipodia
P-Editor: Zhang L

REFERENCES

1 **Mark EJ**, Meng F, Kradin RL, Mathisen DJ, Matsubara O. Idiopathic tracheal stenosis: a clinicopathologic study of 63 cases and comparison of the pathology with chondromalacia. *Am J Surg Pathol* 2008; **32**: 1138-1143 [PMID: 18545144 DOI: 10.1097/PAS.0b013e3181648d4a]
2 **Oberg CL**, Holden VK, Channick CL. Benign Central Airway Obstruction. *Semin Respir Crit Care Med* 2018; **39**: 731-746 [PMID: 30641591 DOI: 10.1055/s-0038-1676574]
3 **Guibert N**, Saka H, Dutau H. Airway stenting: Technological advancements and its role in interventional pulmonology. *Respirology* 2020; **25**: 953-962 [PMID: 32162394 DOI: 10.1111/resp.13801]
4 **Rousseau H**, Dahan M, Lauque D, Carré P, Didier A, Bilbao I, Herrero J, Blancjouvant F, Joffre F. Self-expandable prostheses in the tracheobronchial tree. *Radiology* 1993; **188**: 199-203 [PMID: 8511297 DOI: 10.1148/radiology.188.1.8511297]
5 **Dasgupta A**, Dolmatch BL, Abi-Saleh WJ, Mathur PN, Mehta AC. Self-expandable metallic airway stent insertion employing flexible bronchoscopy: preliminary results. *Chest* 1998; **114**: 106-109 [PMID: 9674455 DOI: 10.1378/chest.114.1.106]
6 **Fortin M**, Lacasse Y, Elharrar X, Tazi-Mezalek R, Laroumagne S, Guinde J, Astoul P, Dutau H. Safety and Efficacy of a Fully Covered Self-Expandable Metallic Stent in Benign Airway Stenosis. *Respiration* 2017; **93**: 430-435 [PMID: 28448981 DOI: 10.1159/000472155]
7 **Madden BP**, Datta S, Charokopos N. Experience with Ultraflex expandable metallic stents in the management of endobronchial pathology. *Ann Thorac Surg* 2002; **73**: 938-944 [PMID: 11899205 DOI: 10.1016/s0003-4975(01)03460-9]
8 **Saad CP**, Murthy S, Krizmanich G, Mehta AC. Self-expandable metallic airway stents and flexible bronchoscopy: long-term outcomes analysis. *Chest* 2003; **124**: 1993-1999 [PMID: 14605078 DOI: 10.1378/chest.124.5.1993]
9 **Food and Drug Administration**. FDA public health notification: complications from metallic tracheal stents in patients with benign airway disorders. 2005. Available from: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062115.htm
10 **Abdel-Rahman N**, Kramer MR, Saute M, Raviv Y, Fruchter O. Metallic stents for airway complications after lung transplantation: long-term follow-up. *Eur J Cardiothorac Surg* 2014; **45**: 854-858 [PMID: 24042147 DOI: 10.1093/ejcts/ezt458]
11 **Andreetti C**, D'Andrilli A, Ibrahim M, Ciccone AM, Maurizi G, Mattia A, Venuta F, Rendina EA. Effective treatment of post-pneumonectomy bronchopleural fistula by conical fully covered self-expandable stent. *Interact Cardiovasc Thorac Surg* 2012; **14**: 420-423 [PMID: 22268070 DOI: 10.1093/icvts/ivr077]
12 **Asopa S**, Moorjani N, Saad RA, Turner JT, Amer KM. Rare and fatal complication of Gianturco tracheobronchial stent. *Ann Thorac Surg* 2007; **84**: 1758-1760 [PMID: 17954110 DOI: 10.1016/j.athoracsur.2007.03.092]
13 **Avasarala SK**, Sethi S, Machuzak M, Almeida FA, Gildea TR. A Single-Center Case Series Describing Tracheobronchial Bonastent Implantation. *J Bronchology Interv Pulmonol* 2019; **26**: 265-272 [PMID: 30829896 DOI: 10.1097/LBR.0000000000000567]
14 **Bi Y**, Yu Z, Ren J, Han X, Wu G. Metallic stent insertion and removal for post-tracheotomy and post-intubation tracheal stenosis. *Radiol Med*

2019; **124**: 191-198 [PMID: 30357596 DOI: 10.1007/s11547-018-0953-9]
15 **Bodhey NK**, Gupta AK, Neelakandhan KS, Neema PK, Kapilamoorthy TR, Purkayastha S, Thomas B, Krishnamoorthy T, Kesavadas C. Fluoroscopic-guided balloon dilatation and stenting in tracheal stenosis with metallic self-expandable stents and long-term follow-up results. *Australas Radiol* 2007; **51**: 351-357 [PMID: 17635472 DOI: 10.1111/j.1440-1673.2007.01749.x]
16 **Bolot G**, Poupart M, Pignat JC, Bertocchi M, Wiesendanger T, Thevenet F, Gamondes JP, Mornex JF. Self-expanding metal stents for the management of bronchial stenosis and bronchomalacia after lung transplantation. *Laryngoscope* 1998; **108**: 1230-1233 [PMID: 9707249 DOI: 10.1097/00005537-199808000-00024]
17 **Bondue B**, Vandermoten G, Sokolow Y, Knoop C, Leduc D. Usefulness of a tailored metallic Y stent for the treatment of complex post-lung transplant bronchial stenosis. *J Heart Lung Transplant* 2015; **34**: 996-998 [PMID: 25851467 DOI: 10.1016/j.healun.2015.01.992]
18 **Burningham AR**, Wax MK, Andersen PE, Everts EC, Cohen JI. Metallic tracheal stents: complications associated with long-term use in the upper airway. *Ann Otol Rhinol Laryngol* 2002; **111**: 285-290 [PMID: 11991577 DOI: 10.1177/000348940211100401]
19 **Burns KE**, Orons PD, Dauber JH, Grgurich WF, Stitt LW, Raghu S, Iacono AT. Endobronchial metallic stent placement for airway complications after lung transplantation: longitudinal results. *Ann Thorac Surg* 2002; **74**: 1934-1941 [PMID: 12643376 DOI: 10.1016/s0003-4975(02)04033-x]
20 **Cao M**, Zhu Q, Wang W, Zhang TX, Jiang MZ, Zang Q. Clinical Application of Fully Covered Self-Expandable Metal Stents in the Treatment of Bronchial Fistula. *Thorac Cardiovasc Surg* 2016; **64**: 533-539 [PMID: 25581102 DOI: 10.1055/s-0034-1396681]
21 **Carré P**, Rousseau H, Lombart L, Didier A, Dahan M, Fournial G, Léophonte P. Balloon dilatation and self-expanding metal Wallstent insertion. For management of bronchostenosis following lung transplantation. The Toulouse Lung Transplantation Group. *Chest* 1994; **105**: 343-348 [PMID: 8306726 DOI: 10.1378/chest.105.2.343]
22 **Chan AL**, Juarez MM, Allen RP, Albertson TE. Do airway metallic stents for benign lesions confer too costly a benefit? *BMC Pulm Med* 2008; **8**: 7 [PMID: 18423035 DOI: 10.1186/1471-2466-8-7]
23 **Charokopos N**, Foroulis CN, Rouska E, Sileli MN, Papadopoulos N, Papakonstantinou C. The management of post-intubation tracheal stenoses with self-expandable stents: early and long-term results in 11 cases. *Eur J Cardiothorac Surg* 2011; **40**: 919-924 [PMID: 21316981 DOI: 10.1016/j.ejcts.2010.12.042]
24 **Chawla RK**, Madan A, Singh I, Mudoiya R, Chawla A, Gupta R, Chawla K, Chhabra R. Removal of self expandable metallic airway stent: A rare case report. *Lung India* 2013; **30**: 64-66 [PMID: 23661920 DOI: 10.4103/0970-2113.106177]
25 **Chen G**, Wang Z, Liang X, Wang Y, Wang Y, Wang Z, Xian J. Treatment of cuff-related tracheal stenosis with a fully covered retrievable expandable metallic stent. *Clin Radiol* 2013; **68**: 358-364 [PMID: 23137611 DOI: 10.1016/j.crad.2012.08.022]
26 **Cheng YJ**, Kao EL. Expandable metal stents as an alternative treatment of cuff-related tracheal stenosis in tracheostomy-dependent ventilated patients: a prospective study of nine cases and description of the complications. *Langenbecks Arch Surg* 2007; **392**: 479-483 [PMID: 17089175 DOI: 10.1007/s00423-006-0110-0]
27 **Chhajed PN**, Malouf MA, Tamm M, Hopkins PM, Plit M, Glanville AR. Resolution of native lung pneumothorax by insertion of a nitinol stent for bronchostenosis in the transplanted lung. *Respirology* 2002; **7**: 377-379 [PMID: 12421249 DOI: 10.1046/j.1440-1843.2002.00412.x]
28 **Chhajed PN**, Malouf MA, Tamm M, Glanville AR. Ultraflex stents for the management of airway complications in lung transplant recipients. *Respirology* 2003; **8**: 59-64 [PMID: 12856743 DOI: 10.1046/j.1440-1843.2003.00425.x]
29 **Choudhary C**, Bandyopadhyay D, Salman R, Gildea T, Mehta A. Broncho-vascular fistulas from self-expanding metallic stents: A retrospective case review. *Ann Thorac Med* 2013; **8**: 116-120 [PMID: 23741275 DOI: 10.4103/1817-1737.109830]
30 **Comer D**, Bedi A, Kennedy P, McManus K, McIlwaine W. Successful Endobronchial stenting for bronchial compression from a massive thoracic aortic aneurysm. *J Surg Case Rep* 2010; **2010**: 2 [PMID: 24946305 DOI: 10.1093/jscr/2010.4.2]
31 **Dahlqvist C**, Ocak S, Gourdin M, Dincq AS, Putz L, d'Odémont JP. Fully Covered Metallic Stents for the Treatment of Benign Airway Stenosis. *Can Respir J* 2016; **2016**: 8085216 [PMID: 27777507 DOI: 10.1155/2016/8085216]
32 **de Mello-Filho FV**, Antonio SM, Carrau RL. Endoscopically placed expandable metal tracheal stents for the management of complicated tracheal stenosis. *Am J Otolaryngol* 2003; **24**: 34-40 [PMID: 12579481 DOI: 10.1053/ajot.2003.6]
33 **Dooms C**, De Keukeleire T, Janssens A, Carron K. Performance of fully covered self-expanding metallic stents in benign airway strictures. *Respiration* 2009; **77**: 420-426 [PMID: 19223681 DOI: 10.1159/000203364]
34 **Ducic Y**, Khalafi RS. Use of endoscopically placed expandable nitinol tracheal stents in the treatment of tracheal stenosis. *Laryngoscope* 1999; **109**: 1130-1133 [PMID: 10401855 DOI: 10.1097/00005537-199907000-00023]
35 **Edwards RD**, Wilkinson LM, Turner MA. Benign bronchial stenosis treated with balloon bronchoplasty and metal stents. *Scott Med J* 1995; **40**: 19-20 [PMID: 7604237 DOI: 10.1177/003693309504000108]
36 **Eller RL**, Livingston WJ 3rd, Morgan CE, Peters GE, Sillers MJ, Magnuson JS, Rosenthal EL. Expandable tracheal stenting for benign disease: worth the complications? *Ann Otol Rhinol Laryngol* 2006; **115**: 247-252 [PMID: 16676820 DOI: 10.1177/000348940611500401]
37 **El Raouf BA**, Kramer MR, Fruchter O. Bronchial anthracofibrosis: treatment using airway stents. *Int J Tuberc Lung Dis* 2013; **17**: 1118-1120 [PMID: 23827039 DOI: 10.5588/ijtld.13.0116]
38 **Faul JL**, Kee ST, Rizk NW. Endobronchial stenting for severe airway obstruction in relapsing polychondritis. *Chest* 1999; **116**: 825-827 [PMID: 10492294 DOI: 10.1378/chest.116.3.825]
39 **Fernandez-Bussy S**, Akindipe O, Kulkarni V, Swafford W, Baz M, Jantz MA. Clinical experience with a new removable tracheobronchial stent in the management of airway complications after lung transplantation. *J Heart Lung Transplant* 2009; **28**: 683-688 [PMID: 19560696 DOI: 10.1016/j.healun.2009.04.014]
40 **Fruchter O**, Raviv Y, Fox BD, Kramer MR. Removal of metallic tracheobronchial stents in lung transplantation with flexible bronchoscopy. *J Cardiothorac Surg* 2010; **5**: 72 [PMID: 20831830 DOI: 10.1186/1749-8090-5-72]
41 **Fruchter O**, Abed El Raouf B, Rosengarten D, Kramer MR. Long-term Outcome of Short Metallic Stents for Lobar Airway Stenosis. *J Bronchology Interv Pulmonol* 2017; **24**: 211-215 [PMID: 28696967 DOI: 10.1097/LBR.0000000000000371]
42 **Geltner C**, Likar R, Hausegger K, Rauter M. Management of Postintubational Tracheal Injury by Endoscopic Stent Placement: Case Report and Review of the Literature. *Thorac Cardiovasc Surg Rep* 2016; **5**: 8-12 [PMID: 28018811 DOI: 10.1055/s-0035-1570376]
43 **George PJ**, Irving JD, Khaghani A, Dick R. Role of the Gianturco expandable metal stent in the management of tracheobronchial obstruction. *Cardiovasc Intervent Radiol* 1992; **15**: 375-381 [PMID: 1477862 DOI: 10.1007/BF02734121]
44 **Gottlieb J**, Fuehner T, Dierich M, Wiesner O, Simon AR, Welte T. Are metallic stents really safe? A long-term analysis in lung transplant recipients. *Eur Respir J* 2009; **34**: 1417-1422 [PMID: 19443535 DOI: 10.1183/09031936.00041909]

45 **Gotway MB**, Golden JA, LaBerge JM, Webb WR, Reddy GP, Wilson MW, Kerlan RK Jr, Gordon RL. Benign tracheobronchial stenoses: changes in short-term and long-term pulmonary function testing after expandable metallic stent placement. *J Comput Assist Tomogr* 2002; **26**: 564-572 [PMID: 12218821 DOI: 10.1097/00004728-200207000-00016]

46 **Han JK**, Im JG, Park JH, Han MC, Kim YW, Shim YS. Bronchial stenosis due to endobronchial tuberculosis: successful treatment with self-expanding metallic stent. *AJR Am J Roentgenol* 1992; **159**: 971-972 [PMID: 1414809 DOI: 10.2214/ajr.159.5.1414809]

47 **Han X**, Al-Tariq Q, Zhao Y, Li L, Cheng Z, Wang H, Liu C, Jiao D, Wu G. Customized Hinged Covered Metallic Stents for the Treatment of Benign Main Bronchial Stenosis. *Ann Thorac Surg* 2017; **104**: 420-425 [PMID: 28499653 DOI: 10.1016/j.athoracsur.2017.01.116]

48 **Harney MS**, Lacy PD, O'Neill S, Walsh M. Nitinol stent insertion for post-pneumonectomy syndrome. *J Laryngol Otol* 2001; **115**: 938-939 [PMID: 11779318 DOI: 10.1258/0022215011909431]

49 **Hautmann H**, Rieger J, Huber RM, Pfeifer KJ. Elastic deformation properties of implanted endobronchial wire stents in benign and malignant bronchial disease: A radiographic in vivo evaluation. *Cardiovasc Intervent Radiol* 1999; **22**: 103-108 [PMID: 10094988 DOI: 10.1007/s002709900343]

50 **Hramiec JE**, Haasler GB. Tracheal wire stent complications in malacia: implications of position and design. *Ann Thorac Surg* 1997; **63**: 209-12; discussion 213 [PMID: 8993267 DOI: 10.1016/s0003-4975(96)00925-3]

51 **Isa AY**, Macandie C, Irvine BW. Nitinol stents in the treatment of benign proximal tracheal stenosis or tracheomalacia. *J Laryngol Otol* 2006; **120**: 32-37 [PMID: 16359154 DOI: 10.1017/S0022215105006456]

52 **Jeong BH**, Ng J, Jeong SH, Kim H. Clinical Outcomes of Complications Following Self-Expandable Metallic Stent Insertion for Benign Tracheobronchial Stenosis. *Medicina (Kaunas)* 2020; **56**: 367 [PMID: 32708022 DOI: 10.3390/medicina56080367]

53 **Kim W**, Lee YC, Rhee YK. Obstruction after self-expanding metallic stents in tuberculous bronchial stenosis. *Korean J Intern Med* 1995; **10**: 64-67 [PMID: 7542914 DOI: 10.3904/kjim.1995.10.1.64]

54 **Kim JH**, Shin JH, Shim TS, Hong SJ, Ko GY, Lim JO, Song HY. Results of temporary placement of covered retrievable expandable nitinol stents for tuberculous bronchial strictures. *J Vasc Interv Radiol* 2004; **15**: 1003-1008 [PMID: 15361571 DOI: 10.1097/01.RVI.0000133857.09327.1A]

55 **Kim JH**, Shin JH, Song HY, Shim TS, Yoon CJ, Ko GY. Benign tracheobronchial strictures: long-term results and factors affecting airway patency after temporary stent placement. *AJR Am J Roentgenol* 2007; **188**: 1033-1038 [PMID: 17377041 DOI: 10.2214/AJR.06.0888]

56 **Madden BP**, Loke TK, Sheth AC. Do expandable metallic airway stents have a role in the management of patients with benign tracheobronchial disease? *Ann Thorac Surg* 2006; **82**: 274-278 [PMID: 16798229 DOI: 10.1016/j.athoracsur.2006.02.028]

57 **Mughal MM**, Gildea TR, Murthy S, Pettersson G, DeCamp M, Mehta AC. Short-term deployment of self-expanding metallic stents facilitates healing of bronchial dehiscence. *Am J Respir Crit Care Med* 2005; **172**: 768-771 [PMID: 15937290 DOI: 10.1164/rccm.200410-1388OC]

58 **Noppen M**, Van Renterghem D, Vanderstraeten P. The wrong stent at the wrong time: a cautionary tale. *Respiration* 2003; **70**: 313-316 [PMID: 12915755 DOI: 10.1159/000072017]

59 **Oryoji D**, Ono N, Himeji D, Yoshihiro K, Kai Y, Matsuda M, Tsukamoto H, Ueda A. Sudden Respiratory Failure due to Tracheobronchomalacia by Relapsing Polychondritis, Successfully Rescued by Multiple Metallic Stenting and Tracheostomy. *Intern Med* 2017; **56**: 3369-3372 [PMID: 29021454 DOI: 10.2169/internalmedicine.8778-16]

60 **Park JH**, Kim PH, Shin JH, Tsauo J, Kim MT, Cho YC, Kim JH, Song HY. Removal of Retrievable Self-Expandable Metallic Tracheobronchial Stents: An 18-Year Experience in a Single Center. *Cardiovasc Intervent Radiol* 2016; **39**: 1611-1619 [PMID: 27417222 DOI: 10.1007/s00270-016-1420-4]

61 **Pizarro C**, Dabir D, Nickenig G, Skowasch D. Nitinol stent insertion in tracheomalacia. *Thorax* 2016; **71**: 770-771 [PMID: 26944511 DOI: 10.1136/thoraxjnl-2015-208143]

62 **Ranu H**, Evans J, Sheth A, Madden BP. Removal of long-term tracheal stents with excellent tracheal healing. *Ann Thorac Surg* 2010; **89**: 598-599 [PMID: 20103350 DOI: 10.1016/j.athoracsur.2009.07.040]

63 **Redmond J**, Diamond J, Dunn J, Cohen GS, Soliman AM. Rigid bronchoscopic management of complications related to endobronchial stents after lung transplantation. *Ann Otol Rhinol Laryngol* 2013; **122**: 183-189 [PMID: 23577571 DOI: 10.1177/000348941312200307]

64 **Satoh S**, Mori M, Inoue Y. Expandable metallic stents applied to benign bronchostenosis. *Chest* 1993; **103**: 1302-1303 [PMID: 8131499 DOI: 10.1378/chest.103.4.1302]

65 **Sendi K**, Al-Khatib T, Ahmed DG, Tonkul AB. Management of embedded metallic stents used in the treatment of grades III and IV subglottic, and upper tracheal stenosis in adults. *Eur Arch Otorhinolaryngol* 2014; **271**: 2991-2995 [PMID: 24777564 DOI: 10.1007/s00405-014-3057-8]

66 **Sesterhenn AM**, Wagner HJ, Alfke H, Werner JA, Lippert BM. Treatment of benign tracheal stenosis utilizing self-expanding nitinol stents. *Cardiovasc Intervent Radiol* 2004; **27**: 355-360 [PMID: 15346210 DOI: 10.1007/s00270-004-0091-8]

67 **Shin JH**, Song HY, Ko GY, Shim TS, Kim SW, Cho YK, Ko HK, Kim YJ, Yoon HK, Sung KB. Treatment of tracheobronchial obstruction with a polytetrafluoroethylene-covered retrievable expandable nitinol stent. *J Vasc Interv Radiol* 2006; **17**: 657-663 [PMID: 16614149 DOI: 10.1097/01.RVI.0000203803.98007.9F]

68 **Swanson KL**, Edell ES, Prakash UB, Brutinel WM, Midthun DE, Utz JP. Complications of Metal Stent Therapy in Benign Airway Obstruction. *J Bronchol Intern Pu* 2007; **14**: 90-94 [DOI: 10.1097/lbr.0b013e318053d445]

69 **Thornton RH**, Gordon RL, Kerlan RK, LaBerge JM, Wilson MW, Wolanske KA, Gotway MB, Hastings GS, Golden JA. Outcomes of tracheobronchial stent placement for benign disease. *Radiology* 2006; **240**: 273-282 [PMID: 16793984 DOI: 10.1148/radiol.2401042169]

70 **Tor M**, Musani AI, Gillespie C, Leh S, Kotloff R, Sterman DH. Short-term Placement of Multiple Self-expandable Metallic Stents for the Treatment of Bilateral Bronchial Dehiscences Complicating Lung Transplantation. *J Bronchology Interv Pulmonol* 2009; **16**: 63-65 [PMID: 23168475 DOI: 10.1097/LBR.0b013e318191f00b]

71 **Xie BX**, Zhu YM, Chen C, Zhao DP, Yang CL, Ding JA, Jiang GN. Outcome of TiNi stent treatments in symptomatic central airway stenoses caused by Aspergillus fumigatus infections after lung transplantation. *Transplant Proc* 2013; **45**: 2366-2370 [PMID: 23953550 DOI: 10.1016/j.transproceed.2013.02.129]

72 **Xiong XF**, Xu L, Fan LL, Cheng DY, Zheng BX. Long-term follow-up of self-expandable metallic stents in benign tracheobronchial stenosis: a retrospective study. *BMC Pulm Med* 2019; **19**: 33 [PMID: 30736856 DOI: 10.1186/s12890-019-0793-y]

73 **Zhou GW**, Huang HD, Sun QY, Xiong Y, Li Q, Dong YC, Zhang W. Temporary placement of metallic stent could lead to long-term benefits for benign tracheobronchial stenosis. *J Thorac Dis* 2015; **7**: S398-S404 [PMID: 26807287 DOI: 10.3978/j.issn.2072-1439.2015.12.65]

74 **Anile M**, Venuta F, Diso D, Liparulo V, Ricella C, De Giacomo T, Pugliese F, Rolla M, Quattrucci S, Pecoraro Y, Rendina EA, Coloni GF. Treatment of complex airway lesions after lung transplantation with self-expandable nitinol stents: early experience. *Transplant Proc* 2010; **42**: 1279-1280 [PMID: 20534280 DOI: 10.1016/j.transproceed.2010.03.092]

75 **Sarodia BD**, Dasgupta A, Mehta AC. Management of airway manifestations of relapsing polychondritis: case reports and review of literature. *Chest* 1999; **116**: 1669-1675 [PMID: 10593793 DOI: 10.1378/chest.116.6.1669]

76 **Shaffer JP**, Allen JN. The use of expandable metal stents to facilitate extubation in patients with large airway obstruction. *Chest* 1998; **114**: 1378-1382 [PMID: 9824018 DOI: 10.1378/chest.114.5.1378]

77 **Spatenka J**, Khaghani A, Irving JD, Theodoropoulos S, Slavík Z, Yacoub MH. Gianturco self-expanding metallic stents in treatment of tracheobronchial stenosis after single lung and heart and lung transplantation. *Eur J Cardiothorac Surg* 1991; **5**: 648-652 [PMID: 1772681 DOI: 10.1016/1010-7940(91)90121-y]

78 **Susanto I**, Peters JI, Levine SM, Sako EY, Anzueto A, Bryan CL. Use of balloon-expandable metallic stents in the management of bronchial stenosis and bronchomalacia after lung transplantation. *Chest* 1998; **114**: 1330-1335 [PMID: 9824010 DOI: 10.1378/chest.114.5.1330]

79 **Tsang V**, Goldstraw P. Self-expanding metal stent for tracheobronchial strictures. *Eur J Cardiothorac Surg* 1992; **6**: 555-559; discussion 560 [PMID: 1389239 DOI: 10.1016/1010-7940(92)90008-l]

80 **Bansal S**, Dhingra S, Ghai B, Gupta AK. Metallic stents for proximal tracheal stenosis: is it worth the risk? *Case Rep Otolaryngol* 2012; **2012**: 450304 [PMID: 22953113 DOI: 10.1155/2012/450304]

81 **Boaron M**, Kawamukai K, Forti Parri SN, Trisolini R. Treatment of an acquired esophageal-bibronchial benign fistula using an original combination of techniques. *Interact Cardiovasc Thorac Surg* 2010; **10**: 156-158 [PMID: 19875513 DOI: 10.1510/icvts.2009.213868]

82 **Gocyk W**, Warmus J, Olechnowicz H, Bik-Multanowski M, Pawlinski L, Kiec-Wilk B. Case report of endoprosthesis -Y implantation in severe respiratory failure in the MPSII patient; comparison with literature data. *BMC Pulm Med* 2020; **20**: 99 [PMID: 32312280 DOI: 10.1186/s12890-020-1143-9]

83 **Chin CS**, Litle V, Yun J, Weiser T, Swanson SJ. Airway stents. *Ann Thorac Surg* 2008; **85**: S792-S796 [PMID: 18222219 DOI: 10.1016/j.athoracsur.2007.11.051]

84 **Sökücü SN**, Özdemir C, Tural Önür S, Dalar L, Altın S. Comparison of silicon and metallic bifurcated stents in patients with malignant airway lesions. *Clin Respir J* 2020; **14**: 198-204 [PMID: 31793225 DOI: 10.1111/crj.13114]

85 **Ayub A**, Al-Ayoubi AM, Bhora FY. Stents for airway strictures: selection and results. *J Thorac Dis* 2017; **9**: S116-S121 [PMID: 28446974 DOI: 10.21037/jtd.2017.01.56]

86 **Harris M**, Chung F. Complications of general anesthesia. *Clin Plast Surg* 2013; **40**: 503-513 [PMID: 24093647 DOI: 10.1016/j.cps.2013.07.001]

87 **Rodriguez AN**, Díaz-jiménez JP, Edell ES. Silicone Stents versus Metal Stents for Management of Benign Tracheobronchial Disease Con: Metal Stents. *J Bronchol Intern Pu* 2000; **7**: 184-187 [DOI: 10.1097/00128594-200007020-00017]

88 **Salguero BD**, Agrawal A, Lo Cascio CM, So M, Chaddha U. How risky is it to remove an airway stent? *Respir Med* 2023; **216**: 107320 [PMID: 37301524 DOI: 10.1016/j.rmed.2023.107320]

89 **Li ZM**, Jiao DC, Han XW, Lu HB, Ren KW, Yang H. Clinical evaluation the success rate and complications of fluoroscopically guided removal of tracheal tube metallic stents. *J Cardiothorac Surg* 2021; **16**: 54 [PMID: 33766043 DOI: 10.1186/s13019-021-01444-8]

90 **Madden BP**, Stamenkovic SA, Mitchell P. Covered expandable tracheal stents in the management of benign tracheal granulation tissue formation. *Ann Thorac Surg* 2000; **70**: 1191-1193 [PMID: 11081868 DOI: 10.1016/s0003-4975(00)01555-1]

91 **Chung FT**, Lin SM, Chou CL, Chen HC, Liu CY, Yu CT, Kuo HP. Factors leading to obstructive granulation tissue formation after ultraflex stenting in benign tracheal narrowing. *Thorac Cardiovasc Surg* 2010; **58**: 102-107 [PMID: 20333573 DOI: 10.1055/s-0029-1186266]

92 **Ching YH**, Geck RD, Andrews AD, Rumbak MJ, Camporesi EM. Argon plasma coagulation in the management of uncovered tracheal stent fracture. *Respir Med Case Rep* 2014; **13**: 37-38 [PMID: 26029557 DOI: 10.1016/j.rmcr.2014.09.004]

93 **Tremblay A**, Marquette CH. Endobronchial electrocautery and argon plasma coagulation: a practical approach. *Can Respir J* 2004; **11**: 305-310 [PMID: 15254614 DOI: 10.1155/2004/216243]

94 **Chen DF**, Chen Y, Zhong CH, Chen XB, Li SY. Long-term efficacy and safety of the Dumon stent for benign tracheal stenosis: a meta-analysis. *J Thorac Dis* 2021; **13**: 82-91 [PMID: 33569188 DOI: 10.21037/jtd-20-2327]

95 **Karush JM**, Seder CW, Raman A, Chmielewski GW, Liptay MJ, Warren WH, Arndt AT. Durability of Silicone Airway Stents in the Management of Benign Central Airway Obstruction. *Lung* 2017; **195**: 601-606 [PMID: 28623537 DOI: 10.1007/s00408-017-0023-4]

96 **Ernst A**, Majid A, Feller-Kopman D, Guerrero J, Boiselle P, Loring SH, O'Donnell C, Decamp M, Herth FJ, Gangadharan S, Ashiku S. Airway stabilization with silicone stents for treating adult tracheobronchomalacia: a prospective observational study. *Chest* 2007; **132**: 609-616 [PMID: 17699133 DOI: 10.1378/chest.06-2708]

97 **Ryu YJ**, Kim H, Yu CM, Choi JC, Kwon YS, Kwon OJ. Use of silicone stents for the management of post-tuberculosis tracheobronchial stenosis. *Eur Respir J* 2006; **28**: 1029-1035 [PMID: 16971412 DOI: 10.1183/09031936.00020906]

98 **Mehta RM**, Singla A, Shah A, Loknath C. The "Hitch Stitch": An Effective Method of Preventing Migration in High Tracheal Stenosis. *Respiration* 2017; **93**: 106-111 [PMID: 27988514 DOI: 10.1159/000453075]

99 **Dumon J**, Cavaliere S, Diaz-jimenez JP, Vergnon J, Venuta F, Dumon M, Kovitz KL. Seven-Year Experience with the Dumon Prosthesis. *J Bronchol Intern Pu* 1996; **3**: 6-10 [DOI: 10.1097/00128594-199601000-00003]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2025 March 18; 13(1): 100523

DOI: 10.13105/wjma.v13.i1.100523

ISSN 2308-3840 (online)

SYSTEMATIC REVIEWS

Nutritional interventions in the treatment of Hashimoto's disease: A systematic review

Carolina S Santos, Randhall B Carteri, Chaline Coghetto, Juliana Czermainski, Carolina B Rosa

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade B

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade B, Grade B

P-Reviewer: Sun CF

Received: August 19, 2024

Revised: November 13, 2024

Accepted: December 9, 2024

Published online: March 18, 2025

Processing time: 206 Days and 23.9 Hours

Carolina S Santos, Randhall B Carteri, Chaline Coghetto, Carolina B Rosa, Department of Nutrition, Centro Universitário CESUCA, Cachoeirinha 94935-630, Brazil

Juliana Czermainski, Postgraduate Program in Hepatology, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre 90430-080, Brazil

Corresponding author: Randhall B Carteri, PhD, Postdoctoral Fellow, Professor, Department of Nutrition, Centro Universitário CESUCA, Silvério Manoel da Silva, 160- Colinas, Cachoeirinha 94935-630, Brazil. randhallcarteri@gmail.com

Abstract

BACKGROUND

Hashimoto's thyroiditis (HT) is an autoimmune dysfunction caused by genetic and environmental changes that attack the thyroid gland. HT affects approximately 2% to 5% of the population, being more prevalent in women. It is diagnosed through a blood test (anti-thyroid peroxidase). Pharmacological treatment consists of daily administration of the synthetic hormone levothyroxine on an empty stomach. The most common signs and symptoms are: Tissue resistance to triiodothyronine T3, weight gain, dry skin, hair loss, tiredness/fatigue, and constipation, and nutritional therapy appears to help reduce these symptoms.

AIM

To analyze nutritional interventions for treating HT.

METHODS

This is an integrative review of original studies on nutritional interventions for treating Hashimoto's disease. Articles were searched in the MEDLINE/PubMed and Latin American and Caribbean Literature on Health Sciences (LILACS) databases *via* virtual health library, using controlled vocabulary and free terms. A total of 70 articles were found: 67 from PubMed and 3 from LILACS. After exclusions, 9 articles met the eligibility criteria, including dietary interventions for maintaining and restoring the patient's quality of life.

RESULTS

The reviewed articles evaluated the nutritional treatment of HT through supplementation of deficient micronutrients, anti-inflammatory diets, gluten-free diets, exclusion of foods that cause food sensitivities, lactose-free diet, paleo diet, and calorie restriction diets. However, some results were controversial regarding the

beneficial effects of HT.

CONCLUSION
In general, it was observed that nutritional interventions for HT are based on the recovery of micronutrient deficiencies, treatment of the intestinal microbiota, diet rich in foods with anti-inflammatory properties, lifestyle changes, and encouragement of healthy habits.

Key Words: Hashimoto's thyroiditis; Nutrition; Health; Autoimmune diseases; Inflammation

Core Tip: The review addresses the efficacy of different dietary approaches in treating Hashimoto's thyroiditis (HT). Although gluten and lactose-free diets may benefit some patients, the evidence is controversial and varies according to individual sensitivity and other associated conditions. Paleo diets, which include lifestyle changes and micronutrient supplementation, have improved inflammatory and metabolic interventions in patients with HT. Nutritional interventions focused on anti-inflammatory diets and management of nutritional deficiencies are recommended as complementary alternatives to drug treatment.

Citation: Santos CS, Carteri RB, Coghetto C, Czermainski J, Rosa CB. Nutritional interventions in the treatment of Hashimoto's disease: A systematic review. *World J Meta-Anal* 2025; 13(1): 100523
URL: https://www.wjgnet.com/2308-3840/full/v13/i1/100523.htm
DOI: https://dx.doi.org/10.13105/wjma.v13.i1.100523

INTRODUCTION

Hashimoto's thyroiditis (HT) is an autoimmune disorder caused by genetic and environmental alterations that are not yet fully understood and attack the thyroid gland. It is the most common form of hypothyroidism, characterized by complications and chronic thyroid edema, which eventually leads to its dysfunction[1-4]. HT is diagnosed by measuring antithyroid antibodies [anti-thyroid peroxidase (TPO)], indicating metabolic alterations in the gland[5].

The thyroid is frequently affected by autoimmune diseases, and patients with autoimmune hyperthyroidism may develop hypothyroidism and vice versa[6].

Subacute thyroiditis may also result in hypothyroidism; however, this condition is usually transient. Approximately 20% to 30% of women with subacute thyroiditis in the postpartum period develop hypothyroidism. The risk increases as anti-TPO antibody levels increase[7].

There is no single definitive cause for this autoimmune disorder, as it involves multiple contributing factors and specific genetic markers. However, early diagnosis can avoid complications, prevent the onset of other autoimmune diseases, and help improve the patient's quality of life with appropriate treatment[8].

The treatment of HT varies according to the clinical manifestations of the disease, which may include diffuse or nodular goiter with euthyroidism, subclinical hypothyroidism, and permanent hypothyroidism. However, in most cases, and under the prescription of an endocrinologist, levothyroxine should be administered daily, preferably on an empty stomach, to improve drug intake[9].

Nutritional treatment of HT is still often neglected. However, some studies recommend supplementation in cases of nutrient deficiencies such as iodine, iron, copper, selenium, zinc, and vitamin D[9]. Micronutrients are often deficient in autoimmune diseases; therefore, it is important to recommend a diet that meets the deficiencies and nutritional needs[10-12]. Anti-inflammatory diets and the elimination or reduction of specific foods to address potential sensitivities are also being explored in the nutritional therapy for HT[5].

The gut microbiota composition plays a key role in the availability of essential micronutrients for thyroid function[10]. With its vast tissue surface and numerous immune cells interacting with the microbiota, the intestine is central to this process. While the microbiota's composition is generally stable in adults, it can be influenced by dietary changes and various diseases. More specifically, patients with HT, often present intestinal dysbiosis, as dysregulation of thyroid hormone levels affects the composition of the microbiota, promoting bacterial overgrowth and increased intestinal permeability, ultimately leading to autoimmune processes[10,13,14].

MATERIALS AND METHODS

This is an integrative review of original studies that investigated nutritional interventions for the treatment of HT patients. Articles were searched in two databases: The National Library of Medicine National Institutes of Health (MEDLINE/PubMed) and the Latin American and Caribbean Literature on Health Sciences (LILACS), *via* the Virtual

Health Library (VHL). The search strategy was developed by combining controlled vocabulary and free terms related to: (1) Nutrition; (2) Nutritional Therapy; and (3) Hashimoto's disease. There was no restriction regarding age group or language. References cited in the articles selected for full reading were reviewed to identify additional studies of interest that may have been missed in the search process (grey literature). Controlled vocabulary was used whenever possible, with health sciences descriptors for VHL and medical subject headings for PubMed. The final search strategy was executed in both databases in June 2024.

RESULTS

This review identified 70 studies, of which 67 were retrieved from MEDLINE/PubMed and 3 from LILACS. Articles that did not focus on nutritional interventions for HT (n = 47) or did not address dietary treatment (n = 20) were excluded. Additionally, 19 articles from grey literature were included, of which 13 did not meet the inclusion criteria. Ultimately, nine articles met the eligibility criteria, exploring dietary interventions for HT and their impact on patients' quality of life. Figure 1 graphically presents the results of the study selection process. The diets analyzed by the authors included: Lactose-free[15], gluten-free[16,17], gluten-free combined with healthy habits and nutritional counseling[18], gluten-free with selenium supplementation[19], calorie-restricted diets with or without food exclusion[20], paleo diets excluding grains and dairy products with micronutrient supplementation[21], autoimmune diets with lifestyle modifications[22], and autoimmune paleo diets with calorie restriction up to 1200 kcal[23].

The parameters investigated included: Thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), parathyroid hormone (PTH), TPO antibodies (TPOAb), thyroglobulin antibodies (TgAb), C-reactive protein, vitamins D and B12, zinc, ferritin, lipid profile (high-density lipoprotein-c, low-density lipoprotein-c, triglycerides), symptom questionnaire, quality of life questionnaire, anthropometry [weight and body mass index (BMI)], fasting glucose, and fasting insulin. Table 1 presents the characteristics of the studies included in this review, organized according to the type of treatment investigated.

DISCUSSION

Firstly, in the study by Asik *et al*[15], a lactose-free diet demonstrated positive results in patients with lactose intolerance, leading to a reduction in TSH levels but no significant effect on other evaluated parameters, such as fT4, calcium, PTH, and TPOAb titers. Excessive lactose consumption can lead to bacterial overgrowth, gas production, and intestinal distension, potentially impairing T4 absorption. This underscores the rationale for excluding lactose in these patients.

In the study by Krysiak *et al*[16], the group that followed a gluten-free diet showed a reduction in TPOAb and TgAb levels and an increase in vitamin D levels. These findings suggest a positive effect of gluten exclusion in patients with HT, possibly through the reduction of autoimmunity and increased thyroid production.

This review observed that gluten-free diets support pharmacological treatment of HT in patients with associated celiac disease, reducing the prescribed oral hormone dose by up to 50%. Poor absorption of thyroid medication is common in these patients due to the high permeability caused by the disease in the digestive tract[17]. Also, a gluten-free diet is often recommended for the dietary management of autoimmune diseases, albeit the effects are not immediately evident. For instance, a study by Pobłocki *et al*[18] examined the effects of a gluten-free diet in combination with healthy habits and nutritional counseling. No significant differences were observed between the control and gluten-free groups until the 12-month mark when the gluten-free group showed reduced TSH levels and increased fT4. These findings suggest that while gluten exclusion is recommended for patients with celiac disease, its use in managing other autoimmune diseases remains controversial, despite its potential to enhance levothyroxine absorption.

Interestingly, Velija *et al*[19] demonstrated that selenium supplementation significantly reduced TPOAb, TgAb, and TSH levels. Additionally, combining selenium supplementation with a gluten-free diet provided more benefits than supplementation alone in women.

Avard and Grant[21] investigated the association between the restriction of gluten, grains, and dairy products and micronutrient supplementation in women following a paleo diet. Similarly, the case report by Al-Bayyari[23], which also used the paleo diet, demonstrated improvements in thyroid levels and a significant improvement in quality-of-life parameters, including regulation of insomnia, chronic fatigue, stress, exhaustion, hair loss, and bowel movements.

The study that evaluated the "modified autoimmune paleo-diet"[23], combined paleo, vegan, and gluten-free diets. The meal plan contained 1200 kcal/day, with 150 g/day of carbohydrates, 45 g/day of protein, and 47 g/day of lipids, distributed over three daily meals. After 6 months, there was an improvement in parameters related to body mass and adiposity, such as TSH, TPOAb, cholesterol, and insulin, without affecting levels of the thyroid hormones fT3 and fT4. These results favor the treatment of HT, as they reduce inflammation, decrease the need for synthetic fT4, and reduce the risk of associated chronic diseases[23].

Similarly, Abbott *et al*[22] reported that an "autoimmune protocol", which is an extension of the paleo diet (removing gluten, and refined sugar, and gradually eliminating pro-inflammatory food groups such as grains, legumes, dairy, eggs, coffee, alcohol, nuts, seeds, sugars, processed foods, oils, and food additives, encouraging the consumption of fresh, nutrient-rich foods, bone broth, and fermentable foods), combined with lifestyle changes, can reduce inflammation and positively assist in the recovery of the immune system weakened by HT. This therapy aims to improve health-related quality of life and reduce disease symptoms.

Table 1 Description of the studies included in the integrative review, according to the type of treatment investigated

Ref.	Country	Type of study	Number of participants, gender and age	Objectives	Groups and treatments	Parameters evaluated	Main results
Lactose-free diet							
Asik *et al* [15]	Türkiye	Case-control	50 patients with HT (Female: 48; Male: 02). Average age: 47.9 ± 8.73 years	To evaluate the prevalence of lactose intolerance in patients with HT and the effects of lactose restriction on thyroid function in these patients	Groups: 1: Lactose intolerant (n = 48); 2: No lactose intolerance (n = 12); Time: 8 weeks	TSH, fT4, calcium, and parathormone (PTH)	The TSH levels decreased in patients with HT and lactose intolerance. Patients without lactose intolerance did not have significant changes in TSH levels. The other parameters did not change after lactose restriction
Gluten-free diet							
Krysiak *et al*[16]	Poland	Case-control	34 women with HT. Average age: Group A = 30 ± 5 years; Group B = 31 ± 6 years	To investigate whether a gluten-free diet affects thyroid function in women with HT	Group A: Gluten-free diet (n = 16); Group B: Gluten-containing diet (n = 18); Time: 6 months	Titers of TPOAb and TgAb; serum levels of TSH, fT3, fT4 and 25-hydroxyvitamin D	In group A, TPOAb and TgAb levels decreased and Vitamin D increased. TSH, fT3, and fT4 levels remained unchanged. In group B, the evaluated parameters remained unchanged
Gluten-free diet for patients with CD and HT							
Virili *et al* [17]	Italy	Case report	103 individuals with HT and/or CD (Female: 92; Male: 11); Age: Patients with HT: 41 (33-51); Patients with HT and CD: 39 (33-50)	To analyze the need to increase fT4 in CD patients adhering to a gluten-free diet	Patients with isolated HT: Gluten-containing diet; Patients with HT and CD: Gluten-free diet; Time: 15 months	TSH, TPOAb, weight and BMI	It was observed that there was a need to increase the fT4 dose by up to 50% in patients with HT and CD who were non-adherent to a gluten-free diet. However, this can be reversed if a gluten-free diet is implemented. Normal thyroid levels were observed after the gluten-free diet, but the same result was obtained after increasing the fT4 dose in patients who were non-adherent to the diet
Gluten-free diet associated with healthy lifestyle and nutritional follow-up							
Pobłocki *et al*[18]	Poland	Case-control	62 women with HT. Average age: 38.86 ± 4.28 years	To evaluate whether the use of a gluten-free diet is effective in patients with HT	Group selection: Gluten-free diet (n = 31); Control group: Average Pole's diet (n = 31); Time: 12 months	Serum levels of TSH, fT3, fT4, and Titers of TPOAb and TgAb, weight and BMI	There was a reduction in TSH in the study group and an increase in fT4 levels, the other parameters did not change in either group
Gluten-free diet with selenium supplementation							
Velija *et al* [19]	United Kingdom	Case-control	98 women with HT. Average age: 39.60 ± 7.36 years	To validate the positive effect of HT patients adhering to a gluten-free diet and selenium supplementation on the recovery of thyroid function	Group A: Receiving 200 µg selenium in the form of L-selenomethionine orally and gluten-free diet (n = 50); Group B: Receiving 200 µg selenium without any dietary treatment (n = 48); Time: 6 months	Titers of TPOAb and TgAb, and serum levels of TSH, fT3, fT4	At the end of the study, euthyroidism was restored in 74% of group A participants, and in 58.3% of group B participants. TSH, TPOAb and TgAb levels were significantly reduced in both group after six months of treatment. Serum TPOAb titer in group A had a more significant decrease (by 49%) than those in group B (by 34%)
Calorie reduction and food exclusion diet							
Ostrowska *et al*[20]	Poland	Case-control	100 women with HT and obesity. Average age: Group A = 42.7 ± 10.51 years;	To evaluate the influence of calorie reduction diets, with and without food exclusion, on thyroid	Group A: Calorie reduction and food exclusion diet (n = 50); Group B: Calorie reduction diet without	Titers of TPOab and TgAb, and serum levels of TSH, fT3, fT4, weight and BMI	In both groups, loss of body mass and decrease in BMI were observed, in group A this loss was greater. Both groups

			Group B = 41.02 ± 11.96 years	parameters in women	excluding foods (n = 50). Average reduction of 1000 kcal/day in both diets. Time: 6 months		obtained decreases in the parameters of TSH, TPOAb, TgAb, and an increase in fT3 and fT4 in group A
Paleo diet with exclusion of gluten, grains, dairy and micronutrient supplementation							
Avard and Grant[21]	Australia	Case report	Woman with HT, 23 years	To validate whether an approach to modulating the intestinal microbiota and reducing inflammation can be used as methods to regulate intestinal permeability and favor the course of HT treatment	Paleo diet with exclusion of gluten, grains, dairy, low-protein with micronutrient supplementation (vitamin C, D, B1, B4, B5, B6, B12, zinc, selenium, iron a N-Acetyl cysteine) and probiotics. Time: 15 months	Serum levels of TSH, fT4, zinc, ferritin, Vitamin D and B12, Titers of TPOAb and TgAb	Reduction in TSH and TgAb levels and significant improvement in the symptoms that most affected the patient (daytime naps, exhaustion, stress and mood swings, excessive fatigue, hair loss, nighttime insomnia), only intestinal transit, which despite improving, remained unstable
Autoimmune diet and lifestyle changes							
Abbott *et al*[22]	United States	Pilot study	16 women with HT. Average age: 35.6 ± 5.7 years	To determine the efficacy of a multidisciplinary diet and lifestyle intervention for improving the quality of life,clinical symptom burden, and thyroid function in a population of middle-aged women with HT	Online health coaching program focused on the implementation of a phased elimination diet known as the Autoimmune Protocol. Time: 10 weeks	Complete metabolic profile, serum levels of TSH fT3, fT4, titers of TPOAb, TgAb, CRP, symptom and quality of life questionnaires	No changes in TSH, fT3, fT4, TPOAb, TgAb. Improvement in health and quality of life. Clinical symptoms with significant decrease. In the CRP test there was a decrease of 29%
Autoimmune and hypocaloric Paleo diet (1200 kcal)							
Al-Bayyari [23]	Jordan	Case report	Woman with HT, 49 years	To observe the effect of a modified paleo immune diet on anthropometry, body composition, insulin, lipid profile and thyroid function of the patient analyzed	Modified autoimmune paleo low-calorie diet (1200 kcal). Time: 6 months	Anthropometric measurements, body composition, fasting blood glucose and insulin, serum levels of HDL-c, LDL-c, triglycerides, fT3, fT4, TSH, and titers of TPOAb	Reduction in anthropometric measurements, body composition, triglycerides, LDL, TSH, TPOAb, and insulin. There were no changes in fT3, fT4. There was an increase in HDL-c

HT: Hashimoto's thyroiditis; fT4: Free thyroxine; fT3: Free triiodothyronine; TPOAb: Anti-thyroid peroxidase antibodies; TgAb: Anti-thyroglobulin antibodies; BMI: Body mass index; CRP: C-reactive protein; TSH: Thyrotropin; CD: Celiac disease; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; PTH: Parathyroid hormone.

A Polish study[20] involving 100 women evaluated a hypocaloric diet of up to 1000 kcal/day, with or without the exclusion of foods such as wheat, egg white, cow's milk, yeast, corn, gluten, peanuts, almonds, egg yolk, shrimp, soy, barley, sheep's milk, goat's milk, rice, apple, tomato, mushrooms, hazelnuts, carrots, walnuts, garlic, sesame, cocoa, vanilla, meat, and pineapple. The diet was established through food sensitivity tests and compared to a hypocaloric diet of up to 1000 kcal/day without dietary restrictions[20]. After 6 months of treatment, both groups showed weight loss and reduced adiposity, albeit the group with food exclusion also showed decreased levels of TSH, TPOAb, and TgAb, as well as increased levels of fT3 and fT4 hormones, and higher rates of BMI reduction. This study demonstrated that weight loss benefits the treatment of HT and that an individualized elimination diet potentiates therapeutic results[20].

According to Mikulska *et al*[24], an anti-inflammatory dietary intervention rich in vitamins and minerals and low in animal-based foods may positively affect the dietary treatment of HT. However, the authors state that no sufficiently reliable studies were found to recommend the exclusion of gluten for all patients with HT. Likewise, Szczuko *et al*[25] corroborate these findings, stating that it is unsafe to recommend that patients with HT follow this nutritional approach. It is worth noting that a gluten-free diet can be extremely restrictive, difficult to adhere to, and present a high risk of inadequate intake of essential nutrients.

A gluten-free diet, aimed at preventing or treating HT, can lead to deficiencies in some nutrients, as the exclusion of this food group generally results in lower quality and variety in the diet[14]. Additionally, the effects of a gluten-free diet in non-celiac patients with autoimmune diseases have not been sufficiently studied. Some publications suggest that thyroid-related antibodies may respond to a gluten-free diet in patients with both conditions[4]. However, there is insufficient scientific evidence to recommend such a diet for patients with autoimmune diseases other than celiac disease.

On the other hand, it has been reported that, in obese women, a restricted diet excluding pro-inflammatory food groups is more effective than a calorie-restricted diet alone[4,20]. Due to the inflammatory process associated with HT, it seems advisable to prescribe an anti-inflammatory diet in parallel with treatment, in addition to investigating associated autoimmune diseases and deficiencies of micronutrients essential for thyroid function[25].

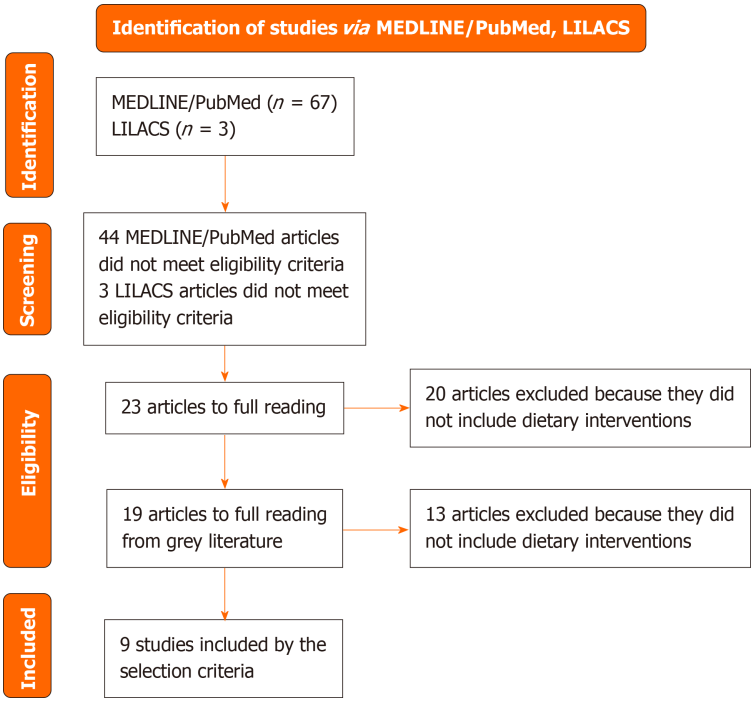


Figure 1 Flowchart of the article selection process. LILACS: Latin American and Caribbean Literature on Health Sciences.

The results of this review indicate that patients with HT should undergo regular medical follow-up, including tests to monitor vitamins and micronutrients, to assist in managing the progression of the disease. The efficacy of a gluten-free diet in patients with HT is controversial; some studies suggest that gluten exclusion may be beneficial, whereas others have indicated that there is no clear positive impact and may even be associated with disease progression. A lactose-restricted diet may be advantageous for patients with lactose intolerance, but it is unjustified for patients lacking this condition.

Paleodiets, including lifestyle changes and weight reduction, associated with appropriate pharmacotherapy and micronutrient supplementation have satisfactory outcomes. These interventions help reduce the inflammation associated with excess weight, contributing to the progression of HT. The "autoimmune protocol", excluding pro-inflammatory foods and foods identified as sensitivities, appears to be a favorable approach for treating autoimmune diseases such as HT. However, these dietary strategies are highly restrictive and may be difficult to adhere to.

CONCLUSION

It is concluded that nutritional interventions based on an anti-inflammatory diet and supplementation of deficient micronutrients may be beneficial alternatives for HT treatment when combined with drug therapy.

FOOTNOTES

Author contributions: Santos CS and Rosa CB were responsible for the conception and design, data collection, and manuscript writing; Rosa CB, Coghetto C, Czermainski J and Carteri RB were responsible for manuscript writing, and critical revision.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: Brazil

ORCID number: Randhall B Carteri 0000-0003-4124-9470; Juliana Czermainski 0000-0002-4628-2467.

S-Editor: Fan M
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Klubo-Gwiezdzinska J**, Wartofsky L. Hashimoto thyroiditis: an evidence-based guide to etiology, diagnosis and treatment. *Pol Arch Intern Med* 2022; **132** [PMID: 35243857 DOI: 10.20452/pamw.16222]
2 **Chaker L**, Razvi S, Bensenor IM, Azizi F, Pearce EN, Peeters RP. Hypothyroidism. *Nat Rev Dis Primers* 2022; **8**: 30 [PMID: 35589725 DOI: 10.1038/s41572-022-00357-7]
3 **Hiromatsu Y**, Satoh H, Amino N. Hashimoto's thyroiditis: history and future outlook. *Hormones (Athens)* 2013; **12**: 12-18 [PMID: 23624127 DOI: 10.1007/BF03401282]
4 **Passali M**, Josefsen K, Frederiksen JL, Antvorskov JC. Current Evidence on the Efficacy of Gluten-Free Diets in Multiple Sclerosis, Psoriasis, Type 1 Diabetes and Autoimmune Thyroid Diseases. *Nutrients* 2020; **12** [PMID: 32752175 DOI: 10.3390/nu12082316]
5 **Tipu HN**, Ahmed D, Bashir MM, Asif N. Significance of Testing Anti-Thyroid Autoantibodies in Patients with Deranged Thyroid Profile. *J Thyroid Res* 2018; **2018**: 9610497 [PMID: 29850012 DOI: 10.1155/2018/9610497]
6 **Vilela LRR**, Fernandes DC. Vitamin D and Selenium in Hashimoto's Thyroiditis: bystanders or players? *Demetra* 2018; **13** [DOI: 10.12957/demetra.2018.30496]
7 **Vargas-Uricoechea H**, Nogueira JP, Pinzón-Fernández MV, Schwarzstein D. The Usefulness of Thyroid Antibodies in the Diagnostic Approach to Autoimmune Thyroid Disease. *Antibodies (Basel)* 2023; **12** [PMID: 37489370 DOI: 10.3390/antib12030048]
8 **Hegedüs L**, Bianco AC, Jonklaas J, Pearce SH, Weetman AP, Perros P. Primary hypothyroidism and quality of life. *Nat Rev Endocrinol* 2022; **18**: 230-242 [PMID: 35042968 DOI: 10.1038/s41574-021-00625-8]
9 **Liontiris MI**, Mazokopakis EE. A concise review of Hashimoto thyroiditis (HT) and the importance of iodine, selenium, vitamin D and gluten on the autoimmunity and dietary management of HT patients.Points that need more investigation. *Hell J Nucl Med* 2017; **20**: 51-56 [PMID: 28315909 DOI: 10.1967/s002449910507]
10 **Gong B**, Wang C, Meng F, Wang H, Song B, Yang Y, Shan Z. Association Between Gut Microbiota and Autoimmune Thyroid Disease: A Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne)* 2021; **12**: 774362 [PMID: 34867823 DOI: 10.3389/fendo.2021.774362]
11 **Knezevic J**, Starchl C, Tmava Berisha A, Amrein K. Thyroid-Gut-Axis: How Does the Microbiota Influence Thyroid Function? *Nutrients* 2020; **12** [PMID: 32545596 DOI: 10.3390/nu12061769]
12 **Ventura A**, Ronsoni MF, Shiozawa MBC, Dantas-corrêa EB, Canalli MHBDS, Schiavon LDL, Narciso-schiavon JL. Prevalence and clinical features of celiac disease in patients with autoimmune thyroiditis: cross-sectional study. *Sao Paulo Med J* 2014; **132**: 364-371 [DOI: 10.1590/1516-3180.2014.1326725]
13 **Ihnatowicz P**, Wątor P, Ewa Drywień M. Supplementation in Autoimmune Thyroid Hashimoto's Disease. Vitamin D and Selenium. *J Food Nutr Res* 2019; **7**: 584-591 [DOI: 10.12691/jfnr-7-8-6]
14 **Ihnatowicz P**, Wątor P, Drywień ME. The importance of gluten exclusion in the management of Hashimoto's thyroiditis. *Ann Agric Environ Med* 2021; **28**: 558-568 [PMID: 34969211 DOI: 10.26444/aaem/136523]
15 **Asik M**, Gunes F, Binnetoglu E, Eroglu M, Bozkurt N, Sen H, Akbal E, Bakar C, Beyazit Y, Ukinc K. Decrease in TSH levels after lactose restriction in Hashimoto's thyroiditis patients with lactose intolerance. *Endocrine* 2014; **46**: 279-284 [PMID: 24078411 DOI: 10.1007/s12020-013-0065-1]
16 **Krysiak R**, Szkróbka W, Okopień B. The Effect of Gluten-Free Diet on Thyroid Autoimmunity in Drug-Naïve Women with Hashimoto's Thyroiditis: A Pilot Study. *Exp Clin Endocrinol Diabetes* 2019; **127**: 417-422 [PMID: 30060266 DOI: 10.1055/a-0653-7108]
17 **Virili C**, Bassotti G, Santaguida MG, Iuorio R, Del Duca SC, Mercuri V, Picarelli A, Gargiulo P, Gargano L, Centanni M. Atypical celiac disease as cause of increased need for thyroxine: a systematic study. *J Clin Endocrinol Metab* 2012; **97**: E419-E422 [PMID: 22238404 DOI: 10.1210/jc.2011-1851]
18 **Pobłocki J**, Pańka T, Szczuko M, Telesiński A, Syrenicz A. Whether a Gluten-Free Diet Should Be Recommended in Chronic Autoimmune Thyroiditis or Not?-A 12-Month Follow-Up. *J Clin Med* 2021; **10** [PMID: 34362024 DOI: 10.3390/jcm10153240]
19 **Velija AZ**, Hadzovic-dzuvo A, Al TD. The effect of selenium supplementation and gluten-free diet in patients with subclinical hypothyroidism affected by autoimmune thyroiditis. *EJEA* 2020 [DOI: 10.1530/endoabs.70.aep906]
20 **Ostrowska L**, Gier D, Zyśk B. The Influence of Reducing Diets on Changes in Thyroid Parameters in Women Suffering from Obesity and Hashimoto's Disease. *Nutrients* 2021; **13** [PMID: 33808030 DOI: 10.3390/nu13030862]
21 **Avard N**, Grant SJ. A case report of a novel, integrative approach to Hashimoto's thyroiditis with unexpected results. *AIMED* 2018; **5**: 75-79 [DOI: 10.1016/j.aimed.2018.03.003]
22 **Abbott RD**, Sadowski A, Alt AG. Efficacy of the Autoimmune Protocol Diet as Part of a Multi-disciplinary, Supported Lifestyle Intervention for Hashimoto's Thyroiditis. *Cureus* 2019; **11**: e4556 [PMID: 31275780 DOI: 10.7759/cureus.4556]
23 **Al-Bayyari NS**. Successful dietary intervention plan for Hashimoto's thyroiditis: A case study. *Rom J Diabetes Nutr Metab Dis* 2020; **27**: 381-385 [DOI: 10.46389/rjd-2020-1055]
24 **Mikulska AA**, Karaźniewicz-Łada M, Filipowicz D, Ruchała M, Główka FK. Metabolic Characteristics of Hashimoto's Thyroiditis Patients and the Role of Microelements and Diet in the Disease Management-An Overview. *Int J Mol Sci* 2022; **23**: 6580 [PMID: 35743024 DOI: 10.3390/ijms23126580]
25 **Szczuko M**, Syrenicz A, Szymkowiak K, Przybylska A, Szczuko U, Pobłocki J, Kulpa D. Doubtful Justification of the Gluten-Free Diet in the Course of Hashimoto's Disease. *Nutrients* 2022; **14**: 1727 [PMID: 35565695 DOI: 10.3390/nu14091727]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2025 March 18; 13(1): 99971

DOI: 10.13105/wjma.v13.i1.99971

ISSN 2308-3840 (online)

META-ANALYSIS

Efficacy of bright light therapy for perinatal depression: A meta-analysis of a randomized controlled trial

Xue Yang, Yuan-Yuan Gao, Shu-Qi Xu, Jin-Cheng Wang, Yu-Jie Ma, Li-Huan Jiao, Lan Wang, Xue-Yi Wang, Shahid Bashir, Cui-Xia An, Ran Wang

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade D
Novelty: Grade C
Creativity or Innovation: Grade C
Scientific Significance: Grade C

P-Reviewer: Liu J

Received: August 4, 2024
Revised: December 13, 2024
Accepted: December 25, 2024
Published online: March 18, 2025
Processing time: 221 Days and 21.9 Hours

Xue Yang, Yuan-Yuan Gao, Shu-Qi Xu, Jin-Cheng Wang, Yu-Jie Ma, Li-Huan Jiao, Lan Wang, Xue-Yi Wang, Cui-Xia An, Ran Wang, Mental Health Center, The First Hospital of Hebei Medical University, Shijiazhuang 050031, Hebei Province, China

Shahid Bashir, Neuroscience Center, King Fahad Specialist Hospital Dammam, Dammam 0096613, Saudi Arabia

Co-first authors: Xue Yang and Yuan-Yuan Gao.

Co-corresponding authors: Cui-Xia An and Ran Wang.

Corresponding author: Ran Wang, MD, PhD, Professor, Mental Health Center, The First Hospital of Hebei Medical University, No. 89 Donggang Road, Shijiazhuang 050031, Hebei Province, China. wr104@hebmu.edu.cn

Abstract

BACKGROUND

Pharmacological treatments are commonly used in individuals experiencing perinatal depression (PPD); however, a debate regarding the reproductive safety of antidepressants is ongoing. Many pregnant women opt to discontinue antidepressant out of concern about potential negative effects on the developing fetus, while slow and ineffective antidepressant medications hinder improved outcomes in women with PPD. In recent years, bright light therapy (BLT) has gained traction as a treatment option for PPD; however, clinical trials findings examining the efficacy of BLT in this population have been inconclusive.

AIM

To validate the feasibility and safety of BLT for the treatment of PPD.

METHODS

We performed a meta-analysis of randomized controlled trials of patients with PPD treated with BLT *vs* placebo following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. We searched PubMed, Embase, the Cochrane Library, and Web of Science for randomized controlled studies published up to December 2023. The results were evaluated using the standardized mean difference of improvement for depression scores and odds ratios (ORs) for remission rate, response rate, incidence of adverse events, and dropout rate.

RESULTS

The BLT group had higher PPD response rate [50.68% *vs* 33.08%; OR = 2.05; 95% confidence interval (CI): 1.25-3.35; P = 0.004; I^2 = 35%] and remission rate (54.10% *vs* 18.52%; OR = 5.00; 95%CI: 2.09-11.99; P = 0.0003; I^2 = 0%) than the placebo group. Improvements in depression scores were higher in the BLT group than the placebo group for the overall efficacy (standardized mean difference = -0.47; 95%CI: -0.80 to -0.13; P = 0.007). No significant differences between the two groups in drop-outs (21.84% *vs* 29.63%; OR = 0.63; 95%CI: 0.31-1.29; P = 0.21; I^2 = 0%) or adverse events (17.89% *vs* 9.68%; OR = 2.01; 95%CI: 0.95-4.25; P = 0.07; I^2 = 0%) were observed.

CONCLUSION

BLT can potentially treat PPD, showing better results than the control group in this study. BLT is effective and safe and could increase the available therapeutic options for PPD.

Key Words: Bright light therapy; Randomized controlled trial; Perinatal depression; Pregnancy; Meta-analysis

Core Tip: Bright light therapy represents a promising intervention for the treatment of perinatal depression, demonstrating significant efficacy and a favorable safety profile. This non-pharmacological approach is particularly well-received among pregnant and postpartum individuals, as well as their support networks, due to its lack of systemic side effects. The integration of bright light therapy into the psychiatric armamentarium for perinatal depression may enhance therapeutic flexibility and patient adherence, thereby contributing to improved mental health outcomes in this vulnerable population.

Citation: Yang X, Gao YY, Xu SQ, Wang JC, Ma YJ, Jiao LH, Wang L, Wang XY, Bashir S, An CX, Wang R. Efficacy of bright light therapy for perinatal depression: A meta-analysis of a randomized controlled trial. *World J Meta-Anal* 2025; 13(1): 99971
URL: https://www.wjgnet.com/2308-3840/full/v13/i1/99971.htm
DOI: https://dx.doi.org/10.13105/wjma.v13.i1.99971

INTRODUCTION

Perinatal depression (PPD) is a mood disorder that occurs during pregnancy and up to 12 months after childbirth[1]. The American Psychiatric Association has categorized PPD as a subtype of major depression, with studies indicating a prevalence rate of 10-15%[2], with over 25% of perinatal women experiencing symptoms of depressed mood[3]. According to the World Health Organization 2020, mental illnesses affect 15.6% of pregnant and 19.8% of postpartum women in developing countries, with depression being the most common. A recent epidemiological review in China found that the prevalence rates of perinatal, prenatal, and postpartum depression were 16.3%, 19.7%, and 14.8%, respectively[4]. The elevated rates of depression underscore its substantial impact on the health outcomes of mothers and infants, influencing the well-being of not only the affected individuals but also their family members[5].

Conventional pharmacological treatments commonly prescribed to women during pregnancy demonstrate notable effectiveness but inherent limitations[6]. Selecting antidepressant medications during the perinatal phase is complex, given the delayed onset of action and suboptimal therapeutic outcomes associated with these drugs[7]. Furthermore, extensive research has evaluated the reproductive safety of antidepressants, with a significant increase in discontinuation rates among pregnant women[8]. Furthermore, individuals with untreated PPD are at an increased risk of suicide[9] and prone to extreme behaviors, such as extended suicide[10]. The infants of women with PPD are more susceptible to adverse outcomes such as low birth weight and perinatal death[7]. Despite the potential efficacy of conventional antidepressants in alleviating PPD symptoms, one-third of patients do not recover effectively[11]. Patients with PPD have relapse rates of around 50% in subsequent pregnancies[12]. Therefore, effective treatment methods and maintenance strategies for PPD need to be identified.

Bright light therapy (BLT) is a type of physical therapy that uses light rays. A patient is placed in a bright light environment and completes light therapy according to the established time and cycle. Its mechanism may be through regulating the neural circuits of brain function, which plays an important role in the patient's clinical symptoms. While the neural mechanisms by which BLT improves mood are currently unknown[13], BLT has gradually been used to treat mental illnesses in recent years, demonstrating therapeutic effects. However, few studies have examined BLT as an adjunctive treatment for patients with PPD. BLT is safe, effective, and relatively inexpensive compared to other treatments, such as pharmacological and psychological treatments[14]. However, studies have been inconsistent, and evidence of its effectiveness in treating PPD needs to be substantiated. Li *et al*[15] conducted a systematic review of depression scale scores after receiving light therapy to treat depression and sleep in pregnant and postpartum women, concluding that light therapy was effective in relieving depression and sleep; however, the results displayed considerable heterogeneity. The purpose of this review was to systematically synthesize existing studies to further assess the efficacy of BLT in treating PPD in terms of remission rate, response rate, and improvement in depression scores before and after the intervention to identify the evidence-based medical basis for BLT in clinical treatment decisions.

MATERIALS AND METHODS

Protocol and registration

This study was registered in PROSPERO (https: //www.crd.york.ac.uk/PROSPERO/; Registration Number CRD420245 60280).

Information sources and search

We systematically searched PubMed, Embase, the Cochrane Library, and Web of Science using a combination of Medical Subject Headings and free-word methods. Studies were published between the database's inception and December 2023. The search terms used were perinatal, pregnancy, depression, postpartum depression, and light therapy (Supplementary Table 1).

Literature eligibility criteria

Inclusion criteria: (1) Randomized control trials (RCTs) written in English; (2) A sample that included perinatal women diagnosed with depression at baseline. All studies excluded patients with other systemic diseases; (3) Experimental groups were treated with BLT, and control groups received dim light therapy (DLT); (4) Outcomes were assessed using the Edinburgh postnatal depression scale, structured interview guide for the Hamilton depression rating scale, and Hamilton depression scale; and (5) The primary outcome was the response to treatment. The secondary outcomes include: Depression remission, improved depression score, adverse events, and treatment drop-out.

Exclusion criteria: (1) Repeated publications; (2) Studies not including outcome indicators; (3) Articles that were case reports, abstracts, comments, letters, and reviews; (4) Studies that used cross-sectional, cohort, case-control, single-arm, and observational designs; and (5) Animal trials.

Literature quality evaluation

We used the Cochrane risk-of-bias tool for randomized controlled studies to evaluate the possibility of bias in specific studies. The risk of bias tool evaluates selection, performance, detection, attrition, and reporting indicators[16]. The risk of bias assessment resulted in each article were classified as "low risk of bias", "unclear", or "high risk of bias", and labeled as "+", "-", and "?". Two reviewers assessed the risk of bias separately. When disagreements emerged between the reviewers from the included studies, a consensus was reached through discussion.

Data extraction and consolidation

Two researchers independently retrieved the first author, sample size, publication date, study site, average age, diagnosis, frequency and intensity of intervention, drug dosage, duration of intervention, depression scale scores, remission rate, response rate, adverse events, and dropouts. Response rate was defined as a drop of 50% or more in depression score from baseline to the completion of therapy, and remission rate was defined for each study.

Statistical methods

We utilized Review Manager 5.3 and Stata 12.0 software for statistical analysis. We used odds ratio (OR) and 95% confidence interval (CI) as the effect size for dichotomous variables. We chose the standardized mean difference and 95%CI as the effect size for the continuous variables because of the differences in the scales used to assess PPD. The meta-analysis indicated significant differences at $P < 0.05$. The heterogeneity of the entries was evaluated using I^2 statistics. $I^2 <$ 50% was not considered significantly heterogeneous using a fixed-effects model. $I^2 > 50\%$ indicated significant heterogeneity; therefore, we used a random-effects model[17]. The sources of significant heterogeneity were investigated using subgroup analysis and univariate meta-regression. We performed a sensitivity analysis to test the stability of the results. Significant publication bias was indicated by $P < 0.05$.

RESULTS

Study selection

Totally 2262 records were retrieved through the search strategy, including PubMed (134), Embase (522), Cochrane Library (354), and Web of Science (1252; Figure 1). We removed 583 duplicate entries using Zotero. Then, the remaining articles were screened for titles and abstracts, and 1630 irrelevant entries were removed. After reading the remaining articles, 43 studies were eliminated because they did not meet the predetermined inclusion and exclusion criteria. Ultimately, six RCTs were chosen to synthesize data.

Characteristics of the study

This study included 168 patients with PPD, 87 in the BLT group and 81 in the control group, incorporating data from a total of six RCTs[18-23] published between 2004 and 2022. In this study, the test group was defined based on their use of the BLT for PPD. The light treatments ranged in intensity from 7000 to 10000 Lux, and all studies were performed in the morning. Daily treatments ranged from 30 minutes to 60 minutes, with treatment duration ranging 3 weeks to 6 weeks. The control group received DLT using dim lights < 1000 Lux. All studies used lightboxes. Tables 1 and 2 show the main features of the included trials.

Table 1 Essential features of the included research

Ref.	Location	Population		Age (years), mean ± SD	T/C (*n*)
Bais *et al*[18], 2020	Netherlands	Pregnant	DSM-V	T: 31.9 ± 4.4	33/34
				C: 31.9 ± 5.3	
Corral *et al*[20], 2007	Spain	Postnatal	DSM-IV; SIGH-SAD ≥ 15	T: 34.6 ± 4.0	5/10
				C: 33.6 ± 2.1	
Donmez *et al*[19], 2022	Marmara	Perinatal	DSM-V; EPDS ≥ 12	T: 29.73 ± 6.57	12/11
				C: 28 ± 3.8	
Epperson *et al*[21], 2004	United States	Pregnant	DSM-IV; SIGH-SAD ≥ 20	T: 32.1 ± 3.9	5/5
				C: 32.1 ± 3.9	
Garbazza *et al*[22], 2022	Multicenter	Perinatal	EPDS ≥ 12	T: 33	11/11
				C: 32	
Wirz-Justice *et al*[23], 2011	Italy and Switzerland	Pregnant	DSM-IV; EPDS ≥ 10	T: 31 ± 4.7	16/11
				C: 32.7 ± 5.4	

T: Treatment group; C: Control group; DSM: Diagnostic and statistical manual of mental disorders, fifth edition; SIGH-SAD: Structured interview guide for the Hamilton depression rating scale; EPDS: Edinburgh postnatal depression scale.

Table 2 Essential features of the included research

Ref.	Test group	Control group	Duration	Main evaluation scales
Bais *et al*[18]	9000 Lux	100 Lux	30 minutes/day, 6 weeks	EPDS; HAMD
Corral *et al*[20]	10000 Lux	600 Lux	30 minutes/day, 6 weeks	EPDS; SIGH-SAD
Donmez *et al*[19]	10000 Lux	< 500 Lux	45 minutes/day, 3 weeks	EPDS; HAMD; SIGH-SAD
Epperson *et al*[21]	7000 Lux	500 Lux	60 minutes/day, 5 weeks	EPDS; HAMD; SIGH-SAD
Garbazza *et al*[22]	10000 Lux	19 Lux	30 minutes/day, 6 weeks	EPDS
Wirz-Justice *et al*[23]	7000 Lux	70 Lux	60 minutes/day, 5 weeks	SIGH-SAD; HAMD

EPDS: Edinburgh postnatal depression scale; HAMD: Hamilton depression scale; SIGH-SAD: Structured interview guide for the Hamilton depression rating scale.

Evaluation of RCT quality

Figure 2 shows the risk of bias evaluation for the six RCTs, which had a low probability of bias overall. Six studies incorporated randomization into their design, and three outlined their randomization method (*i.e.*, random number table or computer randomization). Two provided detailed information on distribution concealment (*i.e.*, the use of envelopes or methods for keeping the shape of the machine identical in appearance). One study had its blinding disrupted, and the remaining 5 studies used double-blinding to avoid bias. Follow-up bias was observed in one study, and a low risk was observed in the other investigations. Four RCTs were broadly in line with the individual design of the study and had a low chance of reporting bias. Two did not mention if any bias was associated with the experimental design in question. All six studies were considered at low risk for other types of bias.

Meta-analysis results

Response rate: We investigated the six studies' treatment response rates, which were defined as a 50% or greater reduction in depression scores from baseline to treatment completion. The pooled data showed a statistically significant difference between the test and control groups (50.68% *vs* 33.08%; OR = 2.05, 95%CI: 1.25-3.35, P = 0.004, I^2 = 35%; Figure 3A).

Remission rate: Four RCTs reported the remission rates of depressive symptoms after the intervention, with remission being defined differently depending on each study's criteria. The results were statistically significant, with higher remission rates in the test group than in the control group (54.10% *vs* 18.52%; OR = 5.00, 95%CI: 2.09-11.99, P = 0.0003; I^2 = 0%; Figure 3B).

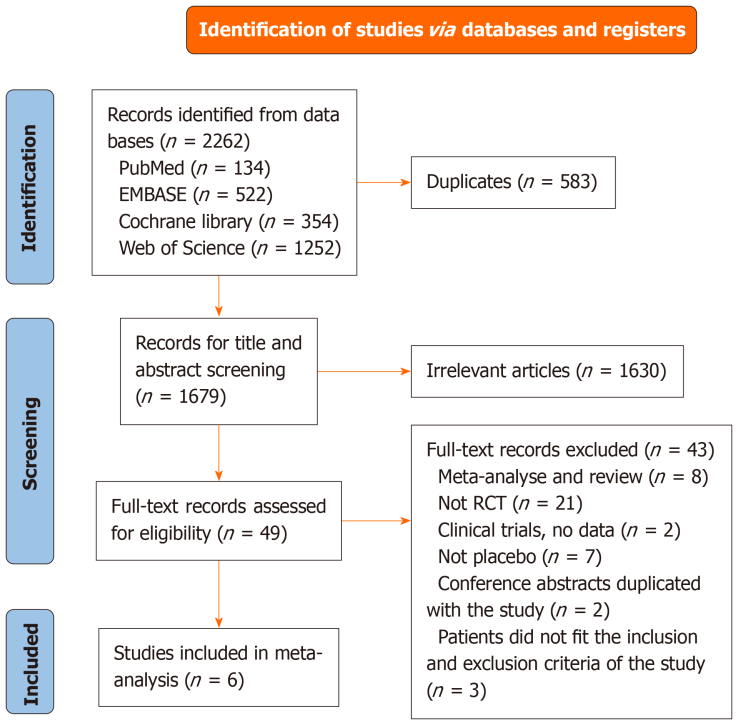


Figure 1 Flowchart for searching and screening literature. RCT: Randomized control trial.

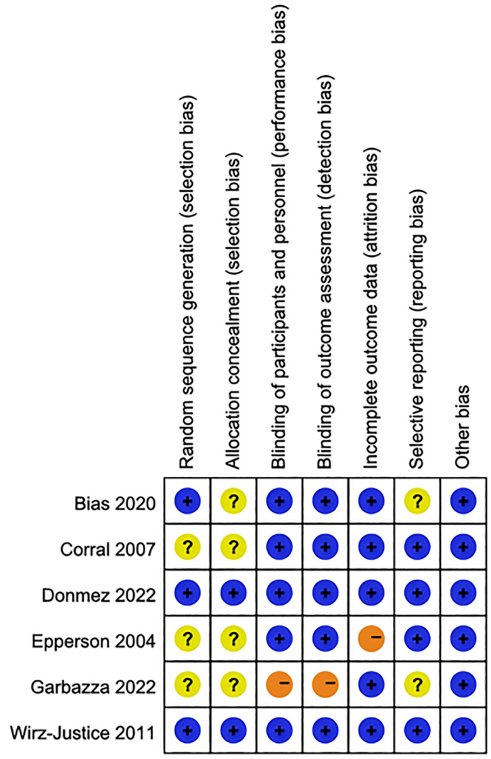


Figure 2 An overview of the methodological quality for included randomized control trials.

Improvements in depression score: Five studies investigated the efficacy of neuromodulation therapies for PPD, which were measured before and after treatment using the structured interview guide for the Hamilton depression rating scale, Edinburgh postnatal depression scale, or Hamilton depression scale. According to the pooled results (standardized mean difference = -0.47, 95%CI: -0.80 to -0.13, P = 0.007, I^2 = 0%), we used a fixed effects model (Figure 3C). The depression scores showed better overall efficacy against PPD in the neuromodulation group than did the control group.

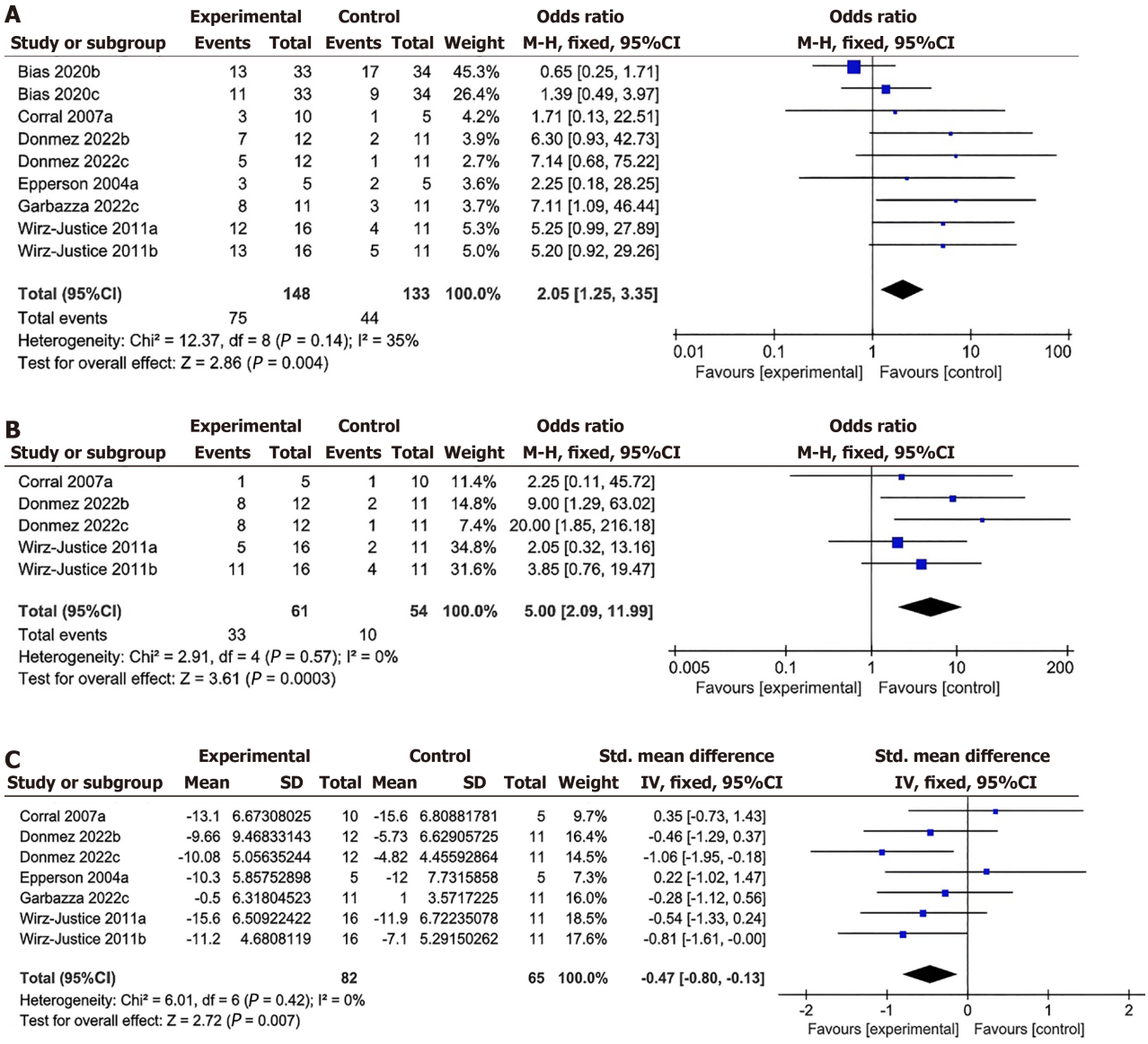


Figure 3 Meta-analysis results. A: Forest plot of response rate; B: Forest plot of remission rate; C: Forest plot of improvement in depression score. The a, b, and c represent the results of one test for Edinburgh postnatal depression scale, structured interview guide for the Hamilton depression rating scale, and Hamilton depression scale, respectively. CI: Confidence interval.

Incidence of adverse events: Two studies reported detailed data on the adverse effects (AEs). Four studies reported no AEs, including headaches, dizziness, sleep problems, nausea, and vomiting, with dizziness being the most common. The two groups in each article were analyzed by adding various adverse reaction times for each article. The combined findings of these two studies found no significant difference in AEs between the trial and control groups (17.89% *vs* 9.68%; OR = 2.01, 95%CI: 0.95-4.25, $P = 0.07$; $I^2 = 0\%$; Supplementary Figure 1).

Drop-outs: We observed no significant difference in drop-outs between the two groups (21.84% *vs* 29.63%; OR = 0.63, 95%CI: 0.31-1.29, $P = 0.21$; $I^2 = 0\%$; $n = 168$; Supplementary Figure 2).

Sensitivity analysis: We performed sensitivity analyses for the response rates, remission rates, and depression score improvement and found that the effect sizes for all studies were within the 95%CI of the total compound effect size, with the overall study results being reliable (Supplementary Figure 3). Our analysis of the PPD remission and response rates using a one-by-one exclusion method also showed that the overall study results were reliable.

Publication bias: Funnel plots were used to determine the remission rate, response rate, and depression score improvement (Supplementary Figure 4). Since this study included fewer than ten papers, Egger's analysis was not performed.

DISCUSSION

In the present meta-analysis, we found that BLT was effective in treating PPD. As we hypothesized, the response rates, remission rates, and depression score improvements in the test group significantly differed from the control group. The present study confirmed the efficacy of 7000-10000 Lux light therapy for PPD, while the corresponding low-intensity light treatment in the control groups showed a non-significant decrease in PPD-related depression scale scores. The 1250 Lux blue-enriched white light has also been shown to be effective in improving depression in postpartum women[24] in several single-arm evaluations[25-28]. However, owing to the limited number of studies and the small sample size in our meta-analysis, further collection of unpublished data is required to provide further support.

BLT for PPD remains a clinical challenge. Current guidelines recommend psychotherapy (*e.g.*, cognitive-behavioral therapy and interpersonal psychotherapy) for mild-to-moderate PPD and medication for severe PPD; however, these treatments have not achieved the desired results. Although some emerging interventions (*e.g.*, transcranial magnetic stimulation, transcranial direct current stimulation, and vagus nerve stimulation) are controversial, research has demonstrated the effectiveness of light therapy in treating PPD. However, some study results were inconsistent. One critical reason for this inconsistency is the small sample sizes of the studies or that they were conducted at a single research site, limiting the credibility of the statistical analysis. Many researchers have reported challenges in enrolling patients, resulting in the studies failing to achieve the expected sample size. However, no statistical differences between the two groups were found in terms of AEs, which were transient and disappeared shortly after treatment. We found no significant differences in the test groups' detachment rates compared to the rates in the control group, suggesting lower AEs or no effect on detachment in the test groups in women with PPD, in response to the better safety and acceptability of BLT.

Follow-up data and literature on prolonged interventions are not currently available. The longest BLT intervention among the studies in this meta-analysis was 10 weeks, and in this intervention, one participant developed hypomania, recovering after decreasing the daily intervention time. Some patients showed improvement without symptomatic relief after increasing their daily irradiation duration, suggesting that individualized treatment for light therapy improves the likelihood of its success[21]. Subgroup analysis of the length of intervention showed better efficacy for interventions lasting three and five weeks than six weeks, similar to previous results. Previous meta-analyses reported greater efficacy among interventions less than 6 weeks[29] or 2-3 weeks[15]. However, a regression analysis of existing literature reported a significant effect for BLT interventions lasting 10 weeks compared to 5 weeks on the mood of patients with PPD[21]. Subgroup analyses for intervention intensity showed that 7000 Lux interventions were more effective than 10000 Lux interventions, which was unexpected (Supplementary Table 2). The relationship between the length of each intervention, the timing of the intervention, and efficacy remains controversial, which may be related to the mechanism of light therapy also affecting mood through hormones due to its alteration of circadian rhythms *via* the eye-brain hormone regulatory pathway[30]. The mechanism of BLT has not been clarified, and further studies on the light information transduction pathways associated with depression are needed.

Light therapy is a non-invasive neuromodulation treatment showing promising results; however, other neuromodulation therapies have been used to treat PPD, with some showing positive effects. Transcranial magnetic stimulation treatment, which stimulates both the right and left dorsolateral prefrontal cortex, effectively improves depressive symptoms in patients with PPD[31-33]. Vigod *et al*[34] concluded that a randomized clinical trial of transcranial direct current stimulation treatment for depression during pregnancy was feasible. Similarly, a case-control study demonstrated the efficacy of electroconvulsive therapy to treat PPD[35], and several case reports and related studies have also reported the feasibility and safety of vagus nerve stimulation in treating PPD[36-39]. Unfortunately, few reliable RCTs are currently available. In addition, several clinical studies on neuromodulation therapies are actively in progress, and we plan to conduct large randomized controlled trials to comprehensively study the efficacy and safety of neuromodulation therapies, including phototherapy, for treating PPD.

Our study had a few limitations, we only included studies that recruited participants diagnosed with PPD who received either BLT or DLT interventions; therefore, the sample size for the meta-analysis was small. Further collection of relevant unpublished results is required to consolidate the results of the current analysis. Although we excluded higher-risk bias studies, other biases may still be present. Additionally, some studies included participants who were also being treated using pharmacotherapy, potentially affecting the results. Third, differences in the timing of BLT existed, but all the included studies showed low heterogeneity in the results; therefore, we did not analyze heterogeneity in this meta-analysis. Our sensitivity analysis suggested stable results.

CONCLUSION

BLT showed significant efficacy in treating PPD. While it was effective in reducing depression symptoms among women with PPD, BLT's long-term outcomes remain unclear. Currently, more randomized controlled trials are required to assess the effectiveness and safety of PPD interventions. In summary, BLT has great potential for treating PPD. Better results are available, which could expand the therapeutic options available to psychiatrists.

FOOTNOTES

Author contributions: Yang X contributed to the conceptualization, data curation, formal analysis, investigation and methodology of the study and the writing of the manuscript; Yang X and Gao YY contributed to the writing the manuscript, they contributed equally to this article, they are the co-first authors of this manuscript; Gao YY, Xu SQ, Wang JC, Ma YJ, and Jiao LH contributed to the investigation of the study; Wang L and Bashir S contributed to the investigation and formal analysis of the study; Wang XY contributed to the quality and professional revision; An CX and Wang R contributed to the conceptualization and funding acquisition of the study, they contributed equally to this article, they are the co-corresponding authors of this manuscript; Wang R contributed to the revision of the manuscript; and all authors thoroughly reviewed and endorsed the final manuscript.

Supported by the Hebei Province Natural Science Foundation, No. H2018206034 and No. H2022206544; Hebei Province clinical medicine outstanding personnel training project, No. ZF2024135.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: China

ORCID number: Yuan-Yuan Gao 0009-0007-2689-147X; Xue-Yi Wang 0000-0002-0798-2049; Ran Wang 0000-0003-1155-2102.

S-Editor: Bai Y
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 ACOG Committee Opinion No. 757: Screening for Perinatal Depression. *Obstet Gynecol* 2018; **132**: e208-e212 [PMID: 30629567 DOI: 10.1097/AOG.0000000000002927]
2 **Stuart-Parrigon K**, Stuart S. Perinatal depression: an update and overview. *Curr Psychiatry Rep* 2014; **16**: 468 [PMID: 25034859 DOI: 10.1007/s11920-014-0468-6]
3 **Gavin NI**, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol* 2005; **106**: 1071-1083 [PMID: 16260528 DOI: 10.1097/01.AOG.0000183597.31630.db]
4 **Nisar A**, Yin J, Waqas A, Bai X, Wang D, Rahman A, Li X. Prevalence of perinatal depression and its determinants in Mainland China: A systematic review and meta-analysis. *J Affect Disord* 2020; **277**: 1022-1037 [PMID: 33065811 DOI: 10.1016/j.jad.2020.07.046]
5 **Yim IS**, Tanner Stapleton LR, Guardino CM, Hahn-Holbrook J, Dunkel Schetter C. Biological and psychosocial predictors of postpartum depression: systematic review and call for integration. *Annu Rev Clin Psychol* 2015; **11**: 99-137 [PMID: 25822344 DOI: 10.1146/annurev-clinpsy-101414-020426]
6 **Simoncelli M**, Martin BZ, Bérard A. Antidepressant use during pregnancy: a critical systematic review of the literature. *Curr Drug Saf* 2010; **5**: 153-170 [PMID: 19534639 DOI: 10.2174/157488610790936114]
7 **Molenaar NM**, Kamperman AM, Boyce P, Bergink V. Guidelines on treatment of perinatal depression with antidepressants: An international review. *Aust N Z J Psychiatry* 2018; **52**: 320-327 [PMID: 29506399 DOI: 10.1177/0004867418762057]
8 **Ray S**, Stowe ZN. The use of antidepressant medication in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2014; **28**: 71-83 [PMID: 24211026 DOI: 10.1016/j.bpobgyn.2013.09.005]
9 **Kobylski LA**, Keller J, Molock SD, Le HN. Preventing perinatal suicide: an unmet public health need. *Lancet Public Health* 2023; **8**: e402 [PMID: 37244671 DOI: 10.1016/S2468-2667(23)00092-0]
10 **Spinelli MG**. Maternal infanticide associated with mental illness: prevention and the promise of saved lives. *Am J Psychiatry* 2004; **161**: 1548-1557 [PMID: 15337641 DOI: 10.1176/appi.ajp.161.9.1548]
11 **Jha MK**, Mathew SJ. Pharmacotherapies for Treatment-Resistant Depression: How Antipsychotics Fit in the Rapidly Evolving Therapeutic Landscape. *Am J Psychiatry* 2023; **180**: 190-199 [PMID: 36855876 DOI: 10.1176/appi.ajp.20230025]
12 **Cohen LS**, Wang B, Nonacs R, Viguera AC, Lemon EL, Freeman MP. Treatment of mood disorders during pregnancy and postpartum. *Psychiatr Clin North Am* 2010; **33**: 273-293 [PMID: 20385337 DOI: 10.1016/j.psc.2010.02.001]
13 **Huang L**, Xi Y, Peng Y, Yang Y, Huang X, Fu Y, Tao Q, Xiao J, Yuan T, An K, Zhao H, Pu M, Xu F, Xue T, Luo M, So KF, Ren C. A Visual Circuit Related to Habenula Underlies the Antidepressive Effects of Light Therapy. *Neuron* 2019; **102**: 128-142.e8 [PMID: 30795900 DOI: 10.1016/j.neuron.2019.01.037]
14 **Huang X**, Tao Q, Ren C. A Comprehensive Overview of the Neural Mechanisms of Light Therapy. *Neurosci Bull* 2024; **40**: 350-362 [PMID: 37555919 DOI: 10.1007/s12264-023-01089-8]
15 **Li X**, Fang L, Guan L, Zhang J, Zheng M, Zhu D. The effects of light therapy on depression and sleep in women during pregnancy or the postpartum period: A systematic review and meta-analysis. *Brain Behav* 2023; **13**: e3339 [PMID: 38031199 DOI: 10.1002/brb3.3339]
16 **Higgins JP**, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**:

d5928 [PMID: 22008217 DOI: 10.1136/bmj.d5928]
17 **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560 [PMID: 12958120 DOI: 10.1136/bmj.327.7414.557]
18 **Bais B**, Kamperman AM, Bijma HH, Hoogendijk WJ, Souman JL, Knijff E, Lambregtse-van den Berg MP. Effects of bright light therapy for depression during pregnancy: a randomised, double-blind controlled trial. *BMJ Open* 2020; **10**: e038030 [PMID: 33115894 DOI: 10.1136/bmjopen-2020-038030]
19 **Donmez M**, Yorguner N, Kora K, Topcuoglu V. Efficacy of bright light therapy in perinatal depression: A randomized, double-blind, placebo-controlled study. *J Psychiatr Res* 2022; **149**: 315-322 [PMID: 35339911 DOI: 10.1016/j.jpsychires.2022.02.027]
20 **Corral M**, Wardrop AA, Zhang H, Grewal AK, Patton S. Morning light therapy for postpartum depression. *Arch Womens Ment Health* 2007; **10**: 221-224 [PMID: 17701271 DOI: 10.1007/s00737-007-0200-1]
21 **Epperson CN**, Terman M, Terman JS, Hanusa BH, Oren DA, Peindl KS, Wisner KL. Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. *J Clin Psychiatry* 2004; **65**: 421-425 [PMID: 15096083 DOI: 10.4088/jcp.v65n0319]
22 **Garbazza C**, Cirignotta F, D'Agostino A, Cicolin A, Hackethal S, Wirz-Justice A, Cajochen C, Manconi M; "Life-ON" study group. Sustained remission from perinatal depression after bright light therapy: A pilot randomised, placebo-controlled trial. *Acta Psychiatr Scand* 2022; **146**: 350-356 [PMID: 35876837 DOI: 10.1111/acps.13482]
23 **Wirz-Justice A**, Bader A, Frisch U, Stieglitz RD, Alder J, Bitzer J, Hösli I, Jazbec S, Benedetti F, Terman M, Wisner KL, Riecher-Rössler A. A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. *J Clin Psychiatry* 2011; **72**: 986-993 [PMID: 21535997 DOI: 10.4088/JCP.10m06188blu]
24 **Verma S**, Quin N, Astbury L, Wellecke C, Wiley JF, Davey M, Rajaratnam SMW, Bei B. Treating postpartum insomnia: a three arm randomised controlled trial of cognitive behavioural therapy and light dark therapy. *Psychol Med* 2023; **53**: 5459-5469 [PMID: 36082412 DOI: 10.1017/S0033291722002616]
25 **Swanson LM**, Burgess HJ, Zollars J, Todd Arnedt J. An open-label pilot study of a home wearable light therapy device for postpartum depression. *Arch Womens Ment Health* 2018; **21**: 583-586 [PMID: 29603017 DOI: 10.1007/s00737-018-0836-z]
26 **Oren DA**, Wisner KL, Spinelli M, Epperson CN, Peindl KS, Terman JS, Terman M. An open trial of morning light therapy for treatment of antepartum depression. *Am J Psychiatry* 2002; **159**: 666-669 [PMID: 11925310 DOI: 10.1176/appi.ajp.159.4.666]
27 **Krzystanek M**, Krupka-Matuszczyk I. [Bright light therapy in pregnant women depression--3 case studies]. *Psychiatr Pol* 2006; **40**: 261-267 [PMID: 17037101]
28 Abstracts of the 23rd Congress of the European Sleep Research Society, 13-16 September 2016, Bologna, Italy. *J Sleep Res* 2016; **25** Suppl 1: 5-376 [PMID: 27570188 DOI: 10.1111/jsr.12446]
29 **Mårtensson B**, Pettersson A, Berglund L, Ekselius L. Bright white light therapy in depression: A critical review of the evidence. *J Affect Disord* 2015; **182**: 1-7 [PMID: 25942575 DOI: 10.1016/j.jad.2015.04.013]
30 **Cui L**, Li S, Wang S, Wu X, Liu Y, Yu W, Wang Y, Tang Y, Xia M, Li B. Major depressive disorder: hypothesis, mechanism, prevention and treatment. *Signal Transduct Target Ther* 2024; **9**: 30 [PMID: 38331979 DOI: 10.1038/s41392-024-01738-y]
31 **Myczkowski ML**, Dias AM, Luvisotto T, Arnaut D, Bellini BB, Mansur CG, Rennó J, Tortella G, Ribeiro PL, Marcolin MA. Effects of repetitive transcranial magnetic stimulation on clinical, social, and cognitive performance in postpartum depression. *Neuropsychiatr Dis Treat* 2012; **8**: 491-500 [PMID: 23118543 DOI: 10.2147/NDT.S33851]
32 **Kim DR**, Epperson N, Paré E, Gonzalez JM, Parry S, Thase ME, Cristancho P, Sammel MD, O'Reardon JP. An open label pilot study of transcranial magnetic stimulation for pregnant women with major depressive disorder. *J Womens Health (Larchmt)* 2011; **20**: 255-261 [PMID: 21314450 DOI: 10.1089/jwh.2010.2353]
33 **Kim DR**, Wang E, McGeehan B, Snell J, Ewing G, Iannelli C, O'Reardon JP, Sammel MD, Epperson CN. Randomized controlled trial of transcranial magnetic stimulation in pregnant women with major depressive disorder. *Brain Stimul* 2019; **12**: 96-102 [PMID: 30249416 DOI: 10.1016/j.brs.2018.09.005]
34 **Vigod SN**, Murphy KE, Dennis CL, Oberlander TF, Ray JG, Daskalakis ZJ, Blumberger DM. Transcranial direct current stimulation (tDCS) for depression in pregnancy: A pilot randomized controlled trial. *Brain Stimul* 2019; **12**: 1475-1483 [PMID: 31257092 DOI: 10.1016/j.brs.2019.06.019]
35 **Haxton C**, Kelly S, Young D, Cantwell R. The Efficacy of Electroconvulsive Therapy in a Perinatal Population: A Comparative Pilot Study. *J ECT* 2016; **32**: 113-115 [PMID: 26479488 DOI: 10.1097/YCT.0000000000000278]
36 **Deligiannidis KM**, Robakis T, Homitsky SC, Ibroci E, King B, Jacob S, Coppola D, Raines S, Alataris K. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder with peripartum onset: A multicenter, open-label, controlled proof-of-concept clinical trial (DELOS-1). *J Affect Disord* 2022; **316**: 34-41 [PMID: 35932937 DOI: 10.1016/j.jad.2022.07.068]
37 **Ding J**, Wang L, Wang C, Gao C, Wang F, Sun T. Is vagal-nerve stimulation safe during pregnancy? A mini review. *Epilepsy Res* 2021; **174**: 106671 [PMID: 34022523 DOI: 10.1016/j.eplepsyres.2021.106671]
38 **Husain MM**, Stegman D, Trevino K. Pregnancy and delivery while receiving vagus nerve stimulation for the treatment of major depression: a case report. *Ann Gen Psychiatry* 2005; **4**: 16 [PMID: 16168055 DOI: 10.1186/1744-859X-4-16]
39 **Salerno G**, Passamonti C, Cecchi A, Zamponi N. Vagus nerve stimulation during pregnancy: an instructive case. *Childs Nerv Syst* 2016; **32**: 209-211 [PMID: 26350804 DOI: 10.1007/s00381-015-2897-x]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2025 March 18; 13(1): 101187

DOI: 10.13105/wjma.v13.i1.101187

ISSN 2308-3840 (online)

META-ANALYSIS

Incidence of luminal gastrointestinal cancers in patients with cirrhosis: A systematic review and meta-analysis

Manisha Jogendran, Kai Zhu, Rohit Jogendran, Nasruddin Sabrie, Trana Hussaini, Eric M Yoshida, Daljeet Chahal

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade D
Novelty: Grade C
Creativity or Innovation: Grade D
Scientific Significance: Grade C

P-Reviewer: Cerwenka H

Received: September 6, 2024
Revised: October 26, 2024
Accepted: December 12, 2024
Published online: March 18, 2025
Processing time: 188 Days and 11.3 Hours

Manisha Jogendran, Department of Medicine, Queens's University, Kingston K7L 2V7, ON, Canada

Kai Zhu, Department of Medicine, University of British Columbia, Vancouver 317-2194, BC, Canada

Rohit Jogendran, Nasruddin Sabrie, Department of Medicine, University of Toronto, Toronto 1 King's College Cir M5S 3H2, ON, Canada

Trana Hussaini, BC Liver Transplant Program, Vancouver General Hospital, Vancouver V5Z 1M9, BC, Canada

Eric M Yoshida, Daljeet Chahal, Department of Gastroenterology, University of British Columbia, Vancouver V5Z 1M9, BC, Canada

Co-corresponding authors: Manisha Jogendran and Daljeet Chahal.

Corresponding author: Manisha Jogendran, MD, Doctor, Department of Medicine, Queens's University, 76 Stuart Street, Kingston K7L 2V7, ON, Canada. 13mj5@queensu.ca

Abstract

BACKGROUND

The global incidence of cirrhosis and luminal gastrointestinal cancers are increasing. It is unknown if cirrhosis itself is a predisposing factor for luminal gastrointestinal cancer. Such an association would have significant clinical implications, particularly for cancer screening prior to liver transplantation.

AIM

To investigate the incidence of luminal gastrointestinal cancers in patients with underlying cirrhosis.

METHODS

An electronic search was conducted to study the incidence of luminal gastrointestinal cancers in patients with cirrhosis. Study-specific standardized incidence ratios (SIR) along with corresponding 95%CI for both overall cancer incidence and luminal cancer incidence were analyzed using a random-effects model. Subgroup analysis was performed based on cirrhosis etiology and location of luminal malignancy.

RESULTS
We identified 5054 articles; 4 studies were selected for data extraction. The overall incidence of all cancers was significantly higher in patients with cirrhosis, with an SIR of 2.79 (95%CI: 2.18–3.57). When stratified by cirrhosis etiology, the incidence of luminal cancers remained significantly elevated for alcohol (SIR = 3.13, 95%CI: 2.24–4.39), Primary Biliary Cholangitis (SIR = 1.40, 95%CI: 1.10–1.79), and unspecified cirrhosis (SIR = 3.52, 95%CI: 1.87–6.65).

CONCLUSION
The incidence of luminal gastrointestinal cancer is increased amongst patients with cirrhosis. Oral cavity, pharyngeal and esophageal cancer had increased incidence across all cirrhosis etiologies compared to gastric and colorectal cancer. Therefore, increased screening of luminal cancers, and in particular these upper luminal tract subtypes, should be considered in this population.

Key Words: Liver disease; Cancer epidemiology; Cirrhosis

Core Tip: Very limited data remains studying the association between luminal gastrointestinal cancers and cirrhosis. We showed that overall incidence of gastrointestinal cancers is higher in patients with cirrhosis. Alcohol related cirrhosis had the highest incidence of oral and pharyngeal cancer. Primary biliary cirrhosis did not demonstrate higher incidence of cancer sites.

Citation: Jogendran M, Zhu K, Jogendran R, Sabrie N, Hussaini T, Yoshida EM, Chahal D. Incidence of luminal gastrointestinal cancers in patients with cirrhosis: A systematic review and meta-analysis. *World J Meta-Anal* 2025; 13(1): 101187
URL: https://www.wjgnet.com/2308-3840/full/v13/i1/101187.htm
DOI: https://dx.doi.org/10.13105/wjma.v13.i1.101187

INTRODUCTION

The global incidence of cirrhosis is rising, paralleled by a growing number of patients with gastrointestinal cancers[1,2]. Notably, patients with gastrointestinal cancer may also have underlying cirrhosis[3,4]. The presence of cirrhosis complicates the management of patients with malignancy, potentially limiting both surgical and chemotherapeutic options due to concerns regarding increased peri-operative hepatic decompensation and hepatotoxicity[5,6]. Importantly, the presence of malignancy would detrimentally impact post liver transplant outcomes, and if detected during transplant assessment, may exclude patients from liver transplantation altogether[7].

While it is widely acknowledged that liver cirrhosis is associated with heightened susceptibility to hepatocellular carcinoma (HCC), there are limited data regarding the incidence of extrahepatic cancers in cirrhosis. As such, we have herein conducted a systematic review and meta-analysis to investigate the incidence of luminal gastrointestinal cancers in patients with underlying cirrhosis.

MATERIALS AND METHODS

Search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. An electronic search of EMBASE (1974–present), MEDLINE (1946–present), EBM Reviews–Cochrane Central Register of Controlled Trials (1946–present) and EBM Reviews–Cochrane Database of Systematic Reviews (2005–present) was conducted to study the incidence of gastrointestinal cancer in cirrhosis. The MeSH searched were "cirrhosis" AND "esophageal cancer" OR "colon cancer" OR "gastric cancer" OR "small bowel cancer" OR "rectal cancer" OR "oropharyngeal cancer". From these initially selected articles, the references were analyzed to identify additional relevant articles. Please refer to our appendix documents for full details regarding our search strategy.

Study selection

Three investigators (Jogendran M, Jogendran R, Sabrie N) conducted the initial screen by independently reviewing study titles and abstracts to identify full text studies examining the incidence of luminal gastrointestinal cancers in patients with cirrhosis. Only studies in English were used in this systematic review. Those that met the criteria were reviewed in full. Disagreements between reviewers were resolved through consensus.

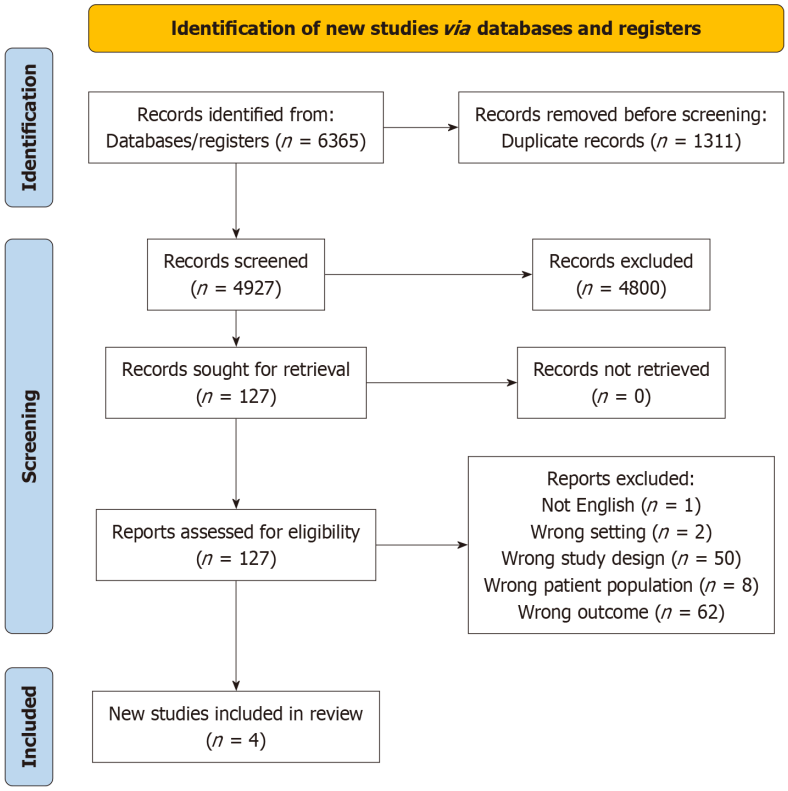


Figure 1 PRISMA flow chart.

Data extraction

Two investigators (Jogendran M, Jogendran R) extracted and tabulated the following data: (1) Study characteristics (title, author, location, type of study, region, study period); (2) Cause of cirrhosis; (3) Demographics (gender and age); and (4) Cancer characteristics [number of cancers, standardized incidence ratio (SIR), and mean follow-up years]. The primary outcome assessed was the incidence of gastrointestinal cancers.

Data synthesis and analysis

Study-specific SIRs along with their corresponding 95%CI for both overall cancer incidence and luminal cancer incidence were synthesized using a random-effects model. We employed the DerSimonian and Laird random-effects model due to expected clinical and methodological diversity among the included studies. The relative weight of each study was determined through generic inverse-variance weighting. However, due to the limited number of included studies, we did not generate a funnel plot to assess publication bias. For a subgroup analysis of the association between cirrhosis and luminal malignancy, we stratified patients based on their cirrhosis etiology, which included alcohol related liver disease, PBC, or unspecified causes. Furthermore, luminal malignancy was further sub-grouped, where reported, into oral cavity and pharynx, esophageal, stomach, and colorectal cancer.

Statistical heterogeneity was assessed using Cochran's Q statistic and I^2 statistic, where $P < 0.10$ and $I^2 > 50\%$ were considered significant indicators of heterogeneity. The significance level for all other statistical tests was set at $P < 0.05$. RevMan version 5.4 (Copenhagen, Denmark) was used for all statistical analyses

RESULTS

Search results

The search strategy identified 5054 articles after duplicates were removed, 4927 were excluded after examining the title and abstract. Full text review of 127 papers was then undertaken. Of these, 4 studies were selected for data extraction. Studies were excluded for various reasons, including being reviews, case reports, wrong outcomes, wrong patient population and not being in the English language (Figure 1). All studies were retrospective studies and conducted in European countries[8-11].

Study characteristics

The study characteristics of the included summaries are outlined in Table 1. A total of 23877 patients were included, comprising 16722 patients with alcohol related cirrhosis, 744 with primary biliary cholangitis (PBC) cirrhosis, 1690 with chronic hepatitis cirrhosis, and 4721 with unspecified cirrhosis. The studies were conducted in Europe, including Finland,

Table 1 Study characteristics of included studies, *n* (%)

Ref.	Study years	Country	Patient population	Sex, female	Age, mean years	Mean follow-up (years)
Sahlman *et al* [8]	1996-2012	Finland	Alcohol related cirrhosis: 7746 (65). Alcoholic hepatitis: 4127 (35)	3077 (26)	N/A	2.9
Kalaitzakis *et al*[9]	1994-2005	Sweden	Alcohol related cirrhosis: 492 (48). Non-specified cirrhosis: 527 (52)	323 (32)	52 (12)	3.3
Goldacre *et al* [10]	1963-1999	England	Alcohol related cirrhosis: 1319 PBC; cirrhosis: 424; non-specified cirrhosis: 1764. Alcohol related cirrhosis: 7165 (62). PBC cirrhosis: 320 (3). Chronic hepatitis cirrhosis: 1690 (14)	1603 (46)	N/A	N/A
Sorensen *et al* [11]	1977-1989	Denmark	Non-specified cirrhosis: 2430 (21)	4547 (39)	N/A	6.4

PBC: Primary biliary cholangitis; N/A: Not applicable.

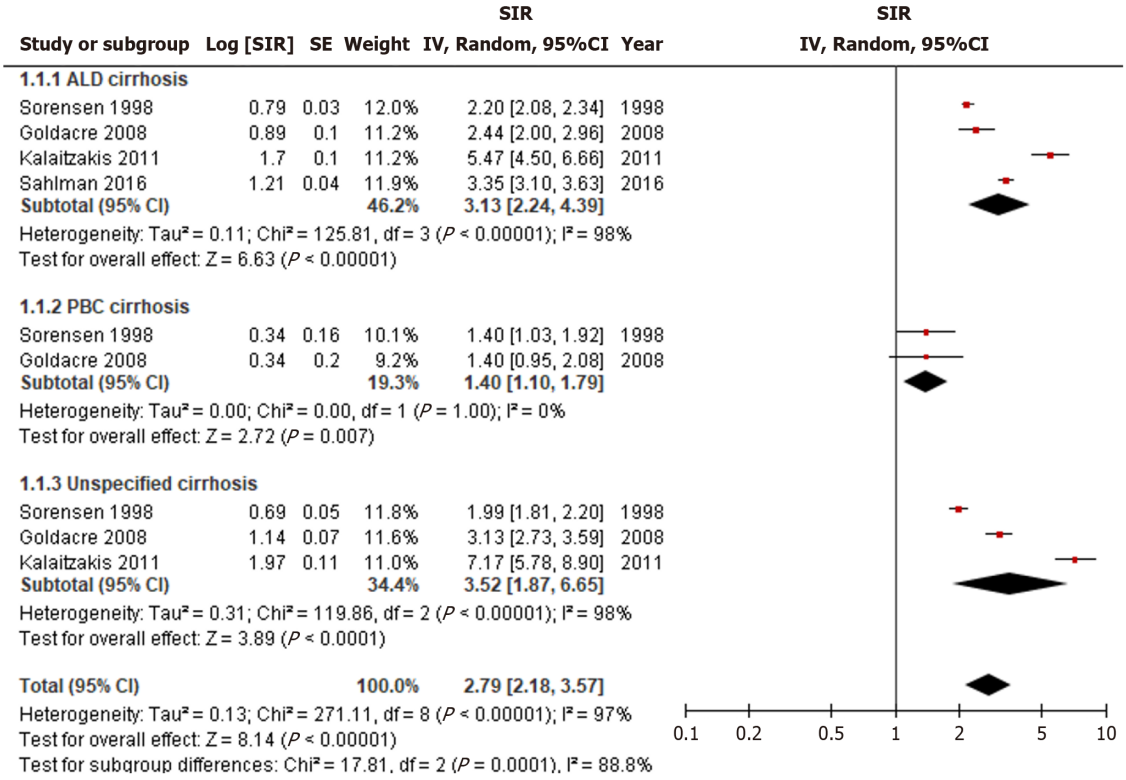


Figure 2 Forest plots of standardized incidence ratio for overall cancer risk in patients with cirrhosis. SIR: Standardized incidence ratio; ALD: Alcoholic liver disease; PBC: Primary biliary cholangitis.

Sweden, England, and Denmark. The study durations ranged from 11 to 36 years, with a mean of 16.6 years.

Cirrhosis and overall risk of cancer

The overall incidence of all cancers was significantly higher in patients with cirrhosis, with a significant SIR of 2.79 (95%CI: 2.18-3.57, I^2 = 97%) (Figure 2). When stratified by cirrhosis etiology, the incidence of all cancers remained significantly elevated for alcohol related (SIR = 3.13, 95%CI: 2.24-4.39, I^2 = 98%), PBC (SIR = 1.40, 95%CI: 1.10-1.79, I^2 = 0%), and unspecified cirrhosis (SIR = 3.52, 95%CI: 1.87-6.65, I^2 = 98%). Unspecified cirrhosis had the greatest overall cancer risk followed by alcohol related cirrhosis, and PBC cirrhosis (P < 0.01). High heterogeneity was observed and persisted even after conducting subgroup analyses based on cirrhosis etiology.

Alcohol related cirrhosis and risk of luminal cancer

Alcohol related cirrhosis was significantly associated with an increased incidence of luminal cancers (SIR = 4.39, 95%CI: 2.84-6.78, I^2 = 92%) (Figure 3). Specifically, the highest incidence was observed for oral cavity and pharyngeal cancer (SIR = 10.44, 95%CI: 8.90-12.24, I^2 = 0%), followed by esophageal cancer (SIR = 7.85, 95%CI: 4.98-12.36, I^2 = 45%), and colorectal

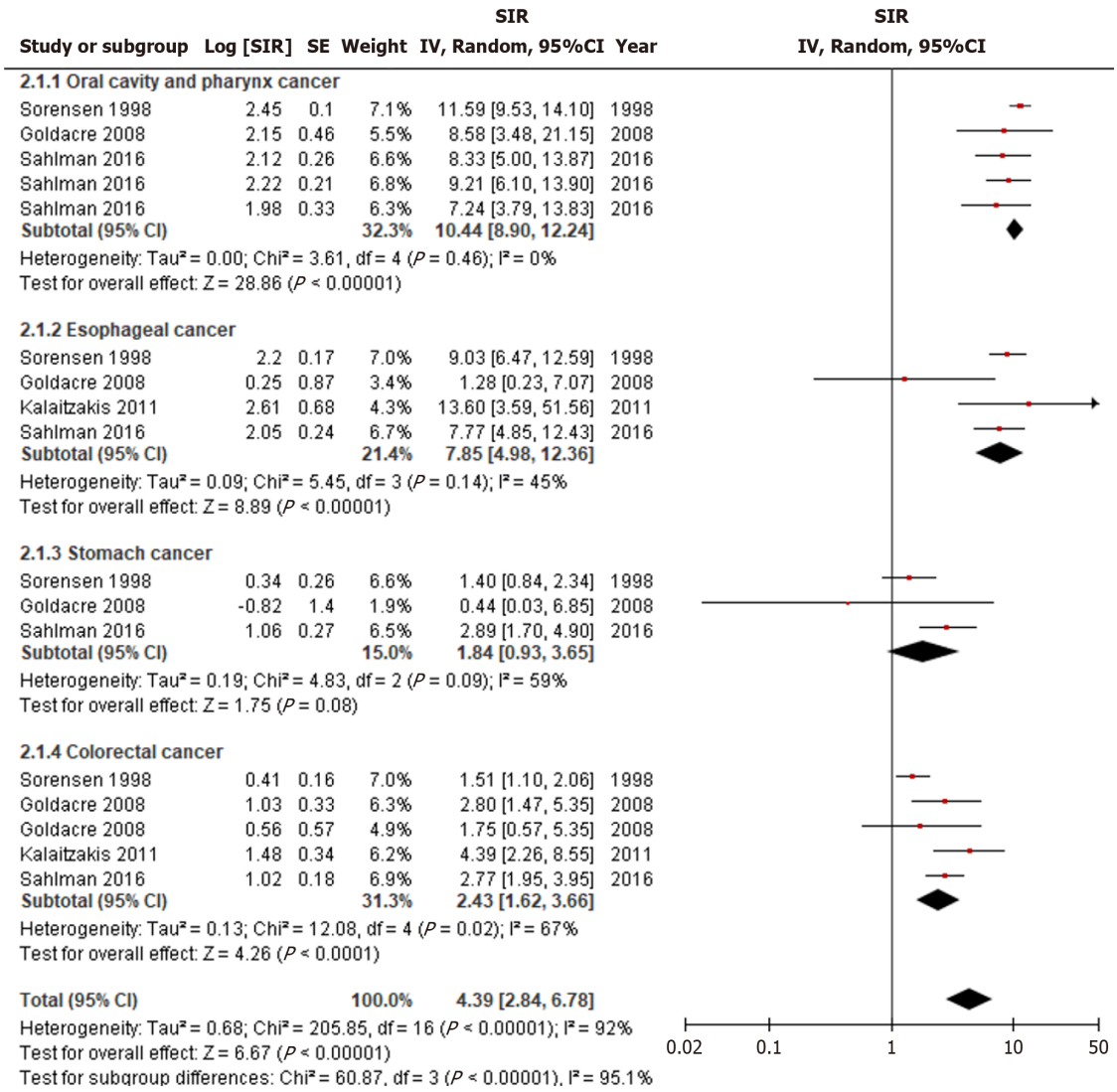


Figure 3 Forest plots of standardized incidence ratio for luminal cancer risk in patients with alcoholic cirrhosis. SIR: Standardized incidence ratio.

cancer (SIR = 2.43, 95%CI: 1.62-3.66, I^2 = 67%) (P < 0.01). The incidence of gastric cancer was not significantly associated with alcohol related cirrhosis (SIR = 1.84, 95%CI: 0.93-3.65, I^2 = 59%). Heterogeneity was less pronounced when subgrouped according to the etiology of luminal cancer, but significant differences remained for the stomach and colorectal cancer subgroups.

PBC cirrhosis and risk of luminal cancer

PBC cirrhosis is significantly associated with an increased incidence of luminal cancers (SIR = 2.11, 95%CI: 1.10-4.04, I^2 = 0%) (Figure 4). However, subgroup analysis did not reveal a significant association with the incidence of any subgroups, including esophageal, stomach, or colorectal cancer. There was no significant statistical heterogeneity among the studies.

Unspecified cirrhosis and risk of luminal cancer

Unspecified cirrhosis was significantly linked to an increased incidence of luminal cancers (SIR = 2.60, 95%CI: 1.65-4.09, I^2 = 78%) (Figure 5). Risk of oral cavity and pharynx cancers (SIR = 4.75, 95%CI: 2.18-10.33, I^2 = 37%) were greatest, followed by esophageal (SIR = 4.52, 95%CI: 1.57-2.99, I^2 = 73%), stomach (SIR = 2.12, 95%CI: 1.31-3.42, I^2 = 0%), and colorectal cancer (SIR = 1.57, 95%CI: 1.14-2.16, I^2 = 0%) (P = 0.03). When stratified by luminal cancer subgroups, only esophageal cancer exhibited statistical heterogeneity, while the others did not.

DISCUSSION

The association between cirrhosis and HCC is well-established[12,13]. Patients diagnosed with cirrhosis undergo routine HCC screening due to increased cancer risk[14]. However, screening remains limited for luminal gastrointestinal cancers in this patient population[15]. Given the growing literature, it is crucial to systematically evaluate the possibility of

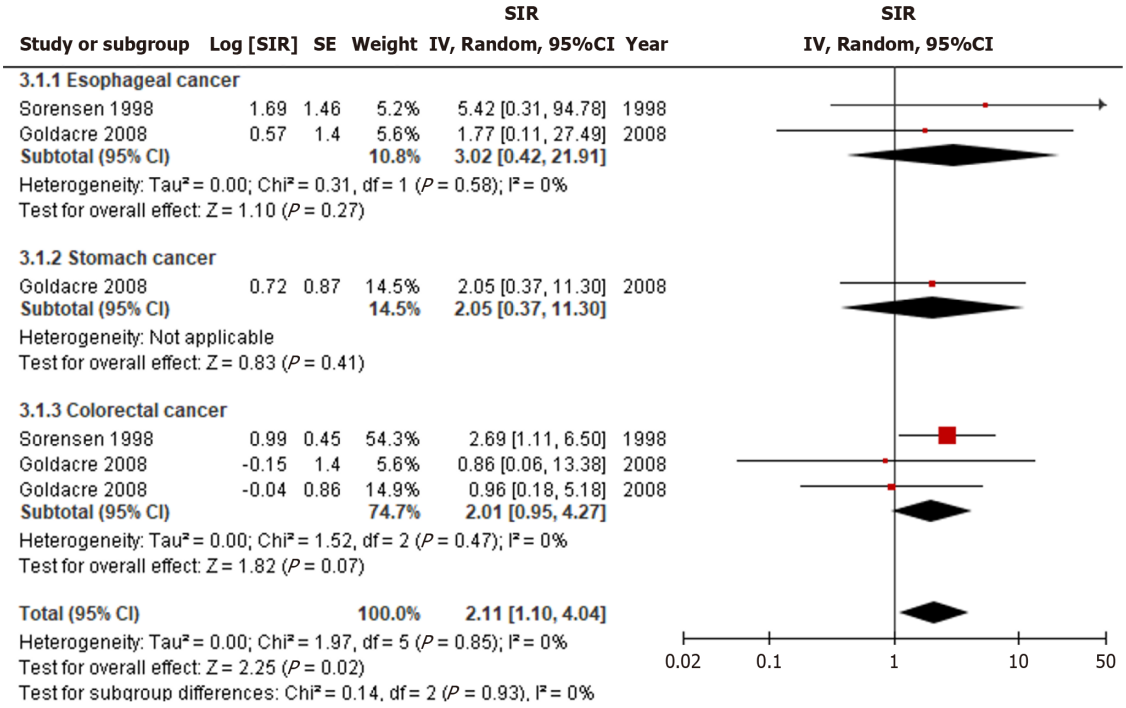


Figure 4 Forest plots of standardized incidence ratio for luminal cancer risk in patients with primary biliary cholangitis cirrhosis. SIR: Standardized incidence ratio.

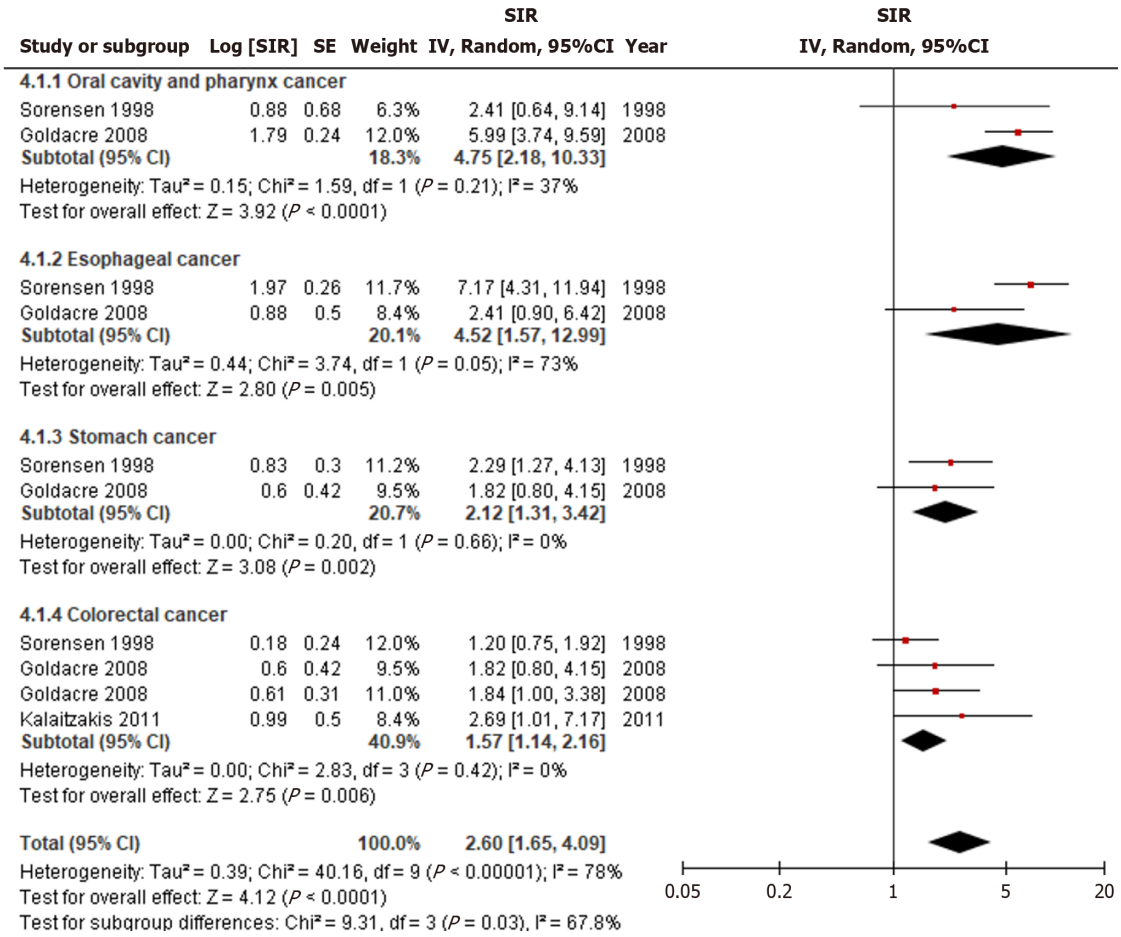


Figure 5 Forest plots of standardized incidence ratio for luminal cancer risk in patients with non-specified cirrhosis. SIR: Standardized incidence ratio.

increased risk of developing luminal gastrointestinal cancers in cirrhosis patients, considering both the etiology of cirrhosis and the specific sites of gastrointestinal cancer. Our meta-analysis incorporated four studies and revealed that the overall incidence of all luminal gastrointestinal cancers was higher in patients with cirrhosis. Notably, alcohol related cirrhosis exhibited the highest incidence of oral and pharyngeal cancer, followed by esophageal and colorectal cancer. On the other hand, PBC did not demonstrate a significantly higher incidence within the specified cancer site subgroups. However, our study had high heterogeneity in our analysis which may limit the validity of these findings.

Prior studies have demonstrated similar findings to our review. For instance, Zullo *et al*[16] concluded a 2.6-fold increase in the prevalence of gastric cancer among individuals with cirrhosis. Additionally, a study led by Pan *et al*[17], encompassing 1391165 admissions for gastrointestinal malignancies, found that 81.7% of cirrhosis cases were associated with HCC, 8.1% with pancreatic cancer, and 5.7% with colorectal cancer. Patients with cirrhosis also exhibited a higher mortality risk, possibly attributed to limited treatment options due to underlying cirrhosis[17]. The increase in cirrhosis and luminal gastrointestinal cancers may be related to shared risk factors between certain gastrointestinal cancers and cirrhosis, such as alcohol and tobacco use. It is also hypothesized that gastric erosive ulcers, congestive gastropathy, zinc deficiency, and alterations in gastrointestinal microbiota, which are all features of cirrhosis, can be associated with malignancy[3].

Despite employing a systematic review and meta-analysis methodology there remain inherent limitations to this study. Our meta-analysis primarily included a diverse range of patients from various study designs, which could potentially impact the interpretation of our results. Moreover, our study primarily focused on a European population, and the findings may not be directly applicable to other regions. Furthermore, the underlying causes of cirrhosis varied, encompassing alcohol related, PBC, and unspecified aetiologies. This lack of specificity in the unspecified group presents a challenge, as it makes it difficult to discern the exact aetiologies within this category. There may be cases that overlap with alcohol related and PBC-related cirrhosis. Ideally, future retrospective or prospective studies should incorporate standardized data on covariates. Finally, all studies included were retrospective in nature. Prospective cohort studies evaluating the incidence of luminal gastrointestinal malignancy in patients with cirrhosis may be of use in the future.

CONCLUSION

In conclusion, our analysis demonstrated a significant increase in luminal gastrointestinal cancers in patients with cirrhosis in comparison to the general population. As such, we believe that screening for luminal gastrointestinal cancers may be needed for patients with cirrhosis. Screening for oropharyngeal malignancy may be of importance during assessment for liver transplantation, particularly in patients with alcohol related disease. Comprehensive, long-term studies will be necessary for potential redevelopment of screening guidelines including, esophageal and oropharyngeal screening.

FOOTNOTES

Author contributions: Jogendran M, Chahal D designed the research study; Jogendran M, Zhu K, Sabrie N, Jogendran R performed the research; Chahal D, Hussaini T, Yoshida EM contributed new reagents and analytic tools; Jogendran M and Zhu K analyzed the data and wrote the manuscript. All authors have read and approved the final manuscript.

Conflict-of-interest statement: All authors have no conflict-of-interest to declare.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: Canada

ORCID number: Manisha Jogendran 0009-0001-1866-1152; Trana Hussaini 0000-0002-6463-6847; Eric M Yoshida 0000-0003-2910-7461; Daljeet Chahal 0000-0003-2486-1449.

Corresponding Author's Membership in Professional Societies: Canadian Association of Gastroenterology, 5520.

S-Editor: Liu H
L-Editor: A
P-Editor: Zheng XM

REFERENCES

1 **Huang DQ**, Terrault NA, Tacke F, Gluud LL, Arrese M, Bugianesi E, Loomba R. Global epidemiology of cirrhosis - aetiology, trends and predictions. *Nat Rev Gastroenterol Hepatol* 2023; **20**: 388-398 [PMID: 36977794 DOI: 10.1038/s41575-023-00759-2]

2 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

3 **Jeng KS**, Chang CF, Sheen IS, Jeng CJ, Wang CH. Upper Gastrointestinal Cancer and Liver Cirrhosis. *Cancers (Basel)* 2022; **14** [PMID: 35565397 DOI: 10.3390/cancers14092269]

4 **Pinter M**, Trauner M, Peck-Radosavljevic M, Sieghart W. Cancer and liver cirrhosis: implications on prognosis and management. *ESMO Open* 2016; **1**: e000042 [PMID: 27843598 DOI: 10.1136/esmoopen-2016-000042]

5 **Kaltenbach MG**, Mahmud N. Assessing the risk of surgery in patients with cirrhosis. *Hepatol Commun* 2023; **7** [PMID: 36996004 DOI: 10.1097/HC9.0000000000000086]

6 **Friedman LS**. Surgery in the patient with liver disease. *Trans Am Clin Climatol Assoc* 2010; **121**: 192-204; discussion 205 [PMID: 20697561]

7 **Benkö T**, Hoyer DP, Saner FH, Treckmann JW, Paul A, Radunz S. Liver Transplantation From Donors With a History of Malignancy: A Single-Center Experience. *Transplant Direct* 2017; **3**: e224 [PMID: 29184912 DOI: 10.1097/TXD.0000000000000738]

8 **Sahlman P**, Nissinen M, Pukkala E, Färkkilä M. Incidence, survival and cause-specific mortality in alcoholic liver disease: a population-based cohort study. *Scand J Gastroenterol* 2016; **51**: 961-966 [PMID: 27181618 DOI: 10.3109/00365521.2016.1157889]

9 **Kalaitzakis E**, Gunnarsdottir SA, Josefsson A, Björnsson E. Increased risk for malignant neoplasms among patients with cirrhosis. *Clin Gastroenterol Hepatol* 2011; **9**: 168-174 [PMID: 21029788 DOI: 10.1016/j.cgh.2010.10.014]

10 **Goldacre MJ**, Wotton CJ, Yeates D, Seagroatt V, Collier J. Liver cirrhosis, other liver diseases, pancreatitis and subsequent cancer: record linkage study. *Eur J Gastroenterol Hepatol* 2008; **20**: 384-392 [PMID: 18403939 DOI: 10.1097/MEG.0b013e3282f4489f]

11 **Sorensen HT**, Friis S, Olsen JH, Thulstrup AM, Mellemkjaer L, Linet M, Trichopoulos D, Vilstrup H, Olsen J. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. *Hepatology* 1998; **28**: 921-925 [PMID: 9755226 DOI: 10.1002/hep.510280404]

12 **Llovet JM**, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, Lencioni R, Koike K, Zucman-Rossi J, Finn RS. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2021; **7**: 6 [PMID: 33479224 DOI: 10.1038/s41572-020-00240-3]

13 **Fattovich G**, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127**: S35-S50 [PMID: 15508101 DOI: 10.1053/j.gastro.2004.09.014]

14 **Demirtas CO**, Ozdogan OC. Surveillance of hepatocellular carcinoma in cirrhotic patients: Current knowledge and future directions. *Hepatol Forum* 2020; **1**: 112-118 [PMID: 35949723 DOI: 10.14744/hf.2020.2020.0003]

15 **Xiang Z**, Li Y, Zhu C, Hong T, He X, Zhu H, Jiang D. Gastrointestinal Cancers and Liver Cirrhosis: Implications on Treatments and Prognosis. *Front Oncol* 2021; **11**: 766069 [PMID: 34746008 DOI: 10.3389/fonc.2021.766069]

16 **Zullo A**, Romiti A, Tomao S, Hassan C, Rinaldi V, Giustini M, Morini S, Taggi F. Gastric cancer prevalence in patients with liver cirrhosis. *Eur J Cancer Prev* 2003; **12**: 179-182 [PMID: 12771554 DOI: 10.1097/00008469-200306000-00002]

17 **Pan C**, Cuartas Mesa MC. Impact of cirrhosis on mortality in gastrointestinal malignancies: A retrospective study from nationwide database. *J Clin Oncol* 2023; **41**: e16324-e16324 [DOI: 10.1200/jco.2023.41.16_suppl.e16324]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2025 March 18; 13(1): 101226

DOI: 10.13105/wjma.v13.i1.101226

ISSN 2308-3840 (online)

META-ANALYSIS

Risk factors associated with the development of chronic pouchitis following ileal-pouch anal anastomosis surgery for ulcerative colitis

Emi Khoo, Robert Gilmore, Alison Griffin, Gerald Holtmann, Jakob Begun

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade B
Novelty: Grade A
Creativity or Innovation: Grade C
Scientific Significance: Grade B

P-Reviewer: Elbarmelgi MY

Received: September 8, 2024
Revised: January 30, 2025
Accepted: February 27, 2025
Published online: March 18, 2025
Processing time: 186 Days and 18.2 Hours

Emi Khoo, Robert Gilmore, Jakob Begun, Department of Gastroenterology, Mater Hospital Brisbane, South Brisbane 4101, Queensland, Australia

Emi Khoo, Robert Gilmore, Jakob Begun, IBD Clinical Trial Unit, Mater Research Institute, South Brisbane 4101, Queensland, Australia

Emi Khoo, Robert Gilmore, Gerald Holtmann, Jakob Begun, Faculty of Medicine, University of Queensland, St Lucia 4067, Queensland, Australia

Alison Griffin, QIMR Berghofer Medical Research Institute, Herston 4006, Queensland, Australia

Gerald Holtmann, Department of Gastroenterology, Princess Alexandra Hospital, Woolloongabba 4102, Queensland, Australia

Corresponding author: Emi Khoo, BMed, FRACP, MBBS, Staff Physician, Department of Gastroenterology, Mater Hospital Brisbane, Raymond Terrace, South Brisbane 4101, Queensland, Australia. emi.khoo@mater.uq.edu.au

Abstract

BACKGROUND

Chronic pouchitis remains a significant and prevalent complication following ileal pouch-anal anastomosis in patients with ulcerative colitis.

AIM

To identify potential risk factors for the development of chronic pouchitis.

METHODS

Predictors of chronic pouchitis were investigated through a systematic review and meta-analysis. A comprehensive search of the Medline, EMBASE, and PubMed databases was undertaken to identify relevant studies published up to October 2023. Meta-analytic procedures employed random-effects models for the combination of estimates, with the I^2 statistic used to assess between-study heterogeneity.

RESULTS

Eleven studies with a total of 3722 patients, comprising 513 with chronic pouchitis and 3209 patients without, were included in the final analysis. Extraintestinal manifestation [odds ratio (OR) = 2.11, 95% confidence intervals (CI): 1.53-2.91, $P < 0.001$, $I^2 = 0\%$], specifically primary sclerosing cholangitis (PSC) (OR = 3.69,

95%CI: 1.40-9.21, P = 0.01, I^2 = 48%), and extensive colitis (OR = 1.96, 95%CI: 1.23-3.11, P = 0.00, I^2 = 31%) were associated with an increased risk of chronic pouchitis. Other factors, including gender, smoking status, family history of inflammatory bowel disease and ileal pouch anal anastomosis surgical indication were not significantly associated with chronic pouchitis.

CONCLUSION
Extraintestinal manifestations, PSC and extensive colitis are associated with the development of chronic pouchitis. These findings underscore the importance of comprehensive pre-operative assessment and tailored post operative management strategies.

Key Words: Ulcerative colitis; Ileal pouch-anal anastomosis; Pouch; Chronic pouchitis; Risk factor

Core Tip: Pouchitis is the most frequent complication after ileal pouch anal anastomosis (IPAA) surgery. This condition can significantly impact a person's quality of life, leading to social isolation. Identifying the risk factors of chronic pouchitis could lead to more personalized patient care, better preoperative counselling, and potential interventions to reduce the risk of chronic pouchitis in patients undergoing IPAA surgery for ulcerative colitis in the future and improve long-term outcomes.

Citation: Khoo E, Gilmore R, Griffin A, Holtmann G, Begun J. Risk factors associated with the development of chronic pouchitis following ileal-pouch anal anastomosis surgery for ulcerative colitis. *World J Meta-Anal* 2025; 13(1): 101226
URL: https://www.wjgnet.com/2308-3840/full/v13/i1/101226.htm
DOI: https://dx.doi.org/10.13105/wjma.v13.i1.101226

INTRODUCTION

Ileal pouch anal anastomosis (IPAA) surgery is frequently performed in patients with ulcerative colitis (UC) who have medically refractory disease, acute severe colitis, or histologically confirmed dysplasia. These conditions represent serious complications of UC that often require surgical intervention. While IPAA provides a valuable option for many patients, the fact that the 10-year colectomy rate of patients with UC has been reported as approximately 10%-30% in Western countries underscores several important points[1]. It highlights the potential for disease progression despite available treatments, the need for ongoing research into more effective therapies, and the importance of close monitoring and follow-up for UC patients. The preferred procedure for these conditions is a total proctocolectomy followed by surgical IPAA creation, but this statistic emphasizes that even with this procedure, some patients may still experience challenges post resection.

The most commonly reported complication following IPAA surgery is pouchitis, which can develop in up to 70% of patients within 5 years of surgery[2]. Pouchitis is diagnosed by active symptoms of pouch dysfunction and endoscopic evidence of inflammatory activity[3]. Antibiotics effectively control inflammation and symptoms for most pouchitis patients in the short term[4]. However, up to 30% of these patients develop chronic pouchitis, which may be responsive or resistant to antibiotics[5-7]. These conditions are termed “chronic antibiotic-refractory pouchitis” and “chronic antibiotic-dependent pouchitis” respectively[8]. While acute pouchitis is typically treatable and does not significantly impact functional pouch outcomes, chronic pouchitis is associated with significant morbidity and an increased incidence of pouch failure.

Treatment of chronic antibiotic-refractory and antibiotic-dependent pouchitis remains challenging due to a lack of evidence guiding therapeutic decisions. A systematic review and meta-analysis of existing literature of real-world experience on currently available therapies for chronic pouchitis published in 2023 by Khoo *et al*[9] found that vedolizumab and ustekinumab are effective in treating chronic pouchitis with a good safety profile. EARNEST is the only well-powered randomized controlled trial demonstrated the positive effects of vedolizumab in treating chronic pouchitis[10]. In the EARNEST trial vedolizumab treatment was associated with a 31% remission rate based on the modified pouchitis disease activity index[10]. This evidence led to vedolizumab's approval by the European Medicines Agency for treating chronic pouchitis. Other treatments used for UC have been used empirically to treat chronic pouchitis with variable efficacy[9]. As a result, in severe cases of intractable chronic pouchitis, it may be necessary to divert or resect the ileal pouch.

The paucity of high-quality studies to date indicates an unmet therapeutic need in the management of chronic pouchitis. Hence, identifying risk factors for chronic pouchitis is crucial for categorizing clinical profiles and predicting disease progression. Early recognition, even prior to IPAA surgery, is important to allow for interventions, such as counselling, risk assessment and postoperative management. These measures are crucial to enhance long-term patient outcomes and prevent complications.

Multiple risk factors for the development of chronic pouchitis have been investigated, including smoking history, male gender, extensive colitis, primary sclerosing cholangitis (PSC), and indication of IPAA surgery[11]. These risk factors were often derived from cohort or case-control studies. The risk factors reported in the literature have been inconsistent and sometimes contradictory. While systematic reviews and meta-analyses have focused on serological markers, microbiota, and extraintestinal manifestations as risk factors for the development of chronic pouchitis, none have evaluated the consistency of the previously reported clinical predictive risk factors which focused specifically on chronic pouchitis[12-14].

The aim of this study is to assess factors, including demographic and clinical characteristics, as well as pathology-based variables, for the development of chronic pouchitis after IPAA surgery in patients with UC. Our meta-analysis offers a more comprehensive and statistically robust assessment of these risk factors compared to previously published individual cohort or case-control studies. Identifying the risk factors of chronic pouchitis could inform more personalised patient management strategies, improve preoperative counselling, and potentially guide interventions to mitigate the risk of chronic pouchitis in patients undergoing IPAA surgery for UC in the future and improve long-term outcomes.

MATERIALS AND METHODS

Search strategy

A systematic literature search of the Medline, EMBASE and PubMed databases was conducted to identify relevant articles published up to October 2023. Studies assessing the risk factors for the development of chronic pouchitis were searched using the Medical Subject Headings terms 'ulcerative colitis' and 'pouchitis', or 'IPAA', along with 'risk factors', 'predictor', 'prevalence' or 'incidence'. The titles and abstracts of the identified studies were independently reviewed by two authors (Khoo E and Gilmore R) to exclude those that did not address the research questions of interest. Each study was assessed for relevance based on predefined inclusion criteria, which included factors such as study design, population, and the specific risk factors examined. Any discrepancies between the authors' assessments were resolved through discussion or consultation with a third reviewer if necessary (Begun J). The full text of the remaining articles was then read in full to determine if they contained relevant information pertaining to the risk factors for the development of chronic pouchitis. This comprehensive review process ensured that only studies with pertinent data were included in the final analysis.

Study selection and data extraction

The studies included in this meta-analysis were observational cohort studies and case control studies, that met the following inclusion criteria: (1) Adult patients (aged 18 and older) who underwent IPAA surgery for UC; (2) Developed chronic pouchitis, either chronic antibiotic refractory pouchitis and/or chronic antibiotic responsive pouchitis; and (3) Provision of raw data or unadjusted odds ratio (OR) with either standard errors or confidence intervals (CI). Articles were excluded from the analysis if they focused on pediatric or other specific populations, lacked raw data or unadjusted odd ratios, or were unable to separate data for patients with Crohn's disease of the pouch or acute pouchitis from patients with chronic pouchitis. When multiple publications from the same population were available, only data from the most recent and comprehensive report were included in the analysis to avoid duplication and ensure data integrity.

Data extraction was conducted by author (Khoo E) and independently verified by author (Griffin A) to ensure accuracy and minimize bias. Any disagreements between the two authors were resolved by consulting a third independent reviewer (Begun J). Once the data extraction was agreed upon, the final data was compiled in an Excel spreadsheet (Microsoft, Redmond, WA, United States) format for statistical analysis.

Risk of bias assessment

The Risk of Bias In Non-Randomized Studies of Exposure Effects (ROBINS-E) tool was employed to evaluate the risk of bias of each study. ROBINS-E assesses seven domains of bias including confounding, measurement of the exposure, selection of participants, post exposure interventions, missing data, measurement of outcomes and selection of reported results. The risk of bias assessment was conducted independently by two authors (Khoo E and Gilmore R). Any conflicts were resolved by reaching a consensus, with reference to the original article when necessary.

Statistical analysis

All predictors of interest were binary categorical. The OR and 95%CI for chronic pouchitis with reference to non-chronic pouchitis (combined normal pouch and acute pouchitis) was calculated for each predictor separately for each study using 2 × 2 tables obtained from the included studies. If raw data in the form of 2 × 2 tables were not available but univariable OR and either 95%CI or standard errors were available, then the latter were used. Estimates were combined using a random effects model to calculate the pooled effect for each predictor. A weighted average effect size was calculated, with weights inversely proportional to the sum of the within-study and between-study variance. The restricted maximum likelihood method was used to estimate the variance. Forest plots including individual study effect size and CI as well as the pooled effect size and CI are presented for each predictor of interest. Between-study heterogeneity was estimated using the I^2 statistic, which describes the percentage of total variability across studies due to heterogeneity. An $I^2 > 50\%$ is considered high and suggests that a substantial portion of the variability in effect size is due to differences between studies. Statistical analysis was completed using Stata v17.0 (Stata Corp, College Station, TX, United States) and a P value < 0.05 was considered statistically significant throughout inferential analysis.

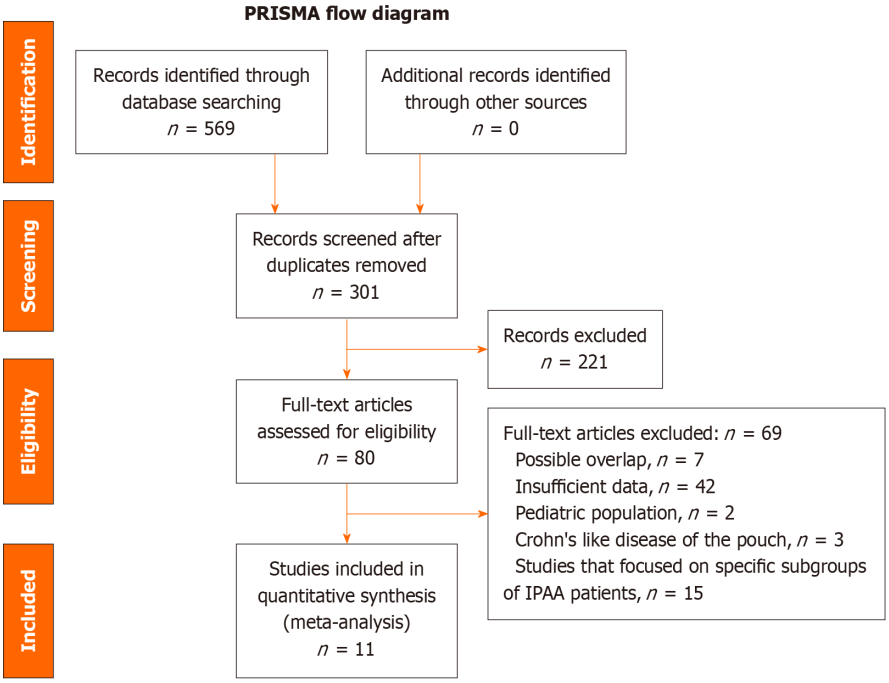


Figure 1 Preferred Items for Systematic Reviews and Meta-Analysis flow diagram for the review. PRISMA: Preferred Items for Systematic Reviews and Meta-Analysis.

RESULTS

Study selection and study characteristics

A total of 569 citations were identified from the database search. Duplicate articles, those studies that focused on specific subgroups of IPAA patients, and those with insufficient data were excluded. The flow diagram illustrating the studies excluded from this analysis is shown in Figure 1. Eleven articles met the inclusion criteria and were included in the meta-analysis. The final analysis included 3722 patients who underwent IPAA surgery. Among them, 3209 patients had either a normal pouch or acute pouchitis, while 513 had developed chronic pouchitis. The cohort with Crohn's like disease of the pouch was excluded. The majority of the studies (10 out of 11) were conducted at single centres. All pouch cases were identified retrospectively, with some (7 out of 11) followed up prospectively. The baseline characteristics, including the study period, sample size, number of patients who developed chronic pouchitis, and the definition of chronic pouchitis, are summarized in Table 1[3,15-24].

Among the eleven studies, the size of the study populations varied significantly, ranging from 36 participants in the study by Werner *et al*[23] to 1564 participants in the study by Wu *et al*[24]. Most of these studies reported similar proportions of patients with chronic pouchitis as have been previously reported, with rates ranging from 11.5% to 31.3% [5]. However, there were notable exceptions: (1) Uchino *et al*[22]; and (2) Werner *et al*[23]. Uchino *et al*[22] reported a low incidence of chronic pouchitis at just 4%, with 90% of patients having a normal pouch. In contrast, Werner *et al*[23] reported a significantly higher incidence of chronic pouchitis at 36%, with only 10% of patients having a normal pouch. It is important to note that Werner *et al*[23] did not specify the study duration or follow-up period.

Each study was assessed for risk of bias using ROBINS-E tool, as shown in Figure 2[3,15-24]. None of the studies were found to have a high risk of bias; one out of eleven studies (Scarpa *et al*[21]) had a moderate risk, and the rest had a low overall risk of bias. The most common bias identified were bias due to confounding and bias due to post-exposure interventions.

Risk factors for chronic pouchitis

Baseline patient characteristics including male gender, family history of inflammatory bowel disease (IBD) and smoking status were the most described risk factors for development of pouchitis (Figure 3A-C)[3,15,17-24]. Male gender was reported as a variable in nine of the studies. While the odds of chronic pouchitis tended to be higher in males, results were inconsistent and this difference did not reach statistical significance (OR = 1.22, 95%CI: 0.94-1.59, P = 0.13, I^2 = 18%). A family history of IBD was reported in five studies. The analysis indicated that the odds of developing chronic pouchitis were not significantly associated with a family history of IBD (OR = 1.02, 95%CI: 0.67-1.54, P = 0.93, I^2 = 0%). Smoking status, comparing current smokers and ex-smokers to those who had never smoked, was described in four studies. The OR was 0.85 with a 95%CI of 0.30-2.47, favouring smoking as a potential protective factor for chronic pouchitis. However, the P value was not significant (P = 0.77) and there was high heterogeneity (I^2 = 71%, P = 0.02), with two studies suggesting that chronic pouchitis is more likely in non-smokers, and two studies indicating it is more likely in smokers (combined active and former smokers). This high heterogeneity means that the combined estimate is of limited value.

Table 1 Studies which were included in meta-analysis, *n* (%)

Ref.	Population	Number of IPAA	Normal pouch[1]	Chronic pouchitis	Follow up period after IPAA	Definition of chronic pouchitis
Abdelrazeq *et al*[3], 2008	York Hospital, Huddersfield Royal Infirmary, Derby Hospitals–prospective	198	134 (68)	29 (15)	Mean 64 months (range: 12-180 months)	Presence of active symptoms continuously for more than 4 weeks despite full dose of standard therapy or required more than 2 weeks of therapy every month for three consecutive months to achieve symptomatic control
Achkar *et al* [15], 2005	Cleveland Clinic Foundation–prospective case control study	120	40 (33)	40 (33)	Mean 5.2 years	Presence of 4 or more episodes of pouchitis per year, or active symptoms lasting continuously for more than 4 weeks despite antibiotic therapy, or chronic antibiotic or anti-inflammatory therapy to control symptoms of pouchitis
Ferrante *et al* [16], 2008	University Hospital Gasthuisberg–retrospective	173	92 (53)	33 (19)	Median 6.5 years (range: 34-9.9 years)	Presence of active symptoms lasted for more than 4 weeks, despite standard therapy
Fleshner *et al* [17], 2007	Cedars-Sinar Medical Centre–prospective	186	127 (68)	23 (12)	Median 24 months (range: 3-117 months)	Required continuous antibiotic treatment for symptom relief or did not respond to antibiotic treatment
Hashavia *et al*[18], 2012	Tel-Aviv Sourasky Medical Centre– prospective	201	-	63 (31)	Mean 107 months	Presence of at least 4 weeks of persistent symptoms and dependent on prolonged therapy of more than two different antibiotics, or those who did not respond to antibiotics
Lian *et al* [19], 2009	Cleveland Clinic Foundation–retrospective	251	35 (14)	29 (12)	-	Failed to respond to a 2-4 weeks course of a single antibiotic, or required therapy over 4 weeks with 2 antibiotics
Okita *et al* [20], 2013	Mie University–retrospective	231	165 (71)	31 (13)	Median 1882.5 days (range: 31-4465 days)	Required long-term, continuous antibiotic therapy to maintain remission, or relapsing episodes (> 3 per year), or failed to respond to antibiotics
Scarpa *et al* [21], 2011	University of Padova–prospective	32	-	6 (19)	Median 23 months	No response to first line antibiotic therapy and required continuous antibiotic treatment for symptom relief or had a treatment resistant form
Uchino *et al* [22], 2013	Hyogo College of Medicine–retrospective	772	695 (90)	29 (4)	Median 5.67 years (range: 152-10.81 years)	Failed to respond to a 4-week course of a single antibiotic, requiring prolonged therapy for ≥ 4 weeks with ≥ 2 antibiotics or topical corticosteroid therapy
Werner *et al* [23], 2013	Tel Aviv Medical Centre–prospective	36	10 (28)	13 (36)	Follow up period was not mentioned	Required antibiotic or anti-inflammatory therapy for at least 4 weeks, or patients having more than 5 flares of pouchitis per year
Wu *et al*[24], 2016	Cleveland Clinic Pouch Centre–prospective	1564	181 (12)	217 (14)	Median 9 years (range: 4-14 years)	Symptoms lasted for 4 weeks or more and failed to respond to a 4-week course of single antibiotic therapy

[1]Normal pouch: Normal pouch cases do not include acute pouchitis.
IPAA: Ileal pouch anal anastomosis.

Immune-related extraintestinal manifestations[25], including joint conditions (sacroiliitis, ankylosing spondylitis and peripheral arthritis), PSC, eye conditions (episcleritis and uveitis) and skin conditions (pyoderma gangrenosum and erythema nodosum) were described in six studies (Figure 3D and E)[3,15-19]. The odds of chronic pouchitis were higher in individuals with extra-intestinal manifestations (OR = 2.11, 95%CI: 1.53-2.91, $P < 0.001$), and this finding was consistent across all six included studies ($I^2 = 0\%$). PSC, in particular, was found to have the highest OR among all risk factors analysed. The OR for chronic pouchitis in individuals with PSC was 3.59, with a 95%CI of 1.40-9.21 ($P = 0.01$). Although all four included studies showed an increase in the risk of chronic pouchitis, there was heterogeneity in the magnitude of the effect ($I^2 = 48\%$).

Distribution of colitis prior to surgery was reported in seven studies (Figure 3F)[3,15,17-20,22]. The odds of chronic pouchitis were higher in people with pancolitis (OR = 1.96, 95%CI: 1.23-3.11, $P < 0.001$, $I^2 = 31\%$). While a single study found lower odds of chronic pouchitis in individuals with pancolitis, this did not reach statistical significance. This discrepancy could be due to chance or differences in population or methodology. The indication for IPAA surgery [refractory disease compared with other indications (acute severe colitis, colonic dysplasia or cancer)] was described in eight studies (Figure 3G)[3,15,17-22]. The odds of chronic pouchitis (OR = 1.17, 95%CI: 0.83-1.66, $P = 0.37$, $I^2 = 0\%$) were

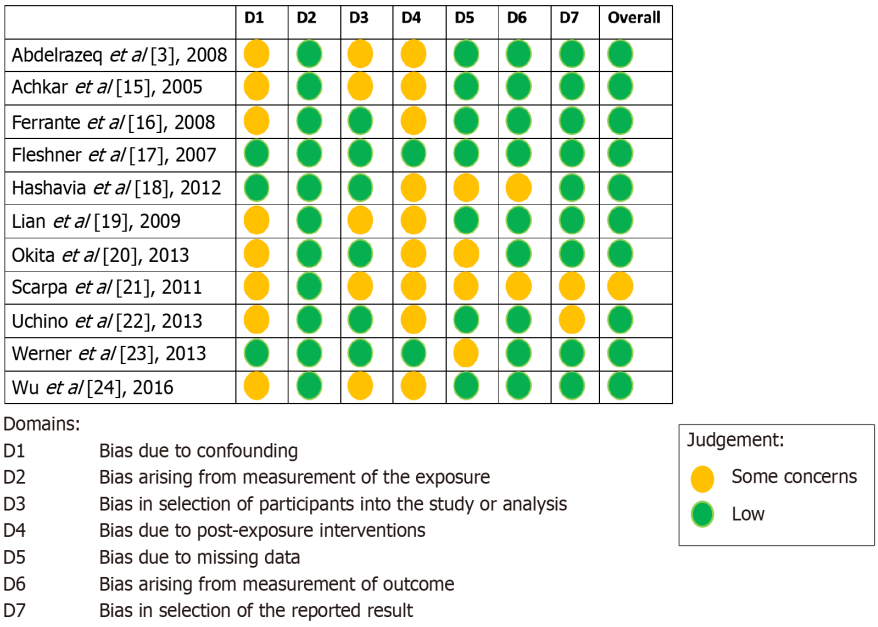
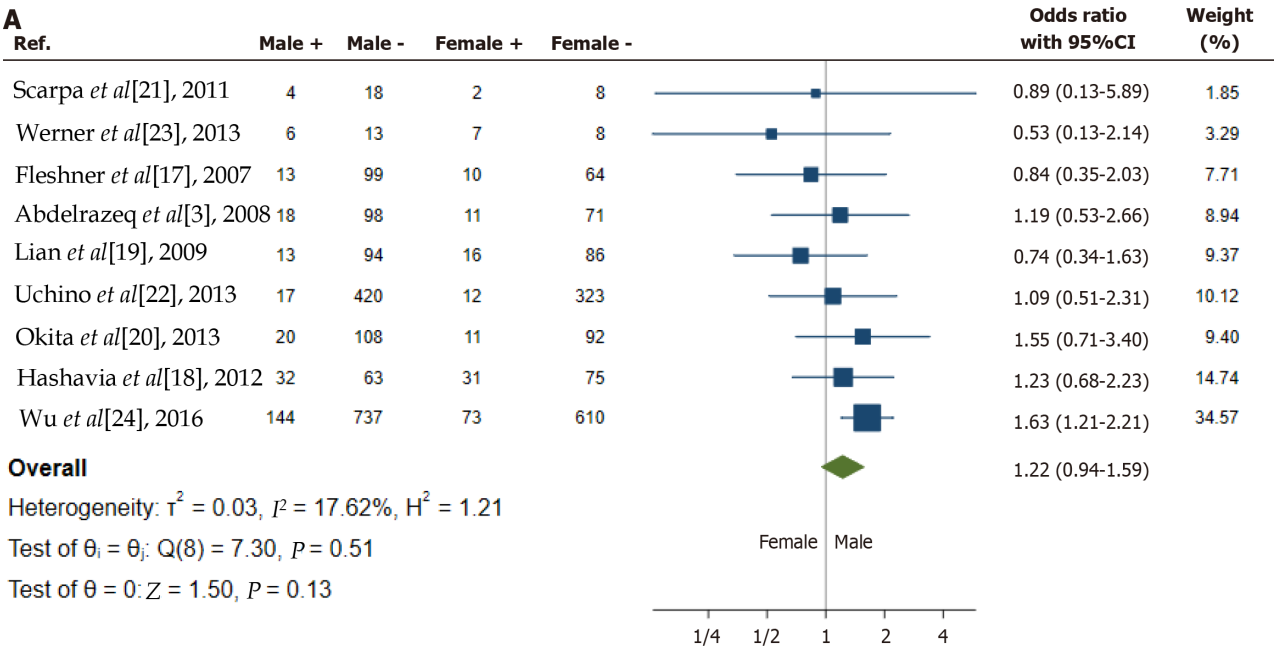
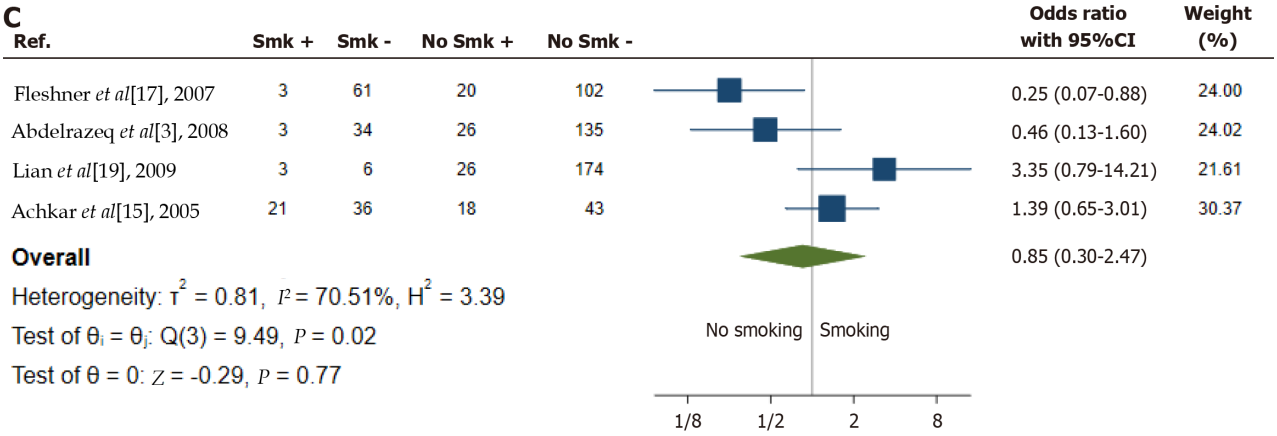


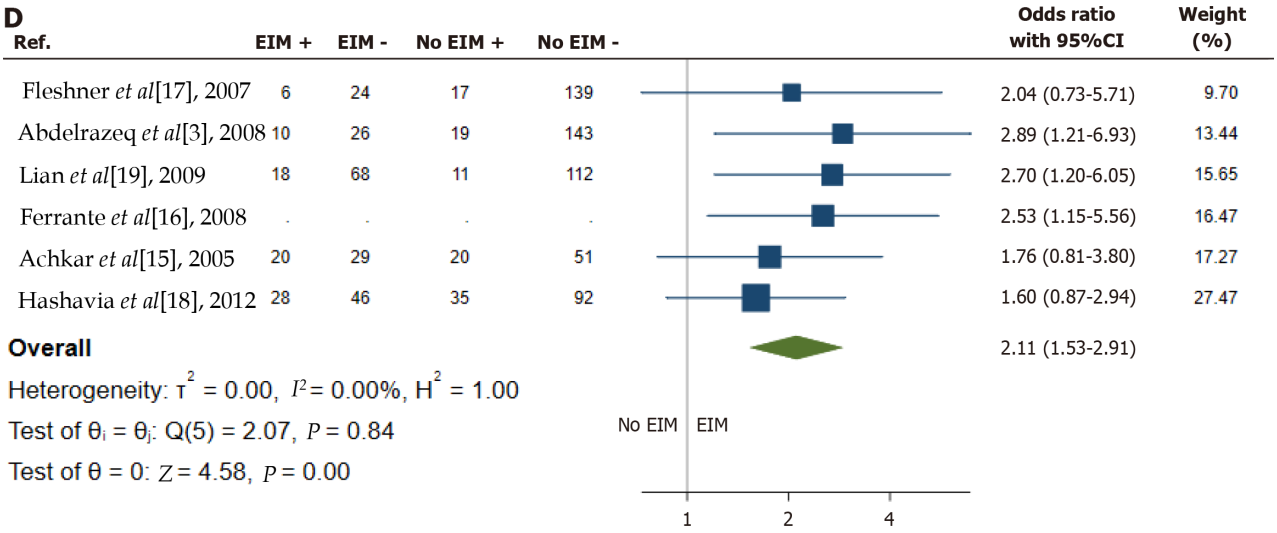
Figure 2 Risk of bias by domain of the included studies using the Risk of Bias In Non-Randomized Studies of Exposure Effects tool.



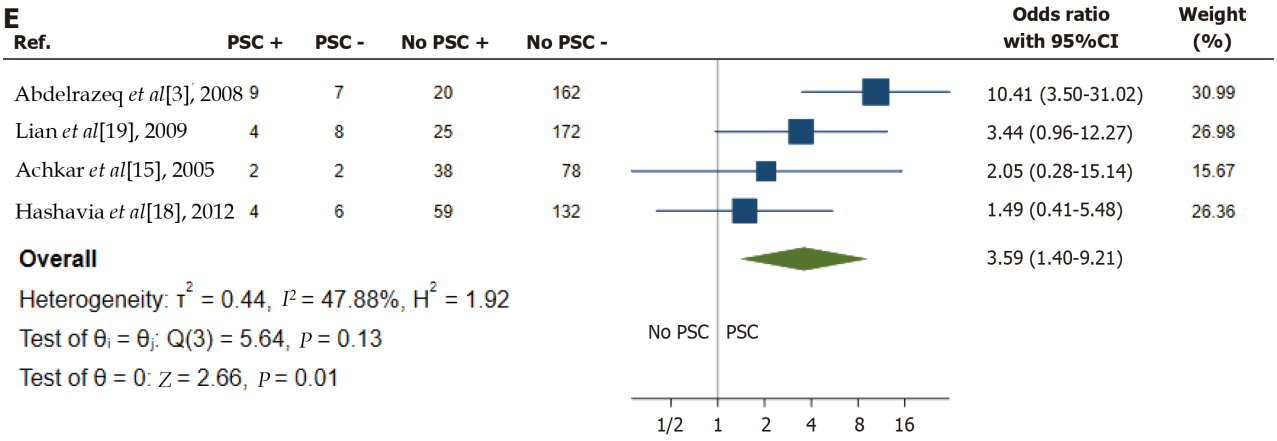
C


Ref. | Smk + | Smk - | No Smk + | No Smk - | Odds ratio with 95%CI | Weight (%)
Fleshner et al[17], 2007 | 3 | 61 | 20 | 102 | 0.25 (0.07-0.88) | 24.00
Abdelrazeq et al[3], 2008 | 3 | 34 | 26 | 135 | 0.46 (0.13-1.60) | 24.02
Lian et al[19], 2009 | 3 | 6 | 26 | 174 | 3.35 (0.79-14.21) | 21.61
Achkar et al[15], 2005 | 21 | 36 | 18 | 43 | 1.39 (0.65-3.01) | 30.37
Overall | 0.85 (0.30-2.47)
Heterogeneity: τ² = 0.81, I² = 70.51%, H² = 3.39
Test of θi = θj: Q(3) = 9.49, P = 0.02
Test of θ = 0: Z = -0.29, P = 0.77
No smoking
Smoking
1/8
1/2
2
8

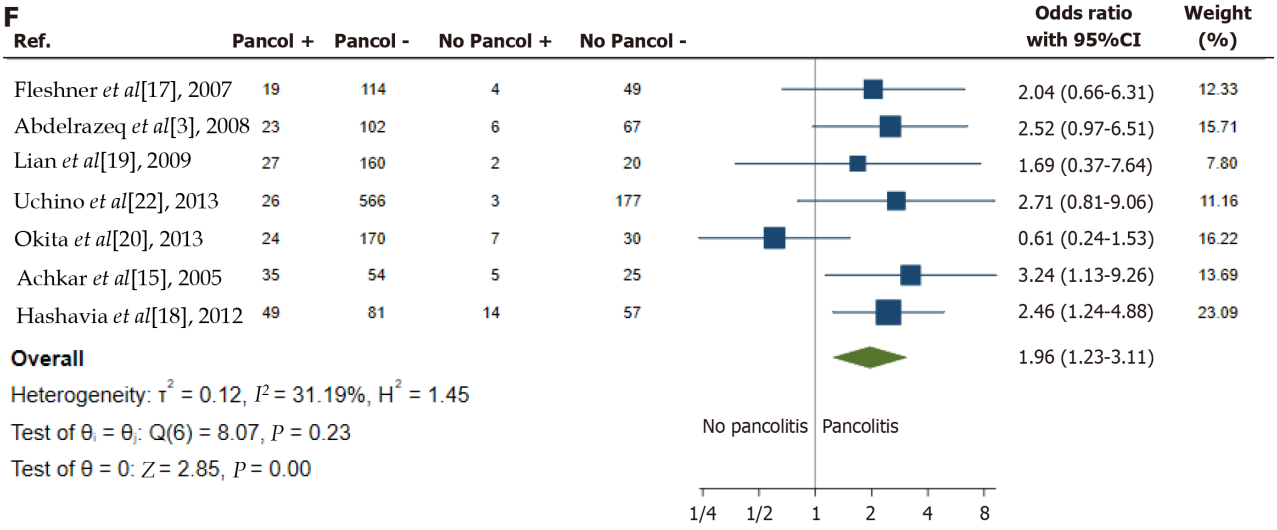
D


Ref. | EIM + | EIM - | No EIM + | No EIM - | Odds ratio with 95%CI | Weight (%)
Fleshner et al[17], 2007 | 6 | 24 | 17 | 139 | 2.04 (0.73-5.71) | 9.70
Abdelrazeq et al[3], 2008 | 10 | 26 | 19 | 143 | 2.89 (1.21-6.93) | 13.44
Lian et al[19], 2009 | 18 | 68 | 11 | 112 | 2.70 (1.20-6.05) | 15.65
Ferrante et al[16], 2008 | . | . | . | . | 2.53 (1.15-5.56) | 16.47
Achkar et al[15], 2005 | 20 | 29 | 20 | 51 | 1.76 (0.81-3.80) | 17.27
Hashavia et al[18], 2012 | 28 | 46 | 35 | 92 | 1.60 (0.87-2.94) | 27.47
Overall | 2.11 (1.53-2.91)
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(5) = 2.07, P = 0.84
Test of θ = 0: Z = 4.58, P = 0.00
No EIM
EIM
1
2
4

E


Ref. | PSC + | PSC - | No PSC + | No PSC - | Odds ratio with 95%CI | Weight (%)
Abdelrazeq et al[3], 2008 | 9 | 7 | 20 | 162 | 10.41 (3.50-31.02) | 30.99
Lian et al[19], 2009 | 4 | 8 | 25 | 172 | 3.44 (0.96-12.27) | 26.98
Achkar et al[15], 2005 | 2 | 2 | 38 | 78 | 2.05 (0.28-15.14) | 15.67
Hashavia et al[18], 2012 | 4 | 6 | 59 | 132 | 1.49 (0.41-5.48) | 26.36
Overall | 3.59 (1.40-9.21)
Heterogeneity: τ² = 0.44, I² = 47.88%, H² = 1.92
Test of θi = θj: Q(3) = 5.64, P = 0.13
Test of θ = 0: Z = 2.66, P = 0.01
No PSC
PSC
1/2
1
2
4
8
16

F


Ref. | Pancol + | Pancol - | No Pancol + | No Pancol - | Odds ratio with 95%CI | Weight (%)
Fleshner et al[17], 2007 | 19 | 114 | 4 | 49 | 2.04 (0.66-6.31) | 12.33
Abdelrazeq et al[3], 2008 | 23 | 102 | 6 | 67 | 2.52 (0.97-6.51) | 15.71
Lian et al[19], 2009 | 27 | 160 | 2 | 20 | 1.69 (0.37-7.64) | 7.80
Uchino et al[22], 2013 | 26 | 566 | 3 | 177 | 2.71 (0.81-9.06) | 11.16
Okita et al[20], 2013 | 24 | 170 | 7 | 30 | 0.61 (0.24-1.53) | 16.22
Achkar et al[15], 2005 | 35 | 54 | 5 | 25 | 3.24 (1.13-9.26) | 13.69
Hashavia et al[18], 2012 | 49 | 81 | 14 | 57 | 2.46 (1.24-4.88) | 23.09
Overall | 1.96 (1.23-3.11)
Heterogeneity: τ² = 0.12, I² = 31.19%, H² = 1.45
Test of θi = θj: Q(6) = 8.07, P = 0.23
Test of θ = 0: Z = 2.85, P = 0.00
No pancolitis
Pancolitis
1/4
1/2
1
2
4
8

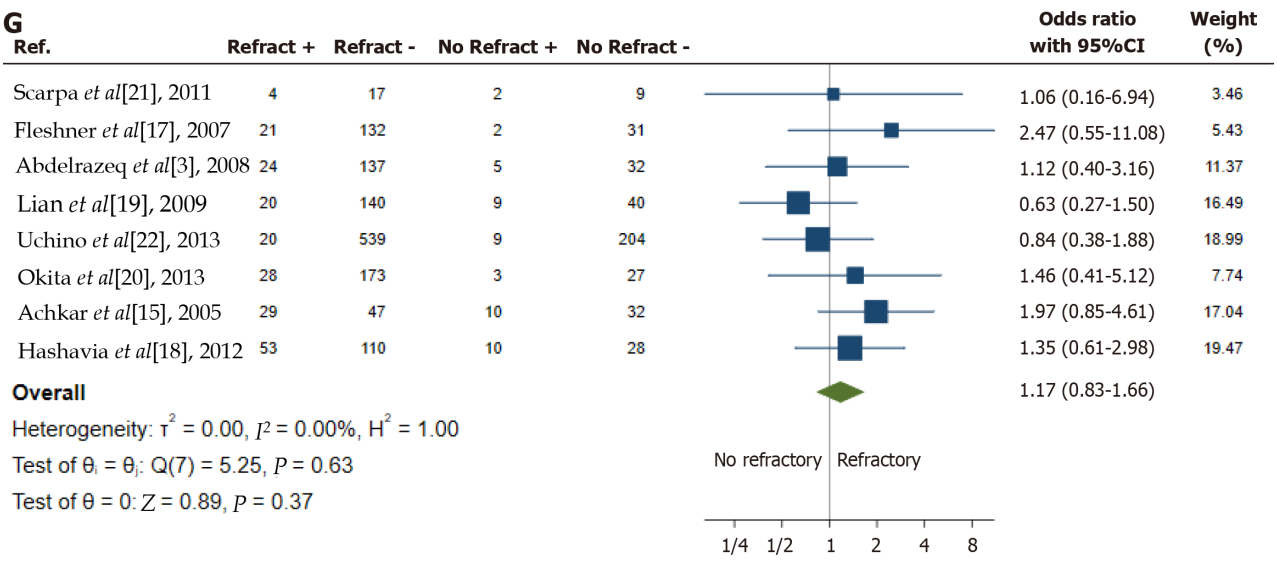


Figure 3 Meta-analysis and forest plots of studies assessing. A: Gender; B: Family history of ulcerative colitis; C: Smoking history; D: Extra-intestinal manifestations; E: Primary sclerosing cholangitis; F: Extent of colitis (pancolitis); G: Indication for surgery (refractory disease). EIM: Extra-intestinal manifestations; FHx: Family history; Pancol: Pancolitis; PSC: Primary sclerosing cholangitis; Refract: Refractory disease as indication for surgery; Smk: Smoking (current or ex-smoker).

not significantly associated with the indication for surgery.

One study suggested that pre-operative use of biologic agents might be associated with a lower risk of chronic pouchitis, although this finding was not statistically significant (OR = 0.38, 95%CI: 0.05-3.00, P = 0.361). Another study reported a possible association between post-operative infection and chronic pouchitis, but this finding was also not statistically significant (OR = 1.41, 95%CI: 0.45-4.46, P = 0.56). Due to the limited number of studies investigating these factors, a meta-analysis could not be performed.

DISCUSSION

To our knowledge, this is the first meta-analysis to evaluate risk factors associated with the development of chronic antibiotic-dependent and antibiotic-refractory pouchitis in patients who underwent IPAA surgery for UC. Eleven studies, comprising a total of 3722 patients, met the inclusion criteria for the final analysis. Within this cohort, 513 patients (13.8%) developed chronic pouchitis, while 3209 patients (86.2%) did not. The latter group comprised patients with a normal pouch and those with acute pouchitis or a history of acute pouchitis; cases resembling Crohn's disease of the pouch were excluded.

Our study corroborates previous findings that extraintestinal manifestations, specifically PSC, are risk factors for chronic pouchitis. This aligns with Hata *et al*[14], who reported an association between both extraintestinal manifestations (EIMs) and PSC with overall pouchitis, particularly chronic pouchitis. Similarly, Penna *et al*[26] observed a cumulative pouchitis risk of 79% in UC patients with PSC, compared to 46% in those without PSC over a ten-year post-IPAA follow up. Additionally, we identified extensive colitis as a pre-operative risk factor for chronic pouchitis, suggesting disease severity may influence its development. In contrast, extraintestinal manifestations, including PSC, and pancolitis did not impact the risk of Crohn's disease of the pouch (CDP)[27].

Other factors, such as male gender and refractory UC as a surgical indication, demonstrated a non-significant trend towards increased chronic pouchitis risk. Family history of IBD did not alter the risk. While smoking may increase acute pouchitis incidence[28], the exposure to cigarette smoking, whether active or former, exhibited a protective trend against chronic pouchitis in two out of four of the studies, albeit non-significant with high heterogeneity between studies. In comparison, Fadel *et al*[27] reported that smoking and family history of IBD were associated with CDP development. A surgical indication of dysplasia or colon cancer was protective against CDP[27], suggesting distinct pathogenic mechanisms for CPD and chronic pouchitis following IPAA for UC.

The precise mechanisms underlying chronic pouchitis remain elusive. However, accumulating evidence suggests that certain serological markers, microbial dysbiosis and genetic polymorphisms may contribute to its development. This condition represents a dysregulated mucosal immune response to intestinal microbiome. High titres of anti-neutrophil cytoplasmic antibody and the presence of microsomal antibody are positively associated with chronic pouchitis[12,29]. Elevated serum immunoglobulin G 4 (IgG4) levels and an increased number of IgG4 expressing plasma cell of more than 10 per high power field within pouch biopsies, have also been identified as risk factors for chronic pouchitis, independent of autoimmune serological markers, when compared to non-chronic pouchitis cohort[29]. Microbiota studies have suggested that mucosal toll like receptor (TLR) 2 and TLR4 expression, as well as increased levels of mucosa associated *Clostridium spp*, are associated with chronic pouchitis[21]. Carrier trait analysis revealed that the presence of TLR9-1237C

and CD14-260T alleles simultaneously occurs significantly higher in patients with chronic pouchitis[21]. Haplotyping of TLR9 has shown that a C allele at TLR9-1237 and an A allele at TLR9+2848 are more frequently observed in patients with chronic pouchitis[30]. These features collectively suggest that a dysregulated immune response to commensal bacteria may predispose individuals to chronic pouchitis. Furthermore, these combined markers could potentially be used to identify a subgroup of IPAA patients at increased risk of developing chronic pouchitis.

Pre-operative predictive factors for chronic pouchitis remain inconclusive. Several studies have investigated the association between different types of pre-operative therapies and chronic pouchitis development, but no significant association has been established. While Okita *et al*[20] suggested a potential risk factor for chronic pouchitis associated with high pre-operative steroid doses (accumulative dose of 500 mg or more per month), the overall effect of pre-operative steroid use on the risk of chronic pouchitis remains uncertain. Similarly, the role of pre-operative immunomodulators and biologic therapies in chronic pouchitis development is unclear. While some studies have suggested a potential link, others have found no association. For example, Esckilsen *et al*[31] reported a possible increased risk with vedolizumab, but this finding has not been consistently replicated. Furthermore, an investigation into other potential pre-operative predictive factors, such as anal pressures and laboratory markers, did not reveal any significant associations with chronic pouchitis development[31].

Post-operative factors were also examined as potential predictors of chronic pouchitis. Studies found that complications following surgery, particularly anastomotic leaks or separations, were linked to a higher risk of developing chronic pouchitis[32]. However, the exact relationship between these complications and chronic pouchitis remains ambiguous. Some experts suggest that patients with anastomotic complications, especially those with additional risk factors, might benefit from preventive treatments for chronic pouchitis. Additionally, imaging evidence revealed that excess fat around the pouch, including mesenteric, visceral, and subcutaneous fat, was strongly associated with chronic pouchitis[33]. Researchers proposed that this fat accumulation might reflect ongoing inflammation and could potentially disrupt blood flow to the pouch, making it a valuable indicator of future pouch health. In contrast, post-operative use of immunomodulators or biologic therapies[34], as well as factors like anal pressure and soiling[31], were not found to increase the risk of chronic pouchitis.

Strengths and limitations

The strengths of our study include the well-defined inclusion and exclusion criteria with a large sample size of chronic pouchitis patients. The overall risk of bias was also deemed low in the eleven included studies. Unfortunately, numerous articles meeting the inclusion criteria were excluded due to incomplete raw datasets. Also, the studies exhibited a substantial range in study population characteristics and follow up duration that range from median of 23 months to 9 years, contributing to heterogeneity across the studies. All these limitations contribute to overall study's validity, generalizability and the strength of its findings.

CONCLUSION

This study identified extraintestinal manifestations, particularly PSC, and extensive colitis as the strongest predictors of chronic pouchitis development in UC patients undergoing IPAA surgery. Conversely, gender, smoking history and IPAA surgical indication did not significantly influence chronic pouchitis incidence. Given the association between these factors and chronic pouchitis, prospective studies are warranted to further elucidate their pathophysiological mechanisms and inform potential targeted interventions. By unravelling these pathways, we can develop targeted and earlier interventions to prevent or treat chronic pouchitis in high-risk patients.

Recommendations

Key risk factors for chronic pouchitis: (1) PSC: This chronic biliary condition, which commonly occurs alongside UC, increases the risk of chronic pouchitis after IPAA surgery; (2) EIMs of IBD: These are symptoms of IBD that occur outside the intestines, such as joint pain (arthritis), skin problems (erythema nodosum, pyoderma gangrenosum), and eye inflammation (uveitis). Having a history of EIMs can increase the risk of chronic pouchitis; and (3) Extensive colitis or pancolitis: The distribution of colitis could reflect the severity of disease and increase the risk of chronic pouchitis after IPAA surgery.

Importance of identifying risk factors: (1) Patient counselling: Healthcare providers can counsel patients about their individual risk of developing pouchitis after IPAA surgery; (2) Early detection and intervention: Patients with risk factors can be monitored more closely for signs of pouchitis, allowing for early intervention and potentially preventing the development of chronic pouchitis; and (3) Research: Further research into these risk factors can help to better understand the causes of pouchitis and develop more effective prevention and treatment strategies.

FOOTNOTES

Author contributions: Khoo E conducted data extraction and wrote the manuscript; Khoo E, Holtmann G and Begun J designed the research study; Khoo E and Gilmore R reviewed literature search and select eligible articles; Griffin A performed statistical analysis and verified data extraction; all authors have read and approved the final manuscript to be published.

Conflict-of-interest statement: Khoo E has received research funding from Pfizer and Celltrion; as well as speaker funding from Ferring. Begun J has received speaking or consulting fees from Ferring, Takeda, Janssen, Pfizer, Abbvie, Dr. Falk, Celltrion, Amgen, and Sandoz. Gilmore R, Griffith A and Holtmann G have nothing to disclose.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: Australia

ORCID number: Emi Khoo 0000-0003-3536-4974; Jakob Begun 0000-0001-5256-7672.

S-Editor: Luo ML
L-Editor: A
P-Editor: Wang WB

REFERENCES

1 **Akiyama S**, Rai V, Rubin DT. Pouchitis in inflammatory bowel disease: a review of diagnosis, prognosis, and treatment. *Intest Res* 2021; **19**: 1-11 [PMID: 33138344 DOI: 10.5217/ir.2020.00047]
2 **Fazio VW**, Kiran RP, Remzi FH, Coffey JC, Heneghan HM, Kirat HT, Manilich E, Shen B, Martin ST. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. *Ann Surg* 2013; **257**: 679-685 [PMID: 23299522 DOI: 10.1097/SLA.0b013e31827d99a2]
3 **Abdelrazeq AS**, Kandiyil N, Botterill ID, Lund JN, Reynolds JR, Holdsworth PJ, Leveson SH. Predictors for acute and chronic pouchitis following restorative proctocolectomy for ulcerative colitis. *Colorectal Dis* 2008; **10**: 805-813 [PMID: 18005192 DOI: 10.1111/j.1463-1318.2007.01413.x]
4 **Magro F**, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, Burisch J, Gecse KB, Hart AL, Hindryckx P, Langner C, Limdi JK, Pellino G, Zagórowicz E, Raine T, Harbord M, Rieder F; European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis* 2017; **11**: 649-670 [PMID: 28158501 DOI: 10.1093/ecco-jcc/jjx008]
5 **Bresteau C**, Amiot A, Kirchgesner J, de'Angelis N, Lefevre JH, Bouhnik Y, Panis Y, Beaugerie L, Allez M, Brouquet A, Carbonnel F, Meyer A. Chronic pouchitis and Crohn's disease of the pouch after ileal pouch-anal anastomosis: Incidence and risk factors. *Dig Liver Dis* 2021; **53**: 1128-1135 [PMID: 33931341 DOI: 10.1016/j.dld.2021.03.027]
6 **Dalal RL**, Shen B, Schwartz DA. Management of Pouchitis and Other Common Complications of the Pouch. *Inflamm Bowel Dis* 2018; **24**: 989-996 [PMID: 29688472 DOI: 10.1093/ibd/izy020]
7 **Bär F**, Kühbacher T, Dietrich NA, Krause T, Stallmach A, Teich N, Schreiber S, Walldorf J, Schmelz R, Büning C, Fellermann K, Büning J, Helwig U; German IBD Study Group. Vedolizumab in the treatment of chronic, antibiotic-dependent or refractory pouchitis. *Aliment Pharmacol Ther* 2018; **47**: 581-587 [PMID: 29266360 DOI: 10.1111/apt.14479]
8 **Madiba TE**, Bartolo DC. Pouchitis following restorative proctocolectomy for ulcerative colitis: incidence and therapeutic outcome. *J R Coll Surg Edinb* 2001; **46**: 334-337 [PMID: 11768572]
9 **Khoo E**, Lee A, Neeman T, An YK, Begun J. Comprehensive systematic review and pooled analysis of real-world studies evaluating immunomodulator and biologic therapies for chronic pouchitis treatment. *JGH Open* 2023; **7**: 899-907 [PMID: 38162843 DOI: 10.1002/jgh3.13000]
10 **Travis S**, Silverberg MS, Danese S, Gionchetti P, Löwenberg M, Jairath V, Feagan BG, Bressler B, Ferrante M, Hart A, Lindner D, Escher A, Jones S, Shen B; EARNEST Study Group. Vedolizumab for the Treatment of Chronic Pouchitis. *N Engl J Med* 2023; **388**: 1191-1200 [PMID: 36988594 DOI: 10.1056/NEJMoa2208450]
11 **Shen B**, Achkar JP, Connor JT, Ormsby AH, Remzi FH, Bevins CL, Brzezinski A, Bambrick ML, Fazio VW, Lashner BA. Modified pouchitis disease activity index: a simplified approach to the diagnosis of pouchitis. *Dis Colon Rectum* 2003; **46**: 748-753 [PMID: 12794576 DOI: 10.1007/s10350-004-6652-8]
12 **Singh S**, Sharma PK, Loftus EV Jr, Pardi DS. Meta-analysis: serological markers and the risk of acute and chronic pouchitis. *Aliment Pharmacol Ther* 2013; **37**: 867-875 [PMID: 23480145 DOI: 10.1111/apt.12274]
13 **Angriman I**, Scarpa M, Castagliuolo I. Relationship between pouch microbiota and pouchitis following restorative proctocolectomy for ulcerative colitis. *World J Gastroenterol* 2014; **20**: 9665-9674 [PMID: 25110406 DOI: 10.3748/wjg.v20.i29.9665]
14 **Hata K**, Okada S, Shinagawa T, Toshiaki T, Kawai K, Nozawa H. Meta-analysis of the association of extraintestinal manifestations with the development of pouchitis in patients with ulcerative colitis. *BJS Open* 2019; **3**: 436-444 [PMID: 31463422 DOI: 10.1002/bjs5.50149]
15 **Achkar JP**, Al-Haddad M, Lashner B, Remzi FH, Brzezinski A, Shen B, Khandwala F, Fazio V. Differentiating risk factors for acute and chronic pouchitis. *Clin Gastroenterol Hepatol* 2005; **3**: 60-66 [PMID: 15645406 DOI: 10.1016/s1542-3565(04)00604-4]
16 **Ferrante M**, Declerck S, De Hertogh G, Van Assche G, Geboes K, Rutgeerts P, Penninckx F, Vermeire S, D'Hoore A. Outcome after proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis. *Inflamm Bowel Dis* 2008; **14**: 20-28 [PMID: 17973304 DOI: 10.1002/ibd.20278]
17 **Fleshner P**, Ippoliti A, Dubinsky M, Ognibene S, Vasiliauskas E, Chelly M, Mei L, Papadakis KA, Landers C, Targan S. A prospective

multivariate analysis of clinical factors associated with pouchitis after ileal pouch-anal anastomosis. *Clin Gastroenterol Hepatol* 2007; **5**: 952-958; quiz 887 [PMID: 17544871 DOI: 10.1016/j.cgh.2007.03.020]

18 **Hashavia E**, Dotan I, Rabau M, Klausner JM, Halpern Z, Tulchinsky H. Risk factors for chronic pouchitis after ileal pouch-anal anastomosis: a prospective cohort study. *Colorectal Dis* 2012; **14**: 1365-1371 [PMID: 22339717 DOI: 10.1111/j.1463-1318.2012.02993.x]

19 **Lian L**, Fazio VW, Lavery IC, Hammel J, Remzi FH, Shen B. Evaluation of association between precolectomy thrombocytosis and the occurrence of inflammatory pouch disorders. *Dis Colon Rectum* 2009; **52**: 1912-1918 [PMID: 19966641 DOI: 10.1007/DCR.0b013e3181b300f4]

20 **Okita Y**, Araki T, Tanaka K, Hashimoto K, Kondo S, Kawamura M, Koike Y, Otake K, Fujikawa H, Inoue M, Ohi M, Inoue Y, Uchida K, Mohri Y, Kusunoki M. Predictive factors for development of chronic pouchitis after ileal pouch-anal anastomosis in ulcerative colitis. *Digestion* 2013; **88**: 101-109 [PMID: 23949485 DOI: 10.1159/000353151]

21 **Scarpa M**, Grillo A, Pozza A, Faggian D, Ruffolo C, Scarpa M, D'Incà R, Plebani M, Sturniolo GC, Castagliuolo I, Angriman I. TLR2 and TLR4 up-regulation and colonization of the ileal mucosa by Clostridiaceae spp. in chronic/relapsing pouchitis. *J Surg Res* 2011; **169**: e145-e154 [PMID: 21601883 DOI: 10.1016/j.jss.2011.04.003]

22 **Uchino M**, Ikeuchi H, Matsuoka H, Bando T, Takesue Y, Tomita N. Clinical features and management of pouchitis in Japanese ulcerative colitis patients. *Surg Today* 2013; **43**: 1049-1057 [PMID: 23076686 DOI: 10.1007/s00595-012-0377-4]

23 **Werner L**, Sturm A, Roggenbuck D, Yahav L, Zion T, Meirowithz E, Ofer A, Guzner-Gur H, Tulchinsky H, Dotan I. Antibodies against glycoprotein 2 are novel markers of intestinal inflammation in patients with an ileal pouch. *J Crohns Colitis* 2013; **7**: e522-e532 [PMID: 23639628 DOI: 10.1016/j.crohns.2013.03.009]

24 **Wu XR**, Ashburn J, Remzi FH, Li Y, Fass H, Shen B. Male Gender Is Associated with a High Risk for Chronic Antibiotic-Refractory Pouchitis and Ileal Pouch Anastomotic Sinus. *J Gastrointest Surg* 2016; **20**: 631-639 [PMID: 26446071 DOI: 10.1007/s11605-015-2976-z]

25 **Mathis KL**, Dozois EJ, Larson DW, Cima RR, Sarmiento JM, Wolff BG, Heimbach JK, Pemberton JH. Ileal pouch-anal anastomosis and liver transplantation for ulcerative colitis complicated by primary sclerosing cholangitis. *Br J Surg* 2008; **95**: 882-886 [PMID: 18496886 DOI: 10.1002/bjs.6210]

26 **Penna C**, Dozois R, Tremaine W, Sandborn W, LaRusso N, Schleck C, Ilstrup D. Pouchitis after ileal pouch-anal anastomosis for ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis. *Gut* 1996; **38**: 234-239 [PMID: 8801203 DOI: 10.1136/gut.38.2.234]

27 **Fadel MG**, Geropoulos G, Warren OJ, Mills SC, Tekkis PP, Celentano V, Kontovounisios C. Risks Factors Associated with the Development of Crohn's Disease After Ileal Pouch-Anal Anastomosis for Ulcerative Colitis: A Systematic Review and Meta-Analysis. *J Crohns Colitis* 2023; **17**: 1537-1548 [PMID: 36961323 DOI: 10.1093/ecco-jcc/jjad051]

28 **Fleshner P**, Ippoliti A, Dubinsky M, Vasiliauskas E, Mei L, Papadakis KA, Rotter JI, Landers C, Targan S. Both preoperative perinuclear antineutrophil cytoplasmic antibody and anti-CBir1 expression in ulcerative colitis patients influence pouchitis development after ileal pouch-anal anastomosis. *Clin Gastroenterol Hepatol* 2008; **6**: 561-568 [PMID: 18378498 DOI: 10.1016/j.cgh.2008.01.002]

29 **Seril DN**, Yao Q, Lashner BA, Shen B. Autoimmune features are associated with chronic antibiotic-refractory pouchitis. *Inflamm Bowel Dis* 2015; **21**: 110-120 [PMID: 25437817 DOI: 10.1097/MIB.0000000000000231]

30 **Lammers KM**, Ouburg S, Morré SA, Crusius JB, Gionchett P, Rizzello F, Morselli C, Caramelli E, Conte R, Poggioli G, Campieri M, Peña AS. Combined carriership of TLR9-1237C and CD14-260T alleles enhances the risk of developing chronic relapsing pouchitis. *World J Gastroenterol* 2005; **11**: 7323-7329 [PMID: 16437636 DOI: 10.3748/wjg.v11.i46.7323]

31 **Esckilsen S**, Kochar B, Weaver KN, Herfarth HH, Barnes EL. Very Early Pouchitis Is Associated with an Increased Likelihood of Chronic Inflammatory Conditions of the Pouch. *Dig Dis Sci* 2023; **68**: 3139-3147 [PMID: 37148442 DOI: 10.1007/s10620-023-07947-9]

32 **Koike Y**, Uchida K, Inoue M, Nagano Y, Kondo S, Matsushita K, Okita Y, Toiyama Y, Araki T, Kusunoki M. Early first episode of pouchitis after ileal pouch-anal anastomosis for pediatric ulcerative colitis is a risk factor for development of chronic pouchitis. *J Pediatr Surg* 2019; **54**: 1788-1793 [PMID: 30446392 DOI: 10.1016/j.jpedsurg.2018.10.056]

33 **Hoda KM**, Collins JF, Knigge KL, Deveney KE. Predictors of pouchitis after ileal pouch-anal anastomosis: a retrospective review. *Dis Colon Rectum* 2008; **51**: 554-560 [PMID: 18266037 DOI: 10.1007/s10350-008-9194-7]

34 **Gao XH**, Yu GY, Khan F, Li JQ, Stocchi L, Hull TL, Shen B. Greater Peripouch Fat Area on CT Image Is Associated with Chronic Pouchitis and Pouch Failure in Inflammatory Bowel Diseases Patients. *Dig Dis Sci* 2020; **65**: 3660-3671 [PMID: 32500285 DOI: 10.1007/s10620-020-06363-7]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2025 March 18; 13(1): 102634

DOI: 10.13105/wjma.v13.i1.102634

ISSN 2308-3840 (online)

SCIENTOMETRICS

Bibliometric analysis of original studies on stereoelectroencephalography from 1990 to 2023

Wei-Lin Yang, Rui Zhou, Xian-Jie Zhang, Wen-Cai Jiang

Specialty type: Critical care medicine

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A, Grade B, Grade D

Novelty: Grade B, Grade B, Grade B

Creativity or Innovation: Grade B, Grade B, Grade C

Scientific Significance: Grade A, Grade B, Grade C

P-Reviewer: Feng XL; Yang WZ; Zhu Q

Received: October 24, 2024

Revised: January 4, 2025

Accepted: February 18, 2025

Published online: March 18, 2025

Processing time: 141 Days and 14.5 Hours

Wei-Lin Yang, Xian-Jie Zhang, Wen-Cai Jiang, Department of Anesthesiology, Deyang People's Hospital, Deyang 618000, Sichuan Province, China

Rui Zhou, Department of Anesthesiology and Perioperative Medicine, Shanghai Fourth People's Hospital, School of Medicine, Tongji University, Shanghai 200434, China

Corresponding author: Wen-Cai Jiang, Department of Anesthesiology, Deyang People's Hospital, No. 173 Taishan Road Section 1, Deyang 618000, Sichuan Province, China. jiang940724@163.com

Abstract

BACKGROUND

Stereoelectroencephalography (SEEG) is a minimally invasive preoperative evaluation of drug-resistant focal epilepsies. Increasing preclinical data show that SEEG has tremendous diagnostic and therapeutic value for epilepsy. There are currently many studies on SEEG.

AIM

To summarize the development and application of SEEG.

METHODS

We conducted a bibliometric analysis of research on SEEG from 2019 to 2023. We obtained publications on SEEG from the Web of Science Core Collection (WoSCC) database. Excel, VOSviewer, and CiteSpace were responsible for the analyses. A variety of bibliographic elements were collected, including annual publications, authors, countries/regions, journals, keywords, *etc.*

RESULTS

A total of 691 publications were included in this study. Professor Fabrice Bartolomei of Timone Hospital in France was the most productive and influential author in the field of SEEG, whereas the authors from the United States were the leaders in general. In addition, we found that deep learning and source localization in SEEG have been popular in recent years.

CONCLUSION

This study provides a comprehensive analysis of SEEG research and highlights the growing interest in SEEG and its deep learning and source localization.

Key Words: Stereoelectroencephalography; Neurology; Bibliometric analysis; Science

Core Collection; VOSviewer; CiteSpace

Core Tip: Stereoelectroencephalography (SEEG) is a popular issue recently. The United States, China, and France are in the leading place. *Epilepsia*, *Clinical Neurophysiology*, *Journal of Neurosurgery*, and *Frontiers in Neurology* are the most popular journals in this field. *Epilepsy* is still the primary clinical application of SEEG, while deep learning and source localization have strongly increased.

Citation: Yang WL, Zhou R, Zhang XJ, Jiang WC. Bibliometric analysis of original studies on stereoelectroencephalography from 1990 to 2023. *World J Meta-Anal* 2025; 13(1): 102634
URL: https://www.wjgnet.com/2308-3840/full/v13/i1/102634.htm
DOI: https://dx.doi.org/10.13105/wjma.v13.i1.102634

INTRODUCTION

Stereoelectroencephalography (SEEG) was first formed in the 1950s at Saint Anne Hospital in France and was designed and developed in the 1960s in France by Talairach *et al*[1]. SEEG uses stereotactic techniques to place intracranial electrodes to record intracranial electrical activity and direct electrical stimulation to identify epileptogenic areas in patients with focal epilepsy[2-4]. SEEG is a diagnostic tool for drug-resistant focal epilepsies, showing precise positioning, minimal trauma, high patient tolerance, and other advantages[5,6]. A recent study demonstrated the performance of deep learning on SEEG signals and demonstrated that the deep learning method was beneficial for the decoding process because it is good at translating brain signals into commands for controlling external devices[7]. Another study showed that SEEG source localization is useful for corroborating the epileptogenic zone because it is inherently three-dimensional and can be modeled through source localization[8]. As a result, SEEG has attracted increasing attention in the research field of deep learning and source localization for drug-resistant focal epilepsies.

Bibliometrics is a technique employed to assess and examine the advancement of a specific field of science[9]. It utilizes computer technologies to present visual representations of literature analysis outcomes in a concise and comprehensible graphical format[10]. Overall, bibliometric analysis offers a comprehensive approach to evaluating academic productivity, summarizing academic frontiers and hotspots, and predicting trends within a particular research field. By understanding the results of bibliometric analysis, researchers can gain valuable insights into the scholarly landscape and make informed decisions regarding their research endeavors.

This study aims to analyze the bibliometric characteristics of the original studies on SEEG over the past 5 years; to analyze the publication trends, popular research topics, and cutting-edge trends in this field; and to provide references for clinicians and researchers.

MATERIALS AND METHODS

Data source and search strategy

The literature was retrieved from the Web of Science Core Collection (WoSCC) on 15 November 2023. After the inclusion and exclusion criteria were determined, the following formula was used as the retrieval strategy: TS = "stereotactic EEG" OR "stereoelectroencephalography" OR "SEEG" OR "stereoelectroencephalography SEEG" OR "intracranial EEG" OR "intracranial encephalography" OR "IEEG". The literature type was restricted to "article", and the publication year was limited to 2019 to 2023. To adequately retrieve the relevant literature, an exact search was not performed.

Inclusion and exclusion criteria

The original research related to SEEG, identified through the WoSCC database and published between 2019 and 2023, was further screened. Conversely, reviews, conference papers, letters, editorials, and notes, as well as retracted papers, were excluded from the analysis. There were no language restrictions.

Data screening and extraction

To ensure the reliability of the results, two independent researchers meticulously selected the literature by reading the abstracts and methods. Divergence in literature selection was settled by discussion or consultation with specialists. Consequently, all retrieved records were downloaded in "plain text" and "Excel" formats. Relevant parameters, such as titles, publication years, citation times, authors, countries/regions, institutions, journals, keywords, usage counts, WoS categories, *etc*., were extracted for further analysis.

Data analysis and visualization

Descriptive statistics from Microsoft Excel (V2021) were used to present the publication trends and cumulative citations. VOSviewer (V. 1.6.20) and CiteSpace (V. 6.2. R6) software were applied to perform knowledge mapping analysis, including the author, institution, country/region, journal, and keywords. Keywords serve as concise summaries of a paper's core content and essence, and through keyword co-occurrence analysis, researchers can gain insights into the research hotspots within a scientific domain. In this study, VOSviewer was employed to construct a network visualization of keyword cooccurrences from the 691 documents. We merged synonyms such as "stereoelectroencephalography", "stereotactic EEG", "stereotactic electroencephalography", "stereoelectroencephalography" and other synonyms into "SEEG".

VOSviewer was employed to conduct coauthorship analyses of the author, institution country/region, and journal. VOSviewer also provided us with the publication and citation counts. The relatedness of the nodes in VOSviewer figures is determined by their number of coauthored publications. In addition, we applied VOSviewer to conduct a co-occurrence analysis for the keywords. Finally, CiteSpace was used to perform the citation burst analysis of keywords.

RESULTS

In the present study, we identified 6453 records by the above formula in the WoSCC on 15 November 2023. A total of 2339 publications were published between 2019 and 2023, of which 1831 records were tagged "Articles". After further screening the document type and relevance, 691 original research publications were ultimately included. The number of articles written in English, German, and Russian are 689, 1, and 1, respectively. The study procedure is shown in Figure 1.

Annual trend of publications

Our analysis revealed that the number of publications markedly increased from 2019 to 2021 (a peak level of 169 in 2021) and then decreased from 2022 to 2023 (Figure 2). The mean number of publications per year was 138.3, and the median was 143 (Figure 2). The cumulative number of citations of these articles increased from 1591 to 4246 during the last five years (Figure 2).

The most productive and influential authors

The publication and citation numbers of the authors were identified *via* VOSviewer software. In total, 3161 authors participated in publishing the articles. The top 10 authors are listed in Table 1. Fabrice Bartolomei (62 publications) was far ahead of the others, emerging as the most prolific author. Other productive authors included Lagarde Stanislas (33 publications), Zhang Kai (25 publications), Carron Romain (24 publications), McGonigal Aileen (23 publications), Zhang Chao (23 publications), Wang Xiu (21 publications), *etc.* With 577 citations, Fabrice Bartolomei was also the most influential researcher in this field, followed by Lagarde Stanislas (387 citations) and McGonigal Aileen (324 citations).

Most productive and influential scientific organizations

VOSviewer software was employed to identify the publication and citation numbers of the scientific organizations. A total of 901 institutions published their works in the last five years. Among the 691 publications, 529 involved multiple institutions, and 196 represented international collaborations. Capital Medical University published 85 articles on SEEG, ranking first, followed by Aix-Marseille University (77 articles), Timone Hospital (48 articles), Fudan University (24 articles), and Shanghai Jiao Tong University (23 articles), and the top 10 organizations are listed in Table 2. Aix-Marseille University had the most citations (n = 701), followed by Timone Hospital (n = 462) and Capital Medical University (n = 378).

Distribution analysis of the country and regions

Country analysis was performed by VOSviewer. Our evaluation revealed that the articles belonged to 45 countries or regions. The United States of America has the highest number of publications (n = 270) on SEEG, far ahead of China (n = 155) and France (n = 132), followed by Italy (n = 53) and Canada (n = 51). The rule of the citation rank was similar to that of the publication number. Figure 3 shows the citation relationships of the countries or regions that had at least 5 publications and Table 3 shows the top 10 countries in terms of the publications. Notably, numerous countries maintain strong connections with both the United States and France. Nevertheless, countries in yellow, including China, Spain, Austria, Belgium, Romania, and the Czech Republic, boomed in this field.

Popular journals

We utilized VOSviewer to analyze the journals that published the articles. These articles were recorded by 156 journals, and 10 journals recorded more than 20 articles. Table 4 shows the top 10 journals in terms of the publications. With 45 documents, Epilepsia published the largest number of articles in this field, followed by *Clinical Neurophysiology* (39 documents) and the *Journal of Neurosurgery* (32 documents). In terms of the total number of citations, *Epilepsia* (n = 549), *Journal of Neurosurgery* (n = 243), and *Clinical Neurophysiology* (n = 224) also ranked in the top 3. However, yellow nodes in the citation analysis map (Figure 4), such as *Epilepsia*, *Neurology*, and *Cortex*, had higher average citations.

Keywords analysis

The results are presented in Figure 5. Keywords with a frequency of 10 or higher were presented. As depicted, the

Table 1 Top 10 authors in stereoelectroencephalography research

Rank	Author	Documents	Citations
1	Fabrice Bartolomei	62	577
2	Lagarde Stanislas	33	387
3	Zhang Kai	25	181
4	Carron Romain	24	301
5	Mcgonigal Aileen	23	324
6	Zhang Chao	23	156
7	Wang Xiu	21	173
8	Trebuchon Agnes	20	278
9	Yu Tao	18	46
10	Hu Wenhan	15	91

Table 2 Top 10 organizations in stereoelectroencephalography research

Rank	Organizations	Count	Citations	Country
1	Capital Medical University	85	378	China
2	Aix-Marseille University	77	701	France
3	Timone Hospital	48	462	France
4	Fudan University	24	100	China
5	Shanghai Jiao Tong University	23	83	China
6	University College London	22	179	United Kingdom
7	University of Pittsburgh	22	86	United States
8	Grande Ospedale Metropolitano Niguarda	21	291	Italy
9	McGill university	20	194	Canada
10	Cleveland clinic	18	186	United States

Table 3 Top 10 countries in stereoelectroencephalography research

Rank	Country	Documents	Citations
1	United States	270	1778
2	China	155	658
3	France	132	1118
4	Italy	53	484
5	Canada	51	394
6	United Kingdom	48	411
7	Germany	29	224
8	Australia	25	153
9	Spain	22	117
10	Japan	18	119

Table 4 Top 10 journals of the number of publications on stereoelectroencephalography studies

Rank	Journal	Documents	Citations
1	*Epilepsia*	45	549
2	*Clinical Neurophysiology*	39	224
3	*Journal of Neurosurgery*	32	243
4	*Frontiers in Neurology*	27	93
5	*Epilepsy Research*	25	117
6	*Epilepsy & Behavior*	24	163
7	*Seizure*	21	125
8	*Journal of Neural Engineering*	21	81
9	*Epilepsy and Behavior Reports*	21	31
10	*Epileptic Disorders*	21	19

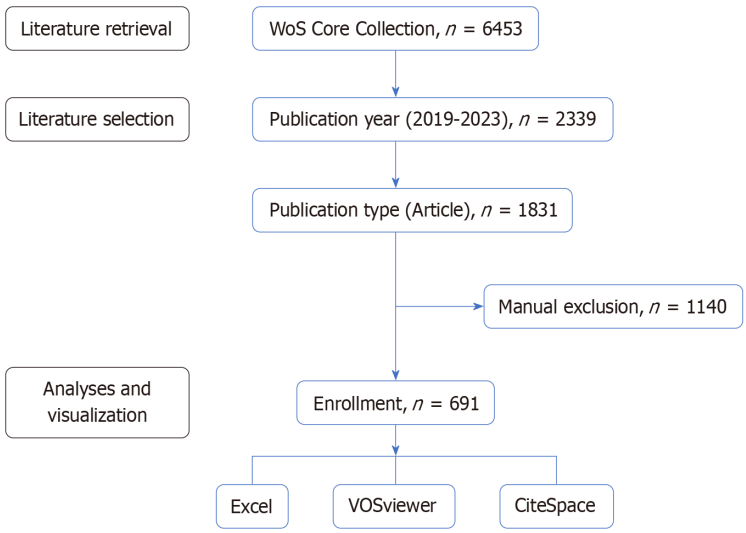


Figure 1 Flow chart of the main steps of this study.

identified keywords are organized into 5 distinct clusters. The green cluster primarily encompasses keywords pertinent to the clinical applications of SEEG, and the red cluster focuses on encephalic regions and functions.

The related research on SEEG encompasses various aspects, such as its working principle, action site, and research object. By utilizing relevant keywords, ten distinct clusters were generated, providing a comprehensive overview of the field. Figure 6 depicts the temporal evolution of keywords *via* the utilization of CiteSpace software, revealing a dynamic research domain marked by evolving topics, including direct electrical stimulation, the epileptogenic zone, and medically refractory epilepsy. Notably, epilepsy was the primary topic of SEEG, other issues such as sleep and memory were also involved. By further analysis with CiteSpace, we obtained the keywords with the strongest citation bursts (Figure 7). Among them, deep learning and source localization have booming tendencies.

DISCUSSION

Bibliometric analysis has emerged as an effective, objective, and reproducible tool for analyzing research output within a specific field[11]. In the present study, we analyzed 691 articles that investigated SEEG. Interestingly, the number of publications in this field remains high. This result highlights the great interest of global researchers in SEEG, underscores the value of SEEG, and highlights its importance across the board. It is therefore likely that the emphasis on SEEG will continue in the future.

In terms of author contributions, more than 3000 researchers have published related articles. Professor Fabrice Bartolomei, an expert on epilepsy from Timone Hospital in France, is the most productive and influential researcher in the field of SEEG. His first studies on epilepsy demonstrated the mechanism of seizure-related humming *via* SEEG techniques[12]. Many clinical investigations on epilepsy have been conducted since then. The most frequently cited study

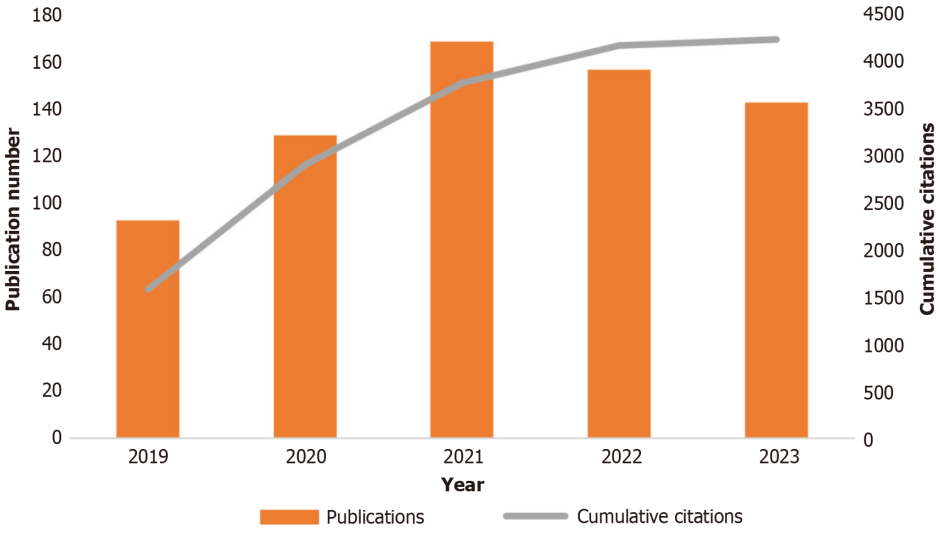


Figure 2 Annual trends of global scientific publications from 2019 to 2023.

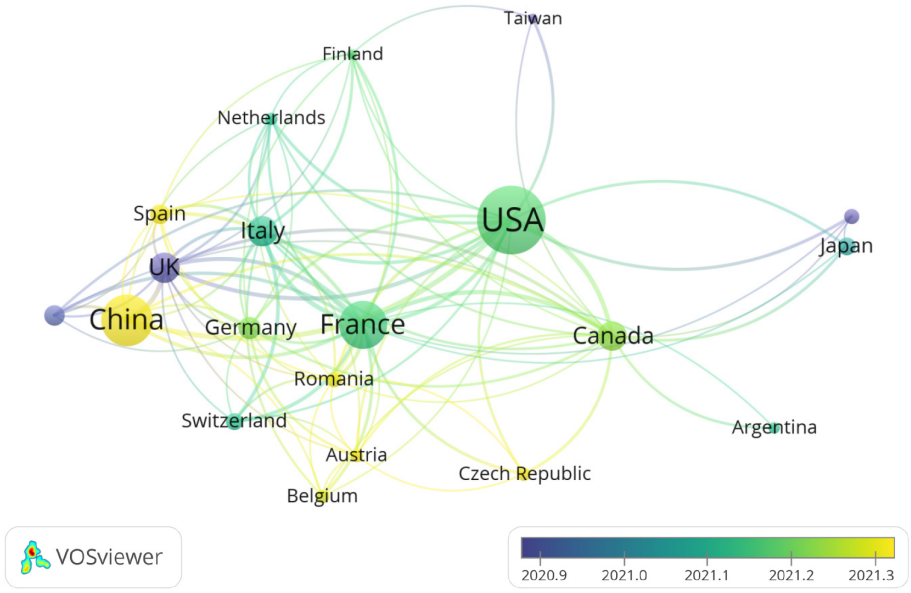


Figure 3 Citation analysis of the countries or regions. The threshold for each node presented in the map is set as 5 publications.

was published in 2019, indicating the determinants and prognosis of seizure onset patterns for focal epilepsies[13]. Recently, his team focused on investigating SEEG markers for epilepsy[14,15].

The United States, China, and France ranked in the top three countries in terms of the number of publications, which means that these three countries represent the highest level of SEEG research worldwide and make the greatest contribution to this field. The co-authorship map of countries revealed global cooperation in this field, with the United States and France exhibiting notably greater centrality. However, China, which ranks in the top three by publications, has relatively less cooperation with other countries. Therefore, China should enhance its international cooperation and carry out more comprehensive and profound research on SEEG.

The present study revealed that the most highly cited journal in this field was *Epilepsia*, with 45 documents and 549 citations, followed by *Clinical Neurophysiology*, the *Journal of Neurosurgery*, and *Frontiers in Neurology*. Therefore, we believe that these journals will continue publishing influential and advanced research in this field in the future. Experts and scholars who have a keen interest in the subject will discover a plethora of novel developments and cutting-edge research in these journals.

Keywords encapsulate the core of papers, revealing the hotspots of research. Keyword co-occurrence analysis pinpoints scientific hotspots. Visual network diagrams clarify evolving trends. Burst keywords track historical development and suggest future research directions. The analyses of keywords revealed that some keywords, such as "surgical technique", "effective connectivity" and "seizure onset patterns", have been researching hotspots in this field in the past. SEEG's accurate identification determines the surgical prognosis, and this characteristic has shifted the research trend toward 'surgical technique'. However, "deep learning" and "source localization" have been the most popular topics

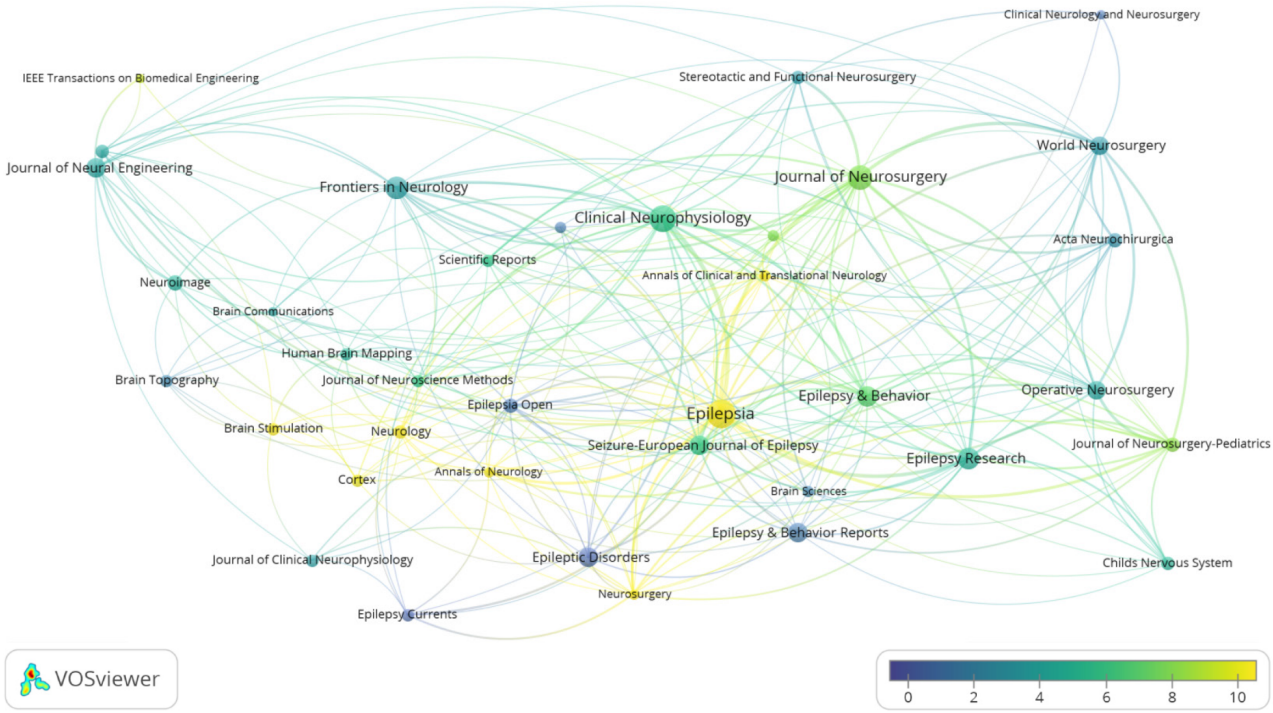


Figure 4 Citation analysis of the journals. The threshold for each node presented in the map is set as 5 publications.

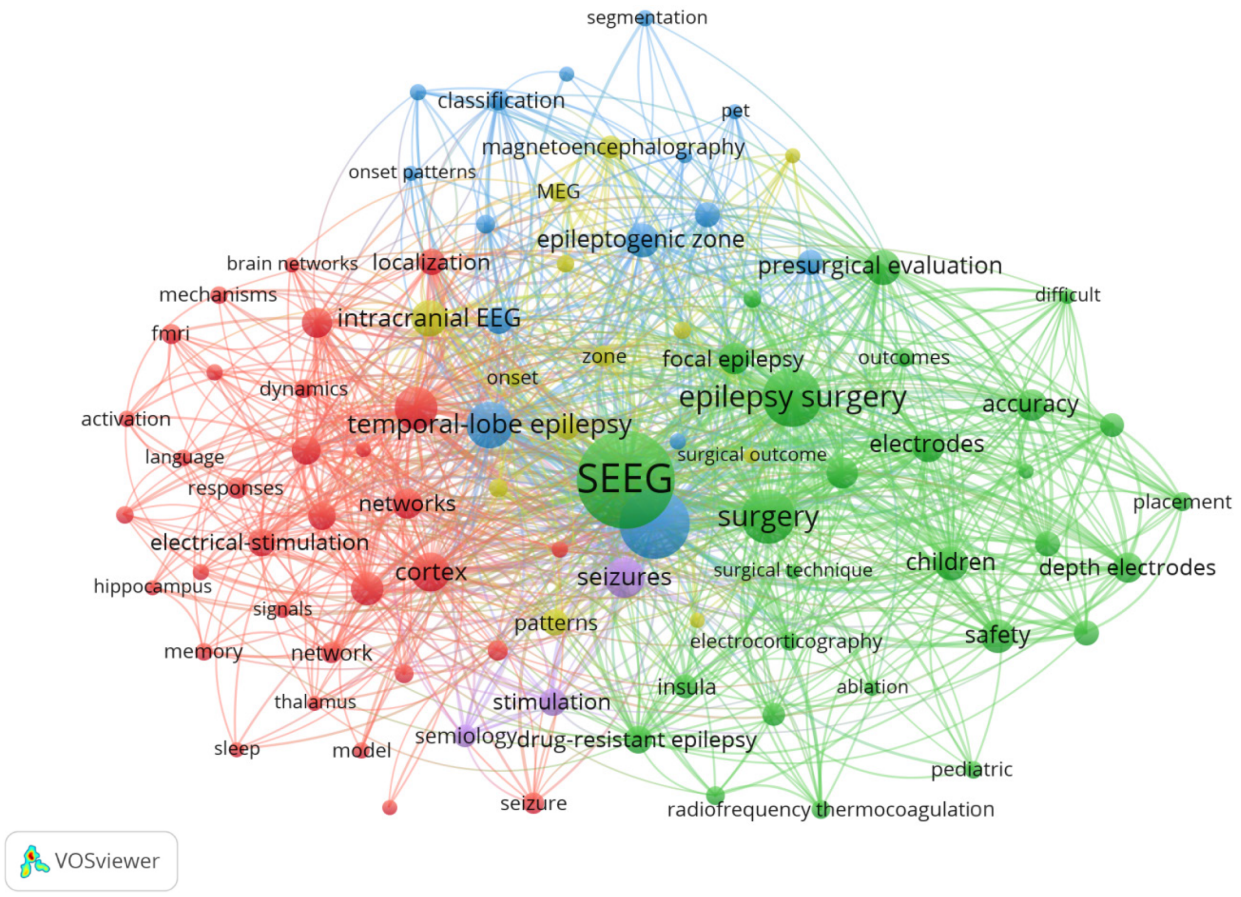


Figure 5 Keywords network. The lowest frequency in the articles of these nodes is 10.

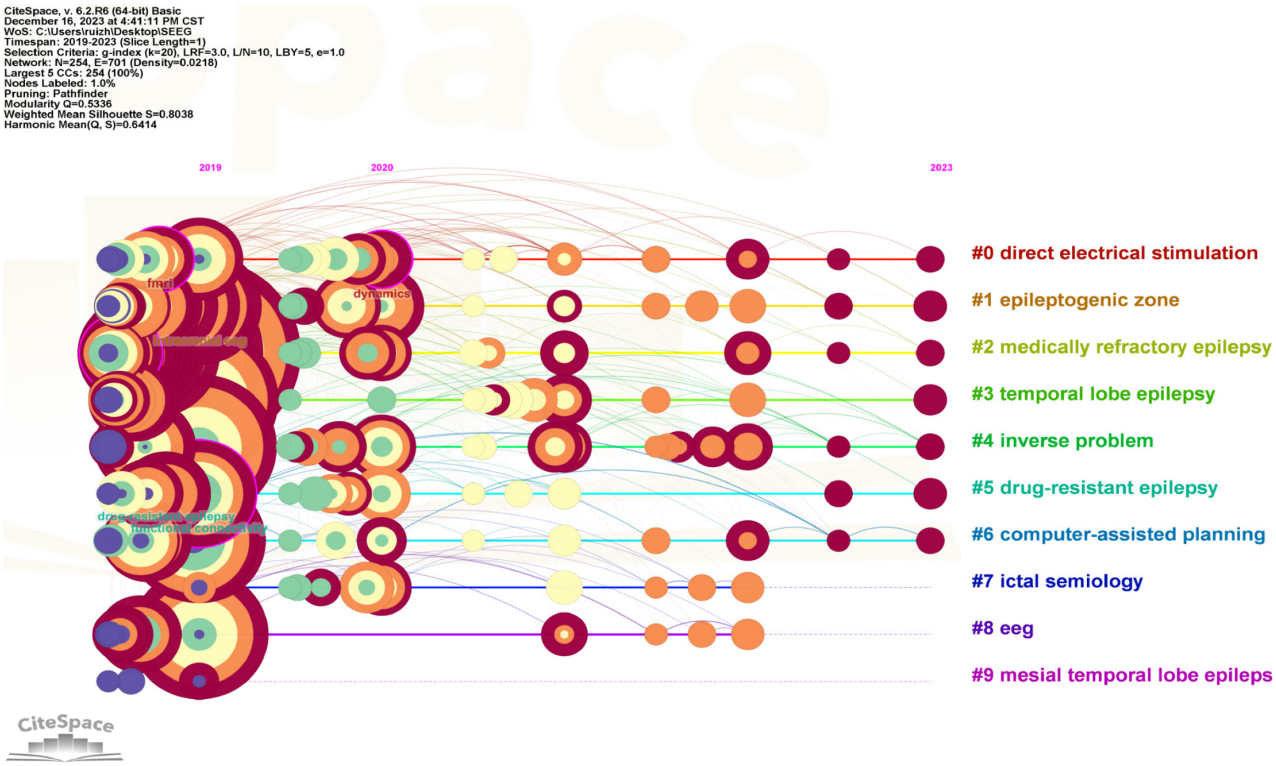


Figure 6 Timeline visualization of keyword analysis. SEEG: Stereoelectroencephalography.

Top 10 keywords with the strongest citation bursts

Keywords	Year	Strength	Begin	End	2019-2023
seizure onset patterns	2019	2.77	2019	2019	
onset patterns	2019	2.77	2019	2019	
effective connectivity	2020	2.39	2020	2020	
surgical technique	2021	2.82	2021	2021	
phase	2021	2.82	2021	2021	
registration	2021	2.35	2021	2021	
temporal lobe	2021	2.35	2021	2021	
surgical outcome	2021	2.35	2021	2021	
deep learning	2022	2.81	2022	2023	
source localization	2022	2.76	2022	2023	

Figure 7 The 10 keywords with the strongest citation bursts in the past 5 years.

in recent years. Clinical research can focus on these aspects. Machine learning is playing an increasingly important role in medical image analysis. In contrast to these traditional decoding techniques, the equivalent or superior performance of deep learning methods has been demonstrated across various studies utilizing SEEG[16,17]. Ictal SEEG source localization is valid and useful for corroborating the epileptogenic zone[18]. Therefore, it is important to develop deep learning and source localization for SEEG, and future research on deep learning and source localization will involve more clinical applications.

Currently, our knowledge regarding epilepsy networks and human brain functional networks remains limited. However, SEEG plays an important role and has emerged as the preferred method for intracranial monitoring in epilepsy patients[4]. As the diagnostic and therapeutic approaches based on SEEG continue to evolve, they promise to significantly increase the quality of life for individuals living with drug-resistant epilepsy[19,20]. Based on these analyses, we predict that these studies on deep learning and source localization will continue to be hotspots in the field of SEEG.

Limitations

This study has certain limitations. First, the exclusive reliance on data from the WoSCC database presents a challenge, as

it inevitably leads to concerns regarding the comprehensiveness of the analyzed data. Nevertheless, the WoSCC database encompasses a vast repository of high-quality academic journals, conference papers, and patents from across the globe. It is the articles of superior quality, rather than those of subpar quality, that catalyze the advancement of scientific research. Second, research results generally reach their peak of citations one to two years after publication or release, which can lead to a lag in the evaluation results of bibliometric analysis and may not reflect the latest research results and trends over time.

CONCLUSION

In this study, 691 articles published in the last 5 years were analyzed *via* bibliometrics to clarify the current status and future trends of SEEG research. The number of publications markedly increased from 2019 to 2023. Fabrice Bartolomei is the most prolific and influential author. The Capital Medical University of China ranks first in terms of publication number. Additionally, the United States has the highest number of publications and citations. *Epilepsia*, *Clinical Neurophysiology*, *Journal of Neurosurgery*, and *Frontiers in Neurology* are the most popular journals in the field of SEEG. *Epilepsy* is still the primary clinical application of SEEG, while deep learning and source localization have strongly increased recently. Overall, our study provides a useful reference for further research on SEEG.

FOOTNOTES

Author contributions: Yang WL, Jiang WC and Zhou R conceived and designed the study; Yang WL and Zhou R participated in data processing and analysis; Yang WL, Jiang WC, Zhou R, Zhang XJ drafted the manuscript; Yang WL and Jiang WC contributed to data analysis and interpretation; Zhang XJ supervised the review of the study. All authors seriously revised and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: China

ORCID number: Wei-Lin Yang 0009-0009-0105-0513; Rui Zhou 0000-0002-1479-4409; Wen-Cai Jiang 0009-0006-5406-233X.

S-Editor: Liu H
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Talairach J**, Bancaud J, Bonis A, Szikla G, Tournoux P. Functional stereotaxic exploration of epilepsy. *Confin Neurol* 1962; **22**: 328-331 [PMID: 13984743 DOI: 10.1159/000104378]

2 **Isnard J**, Taussig D, Bartolomei F, Bourdillon P, Catenoix H, Chassoux F, Chipaux M, Clémenceau S, Colnat-Coulbois S, Denuelle M, Derrey S, Devaux B, Dorfmüller G, Gilard V, Guenot M, Job-Chapron AS, Landré E, Lebas A, Maillard L, McGonigal A, Minotti L, Montavont A, Navarro V, Nica A, Reyns N, Scholly J, Sol JC, Szurhaj W, Trebuchon A, Tyvaert L, Valenti-Hirsch MP, Valton L, Vignal JP, Sauleau P. French guidelines on stereoelectroencephalography (SEEG). *Neurophysiol Clin* 2018; **48**: 5-13 [PMID: 29277357 DOI: 10.1016/j.neucli.2017.11.005]

3 **McGonigal A**. Frontal lobe seizures: overview and update. *J Neurol* 2022; **269**: 3363-3371 [PMID: 35006387 DOI: 10.1007/s00415-021-10949-0]

4 **Buch VP**, Parvizi J. Evolution of SEEG Strategy: Stanford Experience. *Neurosurg Clin N Am* 2024; **35**: 83-85 [PMID: 38000844 DOI: 10.1016/j.nec.2023.08.003]

5 **Tandon N**, Tong BA, Friedman ER, Johnson JA, Von Allmen G, Thomas MS, Hope OA, Kalamangalam GP, Slater JD, Thompson SA. Analysis of Morbidity and Outcomes Associated With Use of Subdural Grids vs Stereoelectroencephalography in Patients With Intractable Epilepsy. *JAMA Neurol* 2019; **76**: 672-681 [PMID: 30830149 DOI: 10.1001/jamaneurol.2019.0098]

6 **Kim LH**, Parker JJ, Ho AL, Feng AY, Kumar KK, Chen KS, Ojukwu DI, Shuer LM, Grant GA, Graber KD, Halpern CH. Contemporaneous evaluation of patient experience, surgical strategy, and seizure outcomes in patients undergoing stereoelectroencephalography or subdural electrode monitoring. *Epilepsia* 2021; **62**: 74-84 [PMID: 33236777 DOI: 10.1111/epi.16762]

7 **Wu X**, Jiang S, Li G, Liu S, Metcalfe B, Chen L, Zhang D. Deep Learning With Convolutional Neural Networks for Motor Brain-Computer Interfaces Based on Stereo-Electroencephalography (SEEG). *IEEE J Biomed Health Inform* 2023; **27**: 2387-2398 [PMID: 37022416 DOI:

10.1109/JBHI.2023.3242262]

8 **Satzer D**, Esengul YT, Warnke PC, Issa NP, Nordli DR Jr. Source localization of ictal SEEG to predict postoperative seizure outcome. *Clin Neurophysiol* 2022; **144**: 142-150 [PMID: 36088217 DOI: 10.1016/j.clinph.2022.08.013]

9 **Ninkov A**, Frank JR, Maggio LA. Bibliometrics: Methods for studying academic publishing. *Perspect Med Educ* 2022; **11**: 173-176 [PMID: 34914027 DOI: 10.1007/s40037-021-00695-4]

10 **He T**, Wang D, Wu Z, Huang C, Xu X, Xu X, Liu C, Hashimoto K, Yang C. A bibliometric analysis of research on (R)-ketamine from 2002 to 2021. *Neuropharmacology* 2022; **218**: 109207 [PMID: 35948160 DOI: 10.1016/j.neuropharm.2022.109207]

11 **Wang L**, Chen Y, Shen W, Fan X, Jia M, Fu G, Chi X, Liang X, Zhang Y. A Bibliometric Analysis of Cardioembolic Stroke From 2012 to 2022. *Curr Probl Cardiol* 2023; **48**: 101537 [PMID: 36529228 DOI: 10.1016/j.cpcardiol.2022.101537]

12 **Bartolomei F**, Wendling F, Vignal JP, Chauvel P, Liégeois-Chauvel C. Neural networks underlying epileptic humming. *Epilepsia* 2002; **43**: 1001-1012 [PMID: 12199725 DOI: 10.1046/j.1528-1157.2002.48501.x]

13 **Lagarde S**, Buzori S, Trebuchon A, Carron R, Scavarda D, Milh M, McGonigal A, Bartolomei F. The repertoire of seizure onset patterns in human focal epilepsies: Determinants and prognostic values. *Epilepsia* 2019; **60**: 85-95 [PMID: 30426477 DOI: 10.1111/epi.14604]

14 **Makhalova J**, Madec T, Medina Villalon S, Jegou A, Lagarde S, Carron R, Scavarda D, Garnier E, Bénar CG, Bartolomei F. The role of quantitative markers in surgical prognostication after stereoelectroencephalography. *Ann Clin Transl Neurol* 2023; **10**: 2114-2126 [PMID: 37735846 DOI: 10.1002/acn3.51900]

15 **Runfola C**, Sheheitli H, Bartolomei F, Wang H, Jirsa V. In pursuit of the epileptogenic zone in focal epilepsy:a dynamical network biomarker approach. *Commun Nonlinear Sci Numer Simul* 2023; **117**: 106973 [DOI: 10.1016/j.cnsns.2022.106973]

16 **Yuan J**, Ran X, Liu K, Yao C, Yao Y, Wu H, Liu Q. Machine learning applications on neuroimaging for diagnosis and prognosis of epilepsy: A review. *J Neurosci Methods* 2022; **368**: 109441 [PMID: 34942271 DOI: 10.1016/j.jneumeth.2021.109441]

17 **Wang Y**, Yang Y, Cao G, Guo J, Wei P, Feng T, Dai Y, Huang J, Kang G, Zhao G. SEEG-Net: An explainable and deep learning-based cross-subject pathological activity detection method for drug-resistant epilepsy. *Comput Biol Med* 2022; **148**: 105703 [PMID: 35791972 DOI: 10.1016/j.compbiomed.2022.105703]

18 **Caune V**, Ranta R, Le Cam S, Hofmanis J, Maillard L, Koessler L, Louis-Dorr V. Evaluating dipolar source localization feasibility from intracerebral SEEG recordings. *Neuroimage* 2014; **98**: 118-133 [PMID: 24795155 DOI: 10.1016/j.neuroimage.2014.04.058]

19 **Feys O**, Goldman S, Lolli V, Depondt C, Legros B, Gaspard N, Schuind S, De Tiège X, Rikir E. Diagnostic and therapeutic approaches in refractory insular epilepsy. *Epilepsia* 2023; **64**: 1409-1423 [PMID: 36869701 DOI: 10.1111/epi.17571]

20 **Kerezoudis P**, Gyftopoulos A, Alexander AY, Keith Starnes D, Nickels KC, Worrell GA, Wirrell EC, Lundstrom BN, Van Gompel JJ, Miller KJ. Safety and efficacy of responsive neurostimulation in the pediatric population: Evidence from institutional review and patient-level meta-analysis. *Epilepsy Behav* 2022; **129**: 108646 [PMID: 35299087 DOI: 10.1016/j.yebeh.2022.108646]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2025 March 18; 13(1): 104644

DOI: 10.13105/wjma.v13.i1.104644

ISSN 2308-3840 (online)

SCIENTOMETRICS

Mapping the current trends and hotspots of transcranial magnetic stimulation-based addiction treatment from 2001-2023: A bibliometric analysis

Hao-Ran Yang, Zheng-Yu Li, Hao Zhu, Hong Wu, Chen Xie, Xin-Qiang Wang, Chang-Shun Huang, Wu-Jun Geng

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade C

Creativity or Innovation: Grade C

Scientific Significance: Grade C

P-Reviewer: Chai R

Received: December 28, 2024

Revised: January 26, 2025

Accepted: February 12, 2025

Published online: March 18, 2025

Processing time: 77 Days and 19.6 Hours

Hao-Ran Yang, School of Educational Sciences, Chongqing Normal University, Chongqing 400030, China

Zheng-Yu Li, Department of Anesthesiology, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, Anhui Province, China

Hao Zhu, Hong Wu, Chang-Shun Huang, Department of Anesthesiology, The First Affiliated Hospital of Ningbo University, Ningbo 315010, Zhejiang Province, China

Chen Xie, Xin-Qiang Wang, Department of Anesthesiology, The First People's Hospital of Huzhou, Huzhou 313000, Zhejiang Province, China

Wu-Jun Geng, Oujiang Laboratory (Zhejiang Laboratory for Regenerative Medicine, Vision and Brain Health), Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China

Wu-Jun Geng, Department of Pain, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China

Co-first authors: Hao-Ran Yang and Zheng-Yu Li.

Co-corresponding authors: Chang-Shun Huang and Wu-Jun Geng.

Corresponding author: Wu-Jun Geng, MD, PhD, Associate Professor, Oujiang Laboratory (Zhejiang Lab for Regenerative Medicine, Vision and Brain Health), Wenzhou Medical University, No. 999 Jinshi Road, Yongzhong Street, Longwan District, Wenzhou 325000, Zhejiang Province, China. gengwujun@ojlab.ac.cn

Abstract

BACKGROUND

The prevalence of addiction makes it a significant public health issue. Recently, transcranial magnetic stimulation (TMS) has garnered significant attention as a promising treatment for addiction.

AIM

To analyze development trends and research hotspots in TMS-based addiction treatment using a bibliometric approach.

METHODS
Articles on TMS-based addiction treatment from 2001 to 2023 were sourced from the Science Citation Index Expanded in the Web of Science Core Collection. CiteSpace software, VOSviewer, the "bibliometrix" R software package, and the bibliometric online analysis platform were used to analyze the current publication trends and hotspots.

RESULTS
Total 190 articles on TMS-based addiction treatment were identified, with clinical studies being the most prevalent. The United States led in both publication volume and international collaborations. Medical University of South Carolina and Zangen A were the most productive institution and author, respectively. Neurobiology, alcohol use disorder, and repetitive TMS were the most recent research hotspots.

CONCLUSION
Future research should focus on the neurobiological mechanisms underlying TMS-based addiction treatment. This study offers comprehensive insights and recommendations for advancing research on TMS-based addiction treatment.

Key Words: Transcranial magnetic stimulation; Addiction; Bibliometric analysis; Transcranial magnetic stimulation-based addiction treatment; Alcohol use disorder

Core Tip: This study presents the inaugural bibliometric analysis of research on addiction treatment using transcranial magnetic stimulation (TMS). From 2001 to 2023, the United States led in both output volume and international collaborations. Medical University of South Carolina and Zangen A were the most productive institution and author, respectively. Neurobiology, alcohol use disorder, and repetitive TMS were the most recent research hotspots.

Citation: Yang HR, Li ZY, Zhu H, Wu H, Xie C, Wang XQ, Huang CS, Geng WJ. Mapping the current trends and hotspots of transcranial magnetic stimulation-based addiction treatment from 2001-2023: A bibliometric analysis. *World J Meta-Anal* 2025; 13(1): 104644
URL: https://www.wjgnet.com/2308-3840/full/v13/i1/104644.htm
DOI: https://dx.doi.org/10.13105/wjma.v13.i1.104644

INTRODUCTION

Addiction is a periodic or chronic toxic state that arises from the continuous use of certain substances. Despite understanding the serious harm of addictive substances, individuals cannot control their use and continue to seek out these substances[1]. According to the 2018 National Survey on Drug Use and Health in America[2], approximately 20.3 million individuals aged 12 or older were reported to suffer from substance use disorders. Despite the availability of therapeutic interventions, relapse rates are high, and addiction is inadequately addressed[3]. Consequently, improved treatment strategies can benefit individuals with addiction globally. Transcranial magnetic stimulation (TMS) is a non-invasive, relatively simple treatment with fewer side effects, making it a significant alternative for addiction[4,5].

TMS stimulates brain activity using a fast and time-varying magnetic field[6]. It can target the prefrontal cortex (PFC) and activate underlying cortical regions[7]. Recently, many studies have found that TMS can be used to effectively treat different types of addiction, such as addiction to nicotine[8,9], alcohol[10], cocaine[11], heroin[12,13], and methamphetamine[14]. TMS is used to treat addiction due to dorsolateral PFC dysfunction in these disorders. Normal function of the dorsolateral PFC is essential for top-down inhibitory control mechanisms and reward mechanisms[15]. Nevertheless, the neurobiological mechanisms of TMS in the treatment of addiction have not been fully elucidated, and the optimal stimulation parameters remain undetermined. Although the high worldwide prevalence of addiction has led to a growing interest in TMS-based treatment of addiction among researchers, few articles have summarized current advances in this field and predicted future research hotspots.

Bibliometric analysis is an in-depth econometric examination of publications within a particular field over a specified timeframe. It includes parameters like article count, author count, country or region, journal, reference, and keyword. It presents a detailed overview of the chosen research area, enabling researchers to gain an in-depth and comprehensive understanding of the latest research trends and potential future hotspots[16-20]. However, there is currently a lack of bibliometric articles analyzing publication characteristics, research trends, and hotspots related to TMS-based treatment of addiction. This bibliometric study analyzed research trends and key areas in TMS-based addiction treatment from 2001 to 2023. In this study, we provided a panoramic overview of the field and identified future research trends and potential hotspots.

MATERIALS AND METHODS

Sources of data and search methodologies

The study utilizes data from publications dated January 1, 2001, to December 31, 2023, sourced from the Web of Science Core Collection (WoSCC) on January 20, 2024. To prevent bias in database updates, we conducted data extraction and downloads within a single day. We conducted a literature search using the strategy: TS = [(Transcranial Magnetic Stimulation) OR (Theta burst stimulation) OR (TMS) OR (TBS)] AND [TS = (addiction) OR (addictive behavior) OR (substance use disorder) OR (substance-related disorders) OR (habituation) OR (dependence) OR (dependency) OR (craving) OR (alcoholism)] AND [DT = (Article)] AND [LA = (English)]. The selection was limited to the Science Citation Index-Expanded (SCI-E). The exclusion criteria included: (1) Studies unrelated to TMS-based addiction treatment; (2) Non-scientific articles, including proceedings, book chapters, reviews, corrections, editorials, letters, news items, meeting abstracts, and retracted publications; (3) Publications not in English; and (4) Duplicate publications. To ensure the accuracy of the bibliometric analysis, researchers Yang HR and Li ZY verified all publications obtained through the search strategy, examining their titles, abstracts, and publication years. Then, raw data were downloaded from WoSCC as text files containing full records. Figure 1 provides a schematic representation of the detailed screening workflow.

Bibliometric analysis

We used the Web of Science to characterize all publications on TMS-based treatment of addiction, analyze the search results, and extract histograms depicting publication trends. Data from WoSCC were converted to TXT format and imported into VOSviewer 1.6.19 and CiteSpace V6.1R6 for analysis. Furthermore, data were analyzed using the "bibliometrix" R software package and the bibliometric online analysis platform.

The annual publication count was obtained from WoSCC, and the publication counts for the top 10 countries/regions and the top 10 most cited journals were sourced from the bibliometric online analysis platform. A word cloud of the top 100 high-frequency keywords was created using the "bibliometrix" R package. Furthermore, the analysis of collaborations between countries/regions was conducted using VOSviewer software, a tool that facilitates the construction of visual bibliometric maps[21]. CiteSpace, a widely recognized bibliometric visualization tool[22], was used to analyze various data, help understand the recent status of research related to TMS-based treatment of addiction, and predict potential hotspots in this field. The data encompassed institutional and author collaborations, reference co-citation analysis, and keywords exhibiting significant citation bursts.

RESULTS

Quantity and trend analysis of published papers

One hundred-ninety articles meeting our inclusion criteria were retrieved from the SCI-E of WoSCC. The total number of articles published per year is displayed at the top of the bar (Figure 2A). Research on TMS-based treatment of addiction was categorized into two periods based on the number of publications. From 2001 to 2014, publications gradually increased, whereas from 2015 to 2023, there was a notable surge in publication numbers. The number of publications in 2022 exceeded that in 2001 by more than 14 times, indicating a significant rise in global interest in research on TMS-based treatment of addiction. Additionally, we assessed the number of clinical research and basic research papers and observed that the majority of the publications were in the realm of clinical research (Figure 2B). Using Microsoft Excel 2021, we formulated a growth trend model represented by the equation: $F(x) = 0.0547x^2 - 218.9x + 219163$ ($R^2 = 0.8513$). This model predicted the publication of approximately 43 articles in 2030 (Supplementary Figure 1).

Using the bibliometric online analysis platform, we identified the leading country/region researching TMS-based addiction treatment from 2001 to 2023 and quantified the publication counts across various countries/regions. Figure 2C illustrates a bar chart showing the top 10 countries with the most published papers from 2001 to 2023. Throughout this period, the United States has maintained its prominent position in studying TMS-based treatment of addiction, with China overtaking the United States in annual publications from 2020 to 2022.

We analyzed the overall citation count for articles published from each country/region and presented the top 10 countries/regions (Figure 2D). The United States and Canada ranked first and second with 1923 and 1718 total citations for all relevant papers published, respectively. By calculating the average number of citations per article (total number of citations/total number of articles) for each country/region, we determined the top 10 countries/regions based on this metric (Table 1). Switzerland, Canada, and Israel ranked as the top three countries with the highest average citations, recording 280.0, 156.2, and 80.1 citations, respectively.

Analysis of collaborating countries/regions and institutions

From 2001 to 2023, 190 articles on TMS-based treatment of addiction were published in 27 countries and regions. The VOSviewer software was applied to explore the collaborative status among these countries or regions. Figure 3A illustrates international academic collaborations in TMS-based addiction treatment research, with circles representing countries/regions and lines indicating collaborative links. Circle size represents the number of articles published by each country/region, while line thickness reflects the collaboration intensity between them. The findings indicated that the United States was the leading nation in international collaboration. The United States collaborated most frequently with Italy, followed by China.

Table 1 The top 10 countries with the highest total citations for research on transcranial magnetic stimulation-based addiction treatment, published between 2001 and 2023 (ranked by average citations)

Rank	Country	Number of publications	Total number of citations	Average number of citations
1	Switzerland	1	280	280.0
2	Canada	10	1718	156.2
3	Israel	8	641	80.1
4	Germany	5	341	68.2
5	India	4	234	58.5
6	England	6	335	55.8
7	United States	43	1923	44.7
8	Belgium	10	388	38.8
9	Italy	29	638	22.0
10	China	40	539	13.5

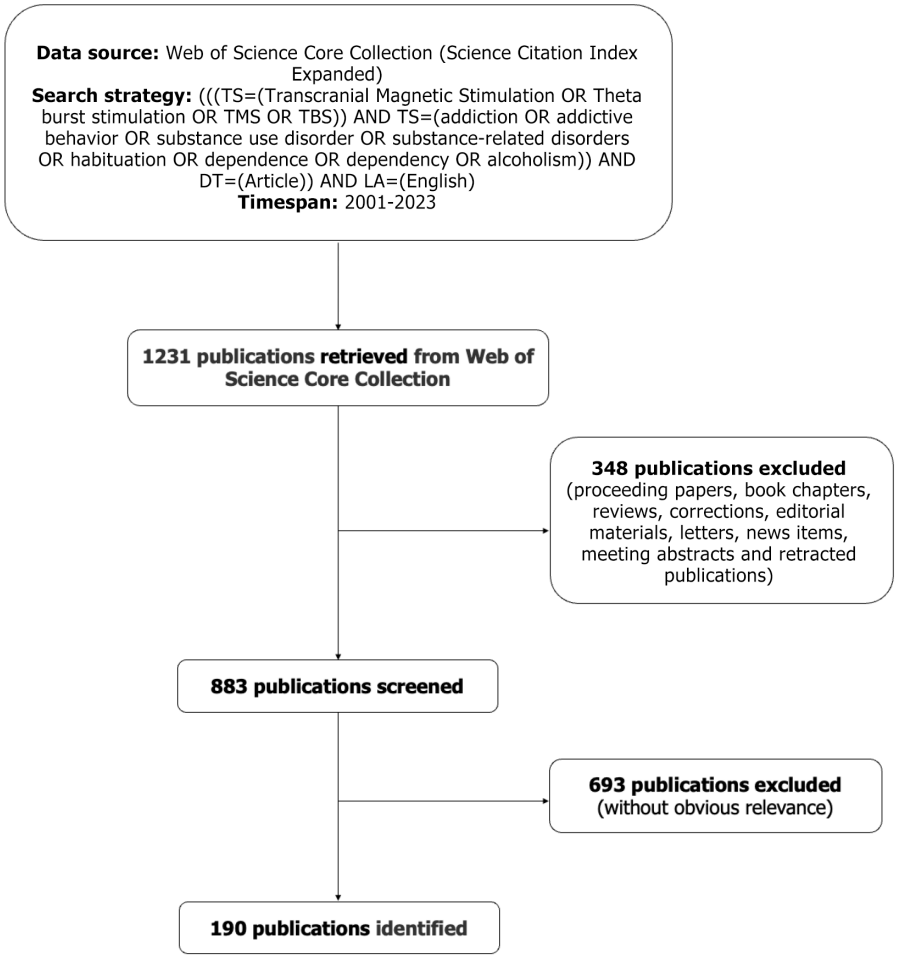
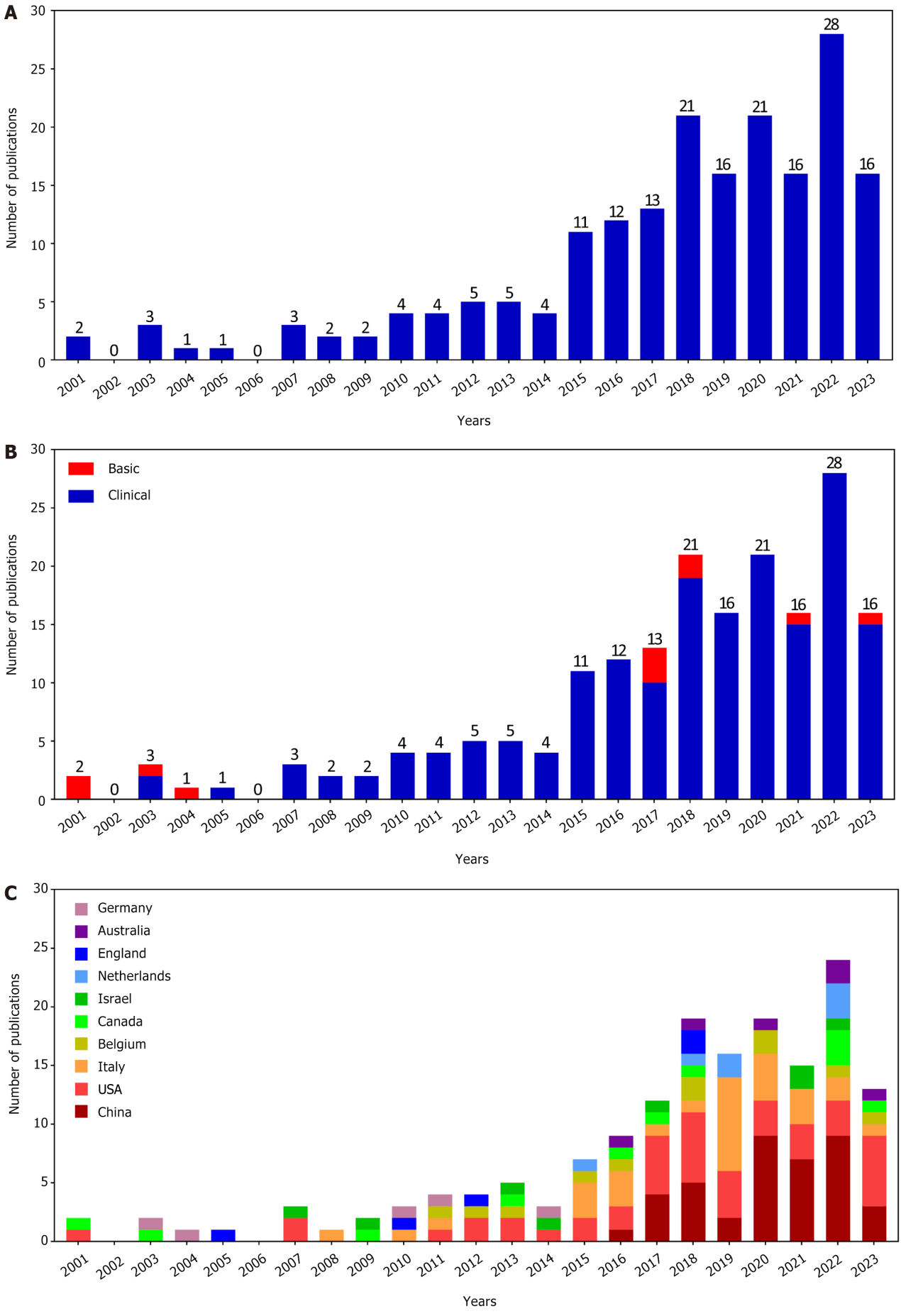


Figure 1 Flowchart describing the inclusion and exclusion criteria used in the present study on transcranial magnetic stimulation-based treatment of addiction. DT: Document type; TBS: Theta-burst stimulation; TMS: Transcranial magnetic stimulation; TS: Topic search.

Data in the TXT format was entered into the CiteSpace software to understand the collaboration status among academic institutions. In total, 229 research institutions participated in studying TMS-based treatment of addiction. Figure 3B visualizes the top 10 most productive institutions, with each concentric circle's size indicating the number of published articles and the thickness of connecting lines representing the extent of inter-institutional collaboration. There were 10 productive institutions with more than 8 publications. The Medical University of South Carolina in the United States published the highest number of articles (n = 20). Five of the top ten most productive institutions were based in the United States, highlighting the country's significant academic influence in this research area.


A
Number of publications
Years
2 0 3 1 1 0 3 2 2 4 4 5 5 4 11 12 13 21 16 21 16 28 16
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023
B
Basic
Clinical
Number of publications
Years
2 0 3 1 1 0 3 2 2 4 4 5 5 4 11 12 13 21 16 21 16 28 16
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023
C
Germany
Australia
England
Netherlands
Israel
Canada
Belgium
Italy
USA
China
Number of publications
Years
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023

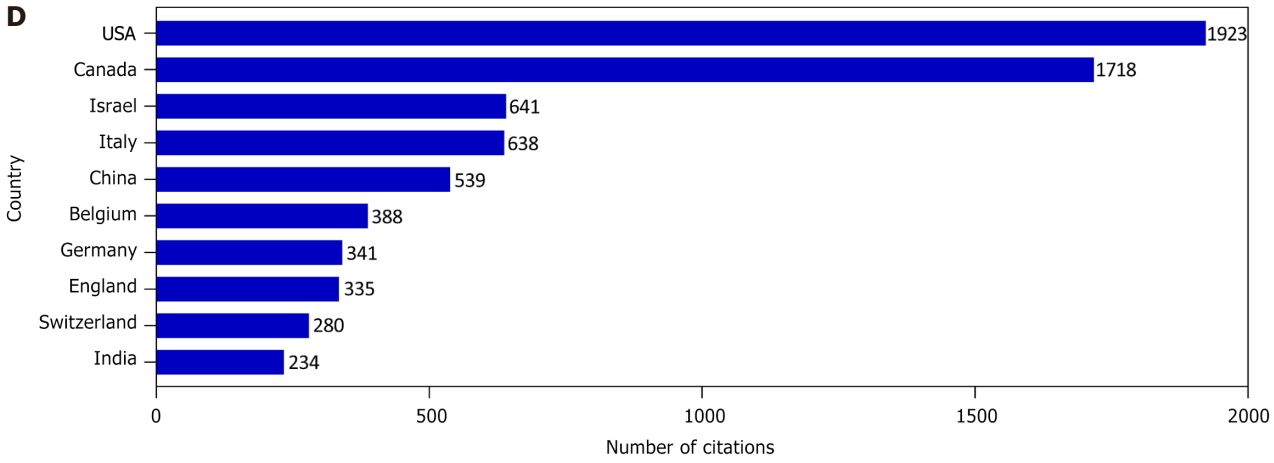


Figure 2 Analysis of the quantity and research trends on transcranial magnetic stimulation-based treatment of addiction from 2001 to 2023. A: The annual number of papers on transcranial magnetic stimulation (TMS)-based treatment of addiction published from 2001 to 2023 was obtained from Web of Science data; B: The proportion of basic and clinical research articles on TMS-based treatment of addiction published from 2001 to 2023; C: Analysis of publication numbers and growth trends for the leading 10 countries/regions in TMS-based addiction treatment, sourced from a bibliometric online platform; D: A bar graph illustrating the total citations from 190 retrieved articles across all countries. This figure displays the top 10 countries ranked by total citation count. Each bar corresponds to a country, with its length directly proportional to the total citation count.

Analysis of co-authorship networks and core author distribution

By analyzing the characteristics of author collaboration networks in a specific field, we can identify the core authors and the extent of collaboration among them[23]. Here, 411 authors were involved in 190 identified articles related to TMS-based treatment of addiction from 2001 to 2023. Figure 4 depicts author collaboration. We identified the top 10 authors based on their publication count. Node and font sizes are directly proportional to publication counts, while line thickness indicates the strength of author collaboration. The visualization map provides intuitive information about the collaboration between different authors, helping researchers identify potential partners. Zangen A, affiliated with the Medical University of South Carolina, authored the highest number of articles (n = 12). The author collaboration network map showed strong collaboration between these prolific authors and other authors.

Journal analysis

The online analysis platform of bibliometrics was used to analyze the influence of journals. The top 10 most cited journals are shown in Table 2, with articles published by *Biological psychiatry* being the most cited (769 citations), followed by articles published by *Drug and alcohol dependence* (675 citations), *European neuropsychopharmacology* (378 citations), *Frontiers in psychiatry* (288 citations), *Brain stimulation* (237 citations), *Neuropsychopharmacology* (218 citations), *Frontiers in neuroscience* (143 citations), *Addiction biology* (98 citations), *Addiction* (69 citations), and *Alcoholism-clinical and experimental research* (56 citations). The publishers of these journals were mainly from the United States (4 of 10). European Neuropsychopharmacology articles had the highest average citations per article, with 126 citations.

Examination of co-citation patterns and network clustering

Literature co-citation identifies articles frequently cited together by multiple authors. Each node symbolizes a reference, with connecting lines indicating that these articles were co-cited by the same article among the 190 articles (Figure 5A). There is a positive correlation between node size and citation frequency. Thicker connecting lines between nodes imply a higher co-citation intensity. Red nodes signify documents frequently cited in recent years, whereas purple nodes represent those cited in earlier years. Citations serve as a key measure of an article's influence within a specific research field. Table 3 indicates the top 10 most cited references from 190 articles. In 2017, a review published in *Nature Reviews Neuroscience* by Diana *et al*[24] Ranked first with 32 citations, the paper reviews TMS mechanisms and proposes that repetitive TMS (rTMS) is pioneering new approaches in addiction treatment. The second-ranked and third-ranked publications were published in *European Neuropsychopharmacology* and *Neuroscience and Biobehavioral Reviews*. They were cited 28 times and 24 times, respectively. The first study indicated the potential therapeutic role of rTMS-mediated PFC stimulation in reducing cocaine use[11], while the second offered guidelines for best practices in researching transcranial electrical and magnetic treatments for substance use disorders[25].

The reference citation burst refers to a rapid increase in citation frequency, which usually reflects the emergence or transformation of a research field. In addition, the higher burst strength of the reference shows greater significance in the field. CiteSpace was used to generate the top 25 references exhibiting the strongest citation bursts (Figure 5B). The blue line indicates the time frame from 2001 to 2023, and the red line indicates the period over which the burst references were maintained. Among the burst references in recent years, the most recent and most cited study was a review, published by *Nature reviews neuroscience* in 2017. The burst began in 2019 and continued until the end of 2023. In this review, the authors described the fundamentals of TMS and its putative mechanisms of action and discussed the pros and cons of TMS. They argued that neural plasticity and connectivity changes may underlie some of the long-term effects of TMS[24].

Table 2 The top 10 most cited journals in the field of transcranial magnetic stimulation-based treatment of addiction, published from 2001 to 2023 (sorted by total number of citations)

Rank	Journal title	Frequency	Total citations	Average citation per paper	Impact factor (2023)	Country	JCR
1	*Biological Psychiatry*	7	769	109.86	9.6	United States	Q1
2	*Drug and Alcohol Dependence*	14	675	48.21	3.9	Switzerland	Q1
3	*European Neuropsychopharmacology*	3	378	126.00	6.1	United States	Q1
4	*Frontiers in Psychiatry*	5	288	57.60	3.2	Netherlands	Q2
5	*Brain Stimulation*	20	237	11.85	7.6	Switzerland	Q1
6	*Neuropsychopharmacology*	6	218	36.33	6.6	United States	Q1
7	*Frontiers in Neuroscience*	4	143	35.75	3.2	England	Q2
8	*Addiction Biology*	6	98	16.33	3.1	Switzerland	Q2
9	*Addiction*	6	69	11.50	5.2	England	Q1
10	*Alcoholism-Clinical and Experimental Research*	3	57	19.00	3.0	United States	Q2

Table 3 The top 10 highly-cited references among 190 retrieved articles on transcranial magnetic stimulation-based treatment of addiction, published from 2001 to 2023 (sorted by citation frequency)

Rank	Title	First author	Journal	Year	Cited frequency	DOI
1	Rehabilitating the addicted brain with transcranial magnetic stimulation	Diana M	*Nature Reviews Neuroscience*	2017	32	10.1038/nrn.2017.113
2	Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: A pilot study	Terraneo A	*European Neuropsychopharmacology*	2016	28	10.1016/j.euroneuro.2015.11.011
3	Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: A consensus paper on the present state of the science and the road ahead	Ekhtiari H	*Neuroscience and Biobehavioral Reviews*	2019	24	10.1016/j.neubiorev.2019.06.007
4	Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: A prospective, randomized controlled trial	Dinur-Klein L	*Biological Psychiatry*	2014	19	10.1016/j.biopsych.2014.05.020
5	High frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex for methamphetamine use disorders: A randomised clinical trial	Su H	*Drug and Alcohol Dependence*	2017	19	10.1016/j.drugalcdep.2017.01.037
6	10-Hz Repetitive Transcranial Magnetic Stimulation of the Left Dorsolateral Prefrontal Cortex Reduces Heroin Cue Craving in Long-Term Addicts	Shen Y	*Biological Psychiatry*	2016	18	10.1016/j.biopsych.2016.02.006
7	Effects of repetitive transcranial magnetic stimulation (rTMS) on craving and substance consumption in patients with substance dependence: A systematic review and meta-analysis	Zhang JJQ	*Addiction*	2019	17	10.1111/add.14753
8	Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex reduces nicotine cue craving	Li XB	*Biological Psychiatry*	2013	17	10.1016/j.biopsych.2013.01.003
9	Transcranial magnetic stimulation in the treatment of substance addiction	Gorelick DA	*Annals of the New York Academy of Sciences*	2014	16	10.1111/nyas.12479
10	Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: A sham-controlled study	Mishra BR	*Addiction*	2010	15	10.1111/j.1360-0443.2009.02777.x

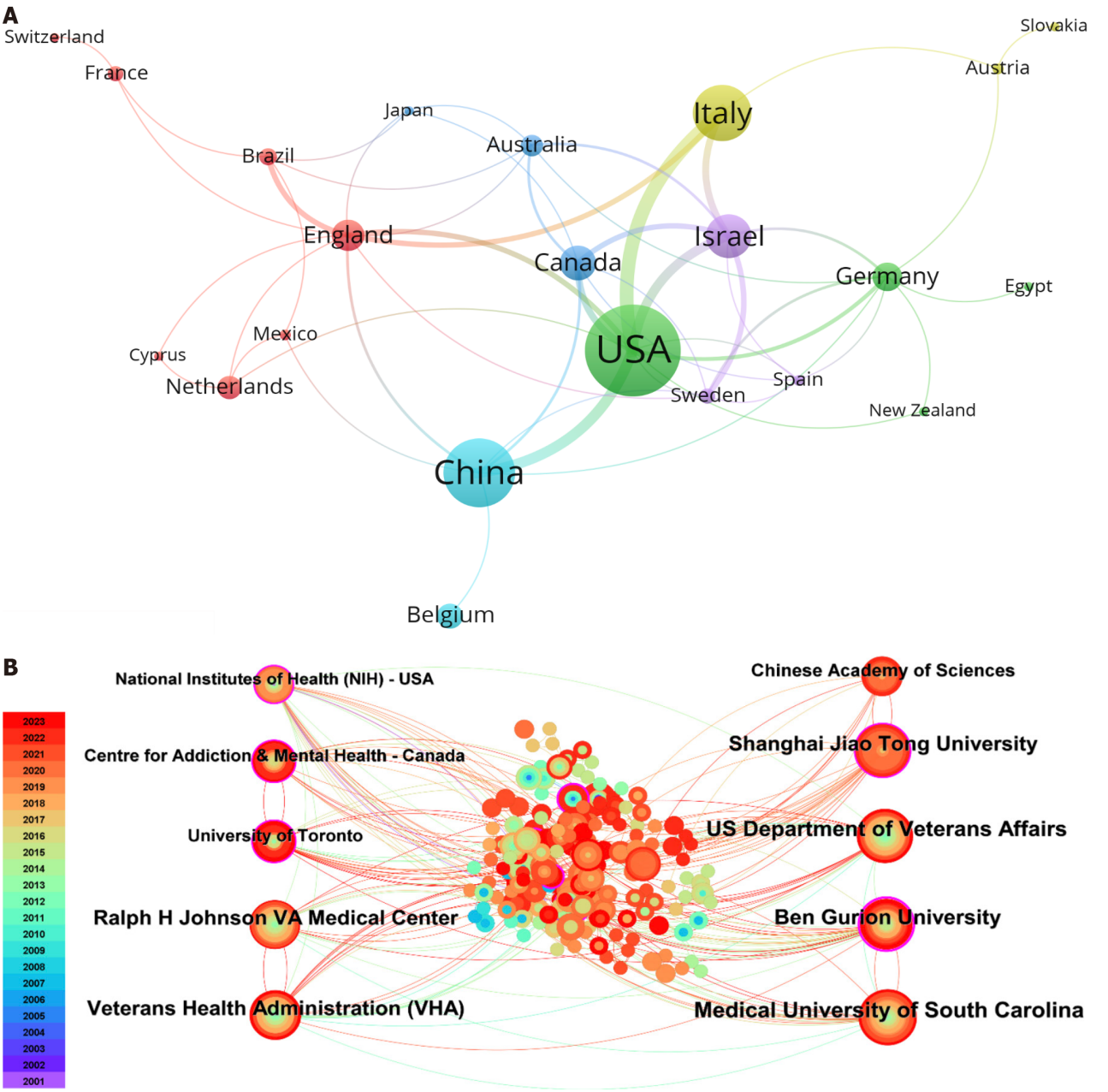


Figure 3 Map of national/regional and institutional cooperation networks in studying transcranial magnetic stimulation-based treatment of addiction. A: Collaborations among 27 countries/regions in studying transcranial magnetic stimulation (TMS)-based treatment of addiction; B: Collaborative network map illustrating institutions engaged in researching TMS-based addiction treatments. The circles represent different countries/regions and institutions. Circle size denotes the number of published articles, while link thickness reflects the level of collaboration.

CiteSpace was used to conduct a co-citation cluster mapping of the references in the 190 articles, based on their keywords. The co-citation cluster analysis showed the most popular terms in studying TMS-based treatment of addiction (Figure 6A), by hierarchical cluster labels was as follows: (1) Dopamine (DA) hypothesis; (2) Gambling disorder; (3) Low frequency; (4) Cigarette craving; (5) DA release; (6) Alcohol-dependent patient; (7) Relapse; (8) Nicotine dependence; (9) Caudate nucleus; and (10) Considering motor excitability. A summary of these clusters is presented in Table 4. The silhouette value of > 0.5 indicated that the clustering results were credible.

Keyword-based analysis of research trends and burst detection

Figure 6B shows a timeline view to clearly depict the changes in research hotspots related to TMS-based treatment of addiction from 2001 to 2023. Each circle denotes a significant cited paper within a particular cluster. The size of the cited tree ring on the timeline represents the citation frequency. Large nodes were frequently cited or were explosively cited in a specific period. The co-cited literature clustering with the keyword "gambling disorder" occurred from around 2010 to 2018. Recent hotspots are "dopamine hypothesis" and "nicotine dependence", which emerged in 2013 and have continued ever since.

Table 4 A summary of 10 clusters of references in publications about transcranial magnetic stimulation-based treatment of addiction

Cluster ID	Term	Size	Silhouette[1]
0	Dopamine hypothesis	99	0.882
1	Gambling disorder	77	0.795
2	Low frequency	56	0.91
3	Cigarette craving	45	0.926
4	Dopamine release	41	1
5	Alcohol-dependent patient	39	0.908
6	Relapse	31	1
7	Nicotine dependence	22	0.972
8	Caudate nucleus	22	1
9	Considering motor excitability	22	0.985

[1]The Silhouette value of > 0.5 indicates that the clustering results are reliable.

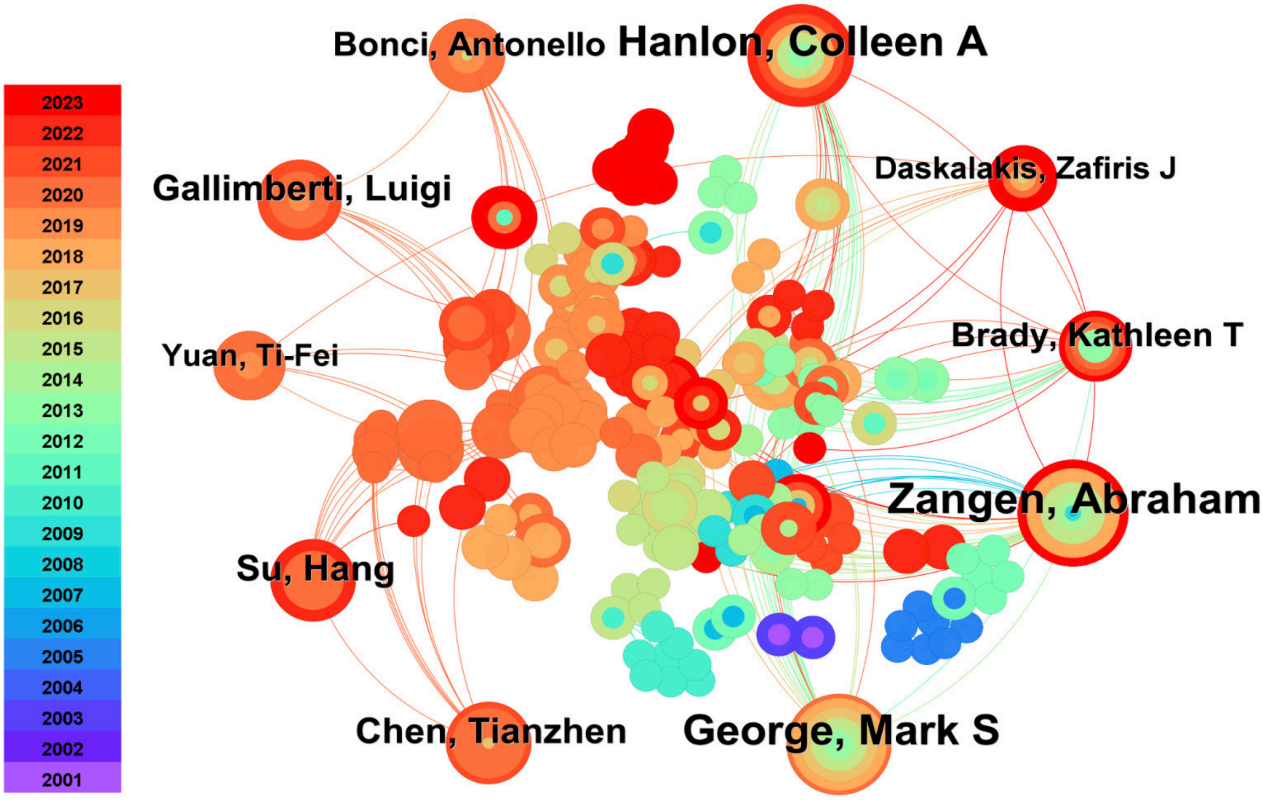
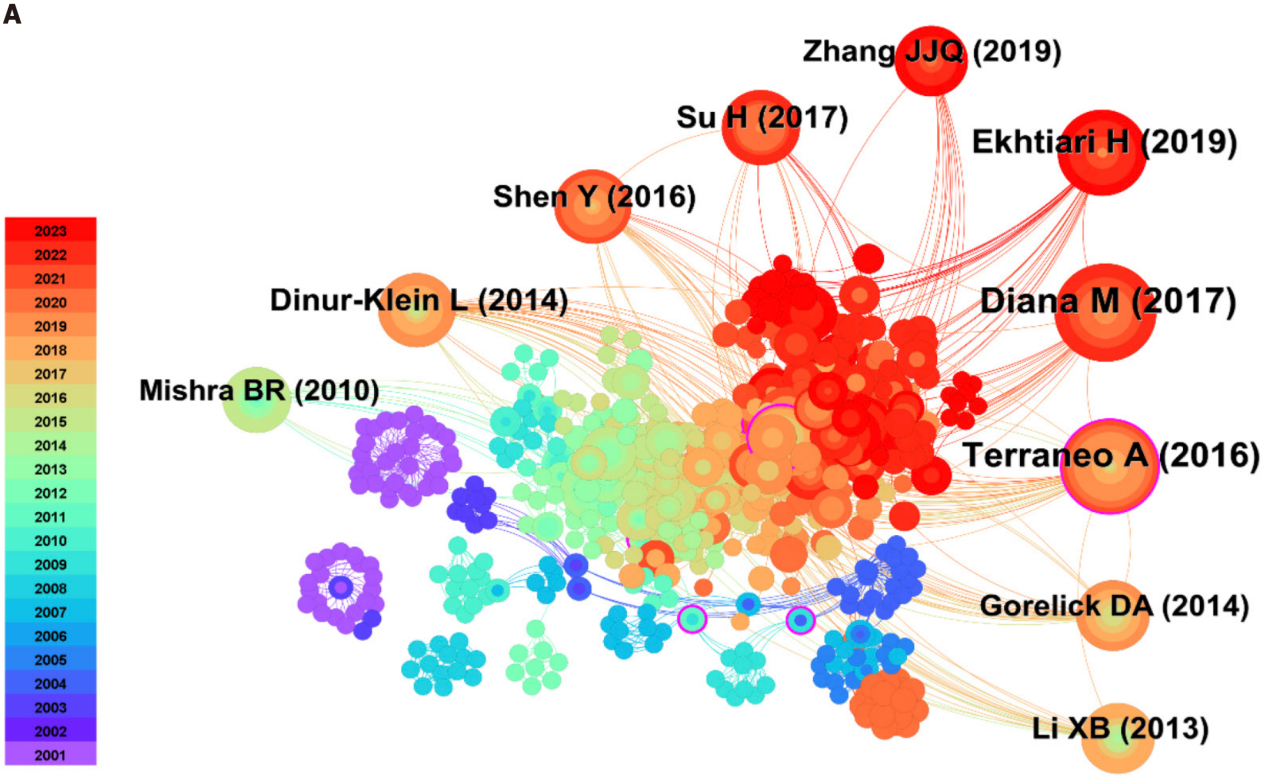


Figure 4 Collaborative network of authors in the field of transcranial magnetic stimulation-based treatment of addiction. This figure displays the top 10 authors with more than five publications. Circles symbolize authors, with links denoting collaborative relationships. There is a positive correlation between font size and the number of published papers.

The word cloud (Figure 7A) represents the top 100 high-frequency keywords in studying TMS-based treatment of addiction. There is a positive correlation between font size and usage frequency. After excluding the keywords with minor practical significance, the following keywords with high frequency were included: (1) Dorsolateral PFC; (2) Addiction, rtms; (3) Drug-addiction; and (4) PFC. Keyword burst detection is a method for swiftly identifying research hotspots. Figure 7B shows the top 15 strongest keywords for the 2001-2023 keyword bursts. The green line represents the period from 2001 to 2023, while the red line indicates the duration associated with the burst keyword among the confirmed keyword bursts, the most recent keywords were "rtms" (4.85), "neurobiology" (2.48), "alcohol use disorder (AUD)" (2.8), and "repetitive transcranial magnetic stimulation" (2.54).

A



B

Top 25 references with the strongest citation bursts

References	Strength	Begin	End	2001 - 2023
Amiaz R, 2009, ADDICTION, V104, P653, DOI 10.1111/j.1360-0443.2008.02448.x, DOI	7.35	2010	2014	
Mishra BR, 2010, ADDICTION, V105, P49, DOI 10.1111/j.1360-0443.2009.02777.x, DOI	7.88	2011	2015	
Feil J, 2010, NEUROSCI BIOBEHAV R, V34, P559, DOI 10.1016/j.neubiorev.2009.11.006, DOI	5.08	2013	2015	
Rose JE, 2011, BIOL PSYCHIAT, V70, P794, DOI 10.1016/j.biopsych.2011.05.031, DOI	3.38	2013	2015	
Li XB, 2013, BIOL PSYCHIAT, V73, P714, DOI 10.1016/j.biopsych.2013.01.003, DOI	7.52	2014	2018	
Bellamoli E, 2014, BEHAV NEUROL, V2014, P0, DOI 10.1155/2014/815215, DOI	5.03	2014	2018	
Jansen JM, 2013, NEUROSCI BIOBEHAV R, V37, P2472, DOI 10.1016/j.neubiorev.2013.07.009, DOI	4.84	2014	2018	
Dinur-Klein L, 2014, BIOL PSYCHIAT, V76, P742, DOI 10.1016/j.biopsych.2014.05.020, DOI	6.72	2015	2019	
Herremans SC, 2012, DRUG ALCOHOL DEPEN, V120, P209, DOI 10.1016/j.drugalcdep.2011.07.021, DOI	3.53	2015	2016	
Höppner J, 2011, WORLD J BIOL PSYCHIA, V12, P57, DOI 10.3109/15622975.2011.598383, DOI	3.53	2015	2016	
Terraneo A, 2016, EUR NEUROPSYCHOPHARM, V26, P37, DOI 10.1016/j.euroneuro.2015.11.011, DOI	6.8	2016	2019	
Gorelick DA, 2014, ANN NY ACAD SCI, V1327, P79, DOI 10.1111/nyas.12479, DOI	6.66	2016	2019	
Hanlon CA, 2015, BRAIN RES, V1628, P199, DOI 10.1016/j.brainres.2015.02.053, DOI	5.06	2017	2019	
Shen Y, 2016, BIOL PSYCHIAT, V80, PE13, DOI 10.1016/j.biopsych.2016.02.006, DOI	5	2017	2021	
Bolloni C, 2016, FRONT PSYCHIATRY, V7, P0, DOI 10.3389/fpsyt.2016.00133, DOI	4.1	2018	2021	
Lefaucheur JP, 2014, CLIN NEUROPHYSIOL, V125, P2150, DOI 10.1016/j.clinph.2014.05.021, DOI	3.48	2018	2019	
Diana M, 2017, NAT REV NEUROSCI, V18, P685, DOI 10.1038/nrn.2017.113, DOI	8.27	2019	2023	
Rapinesi C, 2016, NEUROSCI LETT, V629, P43, DOI 10.1016/j.neulet.2016.06.049, DOI	4.31	2019	2021	
Martinez D, 2018, FRONT PSYCHIATRY, V9, P0, DOI 10.3389/fpsyt.2018.00080, DOI	3.52	2019	2021	
Zack M, 2016, BRAIN STIMUL, V9, P867, DOI 10.1016/j.brs.2016.06.003, DOI	3.28	2019	2020	
Zhang JJQ, 2019, ADDICTION, V114, P2137, DOI 10.1111/add.14753, DOI	5.36	2020	2023	
Su H, 2017, DRUG ALCOHOL DEPEN, V175, P84, DOI 10.1016/j.drugalcdep.2017.01.037, DOI	5.11	2020	2023	
Koob GF, 2016, LANCET PSYCHIAT, V3, P760, DOI 10.1016/S2215-0366(16)00104-8, DOI	4.8	2020	2021	
Liu QM, 2017, AM J ADDICTION, V26, P776, DOI 10.1111/ajad.12638, DOI	3.39	2020	2023	

Figure 5 Reference co-citation network analysis of publications on transcranial magnetic stimulation for addiction treatment, spanning 2001 to 2023. A: CiteSpace co-citation map of 6607 references related to transcranial magnetic stimulation (TMS)-based treatment of addiction. Each node symbolizes a reference. Node size correlates positively with citation frequency, while links between nodes indicate shared references within the same article. Nodes with a deeper red hue indicate papers with high citation frequency in recent years, whereas nodes with a deeper purple hue signify references cited more frequently in earlier years. The top 10 most cited publications are listed with their first author and year of publication; B: The 25 most influential references with significant citation bursts related to TMS-based addiction treatment, spanning publications from 2001 to 2023. The blue bars indicate the period in which the reference has been published, and the red bars represent bursts of citation frequency.

DISCUSSION

This study provides the first comprehensive overview of articles published in the field of TMS-based treatment of addiction from 2001 to 2023. Our analysis indicates a significant rise in the number of articles published in this field over the past nine years. The United States, the Medical University of South Carolina, and researcher Zangen A were identified as the leading contributors in this area through bibliometric and visual analysis. Keyword burst detection indicated that neurobiology, AUD, and rtms are current research hotspots. This bibliometric analysis can help researchers interested in

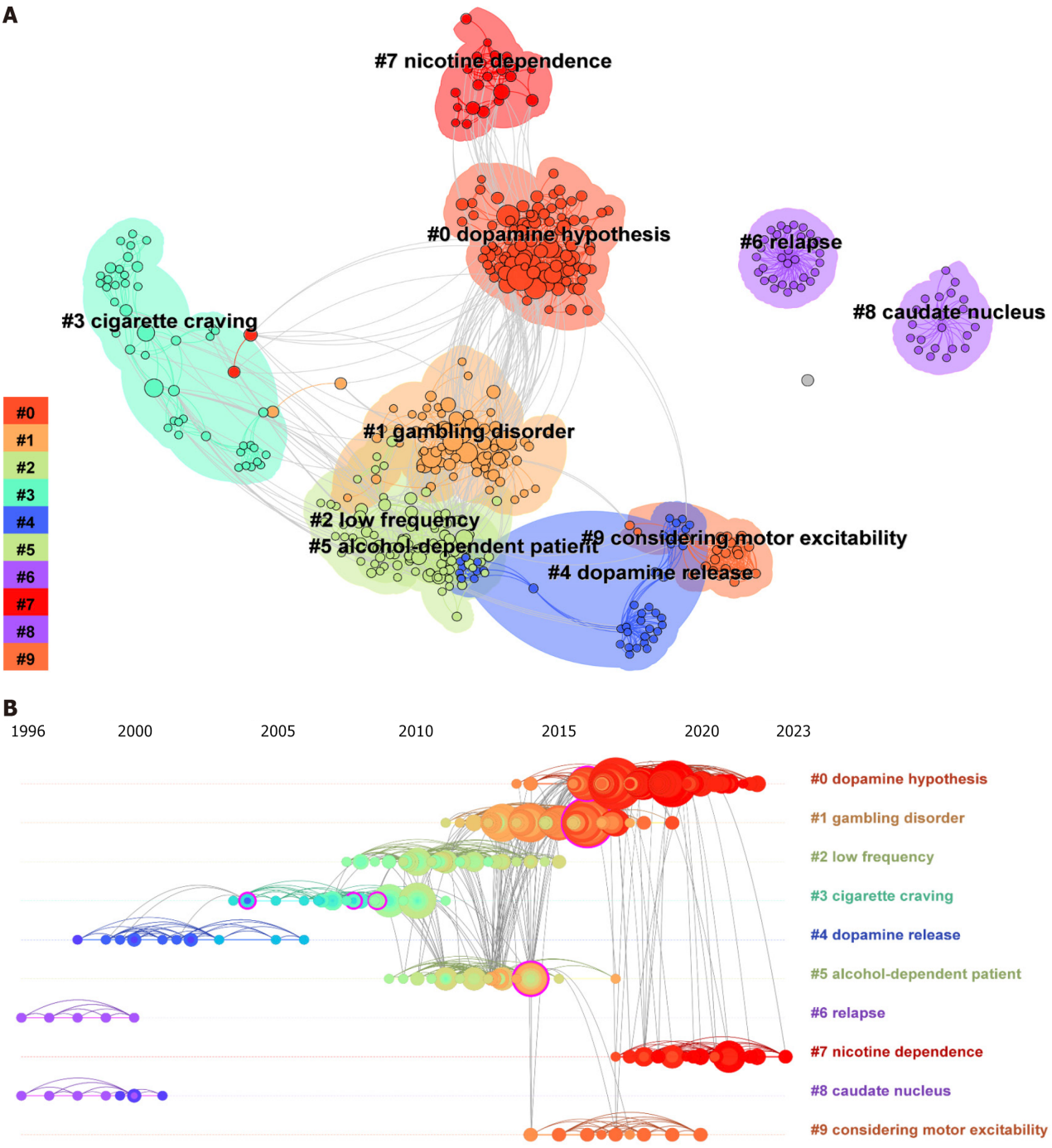
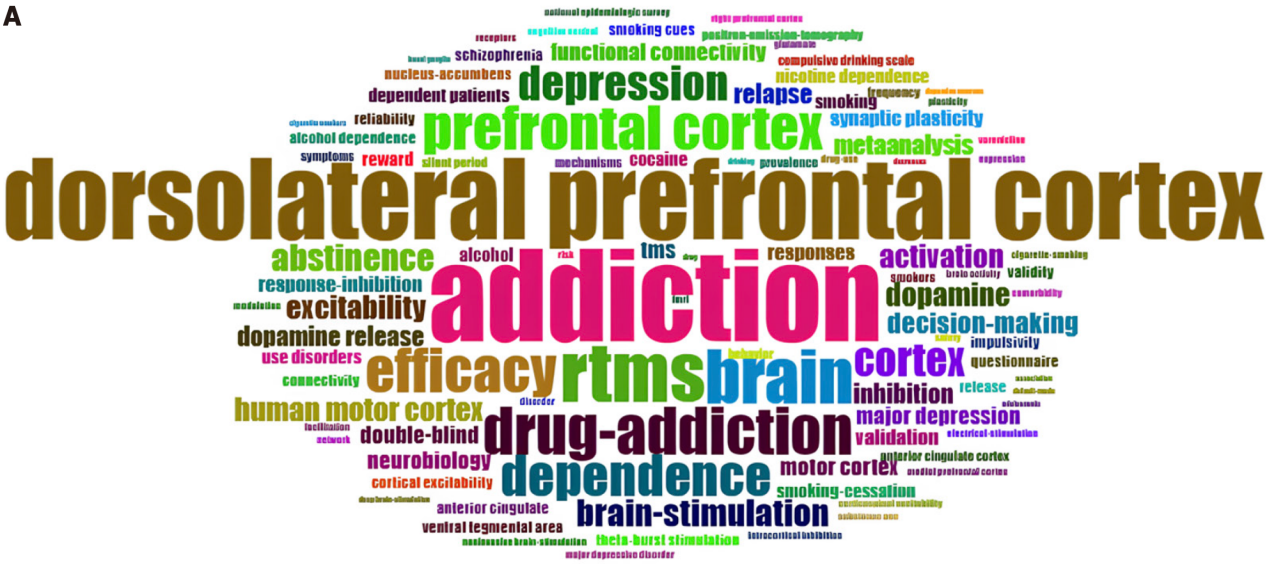


Figure 6 Analysis of the clustered network of publications in on transcranial magnetic stimulation for addiction treatment, covering the period from 2001 to 2023. A: A CiteSpace visual analysis of the co-cited literature clustering network. This figure displays the ten largest citation clusters; B: Timeline visualization of co-cited references concerning transcranial magnetic stimulation-based addiction treatment. Clusters are depicted by horizontal lines, with smaller label numbers indicating larger clusters. Node size represents co-citation frequency, while links denote co-citation relationships. Node and line colors indicate the citing years.

TMS-based treatment of addiction understand the latest research trends and hotspots.

From 2001 to 2023, the United States and China were major contributors to research on TMS-based treatment of addiction. The United States consistently leads in publication volume, citation count, and international collaboration. Half of the top ten research organizations and researchers with the most publications were based in the United States. Four of the ten most active academic journals in the field were from the United States, with the most cited journal coming from the United States. All of these findings show the absolute academic influence and dominance of the United States in this field. China started publishing research papers in this field in 2016 and exceeded the United States in annual publication numbers by 2020. In 2023, China ranked second in the number of published papers, following the United States, but was fifth in total citations, significantly trailing the United States, which held the first position. This suggests that the academic impact of China in this area still requires enhancement, particularly in producing high-quality publications.

A



B

Top 15 keywords with the strongest citation bursts

Keywords	Strength	Begin	End	2001 - 2023
motor cortex	2.21	2001	2016	
human motor cortex	3.36	2007	2017	
dopamine release	3.32	2009	2016	
validation	2.81	2015	2018	
alcohol dependence	2.18	2015	2018	
deep brain stimulation	2.3	2016	2018	
drug addiction	2.13	2016	2019	
anterior cingulate cortex	2.07	2016	2018	
synaptic plasticity	2.66	2017	2018	
nicotine dependence	2.49	2017	2018	
inhibitory control	2.11	2018	2020	
rtms	4.85	2020	2023	
neurobiology	2.48	2020	2023	
alcohol use disorder	2.8	2021	2023	
repetitive transcranial magnetic stimulation	2.54	2021	2023	

Figure 7 Analysis of keywords and burst detection of publications on transcranial magnetic stimulation-based treatment of addiction, published from 2001 to 2023. A: Word cloud illustrating the 100 most frequent keywords from research on transcranial magnetic stimulation-based addiction treatment; B: The 15 keywords with the most significant citation bursts, arranged by the year they began. Keywords marked in red bars indicate a sudden increase in using frequency during the corresponding period, and the blue color represents a relatively unpopular period.

With the process of globalization, there has been a significant trend toward increased international collaboration. This has led to the production of high-quality publications on public health issues. The United States 's closest collaboration is with Italy, followed by China. Research institutions with the most publications predominantly originated from the United States, China, and Canada. In the face of the global burden of addiction, research in this area requires more collaboration among countries and institutions.

The sharp rise in publications over the past nine years indicates heightened interest in TMS-based addiction treatment. Recently, several clinical studies have found that rTMS can reduce craving levels[26] and improve cognitive functions, such as attention, memory, and decision-making, in substance-addicted patients[27], suggesting that TMS is effective in treating addiction. Preclinical and clinical studies suggested that rTMS induces adaptation in specific subcortical neural circuits of the frontal regions of the brain, thereby leading to substantial behavioral changes[27-29]. Basic experiments are more conducive to exploring the neural mechanisms underlying TMS-based treatment of addiction[30-32]. However, they are limited by the absence of TMS devices suitable for small animals.

Zangen A was the leading author in TMS-based addiction treatment research, with George MS and Hanlon CA each contributing 11 articles. Zangen A from Ben Gurion University (Israel) studies electrophysiological and behavioral alterations induced by deep rTMS in depression, addiction, and attention deficit hyperactivity disorder[5,10,33]. Hanlon CA and George MS are affiliated with the Medical University of South Carolina, United States. Using functional and structural brain imaging techniques, along with TMS, they investigated cortico-striatal connectivity in substance-dependent populations[5]. Recent research employed functional magnetic resonance imaging to examine the impact of 10 rTMS sessions on cortical activity and neural networks in smokers seeking treatment. They demonstrated that diminished drive-reward and executive control functional connectivity correlate with the smoking cessation effects of rTMS[15].

Using a timeline view of changes in research fields, we found that the latest research trends in the field of TMS-based treatment of addiction included the DA hypothesis and nicotine dependence, as shown by the red nodes in Figure 6B.

The DA hypothesis cluster started to appear in 2013 and remained a hot research topic until recent years. Dopaminergic activity is reduced in rodent models and in people with addiction. Brain stimulation has been shown to "boost" DA signaling in human brain, thereby providing a path for restoring neural homeostasis[34]. In addition, rTMS of frontal brain regions selectively stimulates DA release from the hippocampus[35], positioning DA as a key candidate neurotransmitter directly and selectively modulated by rTMS. Moreover, high-frequency rTMS also increases DA levels in the nucleus accumbens, anterior cingulate cortex, and PFC[24]. The nicotine dependence cluster was closely linked to the DA hypothesis cluster (Figure 6B), indicating that research on TMS-based treatment of patients with tobacco addiction has received much attention in recent years[15,36,37].

Keyword bursts are considered indicators of important research hotspots or emerging trends. The top 15 most cited keyword bursts are listed in Figure 7B. The time period of the listed keyword bursts was scattered but completely covered the 2001-2023 period, indicating that major research interests have evolved over time. Among the four most recent keywords, the outburst of "rtms", also "repetitive transcranial magnetic stimulation", began in 2020 and ranked first, with an intensity of 4.85. Studies related to this keyword focused on the safety and efficacy of rTMS, a new neuroelectrophysiological technique developed based on TMS for treating addiction[4]. Second, the burst of "neurobiology" originated from studies targeting the neurobiological mechanisms associated with addiction. They showed adaptive changes in neuronal circuits involved in reward and fear processing due to chronic substance use and abuse[38]. In addition to acute effects, TMS can induce long-term plasticity, which alleviates addiction. The frequency and pattern of the TMS pulse sequence determine whether the long-term plasticity effects of TMS are facilitatory or suppressive[39-42]. Most clinical trials on rTMS employ relatively strong intensities (approximately 100%-120% of the motor threshold); however, relatively weak rTMS intensities, which do not induce pyramidal cell action potentials, can also modulate cortical excitability. This modulatory effect may be due to the altered synaptic strengths between interneurons and pyramidal cells[43]. The third keyword burst was "AUD". As the most prevalent form of addiction, AUD brings a serious burden to individuals and society[44]. The neural mechanism of AUD has always been a hot spot in treating addiction[45], and investigating the neurobiological mechanism of TMS-based treatment of AUD[10]. To sum up, these keywords suggest that the neurobiological mechanisms of TMS-based treatment of addiction, such as AUD, nicotine dependence, and drug addiction, will continue to be research hotspots in the future. This finding can help better understand the disease-specific pathophysiology of addiction and select optimal cortical and network-level targets for TMS.

Our study has limitations. First, only data retrieved from WoSCC contained the complete information needed for co-citation analysis by CiteSpace. Consequently, data were exclusively sourced from the WoSCC SCI-E database, omitting records from other significant search engines such as PubMed, EMBASE, and Ovid. This choice might have resulted in an incomplete literature sample on TMS-based treatment of addiction published from 2001 to 2023. Secondly, we chose papers published in English, as it is the dominant language in contemporary academic journals. Consequently, articles published in languages other than English were excluded. Furthermore, despite the increasing number of articles related to TMS-based treatment of addiction, the total number of articles remains relatively small. Hence, our analysis results may be somewhat biased due to reliance on existing literature. Future studies should overcome these limitations.

CONCLUSION

This study presents the inaugural bibliometric and visual analysis of publications on TMS-based addiction treatment. The number of papers in this field has rapidly increased since 2015, with the United States and China being the primary contributors. The neurobiological mechanisms of TMS-based treatment of addiction are expected to remain a prominent research direction in the future. The current study offers valuable insights to explore the therapeutic parameters and neurobiological mechanisms involved in TMS-based treatment of addiction.

ACKNOWLEDGEMENTS

We thank the databases that provide access to the data. We also would like to thank the bibliometric analysis softwares for help in analyzing the results.

FOOTNOTES

Author contributions: Yang HR and Li ZY screened articles and wrote original manuscript, conducted CiteSpace and VOSviewer analysis; Yang HR, Li ZY, Zhu H, Wu H, Xie C, Wang XQ, Huang CS, and Geng WJ revised and critically edited the manuscript; Wang XQ, Huang CS, and Geng WJ put forward the concept of this study and designed this study; all authors contributed to this article and approved the submitted version.

Supported by National Natural Science Foundation of China, No. 81973620; and Wenzhou Municipal Science and Technology Bureau, No. Y20220091.

Conflict-of-interest statement: The authors declare no competing interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: China

ORCID number: Hao-Ran Yang 0009-0002-7628-1913; Zheng-Yu Li 0009-0008-9507-7292; Wu-Jun Geng 0000-0001-5599-3036.

S-Editor: Luo ML
L-Editor: A
P-Editor: Zhang XD

REFERENCES

1 **Poisson CL**, Engel L, Saunders BT. Dopamine Circuit Mechanisms of Addiction-Like Behaviors. *Front Neural Circuits* 2021; **15**: 752420 [PMID: 34858143 DOI: 10.3389/fncir.2021.752420]
2 **Center for Behavioral Health Statistics and Quality**, Substance Abuse and Mental Health Services Administration, United States Department of Health and Human Services. Results from the 2018 National Survey on Drug Use and Health: Graphics from the Key Findings Report. Available from: https://mamh-web.files.svdcdn.com/production/files/NSDUHffrBriefingSlides2018.pdf
3 **Kalin NH**. Substance Use Disorders and Addiction: Mechanisms, Trends, and Treatment Implications. *Am J Psychiatry* 2020; **177**: 1015-1018 [PMID: 33135466 DOI: 10.1176/appi.ajp.2020.20091382]
4 **Lefaucheur JP**, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, Filipović SR, Grefkes C, Hasan A, Hummel FC, Jääskeläinen SK, Langguth B, Leocani L, Londero A, Nardone R, Nguyen JP, Nyffeler T, Oliveira-Maia AJ, Oliviero A, Padberg F, Palm U, Paulus W, Poulet E, Quartarone A, Rachid F, Rektorová I, Rossi S, Sahlsten H, Schecklmann M, Szekely D, Ziemann U. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clin Neurophysiol* 2020; **131**: 474-528 [PMID: 31901449 DOI: 10.1016/j.clinph.2019.11.002]
5 **Li X**, George MS, Zangen A. Brain stimulation therapeutics. *Addict Neurosci* 2023; **6**: 100080 [PMID: 38770029 DOI: 10.1016/j.addicn.2023.100080]
6 **Barker AT**, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1985; **1**: 1106-1107 [PMID: 2860322 DOI: 10.1016/s0140-6736(85)92413-4]
7 **Hallett M**. Transcranial magnetic stimulation: a primer. *Neuron* 2007; **55**: 187-199 [PMID: 17640522 DOI: 10.1016/j.neuron.2007.06.026]
8 **Ibrahim C**, Tang VM, Blumberger DM, Malik S, Tyndale RF, Trevizol AP, Barr MS, Daskalakis ZJ, Zangen A, Le Foll B. Efficacy of insula deep repetitive transcranial magnetic stimulation combined with varenicline for smoking cessation: A randomized, double-blind, sham controlled trial. *Brain Stimul* 2023; **16**: 1501-1509 [PMID: 37806524 DOI: 10.1016/j.brs.2023.10.002]
9 **Li X**, Hartwell KJ, Henderson S, Badran BW, Brady KT, George MS. Two weeks of image-guided left dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation improves smoking cessation: A double-blind, sham-controlled, randomized clinical trial. *Brain Stimul* 2020; **13**: 1271-1279 [PMID: 32534252 DOI: 10.1016/j.brs.2020.06.007]
10 **Selim MK**, Harel M, De Santis S, Perini I, Sommer WH, Heilig M, Zangen A, Canals S. Repetitive deep TMS in alcohol dependent patients halts progression of white matter changes in early abstinence. *Psychiatry Clin Neurosci* 2024; **78**: 176-185 [PMID: 38085120 DOI: 10.1111/pcn.13624]
11 **Terraneo A**, Leggio L, Saladini M, Ermani M, Bonci A, Gallimberti L. Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: A pilot study. *Eur Neuropsychopharmacol* 2016; **26**: 37-44 [PMID: 26655188 DOI: 10.1016/j.euroneuro.2015.11.011]
12 **Shen Y**, Cao X, Tan T, Shan C, Wang Y, Pan J, He H, Yuan TF. 10-Hz Repetitive Transcranial Magnetic Stimulation of the Left Dorsolateral Prefrontal Cortex Reduces Heroin Cue Craving in Long-Term Addicts. *Biol Psychiatry* 2016; **80**: e13-e14 [PMID: 26995024 DOI: 10.1016/j.biopsych.2016.02.006]
13 **Liu X**, Zhao X, Liu T, Liu Q, Tang L, Zhang H, Luo W, Daskalakis ZJ, Yuan TF. The effects of repetitive transcranial magnetic stimulation on cue-induced craving in male patients with heroin use disorder. *EBioMedicine* 2020; **56**: 102809 [PMID: 32512513 DOI: 10.1016/j.ebiom.2020.102809]
14 **Liu T**, Li Y, Shen Y, Liu X, Yuan TF. Gender does not matter: Add-on repetitive transcranial magnetic stimulation treatment for female methamphetamine dependents. *Prog Neuropsychopharmacol Biol Psychiatry* 2019; **92**: 70-75 [PMID: 30605708 DOI: 10.1016/j.pnpbp.2018.12.018]
15 **Li X**, Caulfield KA, Hartwell KJ, Henderson S, Brady KT, George MS. Reduced executive and reward connectivity is associated with smoking cessation response to repetitive transcranial magnetic stimulation: A double-blind, randomized, sham-controlled trial. *Brain Imaging Behav* 2024; **18**: 207-219 [PMID: 37996557 DOI: 10.1007/s11682-023-00820-3]
16 **Li J**, Wang L, Yin S, Yu S, Zhou Y, Lin X, Jiao Y, Yu W, Xia X, Yang L, Gao P. Emerging trends and hotspots of the itch research: A bibliometric and visualized analysis. *CNS Neurosci Ther* 2024; **30**: e14514 [PMID: 37902196 DOI: 10.1111/cns.14514]
17 **Zhou Y**, Lin X, Yin S, Zhu L, Yang Y, Li Y, Wang B, Jiao Y, Yu W, Gao P, Yang L. Emerging Trends and Hot Spots in Hepatic Glycolipid Metabolism Research From 2002 to 2021: A Bibliometric Analysis. *Front Nutr* 2022; **9**: 933211 [PMID: 35911114 DOI: 10.3389/fnut.2022.933211]
18 **Li Y**, Zhou Y, Wang L, Lin X, Mao M, Yin S, Zhu L, Jiao Y, Yu W, Gao P, Yang L. Emerging trends and hotspots in the links between the gut microbiota and MAFLD from 2002 to 2021: A bibliometric analysis. *Front Endocrinol (Lausanne)* 2022; **13**: 990953 [PMID: 36329894 DOI: 10.3389/fendo.2022.990953]

19 **Liao Y**, Wang L, Liu F, Zhou Y, Lin X, Zhao Z, Xu S, Tang D, Jiao Y, Yang L, Yu W, Gao P. Emerging trends and hotspots in metabolic dysfunction-associated fatty liver disease (MAFLD) research from 2012 to 2021: A bibliometric analysis. *Front Endocrinol (Lausanne)* 2023; **14**: 1078149 [PMID: 36761200 DOI: 10.3389/fendo.2023.1078149]

20 **Lin X**, Zhou Y, Ye L, Wang B, Jiao Y, Yu W, Gao P, Yang L. A bibliometric and visualized analysis of hepatic ischemia-reperfusion injury (HIRI) from 2002 to 2021. *Heliyon* 2023; **9**: e22644 [PMID: 38074868 DOI: 10.1016/j.heliyon.2023.e22644]

21 **van Eck NJ**, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics* 2010; **84**: 523-538 [PMID: 20585380 DOI: 10.1007/s11192-009-0146-3]

22 **Chen C**. Searching for intellectual turning points: progressive knowledge domain visualization. *Proc Natl Acad Sci U S A* 2004; **101** Suppl 1: 5303-5310 [PMID: 14724295 DOI: 10.1073/pnas.0307513100]

23 **Ghorbani F**, Feizabadi M, Farzanegan R, Vaziri E, Samani S, Lajevardi S, Moradi L, Shadmehr MB. An Investigation of Topics and Trends of Tracheal Replacement Studies Using Co-Occurrence Analysis. *Tissue Eng Part B Rev* 2017; **23**: 118-127 [PMID: 27758155 DOI: 10.1089/ten.TEB.2016.0254]

24 **Diana M**, Raij T, Melis M, Nummenmaa A, Leggio L, Bonci A. Rehabilitating the addicted brain with transcranial magnetic stimulation. *Nat Rev Neurosci* 2017; **18**: 685-693 [PMID: 28951609 DOI: 10.1038/nrn.2017.113]

25 **Ekhtiari H**, Tavakoli H, Addolorato G, Baeken C, Bonci A, Campanella S, Castelo-Branco L, Challet-Bouju G, Clark VP, Claus E, Dannon PN, Del Felice A, den Uyl T, Diana M, di Giannantonio M, Fedota JR, Fitzgerald P, Gallimberti L, Grall-Bronnec M, Herremans SC, Herrmann MJ, Jamil A, Khedr E, Kouimtsidis C, Kozak K, Krupitsky E, Lamm C, Lechner WV, Madeo G, Malmir N, Martinotti G, McDonald WM, Montemitro C, Nakamura-Palacios EM, Nasehi M, Noël X, Nosratabadi M, Paulus M, Pettorruso M, Pradhan B, Praharaj SK, Rafferty H, Sahlem G, Salmeron BJ, Sauvaget A, Schluter RS, Sergiou C, Shahbabaie A, Sheffer C, Spagnolo PA, Steele VR, Yuan TF, van Dongen JDM, Van Waes V, Venkatasubramanian G, Verdejo-García A, Verveer I, Welsh JW, Wesley MJ, Witkiewitz K, Yavari F, Zarrindast MR, Zawertailo L, Zhang X, Cha YH, George TP, Frohlich F, Goudriaan AE, Fecteau S, Daughters SB, Stein EA, Fregni F, Nitsche MA, Zangen A, Bikson M, Hanlon CA. Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: A consensus paper on the present state of the science and the road ahead. *Neurosci Biobehav Rev* 2019; **104**: 118-140 [PMID: 31271802 DOI: 10.1016/j.neubiorev.2019.06.007]

26 **Damoiseaux JS**, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF. Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A* 2006; **103**: 13848-13853 [PMID: 16945915 DOI: 10.1073/pnas.0601417103]

27 **Liang Q**, Lin J, Yang J, Li X, Chen Y, Meng X, Yuan J. Intervention Effect of Repetitive TMS on Behavioral Adjustment After Error Commission in Long-Term Methamphetamine Addicts: Evidence From a Two-Choice Oddball Task. *Neurosci Bull* 2018; **34**: 449-456 [PMID: 29340869 DOI: 10.1007/s12264-018-0205-y]

28 **Keck ME**, Welt T, Müller MB, Erhardt A, Ohl F, Toschi N, Holsboer F, Sillaber I. Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system. *Neuropharmacology* 2002; **43**: 101-109 [PMID: 12213264 DOI: 10.1016/s0028-3908(02)00069-2]

29 **Zangen A**, Hyodo K. Transcranial magnetic stimulation induces increases in extracellular levels of dopamine and glutamate in the nucleus accumbens. *Neuroreport* 2002; **13**: 2401-2405 [PMID: 12499837 DOI: 10.1097/00001756-200212200-00005]

30 **Hawes SL**, Salinas AG, Lovinger DM, Blackwell KT. Long-term plasticity of corticostriatal synapses is modulated by pathway-specific co-release of opioids through κ-opioid receptors. *J Physiol* 2017; **595**: 5637-5652 [PMID: 28449351 DOI: 10.1113/JP274190]

31 **Huang X**, Chen YY, Shen Y, Cao X, Li A, Liu Q, Li Z, Zhang LB, Dai W, Tan T, Arias-Carrion O, Xue YX, Su H, Yuan TF. Methamphetamine abuse impairs motor cortical plasticity and function. *Mol Psychiatry* 2017; **22**: 1274-1281 [PMID: 28831198 DOI: 10.1038/mp.2017.143]

32 **Wu XQ**, Zan GY, Ju YY, Chen TZ, Guo LB, Jiao DL, Jiang HF, Deng YZ, Liu JG, Zhao M. Low-frequency repetitive transcranial magnetic stimulation inhibits the development of methamphetamine-induced conditioned place preference. *Behav Brain Res* 2018; **353**: 129-136 [PMID: 30003977 DOI: 10.1016/j.bbr.2018.07.004]

33 **Zangen A**, Zibman S, Tendler A, Barnea-Ygael N, Alyagon U, Blumberger DM, Grammer G, Shalev H, Gulevski T, Vapnik T, Bystritsky A, Filipčić I, Feifel D, Stein A, Deutsch F, Roth Y, George MS. Pursuing personalized medicine for depression by targeting the lateral or medial prefrontal cortex with Deep TMS. *JCI Insight* 2023; **8**: e165271 [PMID: 36692954 DOI: 10.1172/jci.insight.165271]

34 **Strafella AP**, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J Neurosci* 2001; **21**: RC157 [PMID: 11459878 DOI: 10.1523/JNEUROSCI.21-15-j0003.2001]

35 **Rapinesi C**, Del Casale A, Di Pietro S, Ferri VR, Piacentino D, Sani G, Raccah RN, Zangen A, Ferracuti S, Vento AE, Angeletti G, Brugnoli R, Kotzalidis GD, Girardi P. Add-on high frequency deep transcranial magnetic stimulation (dTMS) to bilateral prefrontal cortex reduces cocaine craving in patients with cocaine use disorder. *Neurosci Lett* 2016; **629**: 43-47 [PMID: 27365134 DOI: 10.1016/j.neulet.2016.06.049]

36 **GBD 2019 Tobacco Collaborators**. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. *Lancet* 2021; **397**: 2337-2360 [PMID: 34051883 DOI: 10.1016/S0140-6736(21)01169-7]

37 **Le Foll B**, Piper ME, Fowler CD, Tonstad S, Bierut L, Lu L, Jha P, Hall WD. Tobacco and nicotine use. *Nat Rev Dis Primers* 2022; **8**: 19 [PMID: 35332148 DOI: 10.1038/s41572-022-00346-w]

38 **Koob GF**, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology* 2010; **35**: 217-238 [PMID: 19710631 DOI: 10.1038/npp.2009.110]

39 **Pascual-Leone A**, Valls-Solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain* 1994; **117** (Pt 4): 847-858 [PMID: 7922470 DOI: 10.1093/brain/117.4.847]

40 **Chen R**, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 1997; **48**: 1398-1403 [PMID: 9153480 DOI: 10.1212/wnl.48.5.1398]

41 **Valls-Solé J**, Pascual-Leone A, Wassermann EM, Hallett M. Human motor evoked responses to paired transcranial magnetic stimuli. *Electroencephalogr Clin Neurophysiol* 1992; **85**: 355-364 [PMID: 1282453 DOI: 10.1016/0168-5597(92)90048-g]

42 **McDonnell MN**, Orekhov Y, Ziemann U. The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. *Exp Brain Res* 2006; **173**: 86-93 [PMID: 16489434 DOI: 10.1007/s00221-006-0365-2]

43 **Romero JR**, Anschel D, Sparing R, Gangitano M, Pascual-Leone A. Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. *Clin Neurophysiol* 2002; **113**: 101-107 [PMID: 11801430 DOI: 10.1016/s1388-2457(01)00693-9]

44 **GBD 2016 Alcohol Collaborators**. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global

Burden of Disease Study 2016. *Lancet* 2018; **392**: 1015-1035 [PMID: 30146330 DOI: 10.1016/S0140-6736(18)31310-2]
45 **Witkiewitz K**, Litten RZ, Leggio L. Advances in the science and treatment of alcohol use disorder. *Sci Adv* 2019; **5**: eaax4043 [PMID: 31579824 DOI: 10.1126/sciadv.aax4043]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com