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Volume 1, Number 1 (January 2025)

Contents

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SLC2A14 In Hepatoblastoma Clinical Significance And Potential Roles In Ferroptosis

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KEYWORDS

Hepatoblastoma, SLC2A14, Ferroptosis, GLUT Family, Pediatric Oncology, Tumor Metabolism

ABSTRACT

The study aimed to investigate the role of SLC2A14 in hepatoblastoma (HB), a prevalent pediatric liver tumor.Through RNA-seq analysis of public and in-house datasets,we found SLC2A14 upregulated in HB and linked to ferroptosis.Our analysis revealed SLC2A14s potential as a diagnostic marker and its association with tumor metabolism,suggesting it may be a therapeutic target.The study concludes that SLC2A14s role in HB should be further explored for clinical applications.

1. Introduction

Hepatoblastoma (HB) is the most common liver malignant tumor in children, accounting for 80% of liver malignancies together with hepatocellular carcinoma in children [1]. In the recent decades, the survival time and survival quality had been increased significantly thanks to the technological progress of surgery and new chemoradiotherapy [2]. However, an effective treatment must be based on effective diagnosis. The early detection of HB also mainly depends on the expression level of alpha fetoprotein (AFP) except imaging examination [3]. Nevertheless, the expression of AFP often increases physiologically in a period of time after birth, which decreased the accuracy of AFP in detecting HB [4]. Therefore, we hoped to find a new target and applied it to diagnosis and treatment of HB.

Solute carrier family 2 member 14 (SLC2A14, also known as GLUT14) is a member of glucose transporter (GLUT) family, located on 12p13.31 and was first reported to be related to hexose transport [5]. In the previous study, researchers had reported the clinical significance of SLC2A14 in a variety of malignant tumors. Chai et al. reported expression of SLC2A14 was upregulated in patients with thyroid papillary carcinoma, and had a significant positive correlation with the mortality [6]. Through analyzing the expression levels of GLUT family members, Januchowski et al. thought downregulated SLC2A14 was related to chemoresistance of ovarian cancer cells [7]. In a research managed by Valli et al., the researchers pointed out upregulated SLC2A14 was able to promote ingestion of glucose in hypoxic conditions, so then regulating the metabolic process of tumor cells, which could provide a new target to targeted therapy

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[8]. Sharpe et al. indicated that glioblastoma cells could metabolize galactose by upregulated expression of SLC2A14 and other key enzymes, and replaced low concentration glucose as a new energy source [9]. Through years of researches in various cancers, the researchers had further understood the mechanisms of SLC2A14 in glucose metabolism of tumor cells. Interestingly, some researchers had put forward new ideas. Li et al. reported overexpressed SLC2A14 and its family members would influence the activity of GPX4, and reduced Malt-PEG-Abz@RSL3 Into tumor cells, then induced iron accumulated in tumor cells and ferroptosis [10].

As a newly discovered process of apoptosis in recent years, ferroptosis was increasingly reported in cancer. Lee et al. found upregulated ELOVL5 and FADS1 could reduce the resistance of gastric cancer cells to iron accumulation, which promoted ferroptosis occurred [11]. Liang et al. also reported that ruscogenin was able to increased the concentration of ferrous ions in pancreatic cancer cells and caused excessive iron accumulation and ferroptosi [12]. To date, researchers have invested a lot of energy in exploring the application of ferroptosis as a result of recent studies had shown that the effect of inducing ferroptosis in tumor cells that have become resistant to traditional therapy is superior [13]. Wang et al. thought the occurrence of ferroptosis might be related to anti tumor immunity mediated by CD8+ T cells, it was conducive to the application of ferroptosis in the treatment of malignant tumors by blocking checkpoint of this pathway [14]. Lee et al. found ferroptosis induced by AMPK had a high correlation with acetyl CoA carboxylase phosphorylation and polyunsaturated fatty acid biosynthesis, which indicated that there is a coupling between ferroptosis and energy emergency signal mediated by AMPK [15]. Unfortunately, how ferroptosis influences HB had never been reported, rhe relationship between ferroptosis and SLC2A14 in HB is unknown.

Therefore, we herein first used RNA-seq and mRNA-seq to explore the expression level and clinical significance of SLC2A14 in HB, and we also predicted the potential signal pathway of differentially expressed SLC2A14 regulating HB. Moreover, the presented study discussed the relationship between SLC2A14 and ferroptosis in HB.

2. Method

2.1. Expression Level and Discrimination Potential of SLC2A14 in HB

In the present study, the authors first searching datasets from public databases including Gene Expression Omnibus (GEO), Sequence Read Archive (SRA) and ArrayExpress with “Hepatoblastoma” as keyword. The included series should meet the following conditions: (1) The series must be containing mRNA-seq or RNA-seq data; (2) The data should contain normal and HB tissues or body fluid groups; (3) Presence of SLC2A14 expression data. Finally, a total of 311 samples from 7 series were included. Then, we performed $\log_2(x+1)$ conversion for above data in order to make the results more objective. Moreover, 3 pairs of samples from the First Affiliated Hospital of Guangxi Medical University was also included for analyzing.

Next, we estimated standard mean difference (SMD) of 7 studies and in-house data with Stata 14.0. The studies would be considered to be heterogeneous and applied a random-effect model if $P < 0.05$ or $I2 > 50\%$, otherwise a fixed-effects model would be adopted. Moreover, diagnostic test was applied to assess the discrimination potential of SLC2A14 in HB. IBM SPSS Statistics v23.0 and Graphpad Prism 8.0 were preformed to plot Receiver operating characteristic (ROC) curves. Additionally, in order to objectively evaluate the potential of SLC2A14 in the diagnosis of HB, a summary receiver operating characteristic (sROC) was plotted. The area under the curve (AUC) of sROC represents the diagnostic value of SLC2A14. In order to explore the relationship between SLC2A14 and patients with difference clinical parameters, we collected and analyzed the expression levels of SLC2A14 in patients with difference clinical parameters.

2.2. The Identified of SLC2A14 DCEGs

2.2.1. Identification of SLC2A14 Co-Expressed Genes in HB

Co-expressed genes (CEGs) means genes had similar expressed tendency with SLC2A14, aiming to find out those genes had close relationships with SLC2A14 and probably influence SLC2A14 in HB. Genes expression data from the above studies was extracted and evaluated Pearson’s coefficient between SLC2A14 and other genes. Those genes were considered as CEGs when $|r| > 0.3$ and $P < 0.05$, and

CEGs of SLC2A14 would be chosen for subsequent research if they appeared more than 5 times in 8 series.

2.2.2. Identification of SLC2A14 Differential Expressed Genes in HB

We estimated SMD of all genes from the above series. If lower 95%CI > 0 and SMD > 0, the gene would be considered to upregulate in HB. In the same light, If higher 95%CI < 0 and SMD < 0, the gene would be considered to downregulate in HB. Genes would be chosen as differential expressed genes (DEGs) for follow-up research if they appeared more than 5 times in 8 series.

The screened CEGs and DEGs of were intersected and identified as SLC2A14 DCEGs.

2.3. Functional Enrichment Analysis of SLC2A14 DCEGs

In order to further explore the mechanisms of overexpressed SLC2A14 regulated development of HB, the screened upregulated and downregulated DCEGs were entered into Database for Annotation, Visualization, and Integrated Discovery (DAVID) v6.8. separately. Gene ontology (GO) analysis was chosen to explore their potential pathways. Then, Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were performed to explore the potential signaling pathways of SLC2A14 DCEGs. When $P < 0.05$, the GO terms and KEGG signaling pathways were identified. In addition, we constructed PPI networks with Search Tool for the Retrieval of Interacting Genes (STRING), and screened hubgenes of SLC2A14 by applying Cytoscape v3.8.2. Moreover, Bgee is a database included gene expression data in various animal, was also used to explore expression levels of hubgenes.

2.4. The Exploring of Relationship Between SLC2A14 and Ferroptosis in HB

We found SLC2A14 was reported that had a correlation with ferroptosis, so we determined to explore the relationship between SLC2A14 and ferroptosis in HB. GSE104462 was a study containing with HepG2 cell line, researchers divided 6 samples into 2 groups and treated with DMSO and erastin. By comparing expression level of SLC2A14 in DMSO group with erastin group, we revealed the different expression of SLC2A14 in ferroptosis. Moreover, we herein extracted expression data of ferroptosis-related genes from the above series and evaluated Pearson's coefficient between SLC2A14 and ferroptosis-related genes. A heatmap was plotted to show the results.

2.5. Immune Infiltration of SLC2A14

To discuss the immune infiltration of SLC2A14 in varieties of adults' tumors, TISIDB was also performed to analyze the correlation between SLC2A14 and immune-related genes in various of tumors in present study.

Different from adult's tumors, a simple analytical tool for analyzing the immune infiltration of SLC2A14 in HB had never been seen. To explore the Immune infiltration of SLC2A14 in HB, we extracted immune-related genes from the above series and calculated Pearson's coefficient between immune-related genes and SLC2A14. A heatmap was plotted to show our results.

2.6. Clinical Significnce of SLC2A14 in Common Adults' and Children's Tumors

we were trying to reveal the expression levels of SLC2A14 in adults' and children's pan-cancer, so we download and analyzed data from public databases. The Cancer Genome Atlas (TCGA) was managed by National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI), is a database which collected more than 10 thousands patients with 39 types of cancers. Therapeutically Applicable Research To Generate Effective Treatments (TARGET) was an available database containing data of children's cancer, which included 7 types of cancer common in children. We downloaded mRNA-seq series from the above database and analyzed SLC2A14 expression levels.

3. Results

3.1. Expression Level and Discrimination Potential of SLC2A14 in HB

In the present study, we collected 7 public series from databases, combining with sequencing data from our hospital, we revealed the expression level and discrimination potential of SLC2A14 in HB for the first time. 8 pairs of scatter plots and ROC curves were showed on Fig.1. To observe the expression of SLC2A14 in all HB series comprehensively, a SMD was estimated (Fig.2 A). Due to $I2 = 86.1\%$ and $P < 0.001$, a random-effect model was chosen, and the

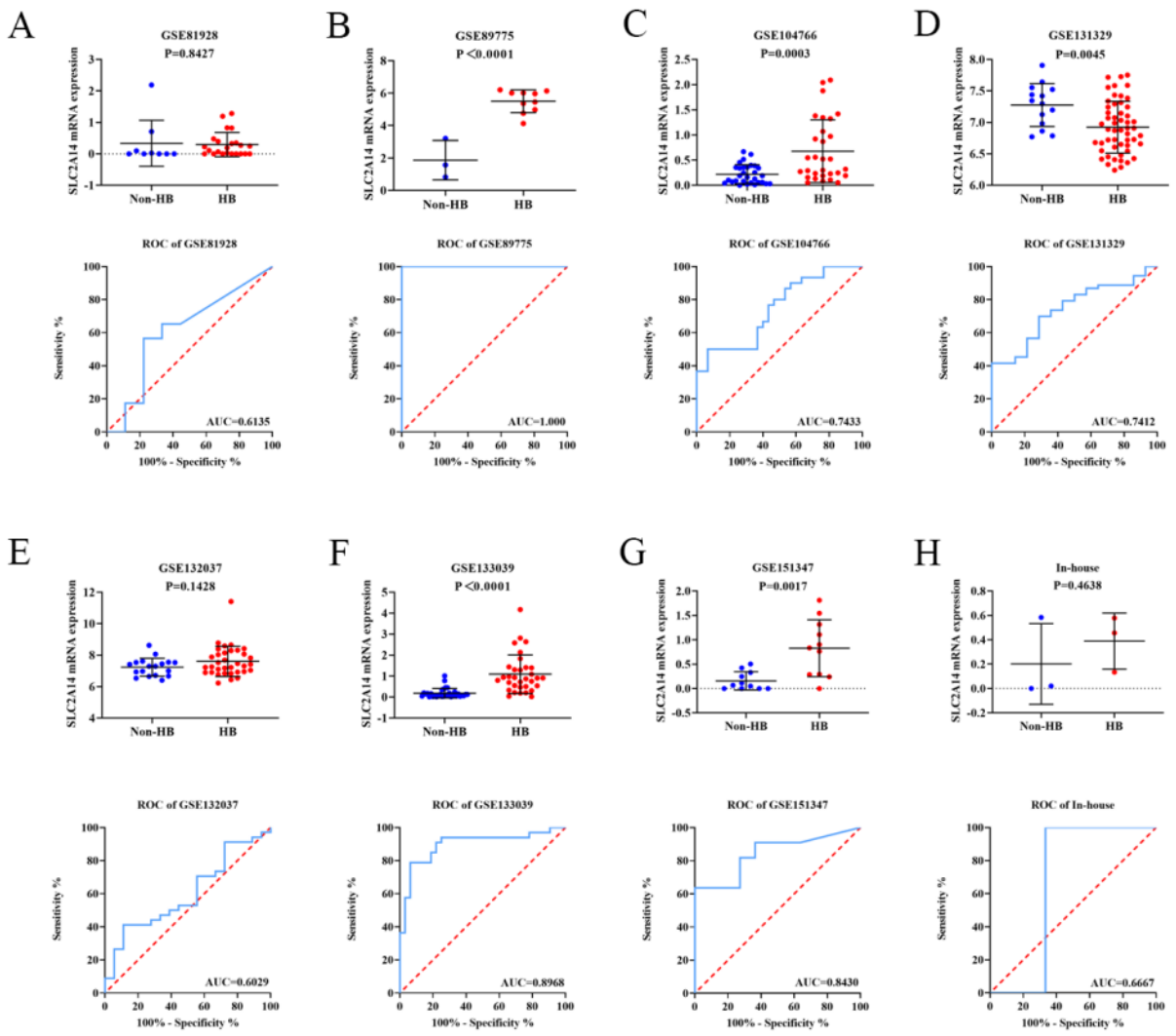

Figure 1

Illustrates the Receiver Operating Characteristic (ROC) curves for the expression levels of SLC2A14 in Hepatoblastoma (HB) samples compared to non-HB samples across various datasets.The scatter plot illustrates the differences in SLC2A14 mRNA expression levels between HB samples and non-HBnormal or control-samples.. With the x-axis showing the false positive rate and the y-axis showing the true positive rate. The Area Under the Curve (AUC) values are provided, indicating the diagnostic potential of SLC2A14.

result showed that SLC2A14 expression was upregulated in HB (SMD = 0.80, and 95%CI = 0.07 to 1.53). Heterogeneity analysis did not provide heterogeneity for us (Fig.2 B). And no publication bias was observed in funnel plots (Fig.2 C-E). Moreover, a sROC curve was plotted and showed the discrimination potential of SLC2A14 in HB intuitively. With a 0.91 (95%CI = 0.88 to 0.93) AUC value, we thought SLC2A14 had a high discrimination potential in HB (Fig.2 F). Additionally, our results got a high credibility because a high positive diagnostic likelihood ratio (DLR) and low negative DLR (Fig.2 G).

To make SLC2A14 more conducive to clinical diagnosis and treatment, we tried to explore whether SLC2A14 expressed differently in patients with different clinical parameters. We collected clinical information of patients and extracted expression data of SLC2A14. Then violin plots were showed on Fig.3.

3.2. Functional Enrichment Analysis of SLC2A14 DCEGs

Upregulated and downregulated DCEGs were entered into DAVID and predicted potential GO pathway, bubble plots were used to show our results (Fig.4 A,B). Then, upregulated and downregulated DCEGs were entered into STRING to construct PPI network and show the connectedness among them (Fig.4 A,B). In addition, all of the DCEGs were en-

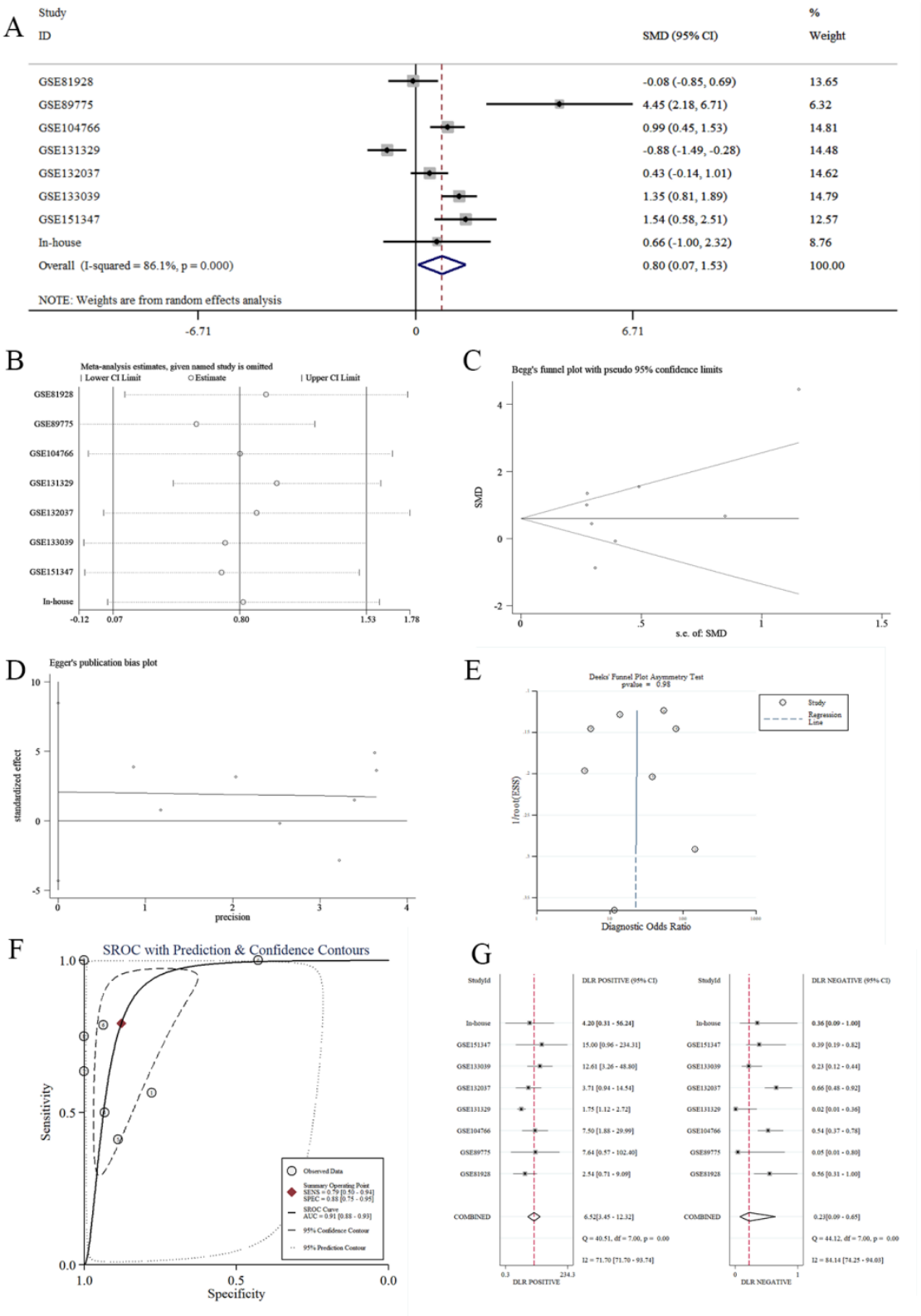

Figure 2

(A) The standardized mean differences (SMD) and their 95% confidence intervals for each study, showing the differences in SLC2A14 mRNA expression levels between HB and non-HB samples.(B) Meta-analysis estimates after omitting each study, showing the impact on the overall estimate.(C) A forest plot displaying the effect size estimates and confidence intervals for each study.(D)A forest plot displaying the effect size estimates and confidence intervals for each study.(E) Precision of studies and diagnostic odds ratios.(F) SROC curve with prediction and confidence contours.(G) The pooled effect size and its confidence interval, showing the overall diagnostic performance of SLC2A14 as a biomarker.

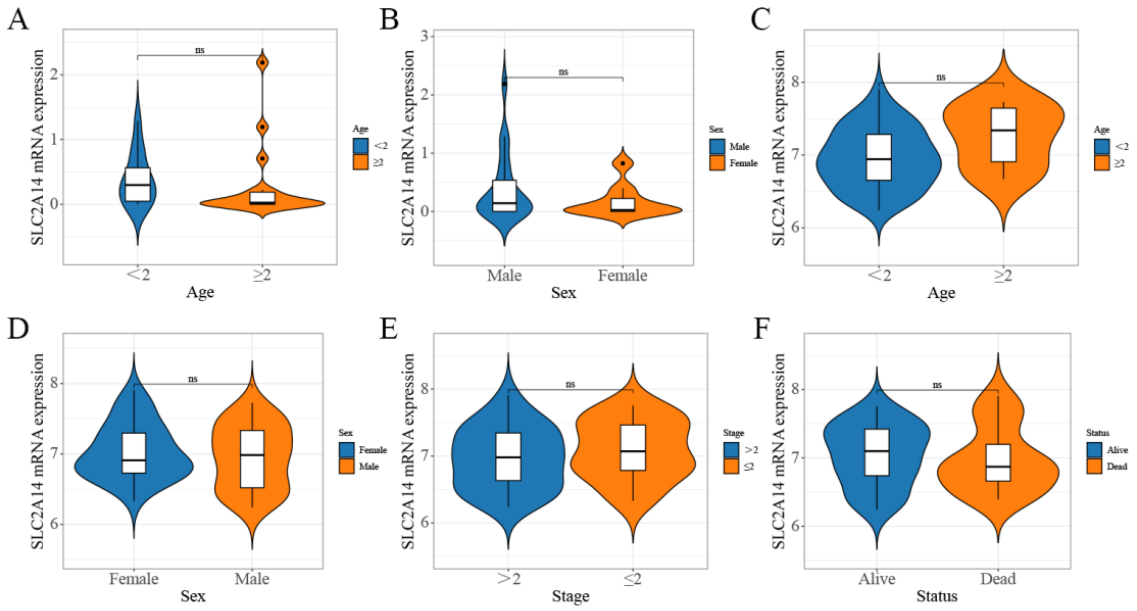

Figure 3

Illustrates the impact of SLC2A14 mRNA expression levels on patient characteristics such as gender,age,tumor staging,and survival status across various subgroups.

tered into DAVID and performed a KEGG enrichment analysis, PPI network also been structured (Fig.5 A,B).

After identified H2AFZ, C3, POLR2A, CDK7, CENPK, CCNA2, BUB1B, MAPRE1, CCNB1 and DSN1 as hubgenes of SLC2A14, we determined to further explore these potential hubgenes (Fig.5 C). We herein discussed expression level of hubgenes in liver, and the results indicated that the above hubgenes had high expression scores in liver (Fig.6 A,B). Then, as the most probably be target gene, the expression H2AFZ was considered had correlations with SLC2A14 (Fig.6 C-J).

3.3. The Relationship Between SLC2A14 and Ferroptosis in HB

In the previous study, SLC2A14 was reported had a correlation with ferroptosis, we wondered if SLC2A14 also regulated development of HB through regulating ferroptosis. First, we downloaded GSE104462, a study including 2 group treated with DMSO and erastin. After screened out DEGs from GSE104462, we surprised to find SLC2A14 was on the list, which indicated that SLC2A14 was downregulated after treated with ferroptosis inducer (Fig.7 A). Thus, we extracted expression data of SLC2A14 from GSE104462 and analyzed its expression level (Fig.7 B).

3.4. Immune Infiltration of SLC2A14 in HB

We herein wanted to further explore clinical significance of SLC2A14 in various types of cancer. Correlation analysis between SLC2A14 and immune cells in various of cancers also be performed. Through TISIDB, the results indicated SLC2A14 was related to a various kinds of immune-related cells in adults' cancers (Fig.8 B-E). However, data of children's cancers were different from adults' cancers, we need to extracted expression data of immune-related genes. The correlated heatmap was showed on Fig.2 B.

3.5. Clinical Significnce of SLC2A14 in Common Adults' and Children's Tumors

Based on TCGA database, the expression of SLC2A14 in common adults' tumors were extracted and assessed, the results show that SLC2A14 was differential expressed in multiple types of tumors. The scatter and box plot displayed the results intuitively (Fig.8 A). Showing only the expression levels of SLC2A14 in adults' tumors were still not convincing, so we collected and analyzed data from TARGET. The results were showed on Fig.9 A. Unfortunately, due to lacking of healthy samples, we were not able to show whether the expression of SLC2A14 in tumors is different from that in normal tissues.

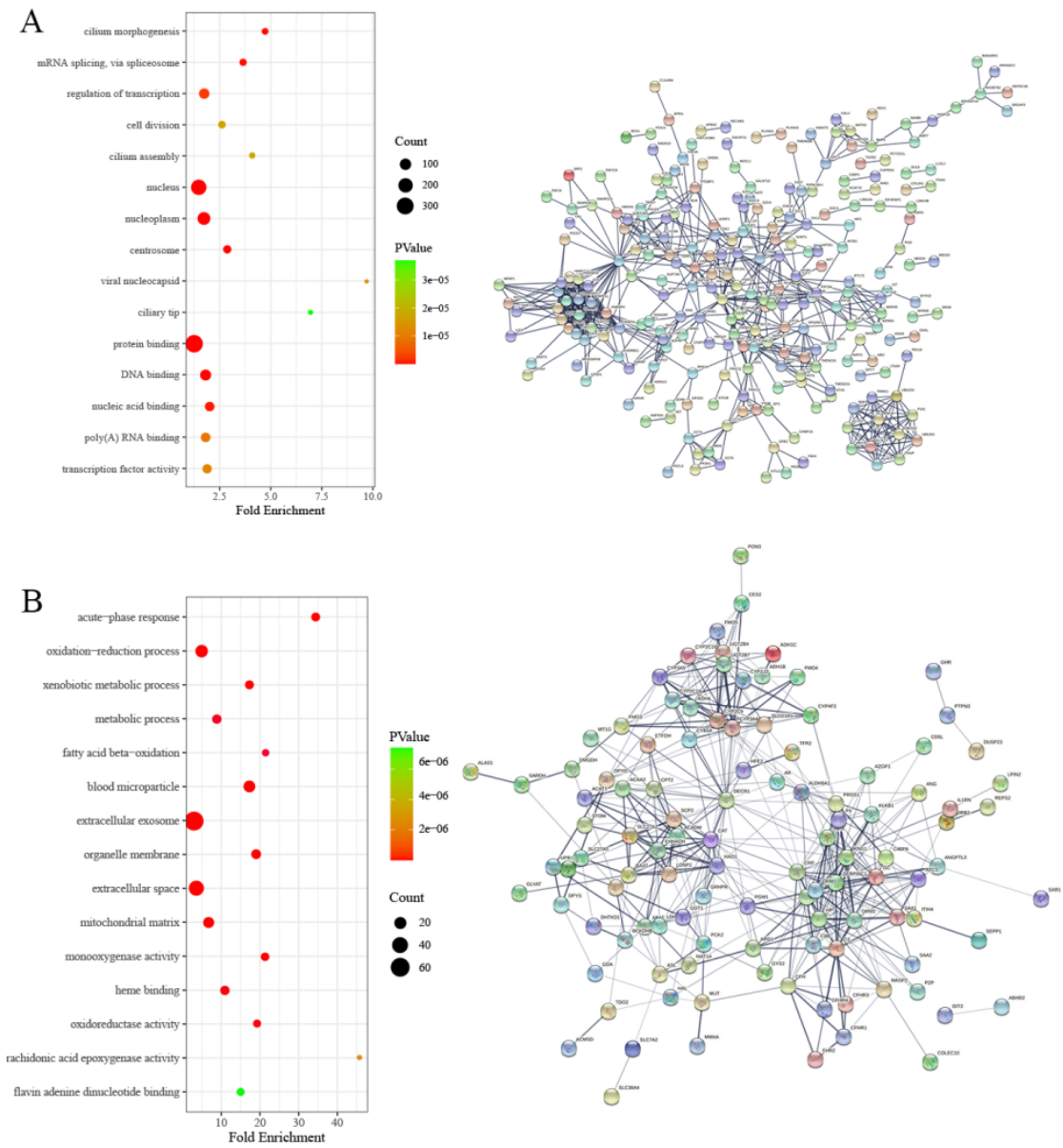

Figure 4

(A) Illustrates the biological processes and functions associated with SLC2A14, such as cilium morphogenesis, mRNA splicing, transcription regulation, and cell division, along with their statistical significance.(B) Depicts functions related to metabolic processes, including oxidation-reduction reactions, xenobiotic metabolism, and fatty acid beta-oxidation, along with their enrichment levels.

4. Discussion

The present study explored the clinical significance and potential molecular mechanisms of SLC2A14 in development of HB. Our results showed overexpressed SLC2A14 had a potential to be a signal of existed HB. We herein provided some highlights. We collected 7 series from public databases to show mRNA expression level of SLC2A14 in HB. Moreover, SLC2A14 expression levels of tissues from HB patients in our hospital were also included into SMD. Then, the relationship between SLC2A14 and immune-related genes was revealed. We also discussed the relationship between SLC2A14 and ferroptosis in HB. In our study, metabolic pathway was considered to play an important role in development of HB regulated by SLC2A14 DCEGs.

As mentioned earlier, SLC2A14 was originally reported to be associated with hexose transport [16]. Some study also found differential expressed SLC2A14 could influence glucose metabolism of tumor cells, including thyroid papillary carcinoma, ovarian cancer and glioblastoma [6,17,18]. To date, there are

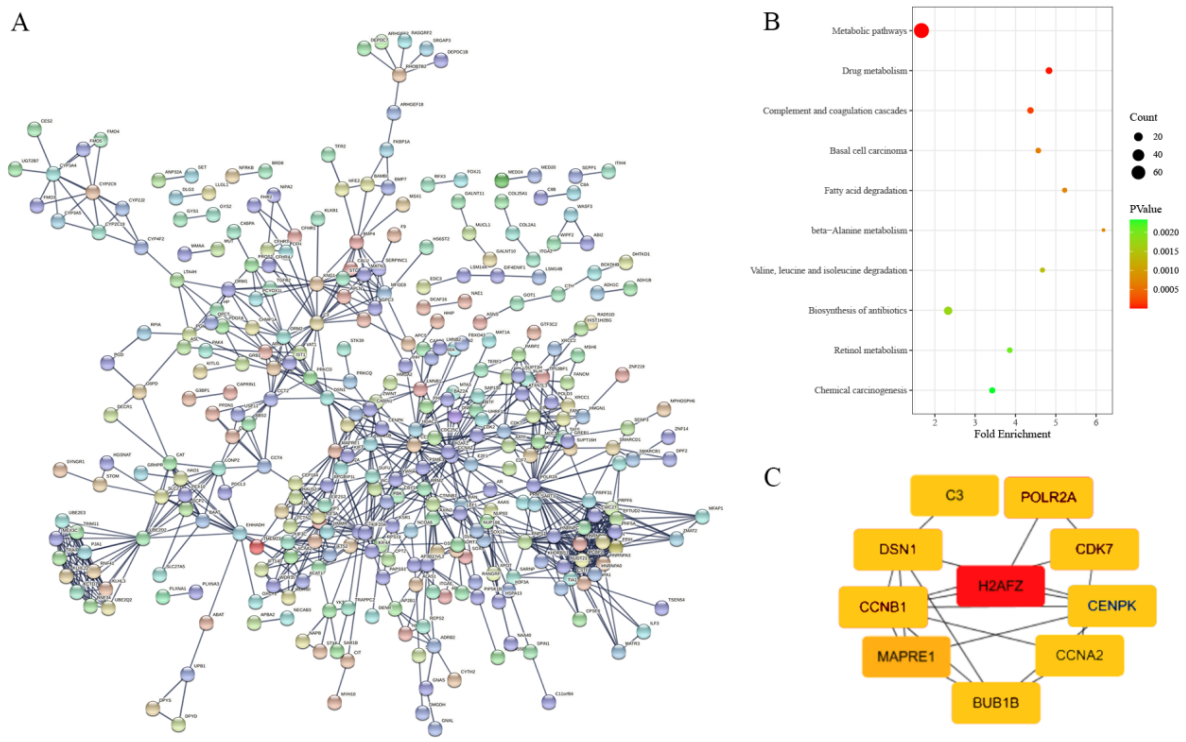

Figure 5

showcases the KEGG pathway enrichment analysis of SLC2A14 DCEGs. (A) Highlights the metabolic pathways associated with SLC2A14 DCEGs, showing the enrichment of these genes in metabolic processes.(B) Displays the enrichment of the complement and coagulation cascade pathways, which may be related to the functions of SLC2A14 DCEGs.(C) Shows other pathways related to SLC2A14 DCEGs, including their roles in various biological processes.

some researches on SLC2A14 in various diseases. In a study included 597 Alzheimer's disease (AD) patients and 605 healthy people, Wang et al. indicated that gene polymorphism of SLC2A14 was probably an important factor causing AD, and this factor was associated with clinical parameters such as ages and sexes [19]. Bitar et al. also reported differential expressed SLC2A14 might influence morbidity of AD [20]. Nag et al. identified the overlapping sites of SLC2A14 were able to regulate intraocular pressure, which could be a target to treat glaucoma, but the researchers thought SLC2A14 expression had no correlation with hypertension [21]. By observing 454 Turner syndrome patients, Prakash et al. thought the lacking of SLC2A14 influenced expression of cardiac development-related genes [22]. In the above study, we found some researches had reported the relationship between the function of SLC2A14 and clinical parameters. In the present study, we showed SLC2A14 expression was upregulated in HB (SMD=0.80, 95%CI=0.07, 1.53), and we indicated that SLC2A14 had a high discrimination potential between HB patients and healthy people (AUC=0.91, 95%CI=0.88, 0.93). Though all of the results showed the expression of SLC2A14 was not related to clinical parameters, these results were instrumental in clinical application of SLC2A14. Additionally, we thought the more accurate results should be obtained in a larger sample sizes.

In summary, after revealing the expression level and discrimination potential of SLC2A14 in HB, to explore the molecular mechanisms of SLC2A14 in regulating HB development, we obtained DCEGs of SLC2A14 by intersecting CEGs and DEGs. Through GO annotation and KEGG pathway enrichment analysis, we found SLC2A14 DCEGs significantly enriched in metabolic pathway, which indicated the correlations between the above genes and material metabolisms had potential research value. In the previous study, intracellular metabolism has been widely reported to be related to the development, metastasis and apoptosis of HB. Wang et al. thought downregulated SLC10A1 could improve viability of HB cells by promoting intracellular metabolism, when SLC10A1 expression was induced by drugs, cell cycle arrest

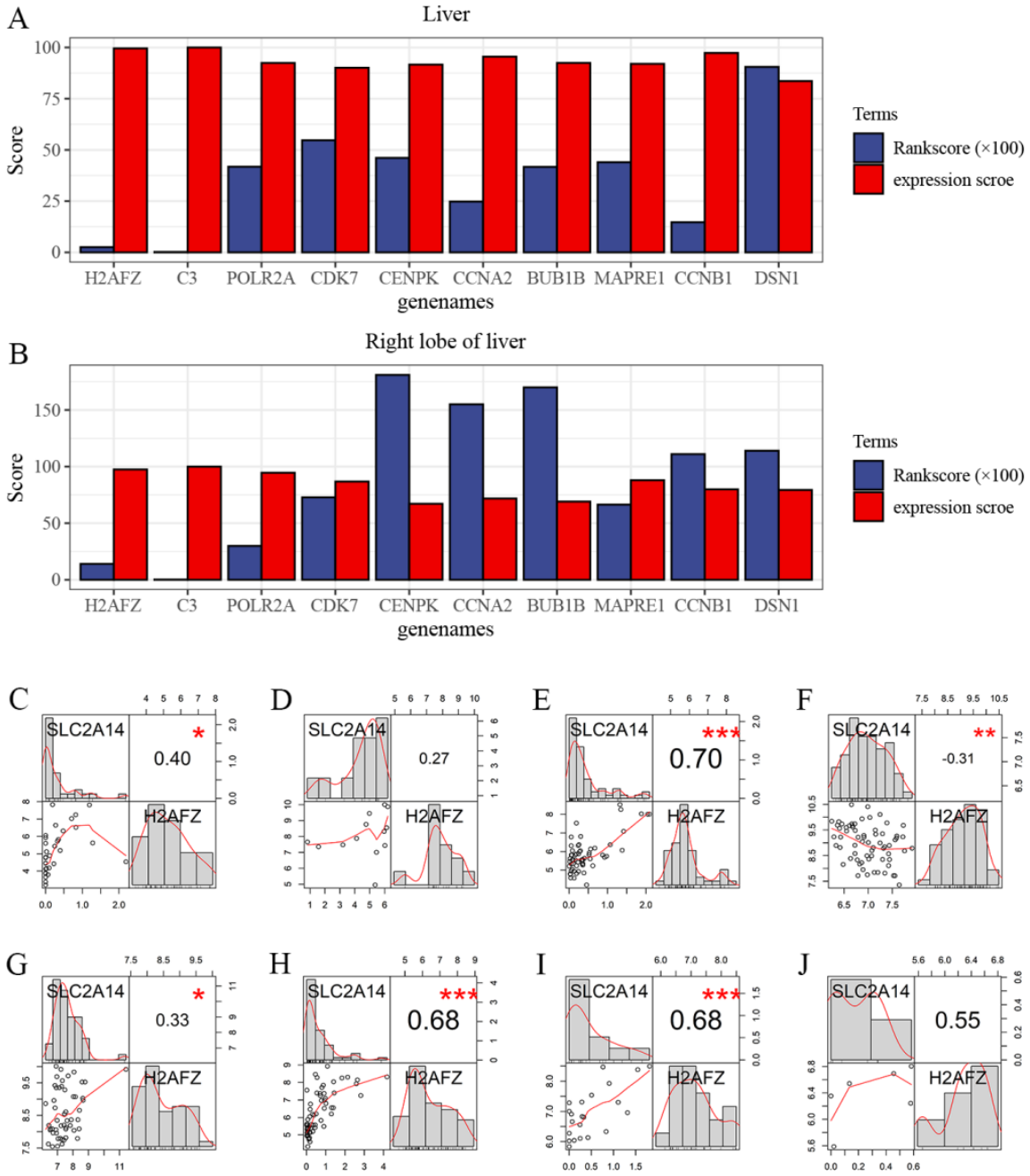

Figure 6

(A) Displays the expression scores and rankscores of specific genes in the liver, highlighting their expression levels within this tissue.(B) Focuses on the expression scores and rankscores of the same genes in the right lobe of the liver, providing region-specific gene expression information.

(C-J)Demonstrates the correlation between SLC2A14 and other genes in hepatoblastoma, with asterisks indicating statistical significance.

and apoptosis would occurred in HB cells [23]. Crippa et al. found HB cells were sensitive to silenced hexokinase-1 through researching glycolytic potential, this study indirectly indicated SLC2A14 hexose transport capacity might affect the glucose metabolism of HB, which coincided with our results [24]. Moreover, in a research managed by Wang et al. researchers found differential expressed Myc would influence metabolic reprogramming and promote growth of tumors [25]. Unfortunately, as for the relationship between SLC2A14 and metabolic pathway in HB, remains to be clarified by the followed research.

We analyzed the PPI network through Cytoscape v3.8.2 and found H2AFZ might be the hubgene of

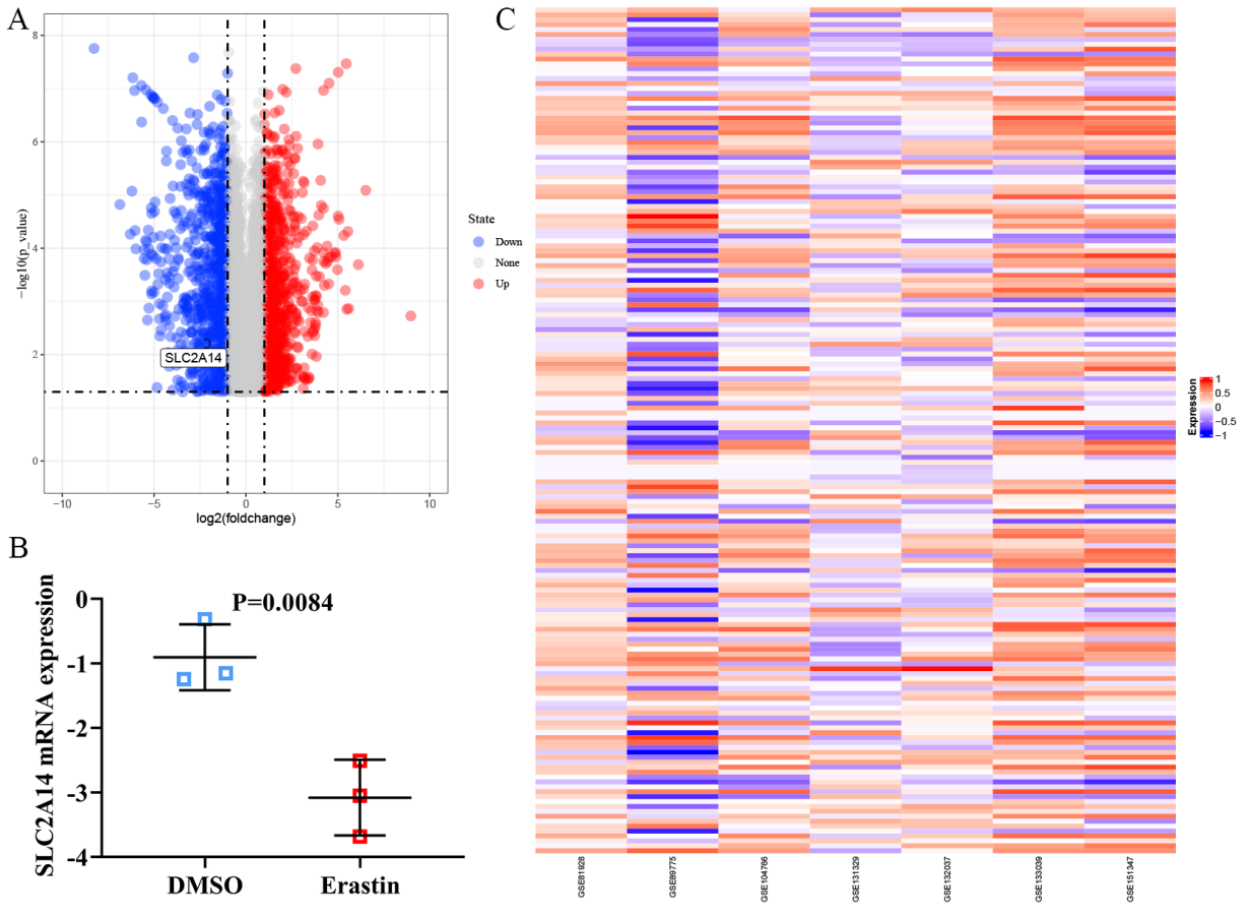

Figure 7

(A)Compares the SLC2A14 mRNA expression levels between samples treated with DMSO and erastin. (B)Presents log2(fold change) values for SLC2A14 across different datasets.(C)Depicts the regulation state of SLC2A14 based on -log10(p_value), indicating upregulation, no change, or downregulation.

SLC2A14 DCEGs. Though there is no researches about H2AFZ in HB, clinical significance of H2AFZ in various malignant tumors had been reported. Qi et al. reported H2AFZ was upregulated in breast tumor, and could be considered as individual adverse prognostic factor [26]. Tang et al. indicated H2AFZ was significantly upregulated in many series of hepatocellular carcinoma, overexpressed H2AFZ regulated the proliferation of hepatocellular carcinoma cells and was related to the poor prognosis of patients [27]. Baptista et al. also indicated nicotinamide would inhibited expression of H2AFZ in prostate cancer, and reduced interaction between sirtuin 1 and H2AFZ, which could also influence proliferation of tumor cells [28]. In the present research, we explore expression levels of H2AFZ and other potential hubgenes in normal liver tissues, and discussed the correlation between H2AFZ and SLC2A14. We indicated potential clinical significance of H2AFZ in HB.

Interestingly, in the process of searching literature, we found SLC2A14 was reported to affect iron metabolism in tumor cells and to regulate ferroptosis of tumor cells [29]. As one of the metabolic types, iron metabolism was also considered to be a part of our research. In a research of Lippmann et al., the researchers reported the effects of different reactive oxygen species modulators and ferroptosis inducers on human HB cells, they thought the activity of HB cells was significantly inhibited by combining use of ferroptosis inducers, the results indicated ferroptosis was expected to be used in the targeted therapy of HB [30]. Up to now, only seldom researches about ferroptosis in HB, but there are many researches reported function of ferroptosis in various of cancers. In many cancers, including gastric cancer, ovarian cancer and lung cancer, the occurrence of ferroptosis was considered to be associated with metabolism of reactive oxygen species and iron, and might be arranged by various of differential expressed mole-

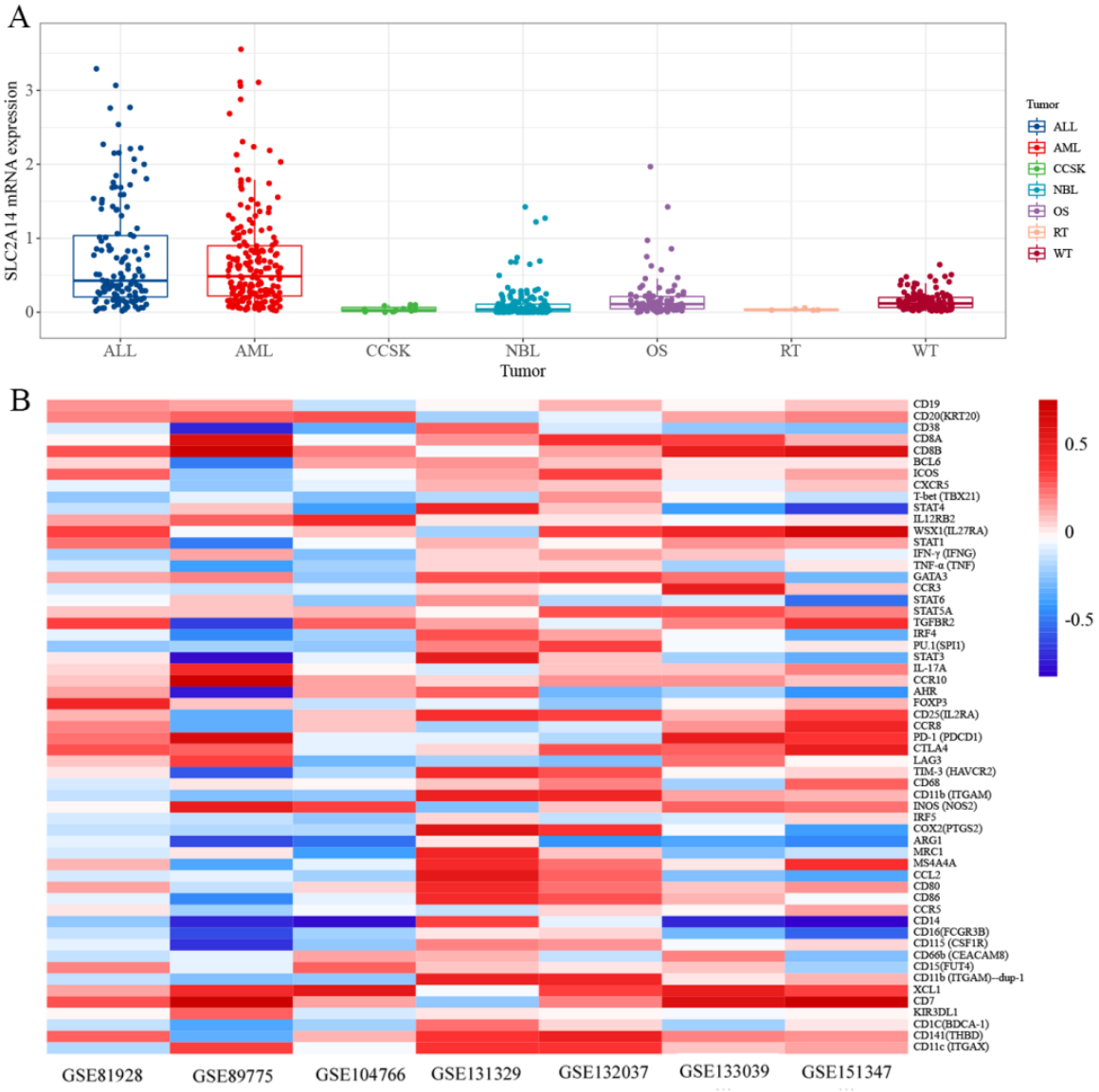

Figure 8

(A)Displays SLC2A14 mRNA expression across different tumor types including ALL, AML, CCSK, NBL, and OS, compared to normal controls (RT and WT).(B)Shows the expression levels of various immune markers such as CD19, CD20, CD38, CD8A, and others, in relation to SLC2A14 mRNA expression.

cules[31–33]. The present study analyzed changes in expression levels of SLC2A14 after being treated with ferroptosis inducer, and the analysis results illuminated downregulated SLC2A14 promoted the development of ferroptosis, then regulated apoptosis of HB cells. Additionally, we also found SLC2A14 expression was related to expression levels of many ferroptosis-related genes.

Some limitations should be pointed out in the present study. The showed results were all collected from HB and paracancerous tissues, we could not simply assume that our results applies to body fluids, so a further research should be managed in the future. In addition, these samples could not necessarily represent the objective situation, larger sample sizes researches are essential.

In conclusion, based on mRNA-seq and sequencing data, we thought SLC2A14 was upregulated in HB, and indicated overexpressed SLC2A14 was associated with occurred of ferroptosis for the first time. Differential expressed SLC2A14 and its DCEGs might regulate ferroptosis by taking part in metabolic pathway, which should be verified in vitro and in vivo.

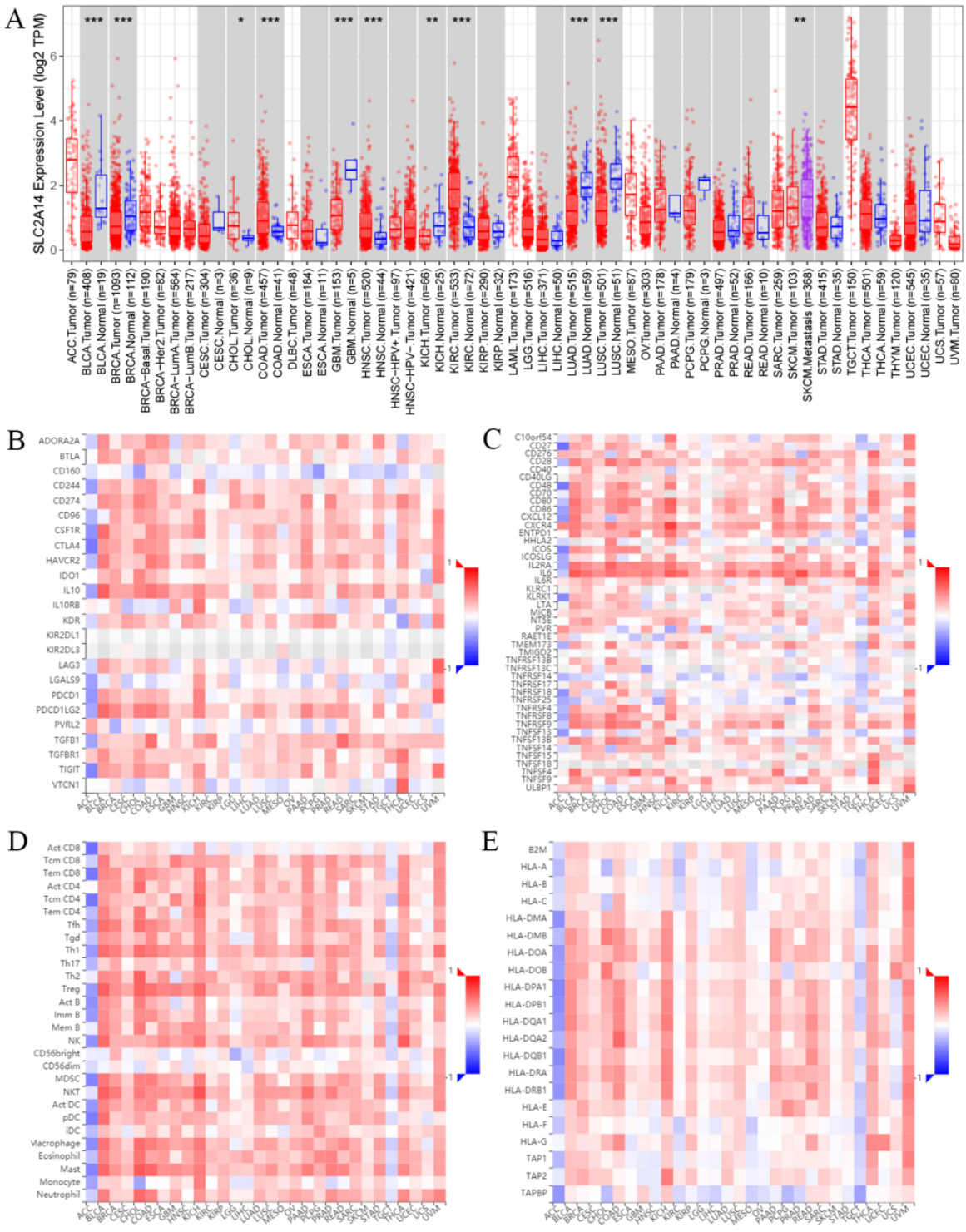

Figure 9

(A)The distribution of SLC2A14 gene expression levels (in log2 TPM) in different tumor types is shown. In the figure, red represents the tumor samples, blue represents the normal samples, each point represents a sample, and the boxplot shows the distribution range of the data.(B)The heat map demonstrates the correlation between different tumor types (rows) and multiple immune-related genes (columns).(C)Presents data on SLC2A14 expression levels (log2 TPM) in a variety of tumor types, comparing tumor samples to normal tissues.(D)Highlights specific immune checkpoint molecules and their potential relationship with SLC2A14 in the tumor microenvironment. (E)Provides an overview of SLC2A14 expression in various cancer types.

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Global Trends and Hotspots in Tongue Cancer Research: A Bibliometric Analysis (2014-2024)

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KEYWORDS

Tongue Cancer,
Bibliometric Analysis,
Research Hotspots,
HPV,
Personalized Treatment

ABSTRACT

This study conducts a bibliometric analysis of 1,553 tongue cancer-related publications from 2014 to 2024, sourced from the Web of Science database, to uncover global research trends, hotspots, key contributors, and future directions in the field. Results indicate a significant rise in research activity, with China, the United States, and Japan leading in output and international collaboration. Emerging hotspots include the use of advanced technologies such as artificial intelligence, deep learning, and radiomics for early diagnosis, prognostic evaluation, and treatment, as well as a growing focus on younger patient populations and immunotherapy strategies. Future research should emphasize interdisciplinary collaboration, integrating bioinformatics, imaging, and clinical studies, while fostering international cooperation and data sharing to advance understanding of tongue cancer pathogenesis and improve treatment outcomes, survival rates, and quality of life for patients.

1. Introduction

Tongue cancer is a malignant tumor that occurs in the oral tongue, and it is one of the most common types of oral squamous cell carcinoma (Sung et al., 2021). It not only jeopardizes the patient's life and health but also severely affects their ability to eat, speak, and socialize. In recent years, the incidence of tongue cancer has been on the rise globally, particularly in regions lacking effective early screening and preventive measures (Sung et al., 2021). According to the World Health Organization's report, tongue cancer ranks among the top five most common malignant tumors of the head and neck, with approximately 300,000 new cases diagnosed annually worldwide (Tan et al., 2023). Because tongue cancer often lacks obvious symptoms in its early stages, most patients are diag nosed at an advanced stage, resulting in a five-year survival rate of less than 50% (Chinn & Myers, 2015; Leemans et al., 2011). Currently, the main treatment for tongue cancer is a

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comprehensive approach, primarily involving surgical resection, supplemented by radiation therapy, chemotherapy, targeted therapy, and immunotherapy (Zanoni, Patel, et al., 2019). Therefore, research on tongue cancer not only helps optimize clinical treatment strategies but also holds the potential to improve patient survival and quality of life through early diagnosis and intervention.

Bibliometric analysis is a statistical method based on public literature databases (such as Web of Science), which uses statistical data to analyze published information (such as books, journal articles, datasets, blogs) and their associated metadata (such as abstracts, keywords, citations). It aims to describe or display the relationships between published works and serves as a practical tool for assessing research trends (Ninkov et al., 2022). This method can analyze frequently occurring keywords in the articles and popular terms that have emerged in recent years, thereby providing supporting evidence for future research trends. Bibliometric analysis helps identify influential researchers, key studies, and emerging trends, promoting strategic planning and decision-making in scientific research (Cheng et al., 2023). The achievements of bibliometric analysis are reflected in its widespread application across various scientific fields, from medicine to environmental science. These analyses play a crucial role in mapping research activities and assessing the contributions of different countries and institutions to global knowledge (Cheng et al., 2023; Wei et al., 2022).

CiteSpace is a tool for bibliometric analysis, designed to visualize and analyze trends and patterns in scientific literature, helping researchers identify key points and emerging trends (Cortese et al., 2022). In this study, CiteSpace software was used to perform co-occurrence analysis of literature related to tongue cancer, constructing a knowledge map to visualize research dynamics, evolving patterns, and development processes. The analysis aims to identify academic research hotspots in this field and provide new insights and references for future related research.

2. Methods

2.1. Data Source and Retrieval Strategy

The Web of Science (WOS) core database, provided by Clarivate Analytics, is widely regarded as the preferred data source for bibliometric analysis, as it covers a wide range of academic fields and high-quality scholarly publications (Liu et al., 2023). Therefore, this study selected the WOS core database as the primary data source. On March 24, 2024, we performed an English-language search in the WOS core database for all articles related to tongue cancer published from January 1, 2014, to March 24, 2024. The search string was: (((((TS=("tongue cancer")) OR TS=("tongue neoplasm")) OR TS=("carcinoma of tongue")) OR TS=("tongue cancers")) OR TS=("tongue squamous cancer")) OR TS=("tongue squamous carcinoma")). The inclusion criteria were: (1) articles written in English; (2) only research articles included, excluding letters, reviews, conference abstracts, etc.; (3) studies focused on tongue cancer; (4) to ensure data consistency and minimize potential bias from daily database updates, all relevant literature was retrieved and screened on the same day.

2.2. Analysis Method

This study used CiteSpace software (version 6.1.6) for visualization analysis and Microsoft Excel (2021) for data management and publication trend analysis. The parameters for CiteSpace were set as follows: time slices from 2014 to 2024, with each slice representing one year, and the selection criteria were based on the g-index (g2≤k σ i≤gci, where k∈Z+, k=25). The literature was visualized and analyzed with respect to countries/regions, institutions, references, and keywords.

In the generated graphs, N represents the number of network nodes, E represents the number of connecting edges, and density refers to the network density. Modularity is an indicator of network modularity. A higher modularity Q value indicates a better clustering effect in the network. A Q value greater than 0.3 suggests that the clustering structure is significant. The silhouette value is used to measure the homogeneity of the network, with values close to 1 indicating higher homogeneity, and values greater than 0.5 suggesting that the clustering structure is reasonable.

This study primarily measures the following: (1) Analysis of the number of publications, collaboration networks between countries/regions, journals, and institutions;(2) Author and co-cited author network analysis, which helps reveal the collaboration patterns and influence among authors;(3) Cited literature analysis, which includes network maps, timeline graphs, and reference burst graphs. Co-citation analysis refers to the situation where two or more articles are simultaneously cited by one or more subse-

quent articles, indicating a co-citation relationship between these articles. This is a method for measuring the strength of relationships between publications;(4) Keyword analysis, which includes keyword clustering analysis, keyword time-zone graph analysis, and keyword burst analysis. The keyword clustering graph focuses on reflecting the structural characteristics between clusters and highlights key nodes and important connections. The keyword time-zone graph shows the evolution of high-frequency keywords over time. Keyword burst analysis helps explore rapidly emerging topics within the field.

Ethical review is not applicable for this type of study.

3. Results

3.1. Publication Trends

A total of 1,553 articles related to tongue cancer were retrieved in this study. The data show that from 2015 to 2016, the number of publications increased slowly. From 2016 to 2019, the number of articles grew steadily, while from 2019 to 2021, there was an explosive growth in publications (Figure 1). This reflects the increasing attention to tongue cancer research over the past decade. Although the number of articles declined after reaching its peak in 2021, it still remained at a high level compared to the previous ten years.

3.2. Country / Region of Publication

This study includes publications from 73 different countries and regions. Among all countries, China leads with 355 articles, accounting for 22.86%, followed by Japan (268 articles, 17.26%) and the United States (219 articles, 14.10%). Despite China's dominance in the number of publications, its centrality is only 0.16, ranking fourth. In contrast, the United States ranks third in total publications, but with a centrality of 0.25, it holds the top position, reflecting its core role in international collaboration. England (centrality 0.23) and India (centrality 0.22) follow closely, highlighting their significant roles in international cooperation. Notably, despite England's relatively small publication count of 26 articles (1.67%, ranked 15th), its centrality is ranked third, indicating its prominent position in international collaboration. The most frequent collaboration occurs between the United States and China.

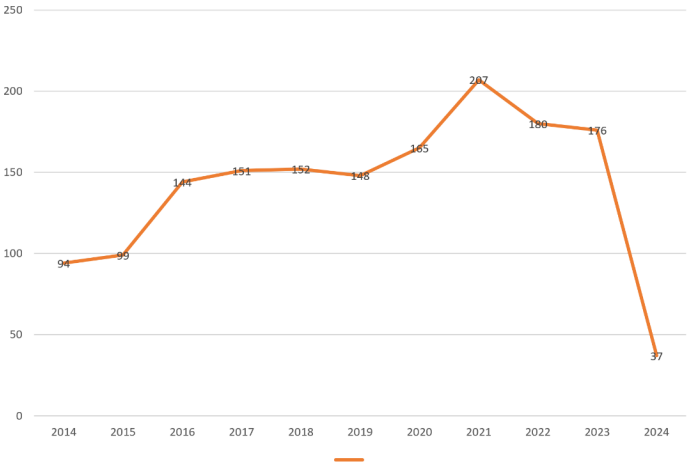
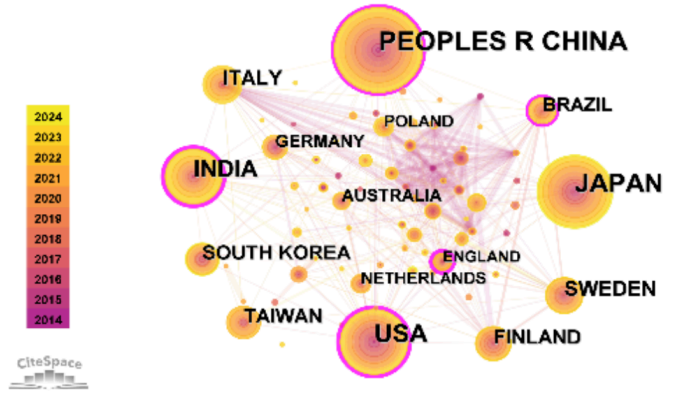


Figure 1 | Number of publications per year



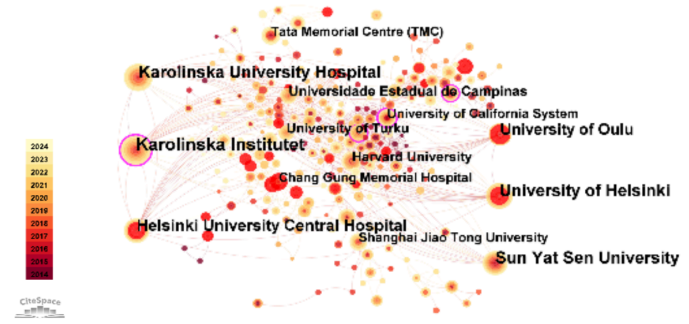


Figure 3 | Analysis of research institutions

3.3. Research Institutions

CiteSpace software was used to analyze 353 institutions contributing to tongue cancer research, as shown in Figure 3. Table 3 lists the top 10 institutions by the number of published studies from 2014 to 2024. The data shows that these top 10 institutions published a total of 415 research articles, accounting for 26.72% of all publications. The institution with the most publications is Karolinska Institutet (73 articles, 4.70%), followed by University of Helsinki (63 articles,

Table 1 | Top 10 Research Institutions

Rank	Count	Centrality	Research Institutions
1	73	0.24	Karolinska Institutet
2	63	0.03	University of Helsinki
3	62	0.05	Karolinska University Hospital
4	58	0.09	Sun Yat Sen University
5	51	0.01	Helsinki University Central Hospital
6	42	0.02	University of Oulu
7	28	0.05	Universidade Estadual de Campinas
8	26	0	University of Turku
9	25	0.07	Harvard University
10	23	0.01	Tata Memorial Centre (TMC)

4.06%) and Karolinska University Hospital (62 articles, 3.99%).

3.4. Analysis of Authors and Co-Cited Authors

A total of 450 researchers have contributed to the publication of relevant literature in this field. Among them, Salo, Tuula ranks first with 37 publications, followed by Dalianis, Tina (29 publications) and Almangush, Alhadi (23 publications). The visual analysis graph displays the influence of each author, where each circle represents an author. The size of the circle reflects the number of publications by that author, and the thickness of the connecting lines between circles indicates the level of collaboration between authors (Figure 4).

In the co-citation analysis, a total of 564 authors formed co-citation relationships. Among these authors, JEMAL A has the highest citation count with 185 citations, followed by DCRUZ AK (132 citations)

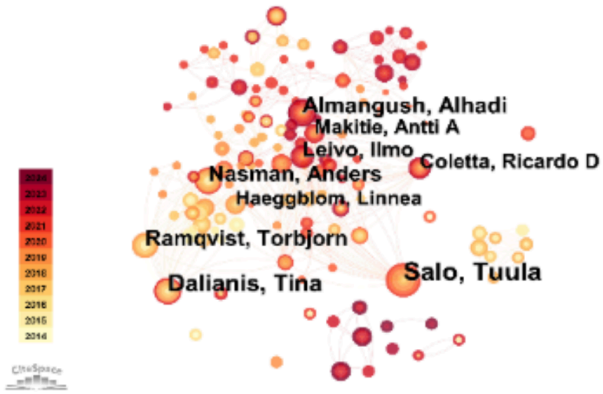


Figure 4 | Analysis of authors

Table 2 | Top 10 Authors and Co-Cited Authors

Rank	Count	Centrality	Authors	Rank	Count	Centrality	Co-Cited Authour
1	37	0.02	Salo, Tuula	1	185	0.02	JEMAL A
2	29	0.01	Dalianis, Tina	2	132	0.05	DCRUZ AK
3	23	0	Almangush, Alhadi	3	123	0.04	GANLY I
4	22	0.01	Nasman, Anders	4	110	0.09	ALMANGUSH A
5	21	0.01	Ramqvist, Torbjorn	5	105	0.02	WARNAKULASURIYA S
6	19	0	Leivo, Ilmo	6	101	0.04	CHATURVEDI AK
7	18	0.01	Coletta, Ricardo D	7	100	0.04	YUEN APW
8	15	0	Makitie, Antti A	8	97	0.02	HUANG SH
9	15	0.01	Haeggblom, Linnea	9	82	0.1	GILLISON ML
10	13	0	Kakimoto, Naoya	10	78	0.02	FERLAY J

and GANLY I (123 citations). In terms of network centrality, COOPER JS has the highest centrality at 0.14, followed by GILLISON ML (0.1), while ALMANGUSH A and BRANDWEIN-GENSLER A share the third position with a centrality of 0.09. This indicates the significant influence and central role of these authors in the field of tongue cancer research (Figure 5).

3.5. Journals of Publication and Co-Cited Journals

In the field of tongue cancer research, ORAL ONCOLOGY is the journal with the highest number of publications, with 71 articles, followed by HEAD AND NECK-JOURNAL FOR THE SCIENCES AND SPECIALTIES OF THE HEAD AND NECK (66 articles) and CANCERS (30 articles). In terms of impact factor, CANCERS ranks first among the top ten academic journals, with an impact factor of 5.2. The number of publications, impact factor, and JCR rankings of the top 10 journals are listed in Table 3.

Among the 638 co-cited journals, ORAL ONCOLOGY has the highest citation count, with 989 citations, followed by HEAD NECK-J SCI SPEC (908 citations) and LARYNGOSCOPE (509 citations). The impact factor and JCR rankings of the top 10 co-cited journals are shown in Table 3.

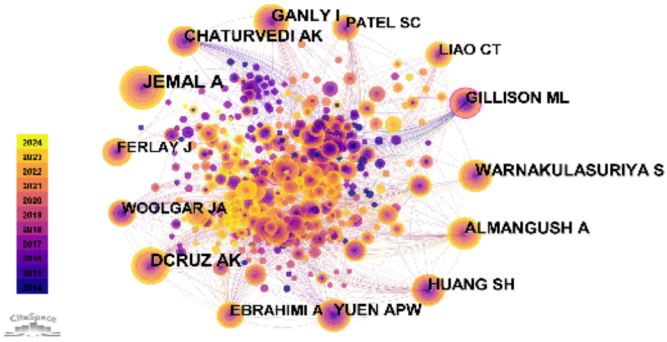


Figure 5 | Analysis of Co-Cited Author

Figure 7 | Co-Cited Journal Analysis

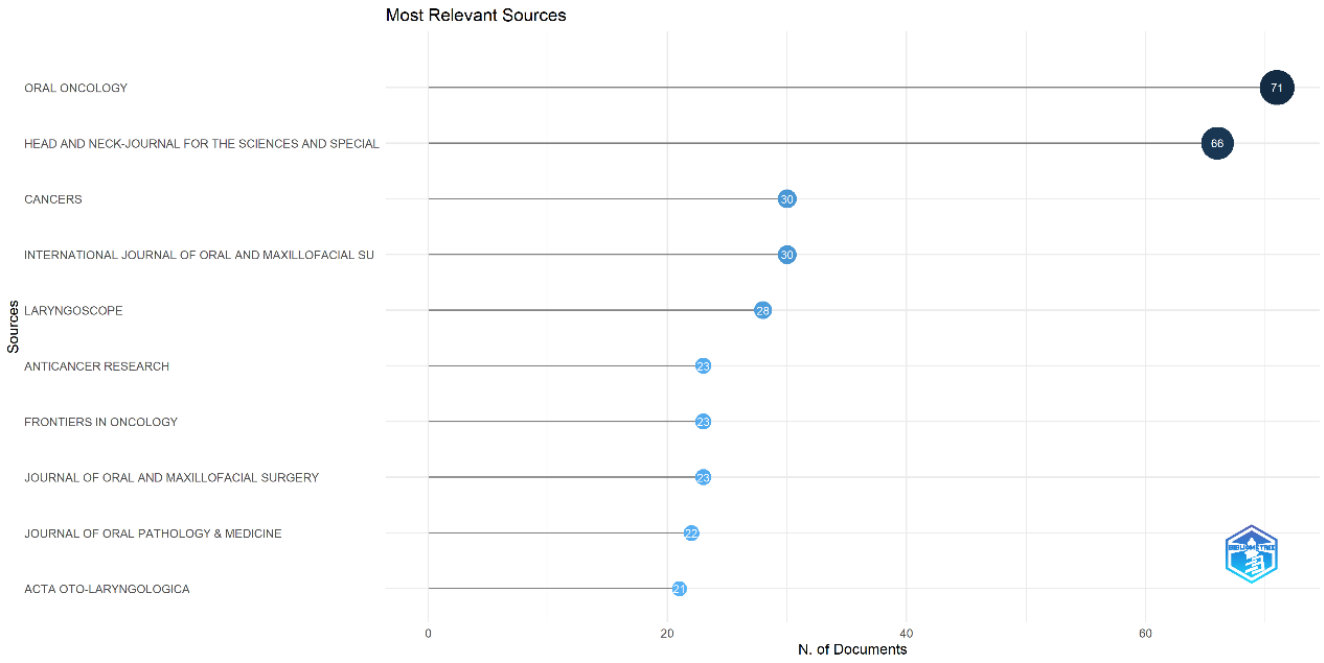


Figure 6 | Number of Publications by Journal

Table 3 | Top 10 Journals by Number of Publications and Co-Citation Count

Rank	Count	Journal	IF	JCR	Rank	Count	Cited Journal	IF	JCR
1	71	ORAL ONCOLOGY	71	4.0	1	71	ORAL ONCOL	4.0	Q2
2	66	HEAD AND NECK-JOURNAL FOR THE SCIENCES AND SPECIALTIES OF THE HEAD AND NECK	66	2.3	2	66	HEAD NECK-J SCI SPEC	2.3	Q2
3	30	CANCERS	30	4.5	3	30	LARYNGOSCOPE	2.2	Q1
4	30	INTERNATIONAL JOURNAL OF ORAL AND MAXILLOFACIAL SURGERY	30	2.2	4	30	CANCER-AM CANCER SOC	6.1	Q1
5	28	LARYNGOSCOPE	28	2.2	5	28	PLOS ONE	2.9	Q1
6	23	ANTICANCER RESEARCH	23	1.6	6	23	J CLIN ONCOL	18.97	Q1
7	23	FRONTIERS IN ONCOLOGY	23	3.5	7	23	INT J CANCER	5.7	Q1
8	23	JOURNAL OF ORAL AND MAXILLOFACIAL SURGERY	23	2.3	8	23	J ORAL MAXIL SURG	2.2	Q2
9	22	JOURNAL OF ORAL PATHOLOGY & MEDICINE	22	2.7	9	22	CANCER RES	12.5	Q1
10	13	ACTA OTO-LARYNGOLOGICA	21	1.2	10	13	CA-CANCER J CLIN	4.0	Q2

Table 4 | Top 10 Cited References

Rank	Count	Cited Reference	Centrality	Year	DOI
1	58	Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer	0.14	2015	10.1056/NEJMoa1506007
2	44	Changing epidemiology of oral squamous cell carcinoma of the tongue: A global study	0.05	2017	10.1002/hed.24589
3	38	Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual	0.05	2017	10.3322/caac.21389
4	33	Rising incidence of oral tongue cancer among white men and women in the United States, 1973-2012	0.16	2017	10.1016/j.oraloncology.2017.02.019
5	31	Depth of invasion, tumor budding, and worst pattern of invasion: Prognostic indicators in early-stage oral tongue cancer	0.08	2014	10.1002/hed.23380
6	25	Classification of GLOSSECTOMIES: Proposal for tongue cancer resections	0.02	2019	10.1002/hed.25466
7	25	Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries	0.01	2021	10.3322/caac.21660
8	24	AJCC CANCER STAGING MANUAL	0.02	2017	-
9	22	Long-term regional control and survival in patients with “low-risk,” early stage oral tongue cancer managed by partial glossectomy and neck dissection without postoperative radiation	0.15	2013	10.1002/cncr.27872
10	21	Survival outcomes after treatment of cancer of the oral cavity (1985-2015)	0.09	2019	10.1016/j.oraloncology.2019.02.001

3.6. Co-Cited Literature Analysis and Citation Burst

Co-citation analysis reflects, to some extent, the key literature in a research field. By analyzing the high-frequency co-cited literature, we identified the top 10 core articles in this field, which are of significant reference value for current research. Among them, the article with the highest citation burst intensity and the most citations was published in 2015 in The New England Journal of Medicine (impact factor 158.5, Q1 level), titled "Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer" (D'Cruz et al., 2015). This study showed that, in oral cancer patients without neck lymph node metastasis, elective neck dissection was more effective in reducing postoperative complications compared to therapeutic neck dissection, without affecting the overall survival rate of patients. This finding provides important guidance for the surgical treatment strategies of tongue cancer and has contributed to the development of personalized treatment plans.

Citation burst analysis is a powerful tool that helps researchers and decision-makers better understand and grasp the development dynamics and trends of a research field, as well as identify the literature that has received significant attention during a specific period of time.

3.7. Analysis of Keywords and Burst Keywords

Keywords play a crucial role in academic articles, as they concisely express the content of the paper, quickly and accurately revealing the topic and research focus, helping readers rapidly understand the scope and core content of the research. In this study, the keywords of the included publications were visualized and analyzed using CiteSpace software (Figure 9). The most frequently occurring keyword was "tongue cancer," appearing 606 times, followed by "head" (553 times), "squamous cell carcinoma" (529 times), "oral cancer" (230 times), and "cancer" (202 times). The co-occurrence analysis of keywords re-

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2014 - 2024
Chaturvedi AK, 2011, J CLIN ONCOL, V29, P4294, DOI 10.1200/JCO.2011.36.4596, DOI	2011	8.03	2014	2016	
Patel SC, 2011, J CLIN ONCOL, V29, P1488, DOI 10.1200/JCO.2010.31.7883, DOI	2011	7.56	2014	2016	
Attner P, 2010, INT J CANCER, V126, P2879, DOI 10.1002/ijc.24994, DOI	2010	7.5	2014	2015	
Siegel R.L., 2020, ANTI-CANCER DRUG, V70, P7, DOI 10.1097/CAD.0000000000000617, DOI	2020	7.37	2020	2016	
Ganly I, 2012, CANCER-AM CANCER SOC, V118, P101, DOI 10.1002/cncr.26229, DOI	2012	7.05	2014	2017	
Ang KK, 2010, NEW ENGL J MED, V363, P24, DOI 10.1056/NEJMoa0912217, DOI	2010	6.96	2014	2015	
Leemans CR, 2011, NAT REV CANCER, V11, P9, DOI 10.1038/nrc2982, DOI	2011	6.13	2014	2016	
Näsman A, 2013, PLOS ONE, V8, P0, DOI 10.1371/journal.pone.0077025, DOI	2013	4.97	2014	2018	
Ganly I, 2013, CANCER-AM CANCER SOC, V119, P1168, DOI 10.1002/cncr.27872, DOI	2013	6.99	2015	2018	
Nordfors C, 2013, EUR J CANCER, V49, P2522, DOI 10.1016/j.ejca.2013.03.019, DOI	2013	5.32	2015	2018	
Almangush A, 2014, HEAD NECK-J SCI SPEC, V36, P811, DOI 10.1002/hed.23380, DOI	2014	8.81	2016	2019	
DCruz AK, 2015, NEW ENGL J MED, V373, P521, DOI 10.1056/NEJMoa1506007, DOI	2015	14.04	2017	2020	
Ebrahimi A, 2014, JAMA OTOLARYNGOL, V140, P1138, DOI 10.1001/jamaoto.2014.1548, DOI	2014	9.02	2018	2019	
[Anonymous], 2017, AMERICAN JOINT COMMITTEE ON CANCER, V0, P0	2017	7.02	2018	2020	
Abu-Ghanem S, 2016, JAMA OTOLARYNGOL, V142, P857, DOI 10.1001/jamaoto.2016.1281, DOI	2016	5.92	2019	2021	
Alsaffar HA, 2016, J OTOLARYNGOL-HEAD N, V45, P0, DOI 10.1186/s40463-016-0172-0, DOI	2016	5.22	2019	2021	
Ng JH, 2017, HEAD NECK-J SCI SPEC, V39, P297, DOI 10.1002/hed.24589, DOI	2017	9.56	2020	2021	
Murakami R, 2019, ACAD RADIOL, V26, PE180, DOI 10.1016/j.acra.2018.08.021, DOI	2019	6.77	2020	2021	
Tota JE, 2017, ORAL ONCOL, V67, P146, DOI 10.1016/j.oraloncology.2017.02.019, DOI	2017	6.6	2020	2021	
Ansarin M, 2019, HEAD NECK-J SCI SPEC, V41, P821, DOI 10.1002/hed.25466, DOI	2019	5.39	2020	2024	
Amin MB., 2017, AJCC CANCER STAGING MANUAL, V0, P0	2017	9.3	2021	2022	
Hussein AA, 2017, EUR J CANCER, V82, P115, DOI 10.1016/j.ejca.2017.05.026, DOI	2017	5.9	2021	2022	
Sung H, 2021, CA-CANCER J CLIN, V71, P209, DOI 10.3322/caac.21660, DOI	2021	8.42	2022	2024	
Zanoni DK, 2019, ORAL ONCOL, V90, P115, DOI 10.1016/j.oraloncology.2019.02.001, DOI	2019	7.3	2022	2024	
Tarabichi O, 2019, LARYNGOSCOPE, V129, P662, DOI 10.1002/lary.27403, DOI	2019	6.56	2022	2024	

Figure 8 | References with the Strongest Citation Bursts

veals the research hotspots and trends. In the keyword co-occurrence map, the size of the nodes and circles reflects the frequency of keyword occurrence. The larger the node, the more concentrated and frequent the research on that keyword.

In the burst keyword analysis, "young patients" is the keyword with the longest burst duration. In recent years, keywords such as "machine learning," "MRI," "accuracy," "interstitial brachytherapy," and "disease-free survival" have also significantly increased, indicating that research on tongue cancer in young patients has become a research hotspot over the past decade. Future research trends are likely to focus on more advanced and precise diagnostic methods for tongue cancer, such as the application of machine learning and radiomics in tongue cancer diagnosis, as well as studies on interstitial brachytherapy and disease-free survival rates.

Figure 9 l Analysis of Keyword

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2014 - 2024
overexpression	2014	4.7	2014	2016	
favorable prognostic factor	2014	3.92	2014	2015	
e cadherin	2014	3.29	2014	2017	
neck cancer	2014	3.08	2014	2015	
speech	2014	2.86	2014	2015	
prognostic significance	2014	2.79	2014	2017	
breast cancer	2014	4.56	2015	2017	
down regulation	2015	4.12	2015	2017	
prostate cancer	2015	3.88	2015	2017	
colorectal cancer	2016	4.23	2016	2018	
radiation	2017	3.01	2017	2019	
nasopharyngeal carcinoma	2017	3.01	2017	2019	
floor	2015	3.62	2018	2021	
total glossectomy	2018	3.34	2018	2019	
biomarkers	2018	2.97	2018	2020	
defects	2018	2.78	2018	2021	
resistance	2019	4.63	2019	2022	
young patients	2020	3.62	2020	2024	
head and neck	2017	2.84	2020	2021	
machine learning	2021	3.64	2021	2024	
tonsillar	2021	3.25	2021	2022	
mri	2018	3.01	2021	2024	
accuracy	2019	3.24	2022	2024	
interstitial brachytherapy	2022	3.24	2022	2024	
disease-free survival	2022	2.89	2022	2024	

Figure 10 l Top 25 Keywords with the Strongest Citation Bursts

4. Discussion

4.1. General Information

In recent years, despite significant progress made by numerous researchers in the study of tongue cancer, it remains a global challenge. Over the past decade, the number of publications on this disease has steadily and rapidly increased, with 1,553 relevant publications selected from the WOS database. Visualization analysis indicates that Sweden, Finland, China, and the United States have made the most significant contributions to tongue cancer research in the past decade. China not only has the highest number of publications (n=355) but is also one of the most frequent collaborators with other countries. In terms of centrality, the United States ranks first. However, the collaboration between these countries has yet to reach an ideal level.

These studies include the work of 450 authors from 73 different countries. Among them, Salo, Tuula from Finland is the most influential author in the field, having published the most research.Salo, Tuula's significant contributions to tongue cancer research have greatly advanced the understanding of the disease's pathology and molecular mechanisms. Her research has provided important insights into prognostic markers and histopathological features, which are key to optimizing treatment decisions. In particular, her collaborative study with Almangush A. on the discovery of prognostic markers, such as invasion depth, has played a crucial role in improving patient prognostic prediction (Almangush, Bello, et al., 2015; Almangush et al., 2017).

Additionally, her research on the molecular basis of tongue cancer, in collaboration with Zlotogorski-Hurvitz A. and Alabi RO., has enhanced diagnostic and monitoring strategies (Alabi et al., 2020; Zlotogorski-Hurvitz et al., 2016). Salo's interdisciplinary approach has facilitated a comprehensive understanding of tongue cancer, from clinical characteris-

tics to treatment interventions, as reflected in her numerous high-impact publications.

The Karolinska Institutet in Sweden and the University of Helsinki in Finland are the highest-producing institutions. The Karolinska Institutet has a significant impact in the field of tongue cancer research, with studies spanning from virology to clinical outcomes and epidemiology. In 2014, Dalianis T. provided insights into carcinogenic viruses associated with tongue cancer, opening new avenues for understanding cancer mechanisms and potential therapeutic targets (Dalianis, 2014). Alabi RO., in studies from 2020 and 2019 on digital health technologies and molecular characteristics of tongue cancer, not only revealed innovative diagnostic and monitoring methods but also highlighted the molecular diversity in tongue cancer cases (Alabi et al., 2019, 2020).

Nasman A., in studies conducted in 2015 and 2020, explored the epidemiology and clinical outcomes of HPV-positive tongue cancer, significantly impacting clinical practice and patient management strategies (Näsman et al., 2015; Stephen et al., 2010). Nordfors C.'s 2014 study contributed to the understanding of genetic mutations associated with tongue cancer, which is crucial for personalized medical approaches (Nordfors et al., 2014).

Additionally, Ramqvist T.'s 2015 research focused on the role of viruses in tongue cancer, providing foundational knowledge for the field, with significant implications for prognosis and treatment strategies (Näsman et al., 2015). Almangush A.'s 2018 study concentrated on histopathological factors in prognosis (Almangush et al., 2018), while Haeggblom L. and Heikkinen I.'s 2019 research further explored the clinical and pathological impacts of tongue cancer treatment (Haeggblom et al., 2019; Heikkinen et al., 2019).

The Helsinki institution has played a significant leadership role in the field of tongue cancer research, particularly in the areas of disease diagnosis, pathological features, surgical treatment, and the optimization of treatment strategies. Almangush A.'s series of studies have provided important insights into the understanding and treatment of tongue cancer. For example, his 2017 study introduced new prognostic markers for tongue cancer (Almangush et al., 2017), his 2015 research delved into the histopathological features of tongue cancer (Almangush, Bello, et al., 2015), and another 2015 study analyzed the impact of surgical resection margins on treatment outcomes (Almangush, Coletta, et al., 2015). Additionally, his 2018 research focused on the microenvironmental factors of the disease, laying the foundation for the development of new therapeutic targets (Almangush et al., 2018). These studies have not only advanced the understanding of the biological characteristics of tongue cancer but also facilitated innovations in clinical treatment methods, improving disease management outcomes.

Co-citation analysis reflects, to some extent, the key literature in this research field. By analyzing high-frequency co-cited literature, we identified the top 10 core articles in this field, which showcase the multifaceted progress in tongue cancer research. DCruz AK's 2015 study, published in The New England Journal of Medicine, reported a comparison between surgery and radiation therapy for tongue cancer, emphasizing the potential advantages of precise surgical treatment (D'Cruz et al., 2015). Ng JH's 2017 study, published in Head and Neck-Journal for the Sciences and Specialties of the Head and Neck, explored the impact of treatment method selection on patient survival (Ng et al., 2017). Lydiatt WM's 2017 work, published in Cancer Journal, summarized the epidemiological data and prevention strategies for tongue cancer (Lydiatt et al., 2017). Tota JE's 2017 research, published in Oral Oncology Journal, investigated the role of HPV in the development of oral cancer (Lydiatt et al., 2017), while Almangush A.'s 2014 study focused on the application of molecular markers in prognostic evaluation (Almangush et al., 2014). Ansarin M's 2019 study explored how innovative surgical techniques can improve treatment outcomes (Ansarin et al., 2019). Sung H.'s 2021 article in Cancer Journal provided the latest global statistics and trends on oral cancer (Sung et al., 2021).

The AJCC Cancer Staging Manual, 8th Edition (published in 2017 by the American Joint Committee on Cancer) provides detailed guidance for clinicians on the staging of tongue cancer (Edition et al., 2017). Ganly I's 2013 study revealed the cytogenetic characteristics of tongue cancer and their association with patient prognosis (Ganly et al., 2013). Zanoni DK's 2019 research, published in Oral Oncology Journal, assessed the effect of neoadjuvant therapy on improving survival rates in patients with locally advanced tongue cancer (Zanoni, Montero, et al., 2019).

4.2. Research Hotspots or Trends

As a core summary of the research content, keyword analysis is an important method for identifying research hotspots and development trends. Keyword co-occurrence analysis reveals the relationships between various research topics by examining the frequency and patterns of keywords appearing together. The analysis indicates that research in areas such as "young patients," "machine learning," "MRI," and "interstitial brachytherapy" is emerging as a new hotspot in tongue cancer research. The frequent occurrence of these keywords suggests that future research may focus more on young patients with tongue cancer and early diagnostic technologies. The analysis identifies current research hotspots in the field of tongue cancer and possible future development trends.

In recent years, artificial intelligence (AI) and deep learning methods have gained widespread attention in the early diagnosis and prognostic prediction of tongue cancer. The study by Ting-Guan Sun et al. demonstrated the potential of using AI in CECT imaging to non-invasively predict the proliferation status of TSCC before surgery (Sun et al., 2022). Mingxin Yu et al. proposed a novel classification method using deep convolutional neural networks and optical fiber Raman spectroscopy to distinguish between tongue squamous cell carcinoma (TSCC) and non-tumor tissue (Yu et al., 2019). The integration of artificial intelligence has significantly improved the diagnostic accuracy of imaging and reduced subjective bias to some extent. Umberto Committeri et al. combined clinical data with radiomics features from CT scans to predict the risk of metastatic lymph nodes and tumor grading related to tongue cancer, and developed a supportive approach for managing lymph nodes (Committeri et al., 2022). Radiomics-based analysis techniques, which extract a large number of quantitative features from medical imaging, can predict the treatment response and prognosis of tongue cancer, offering valuable insights for the development of personalized treatment plans.

An increasing number of studies have found that the incidence of tongue cancer is rising among young patients, a trend that has attracted widespread attention globally. Research suggests that the rising incidence of tongue cancer in young populations may be related to lifestyle, environmental factors, and genetic susceptibility (Ferreira E Costa et al., 2022). For instance, smoking, alcohol consumption, and human papillomavirus (HPV) infection have all been directly linked to the occurrence of oral cancer, and the widespread presence of these factors in young individuals may partially explain this trend (Hübbers & Akgül, 2015). Studies also indicate that the clinical behavior and prognosis of HPV-positive tongue cancer differ from those of HPV-negative tongue cancer, with HPV-positive patients typically having a better prognosis. Based on this, early screening and detection strategies for HPV infection biomarkers (such as salivary biomarkers) are becoming a key focus of research.

In the treatment strategy for tongue cancer, the depth of surgical resection and the status of the resection margins are considered key indicators for prognostic prediction. Previous studies have shown that the degree of margin clearance is closely related to local recurrence rates. In addition, innovative adjuvant therapies, such as immunotherapy and targeted therapy, have been shown to improve survival rates in patients at high risk of recurrence. For HPV-positive tongue cancer patients, the response rate to immunotherapy is significantly higher than that for HPV-negative patients. This finding provides important insights for the development of personalized treatments and novel therapies.

In recent years, the tumor microenvironment and immune microenvironment have been found to play a critical regulatory role in the occurrence and progression of tongue cancer. Studies have shown that cancer-associated fibroblasts (CAFs) in the tongue cancer microenvironment play a key role in regulating the migration and invasion of tumor cells (Ba et al., 2019). Additionally, epigenetic modifications (such as DNA methylation and histone modifications) have become key molecular regulatory mechanisms in tongue cancer (Lu et al., 2015), providing new research directions for the development of personalized and targeted therapies.

With advancements in diagnostic technology, an increasing number of early tongue cancer cases are being identified in young patients. This highlights the importance of early diagnosis and treatment, as early diagnosis not only significantly improves cure rates but also enhances the quality of life for patients (Khijmatgar et al., 2024). Therefore, understanding the trend of younger patients is crucial for public health policymakers, healthcare professionals, and researchers, in order to develop effective prevention, screening, and intervention strategies.

4.3. Limitations

Although this study successfully revealed global trends and hotspots in tongue cancer research through the comprehensive analysis of a large number of publications, it also has some notable limitations. One limitation is the single data source, restricted to the WOS database, which may lead to the neglect of some high-quality studies not included in the database, potentially affecting the representativeness of the research. Future studies should consider a multi-database strategy, incorporating data from other databases such as Scopus and PubMed. In addition, while keyword co-occurrence analysis can reveal research trends, it still has limitations in capturing more subtle dynamic changes. To address this, future research could introduce deep learning-based topic modeling methods to more comprehensively capture research trends and hotspots in the field of tongue cancer.

5. Conclusion

This study systematically analyzed the research achievements in the field of tongue cancer using bibliometric tools, revealing the research hotspots, key contributors, international collaboration networks, and future development trends. The analysis indicates that global attention to tongue cancer research has significantly increased over the past decade, with China, the United States, and Japan playing important roles in research output and international collaboration in this field. Through keyword co-occurrence and burst analysis, this study identified several research hotspots in the field of tongue cancer, including the application of new technologies such as artificial intelligence and deep learning in early diagnosis and prognostic evaluation, as well as the trends of younger patients and immunotherapy strategies.

In the future, tongue cancer research should place greater emphasis on interdisciplinary collaboration, integrating bioinformatics, imaging, and clinical research to further explore the pathogenesis and treatment strategies of tongue cancer. At the same time, strengthening international research collaboration and data sharing will help promote the global development of tongue cancer research and ultimately achieve the goal of improving patient survival rates and quality of life.

Conflict of Interest:

None declared.

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Two Cases of Maxillofacial Vascular Malformations Associated with Blue Rubber Bleb Nevus Syndrome And Literature Review

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KEYWORDS

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ABSTRACT

Blue Rubber Bleb Nevus Syndrome (BRBNS) is a rare systemic vascular malformation-related disorder that primarily affects the skin, gastrointestinal tract, and central nervous system. Approximately 55.9% of patients have lesions involving the oral and maxillofacial region. Due to the potential risks of gastrointestinal hemorrhage and intracerebral hemorrhage, it is crucial for dental practitioners to promptly identify and refer such cases to relevant departments to improve patient prognosis and enhance quality of life. This paper reports two cases of BRBNS associated with maxillofacial vascular malformations treated at the Oral and Maxillofacial Surgery Department of Henan Provincial People's Hospital. In conjunction with a literature review, this study discusses the clinical features, diagnosis, and treatment strategies of BRBNS, aiming to raise awareness among dental practitioners to avoid missed or incorrect diagnoses.

1. Introduction

Blue Rubber Bleb Nevus Syndrome (BRBNS) is a rare systemic vascular malformation disorder that primarily affects the skin, gastrointestinal tract, and central nervous system. It is characterized by multiple vascular malformations in the skin and digestive system, with clinical manifestations commonly including multiple cutaneous vascular malformations, gastrointestinal bleeding, and secondary iron-deficiency anemia(Martinez et al., 2014).

The distribution of BRBNS lesions varies among patients. According to a study by Kozai L et al., the most commonly affected site is the oral cavity (55.9%), followed by the small intestine (49.5%), colorectum (35.6%), and stomach (26.7%) (Kozai & Nishimura, 2023). This indicates that some BRBNS

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patients may initially present to the dental department due to maxillofacial vascular malformations.

Given this, the present study reports two cases of BRBNS with maxillofacial vascular malformations as the primary clinical presentation, which were diagnosed and treated at the Department of Oral and Maxillofacial Surgery, Henan Provincial People's Hospital. A review of the relevant literature is also provided to discuss the clinical features, diagnostic criteria, and treatment strategies for BRBNS. The aim is to raise awareness among dental practitioners, reduce the risk of missed or misdiagnosed cases, and ultimately improve patient outcomes.

Both cases reported in this study obtained informed consent from the patients or their guardians. The study protocol was reviewed and approved by the Ethics Committee of the School of Medicine, Henan University (Approval No. HUSOM2024-452).

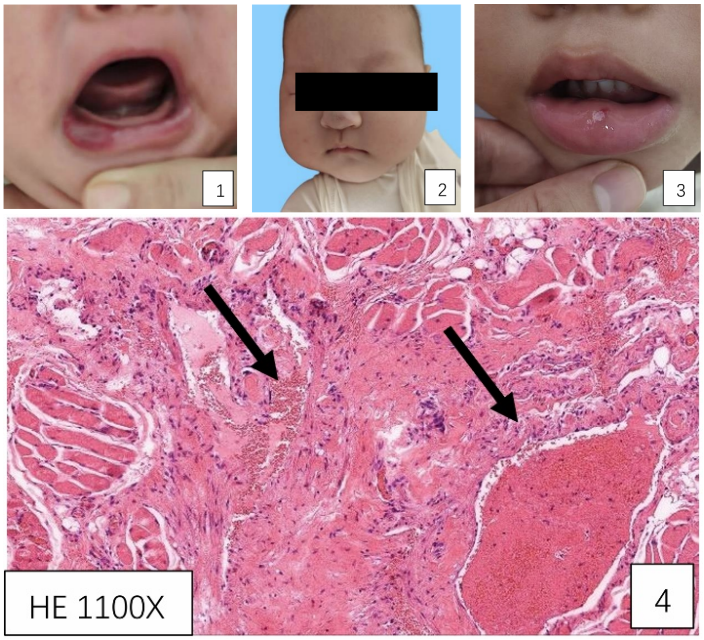


Figure 1-4

1. Right lower lip; 2. Nasal tip; 3. Central lower lip; 4. Microscopic view showing dilated lumens of varying sizes, with possible thrombus formation within the lumens.

2. Patients

2.1. Case 1

A 3-month-old male infant presented with a chief complaint of "red-blue masses on the nasal tip and right lower lip for over one month." The parents noticed the appearance of red-blue discoloration and localized swelling on the nasal tip and the right lower lip, which showed no significant improvement after one month of observation, prompting them to seek medical attention.

Physical examination revealed a red-blue soft mass measuring approximately 1.5 × 1.5 × 1 cm on the nasal tip and another on the right lower lip measuring 1.5 × 1 × 0.5 cm (Figures 1, 2). Both lesions were soft in texture, homogeneous, and non-hemorrhagic. The patient had no family history of hereditary diseases.

Upon admission, routine blood tests revealed hemoglobin levels of 117.3 g/L, while fecal occult blood test (FOBT) was weakly positive. No other abnormalities were detected in the standard laboratory workup. Abdominal computed tomography (CT) revealed no significant abnormalities.

A multidisciplinary discussion (MDT) was held involving specialists from oral and maxillofacial surgery, pediatric surgery, gastroenterology, and vascular anomaly departments. The initial diagnosis was multiple vascular malformations of the maxillofacial region, with the possibility of Blue Rubber Bleb Nevus Syndrome (BRBNS) not being excluded. The patient's family was informed of the condition, and oral iron supplementation was recommended to correct anemia. Although endoscopic examination of the gastrointestinal tract was suggested, the procedure was deemed too risky due to the patient's young age. The parents opted for surgical treatment of the mass on the right lower lip only.

Under general anesthesia, a "right lower lip mass excision" was performed. Postoperative histopathological examination revealed features consistent with venous malformation with thrombosis (Figure 4). The patient was treated with oral iron supplements following surgery and was followed up at 1, 3, and 6 months postoperatively. No recurrence of the mass was observed, and the patient's hemoglobin levels gradually increased from 136.8 g/L to 143.9 g/L.

Two years after surgery, a new mass reappeared on the patient's lower lip (Figure 3). The patient was referred to a pediatric specialist hospital for gastrointestinal endoscopic examination. Endoscopy revealed hemorrhagic and bluish lesions in the small intestinal wall. The lesions were excised, and hemostasis was achieved via ligation. Histopathological analysis confirmed venous malformation, leading to a definitive diagnosis of BRBNS.

The lesions on the lower lip and nasal tip were treated with local injections of pingyangmycin, a sclerosing agent. One year after treatment, follow-up re-

vealed that the patient had normal hemoglobin levels, a negative fecal occult blood test (FOBT), and significant reduction in the size of the masses on the lower lip and nasal tip.

2.2. Case 2

A 14-year-old male patient was referred to our hospital with a chief complaint of "bilateral temporal masses for 10 years and a tongue mass for 1 year."

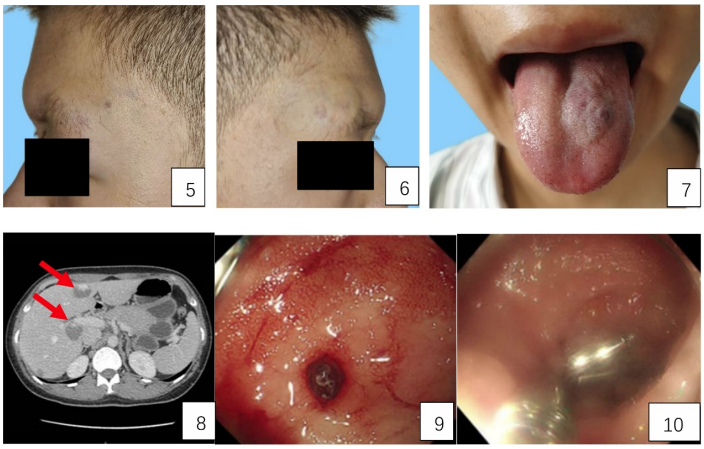
Physical examination revealed multiple bluish-purple masses on both temporal regions and the dorsal surface of the left side of the tongue (Figures 5-7). The masses were soft in texture, with no signs of bleeding, ulceration, or significant tenderness. The patient had a history of chronic anemia and had previously received treatment with traditional Chinese herbal decoctions at a local clinic, with limited therapeutic effect. There was no family history of hereditary diseases.

Upon admission, routine blood tests revealed a white blood cell count of 9.59 × 10^9/L and hemoglobin level of 104.1 g/L. The fecal occult blood test (FOBT) was weakly positive, while other routine laboratory tests were unremarkable. Abdominal computed tomography (CT) suggested the presence of multiple hepatic hemangiomas (Figure 8).

A multidisciplinary team (MDT) composed of specialists from oral and maxillofacial surgery, gastroenterology, spinal surgery, and vascular anomaly departments convened to discuss the case. The initial diagnosis was Blue Rubber Bleb Nevus Syndrome (BRBNS). Endoscopic examination of the gastrointestinal tract revealed bleeding at the terminal ileum, for which an endoscopic hemostasis procedure was performed (Figures 9, 10). The biopsy results confirmed the diagnosis of BRBNS.

The patient underwent local sclerotherapy with pingyangmycin injections targeting the masses in the bilateral temporal regions and the tongue. Following treatment, the patient's condition improved, and he was discharged from the hospital.

Follow-up visits were conducted at 1, 2, and 3 months post-discharge. Significant reduction in the size of the masses on the bilateral temporal regions and tongue was observed, and the patient received additional local sclerotherapy with pingyangmycin injections during this period. At 3 months post-discharge, the patient's overall health continued to improve. His hemoglobin level increased to 109.3-126.5 g/L, and the fecal occult blood test (FOBT) turned



Figures 5-10

5. Vascular malformation in the left temporal region; 6. Vascular malformation in the right temporal region; 7. Vascular malformation on the dorsal surface of the left side of the tongue; 8. CT showing multiple hepatic hemangiomas; 9. Active thrombus head observed at the terminal ileum;10. Thrombus head closed with metal clips.

negative. At 6 months and 1 year post-discharge, follow-up evaluations revealed no recurrence of anemia, normal blood test results, and persistently negative FOBT.

3. Discussion

3.1. Etiology

Blue Rubber Bleb Nevus Syndrome (BRBNS) was first described by Gascoyen in 1860(Gascoyen, n.d.). Later, in 1958, Bean provided a detailed description of its clinical features and officially named it Blue Rubber Bleb Nevus Syndrome (also known as Bean Syndrome)(Bean, 1958). To date, more than 400 cases of BRBNS have been reported in the literature. However, the exact etiology and pathogenesis of this disorder remain incompletely understood.

Recent advances in molecular genetics have provided new insights into the etiology of BRBNS. Studies have suggested that BRBNS may be closely associated with mutations in the TEK gene (also known as the TIE2 gene) (Nobuhara et al., 2006). Mutations in the TEK gene can lead to abnormal proliferation and migration of vascular endothelial cells, ultimately resulting in vascular malformations. Additionally, upregulation of c-kit expression has been observed in some BRBNS patients. Researchers hypothesize that c-kit plays a pivotal role in the pathogenesis of BRBNS, and specific inhibitors of c-kit may provide a nov-

el targeted therapeutic approach for the treatment of this disease (Mogler et al., 2010).

The majority of BRBNS cases are sporadic, with no family history of the disease. However, in rare cases, family-based studies have revealed a potential association between mutations on the short arm of chromosome 9 (9p) and BRBNS, suggesting that it may exhibit characteristics of autosomal dominant inheritance (Gallione et al., 1995). This finding implies that BRBNS may have a genetic predisposition in certain families, but large-scale genome-wide association studies (GWAS) have yet to identify specific pathogenic genes.

Research on the pathogenesis of BRBNS is ongoing, and the potential role of genetic-epigenetic interactions is drawing increasing attention. Whether signaling pathways associated with the TEK gene and c-kit (such as the PI3K-Akt pathway) play a key role in the pathogenesis of BRBNS remains to be elucidated. Furthermore, the potential role of external environmental factors and molecular epigenetic modifications in the onset and progression of BRBNS is another area of interest. Future studies on these mechanisms may offer new insights into disease development and therapeutic strategies.

3.2. Clinical Manifestations

The clinical manifestations of Blue Rubber Bleb Nevus Syndrome (BRBNS) are diverse, with the most prominent features being vascular malformations of the skin and gastrointestinal tract. According to a statistical analysis of 106 BRBNS cases reported by RIMONDI A et al., 57.5% of patients develop symptoms before the age of 18 (Rimondi et al., 2024). The two cases reported in this study, involving a 3-month-old infant and a 14-year-old adolescent, are consistent with these findings.

BRBNS-related cutaneous lesions typically present as multiple bluish-purple, rubber-like blebs distributed across the body. These lesions are soft and compressible, and upon compression, they flatten temporarily but rebound quickly after pressure is released (Chen et al., 2022). While the cutaneous lesions of BRBNS generally do not cause bleeding or other life-threatening conditions, and no reports of malignant transformation have been published to date, these lesions can affect a patient's appearance, leading many patients to seek medical attention for cosmetic reasons.

A retrospective study by RIMONDI A et al. reported that more than 50% of patients with BRBNS underwent multiple treatments during the disease course (Rimondi et al., 2024), reflecting the long-term treatment needs associated with this condition.

BRBNS-related gastrointestinal (GI) lesions are most frequently observed in the stomach and intestines, where they appear as multiple vascular malformations. The primary clinical manifestation is recurrent gastrointestinal bleeding, which is also a major cause of anemia in these patients. Other symptoms include abdominal pain and discomfort (da Fonseca et al., 2009). Due to the extensive distribution of vascular malformations in the gastrointestinal tract, some patients may experience acute complications such as intussusception, volvulus, or bowel infarction (Wang et al., 2014).It is worth noting that mild symptoms, such as mild anemia or positive fecal occult blood test (FOBT), often go unnoticed by patients or their families. This can lead to delays in diagnosis and treatment, particularly in patients without obvious gastrointestinal bleeding.

In addition to the skin and gastrointestinal tract, BRBNS can also affect multiple organs and systems, including the liver, spleen, heart, eyes, and central nervous system (CNS) (R et al., 2014).When the CNS is involved, patients may present with headaches (R et al., 2014), seizures [14], or even intracranial hemorrhage (G et al., 2010), which are serious and potentially life-threatening complications.

Other uncommon systemic manifestations include pain (5%) and localized hyperhidrosis (2%) (McCarthy et al., 1982). When the disease affects the joints, patients may develop movement disorders or, in severe cases, joint deformities, which can significantly impact their quality of life (McCarthy et al., 1982).

The histopathological features of BRBNS lesions are typically consistent with venous malformations and cavernous venous dilation. Under the microscope, the affected areas show a simple layer of endothelial cells lining a thin layer of smooth muscle cells (Hasosah et al., 2010). This distinctive histopathological profile provides important clues for disease identification and diagnosis.

The diagnosis of BRBNS relies on a combination of physical examination and gastrointestinal endoscopy. The presence of typical cutaneous lesions is often sufficient to raise clinical suspicion. Gastrointestinal endoscopy can reveal characteristic vascular malformations in the gastrointestinal tract, confirming

the diagnosis.In most cases, biopsy for diagnostic purposes is not necessary, as the combined evidence from clinical presentation and endoscopic findings is sufficient for diagnosis (Atten et al., 2000).

3.3. Clinical Diagnosis

The diagnosis of Blue Rubber Bleb Nevus Syndrome (BRBNS) primarily relies on clinical examination, especially the identification of characteristic lesions in the skin, oral cavity, and gastrointestinal tract. The typical bluish-purple, rubber-like blebs on the skin often serve as early diagnostic clues for BRBNS. Lesions in the oral and maxillofacial regions also provide additional diagnostic support, especially in patients with facial abnormalities or oral ulcers.

Endoscopy is considered the gold standard for both the diagnosis and treatment of BRBNS(Nishiyama et al., 2012), particularly for the evaluation and management of gastrointestinal vascular malformations. Among the available endoscopic methods, capsule endoscopy (CE) has become an effective tool for evaluating small intestinal lesions due to its non-invasiveness, good patient tolerance, and high acceptance rate (Barlas et al., 2008; Kassarjian et al., 2003; Kopácová et al., 2007).

Compared with balloon-assisted enteroscopy (BAE), capsule endoscopy is simpler to operate and more acceptable to patients, especially for children and those who are unable to tolerate conventional endoscopy.Endoscopic examination not only plays a role in diagnosis but also facilitates endoscopic hemostasis and lesion resection. For instance, in cases of bleeding from the terminal ileum, endoscopic hemostasis can significantly improve the patient's prognosis.

In the initial screening for BRBNS, the fecal occult blood test (FOBT) serves as a simple and cost-effective screening tool, particularly for patients without obvious signs of gastrointestinal bleeding. The FOBT can detect occult gastrointestinal bleeding, even when the volume of blood loss is small.Given that recurrent gastrointestinal bleeding is one of the major clinical manifestations of BRBNS, a positive FOBT result is often an important early clue for diagnosing the disease. Therefore, for patients with chronic anemia or a history of gastrointestinal bleeding, FOBT should be considered a routine screening test.

Imaging examinations play a crucial role in localizing lesions and assessing the extent of disease in patients with BRBNS.Computed Tomography (CT) scans provide clear visualization of lesions in the gastrointestinal tract and abdominal solid organs, such as multiple hepatic hemangiomas. CT is also useful for assessing the number, size, and distribution of lesions (Agnese et al., 2010). Furthermore, CT scans play an important role in the detection of acute complications, such as intussusception, volvulus, and bowel infarction, which may require immediate medical intervention.

Compared with CT, Magnetic Resonance Imaging (MRI) has higher soft-tissue resolution, making it more effective for the detailed assessment of soft-tissue lesions. MRI is particularly useful in the evaluation of lesions in the central nervous system (CNS) and in determining the extent and depth of vascular abnormalities. For the liver, spleen, and other parenchymal organs, MRI has a higher sensitivity than CT (Certo et al., 2007). This makes MRI a valuable tool for identifying small or subtle lesions that may be missed on CT scans.

3.4. Clinical Treatment

Currently, there is no unified, systematic treatment guideline for Blue Rubber Bleb Nevus Syndrome (BRBNS). Clinical treatment strategies are primarily based on the patient's clinical presentation and specific symptoms, employing an individualized, symptom-targeted approach. Oral and cutaneous lesions generally do not require special treatment; however, if lesions affect aesthetics or local function, local treatments such as sclerotherapy, laser therapy, or surgical resection may be considered (Dwivedi & Misra, 2002).

For oral and cutaneous BRBNS lesions, the primary treatment goals are to restore appearance and local function. The injection of bleomycin, polidocanol, or absolute ethanol into the lesion can induce local fibrosis and vascular occlusion, leading to lesion shrinkage or regression (Dwivedi & Misra, 2002). Pulsed dye laser (PDL) or Nd:YAG laser can reduce the size of cutaneous lesions, thereby improving appearance. For localized or recurrent lesions, surgical resection is a direct and effective treatment. However, surgery carries a higher risk of trauma, and there is a possibility of lesion recurrence after the procedure.

The treatment of gastrointestinal (GI) lesions depends on the number, size, shape, location, and bleeding status of the vascular malformations. Treatment strategies generally include endoscopic, interventional, and surgical approaches. In this study,

Case 1 underwent an "endoscopic hemostasis procedure for gastrointestinal bleeding," which achieved satisfactory hemostatic results. This method plays a crucial role in controlling acute GI bleeding. Injection of absolute ethanol or polidocanol into the lesion under endoscopy can occlude abnormal blood vessels, achieving hemostasis (Dieckmann et al., 1994). High-frequency electrocoagulation or laser energy can directly seal abnormal blood vessels, making it particularly suitable for diffuse lesions and small vascular abnormalities. Embolization therapy involves the injection of embolic agents (e.g., gelatin sponge or microparticle embolic agents) into the affected vessels via an interventional catheter, enabling precise occlusion of blood supply to the lesion (Jin et al., 2014). Embolization therapy serves as a supplementary method for endoscopic treatment, especially for severe GI bleeding from deep small bowel lesions.

Surgical treatment is typically a last-resort option, mainly used for cases where endoscopic and interventional therapies are ineffective. Indications for surgery include localized lesions, such as focal lesions in the stomach or small intestine; massive GI bleeding that is unresponsive to endoscopic treatment; and acute complications such as bowel ischemia, intussusception, and intestinal infarction (Choi et al., 2012). However, surgery is associated with higher trauma and recurrence rates, so the risks and benefits must be weighed carefully. Endoscopic or interventional therapy is generally preferred, and surgery is reserved for life-threatening situations.

The goal of pharmacological treatment is to control GI bleeding and disease progression by reducing endothelial cell proliferation and angiogenesis. Commonly used drugs include Glucocorticoids: Prednisone can inhibit inflammation and endothelial cell proliferation, providing temporary symptom relief for certain patients (Dieckmann et al., 1994).

Interferon-α: This agent modulates immune responses and inhibits angiogenesis, showing efficacy in some refractory cases, but its adverse effects are significant.

Vincristine: As an anti-mitotic agent, it reduces endothelial cell proliferation. However, its clinical use is limited by adverse effects such as bone marrow suppression (Aihara et al., 1991).

Octreotide: As a somatostatin analog, it reduces visceral blood flow, thereby decreasing the frequency of GI bleeding (Boente et al., 1999).

In recent years, sirolimus (rapamycin) has emerged as a breakthrough drug for BRBNS treatment. Sirolimus, an mTOR pathway inhibitor, reduces venous malformation size and controls GI bleeding by inhibiting endothelial cell proliferation and angiogenesis (Gonzalez-Magaña et al., 2024; Pi et al., 2023).

According to a retrospective study by Quan Xu et al. on 26 BRBNS patients treated with sirolimus, all patients experienced significant clinical improvement, with no severe drug-related adverse reactions. The adverse effects of sirolimus are relatively mild, mainly including oral ulcers, rashes, and mild liver function impairment. Its high safety profile and good patient compliance make it a promising option for children and refractory cases.

With the advancement of pharmacological and interventional therapies, multidisciplinary individualized treatment (MDT) has become the standard treatment strategy for BRBNS. MDT treatment plans can be customized based on the severity of the patient's symptoms, lesion location, and treatment risk. For GI lesions, endoscopic treatments (e.g., hemostasis, laser coagulation) are generally the first-line options. When multiple endoscopic treatments fail, interventional therapy or surgical treatment may be considered.

4. Conclusion

As the starting point of the digestive tract, oral involvement in Blue Rubber Bleb Nevus Syndrome (BRBNS) accounts for up to 55.9% of cases (Kozai & Nishimura, 2023). However, due to insufficient awareness of this disease among oral clinicians, detailed auxiliary examinations are often overlooked, leading to missed or incorrect diagnoses. This delay in diagnosis hampers early detection, timely treatment, and prognosis improvement, while also increasing the risk of emergency medical events.

Although BRBNS is a rare disorder, patients face an ongoing risk of life-threatening gastrointestinal (GI) bleeding and cerebral hemorrhage. For patients presenting with multiple vascular malformations across the body or a history of multiple vascular malformation treatments, physicians should maintain a high degree of vigilance. A detailed medical history should be obtained, especially focusing on symptoms of gastrointestinal bleeding and a history of anemia. In such cases, routine blood tests and fecal occult blood tests should be conducted to assess for the presence of anemia or GI bleeding. If clear indications of anemia or GI bleeding are identified, further diagnostic imaging, including gastrointestinal endoscopy, abdominal

and cranial CT scans, and abdominal ultrasound, should be performed to determine the presence of vascular malformations in other systems.

Once a diagnosis of BRBNS is confirmed, a multidisciplinary team (MDT) consultation involving specialists from gastroenterology, pediatric surgery, pathology, and vascular anomaly units should be convened. This collaborative approach aims to develop an individualized treatment strategy. If necessary, the patient should be referred to a specialized department, such as gastroenterology or vascular anomaly centers, for further treatment. Early detection and timely intervention for vascular malformations in the gastrointestinal system, nervous system, or other organs can alleviate patient suffering, reduce the occurrence of emergency medical events, and improve both prognosis and quality of life.

Oral and maxillofacial surgeons often encounter patients with vascular malformations or masses in the head, neck, and oral cavity. It is essential to differentiate BRBNS from other syndromes associated with vascular malformations, including Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia, HHT), Klippel-Trenaunay syndrome, and Maffucci syndrome (Choi et al., 2012; Marín-Manzano et al., 2010). While these conditions share the feature of vascular anomalies, they present distinct clinical manifestations and diagnostic criteria.

Osler-Weber-Rendu syndrome (HHT) is characterized by punctate hemorrhagic telangiectasia, recurrent epistaxis, and capillary dilatation, often with a positive family history (Gallo & McClave, 1992; Shovlin et al., 2000).Maffucci syndrome typically presents with diffuse vascular malformations of the skin and soft tissues, skeletal deformities, and enchondromas (Sakurane et al., 1967; Shepherd et al., 2005).Klippel-Trenaunay-Weber syndrome is primarily characterized by venous varicosities, soft tissue and bone hypertrophy, and limb enlargement (Arguedas et al., 2001).

In summary, the hallmark clinical features of BRBNS include multiple vascular malformations of the skin and oral cavity, as well as gastrointestinal bleeding, which frequently results in iron deficiency anemia (IDA). To date, there is no universally accepted systematic treatment guideline for BRBNS. This study aims to raise awareness of BRBNS among oral clinicians to prevent misdiagnosis and missed diagnoses. Based on the analysis of this case, clinicians should consider the possibility of BRBNS when patients present with multiple vascular malformations in the maxillofacial region and other parts of the body, especially if they have a positive fecal occult blood test or a history of anemia. Early diagnosis and timely intervention are essential to prevent emergency medical events, improve prognosis, and enhance patients' quality of life.

Conflict of Interest

None declared.

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The efficacy and safety of acupoint application for cirrhotic ascites: A protocol for systematic review and meta-analysis

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KEYWORDS

Acupoint Application,
Cirrhotic Ascites,
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Protocol,
Systematic Review

ABSTRACT

Cirrhotic ascites significantly impacts patients' quality of life and poses serious clinical challenges. Conventional treatments, such as diuresis and abdominocentesis, are costly and prone to recurrence. Acupoint application, a traditional Chinese medicine (TCM) external therapy, offers a safe, painless, and cost-effective alternative widely used in clinical practice. However, its efficacy and safety lack systematic evaluation. This study aims to comprehensively assess the effectiveness and safety of acupoint application for treating cirrhotic ascites through a meta-analysis of randomized controlled trials retrieved from databases including CNKI, VIP, WanFang, PubMed, Embase, and the Cochrane Library. The findings will provide evidence to guide clinical decision-making.

1. Introduction

Cirrhotic ascites is caused by degeneration, necrosis, and regeneration of hepatocytes, which contribute to the proliferation of fibrous tissue and contraction of scarring, resulting in the hardening of the liver texture to form cirrhosis, causing portal hypertension and impairment of liver function, leading to the generation of ascites. The mechanism of ascites formation is complex, mainly due to portal hypertension caused by cirrhosis, which leads to obstruction of portal blood flow; increased intravascular pressure and capillary hydrostatic pressure in the portal venous system, which leads to fluid leakage into the abdominal cavity[1]; Portal hypertension also enhances renin-angiotensin-aldosterone system (RAAS) activity by triggering splanchnic and systemic circulatory changes, leading to sodium and water retention[2, 3]; Ascites formation is also closely associated with increased vasoactive substances and hypoproteinemia[4], After the onset of cirrhosis, secretion and activity of atrial natriuretic peptide, prostaglandins and other vasoactive substances increase, stimulating extensive dilation of small splenic arteries and thus increasing venous inflow. After the impaired liver function, albumin synthesis is significantly reduced, leading to a decrease in plasma colloid osmotic pressure, which promotes the leakage of fluid from the plasma into the peritoneal cavity and the formation of ascites[5]. At the stage of cirrhotic ascites, patients will have symptoms such as abdominal distension, loss of appetite, weakness, low urine, etc., and are often accompanied by swelling of the lower limbs, dyspnea, chest tightness, etc. About 60% of patients develop

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ascites within 10 years after the diagnosis of cirrhosis, and the mortality rate is about 15% at 1 year and 44% to 85% at 5 years after the occurrence of cirrhotic ascites[6, 7]. There is no doubt that cirrhotic ascites seriously affect patients' quality of life and threaten their life safety, which is a major clinical challenge. The current main treatments for cirrhotic ascites include diuretics, salt restriction, albumin supplementation and invasive therapies such as abdominocentesis, transjugular intrahepatic portosystemic shunt (TIPS) and even liver transplantation[8, 9], but 10% of patients will develop diuretic resistance[10]. Long-term repeated abdominocentesis causes great pain to patients, while TIPS and liver transplantation are effective treatments for cirrhotic ascites but are difficult, risky, and expensive.

Acupoint application is a unique Chinese medicine external treatment method based on the theory of Chinese medicine meridian science by mixing specific Chinese medicine into a paste or boiling Chinese medicine soup into a paste and applying it to the acupuncture points on the surface of the body, usually for several hours, so that the acupuncture points are stimulated. The medicine is absorbed through the body's surface, which has achieved the purpose of treating diseases. Acupoint application is easy to learn, safe and painless, widely applicable and inexpensive, especially for the treatment of chronic diseases. In recent years, acupoint application has been widely used for cirrhotic ascites, but its efficacy and safety are still controversial. Therefore, we will study the efficacy and safety of acupressure in the treatment of cirrhotic ascites and objectively evaluate its efficacy and safety in order to provide evidence-based medical evidence for clinical practice and further clinical research.

2. Methods and Analysis

2.1. Study Registration

This study protocol was registered on the PROSPERO website (https://www.crd.york.ac.uk/PROSPERO/) on September 25, 2022 (registration number: CRD42022360397) and is authentically available.We will write the study protocol in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) statement guidelines[11].

2.2. Eligibility Criteria

2.2.1. Type of Studies

All the randomized controlled clinical trials (RCTs) that report using acupoint application for cirrhotic ascites will be included.

Inclusion:

1. Studies must be randomized controlled clinical trials;
2. Developed by treatment guidelines[10, 12] .The diagnosis of cirrhotic ascites needs to meet the following three conditions: 1) imaging examination indicates cirrhosis and peritoneal fluid; 2) positive mobile turbid sounds on physical examination; 3) exclusion of ascites due to cancer, cardiogenic, nephrogenic, tuberculosis and other causes；
3. Patients in the treatment group will be given acupoint application whether or not combined with treatments received in the control group, while patients in the control group will be given no acupoint application treatment;
4. Trials must have reported at least one outcome indicator of cirrhotic ascites;
5. Studies must be published in English or Chinese language.

Exclusion:

1. The diagnostic criteria of the original study did not meet the clinical diagnosis of cirrhotic ascites;
2. Studies without consistent diagnostic criteria or relevant outcome indicators;
3. Non-English or Chinese-language articles;
4. Duplicate reports, or the data cannot be extracted.

2.2.2. Type of Participants

Subjects had a clinical diagnosis of cirrhotic ascites and no other acute or chronic disease. Patients were not restricted by age, sex, or source.

2.2.3. Type of Intervention

Patients in the treatment group will all receive acupoint application treatment regardless of whether they receive conventional Western medical treatment (e.g. diuretics and albumin supplementation); There is no restriction on the acupuncture points, types of herbs and duration of acupoint application treatment in our study.

2.2.4. Type of Comparators

Patients in the control group will be given treatment, including simple routine western medicine treatment compared with the acupoint application treatment group.

2.2.5. Type of Outcome Measures

2.2.5.1. Main Outcomes

Ascites volume (obtained by ultrasound or other ancillary tests)

2.2.5.2. Additional Outcomes

1. Body weight; 2. Abdominal circumference; 3. Aspartate aminotransferase(AST); 4. Alanine aminotransferase(ALT); 5. Incidence of adverse events

2.3. Search Strategy

Computerized comprehensive searches of databases such as China Knowledge Network (CNKI), Chinese Science and Technology Journal Database (VIP), WanFang Database (WangFang), China Biomedical Literature Database (CBM), PubMed, SCI, Embase, and Cochrane Library were conducted for the period of establishment to September 2022. The search terms included: "cirrhotic ascites," "live cirrhosis with ascites," "portal hypertension, " "ascites," " acupoint application," "point application, "and "randomized controlled trial." The search strategy (Table 1) was tailored to the specific database.

2.4. Data Collection and Analysis

2.4.1. Selection of Studies

We will strictly follow the flowchart shown in Figure 1 to filter the final eligible literature. The specific process is as follows: ①We will import all the retrieved literature into the literature management software NoteExpress (3.2.0.7535) to check and eliminate duplicate literature according to the above 2.3 search strategy. ②Subsequently, we will review the titles, abstracts and keywords of the literature and screen out the literature that seriously does not meet the inclusion criteria and those that meet the exclusion criteria. ③The remaining literature was downloaded one by one and evaluated for the level of methodological quality evidence for each literature according to the Jadad scale[13]. Literature suspected of data falsification or serious data errors was excluded from obtaining the final included literature. Two researchers (Yulan Gao and Xiaoying Yao) screened the literature separately, and if differences of opinion arose, they were determined by discussion or consultation with a third researcher (Liuping Zhang).

2.4.2. Data Extraction and Management

Two researchers extracted information from the final included literature separately using an Excel sheet, which which had: the study title, first author, time of publication, sample size, basic information about the study population (gender, age), interventions, duration of treatment, and outcome indicators, and cross-checked, and in case of disagreement was determined by discussion or consultation with a third researcher (Liuping Zhang). If important information or data needed were missing from the article, they would be obtained by contacting the authors by phone or email.

2.4.3. Risk of Bias Assessment

We will assess the quality of the included literature by using the Cochrane Risk of Bias Assessment Tool and GRADE evidence grading method[14]. This includes method of random allocation; allocation protocol concealment; blinding of investigators and subjects; blinding of judges of randomized trial results; completeness of outcome data; selective description of trial results, and other sources of bias. The above situations in the literature were judged as "unknown risk of bias," "low risk of bias," and "high risk of bias.

2.4.4. Measures of Treatment Effect

Meta-analysis of the data was performed using Review Manager 5.4 software. Dichotomous data were subjected to Meta-analysis using relative risk (RR) to indicate effect indicators. As for the measurement data, the mean difference (WMD) was chosen if all data had the same unit of measure; the standard deviation (SMD) was used if the unit of the measure did not agree. Both data types had 95% confidence intervals (95% CI).

2.4.5. Assessment Of Heterogeneity

Heterogeneity analysis was performed on the study data, and its P value and I2 were calculated. If $P>0.1, I^2 \leq 50\%$, it means that there is no statistically significant heterogeneity among the included study

groups, then the fixed-effect model was selected for statistical analysis; if P<0.1, I^2>50%, it means that there is statistically significant heterogeneity, then the random-effect model was selected for statistical analysis.

2.4.6. The Publication Bias

If more than 10 papers were eventually included, funnel plots were drawn using Review Manager 5.4 software to assess publication bias among the studies. If the distribution was symmetrical on both sides of the funnel plot, it indicated no significant publication bias; if the funnel plot was asymmetrical on both sides, it indicated some publication bias.

2.4.7. Subgroup Analysis

Subgroup analyses will be performed according to the degree of the patient's condition and the control group intervention.

2.4.8. Sensitivity Analysis

A sensitivity analysis using STATA software will be performed to verify the robustness of the review conclusions.

2.5. Ethics and Dissemination

This study is not a human or animal test and does not involve personal information or personal data, so there is no need to undergo ethical review. The results of this Meta-analysis will be published in a peer-reviewed journal.

3. Discussion

Ascites is the most common complication of cirrhosis and a hallmark of the decompensated stage of cirrhosis. The formation mechanism of ascites in cirrhosis is complex and is related to portal hypertension, RAAS system activity, increased vasoactive substances and hypoproteinemia. Currently, treatment is mainly includes the use of diuretics, salt restriction, albumin supplementation and treatment by abdominocentesis, TIPS and even liver transplantation. However, long-term diuretic use and ascites discharge may bring side effects such as diuretic resistance, electrolyte disorders, gynecomastia, and hepatic encephalopathy, while the risks and costs of surgery are difficult for patients to bear.

This disease has been documented in ancient Chinese medical texts, and acupoint application has been one of the main tools in treating cirrhotic ascites in Chinese medicine. Acupoint application, as an external Chinese medicine treatment, has been proven to treat many chronic diseases[15-17]. On the one hand, many acupuncture points themselves have the effect of reducing ascites, which can be eliminated by stimulating specific acupuncture points[18]; On the other hand, the selection of diuretic Chinese medicine made into ointment, the drug can be absorbed by the body through the skin, to achieve the purpose of eliminating ascites[19]. Acupoint application is inexpensive, easy to use, non-invasive, and can be used according to the patient's different symptoms of different points and drugs. And has become an important treatment of cirrhotic ascites, especially for refractory ascites, with excellent efficacy. Acupoint application is rarely associated with adverse reactions, and the main adverse event of acupoint application was local skin reaction without systemic side effects.[20] However, there is a lack of systematic evaluation and discussion on the efficacy and safety of acupoint application in the treatment of cirrhotic ascites, so this study aims to evaluate the efficacy and safety of acupressure in the treatment of cirrhotic ascites and provide a basis for the clinical decision of physicians.

There are still limitations in this study; for example, the included studies were biased by choice of acupuncture points, the type of drug preparation resulting in efficacy, and studies or reports in other languages may be overlooked due to the search of English and Chinese literature, which we will try to avoid and improve in subsequent studies.

Abbreviations

CNKI = China National Knowledge Infrastructure, VIP = Chinese Scientific Journals Database,CBM = China BioMedical Literature, TIPS = transjugular intrahepatic portosystemic shunt, RAAS = renin-angiotensin-aldosterone system, PRISMA-P = preferred reporting items for systematical reviews and meta-analyses protocols, RCTs = randomized controlled clinical trials, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, RR = risk ratio, SMD = standardized mean difference, WMD = weighted mean difference, 95%CI = 95% confidence interval, OR = odds ratio.

Author Contributions

Conceptualization: Liuping Zhang, Xiaoying Yao,

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Methodology: Liuping Zhang, Yulan Gao, He Li, Fangyu Long

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Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or

analyzed during the current study.

Conflict of Interest

declare no conflicts

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Advances in Personalized Diagnosis and Treatment Strategies for Temporomandibular Disorders

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KEYWORDS

Temporomandibular Joint Disorders, Personalized, Diagnosis, Treatment

ABSTRACT

Temporomandibular joint disorders (TMDs) is a broad term encompassing pain and/or functional impairment of the masticatory muscles and the temporomandibular joint. Currently, the clinical treatment principles for TMDs mainly include etiological treatment and symptomatic treatment. In addition, the development of personalized diagnostic and treatment plans is crucial for the effective management of TMDs. This review systematically outlines the patient intake process for TMDs and discusses the importance and methods of developing personalized etiological and symptomatic treatment plans based on patient characteristics such as age and symptoms, aiming to provide clinical practitioners with guidance on patient management.

1. Introduction

Temporomandibular disorders (TMDs) are the fourth most common oral disease following dental caries, periodontal diseases, and malocclusions. This condition significantly affects patients' physical and mental health, as well as their quality of life, and has gradually received increasing attention (Ohrbach et al., 2013). Numerous reviews have been published regarding treatment methods for TMDs; however, there are fewer articles discussing the personalized treatment approaches for TMD patients. In clinical practice, although clinicians have a general understanding of the dual-axis diagnosis of TMDs, it is often challenging to select the appropriate treatment approach based on treatment principles for patients with varying demographics and symptoms. Therefore, this review combines diagnostic methods and treatment principles for TMDs from both China and abroad, with a focus on how to tailor personalized treatment strategies for patients of different ages and symptom profiles. The aim is to provide clinicians with scientifically sound and reasonable approaches for patient management.

2. Diagnostic Approach

The classification of TMDs is highly diverse, with the dual-axis diagnostic criteria occupying a dominant position in China. This diagnostic framework includes two axes: Axis I for the assessment of physical condi-

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tions and Axis II for evaluating pain-related disability and psychological status. Accurate diagnosis is crucial for successful treatment. Chinese scholars advocate for a comprehensive diagnostic approach that combines disease classification, imaging-based diagnosis, and etiological assessment. This integrative method enables a clear characterization of the affected region, the nature and severity of the disease, as well as its potential triggers.

Typically, clinicians perform a thorough medical history review and specialized examination of the temporomandibular joint (TMJ) to make a preliminary determination of the TMD subtype based on the Axis I classification of the Chinese dual-axis diagnostic criteria. Beyond physical assessment, psychological factors such as anxiety, depression, and somatization are considered key susceptibility factors for TMDs. Therefore, a comprehensive evaluation of mental health, psychological status, and physical comorbidities is deemed essential before determining the treatment plan, aligning with the Axis II diagnostic framework.

In clinical practice, commonly utilized tools for Axis II diagnosis include the Patient Health Questionnaire-9 (PHQ-9) for assessing depression, the Generalized Anxiety Disorder-7 (GAD-7) for anxiety evaluation, and the Patient Health Questionnaire-15 (PHQ-15) for somatic symptom assessment. These tools enable a systematic evaluation of TMD patients' psychological and somatic conditions, facilitating individualized treatment planning.

In addition to classifying the disease according to the dual-axis diagnostic criteria and evaluating the psychological status of the patient, it is also essential to conduct an etiological assessment. This involves inquiring about harmful chewing habits, the presence of nocturnal bruxism, and the patient's occlusal condition. These evaluations provide critical insights into the underlying causes of temporomandibular disorders (TMDs), enabling a more targeted and personalized treatment approach (Murphy et al., 2013).

Current imaging modalities for TMDs include panoramic X-rays, CBCT, and magnetic resonance imaging (MRI) (Singer & Mupparapu, 2023).With advancements in imaging techniques for the temporomandibular joint (TMJ), MRI has gradually become the preferred diagnostic method, offering significant clinical value. Beyond X-ray imaging, arthroscopy has also gained increasing attention in the diagnosis and management of refractory TMJ conditions, proving to be indispensable (Verhelst et al., 2021). Professor Ma Xuchen proposed that in clinical practice, the dual-axis diagnostic approach should be adopted as the standard. Before formulating treatment plans, it is essential to conduct a comprehensive evaluation of patients' physical conditions and psychological status using the dual-axis diagnostic framework. This approach facilitates the development of personalized treatment strategies tailored to the individual characteristics of each patient. Nevertheless, TMDs are inherently complex. Some researchers advocate for the use of a "triple diagnostic approach," which integrates: Dual-axis diagnosis (assessment of physical and psychological conditions), Imaging diagnosis (evaluation of anatomical structures), and Etiological diagnosis (identification of underlying causes).

This comprehensive diagnostic framework helps elucidate the disease type, etiology, and anatomical abnormalities. Regarding treatment, it is recommended to address both symptoms and underlying causes, developing an effective management plan. Treatment strategies can be broadly classified into two categories: Definitive or etiological treatments, which target the root cause, and Supportive or symptomatic treatments, which focus on symptom relief. This integrated treatment strategy can be tentatively termed the "dual-axis therapy model" (Cadden, 2009).

3. Treatment Principles

Over the past few decades, the principles guiding the treatment of temporomandibular disorders (TMDs) in China have undergone significant evolution. Initially dominated by conservative approaches, the field later saw an expansion of surgical indications before ultimately r eturning to a conservative-first paradigm. Extensive clinical trials and controlled studies have demonstrated that many TMD patients can achieve symptom relief through appropriate self-management, patient education on joint health, and psychological support (Penlington et al., 2022), This phenomenon underscores the self-limiting nature of TMDs (Buescher, 2007). China currently advocates for a "graded intensification" treatment strategy for temporomandibular disorders (TMDs). This approach begins with reversible conservative treatments, followed by irreversible conservative treatments, and ultimately progresses to arthroscopic surgery or other invasive procedures if the aforementioned methods prove ineffective and the symptoms significantly impair the patient's quality of life. This treatment principle must be strictly adhered to.

Under this primary principle, several detailed treatment guidelines should also be followed: Strictly adhere to treatment indications: Avoid over-diagnosis and overtreatment.Emphasize personalized treatment: Focus on restoring joint function while tailoring interventions to individual patient needs.Ensure accurate diagnosis and classification. Conduct comprehensive patient evaluations. Address psychological health promptly.Emphasize health education and rehabilitation.Among these, personalized treatment is often overlooked by clinicians and is a key focus of this review. It highlights the importance of individualized care, which not only aligns with modern medical principles but also ensures optimized outcomes for patients with TMD.

4. Symptom-Based Treatmeny

4.1. Diagnosis and Treatment of Patients With Pain as the Primary Symptom in TMDs

Pain is often the primary reason for patients with TMDs to seek medical attention. In developed countries, TMDs are among the most common causes of chronic orofacial pain, significantly affecting patients' daily lives (Wieckiewicz et al., 2015). Patients commonly report various pain-related symptoms during consultations, including pain while chewing hard foods, pain during wide mouth opening, pain associated with mandibular movements, spontaneous joint pain around the temporomandibular region, muscle soreness or fatigue, and even referred pain in the temporal region, neck and shoulders, or around the external auditory canal.

Although the manifestations of pain are highly diverse and its underlying causes remain a topic of debate, TMD-related pain is generally classified into two major categories: myofascial pain involving the masticatory muscles and arthralgia originating from the joint itself (Christidis et al., 2019).

4.1.1. Myofascial Pain in TMDs

The most common method for diagnosing myalgia in TMDs is palpation of the masticatory muscles, typically focusing on the temporalis and masseter muscles. Palpation is performed by applying pressure perpendicular to the muscle fibers while moving the fingertips anteriorly and posteriorly(Schiffman et al., 2014). The overarching treatment principles for myofascial TMDs are pain relief and muscle relaxation. Stepwise management of myalgia typically begins with conservative approaches. During the acute pain phase, patients are advised to limit mandibular functional movements, consume soft foods, and avoid activities that could strain the joint. Subsequent conservative treatments may include physical therapy, pharmacotherapy, and cognitive behavioral therapy(Wieckiewicz et al., 2015). These interventions primarily aim to strengthen specific muscle groups while reducing the activity of others(Kijak et al., 2013), This facilitates isometric contraction of the bilateral masticatory muscles during functional activities, ultimately alleviating the symptoms of myalgia.

4.1.2. Physical Therapies

Currently, widely adopted physical therapies for TMDs can be broadly categorized into physical modality therapy, manual therapy, and movement therapy, collectively referred to as the "3M techniques." Among these, manual therapy and movement therapy are extensively utilized due to their pain-free, cost-effective, and repeatable nature (Shimada et al., 2019). Manual therapy involves interventions targeting the cervical muscle groups, suboccipital muscles, facial muscles, and joints to promote overall improvement in the temporomandibular joint (TMJ) region and alleviate myalgia symptoms(Asquini et al., 2021). The effectiveness of manual therapy, either as a standalone treatment or in combination with other modalities, in reducing TMD pain and surrounding muscle spasms, has been well-established. Therefore, it is frequently combined with other therapeutic approaches in clinical practice.Movement therapy aims to balance bilateral muscle strength and improve natural mouth opening by employing techniques such as stretching, relaxation, and isometric contraction exercises. This approach addresses imbalances in muscle tone or contraction intensity between the two sides (Wieckiewicz et al., 2015). Key techniques include muscle strengthening exercises (resistance training), coordination exercises, and myofascial release(Kalamir et al., 2012).

4.1.3. Invasive Muscle Therapies

Invasive muscle therapies have been shown to effectively alleviate myogenous pain associated with TMDs. The beneficial effects of masticatory muscle needling and low-concentration botulinum toxin injections are well-supported by the literature(Romero-Morales et al., 2021), Botulinum toxin, a biological neuromuscular blocker used as a muscle relaxant,

can relieve pain in the head and neck region. Additionally, it has been proven effective in reducing neuromuscular tension and nighttime bruxism (Ho & Tan, 2007; Schwartz & Freund, 2002). Consequently, invasive muscle therapies can serve as supportive or alternative treatments for myofascial pain.

4.2. Pain due to Osteoarthritic and Inflammatory Joint Diseases

Temporomandibular joint osteoarthritis (TMJOA) represents the most severe form of TMDs, characterized by structural degeneration and non-inflammatory deterioration of joint tissues, including wear and degradation. Clinically, TMJOA is primarily manifested by joint pain, joint sounds, and functional impairment (Zarb & Carlsson, 1999). Inflammatory joint conditions, such as synovitis and/or capsulitis, can present in acute or chronic phases. These conditions are typically characterized by localized joint pain, which intensifies with posterior and superior movement of the condyle or upon palpation in the preauricular region. In many cases, inflammatory joint diseases co-occur with TMJOA, leading to a range of debilitating symptoms that severely impact patients' quality of life. Therefore, this article focuses on TMJOA for an in-depth discussion.

The most commonly utilized diagnostic modality for TMJOA is CBCT. The radiographic features of TMJOA include erosive resorption, sclerosis, attrition, osteophyte formation, and cystic changes of the condyle(Wang et al., 2015).The primary goals of TMJOA treatment are to alleviate pain, slow disease progression, and restore temporomandibular joint function(de Souza et al., 2012).Pain management can be effectively achieved with non-steroidal anti-inflammatory drugs (NSAIDs) or therapeutic interventions such as arthrocentesis(Machon et al., 2011).

4.2.1. Pharmacotherapy Treatment

Oral pharmacotherapy is a common non-invasive treatment modality for TMJOA. Frequently used medications include NSAIDs, opioids, corticosteroids, and benzodiazepines (Freesmeyer et al., 2005; Ouanounou et al., 2017; Wieckiewicz et al., 2015). NSAIDs and analgesics are effective in alleviating pain in the head, mandibular muscles, face, neck, or shoulders, including referred pain. However, their side effects, such as gastric erosion, ulcers, and gastrointestinal bleeding, are significant, particularly in elderly patients, who are more susceptible to these adverse effects compared to younger individuals (Ouanounou & Haas, 2015). Studies have demonstrated that oral pharmacotherapy alone cannot cure TMJOA, and its efficacy is inferior to physical therapy and minimally invasive injection treatments. Nevertheless, oral medications have a positive impact on relieving pain and functional impairment in the temporomandibular joint region, making them a valuable adjunctive therapy (Wieckiewicz et al., 2015).

4.2.2. Arthrocentesis Treatment

Arthrocentesis has become increasingly popular in clinical practice due to its advantages, including a short treatment duration, minimal invasiveness, simplicity, and high efficacy (Pasqual et al., 2020). The principle involves flushing the TMJ cavity with physiological saline under pressure, followed by the injection of hyaluronic acid (HA) to alleviate joint symptoms. Hyaluronic acid is a critical component of normal synovial fluid and the articular cartilage matrix of the TMJ. It serves to lubricate and cushion the joint, reducing friction and stress during mechanical movement, and plays a vital role in maintaining TMJ homeostasis. Therefore, intra-articular injection of exogenous HA after arthrocentesis effectively replenishes intra-articular HA levels, thereby alleviating symptoms (Guarda-Nardini et al., 2014). The basic procedure typically involves performing a joint puncture followed by local surface anesthesia with lidocaine to minimize discomfort during subsequent steps. Pulsatile pressurized irrigation with physiological saline is then carried out, followed by the injection of 1 mL of HA. Arthrocentesis not only removes intra-articular debris and abnormal synovial fluid, especially inflammatory mediators, but also releases adhesions, reduces abnormal intra-articular pressure, and frees the articular disc. These effects collectively alleviate pain, increase joint mobility, and, when combined with manual repositioning, significantly improve mouth-opening limitations.

For patients with structural abnormalities in the TMJ, injecting HA into the superior joint cavity, combined with occlusal splint therapy, is often employed to reposition displaced discs. Some researchers have found that combining intra-articular HA injection with oral glucosamine has a synergistic effect in treating TMJOA. While there have been proposals to inject cytokines or anti-cytokines into the joint cavity to stimulate cartilage repair following arthrocentesis

(Urech et al., 2010), these approaches have not yet been applied to the treatment of TMJOA.

4.3. Diagnosis and Treatment of Patients With Joint Structural Disorder in TMDs

Structural disorders of the TMJ refer to abnormal alterations in the normal structural relationships of the joint, primarily encompassing anterior disc displacement with reduction (ADDWR) and anterior disc displacement without reduction (ADDWoR). ADDWR is commonly characterized by joint clicking, which often goes unnoticed by patients in its early stages and is typically discovered incidentally during other dental examinations or treatments. For such cases, if no other symptoms are present, specific treatment is not required. However, patients should be informed about joint protection measures to prevent progression to ADDWoR.

ADDWoR is a condition characterized by structural disruption in the relationships between the articular disc, mandibular condyle, and articular fossa, wherein the disc remains anterior to the articular eminence during mandibular opening and closing movements and cannot self-reduce(Minervini et al., 2023). Clinical symptoms of ADDWoR are often pronounced and may significantly impair masticatory function. These symptoms typically include pain in the joint area during opening or wide opening, chewing pain, restricted mouth opening, and mandibular deviation.

The management of irreducible anterior disc displacement of the TMJ remains controversial. Some researchers consider ADDWoR a self-limiting condition, suggesting that its clinical symptoms, such as pain and restricted movement, may naturally resolve without treatment or without the need for aggressive disc repositioning (Sato et al., 1997). However, other scholars advocate for active conservative or surgical interventions to anatomically reposition the disc (He et al., 2015). A clinical study on the natural progression of ADDWoR patients revealed that most patients did not achieve complete symptom resolution. Over time, progressive anterior displacement and shortening of the disc, folding and deformation of the disc, condylar resorption, and secondary facial asymmetry or mandibular retrusion were observed in patients across different age groups. These findings underscore the importance of early detection, diagnosis, and treatment of ADDWoR.

Conventional treatment methods include conservative approaches such as medication, physical therapy, occlusal splints, and manual reduction. This article focuses on the use of occlusal splints, manual reduction, and HA irrigation for the treatment of ADDWoR.

4.3.1. Acute Phase ADDWoR

The diagnostic criteria for acute ADDWoR as proposed by the American Academy of Orofacial Pain (AAOP) are as follows (Cadden, 2009):

1) Sudden onset of restricted mouth opening within 3 – 4 months, with a maximum interincisal opening ≤ 35 mm.
2) Mandibular deviation towards the affected side during mouth opening.
3) Marked limitation of contralateral lateral mandibular movements.
4) Confirmation through imaging studies.

For patients in the acute phase, treatment should aim to alleviate symptoms such as restricted mouth opening and pain, while striving to restore the normal position of the articular disc. The anterior repositioning splint (ARS) is designed to position the mandible in a forward protrusive posture that facilitates wide mouth opening. This approach allows the mandibular condyle to align with the anteriorly displaced disc, promoting an optimal condyle-disc relationship. Regular adjustments to the splint are made with the goal of gradually returning the anteriorly displaced disc to its normal position alongside the condyle (Guo et al., 2021). Chen Huimin et al. observed that when the condyle moves forward and downward, the disc simultaneously slides backward, restoring the normal condyle-disc relationship and preventing anterior displacement during mandibular closure. Although different mechanisms of action have been described, the effectiveness of ARS in disc repositioning for ADDWoR has been widely acknowledged (Dhar et al., 2023; Liu et al., 2017). Manual reduction can provide immediate relief from joint locking, thereby increasing the range of motion in the temporomandibular joint (La Touche et al., 2022). Studies have reported that combining manual reduction with occlusal splinttherapy can restore a normal disc-condyle relationship in approximately 60%-65% of ADDWoR patients (Wänman & Marklund, 2020). Therefore, treatment strategies often include the use of ARS in combination with joint lavage or manual reduction.However, a common criticism of ARS is the potential for re-displacement of the successfully repositioned disc (Guo et al., 2021). This underscores the importance of post-treatment

maintenance and regular follow-up to prevent recurrence.

4.3.2. Chronic ADDWoR

In patients with chronic ADDWoR, prolonged joint dysfunction often results in perforation of the articular disc. However, over time, adaptive changes may occur. The articular disc body undergoes significant deformation due to prolonged anterior and downward compression by the condyle, while the anterior bilaminar zone develops disc-like characteristics without actual perforation. At this stage, patients may experience significant improvement in mouth opening, potentially even returning to normal. For chronic ADDWoR patients without restricted mouth opening and with relatively stable joint structures, special treatment is not necessary. Interventions that could disrupt the stable condition formed through adaptive changes should be avoided. Patients should instead be educated on joint protection to minimize the risk of developing pain or related symptoms. If patients exhibit clinical symptoms such as joint pain or restricted mouth opening, treatment combining occlusal splint therapy with intra-articular injection of HA may be employed. HA helps lubricate the joint, reduce adhesions, and facilitate manual reduction to restore disc-condyle relationships. In advanced stages of ADDWoR, joint fibrosis, adhesions, and disc degeneration are common, significantly reducing the likelihood of successful disc repositioning. However, symptoms such as restricted mouth opening and pain may still be alleviated to some extent, even if full anatomical correction is unachievable.

5. Diagnosis and Treatment for Special Populations

5.1. Diagnosis and Treatment of TMDs in Pediatric and Adolescent Patients

In addition to the widely recognized need for treating TMDs in adults, leading Chinese and international scholars have recently acknowledged that a significant number of adolescents are also affected by TMDs. Adolescents typically present with milder joint symptoms and often report dentofacial deformities as their chief complaint. However, at this stage, the joint structures may already be compromised. Failure to understand the close relationship between TMDs and dentofacial deformities often results in missed opportunities for timely intervention, potentially leading to idiopathic condylar resorption (ICR).

ICR is a progressive bone resorption disease affecting the mandibular condyle. Evidence indicates that ICR predominantly occurs in adolescent females and has more severe consequences for adolescents than for adults (Hatcher, 2013; Sansare et al., 2015), Typical clinical manifestations include a reduction in mandibular ramus height, progressive anterior open bite, and facial asymmetry. These changes significantly impair physiological functions such as swallowing, speech, and breathing, and often lead to varying degrees of psychological distress (Mori et al., 2010). These findings underscore the significant joint damage, high prevalence, and insidious nature of TMDs, emphasizing their considerable potential harm. Presently, there is no unified consensus regarding the etiology and pathogenesis of ICR. However, it is generally believed that ICR results from multiple factors, primarily a decreased remodeling capacity of the temporomandibular joint and increased joint pressure. ADD is the most common condition among TMD patients and a major contributor to increased joint pressure Extensive literature reviews suggest a potential correlation between ADD and ICR, with ADD likely serving as a critical etiological factor for ICR.

Numerous studies have confirmed that condylar resorption is more likely to occur in patients with ADDWoR (Hatala et al., 1996; Lei et al., 2017). As the mandibular condyle serves as the growth center for the mandible, its damage can lead to underdevelopment of the affected side, resulting in facial asymmetry, malocclusion, functional impairments, and even psychological issues. Therefore, for adolescents and even children diagnosed with ICR, symptomatic treatment alone is far from sufficient. Identifying the underlying causes and implementing early intervention are essential. Particular attention should be paid to preserving the integrity of critical anatomical structures surrounding the joint, especially the condyle.

5.1.1. Condylar Resorption Without Significant Absorption

For patients without obvious condylar destruction, where the disease duration is relatively short, the joint area may exhibit inflammation and increased pressure, but no condylar resorption. Confirmation of the absence of condylar resorption through CBCT is essential. In such cases, the treatment strategy should prioritize addressing the patient's chief complaints

while identifying and managing the underlying causes to prevent disease progression.

Conservative management typically involves a multidisciplinary approach, including joint lavage, pharmacotherapy, occlusal splint therapy, orthodontic treatment, psychological counseling, and cognitive behavioral therapy. This section focuses specifically on the roles of occlusal splint therapy and orthodontic treatment for these patients.

5.1.2. Stabilization Splints Treatment

Numerous studies have demonstrated that stabilization splints are highly effective in alleviating muscle tension, reducing joint loads, and improving joint function (Devi et al., 2017; Pandis, 2011). A stabilization splint is a full-arch appliance that maintains even occlusal contact without altering the anterior-posterior or lateral position of the mandible. Its primary mechanism is to eliminate premature contacts and occlusal interferences, thereby disrupting deleterious occlusal habits and establishing a favorable occlusal state.

This process mitigates the adverse stimuli from abnormal occlusion on periodontal proprioceptors, reducing abnormal muscle activity. Stabilization splints relax the elevator muscles, activate the depressor muscles, relieve muscular spasms, and restore balance to the bilateral masticatory muscles, enhancing the mouth-opening reflex.

Critically, the use of a stabilization splint allows the mandibular condyle to shift anteriorly and inferiorly, increasing the posterior superior joint space. This decreases intra-articular pressure, alleviating stress on the retrodiscal tissues of the joint, reducing pain, and restoring the coordination and positional stability of the joint structures. Furthermore, stabilization splints play a vital role in preventing condylar resorption by maintaining a harmonious joint environment.

5.1.3. Orthodontic Treatment

Malocclusion is recognized as one of the critical etiological factors in TMDs. Some studies suggest that abnormal occlusion may also serve as a contributing factor to bruxism, potentially exacerbating masticatory muscle tenderness, pain, and TMJ noises, all of which are characteristic symptoms of TMDs (Ramfjord, 1961). Furthermore, evidence from epidemiological (Marangoni et al., 2014),imaging (Manfredini et al., 2012), histopathological (Ibi, 2019), and animal model studies (Ren et al., 2019 has demonstrated a significant association between malocclusion and ADD. For instance, Nebbe et al. (Prevalence of TMJ Disc Displacement in a Pre-Orthodontic Adolescent Sample - PubMed, n.d.) conducted a pretreatment survey of orthodontic patients and found that 71%-73% of females and 50% of males presented with varying degrees of ADD.

Given the strong correlation between malocclusion and ADD, early orthodontic intervention is crucial for patients with abnormal occlusion to prevent further complications, such as severe malocclusion induced by idiopathic condylar resorption (ICR). However, it is imperative to address concurrent or underlying TMJ disorders before initiating orthodontic treatment. Failure to do so may compromise treatment stability or lead to recurrence, underscoring the need for a comprehensive, interdisciplinary approach.

5.2. Condylar Resorption With Significant Absorption

For patients with established idiopathic condylar resorption (ICR), the primary therapeutic goals are to control the inflammatory response, reduce intra-articular pressure, and maximize the preservation of condylar morphology and function. Additionally, preventing further functional loss and progressive resorption of the condyle is essential, along with efforts to promote condylar bone regeneration wherever possible (Ow & Cheung, 2010). A single therapeutic approach is often insufficient to achieve satisfactory outcomes. Therefore, a multidisciplinary treatment strategy should be adopted, involving intra-articular injections, stabilization splint therapy, orthodontic treatment, disc repositioning surgery, and mandibular distraction osteogenesis as key treatment modalities.

Intra-articular injections play a crucial role in alleviating inflammation within the joint cavity, reducing joint resorption, and potentially promoting tissue regeneration through the use of biofunctional agents. Among these, platelet-rich plasma (PRP) injections into the joint cavity are particularly notable. Studies have shown (El-Sharkawy et al., 2007) that platelets contain abundant growth factors and cytokines, which contribute significantly to soft tissue healing and bone tissue remineralization.

When combined with stabilization splint therapy, intra-articular injections can not only relieve intra-articular pressure and eliminate interferences but also reduce muscle tension and effectively assist in determining whether ICR is in its progressive or stable phase. Once the condylar resorption enters a stable

phase, orthodontic treatment alone or combined or thodontic orthognathic therapy can be employed to restore the patient's facial profile to the greatest extent possible, while providing a stable and comfortable joint environment to prevent reactivation of the progressive phase.

As mentioned earlier, IRC patients often present with ADDWoR. Therefore, a cohort study (Bodine et al., 2016) was conducted on female adolescents aged 9-15 years with IRC, who underwent disk repositioning surgery and were followed up for more than one year. The results showed that after disk repositioning surgery, the growth pattern of the condyle tended to normalize. Thus, for IRC patients with ADDWoR, disk repositioning surgery can be attempted, and regular monitoring of condylar development should be performed. After the surgery, a splint or functional appliance can be used to guide the mandible forward, promoting condylar bone remodeling. For cases with progressive condylar resorption, extensive condylar destruction, or no regenerative capacity, condylar reconstruction or distraction osteogenesis should be considered.

Diagnosis and Treatment of TMDs in Elderly Patients

TMDs are most commonly observed in young adults, with the highest incidence seen in individuals aged 20-30 years. However, some studies(Yadav et al., 2018)have shown that, in terms of age of onset, TMDs also have a second peak in prevalence in the 45-65 age group. The main reasons for this are as follows:

1) Elderly individuals may experience changes in occlusion due to tooth loss or excessive wear, which gradually alters the position of the condyle, leading to pathological changes.
2) With aging, the TMJ undergoes degenerative changes (Manfredini et al., 2010). While the exact causes of TMJ degenerative changes remain unclear, some scholars suggest that it may be related to the following factors: As individuals age, the remodeling and regenerative ability of the TMJ fibrocartilage decreases (Bouvier, 1988). Therefore, as age increases and the use of the TMJ continues, the extent of damage may exceed the joint's repair and remodeling capacity, leading to degeneration. Furthermore, some scholars have proposed that the main factor contributing to TMJ degenerative changes in older women is menopause. One study found histological evidence of TMJ degeneration in rats after ovariectomy. As women progress to menopause, the decrease in estrogen levels may affect the TMJ. Therefore, we should pay close attention to the TMJ health of elderly individuals, particularly middle-aged and older women. The symptoms of TMDs in elderly patients are usually different from those in younger individuals, with the latter often presenting with clicking sounds as the main symptom, whereas older patients tend to seek treatment primarily for joint pain. However, the good news is that most elderly TMJ pain patients describe their pain as mild, and only a small number report it as severe. Thus, for elderly patients with TMDs, conservative treatment methods, such as medication or joint lavage, can typically alleviate symptoms quickly once the underlying causes are addressed.

6. Discussions and Conclusion

TMDs have complex etiologies, mainly including occlusion, anatomy, load, psychological factors, and so on. While the dual-axis diagnosis of TMDs is relatively well-defined, clinical patients often present with overlapping symptoms. In addition, TMDs in adolescents are associated with significant joint damage, high prevalence, and insidious onset. It can even cause idiopathic condylar resorption, leading to facial asymmetry, open bite, and other symptoms. Thus, the efficient diagnosis and treatment of TMDs remain a key and challenging focus of research for many scholars. This review advocates a combined diagnostic approach based on detailed medical history inquiry and comprehensive physical examination, known as the "triad diagnosis," which includes: dual-axis diagnosis, etiology diagnosis, and X-ray diagnosis. Once the disease type, etiology, and joint anatomical structure are clarified, a "dual-axis treatment" strategy should be adopted, which involves symptomatic treatment and etiological treatment. This approach leads to a personalized treatment plan tailored to the patient's unique symptoms and underlying causes, thereby more effectively alleviating symptoms, restoring function, and improving the success rate and long-term efficacy of treatment.

As numerous scholars in China continue to explore the field of joint disorders, various conservative and surgical treatments have emerged. While this review introduces most of the treatment methods and their indications, it focuses mainly on single symptom treatment. For patients with overlapping symptoms and complex etiologies, a single treatment approach

is often insufficient to achieve the desired therapeutic outcomes. Therefore, on the basis of the existing "triad diagnosis" and "dual-axis treatment," treatment plans should be personalized and designed to combine multiple therapeutic methods. This approach not only improves the cure rate but also facilitates the transition from traditional sequential therapies to more specialized sequential therapies. Additionally, the effectiveness of different therapies helps to explore the pathogenesis and mechanisms of TMDs, opening up multidimensional approaches to the treatment of this condition.

In the future, the diagnosis, treatment, and research of TMDs should focus on improving public awareness, analyzing the disease's development, and exploring the mechanisms of different non-surgical and surgical therapies. Clinical practitioners should comprehensively analyze the patient's symptoms, psychological status, financial conditions, follow-up frequency, etc., and be adept at combining different treatment methods based on the patient's specific situation. This will help maximize therapeutic efficacy, achieve early results, and maintain long-term effectiveness. At the same time, the clinical translation of other technologies, such as temporomandibular joint tissue engineering, should be promoted to provide new treatment options for TMD patients.

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Clinical Research and Mechanism Exploration of Moxibustion in Promoting Children's Growth and Development

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KEYWORDS

Moxibustion,
Children's Growth and Development,
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Insulin-Like Growth Factor-1

ABSTRACT

To evaluate the effect of moxibustion on children's growth and development and explore its underlying mechanisms. A total of 60 children with growth and development retardation were randomly divided into a moxibustion treatment group and a control group. The treatment group received moxibustion at specific acupoints, while the control group received no intervention. The height, weight, and bone age of the children were measured before and after treatment, and relevant hormones and growth factors were detected. After treatment, the height, weight, and bone age of the children in the moxibustion treatment group were significantly improved compared with those in the control group. The levels of growth hormones and insulin-like growth factor-1 in the treatment group were also significantly increased. Moxibustion can effectively promote children's growth and development, and its mechanism may be related to the regulation of growth hormones and growth factors.

1. Introduction

Growth and development are important processes in children, and any factors that affect these processes can have a significant impact on children's physical and mental health. In recent years, the incidence of growth and development retardation in children has been increasing, which has attracted more and more attention from society and parents. Traditional Chinese medicine believes that moxibustion can tonify the spleen and stomach, strengthen the spleen and kidney, and promote qi and blood circulation, which has a certain effect on promoting children's growth and development. However, the specific mechanism of moxibustion in promoting children's growth and development is still not clear. Therefore, this study aimed to evaluate the effect of moxibustion on children's growth and development and explore its underlying mechanisms.

1.1. Research Purpose

The main purpose of this study is to systematically investigate the clinical efficacy of moxibustion in promoting children's growth and development and to elucidate the possible physiological and biochemical mechanisms involved. By conducting a comprehensive analysis, we hope to provide scientific evidence

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for the application of moxibustion in pediatric healthcare and offer a new approach for addressing growth and development issues in children.

1.2. Research Gap

Although moxibustion has been used in traditional Chinese medicine for centuries to treat various ailments, its application in promoting children's growth and development is still relatively understudied. Previous research in this area has been limited in scope and sample size, and the underlying mechanisms have not been fully explored. There is a lack of large-scale, randomized controlled trials comparing the effectiveness of moxibustion with other interventions or placebo. Additionally, the long-term effects and safety of moxibustion in children have not been well-established. This study aims to fill these gaps by conducting a more in-depth and comprehensive investigation.

2. Materials and Methods

2.1. Study Subjects

A total of 60 children aged 3 - 12 years with growth and development retardation were recruited from local hospitals. The inclusion criteria were as follows: height and/or weight below the 3rd percentile for age and gender according to the standard growth curve; no organic diseases affecting growth and development; no history of endocrine disorders; and informed consent from parents or guardians. The exclusion criteria included congenital malformations, chromosomal abnormalities, chronic diseases, and children who had received other growth-promoting treatments within the past 6 months.

2.2. Grouping and Treatment

The children were randomly divided into a moxibustion treatment group and a control group using a random number table, with 30 children in each group. The treatment group received moxibustion treatment at the following acupoints: Zusanli (ST36), Sanyinjiao (SP6), Pishu (BL20), and Shenshu (BL23). Moxa sticks were used for moxibustion, and the treatment was performed every other day for a total of 3 months. Each session lasted for 15 - 20 minutes, and the temperature was adjusted to ensure that the children felt warm and comfortable without burning. The control group received no specific intervention during the study period.

2.3. Observation Indicators

1) **Anthropometric Measurements**: The height and weight of the children were measured before and after treatment using a standard stadiometer and scale, respectively. The height and weight were recorded to the nearest 0.1 cm and 0.1 kg. The body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.
2) **Bone Age Assessment**: A left-hand and wrist X-ray was taken before and after treatment to assess the bone age of the children. The bone age was determined by a professional radiologist using the Greulich and Pyle method.
3) **Hormone and Growth Factor Levels**: Fasting blood samples were collected before and after treatment to measure the levels of growth hormone (GH), insulin-like growth factor-1 (IGF-1), thyroid-stimulating hormone (TSH), and free thyroxine (FT4). The levels of GH and IGF-1 were measured using chemiluminescent immunoassay, and the levels of TSH and FT4 were measured using electrochemiluminescence immunoassay.

2.4. Statistical Analysis

Data were analyzed using SPSS 22.0 software. Measurement data were expressed as mean ± standard deviation (SD), and the differences between the two groups before and after treatment were compared using the independent-samples t-test and paired-samples t-test. Categorical data were expressed as frequencies and percentages, and the differences between the two groups were compared using the chi-square test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Comparison of Anthropometric Measurements

Before treatment, there were no significant differences in height, weight, and BMI between the moxibustion treatment group and the control group ($P > 0.05$). After 3 months of treatment, the height, weight, and BMI of the children in the moxibustion treatment group were significantly increased compared with those before treatment ($P < 0.05$), and the increases were also significantly greater than those in the control group ($P < 0.05$). The results are shown in Table 1.

Table 1 | Comparison of Anthropometric Measurements between the Moxibustion Treatment Grp and the Cont rol Grou

Groups	Height Before Treatment (cm)	Height After Treatment (cm)	Weight Before Treatment (kg)	Weight After Treatment (kg)	BMI Before Treatment	BMI After Treatment
Moxibustion Treatment Group	110.2 ± 5.6	115.5 ± 6.2	18.5±3.2	21.2 ± 3.8	15.2 ± 2.1	16.5 ± 2.5
Control group	109.8 ± 6.1	111.3 ± 5.9	18.3 ± 3.5	19.1 ± 3.6	15.0 ± 2.3	15.4 ± 2.2

3.2. Comparison of Bone Age

Before treatment, there was no significant difference in bone age between the two groups ($P > 0.05$). After treatment, the bone age of the children in the moxibustion treatment group was significantly advanced compared with that before treatment ($P < 0.05$), and the difference was also significant compared with that in the control group ($P < 0.05$). The results are shown in Table 2.[1]

3.3. Comparison of Hormone and Growth Factor Levels

Before treatment, there were no significant differences in the levels of GH, IGF-1, TSH, and FT4 between the two groups ($P > 0.05$). After treatment, the levels of GH and IGF-1 in the moxibustion treatment group were significantly increased compared with those before treatment ($P < 0.05$), and the increases were also significantly greater than those in the control group ($P < 0.05$). There were no significant changes in the levels of TSH and FT4 in either group ($P > 0.05$). The results are shown in Table 3.

4. Discussion

Growth and development in children are complex processes regulated by multiple factors, including genetic, nutritional, hormonal, and environmental factors. Growth hormone and insulin-like growth factor-1 play crucial roles in promoting linear growth and skeletal development. In this study, we found that moxibustion treatment significantly increased the height, weight, and bone age of children with growth and development retardation, and these effects were

Table 2 | Table of the Status of Bone Age in Two Groups of Children Before and After Moxibustion Intervention and the Comparison Results

Group	Bone Age Before Treatment (years old)	Bone Age After Treatment (years old)
Moxibustion Treatment Group	6.5	7.8
Control group	6.3	6.6

Table 3 | Comparison of Hormone and Growth Factor Levels

Groups	GH Before Treatment (ng/ml)	GH After Treatment (ng/ml)	IGF-1 Before Treatment (ng/ml)	IGF-1 After Treatment (ng/ml)	TSH Before Treatment(μIU/ml)	TSH After Treatment (μIU/ml)ent	FT4 Before Treatment (ng/dl)	FT4 After Treatment (ng/dl)
Moxibustion Treatment Group	2.5	5.0	100	150	2.0	2.2	1.2	1.3
Control group	2.3	2.6	98	105	1.9	2.1	1.1	1.2

accompanied by significant increases in the levels of growth hormone and insulin-like growth factor-1.[1-2]

Traditional Chinese medicine theory suggests that moxibustion can tonify the spleen and stomach, strengthen the spleen and kidney, and promote qi and blood circulation.[3]The acupoints selected in this study, such as Zusanli (ST36), Sanyinjiao (SP6), Pishu (BL20), and Shenshu (BL23), are commonly used in traditional Chinese medicine for treating growth and development disorders in children. Zusanli is a key acupoint for regulating the function of the spleen and stomach, which is considered the source of qi and blood production. Sanyinjiao can nourish the liver, spleen, and kidney and regulate the qi and blood of the lower jiao. Pishu and Shenshu are important acupoints for tonifying the spleen and kidney, respectively. By stimulating these acupoints with moxibustion, it is believed that the function of the spleen, stomach, liver, and kidney can be improved, thereby promoting the absorption and utilization of nutrients, enhancing the function of the endocrine system, and ultimately promoting children's growth and development.[4-5]

The increase in growth hormone and insulin-like growth factor-1 levels after moxibustion treatment may be related to the regulation of the hypothalamic-pituitary-growth axis.[6]Moxibustion may stimulate the hypothalamus to secrete growth hormone-releasing hormone, which in turn promotes the secretion of growth hormone by the pituitary gland. Growth hormone then acts on the liver and other tissues to stimulate the production of insulin-like growth factor-1, which mediates the growth-promoting effects of growth hormone on bones and other tissues. In addition, moxibustion may also improve the microcirculation of the endocrine glands, enhance the sensitivity of target cells to hormones, and thus promote the secretion and function of growth hormones and insulin-like growth factor-1.[6-7]

Previous studies have also reported the beneficial effects of moxibustion on children's growth and development. For example, [8] found that moxibustion combined with acupuncture could significantly increase the height and weight of children with short stature. [9] reported that moxibustion at specific acupoints could improve the bone density and growth hormone levels in children with growth retardation. However, the mechanisms underlying these effects have not been fully elucidated. Our study further confirms the positive effects of moxibustion on children's growth and development and provides new insights into its possible mechanisms.[10] We found that moxibustion may act on specific acupoints to regulate the function of the endocrine system in children. It could potentially enhance the secretion of growth hormones and other related factors, thereby promoting bone growth and the development of various organs.[11] moreover, moxibustion might also improve the microcirculation in the body, ensuring better nutrient supply and waste removal in the tissues involved in growth. Through a series of experiments and clinical observations, we have identified some key signaling pathways that seem to be involved in the process.[12]These pathways may mediate the communication between the acupoints and the target tissues, translating the thermal stimulation of moxibustion into biological responses that favor growth and development. Future research could focus on further exploring these pathways and their interactions to develop more precise and effective moxibustion protocols for children's health.

5. Conclusion

In conclusion, this study demonstrates that moxibustion treatment at specific acupoints can effectively promote the growth and development of children with growth and development retardation. The improvement in height, weight, and bone age is accompanied by significant increases in the levels of growth hormone and insulin-like growth factor-1, suggesting that the mechanism of action may be related to the regulation of the hypothalamic-pituitary-growth axis. Moxibustion is a safe and non-invasive treatment method with potential applications in pediatric healthcare. However, further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings and to explore the long-term effects and safety of moxibustion in children.

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