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Global Trends on β-Thalassemia Research Over 10 Years: A Bibliometric Analysis

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Purpose: Thalassemia, an inherited quantitative globin disorder, is the most prevalent monogenic disease globally. While severe alpha thalassemia results in intrauterine death, β-thalassemia manifests during childhood due to the "second conversion of hemoglobin", garnering increased attention in recent decades.

Methods: In this study, a bibliometric analysis was conducted of thalassemia articles published in the Web of Science Core Collection database between 2013 and 2023 to establish a comprehensive overview and to identify emerging trends. A total of 5655 studies published between 2013 and 2023 were systematically retrieved, and annual publications demonstrated a steady increase, maintaining a high level over the past decade.

Results: The United States contributed the highest number of publications, followed by China. Notably, the journal *Blood* emerged as the leading authority in β-thalassemia research. Analysis of research hotspots revealed that the pathogenesis of β-thalassemia is primarily linked to iron overload, anemia, gene mutations, and ineffective erythropoiesis. Furthermore, recent studies focusing on gene editing therapies present promising avenues for future investigation.

Conclusion: These findings grasp the research status of β-thalassemia and shed new light on future research frontiers.

Keywords: bibliometric, citespace, hotspots, thalassemia, VOSviewer

Introduction

Thalassemia, a hereditary disorder characterized by quantitative abnormalities in globin, is the most widespread monogenic disease globally. The prevalence of thalassemia genetic mutations among carriers is estimated to be between 1.5–7% of the world's population.[1] The high incidence of inherited hemoglobin variants in certain regions is attributed to the heterozygote resistance to Plasmodium falciparum malaria. Thalassemia is most prevalent in the Mediterranean regions, parts of North and sub-Saharan Africa, the Middle East, the Indian subcontinent, and Southeast Asia.[2–4] The emergence of these disorders in large multiethnic cities across Europe and North America due to ongoing migration presents a global health concern.[5,6] The mutations in β-thalassemia result in a decrease, abnormal structure, or complete absence of β-globin chain expression, leading to an imbalance of the α- and β-subunits that comprise the hemoglobin (Hb) tetramer, thereby hindering adequate oxygen transport.[7] Excess accumulation of stem cells in developing erythrocytes causes ineffective erythropoiesis (IE), chronic hemolytic anemia, and compensatory hematopoiesis.[8]

In recent decades, there has been substantial progress in understanding the physiological aspects of normal erythropoiesis, hemoglobin switching, and the pathogenic mechanisms underlying β-thalassemia.[9] However, the increasing number of publications makes it challenging for researchers and clinicians to keep up with the latest advancements. While meta-analyses and systematic reviews on thalassemia offer consolidated findings, they often focus on specific aspects and may not capture evolving publication trends, or predict emerging research hotspots.

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Bibliometrics is an interdisciplinary science that combines mathematics, statistics, and bibliography to examine the characteristics of literature systems. It involves the statistical and mathematical analysis of written publications, such as those originating from different countries, institutions, journals, and authors within a specific research field. This analysis is often presented visually through graphical representations, enabling the identification of research trends and patterns over time.[10] As an adjunct research method, bibliometrics has been employed to investigate research trends in various areas, including antiphospholipid syndrome,[11] heart failure,[12] chronic heart failure,[13] and femoral head necrosis.[14] However, there is currently a lack of targeted bibliometric analysis focusing on the literature on β-thalassemia.

A bibliometric analysis of articles contained in the Web of Science Core Collection database for the period 2013-2023 was conducted. The goal was to provide a general overview of the current research status and offer valuable insights for researchers working on β-thalassemia and its treatments.

Materials and Methods

Data Selection and Search Methods

The Web of Science (WoS) database was utilized as the primary source of international academic literature, encompassing over 12,000 scholarly journals.[15] Thalassemia-related literature was retrieved from the Science Citation Index Expanded (SCI-Expanded) within the WoS Core Collection (WoSCC) and downloaded on May 1, 2023. The search query was formulated as follows: TI = ("β-Thalassemia*" OR "β-Mediterranean anemia*" OR "Cooley anaemia*" OR "beta thalassemia*") AND publishing year= (2013-01-01 to 2023-05-01) AND Language = (English). The document types were restricted to articles and reviews. A total of 4550 documents were obtained after thorough screening, and the results are presented in Figure 1.

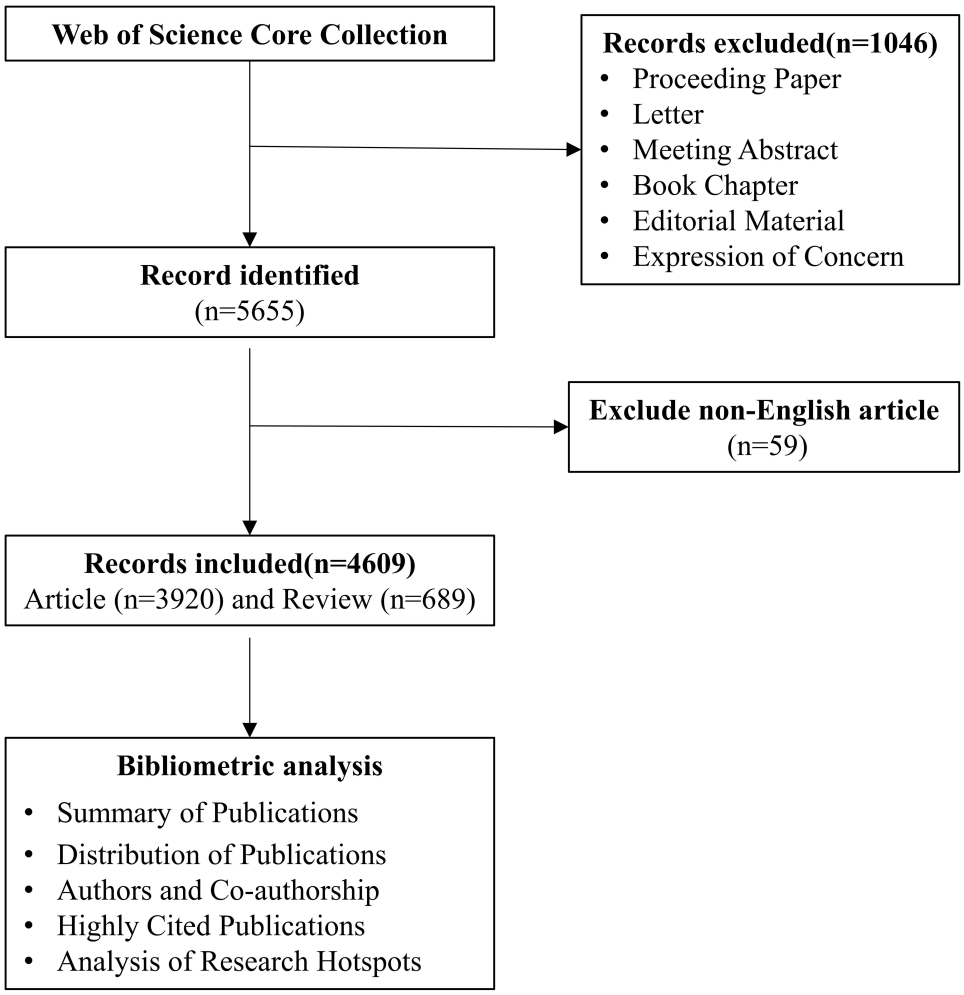

Figure 1 Flowchart of literature retrieval and selection.

Bibliometric Analysis

Microsoft Excel 2022 was utilized to generate a line chart to visualize the annual publications related to β-thalassemia research. Further analysis of the data was conducted using CiteSpace (v.5.7.R2) and VOSviewer (v.1.6.19.0). CiteSpace, a powerful bibliometric tool, was employed in this analysis to examine scientific publications and create visualizations that map the knowledge structure. Specifically, it was used to analyze collaboration patterns among institutions and authors, perform co-citation analysis of references, and identify significant burst references and keywords. VOSviewer is a free software tool that maps scientific knowledge based on co-occurrence clustering. It enables the visualization of the structure, evolution, and cooperation of knowledge domains.[16] VOSviewer version 1.6.19 was employed to construct network visualization maps of institutions, authors, co-cited authors, and journals to gain insights into the general landscape of thalassemia research in this study.[17]

Results

Summary of β-Thalassemia Publications

The analysis of scholarly output reveals the annual number of publications in the field of β-thalassemia. Following the literature selection process outlined in Figure 1. A total of 5655 articles about β-thalassemia that were published between 2013 and 2023 were found. Among these, there were 3920 articles and 689 reviews. Figure 2A illustrates the distribution of annual publications. The general trend indicates a rise in the number of publications on β-thalassemia, from 391 in 2013 to 471 in 2022, despite periodic reductions in some years. At 499 articles, 2021 was the year with the largest number of publications. There have been 95 articles published so far this year as of May 1, 2023. The analysis of annual publications indicates a sustained growth in researchers' interest in β-thalassemia over the past decade.

Distribution of Publications

Examining the annual publications of the top 10 countries/regions over the past decade (Figure 2B), China (108 publications) gradually surpassed the USA (72 publications) starting in 2022. Regarding the geographical distribution, out of the 4550 articles analyzed, they originated from 116 different countries/regions and were affiliated with 5133 different institutions. To visualize the spatial distribution, a heatmap was generated (Figure 2C). According to Table 1, the United States of America (USA) is the most productive country, with 837 publications, accounting for 18.40% of the total. It was followed by China (502 publications, 11.03%), Italy (454 publications, 9.98%), Thailand (376 publications, 8.26%), and Iran (336 publications, 7.38%). International collaborations played a significant role in facilitating academic exchange and development. Among the top 10 research institutions in Table 2, three were based in Thailand and two in China. Mahidol University contributed the most publications (227 publications, 4.99%), followed by Chiang Mai University (104 publications, 2.29%). Collaboration between research institutions was extensive, as depicted in Figure 2D. Mahidol University demonstrated close collaborations with various universities in Thailand, as well as institutions from Italy, China, and the United States, as shown in Figure 2E.

Authors and Co-Authorship

The last ten years have seen 20,044 authors publish articles on the area of β-thalassemia. Table 3 lists the top 10 authors with the highest number of publications, including 2 authors from Iran and 4 from Thailand. The most productive author was Suthat Fucharoen from Mahidol University, Thailand, with 83 publications, followed by DONGZHI LI from Guangzhou Medical University, China, with 54 publications. The collaboration between authors is shown in Figure 3A. Co-cited authors are authors who are simultaneously cited in several articles at the same time. Table 3 shows that of the top 10 co-cited authors, 5 were from Italy and 3 were from the UK. The most widely co-cited author was David J. Weatherall (968 co-citations), who was followed by Renzo Galanello (616 co-citations) and Ali T. Taher (562 co-citations). Figure 3B shows the co-citation links among the authors.

There are 1060 journals has publications on β-thalassemia between 2013 and 2023. Analysis of these journals helps identify the most prominent journals in this field. A list of the top 10 journals with the most publications is shown in Table 4 and Figure 4A, along with their impact factors (IFs) and H-index. An average IF of 4.27 can be found in these

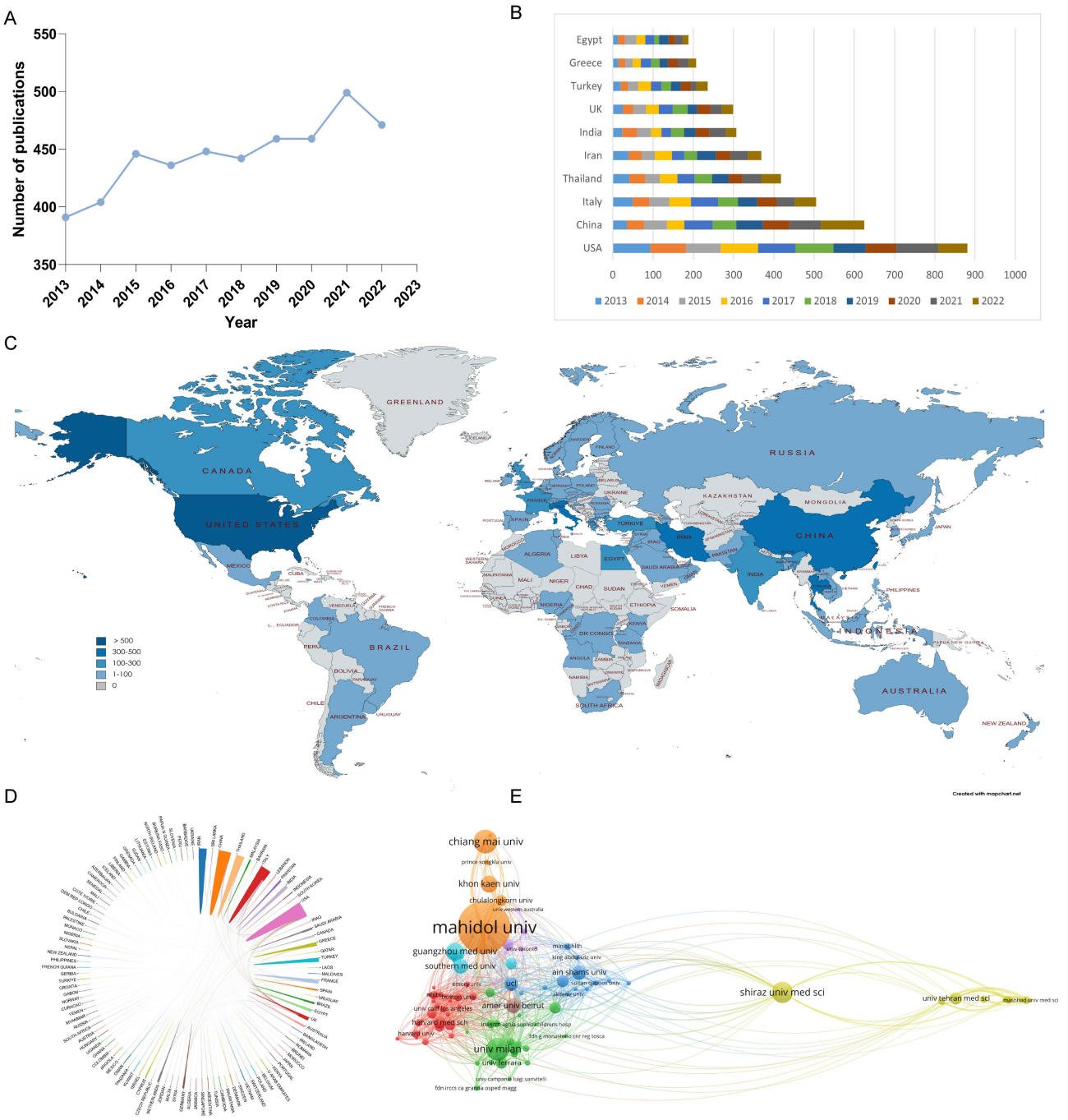

Figure 2 Summary of β-thalassemia Publications. (**A**) Annual publications of β-thalassemia from 2013 to 2022. (**B**) Percentage of publications in the 10 most productive countries/regions over the last 10 years. (**C**) An illustration of the geographical distribution of global publications. Gray represents countries with no publications. (**D**) Analysis of international collaboration in the field of β-thalassemia among various nations/regions. (**E**) Collaboration between institutions in the field of β-thalassemia.

journals, ranging from 0.7 to 21.0. The journal *Hemoglobin* ranked first in terms of productivity with 488 papers, an IF of 1.2, and an H-index of 41. It was followed by *Annals of Hematology* with 103 papers, an IF of 3.0, and an H-index of 88, and *Journal of Pediatric Hematology Oncology* with 96 papers, an IF of 1.2, and an H-index of 83.

Co-citation analysis reveals the relationships among various journals, with the number of citations a journal receives serving as an indicator of its significance and influence within the research field. According to Table 4 and Figure 4B, four out of the top 10 journals were also among the most frequently cited ones. These include *Blood* (16620 citations), *British Journal of Hematology* (6022 citations), *Hemoglobin* (4961 citations), and *Blood Cells Molecules and Disease*

Table 1 Top 10 Productive Countries in the Field of β-Thalassemia

Rank	Country	Count	Proportion	Rank	Country	Count	Proportion
1	USA	837	18.40%	6	India	255	5.60%
2	China	502	11.03%	7	UK	217	4.77%
3	Italy	454	9.98%	8	Turkey	194	4.26%
4	Thailand	376	8.26%	9	Greece	178	3.91%
5	Iran	336	7.38%	10	Egypt	173	3.80%

Abbreviations: USA, the United States of America; UCL, University College London; UK, The United Kingdom.

Table 2 Top 10 Productive Institutions in the Field of β-Thalassemia

Rank	Institution	Count	Proportion	Rank	Institution	Count	Proportion
1	Mahidol Univ(Thailand)	227	4.99%	6	Khon Kaen Univ(Thailand)	72	1.58%
2	Chiang Mai Univ(Thailand)	104	2.29%	7	Amer Univ Beirut(Lebanon)	69	1.52%
3	Milan Univ (Italy)	102	2.24%	8	Southern Med Univ(China)	63	1.38%
4	Shiraz Univ Med Sci(Iran)	89	1.96%	9	Ain Shams Univ(Egypt)	63	1.38%
5	Guangzhou Med Univ(China)	77	1.69%	10	UCL(The United Kingdom)	60	1.32%

Table 3 Top 10 Productive Authors and Co-Cited Authors in the Field of β-Thalassemia

Rank	Author	Count	Institution	Country	Co-cited author	Citation	Institution	Country
1	Suthat F, et al	83	Mahidol Univ	Thailand	Weatherall DJ, et al	968	Oxford Univ	UK
2	DongZhi L, et al	54	Guangzhou Med Univ	China	Galanello R, et al	616	Cagliari Univ	Italy
3	Supan F, et al	53	Khon Kaen Univ	Thailand	Taher AT, et al	562	Amer Univ Beirut	Lebanon
4	Mehran K, et al	50	Semnan Univ	Iran	Cappellini MD, et al	557	Milan Univ	Italy
5	Saovaros S, et al	49	Mahidol Univ	Thailand	Borgna P, et al	532	Ferrara Univ	Italy
6	Taher AT, et al	48	Amer Univ Beirut	Lebanon	Modell B, et al	513	University College London	UK
7	Maria, DC, et al	46	Milan Univ	Italy	Thein SL, et al	472	King's College Hospital	UK
8	Rivella S, et al	44	Pennsylvania Univ	USA	Cao A, et al	465	Ferrara Univ	Italy
9	Fucharoen G, et al	42	Khon Kaen Univ	Thailand	Olivieri NF, et al	437	Toronto Univ	Canada
10	Haghpanah S, et al	42	Shiraz Univ	Iran	Musallam KM, et al	414	Milan Univ	Italy

(2325 citations). Furthermore, based on the Journal Citation Reports of 2022, eight out of the top ten co-cited journals belonged to Q1, except for *Hemoglobin* and *Blood Cells Molecules and Disease*. A dual-map overlay of journals is shown in Figure 4C, with cited on the right and citing on the left. On the map, the lines represent the citation links between the journals. The visualization shows four main citation paths within the map.

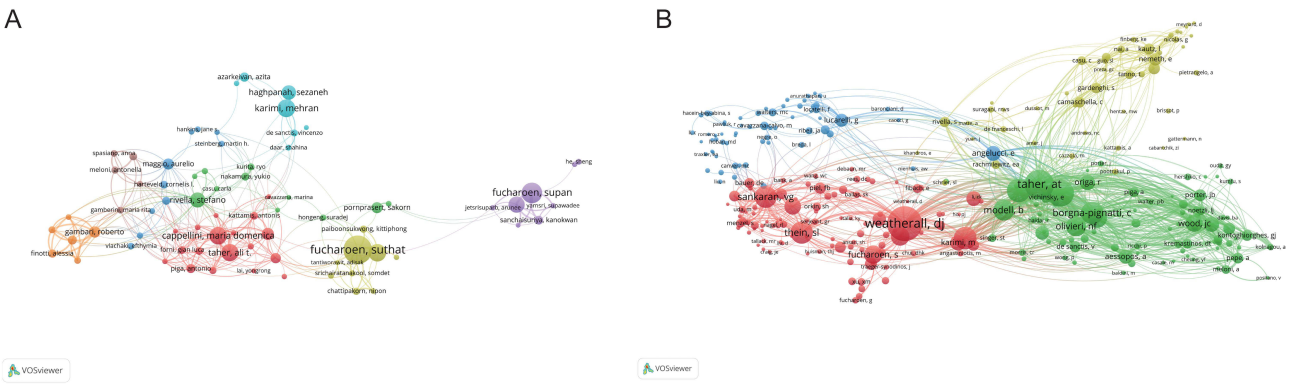

Figure 3 The collaboration of different authors in the field of β-Thalassemia. (**A**) VOSviewer network visualization map of the cooperation network of authors in the field of β-thalassemia. (**B**) VOSviewer network visualization map of the co-citation network of authors in the field of β-thalassemia.

Table 4 Top 10 Productive Journals and Co-Cited Journals in the Field of β-Thalassemia

Rank	Journal	Count	IF(2023)	H-Index	JCR	Co-Cited Journal	Citation	IF(2023)	H-Index	JCR
1	*Hemoglobin*	488	1.2	41	Q4	*Blood*	16620	21.0	506	Q1
2	*Annals of hematology*	103	3.0	88	Q2	*British Journal of Haematology*	6022	5.1	201	Q1
3	*Journal of pediatric hematology*	96	0.9	83	Q4	*Hemoglobin*	4961	1.2	41	Q4
4	*PLoS one*	85	2.9	404	Q1	*NEJM*	4107	96.2	1130	Q1
5	*BCMD*	85	2.1	95	Q3	*American Journal of Hematology*	3714	10.1	121	Q1
6	*Blood*	84	21.0	506	Q1	*Haematologica*	3128	8.2	155	Q1
7	*Hematology*	78	2	46	Q4	*PNAS*	2855	9.4	838	Q1
8	*Indian Journal of Hematology and Blood Transfusion*	71	0.7	20	Q4	*Nature*	2554	50.5	1331	Q1
9	*Scientific reports*	66	3.8	282	Q1	*BCMD*	2325	2.1	95	Q3
10	*British Journal of hematology*	61	5.1	201	Q1	*Lancet*	2314	98.4	855	Q1

Abbreviations: NEJM, The New England Journal of Medicine; PNAS, Proceedings of the National Academy of Sciences of the United States of America; BCMD, Blood cells molecules and disease.

Highly Cited Publications

The Timeline view of references illustrates the rapid increase in citations of specific publications during certain periods, making it a useful tool for identifying emerging issues that are attracting significant attention at a particular time. The

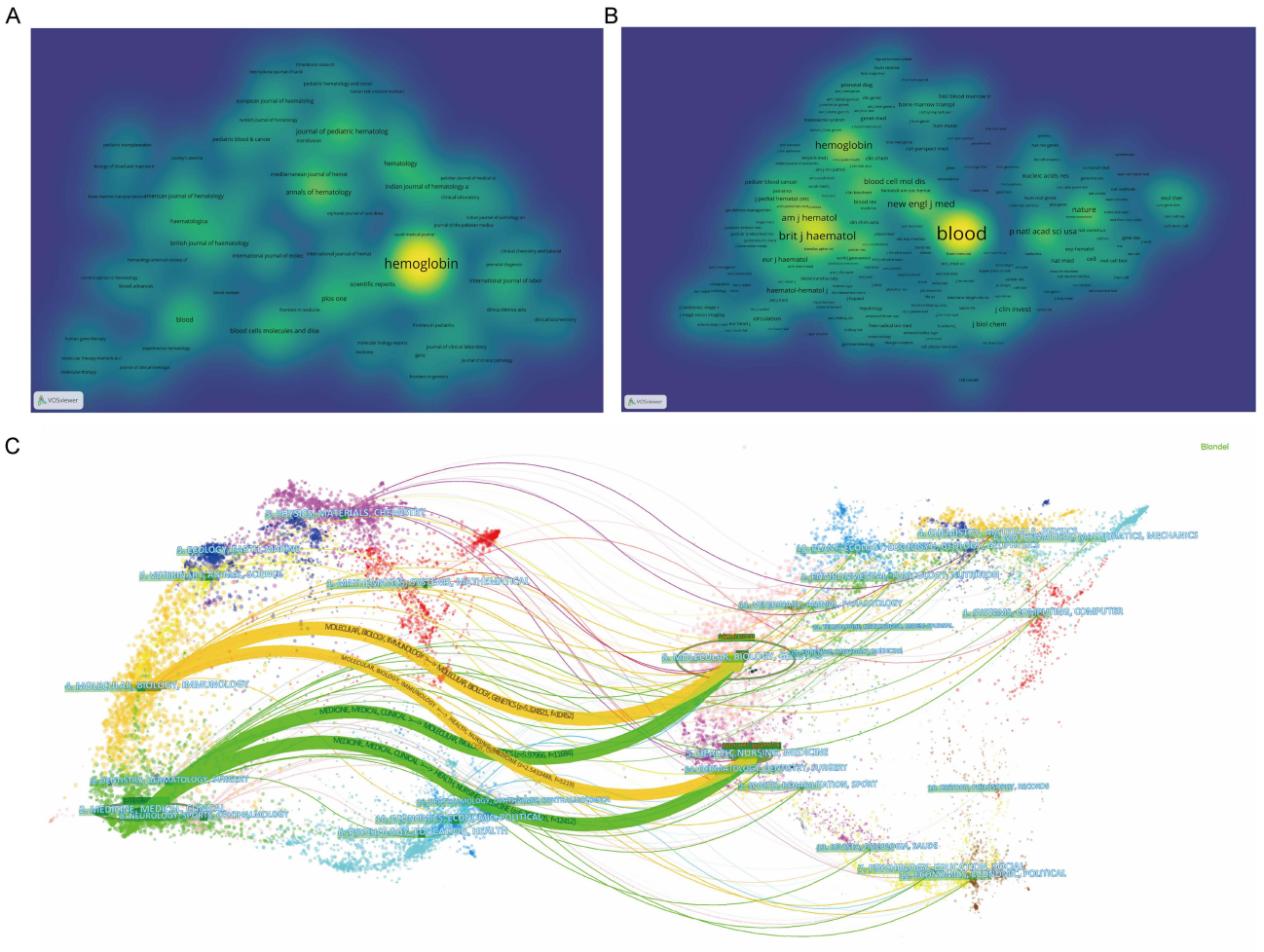

Figure 4 Co-citation maps and visualizations of the most productive journals on the subject of β-thalassemia. (**A**) VOSviewer density visualization map of the most productive journals. (**B**) VOSviewer density visualization map of the co-citation of journals. (**C**) Dual-map overlay of journals related to β-thalassemia. The visualization highlights four main citation paths: The top yellow path indicates that papers published in molecular/biology/immunology journals primarily cited journals in the molecular/biology/genetics area. The middle yellow path shows that papers published in molecular/biology/immunology journals partially cited journals in the health/nursing/medicine area. The middle green path demonstrates that papers published in medicine/medical/clinical journals partially cited journals in the molecular/biology/genetics area. The bottom green path reveals that articles published in medicine/medical/clinical journals partially cited journals in the health/nursing/medicine area.

timeline view map in Supplementary Figure 1 provides insights into the burst of citations for specific publications during different periods. It helps identify emerging themes that attract significant interest within a given timeframe. Notably, while most references experienced bursts earlier, documents focusing on fetal hemoglobin expression and third-generation sequencing continue to be in a state of burst, indicating that these research topics are currently the most up-to-date and relevant. The most highly cited publications is the article titled "Thalassemia" published by Ali T. Taher in the Lancet in 2018. This review summarizes the clinical treatment and management of β-thalassemia, covering aspects such as blood transfusion, iron chelation, splenectomy, and hemopoietic stem-cell transplantation.[18] Another highly cited article is titled "Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia", published in *The New England Journal of Medicine* in 2018. This study focused on transducing autologous $CD34^+$ cells with the LentiGlobin BB305 vector in 22 patients with TDT. Based on the results, 12 patients with a non-β^0/β^0 genotype were able to stop receiving red blood cell transfusions, and 9 patients with a β^0/β^0 genotype or two copies of the IVS1-110 mutation, the median annualized transfusion volume was reduced by 73%.[19] Top 10 highly cited publications in the field of β-thalassemia are listed in Table 5.

Analysis of Research Hotspots

Reference co-citation analysis is a valuable method for assessing progress and identifying research hotspots within a specific field. After the consolidation process, a total of 1288 keywords were identified. The top 30 most popular terms are shown in Table 6, which may be divided into four categories: pathophysiological processes, therapeutic approaches, clinical diagnosis, and risk populations. As depicted in the CiteSpace Strongest Citation Burst Map (Figure 5A), the keywords are presented based on their average appearing year (AAY). Several keywords such as HPLC, polymerase chain reaction, myocardial iron (AAY 2014), transfusion-dependent thalassemia, and mixed chimerism experienced frequent appearances around 2017. Keywords like genome, guideline, and target showed high frequency around 2019. The keywords gene editing, hematopoietic stem, and coronavirus disease 2019 (COVID-19) were frequently mentioned between approximately 2020 and 2021. Additionally, Figure 5B illustrates the VOSviewer overlay visualization map of the high-frequency keywords. Each keyword is assigned a color that indicates its density.

Table 5 Top 10 Highly Cited Publications in the Field of β-Thalassemia

Rank	Title	Author	Journal	Year	Citation	ACY,
1	Thalassemia	Taher AT, et al	*Lancet*	2018	177	35.40
2	Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia	Thompson AA, et al	*NEJM*	2018	121	24.20
3	Updates of the HbVar database of human hemoglobin variants and thalassemia mutations	Belinda G, et al	*Nucleic Acids Research*	2014	118	13.11
4	Identification of erythroferrone as an erythroid regulator of iron metabolism	Léon K, et al	*Nature Genetics*	2014	82	9.11
5	β-Thalassemia	Raffaella O, et al	*Genetics in Medicine*	2017	74	12.33
6	Transcription factors LRF and BCL11A independently repress expression of fetal hemoglobin	Takeshi M, et al	*Science*	2016	72	10.29
7	Gene Therapy in a Patient with Sickle Cell Disease	Jean AR, et al	*NEJM*	2017	72	12.00
8	Thalassemia	Douglas RH, et al	*Lancet*	2012	71	6.45
9	Reducing TMPRSS6 ameliorates hemochromatosis and β-thalassemia in mice	Shuling G, et al	*JCI*	2013	67	6.70
10	BCL11A enhancer dissection by Cas9- mediated in situ saturating mutagenesis	Matthew CC, et al	*Nature*	2015	63	7.88

Abbreviations: NEJM, The New England Journal of Medicine; ACY, average citations per year; JCI, The Journal of Clinical Investigation.

Table 6 Top 30 Keywords in the Field of β-Thalassemia

Rank	Keywords	Occurrences	Total link strength	Rank	Keywords	Occurrences	Total link strength
1	Beta thalassemia	2222	7837	16	Intermedia	175	804
2	Thalassemia	1753	7051	17	Gene	169	603
3	Iron overload	848	4068	18	Ineffective erythropoiesis	168	791
4	Disease	429	1745	19	Population	164	718
5	Anemia	425	1723	20	Deferasirox	163	980
6	Children	384	1451	21	Hydroxyurea	161	768
7	Diagnosis	287	1047	22	Bone marrow transplantation	155	669
8	Sickle cell disease	550	2333	23	Erythropoiesis	154	604
9	Hemoglobinopathies	261	1001	24	Hepcidin	147	710
10	Prevalence	256	1039	25	Deferoxamine	255	1618
11	Mutations	403	1537	26	Mouse model	128	569
12	Hemoglobin	479	2959	27	Survival	125	684
13	Oxidative stress	223	774	28	Disorders	124	539
14	Therapy	209	915	29	Prenatal-diagnosis	124	501
15	Complications	195	1032	30	Serum ferritin	120	686

Discussion

Principal Information

The analysis of scientific publications related to β-thalassemia using CiteSpace and VOSviewer software reveals several important findings. Firstly, it has been steadily increasing over the past decade, with a peak in 2021. This indicates a growing interest and focus on β-thalassemia among researchers. In terms of country productivity, the United States and China emerge as the leading contributors, with a significant number of publications. Italy follows closely as the third-ranked country. Thailand and Iran have notable presences among the top institutions with the most publications. Collaboration between countries, particularly between Thailand and China, is evident in the research output. Notably, China has surpassed the United States in terms of annual publications since 2022, highlighting the increasing attention and research efforts in β-thalassemia from Chinese researchers.

However, when considering the impact and citations of publications, it is observed that authors from Italy and the United Kingdom dominate the top-cited authors' list, while none of the most cited authors are from China. This suggests

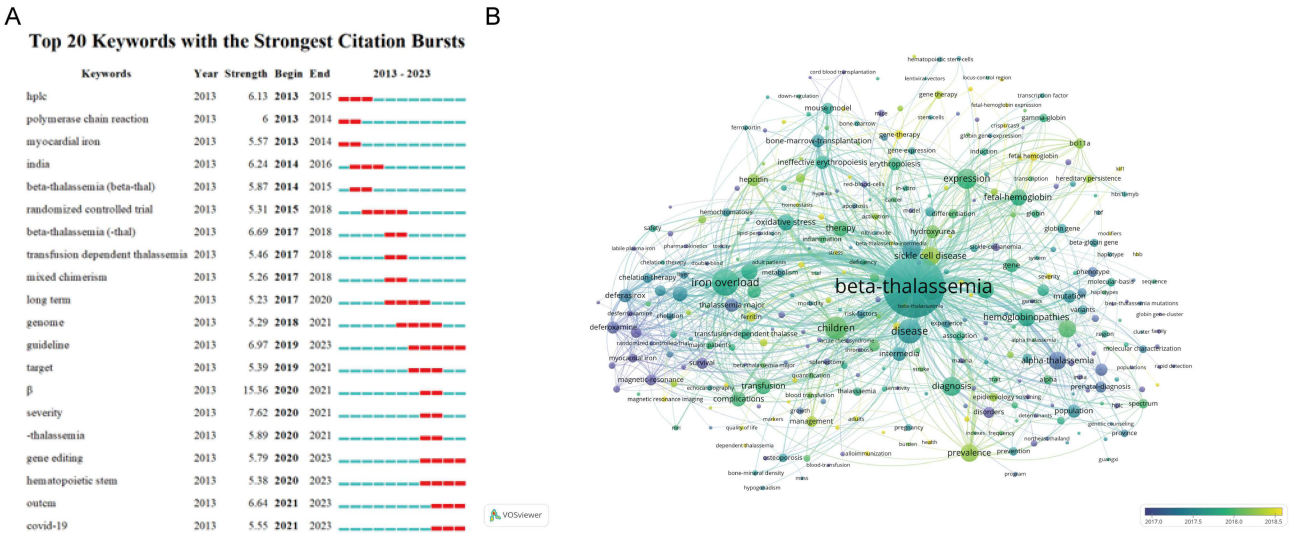

Figure 5 Keyword overlay visualization map for the field of β-thalassemia using VOSviewer. (**A**) Top 20 keywords with the strongest citation bursts by CiteSpace. A rectangle represents a year. Green rectangles represent time intervals, whereas red rectangles indicate burst duration. (**B**) Visualization of keywords in an overlay in VOSviewer.

that although Chinese researchers are publishing more papers, their research impact and influence in the field are still limited. To enhance their international influence, Chinese researchers need to focus on improving the quality of their research. Regarding journals, Hemoglobin emerges as the most productive journal in terms of the number of publications. However, the quality of these publications may not be particularly high due to the prevalence of spontaneous gene mutation cases in β-thalassemia. On the other hand, Blood stands out as the most cited journal, indicating its prominence and authority in the field of β-thalassemia. Researchers in this field should consider targeting high-impact journals like *Blood* to maximize the reach and visibility of their work.

Research Hotspots and Frontiers

Among the high-frequency keywords, risk population, children, and prevalence stand out as representatives of the research hotspots in the field of β-thalassemia. Thalassemia is a group of genetic disorders of hemoglobin that were originally endemic in the tropics but are now found worldwide due to migration patterns.[20] Understanding the population at risk, particularly children is crucial in addressing the challenges associated with thalassemia. During the early stages of fetal development, different types of hemoglobins, such as $\beta_2\varepsilon_2$, $\alpha_2\varepsilon_2$, and $\beta_2\gamma_2$, are formed in erythroid cells primarily located in the yolk sac. The erythropoiesis site shifts from the liver and spleen to the bone marrow during fetal development. This transition, known as "the switch of hemoglobin", involves a shift from γ-globin to β-globin expression and is completed by the time the baby reaches 6 months.[21] Severe forms of α-thalassemia can lead to intrauterine death unless advanced measures are taken to save the fetus. In contrast, β-thalassemia typically manifests in childhood due to "the second switch of hemoglobin". In the past, due to limitations in diagnostic and therapeutic techniques, most affected children faced significant challenges in surviving into adulthood. However, with advancements in screening and prevention programs for thalassemia, the landscape has improved.

In terms of pathophysiological mechanisms, the high-frequency keywords in β-thalassemia research include iron overload, anemia, gene mutations, and IE These factors have been reported to contribute to the development of pathological β-thalassemia, with iron overload being a particularly vital factor. Research has shown that unstable α-globin chain tetramers accumulate in erythroid cells in β-thalassemia, leading to premature cell death both inside and outside the bone marrow. This process also involves the formation of reactive oxygen species and structural membrane deformities, which result in the exposure of senescence antigens.[22,23] Changes in the concentrations of several mediators involved in the control of erythropoiesis have also been noted in circumstances of inefficient erythropoiesis, in addition to changed signal pathways such as overexpression of Janus kinase (JAK)/ Protein Kinase B(AKT)/(Target of Rapamycin) mTOR and (Mothers Against Decapentaplegic 2/3)SMAD2/3. Molecular regulators like heat shock protein 70 (HSP70) and the α-Hb stabilizing protein exert a protective role, according to a recent study.[24] Medullary expansion, bone deformities, and a decrease in bone mass are caused by increased proliferation of erythroid precursors in the bone marrow. Additionally, compensatory hematopoietic points in the spleen, liver, and other tissues with hematopoietic potential are activated, resulting in splenomegaly and hepatomegaly.[25] Reticuloendothelial cells release more iron when hepcidin levels are lower because this promotes iron redistribution and dietary absorption. Ultimately, this leads to iron overload, causing cellular and organ damage.[26,27] The non-transferrin-bound iron enters various cell types, such as cardiomyocytes, hepatocytes, pancreatic β-cells, and anterior pituitary cells. The accumulation of iron generates reactive oxygen species, leading to damage to lipids, proteins, DNA, and subcellular organelles, as well as cellular dysfunction, apoptosis, and toxicity in target organs.[28]

In the first decade of life, β-thalassemia major is fatal due to the complex pathophysiology underlying its symptoms. Understanding these pathophysiological mechanisms is crucial for developing effective therapeutic strategies to reduce the impact of β-thalassemia. Additionally, chronic hemolytic anemia resulting from β-thalassemia can lead to acute complications, including cholelithiasis and negatively affect growth, organ function, and vascular health.[29] Erythroid cells are exposed to senescence antigens such as phosphatidylserine due to IE, which has the potential to cause thrombosis. Patients with thalassemia have hypercoagulability and vascular symptoms such as venous thrombosis and pulmonary hypertension as a result of dysfunctional platelets and coagulation systems.[30] Furthermore, recent research has uncovered an association between thalassemia and autoimmune diseases, implicating specific mutations and molecular pathways. Rheumatoid arthritis, multiple sclerosis, celiac disease, and autoimmune hemolytic anemia have all been

linked to thalassemia.[31] The underlying cause of this hyperlink may be abnormalities in cellular immunity in thalassemia patients, including altered $CD8^+/CD4^+$ lymphocyte ratios, impaired innate effector activities of phagocytes, and suppression of lymphocyte development. These findings highlight the broader impact of β-thalassemia beyond its primary pathophysiological mechanisms, encompassing complications related to coagulation, vascular function, and the potential involvement of autoimmune processes.

The keywords with the strongest citation bursts, identified by CiteSpace, highlight key areas of hot research in the field of β-thalassemia. High-performance liquid chromatography (HPLC), polymerase chain reaction (PCR), and myocardial iron have emerged as important topics of investigation. Full blood count (FBC), reticulocytes, hepatorenal function assessment, iron, ferritin, and transferrin levels are all used in thalassemia screening. The mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) derived from automated analyzers are useful for rapidly and cost-effectively identifying cases that require further investigation. Most carriers of β-thalassemia exhibit MCV <79 fl and MCH <27pg. HPLC is a diagnostic technique used to assess HbA_2, HbF, and discover abnormal hemoglobins. It is frequently used in the diagnosis of thalassemia and the detection of pathogenic variations.[18] To determine α- and β-globin mutations, PCR-based molecular analysis or DNA sequencing is used, validating the diagnosis and allowing genotype/phenotype correlations. β-thalassemia is linked to over 350 mutations, while gene deletions occurring less commonly.[32,33] For validating the diagnosis, determining mutant hemoglobins, clarifying difficult cases, and enabling prenatal diagnosis, molecular techniques have emerged as the gold standard.[34]

Among the treatment strategies, two prominent keywords that emerged were drug therapy and hematopoietic stem cell transplantation (HSCT). The combination of iron-chelation therapy with regular blood transfusion has significantly increased the survival rate and lifespan of transfusion-dependent thalassemia (TDT) patients. Currently, there are three available iron chelators: deferoxamine, which was the first clinically approved chelator and has been in use since the 1980s; oral deferasirox and deferiprone. These chelators help in reducing iron overload, a major concern in thalassemia patients. Studies have also explored the potential of JAK_2 as a target for treating IE Preclinical studies have shown promising results, and a clinical trial involving 30 TDT patients demonstrated that treatment with ruxolitinib, a JAK_2 inhibitor, led to a sustained reduction in spleen size with manageable adverse reactions.[35] The only curative therapy available for people with β-thalassemia is HLA-matched HSCT. However, for patients without matched sibling donor, the use of unrelated donors and umbilical cord blood as alternative sources of hematopoietic stem cells is increasingly being considered.[36] However, HSCT carries significant risks, including Graft-versus-Host Disease (GVHD) and graft failure, making it a high-risk and costly procedure.[37]

The discovery and development of the CRISPR-Cas9 gene-editing system in 2012 have revolutionized the field of gene editing and sparked numerous clinical trials. CRISPR entered its first human clinical trial in 2020 to remove mutations causing Leber's congenital amaurosis, a major breakthrough.[38] Gene therapy for β-thalassemia is inserting a vector containing the healthy β-globin or γ-globin gene into hematopoietic stem cells to promote the formation of normal red blood cells. Several clinical trials have been conducted and are ongoing to explore the potential of gene therapy in treating β-thalassemia. A young male patient with transfusion-dependent β^E/β^0-thalassemia participated in the first clinical trial in 2007. Hemoglobin levels in the patient ranged from 8.5 to 9 g/dl one year later, when they were no longer dependent on blood transfusions.[39] Subsequent clinical trials, such as HGB-204 and HGB-205 sponsored by Bluebird Bio, utilized an improved vector called LentiGlobin BB305. The early results of these trials have shown promising efficacy and a favorable safety profile.

Techniques for genome editing have been created to disrupt or directly correct certain genetic mutations found in the DNA of cells. Researchers are exploring genome editing to replicate mutations that cause hereditary persistence of fetal hemoglobin (HPFH), a condition that may help alleviate anemia symptoms in β-thalassemia patients.[40,41] These strategies include targeting the BCL11A gene, making small deletions in the β-globin gene promoter region to prevent transcription factors binding, introducing point mutations in the β-globin promoter region, and altering other transcription factors such as KLF1, MYB, SOX6, and GATA-1 to reduce their effectiveness in suppressing β-globin gene expression and globin gene switching.[37] Clinical studies utilizing CRISPR-Cas9 gene editing for the treatment of β-thalassemia have shown encouraging results. In one such study, autologous $CD34^+$ hematopoietic stem cells were edited with CRISPR, resulting in the creation of CTX001, which was used in the treatment process. In a trial involving 15 individuals,

including those with severe genotypes, results showed transfusion independence and significant increases in both total hemoglobin and fetal hemoglobin levels.[42,43] In two patients with the most severe genotype of β-thalassemia, a second Phase 1/2 trial conducted in China showed that gene editing was effective, producing high quantities of HbF, bringing hemoglobin levels back to normal, and enabling the patients to stop receiving blood transfusions.[44] Base editing is another emerging tool in genome editing that allows for specific editing of DNA sequences without DNA template or double-stranded breaks. The −28 (A > G) mutation in β-thalassemia has been successfully corrected using base editing methods, which has also increased the synthesis of β-globin in hematopoietic stem and progenitor cells.[45] Similarly, base editing was used to carry out particular mutations that undermined the BCL11A and KLF1 binding sites, increasing the quantity of γ-globin.[46,47] However, gene therapy and genome editing still face challenges and concerns. These include vector-triggered immune responses, technological limitations, high costs, regulatory issues, and ethical considerations regarding the heritability of edited genes.[48,49]

Among the top 20 burst keywords identified between 2013 and 2023, it is noteworthy that topics related to coronavirus disease 2019 (COVID-19) have seen a significant surge since 2019. Patients with thalassemia may be more susceptible to infections due to the dysfunctional immune system, splenectomy, and adrenal hypofunction.[50] The COVID-19 epidemic has had a severe influence on various countries' critical healthcare systems, which has a direct or indirect impact on the lives of thalassemia patients. Due to transportation restrictions, patients have difficulties in accessing necessary medications and blood transfusions. Delays in referral to healthcare centers are particularly concerning, as regular blood transfusions are vital for the survival of TDT patients. Furthermore, the economic hardships caused by the pandemic have worsened the financial struggles of TDT patients, with job losses making it even more challenging for them to seek necessary treatment.[51] The challenges faced by patients undergoing long-term blood transfusion and iron chelation therapy during the COVID-19 pandemic highlight significant access to care issues that merit further study and discussion.

Conclusions

In conclusion, the quantity of publications and citations indicates that β-thalassemia research has garnered significant scientific interest over the past decade. Notably, the University of Mahidol, Chiang Mai, and Milan have been the most productive institutions, making substantial contributions to the advancement of this field. Although Hemoglobin is the main journal for β-thalassemia research publications, Blood is the journal that receives the most co-citations, indicating the need for more high-quality studies in the area. The analysis of research hotspots highlights the importance of iron overload, anemia, gene mutations, and IE in the pathogenesis of β-thalassemia. Exploring the interactions between these mechanisms may provide valuable insights for future research endeavors. The application of gene editing therapy in the treatment of β-thalassemia has become an increasing concern, suggesting that this is an attractive field for further research. This bibliometric analysis provides a comprehensive overview of the current state of β-thalassemia research and its future directions. By highlighting key research hotspots and suggesting areas for further exploration, it offers valuable guidance to both clinicians and researchers in advancing the field.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Statement

This article does not contain any studies with human or animal participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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