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GLOBAL TRENDS IN HEMOPHILIA RESEARCH

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Abstract: The hemophilias are the most common X-linked inherited bleeding disorders, and if not managed properly, they can lead to chronic disease and lifelong disabilities. The hemophilias remains a hot topic in the field of hematology. This bibliometric study aimed to investigate the current status of publications on haemophilia. The goal of this study was to retrieve data from journals that were indexed in the Web of Science (WoS; Thomson Reuters, New York, NY, USA) database. Keywords related to "Hemophilia" were used. The time span was set from 1970 to 2021. Data pertaining to growth of publications, the most active countries and institutions, the most cited journals, and mapping of publications and keywords were analyzed. Retrieved data were analyzed to present various bibliometric indicators while maps were visualized using the VOS viewer technique. The Hirsch (H) index and the impact factor (IF) of the publishing journal were used as indicators of impact of publications. A total of 7.736 articles were retrieved with an average of 22.06 and total of 170.624 citations. H index was found as 149. Study searches the publications in the period between 1970 and 2020 first article was in the year 1970. The leading country on journal number is the United States of America (USA) with (n=2474; 31.98%), followed by England (11.69%), Germany (9.76%), Italy (8.59%), Canada (6.81%), France (6.67%). Most of the retrieved articles were from research areas of Hematology (n=4706; 60.83%), Cardiovascular System/Cardiology (11.46%), General Internal Medicine (10.12%), Pediatrics (4.52%), Genetics Heredity (n4.25%). The number of publications from the development countries should be increased and research on hemophilia should be supported. The landscape of this illness is changing continuously, and bibliometric studies like the one presented are a useful tool for highlighting developments inside this field.

Keywords: Bibliometric analysis, Citation analysis, Hemophilia

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1. Introduction

Plasma deficits of coagulation proteins are of enormous concern to the hematologist, entailing a lifelong bleeding tendency with significant morbidity and death if not effectively treated, among the more than 6000 human disorders caused by single gene defects (Jackson, et al., 2018). According to the standards used in the United States (less than 200000 instances countrywide) and Europe, inherited coagulation deficits are rare disorders (less than 5 cases per 10,000 persons in the general population) (Khosla et al., 2018).

Haemophilia A and B are X-linked congenital illnesses caused by a loss or shortage of clotting factor VIII (FVIII) or IX (FIX). The severity of the condition is dictated by the amount of FVIII or FIX that is reduced, which is determined by the sort of causal mutation in the genes that encode the factors (F8 and F9, respectively). Bleeding (spontaneous or after trauma) into major joints such as ankles, knees, and elbows is a defining clinical feature, especially in untreated severe forms, and can lead to the development of arthropathy. Intracranial hemorrhage, as well as bleeds into internal organs, can be fatal (Berntorp et al., 2021). According to a recent report on the global distribution of hemophilias, the disease is more common than previously thought: 17.1 cases per 100,000 males with HA for all degrees of FVIII deficit, 3.8 cases per 100000 of HB, and a prevalence of 6 cases per 100000 for HA and 1.1 cases per 100000 for HB of individuals with total plasma factor insufficiency, indicating a more severe clinical phenotype (Iorio et al, 2019).

Hemophilia treatment became a success story in the 1970s, when plasma-derived concentrates of coagulation factor VIII (FVIII) and factor IX (FIX) became available for the treatment of bleeding in patients with hemophilia A and B. When the first recombinant coagulation factors were developed in the 1990s, this optimistic scenario was solidified in terms of increased safety and availability. This meant that prophylactic regimens might be used to avoid bleeding instead of only treating it when it happened. Prophylaxis became the evidence-based standard of care after its superiority was demonstrated in two randomized clinical trials. These advancements have resulted in a patient's life expectancy approaching that of the general male population in high-income countries (Mannucci, 2020).

This bibliometric study aimed to investigate the current status of publications on hemophilia.

2. Material and Methods

The goal of this study was to retrieve data from journals that were indexed in the Web of Science (WoS; Thomson Reuters, New York, NY, USA) database. The WOS Core Collection was used to retrieve comprehensive bibliometric data and the SCI-EXPANDED, SSCI, A & HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI indexes database, which has previously been regarded the optimal database for bibliometrics (Alkan et al., 2021; Öntürk et al., 2021; Özlü, 2022).

Keywords related to "Hemophilia" were used in a search query in the WOS search engine. For more accurate results "United Kingdom English and United States English words used. The time span was set from 1970 to 2021. Data pertaining to growth of publications, the most active countries and institutions, the most cited journals, and mapping of publications and keywords were analyzed.

This study was carried out to retrieve data about the journals with dataset as in the title "dataset: TI=(hemophilia)" in the WOS search engine searched between 1970 and 2021. In this study, the selected keywords to be used in the WOS search engine were those related to the "hemophilia". We used the search query and got 20645 different type of results and analyzed according to documents types and year they published. After we deducted from 20645 entries to only the journal articles 7736. Retrieved data were analyzed to present various bibliometric indicators while maps were visualized using the VOS viewer technique. The Hirsch (H) index and the impact factor (IF) of the publishing journal were used as indicators of impact of publications.

3. Results

3.1. General Information

A total of 20645 publications were retrieved, and 37.472% of them articles. Search the publications in the period between 1970 and 2020 first article was in the year 1970. Distribution of publication showed in Figure 1.

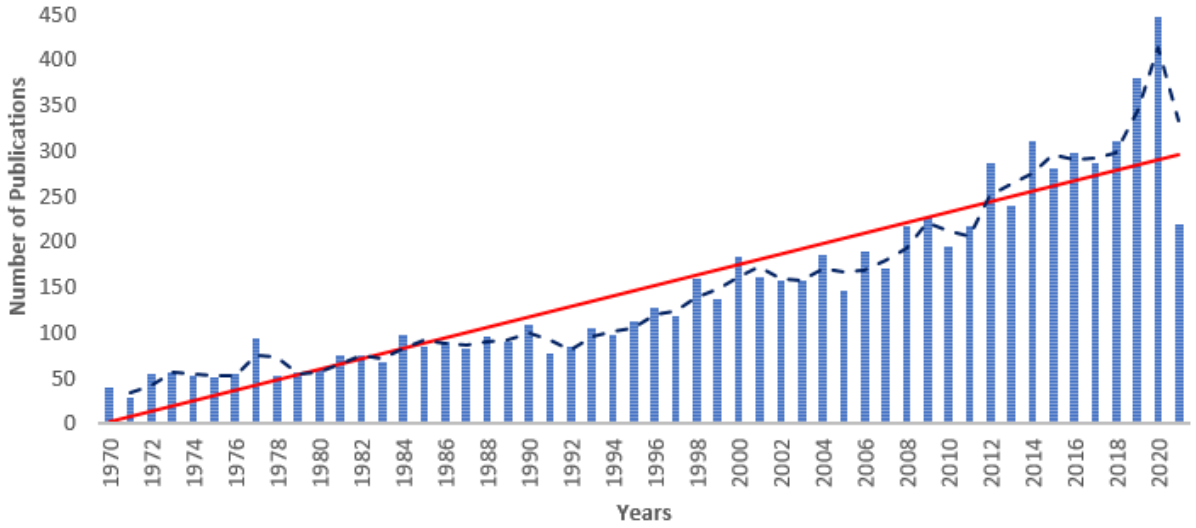

Figure 1. Graphics of publication frequency by years between 1970 and 2021. Black dashed line express the moving median. Red line express the trend line.

3.2. Detailed Information

3.2.1. Detailed analysis of the articles

A total of 7736 articles were retrieved with an average of 22.06 and total of 170624 citations. H index was found as 149. Study searches the publications in the period between 1970 and 2020 first article was in the year 1970. 39 Article was published in 1970 (Figure 2).

Most of the retrieved articles were from research areas of Hematology (n=4706; 60.83%), followed by Cardiovascular System/Cardiology (n=887; 11.46%), General Internal Medicine (n=783; 10.12%), Pediatrics (n=350; 4.52%), Genetics Heredity (n=329; 4.25%) and the rest was various areas (Table 1).

3.2.2. Active countries and organizations

The leading country on journal number is the United States of America (USA) with (n=2474; 31.98%), followed by England (n=905; 11.69%), Germany (n=755; 9.76%), Italy (n=665; 8.59%), Canada (n=527; 6.81%), France (n=516; 6.67%). Other 113 countries which around the globe were (n=5385; 69.61%) (Table 2).

The University of London was the leader organisation on hemophilia research (Table 3).

3.2.3. Citing analysis and international collaborations

The list of active countries includes countries from all over the world, including North and South America, Europe, Asia, and Africa.

Papers co-authored by authors from multiple countries were designated as "international collaborations." The map depicts the international collaborative network (Figure 3) Using the VOSviewer approach, an investigation of international cooperation for active nations with at least one document revealed that there were clusters of international collaboration (Figure 3).

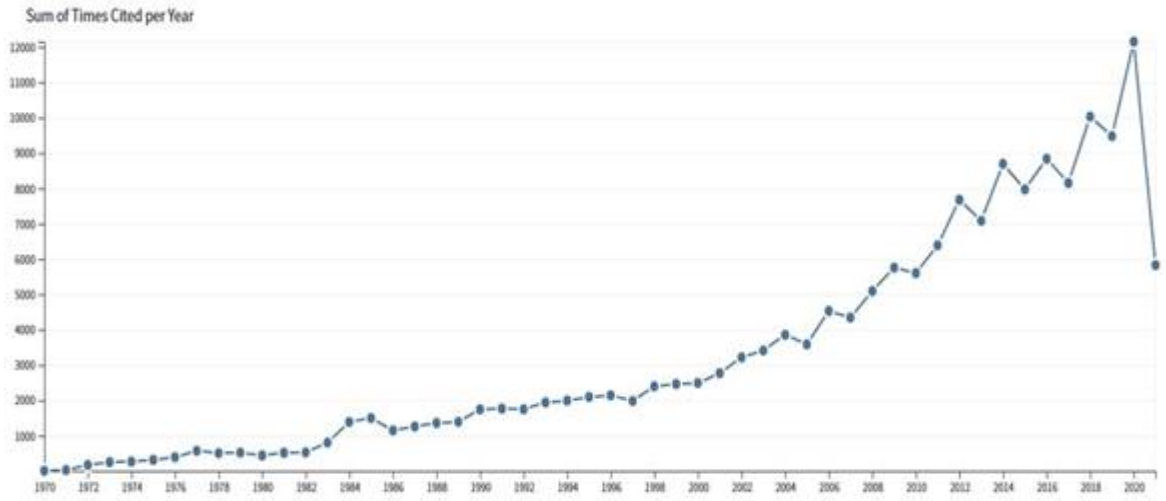

Figure 2. Graphics of citation by years between 1996 and 2021. Line express the cite number.

Table 1. The top 10 research areas of the articles

Research Areas	Frequency	% of 7736
Hematology	4706	60.832
Cardiovascular System/ Cardiology	887	11.466
General Internal Medicine	783	10.122
Pediatrics	350	4.524
Genetics Heredity	329	4.253
Research Experimental Medicine	301	3.891
Surgery	199	2.572
Health Care Sciences Services	166	2.146
Immunology	150	1.939
Oncology	141	1.823

Table 2. The ranked countries on hemophilia research

SCR	Country	Frequency	Percentage of total publications (n=7736)
1st	USA	2474	31.98
2nd	England	905	11.699
3rd	Germany	755	9.76
4th	Italy	665	8.596
5th	Canada	527	6.812
6th	France	516	6.67
7th	Netherlands	483	6.244
8th	Japan	400	5.171
9th	Sweden	392	5.067
10th	Spain	319	4.124

SCR= Standard Competition Ranking. Equal countries were given the same ranking number.

The total number of citations for the articles that were found was 170.624, with an average of 22.06 citations per article. The Hirsch index of the articles that were found was 149. The number of citations increased with time, and annual citation growth of "haemophilia" and "hemophilia" was modest until 2012, then increased in the last decade. The annual increase of the terms "haemophilia" and "hemophilia" is depicted in the graph. The year with the most citations was 2020, with a total of 12154 citations (Figure 2). The United States of America was the most frequently mentioned country (Table 4 and Figure 4).

3.2.4. Journals

The articles from the journal of New England Journal of Medicine were cited mostly. The detailed information on top 20 of the most cited articles and journals were given in Table 5.

4. Discussion and Conclusion

The hemophilias are the most common X-linked inherited bleeding disorders, and if not managed properly, they can lead to chronic disease and lifelong disabilities. Children encounter challenges and issues that are distinct from those faced by older children and adults.

Table 3. The top ranked organizations on hemophilia research

Organizations-Enhanced	Frequency	% of 7737
University of London	382	4.937
University College London	293	3.787
Lund University	275	3.554
Utrecht University	263	3.399
Irccs Ca Granda Ospedale Maggiore Policlinico	246	Mar.18
University of North Carolina	242	3.128
University of North Carolina Chapel Hill	232	2.999
Utrecht University Medical Center	227	2.934
University of Bonn	216	2.792
Skane University Hospital	207	2.675
University of Pennsylvania	200	2.585
Assistance Publique Hopitaux Paris	196	2.533
Novo Nordisk	191	2.469
Mcmaster University	178	2.301
University of Toronto	178	2.301
University of Milan	177	2.288
University of California System	166	2.146

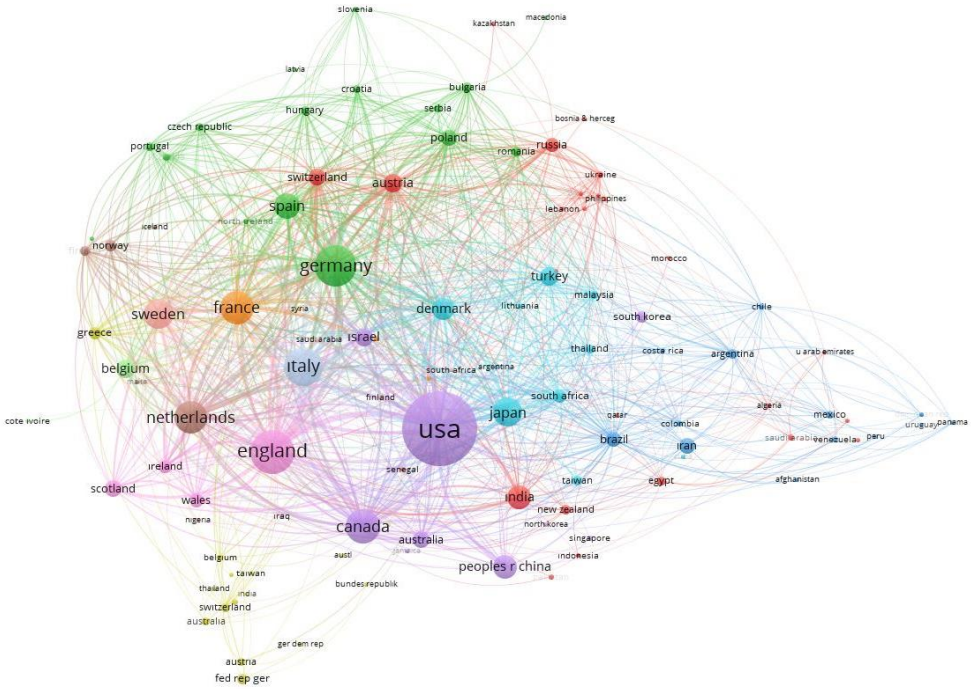

Figure 3. Co-authorship network visualization map across nations with at least one publication on "hemophilia" and "haemophilia." Collaboration is indicated with lines connecting countries. Stronger cooperation are indicated by thicker lines. Countries with a larger circle or text size had a higher level of international collaboration.

Table 4. Top 10 countries according to citations

Country	Number of documents	Number of citations
USA	2358	80390
England	832	30263
Germany	732	19879
Italy	644	18828
Netherlands	464	17352
Sweden	373	14681
Canada	513	14557
France	480	14053
Spain	288	6913
Japan	363	6760

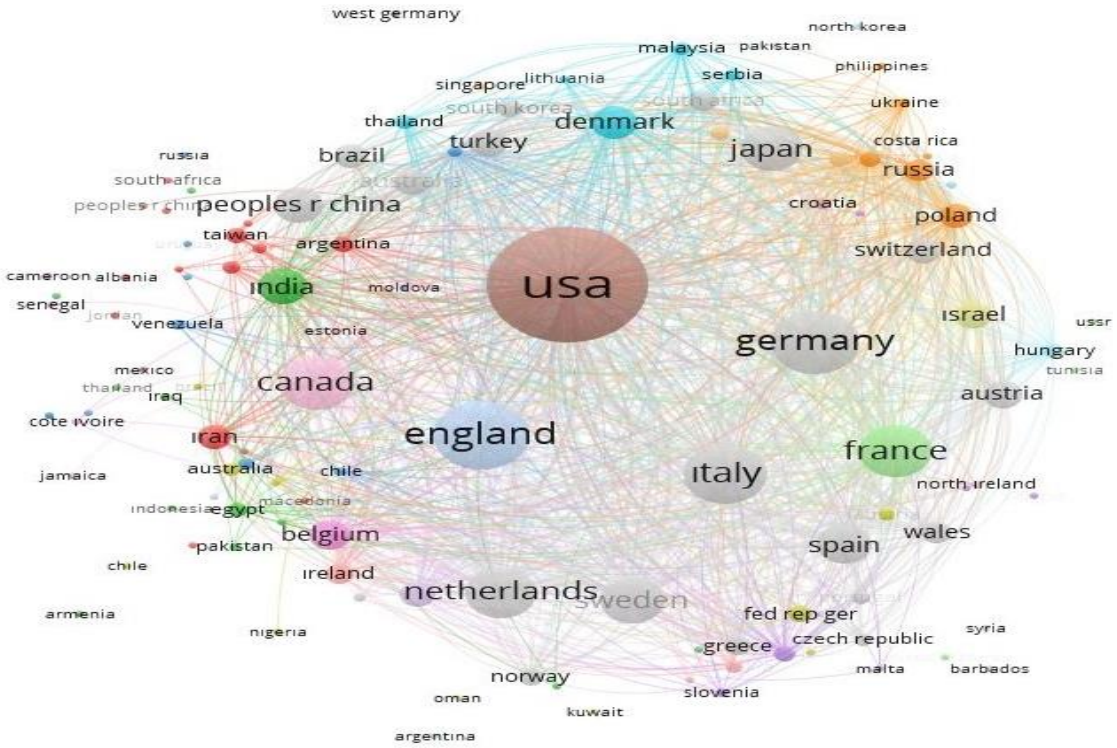

Figure 4. Countries having at least one publication on "haemophilia" are represented by a network visualization map of citations. Collaboration is indicated with lines connecting countries. Stronger cooperation are indicated by thicker lines. Countries with a larger circle or text size had a higher level of international collaboration.

Table 5. Top 20 of most cited articles and journals

Source Title	Article Title	Times Cited
Nature Medicine	Successful transduction of liver in hemophilia by AAV-factor IX and limitations imposed by the host immune response	1308
New England J Medicine	Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia	1238
New England J Medicine	Adenovirus-Associated Virus Vector-Mediated Gene Transfer in Hemophilia B	1111
Haemophilia	Guidelines for the management of hemophilia	1076
New England J Medicine	An Improved Method For Prenatal-Diagnosis Of Genetic-Diseases By Analysis Of Amplified Dna-Sequences - Application To Hemophilia-A	781
Nature Genetics	Evidence for gene transfer and expression of factor IX in haemophilia B patients treated with an AAV vector	777
J Clinical Investigation	Immunologic Differentiation Of Classic Hemophilia (Factor-Viii Deficiency) And Von-Willebrands Disease - With Observations On Combined Deficiencies Of Antihemophilic Factor And Proaccelerin (Factor V) And On An Acquired Circulating Anticoagulant Against Antihemophilic Factor	765
J Internal Medicine	25 years experience of prophylactic treatment in severe hemophilia-a and hemophilia-b	741
New England J Medicine	Long-Term Safety And Efficacy Of Factor Ix Gene Therapy In Hemophilia B	669
Nature Genetics	Inversions Disrupting The Factor-Viii Gene Are A Common-Cause Of Severe Hemophilia-A	648
Nature	Hemophilia-a resulting from denovo insertion of l1 sequences represents a novel mechanism for mutation in man	642
New England J Medicine	A Prospective-Study Of Human Immunodeficiency Virus Type-1 Infection And The Development Of Aids In Subjects With Hemophilia	547
Blood	AAV-mediated factor IX gene transfer to skeletal muscle in patients with severe hemophilia B	526
Lancet	1-deamino-8-d-arginine vasopressin - new pharmacological approach to management of hemophilia and von-willebrands disease	516
Haemophilia	The epidemiology of inhibitors in haemophilia A: a systematic review	475
Nature Medicine	Long-term correction of canine hemophilia B by gene transfer of blood coagulation factor IX mediated by adeno-associated viral vector	439
New England J Medicine	Targeting of Antithrombin in Hemophilia A or B with RNAi Therapy	434
New England J Medicine	Recombinant Factor-Viii For The Treatment Of Previously Untreated Patients With Hemophilia-A - Safety, Efficacy, And Development Of Inhibitors	418
New England J Medicine	Emicizumab Prophylaxis in Hemophilia A with Inhibitors	395
Blood	Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation	384

Bleeding episodes are still the most prevalent diagnostic trigger in children, but bleeding sites vary by age. Intracranial hemorrhage (ICH), circumcision, and venipuncture bleeding are prevalent in newborns, whereas joint disease and head trauma are common in older children and adolescents. In order to institute effective care and adopt preventative efforts, it is critical to be aware of clinical symptoms and therapeutic problems. The most difficult consequences are now inhibitors and ICH, and prophylaxis is emerging as the best preventive management technique (Kulkarni and Soucie, 2011). Until the 1960s, the median life expectancy was 30 years, but improved understanding of the disorder and the development of effective therapy based on prophylactic replacement of the missing factor resulted in a paradigm shift, and today, people with haemophilia can expect a nearly normal life expectancy and quality of life. Nonetheless, in a significant proportion of patients, the formation of inhibitory antibodies to infused factor remains a significant challenge to overcome. Finally, gene therapy for both types of haemophilia has made significant progress and is on the verge of becoming a reality (Berntorp et al., 2021).

This study sought to give a bibliometric perspective of literature on haemophilia between the years 1970 - 2021. To accomplish this, we used the well-known WOS database, which has been used in previously published bibliometric studies (Alkan et al., 2021; Alkan-Çeviker et al., 2021; Köse et al., 2021; Öntürk et al., 2021; Mızrakçı, 2022; Özlü, 2022; Yıldız, 2022).

In the area of hematology, similar bibliometric studies were also conducted (Latif et al., 2018; Okoroiwu et al., 2020; Seo et al., 2020; Chen et al., 2021). However, there was no relevant study on haemophilia in the literature available.

Bibliometric analysis has recently been used to identify field frontiers and evaluate the achievements of publications, organisations, and nations. In the bibliometric analysis method, internet databases are frequently utilised. It can also provide details on research clusters, current topics of interest, and emerging topic trends. Visualization techniques can be used to analyse and map a variety of databases (Dindar Demiray et al., 2021; Gürler et al., 2021; Köylüoğlu et al., 2021; Küçük et al., 2021; Mızrakçı et al., 2021; Özlü, 2021; Akyüz et al., 2022; Durgun et al., 2022). In this study both visualization techniques and data analyses were done.

Although this disease has been known since since the 1800s, as the main developments in medicine are in recent years, publications after 1970s were analyzed in this study. Our study showed that publications "haemophilia" have been increasing and growing rapidly in the past decade and in the past ten years, over two-thirds of all documents have been published.

Altough the University of London was the leader organisation on hemophilia research, the USA was the most cited and most productive country on hemophila research. This may be due to the excess of institutions and economic support in the USA. In addition, there were no development countries in the list of top 10 ranked countries.

An article's overall impact to the clinical world is measured by the number of citations it receives (Chen et al., 2021; Latif, et al., 2018). This study showed that the articles on haemophilia had increasing number of citations. This shows that this topic is an important research area.

In conclusion, the number of publications from the development countries should be increased and research on hemophilia should be supported. The landscape of this illness is changing continuously, and bibliometric studies like the one presented are a useful tool for highlighting developments inside this field.

Limitations

This bibliometric analysis has a lot of disadvantages. PubMed, Embase, Scopus, and the Cochrane Library are among the electronic databases that are not searched or evaluated. Articles written in languages other than English were also excluded. Despite the fact that the majority of the research in this study are written in English, this limitation may lead to a publishing bias. Finally, because several potentially influential articles were published recently and could not be mentioned frequently, influential publications were not referred to frequently enough.

Author Contributions

Concept: C.Ö. (50%) and G.C. (50%), Design: C.Ö. (50%) and G.C. (50%), Supervision: C.Ö. (50%) and G.C. (50%), Data collection and/or processing: C.Ö. (50%) and G.C. (50%), Data analysis and/or interpretation: C.Ö. (50%) and G.C. (50%), Literature search: C.Ö. (50%) and G.C. (50%), Writing: C.Ö. (50%) and G.C. (50%), Critical review: C.Ö. (50%) and G.C. (50%), Submission and revision C.Ö. (50%) and G.C. (50%). All authors reviewed and approved final version of the manuscript.

Conflict of Interest

The authors declared that there is no conflict of interest.

Ethical Approval/Informed Consent

The study complied with the Helsinki Declaration, which was revised in 2013. Ethics committee approval is not required as there is no human or animal research.

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