Anesthesiology and
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The 100 most cited articles in malignant hyperthermia

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Abstract

Bibliometric analysis is a widely used method to identify and evaluate the trends and characteristics of the scientific publications in a specific research field. A large volume of literature has been published in the field of malignant hyperthermia (MH). However, no bibliometric studies have been conducted to describe the characteristics of highly cited articles on MH. Therefore, this study aims to identify the 100 most frequently cited articles about malignant hyperthermia, describe their characteristics, and investigate research trends. Searches were performed in Web of Science Core Collection, Google Scholar, and Scopus from January 1900 to March 2023, with no language limitation. The 100 most frequently cited articles were selected and analyzed. Characteristics including publication year, journal, impact factor, authors, authors countries, citation number, journal citation indicator, study design, and topics were analyzed. For the 100 most cited articles, the number of times each article was cited ranged from 84 to 1254, with a median of 133. The number of articles published peaked in the decade of 1990s (*n* = 30). The articles were published in 39 journals, with Anesthesiology leading with 13 publications and then the British Journal of Anaesthesia with 12 publications. The authors were from 21 countries, led by the United States (*n* = 37). Forty articles focused on genetic susceptibility screening, 27 articles were about MH etiology, and 11 articles were about diagnosis and treatment. The mortality rate of MH and dantrolene availability are known to be uneven worldwide. This may partly be explained by the fact that scientific publications primarily report by authors from developed countries. This bibliometric analysis highlights the characteristics of the most influential research related to malignant hyperthermia, providing a reference for conducting future research.

Keywords Bibliometric analysis, Malignant hyperthermia, General anesthesia, Volatile anesthetic agents, Most-cited articles

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1 Introduction

Malignant hyperthermia (MH) is an uncommon, progressive, and life-threatening crisis that occurs in genetically susceptible individuals. MH is usually triggered by volatile inhalational anesthetics and/or succinylcholine use [1]. The reported incidence of MH ranging from 1:10,000 to 1:250,000, with the mortality rate up to 60%–90% if left untreated [2]. In June 1962, Denborough et al. reported in British Journal of Anaesthesia a familial clustering of MH in 10 of 38 members following anesthesia [3]. The mechanism of MH involves uncontrolled release of calcium from the sarcoplasmic reticulum of skeletal muscle after administration of triggering

agents [2]. Clinical features of MH are characterized by rapid progression of hypermetabolic hypercapnia, persistent contraction of the skeletal muscle, tachycardia, and rapid elevation of the body temperature over 40 °C. The severity of MH is variable; however, patients may develop myoglobinuria with subsequent acute kidney injury, compartment syndrome, severe acidosis and hyperkalemia, refractory arrhythmias with circulatory failure, disseminated intravascular coagulation, coma, and death without timely and effective therapy [4]. However, much about the pathogenesis and mechanisms still needs to be elucidated. Therefore, it is essential to quantitatively identify the state of current MH research.

Bibliometric analysis evaluates research performance by analyzing the citation data of published articles in a quantitative manner [5]. With the citation data, the impact of the articles and the authorship of highly cited articles can be accurately determined. Bibliometrics can not only help scholars quickly comprehend important research areas and trends within a particular field of research, but also allows evaluation of characteristics such as the key authors, journals, and significant topics within the research field, and more importantly, builds a foundation for further research [6]. Influential articles that have shaped medical practice and inspired new research ideas can also be identified.

Bibliometric analysis has been applied in many fields to identify the most frequently cited articles. These research fields include neuroscience [7], critical care medicine [8], pain medicine [9], orthopedics [10], enhanced recovery after surgery [11], and COVID-19 vaccines [12]. To our knowledge, no bibliometric studies have been conducted on MH, and a search of PubMed using the medical subject headings (MeSH) 'Bibliometrics' and 'Malignant hyperthermia' retrieved no articles. Therefore, this study aimed to perform a bibliometric analysis of the 100 most frequently cited articles in MH, hoping to gain an overview picture of the current research status and identify future research opportunities.

2 Materials and methods

We searched for articles from the ISI Web of Science Core Collection (Philadelphia, PA, USA), Google Scholar, and Scopus with the search strategy: TS (Topic) = ("malignant hyperthermia" OR "malignant hyperpyrexia") OR ("hyperthermia" AND "anesthesia") OR ("hyperthermia" AND "anaesthesia") OR ("anesthesia" AND "hyperthermia") OR ("anaesthesia" AND "hyperthermia") OR ("hyperthermia" AND "malignant") OR ("porcine stress syndrome") OR ("caffeine halothane muscle contracture test") OR ("in vitro contracture test") OR ("anaesthetic death" AND "family") OR ("anesthetic death" AND "family"), from January 1900 to March 2023, no language

limitation. Items were searched in title, abstract, and author keywords fields. The inclusion criteria were scientific articles and review publications from index journals. Letters, editorial materials, notes, abstracts, proceeding papers, case reports were excluded. The first 500 records were selected and sorted in descending order of citations.

A complete literature list and full text of all the articles were downloaded. Two independent researchers (Y.H. and Y.Q.) reviewed the titles and abstracts of all the articles and removed irrelevant ones. The irrelevant articles were defined as the articles that contains no information in the title or abstract related to malignant hyperthermia, in vitro contracture test (IVCT), and caffeine halothane muscle contracture test (CHCT); and articles beyond the scope of anesthesia specialty. After data screening, a database containing the top 100 most cited articles was established (Fig. 1).

The 100 most frequently cited articles related to MH were identified and then manually reviewed with a modified approach to the methods described by Xue et al. [13]. Characteristics of each article were evaluated. These characteristics include publication year, authors' countries, journal, Impact Factor (takes 2021 as the standard), Journal Citation Indicator (JCI), authors, study design, and citation number. If multiple authors or countries were involved in a study, all authors and counties listed in each study were entered into the research database and calculated in the analysis. JCI is a new metric designed by Clarivate for comparing the relative citation performance of journals across different disciplines.

The data used in this study are publicly available and contain no protected health information. Therefore, Peking University Third Hospital review board approval was not sought.

### 2.1 Patient and public involvement
No patient was involved.

2.2 Statistical analysis
SPSS software (version 21.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. The data were expressed as the median (interquartile range) or number (%). Continuous variables were analyzed with the independent sample t-test and categorical variables with the χ^2 test. Correlation coefficients (r) were calculated with Pearson's test. A P value of < 0.05 was considered statistically significant.

3 Results
After the initial search with the publication date limit set from January 1900 to March 2023, 10,893 publications were retrieved from the ISI Web of Science Core Collection. 29,700 and 10,715 records were retrieved from the
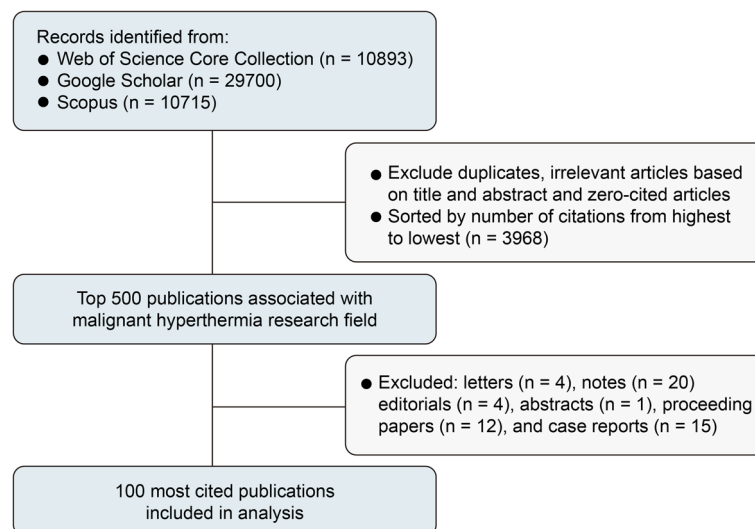
Fig. 1 Flowchart of the screening process

Google Scholar and Scopus, respectively. After literature retrieval and screening for duplication, the 100 most frequently cited articles (Online Resource 1) were selected for further review and their characteristics were analyzed. The 10 most frequently cited articles focusing on MH are listed in Table 1.

3.1 Year of publication and country of origin

The publication year of the 100 most frequently cited articles on MH ranged from 1962 to 2015. Four articles were published before 1970, and three articles were published after 2010. The 1990s were the most productive decade, with 30 articles published (Fig. 2A). The largest number of citations ($n = 1254$) for a single article was for an article published in 1991 [14]. The number of citations was highest (6190) in the decade from 1991 to 2000.

Authors from the United States published the most articles ($n = 37$), followed by Canada ($n = 20$), England ($n = 20$), Germany ($n = 16$), Ireland ($n = 10$), Switzerland ($n = 10$) and Australia ($n = 10$) (Fig. 2B). In total, the authors who contributed to the 100 most frequently cited articles were from 21 countries (Fig. 2C).

3.2 Journals publishing the 100 most frequently cited articles

These articles were published in 39 journals with the top 10 journals listed in Table 2. The journals were predominantly within the field of anesthesia, led by Anesthesiology with 13 articles, followed by the British Journal of Anaesthesia with 12. In addition, Journal of Biological Chemistry, Canadian Anaesthetists Society Journal, and Genomics published eight, five, and five articles, respectively. The impact factor of these journals ranged from

1.375 to 202.731. Fifteen of the 100 most cited articles were published in journals with an impact factor > 20.

3.3 Authorship

The 10 authors with the largest number of published articles about MH within this study are shown in Table 3. The author who published the largest number of articles was Britt ($n = 9$, five as the first author) and Maclennan ($n = 9$, six as the last author).

Maclennan's articles received the highest number of total citations (3027). In third place was McCarthy with eight articles (three as the last author). In fourth place were Heffron who had seven articles, with a considerable number of total citations of 1410.

3.4 Study design and topics

The 100 most frequently cited articles covered a range of topics. Forty articles focused on genetic susceptibility screening, 27 articles on MH etiology study, and 11 on diagnosis and treatment. Among the eight articles related to MH diagnosis, four involved caffeine halothane contracture test, two focused on in vitro contracture test; one was intended for the non-invasive molecular genetic tools based on ryanodine receptor gene mutation, and the other one focused on the development of a clinical grading scale. The other articles included 25 reviews and three clinical guidelines (Fig. 3). The number of times each article was cited ranged from 86 to 1254 (median, 111) for articles about genetic susceptibility screening, from 87 to 553 (median, 142) for reviews, and from 96 to 356 (median, 141) for articles focusing on diagnostic and treatment.

Han *et al. Anesthesiology and Perioperative Science*   (2023) 1:32

Page 4 of 9

Table 1 Top 10 most cited articles focusing on malignant hyperthermia

Rank	Citation	Title	Corresponding author	Country	ACR	JCI
1	1254	Fujii J, Otsu K, Zorzato F, et al. Identification of a mutation in porcine ryanodine receptor associated with malignant hyperthermia. Science. 1991,253(5018):448–451 [14].	D.H. Maclennan	Canada	38.0	10.15
2	553	Gronert GA. Malignant hyperthermia. Anesthesiology. 1980,53(5):395–423 [15].	G.A. Gronert	United States	12.6	2.84
3	483	MacLennan DH, Duff C, Zorzato F, et al. Ryanodine receptor gene is a candidate for predisposition to malignant hyperthermia. Nature. 1990,43(6258):559–561 [16].	D.H.MacLennan	Canada	14.2	10.86
4	430	Britt BA, Kalow W. Malignant hyperthermia: a statistical review. Canadian Anaesthetists Society Journal. 1970,17(4):293–315 [17].	B. A. Britt	Canada	8.0	1.66
5	401	MacLennan DH, Phillips MS. Malignant hyperthermia. Science. 1992,256(5058):789–794 [18].	D.H.MacLennan	Canada	12.5	10.15
6	371	McCarthy TV, Healy JM, Heffron JJ, et al. Localization of the malignant hyperthermia susceptibility locus to human chromosome 19q12-13.2. Nature. 1990,343(6258):562–564 [19].	T.V. McCarthy	Ireland, Germany, England	10.9	10.86
7	356	Kalow W, Britt BA, Terreau ME, et al. Metabolic error of muscle metabolism after recovery from malignant hyperthermia. Lancet. 1970,2(7679):895–898 [20].	W. Kalow	Canada	6.6	21.87
8	354	Larach MG, Localio AR, Allen GC, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology. 1994,80(4):771–779 [21].	M.G. Larach	United States, Canada, Australia, England, Denmark	11.8	2.84
9	349	Krause T, Gerbershagen MU, Fiege M, et al. Dantrolene–a review of its pharmacology, therapeutic use and new developments. Anaesthesia. 2004,59(4):364–373 [22].	T. Krause	Germany	17.5	3.03
10	343	Ellis FR, Halsall PJ, Ording H, et al. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. British Journal of Anaesthesia. 1984,56(11):1267–1269 [23].	F. R. Ellis	England, Denmark, Sweden, Ireland, Germany, Austria, France, Netherlands	8.6	2.63

ACR (annual citation rate) was defined as the number of citations divided by the number of years since the article was published up to 2023

JCI Journal Citation Indicator

Among the articles focusing on screening for susceptibility to MH, 25 articles focused on ryanodine receptor 1 (RYR1) gene mutations, six on chromosome analysis, and three on other methods. The first article about the caffeine halothane contracture test within the list was published in Lancet in 1970 [20], while the earliest report of dantrolene therapy was published in Anesthesiology in 1982 [24]. In terms of animal models, 22 articles used the swine model, and four articles used the mouse model. The first article using the swine model was published in British Journal of Anaesthesia in 1969 [25]. The first murine model of MH was reported by Chelu et al. in FASEB Journal in 2006 [26] and this article was cited 133 times.

3.5 Citation numbers

The number of times each article was cited ranged from 84 to 1254, with a median of 133. The annual citation rate (ACR) was defined as the number of citations divided by the number of years since the article was published up to 2023. The ACR of the articles ranged from 1.7 to 38.0 citations/year.

There was one article that had been cited over 1,000 times, 26 articles cited more than 200 times, and 80 articles cited more than 100 times. The article with the highest citation and annual citation rate was a comparative study by Fujii et al. published in Science in 1991 [14], and the article had 1254 citations and an annual citation rate of 38.0 citations/year. The second most
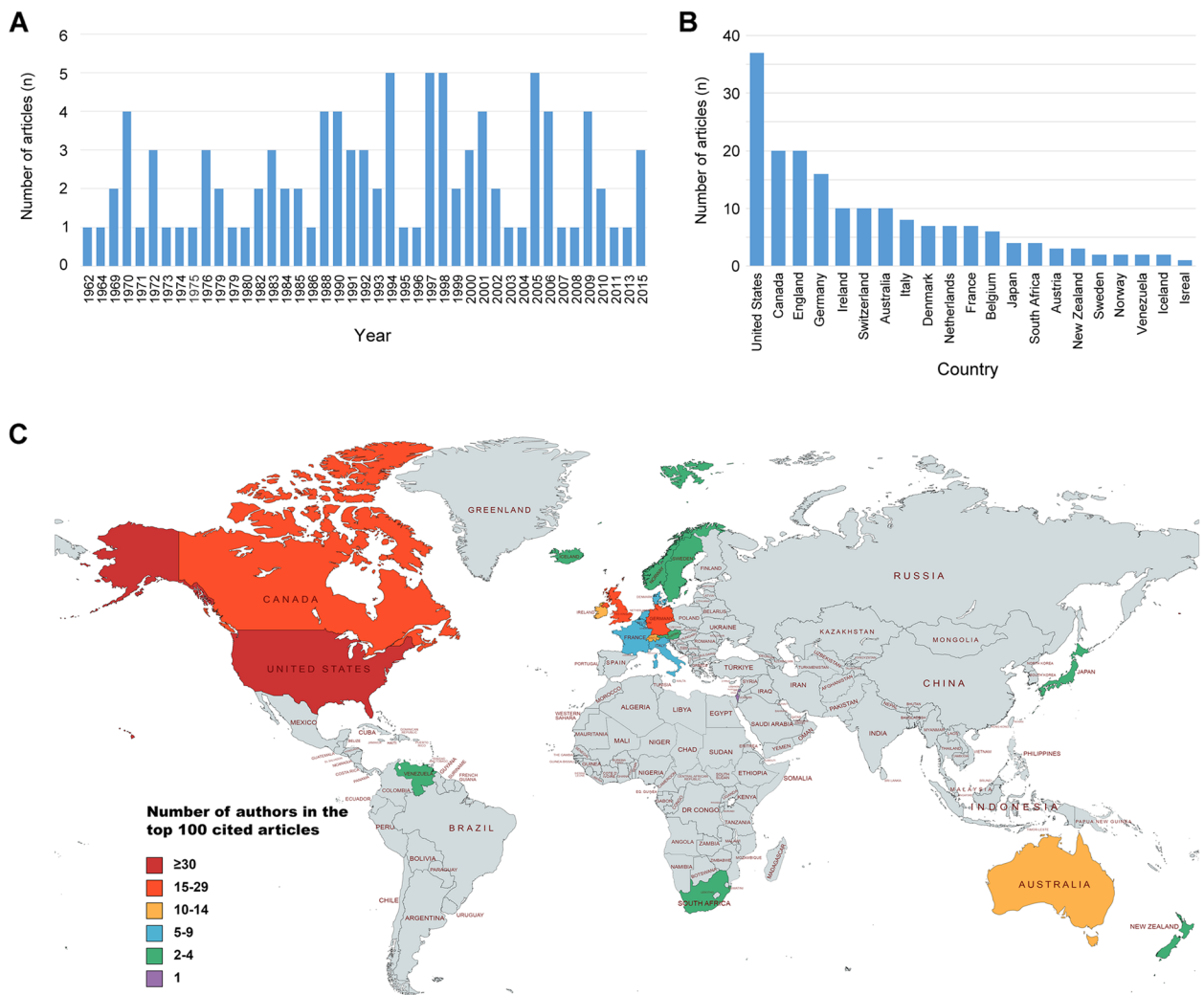
Fig. 2 Overview of the publication year and country origin distribution. **A** Publication year of the 100 most cited articles; **B**, **C** Number of articles contributed by authors from a particular country in the top 100 cited articles

Table 2 The top 10 sources contributing to the top 100 publications

Rank	Journal	No. of top 100 articles	Country	Impact factor-2021	JCI
1	Anesthesiology	13	United States	9.198	2.84
2	British Journal of Anaesthesia	12	United Kingdom	11.719	2.63
3	Journal of Biological Chemistry	8	United States	5.485	0.91
4	Canadian Anaesthetists Society Journal	5	Canada	2.306	1.66
5	Genomics	5	United States	4.310	1.21
6	Anesthesia and Analgesia	4	United States	6.627	1.95
7	Human Molecular Genetics	4	United Kingdom	5.121	1.12
8	Lancet	4	United Kingdom	202.484	21.87
9	American Journal of Human Genetics	3	United States	11.043	2.52
10	British Medical Journal	3	United States	17.215	7.15

JCI Journal Citation Indicator

cited article was by Gronert (cited 553 times and 12.6 citations/year) and was published in Anesthesiology in 1980 [15].

The most productive decade was the 1990s with the total number of citations peaking at more than 1000 in 1990 and 1991 (Fig. 4A).
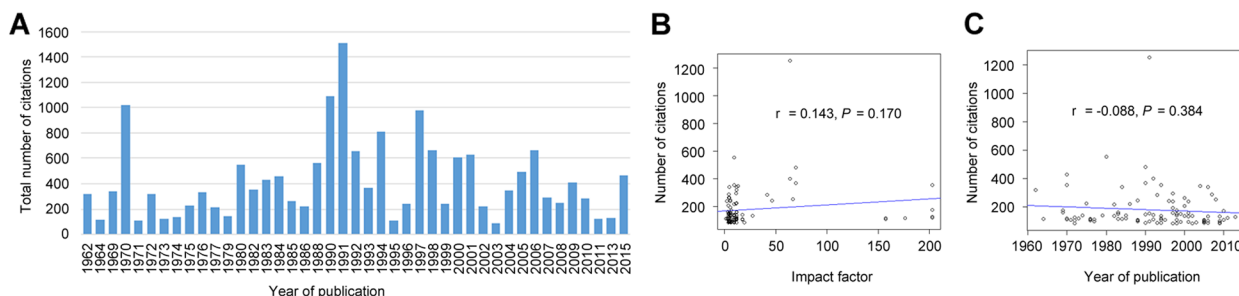
3.6 Correlation analysis

The impact factor of the journal showed no significant association with the number of top-cited articles ($r=0.143$, $P=0.170$; Fig. 4B). Similarly, no correlation was found between citation numbers and the year of publication ($r=-0.088$, $P=0.384$; Fig. 4C).

Table 3 Authors with top-10 number of papers included in the 100 most-cited

Rank	Name	Total publications	First author	Co-author	Last author	Total citations	Mean citations/ paper
1	B. A. Britt	9	5	4	0	2069	283
2	D.H. MacLennan	9	2	1	6	3027	336
3	T.V. McCarthy	8	2	3	3	1585	198
4	J. A. Heffron	7	0	6	1	1410	201
5	G.A. Gronert	6	3	2	1	1454	242
6	M. Denborough	6	3	2	1	1236	206
7	W. Kalow	6	2	1	3	1298	216
8	F. R. Ellis	6	1	5	0	1062	177
9	C.F. Louis	6	0	2	4	1145	191
10	H. Rosenberg	6	2	3	1	1225	204
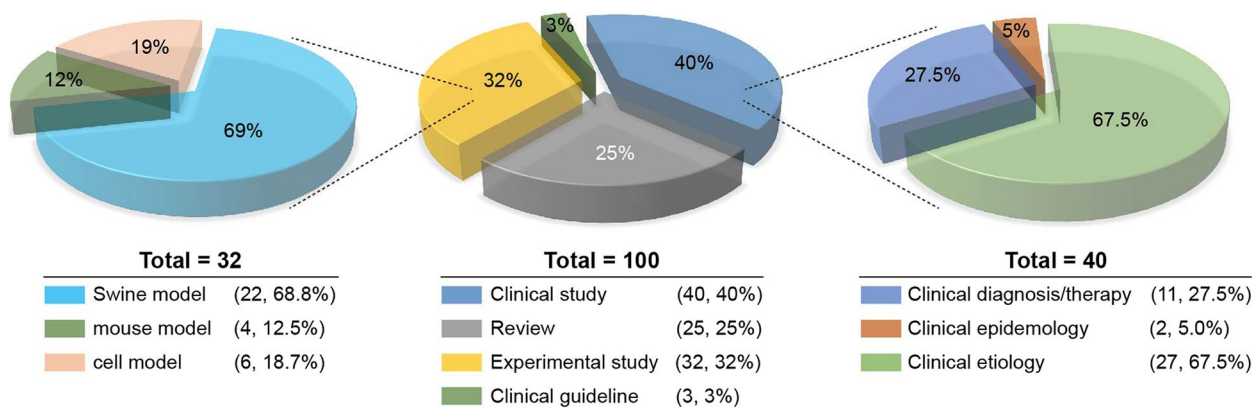
Fig. 3 Distribution of the different categories of the 100 most cited articles in malignant hyperthermia

Fig. 4 Citation analysis. **A** The total number of citations of the 100 most cited articles. **B** Linear correlation between impact factors of journals and the number of citations of articles included in the 100 most cited list. **C** Linear correlation between year of publication and the number of citations of the 100 most cited articles

3.7 Anesthesiology journals versus non-specialty journals

We compared top-cited articles published in anesthesiology journals and non-specialty journals (Table 4). There was no significant difference in total citation numbers, annual citation rate, journal citation indicator, number of authors per article, or multiple institutions between anesthesiology and non-specialty journals. There was no significant difference in study design between anesthesiology and non-specialty journals. However, all the three guidelines were published in journals of the anesthesiology specialty.

4 Discussion

The 100 most frequently cited articles on MH up to March 2023 were identified. The results indicate that both the number of top-cited articles and the citation rate peaked in the 1990s. To our knowledge, our study is the first to analyze the influential articles in MH research and will help scholars to identify the important achievements in this field and clarify the developing trends in future research.

Bibliometric analysis is a useful quantitative method to help scholars review the research history of a certain field, recognize the progress of important research, and inspire the direction of further research. However, because the citation number for any given article is strongly affected by the influence of the journal, the number of citations of any given article may not be proportionally associated with the scientific value of the article [27]. Other factors such as the country of author, language, and gender may also affect the citation number [28]. Still, citation analysis

Table 4 Comparison of articles from anesthesiology journals and non-specialty journals

Parameter	Anesthesiology (*n* = 37)	Non-specialty (*n* = 63)	*P* value
Quantitative [median, (interquartile range)]			
Total Citations, number	1718 (110)	184 (163)	0.687
ACR, number	6.0 (3.7)	6.9 (6.3)	0.417
JCI	2.54 (0.50)	4.35 (6.37)	0.113
Author, number	6 (5)	7 (5)	0.275
Qualitative (n, %)			
Multiple institutions	23 (62.2%)	44 (69.8%)	0.570
Article focus			0.062
Clinical study	16 (43.2%)	24 (38.1%)	
Review article	10 (27.0%)	15 (23.8%)	
Experimental study	8 (21.6%)	24 (38.1%)	
Clinical guideline	3 (8.1%)	0 (0)	

ACR (annual citation rate) was defined as the number of citations divided by the number of years since the article was published up to 2023

JCI Journal Citation Indicator

is a widely accepted method of determining the merits of an article or journal despite these disadvantages.

The initial report on MH was published by Denborough MA in The Lancet in 1960, which we did not exclude due to its letter format. Subsequently, the authors provided a more comprehensive case report in the British Journal of Anaesthesia in 1962. While our methodology involved excluding case reports, we made an exception for these earliest descriptions of MH as they hold significant importance and have received substantial citations. Therefore, we included Denborough MA's report from the British Journal of Anaesthesia and Saidman LJ's report from the Journal of the American Medical Association in our analysis. The 100 most frequently cited articles were published between 1962 to 2015. The most productive decade was 1991 to 2000 when 30 articles were published and this is the decade when the highest number of citations (6190) appeared, indicating that this field gained great attention at that time. This increase in the number of MH articles may be associated with the comparative study published by Fujii et al. in 1991 that focused on a single point mutation of the RYR1 gene in swine skeletal muscle [14]. This article was the most cited in the field of MH and marked a new level of genetic susceptibility research.

Some of these impactful articles were groundbreaking; one important article by Larach et al. in 1994 highlighted a clinical grading scale for the diagnosis of MH [21]. Because the clinical signs and laboratory findings with MH can be variable, the clinical diagnosis of MH is difficult. They developed a standardized method, clinical grading scale, for qualitatively estimating the possibility of MH. However, the value of this clinical grading scale is dependent on the typical presentations including rigidity, muscle breakdown, respiratory acidosis, temperature increase, and cardiac involvement. Therefore, early diagnosis of MH event remains a great challenge and a reliable perioperative diagnostic tool needs to be developed in the future. A multicenter study by Kolb et al. in 1982 introduced dantrolene therapy for MH and was published in Anesthesiology [24]. This article demonstrated that dantrolene therapy effectively reverses the pathophysiology of MH and resulted in a significant reduction in mortality that would be expected otherwise in MH patients. The therapeutic effects of dantrolene on MH are mediated by the muscle relaxant effect via inhibition of the calcium release from the sarcoplasmic reticulum into cytoplasm of skeletal muscle [29].

Authors from the United States published the most top-cited articles, followed by Canada, England, and Germany. Ten journals published the majority (61/100) of the 100 most cited articles. Among these journals, six were from the United States (36 published articles), two from

the United Kingdom (20 published articles), and one from Canada (five published articles). The majority of the 100 most cited articles originated from North America, Europe, and Oceania, followed by Asia, Africa, and South America. The distribution of the authors of the 100 most cited articles is relatively concentrated in a few developed countries. Ranking by the number of published articles, the top 10 authors published a total of 69 articles, contributing nearly one-third of the 100 most cited articles. In recent years, researchers have explored the role of multiple genetic variants in the progress of MH [30]. This emphasizes the urgent need for future research focused on the pedigree analysis for genetic variants and functional analysis.

The impact factor of the journal and the year of publication are generally suspected to influence the number of citations. We then performed the linear correlation to evaluate the influence of these two factors on the number of citations. A r value of 0.143 ($P = 0.170$, Fig. 4B) implies that there is no linear correlation between the impact factor and the number of citations. Also, no significant correlation ($r = -0.088$, $P = 0.384$, Fig. 4C) existed between the year of publication and the number of citations. These data indicate that the number of citations selected as a reliable index to evaluate the influence of the publications.

Influential journals (with high-impact factor) tend to receive more manuscripts from scholars. This is likely because they may better highlight research results and prompt acknowledgement of the authors' work. The impact factor of journals is a crucial predictor for citations. Fifteen articles were published in the high-impact factor journals (impact factor > 20). Twenty-one articles were published in journals with an impact factor between 10 and 20. Thirty-three articles were published in journals with an impact factor between 5 and 10. Anesthesiology ranks first with 13 articles, of which seven were clinical research, covering a wide topic of genetic, diagnostic, therapeutic studies. Second in line is the British Journal of Anaesthesia, who published the most clinical guidelines ($n = 3$). The Journal of Biological Chemistry came third, publishing early (1988 to 2005) experimental studies ($n = 8$) of swine MH models. These results further indicate that scholars prefer to cite articles from certain core journals within their specialty.

Among the 100 most frequently cited articles, most of the articles were published from limited number of authors from a few countries. The mortality rate of MH and dantrolene availability are known to be uneven worldwide. Most of the highly cited articles on MH appeared in the 1990s which reflects the in-depth study of the pathogenesis of MH and the discovery of gene mutations in individuals susceptible to MH during

that period. Over the past decade, scientists have been working to identified novel genetic variants associated with MH and enhancing its genetic screening and diagnosis [31]. The emergence of dantrolene as an effective treatment for MH has contributed to the decreased mortality rate in this field to a certain extent. However, dantrolene was not available until October 2020 in China, and globally, many patients in most countries still do not have access to dantrolene [32]. A large volume of clinical studies so far has focused on the genetic variants and development of rapid and non-invasive diagnostic tools. Researchers are also committed to the deeper insight into the mechanisms of MH and effective treatment.

Therefore, based on this bibliometric analysis, the future research directions should be the development of rapid and non-invasive diagnostic tools, and raising the public concern with the availability of dantrolene.

4.1 Research limitations

There are inherent limitations to this bibliometric analysis. First, some potentially high-quality articles were published recently and thus were not cited enough times to appear in the 100 most cited articles list [33]. Thus, this study may under-estimate the impact of the articles published after 2015. Second, the topics of articles were limited to the title and keywords, which may not cover all the research fields.

5 Conclusions

The present study reviewed the development of MH research from a historical perspective. Research trends and academic milestones in this field were illustrated. Research on developing a rapid and non-invasive perioperative diagnostic tool is needed. Our study provides scholars who wish to join the field of MH with the direction to retrieve important literature.

Abbreviations

ACR	Annual citation rate
CHCT	Caffeine halothane muscle contracture test
IVCT	In vitro contracture test
JCI	Journal Citation Indicator
MeSH	Medical subject headings
MH	Malignant hyperthermia
RYR1	Ryanodine receptor 1

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s44254-023-00030-6.

Additional file 1: Table S1. List of the top 100 most cited articles in malignant hyperthermia (1900-2023).

Han *et al. Anesthesiology and Perioperative Science*   (2023) 1:32

Page 9 of 9

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
All authors declare no conflict of interests.

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