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A Bibliometric and Visual Analysis of Publications on Low-Density Lipoprotein Cholesterol Estimating Equations

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ABSTRACT

The concentration of low-density lipoprotein cholesterol (LDL-C) is recognized as a crucial factor in cardiovascular health. This study aims to conduct a comprehensive bibliometric and visual analysis to provide a comprehensive review of current research trends and patterns in this research area. We retrieved the publications from the Web of Science (WoS) database and conducted the bibliometric analyses using VOSviewer software, bibliometrix R package, and biblioshiny web tool. The analysis was conducted on 620 original articles and review papers published between 1990 and 2023 from institutions located in 62 different countries and published in 329 journals. The countries with the most articles were the US, China, and Japan. The most productive journals were Clinica Chemica Acta, Clinical Biochemistry, and Clinical Chemistry; while the most cited journals were Clinical Chemistry, Circulation, and JAMA-Journal of the American Medical Association. The co-occurrence network visualizations of keywords and terms provided a global overview of LDL-C estimating equations. The study presented provides valuable insights into potential research avenues within the examined field, serving as a foundation for future research initiatives.

Keywords: Bibliometric analysis, Cardiovascular disease, Low-density lipoprotein cholesterol, LDL-C, VOSviewer.

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Introduction

Cardiovascular diseases (CVD) cover a wide range of conditions affecting the heart and blood vessels, posing a significant global health challenge [1]. Several risk factors contribute to CVD development, including high blood pressure, diabetes, and dyslipidemia [2]. Dyslipidemia refers to irregularities in lipid levels, specifically an increase in low-density lipoprotein cholesterol (LDL-C). LDL-C concentration is recognized as a crucial factor in cardiovascular health, with higher levels associated with an increased risk of atherosclerosis and coronary artery disease. Several studies emphasize the importance of managing LDL-C levels to mitigate cardiovascular risk. As an essential component of lipid profiles, understanding and controlling LDL-C concentration play a pivotal role in cardiovascular risk assessment and preventive strategies [3, 4].

The gold standard for LDL-C measurement is ultracentrifugation followed by beta-quantification, which accurately isolates the LDL-C fraction [5]. However, this method is impractical for routine use due to its high cost, time requirements, and the need for large sample volumes and specialized equipment. The Friedewald formula, introduced in 1972, has become a global standard for LDL-C estimation in clinical practice due to its convenience and cost-effectiveness [6]. Despite its widespread use, the Friedewald formula has several limitations. It is sensitive to triglyceride levels, leading to inaccuracies, particularly in high triglyceride concentrations [7]. It tends to be less accurate in cases with low LDL-C levels, potentially resulting in unreliable LDL-C estimates [8]. Additionally, its fixed triglyceride (TG)—very low-density lipoprotein (VLDL-C) ratio does not account for individual variations, resulting in further inaccuracies in LDL-C estimation [9]. This may lead to overestimation of hypercholesterolemia prevalence compared to direct measurement methods [10]. Alternative methods like the Martin/Hopkins and Sampson formulas provide improved accuracy, particularly in cases with high triglycerides and non-fasting samples, making them valuable alternatives in clinical settings [6, 7, 11].

In Turkey, there has been a significant increase in studies focused on the validation of LDL-C formulas [6, 12]. Notably, there is a growing trend towards developing new methodologies utilizing machine models, including linear regression, artificial neural networks, Bayesian-

regularized neural networks, random forests, decision trees, and gradient-boosted trees [13-15]. These investigations indicate that machine learning algorithms offer more reliable predictions and classifications of LDL-C levels compared to traditional formulas, thereby facilitating personalized healthcare interventions with more accurately assessed cardiovascular risks in clinical applications.

Bibliometric analysis is a quantitative method for assessing scientific publications within a specific field. By applying statistical techniques to bibliographic data, it reveals patterns, trends, and relationships among academic works. This method provides insights into scholarly communication dynamics and evaluates the impact, productivity, and influence of authors, journals, institutions, and research topics. Ultimately, bibliometric analysis serves as a valuable tool for exploring scholarly publications and offers critical insights for researchers, policymakers, and institutions [16-18].

Only one systematic review and meta-analysis on LDL-C estimation has been identified in the literature. Ephraim et al. (2023) evaluated existing equations for LDL-C estimation using a random-effects meta-analysis approach [19]. To our knowledge, no bibliometric analysis specifically addressing LDL-C estimation equations exists in the literature. This study aims to provide a global overview of LDL-C estimating equations through bibliometric analysis, focusing on i) trends in article and citation volume over time, ii) prevalent research areas, iii) the most productive countries and institutions, iv) leading journals, v) highly cited papers and author collaborations, and vi) frequently used keywords and their co-occurrence networks within the field.

Materials and Methods

Data Collection and Search Strategy

The data for the analysis was retrieved from the Web of Science (WoS) database on January 1, 2024. The query employed during the scan of publications is outlined below:

(AB=("LDL-C" AND "equation") OR AB=("LDL-C Estimation") OR AB=("LDL-C estimating equation") OR AB=("Martin-Hopkins" AND "formula") OR AB=("Martin-Hopkins" AND "equation") OR AB=("Sampson" AND "formula") OR AB=("Sampson" AND "equation") OR AB=("LDL-C calculation") OR AB=("novel formula" AND "LDL-C") OR AB=("novel equation" AND "LDL-C") OR AB=("calculation of LDL-C") OR AB=("estimation of LDL-C") OR AB=("Friedewald's") OR QMTS=("Friedewald Formula") OR QMTS=("Friedewald Equation") OR QMTS=("Friedewald S Formula") OR QMTS=("Friedewald S Equation") OR QMTS=("Sampson Equation") OR QMTS=("Sampson Formula") OR QMTS=("Martin Hopkins Equation") OR QMTS=("Anandaraja S Formula"))

The pertinent data from the literature was exported to a Plain Text File (.txt) by selecting the record content, specifically, 'Full Record and Cited References'.

Bibliometric Analysis

As a result of the search query, we obtained 734 records published in the literature on LDL-C estimating equations between 1990 and 2023. Of these records, 74 records in the document types meeting abstracts, proceeding papers, editorial materials, early access, letters, book chapters and reviews, data papers, and notes were filtered. Of the remaining 660 original research and review articles, 40 were filtered because they were not written in the English language. After filtering, the remaining 620 original research and review articles in English were included in the bibliometric analyses (Figure 1). These articles had 12,347 citations, each article was cited an average of 25.6 times, and the H-index was 59. Figure 2 shows the changes in the number of articles and citations in this field over the years. It is seen that there is a general increase in both the number of articles and citations, and peak values were reached in 2022-2023. An important finding is that 316 articles were published between 2016 and 2023, accounting for 51% of the total number of articles.

For analyses such as research trends, content, and keyword analyses, we utilized biblioshiny 4.1.4 [20], a web interface for the bibliometrix R package, and VOSviewer 1.6.20 software [21].

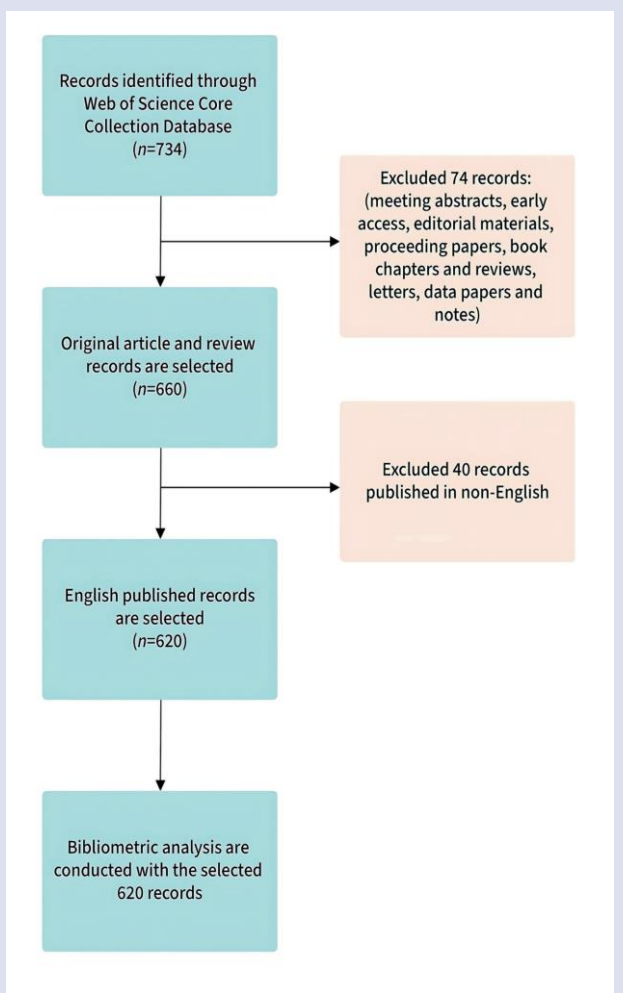

Figure 1. Flow chart of study selection process.

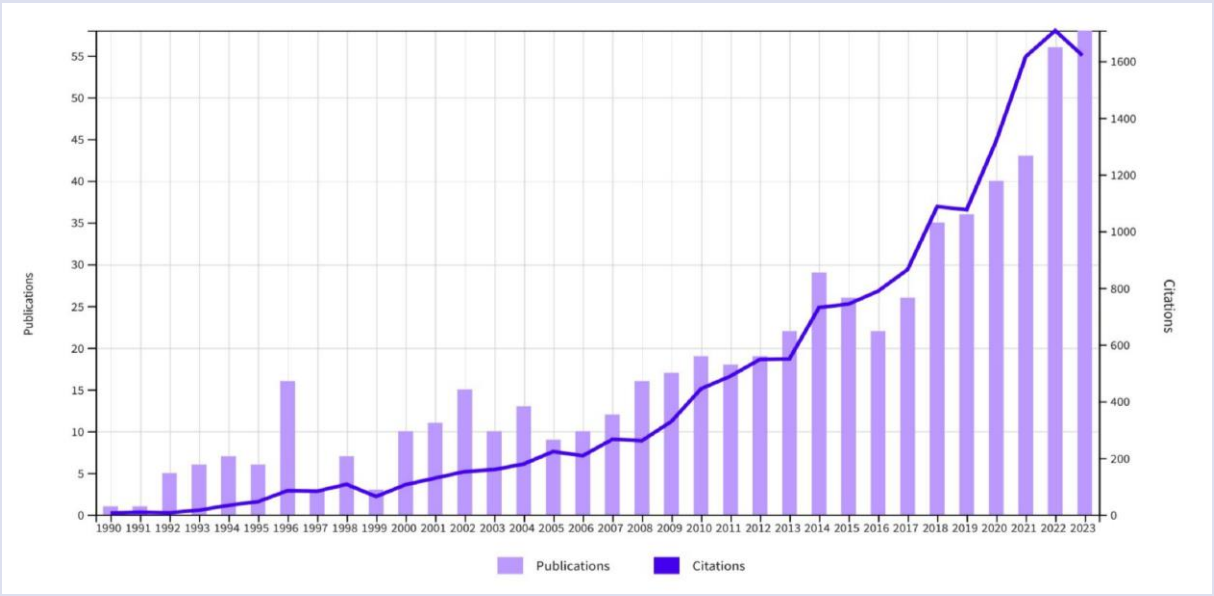

Figure 2. The number of publications per year between 1990 and 2023.

Results

Distribution of Research Areas

The 620 articles included in the bibliometric analyses were related to 57 WoS research areas. The 10 research areas with the highest number of articles were medical laboratory technology (n=120, 19.4%), cardiac & cardiovascular systems (n=114, 18.4%), medicine, general & internal (n=103, 16.6%), endocrinology & metabolism (n=62, 10.0%), nutrition & dietetics (n=47, 7.6%), pharmacology & pharmacy (n=38, 6.1%), biochemistry & molecular biology (n=36, 5.8%), medicine, research & experimental (n=29, 4.7%), science, technology & other topics (n=18, 7.6%), and public, environmental & occupational health (n=17, 2.7%).

Analysis of Main Countries and Top Country Institutions

To better understand the current state of research on LDL-C estimating equations, we conducted country- and institution-level analyses. 620 studies between 1990 and 2023 were conducted by institutions in 62 different countries. The countries with the highest number of publications were the USA (n=436), China (n=248) and Japan (n=224), while the countries with the highest average citations were the USA (n=42.8), UK (n=36.0) and Japan (n=31.5) (Table 1). When analyzed by institutions, the most productive institutes of the countries in Table 1 were Johns Hopkins University (USA, n=48), Yonsei University (South Korea, n=21), and Tehran University of Medical Sciences (Iran, n=20). When ranked based on all institutes, the top 5 universities were as follows: Johns Hopkins University (USA, n=48), Harvard University (USA, n=24), Yonsei University (South Korea, n=21), Tehran University of Medical Sciences (Iran, n=20), and National Taiwan University (Taiwan, n=17).

Table 1. Top ten countries and institutions with the highest number of publications on LDL-C estimating equations (1990-2023)

Country	Number of Articles	Total Citations	Average Article Citations	Top Country Institution	Top Institution Articles
USA	436	4,750	42.8	Johns Hopkins University	48
China	248	667	10.8	Central South University	10
Japan	224	1,450	31.5	Kyoto University	11
Spain	108	422	17.6	Universitat Autònoma de Barcelona	8
Iran	101	353	13.1	Tehran University of Medical Sciences	20
India	95	314	7.5	Carmel Medical Centre	6
South Korea	89	343	13.7	Yonsei University	21
UK	88	720	36.0	Imperial College London	13
Canada	77	602	27.4	Laval University	10
Finland	61	87	14.5	University of Turku	9

LDL-C, low-density lipoprotein cholesterol.

Most Productive and Cited Journals

The conducted analysis showed that the articles were published in 329 different journals. According to Bradford's law, journals in a particular field undergo ranking based on their publication count. Subsequently, these journals are categorized into three segments, each holding an identical number of publications. The segment with the fewest journals is denoted as the core. The core group houses the most productive journals, whereas in the remaining segments, the number of journals rises while maintaining an equivalent publication count to the core group. The Bradford Law Graph, demonstrating the most productive journals located in the core group, is given in Figure 3. According to this plot, the number of core sources with the largest number of LDL-C estimating

equations publications is 17, according to 5.2% of the entire literature.

When the citations in these articles were evaluated, the 10 journals with the highest number of citations were as follows: Clinical Chemistry, Circulation, JAMA-Journal of the American Medical Association, Atherosclerosis, Journal of the American College of Cardiology, Lancet, New England Journal of Medicine, Diabetes Care, Clinica Chimica Acta, and European Heart Journal. The number of records of the most productive and the most cited journals, as well as journal impact factors (JIF), JIF quartiles, and journal citation reports (JCR) research categories, are shown in Table 2. Of these 17 journals in the core group, 2 (12%) had an impact factor above 5, and 13 (76%) were among the top 50%. The journal with the highest number of articles was Clinica Chimica Acta (n=28, 4.5%), while the journal with the highest impact factor was Metabolism-Clinical and Experimental.

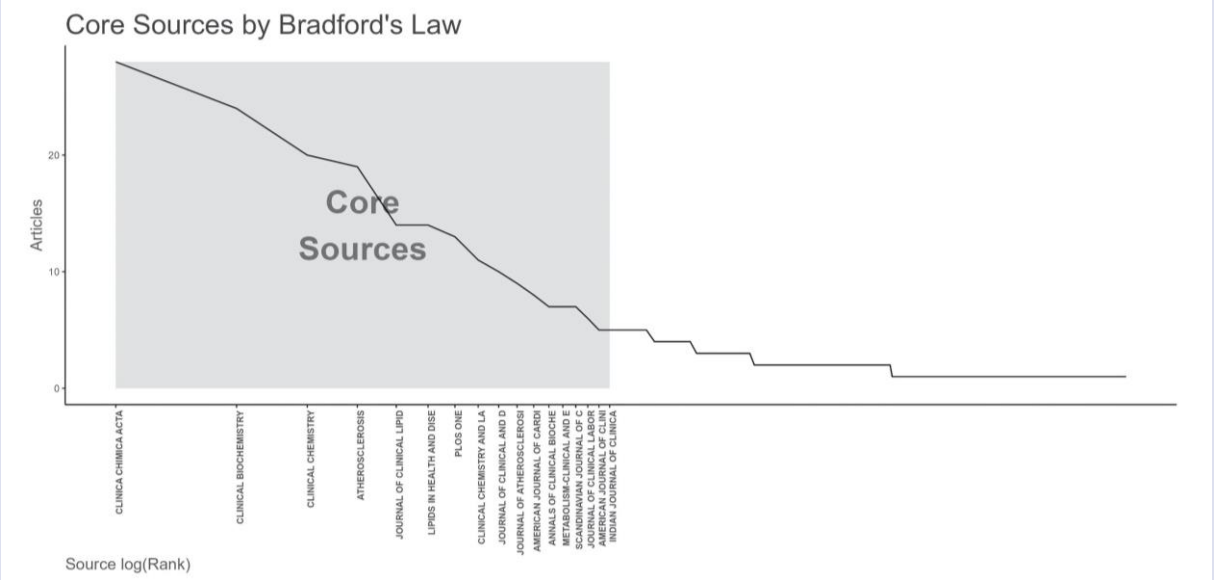

Figure 3. The core journals in the LDL-C estimating equations field based on Bradford's law.

Table 2. The most productive and cited journals for research publications on LDL-C Estimating Equations (1990-2023)

Journal Name	Number of Records	JIF (2023)	JIF Quartile (2023)	JCR Category
Most Productive Journals				
Clinica Chimica Acta	28 art.	3.2	Q2	Medical Laboratory Technology
Clinical Biochemistry	24 art.	2.5	Q2	Medical Laboratory Technology
Clinical Chemistry	20 art.	7.1	Q1	Medical Laboratory Technology
Atherosclerosis	19 art.	4.9	Q1	Cardiac & Cardiovascular Systems, Peripheral Vascular Disea
Journal of Clinical Lipidology	14 art.	3.6	Q2	Pharmacology & Pharmacy
Lipids in Health and Disease	14 art.	3.9	Q2	Biochemistry & Molecular Biology, Nutrition & Dietetics
Plos One	13 art.	2.9	Q1	Multidisciplinary Sciences
Clinical Chemistry and Laboratory Medicine	11 art.	3.8	Q1	Medical Laboratory Technology
Journal of Clinical and Diagnostic Research	10 art.	0.2	Q4	Medicine, General & Internal
Journal of Atherosclerosis and Thrombosis	9 art.	3.0	Q2	Peripheral Vascular Disease
American Journal of Cardiology	8 art.	2.3	Q2	Cardiac & Cardiovascular Systems
Annals of Clinical Biochemistry	7 art.	2.1	Q3	Medical Laboratory Technology
Metabolism-Clinical and Experimental	7 art.	10.8	Q1	Endocrinology & Metabolism
Scandinavian Journal of Clinical & Laboratory Investigation	7 art.	1.3	Q4	Medicine, Research & Experimental
Journal of Clinical Laboratory Analysis	6 art.	2.6	Q2	Medical Laboratory Technology
American Journal of Clinical Pathology	5 art.	2.3	Q2	Pathology
Indian Journal of Clinical Biochemistry	5 art.	1.5	Q4	Biochemistry & Molecular Biology
Most Cited Journals				
Clinical Chemistry	1,930 cit.	7.1	Q1	Medical Laboratory Technology
Circulation	857 cit.	35.5	Q1	Cardiac & Cardiovascular Systems, Peripheral Vascular Disease
JAMA-Journal of the American Medical Association	709 cit.	63.1	Q1	Medicine, General & Internal
Atherosclerosis	551 cit.	4.9	Q1	Cardiac & Cardiovascular Systems, Peripheral Vascular Disease
Journal of the American College of Cardiology	485 cit.	21.7	Q1	Cardiac & Cardiovascular Systems
Lancet	466 cit.	98.4	Q1	Medicine, General & Internal
New England Journal of Medicine	419 cit.	96.2	Q1	Medicine, General & Internal
Diabetes Care	400 cit.	14.8	Q1	Endocrinology & Metabolism
Clinica Chimica Acta	382 cit.	3.2	Q2	Medical Laboratory Technology
European Heart Journal	331 cit.	37.6	Q1	Cardiac & Cardiovascular Systems

LDL-C, low-density lipoprotein cholesterol; JIF, journal impact factor; JCR, journal citation reports; art., articles; cit., citations.

Highly Cited Papers and the Analysis of Main Authors

The most cited 10 studies are presented in Table 3. Of these 10 studies, 7 were published in Q1 ranked and 3 in Q2 ranked journals. It is noteworthy that the lowest journal impact factor of the Q1 ranked journals is 7.1. Seven of the most cited articles were from the USA and 3 articles were published in Clinical Chemistry. In the study published in JAMA-Journal of the American Medical Association, which has the highest impact factor (63.1) and the highest number of citations (481), Martin et al. (2013) proposed an alternative formula to the Friedewald formula, which uses a constant coefficient of 5 for the TG:VLDL-C ratio, and validated the formula in data including 1,350,908 children, adolescents and adults in whom actual LDL-C measurements were made by ultracentrifugation [22]. Another interesting study is the study by Sampson et al. published in JAMA Cardiology where the normalized citations per year statistic is the highest [11]. In this study, Sampson et al. (2020) developed a new formula that works specifically for hypertriglyceridemia and/or a low level of low-density lipoprotein cholesterol and compared their results to the Martin-Hopkins formula.

Table 3. Top 10 most highly cited documents on LDL-C estimating equations (1990-2023)

Authors	Article Name	Published Year	Country	Total Citations	Citations per Year	Normalized Citations per Year	Journal	JIF 2023	JIF Quartile 2023
Martin et al. [22]	Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile	2013	USA	481	40.08	8.91	*JAMA-Journal of the American Medical Association*	63.1	Q1
Warnick et al. [23]	Estimating low-density lipoprotein cholesterol by the Friedewald equation is adequate for classifying patients on the basis of nationally recommended cutpoints	1990	USA	398	11.37	1.00	*Clinical Chemistry*	7.1	Q1
Nauck et al. [24]	Methods for measurement of LDL-cholesterol: a critical assessment of direct measurement by homogeneous assays versus calculation	2002	Germany	271	11.78	4.38	*Clinical Chemistry*	7.1	Q1
Martin et al. [7]	Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications	2013	USA	263	21.92	4.87	*Journal of the American College of Cardiology*	21.7	Q1
McNamara et al. [25]	Change in LDL particle size is associated with change in plasma triglyceride concentration	1992	USA	240	7.27	2.99	*Arteriosclerosis, Thrombosis and Vascular Biology*	7.4	Q1
Sampson et al. [11]	A New Equation for Calculation of Low-Density Lipoprotein Cholesterol in Patients With Normolipidemia and/or Hypertriglyceridemia	2020	USA	203	40.6	16.41	*JAMA Cardiology*	14.8	Q1
Tremblay et al. [26]	Validation of the Friedewald formula for the determination of low-density lipoprotein cholesterol compared with beta-quantification in a large population	2004	Canada	167	7.95	6.17	*Clinical Biochemistry*	2.5	Q2
Frost & Havel [27]	Rationale for use of non-high-density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy	1998	USA	148	5.48	2.66	*American Journal of Cardiology*	2.3	Q2
Chen et al. [28]	A modified formula for calculating low-density lipoprotein cholesterol values	2010	China	140	9.33	5.26	*Lipids in Health and Disease*	3.9	Q2
Rifai et al. [29]	Measurement of low-density-lipoprotein cholesterol in serum: a status report	1992	USA	132	4.00	1.65	*Clinical Chemistry*	7.1	Q1

LDL-C, low-density lipoprotein cholesterol; JIF, journal impact factor.

The authors' productivity over time is shown in Figure 4. It can be seen that these two works have had a significant impact on the literature on LDL-C estimating equations. When we evaluate each article specifically, it can be said that most of the recent studies conducted validation and performance comparison studies of Martin-Hopkins and Sampson formulas in different populations.

The scientific collaborations between the main authors are given in Figure 5. The connections among the main authors represent co-authorships, with the thickness of these connections indicating the different frequencies of collaboration. Wider links signify a higher level of collaboration between the two main authors.

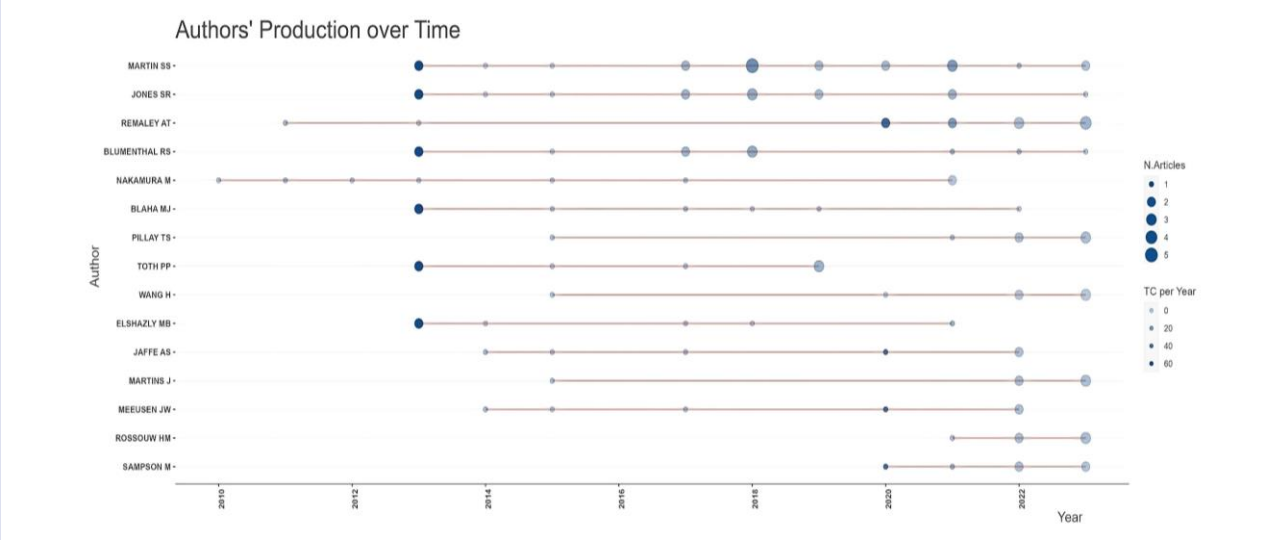

Figure 4. Top authors' production over time (1990-2023).

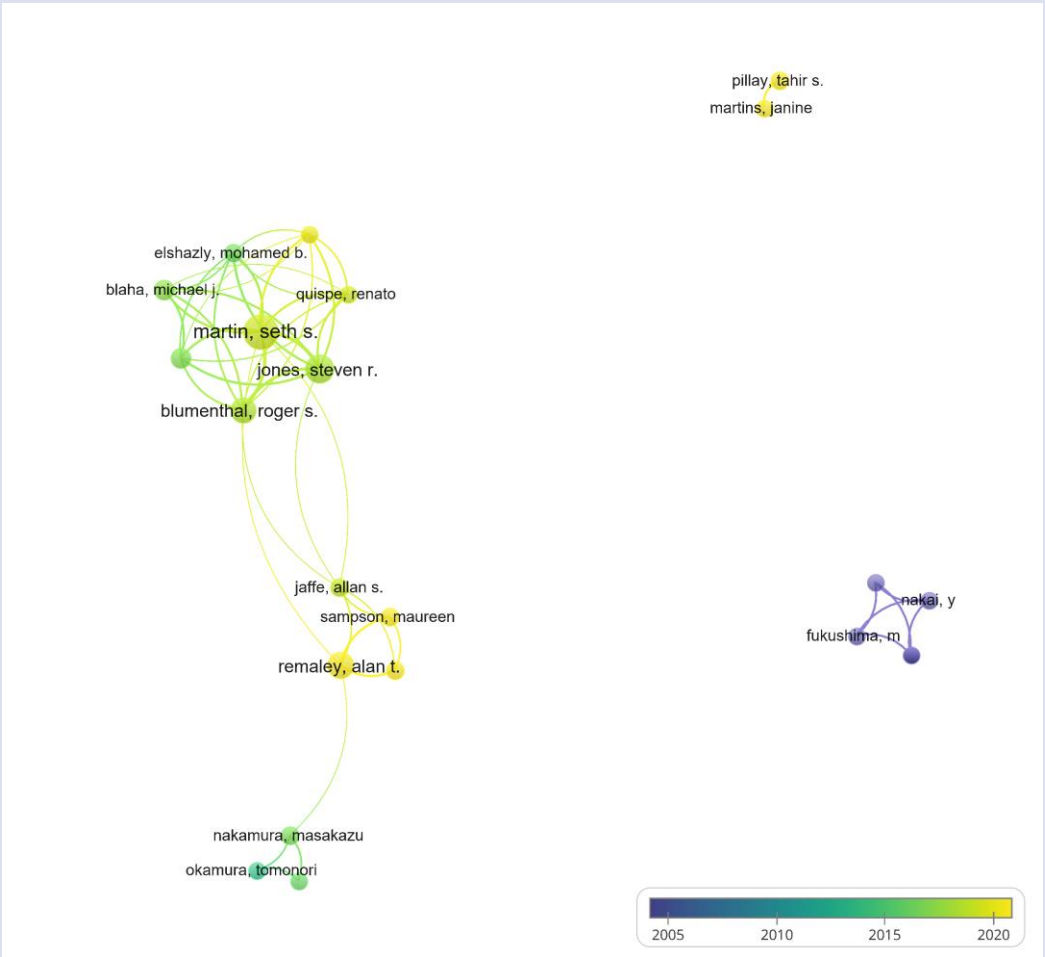

Figure 5. The authors' scientific collaboration network.

Keyword Analysis

Keyword analysis provides a comprehensive understanding of research themes, trends, and the evolving landscape within a particular field. In the analysis of keywords, the keywords specified by the authors in the article were used. The authors identified a set of 1,165 established keywords. The word cloud graph for the most frequently used words in the field of LDL-C estimation equations is given in Figure 6. The most frequently used words in this field were cholesterol (n=75), Friedewald formula (n=52), low-density lipoprotein cholesterol (n=50), triglycerides (n=46), lipids (n=44), Friedewald equation (n=43), LDL-C (n=36), dyslipidemia (n=30), LDL-cholesterol (n=30), and lipid profile (n=29).

Figure 6. Word cloud visualization of authors' keywords.

The co-occurrence analysis of the keywords is given in Figure 7 and Figure 8. Figure 7 shows the interaction between the keywords defined by the authors in different documents and Figure 8 displays the change in the interaction between the two terms over time. It was observed that all of the most frequently used words in the word cloud graph appeared as key nodes in the co-occurrence analysis graph, forming seven different clusters: purple – "cholesterol, LDL-cholesterol, lipoproteins, LDL and HDL", red – "triglycerides, hypertension, total cholesterol, metabolic syndrome, and cardiovascular diseases", blue – "Friedewald formula, LDL-C and non-HDL-C", green – "dyslipidemia, cardiovascular risk, LDL-cholesterol, triglyceride, and lipoprotein (a)", yellow – "Friedewald equation, atherosclerosis, and Sampson equation", light-blue – "Friedewald, non-high density lipoprotein C, beta-quantification, homogeneous assays, equation, and Martin", orange – "low density lipoprotein". These seven clusters were the main themes that stimulated the LDL-C estimating equations research process. The terms "low density lipoprotein", "Friedewald", "Sampson equation", "measurement", "equation", and "Martin" are the keywords with the highest occurrence in current studies. The evaluation of terms is depicted in this item based on their publication years, alongside highlighting the primary interests within the scientific community.

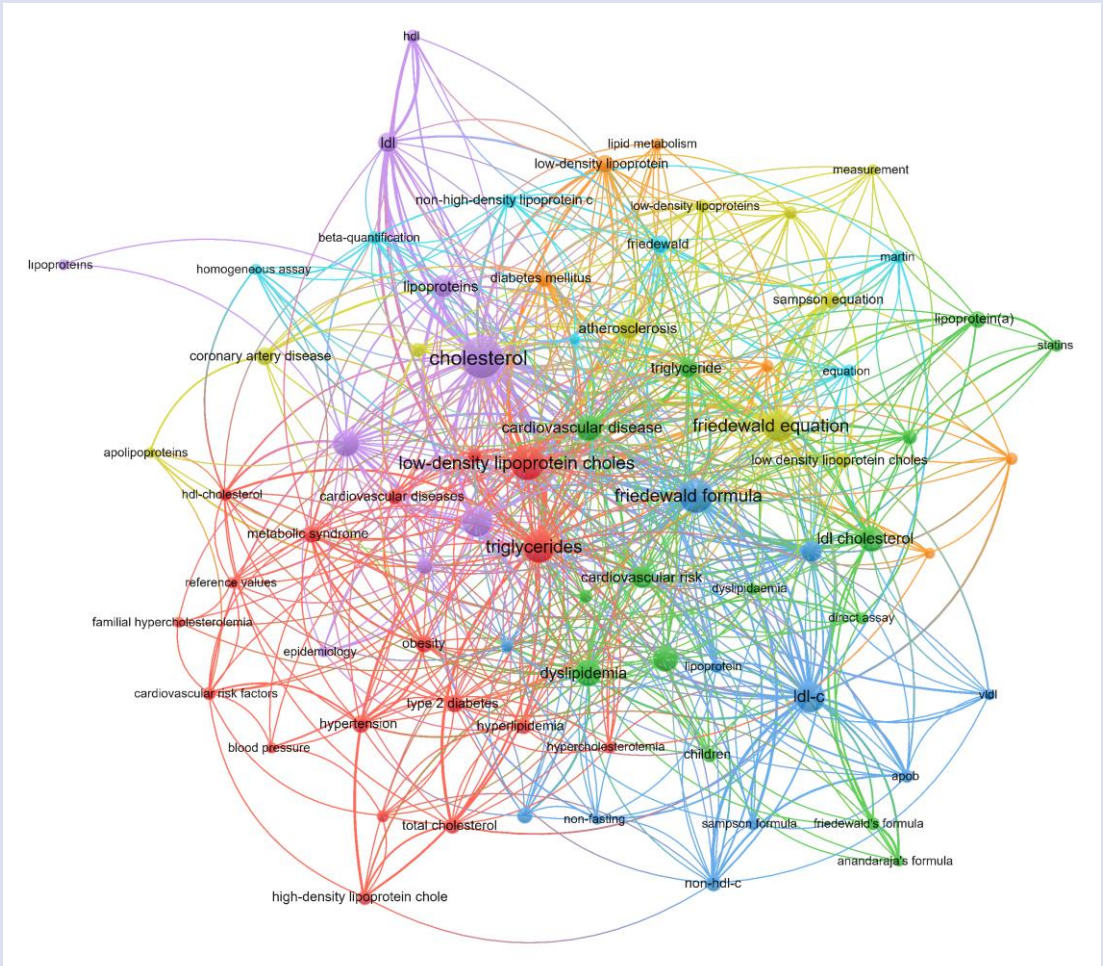

Figure 7. Co-occurrence network plot displaying the relation of authors' keywords.

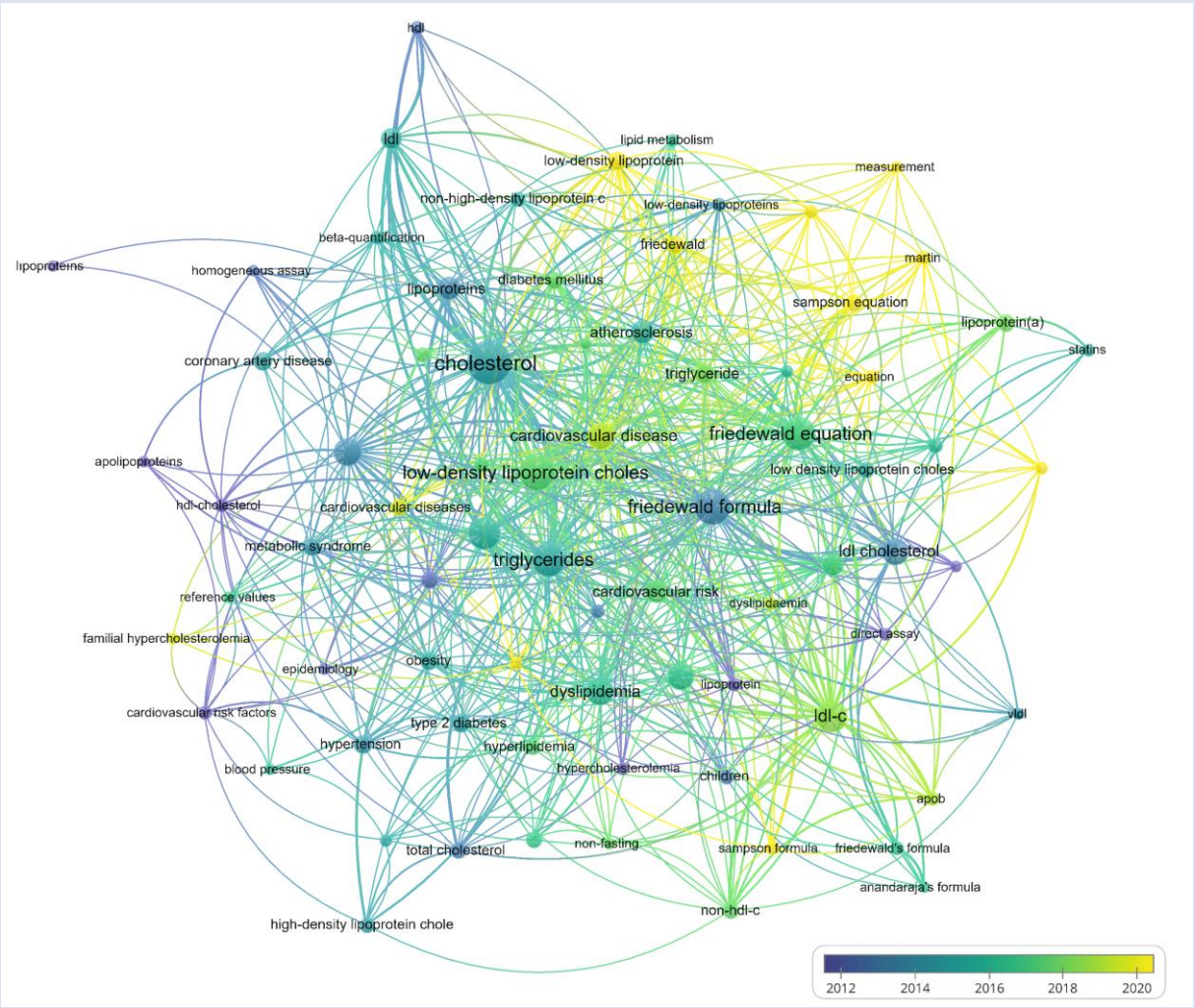

Figure 8. Co-occurrence network plot displaying the evaluation of authors' keywords over time.

Discussion

In this study, a bibliometric analysis of LDL-C estimation equations was performed. This bibliometric analysis was carried out using VOSviewer and Bibliometrix, it is aimed to understand the current state of the literature on LDL-C estimation equations and to present the studies conducted until January 1, 2024 in a global and accessible way. The conducted bibliometric analysis resulted in 620 studies in the WoS database between 1990 and 2023. It is noteworthy that the number of publications in this field has increased by 290% in the last 10 years and 179% in the last 5 years. The WoS research categories of the journals in which these studies were published were medical laboratory technology, cardiac & cardiovascular systems, medicine, general & internal, endocrinology & metabolism, nutrition & dietetics, pharmacology & pharmacy, biochemistry & molecular biology, and medicine, research & experimental. These research areas are the main areas of knowledge where the calculation of LDL-C levels is of importance. The studies were mostly published in journals with high-impact factors in the fields of biochemistry and cardiology such as Journal of the American College of Cardiology, JAMA Cardiology, Clinica Chimica Acta, Clinical Biochemistry, and Clinical Chemistry. The role of LDL-C in the increased risk of cardiovascular disease has been shown by scientific studies [30, 31]. These analyzed studies focused on the development and validation of the most accurate and simple equations to measure LDL-C levels for this problem.

As a result of the study, the top 10 list of articles on LDL-C estimating equations is shared. The top three countries and the top country institutions are the USA (John Hopkins University), China (Central South University), and Japan (Kyoto University). According to the Centers for Disease Control and Prevention, cardiovascular disease is the leading cause of death, with one death from cardiovascular disease every 33 seconds (1 in 5 deaths in total) in the USA [32]. Since LDL-C level is an important risk factor for cardiovascular disease, we believe that studies on LDL-C estimation equations are mostly conducted in the USA. It is observed that LDL-C estimations and subsequent validation studies for different populations are common in the literature.

SS Martin, the author with the highest number of publications on this topic, is also the main author of the most cited study in the field. In this study, Martin et al. (2013) proposed their Martin-Hopkins formula instead of the Friedewald formula, which has an important place in

clinical practice, and validated the formula in data from 1,350,908 children, adolescents, and adults living in the USA [22]. In the other most cited studies, the validity of the Friedewald formula, which is widely accepted in the literature, was investigated and its compatibility with direct methods was evaluated [7, 23, 24, 26]. McNamara et al. (1992) demonstrated the variation of LDL-C particle numbers according to triglyceride levels [25]. The other most cited study is the development of the Sampson formula for low LDL-C levels and/or hypertriglyceridemia (TG levels, ≤800 mg/dL) [11].

When the co-occurrence network graph displaying the evaluation of the authors' keywords over time is analyzed, it is seen that keywords such as "atherosclerosis", "dyslipidemia", "triglycerides", and "cardiovascular risk" used in previous years were replaced by words such as "Sampson equation", "Martin", and "equation". Therefore, it can be said that studies on LDL-C prediction equations have intensified in recent years, and studies on investigating the validity of Martin-Hopkins and Sampson equations in different populations and comparing their performance (including the Friedewald formula) have increased.

One limitation of the study is that only the Web of Science database was used for exporting data. This could have resulted in studies being influenced by bias and having incomplete inclusion.

Conclusions

To the extent of our knowledge, this is the first bibliometric analysis study in the field of LDL-C estimation equations. In this study, we analyzed the sources, countries and institutions, authors, keywords, and themes of LDL-C estimation equations articles published between 1990 and 2023. In addition, the trends in the literature on the topic are shared. The results showed that LDL-C estimating equations research captured significant interest from researchers, especially in the last seven years. In summary, studies on LDL-C estimating equations may receive more and more attention, new equations may be developed or validation of existing equations in different populations or systems may be investigated. This study can guide researchers in this field to quickly understand the knowledge structures in this area.

Conflicts of interest

There are no conflicts of interest in this work.

Ethical Approval Statament

Ethics committee approval is not required as there is no human or animal research.

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