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Original article

Bibliometric analysis of global sickle cell disease research from 1997 to 2017

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ABSTRACT

Introduction: Sickle cell disease is an autosomal recessive genetic disease caused by a single point mutation in the β-globin chain of the hemoglobin. It has been recognized by the World Health Organization as a public health priority since 2006.
Methods: The Scopus database was used in this study with the search descriptors: "*sickle cell*" and "*sickle cell disease*". We applied common bibliometric indicators to evaluate the trend in scientific literature in sickle cell disease research.
Results: We retrieved a total of 19,921 pieces of scientific literature in the repertoire from 1997 to 2017. The Price law was fulfilled in the trend of production of scientific literature on SCD as the growth of scientific literature was more exponential ($r = 0.9751$; $r^2 = 0.9509$) than linear ($r = 0.9721$; $r^2 = 0.9449$). We observed a duplication time of 4.52 years. The Bradford core was made up of 69 journals with *Blood* at the top, publishing the greatest number of articles. The most productive institutions were mostly United States agencies and hospitals. The United States was the most productive country. The National Institute of Health was the most productive institution and also had the highest number of citations. Vichinsky E was the most productive author, while the most cited article was published by *Circulation*.
Conclusion: The growth of scientific literature in Sickle cell disease was found to be high. However, the exponential growth trend shows a "yet-to-be-explored" area of research. This study will be useful for physicians, researchers, research funders and policy-cum-decision makers.

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Introduction

Sickle cell disease (SCD) was first identified in 1910 by James Herrick,[1] followed by the description of the molecular basis of the disease in 1949 by Linus Pauling and colleagues.[2–4] It is an autosomal recessive genetic disease cause by a single point mutation (69 A > T) in the β-globin chain of the hemoglobin in which there is substitution of hydrophobic valine residue for negatively charged glutamic acid residue, consequently resulting in non-covalent polymerization and double strand formation under low oxygen.[3,5] This non-covalent polymerization of the sickle hemoglobin into long fibers under oxygen tension (deoxygenation) is the major pathological event in SCD. The resulting fibers distort red blood cells into atypical and heterogeneous shapes; crescent (classical sickle), elongated, granular and oval shapes[6–8] that lack deformability. These red cells with decreased deformability (loss of membrane elasticity) are rigid and sticky and are usually trapped in narrow capillary blood vessels causing frequent episodes of vaso-occlusion and ischemia.[6,9] In addition, the stiff cells that are unable to return to the normal shape are spotted and destroyed via hemolysis.[9,10] The SCD encompasses sickle cell anemia (which is the inheritance of two S genes), and co-inheritance of hemoglobin C (HbSC) or β-thalassaemia (HbS/β-thalassaemia). However, sickle cell anemia is the most prevalent globally, accounting for an estimated 83% of all newborns with SCD.[11] Conversely, those who inherit a single HbS gene, together with HbA (heterozygotes), are carriers and usually asymptomatic.

The World Health Organization recognized sickle cell anemia as a public health priority in 2006, and subsequently adopted a resolution on the prevention and management of birth defects, including sickle cell disease and thalassemia at the 63rd (2010) World Health Assembly.[12–14] The prevalence of sickle cell disease depends on the sickle cell trait, which is now widespread, reaching its highest prevalence in parts of Africa, the Mediterranean Basin and Saudi Arabia. In countries such as Ghana, Cameroon, Nigeria, Gabon and Republic of Congo, the prevalence is between 20% and 30%, while in some parts of Uganda, it is as high as 45%. In countries where the trait is above 20%, the disease affects about 2% of the population.[15] On a global map of HbS allele frequency distribution with Bayesian geostatistical model using a database of sickle hemoglobin surveys by Piel et al.,[16] it was shown that 50% of the total AS and SS neonates were born in only three countries, namely, Nigeria, India and the Democratic Republic of Congo. Nigeria has the highest incidence of SCD in the world, with approximately 91,011 children born with the defect, accounting for approximately 2% of all newborns annually, followed by the Democratic Republic of Congo, with 39,743 sickle cell births per year.[17]

"Bibliometrics" is a term coined by Allan Pritchad to define the use of mathematical-cum-statistical procedures to the process of the propagation of written communication in the field of scientific discipline through the quantitative study of the varying aspects of this type of communication.[18,19] Bibliometric studies are relevant tools in social and scientific evaluation of a given discipline within a specified time frame. Bibliometric indicators are proxy markers for activity in a field of research.[20,21]

This study aimed at identify the trend in sickle cell disease, as well as to analyze the structure of the evolving sickle cell disease research community network over time. The result of this study will be relevant to clinicians, researchers and government/health policymakers, as well as research finders.

Methods

Data source

The Scopus database was used for this bibliometric study, considering that it is the largest abstract and citation database of peer reviewed literature. It indexes approximately 22,000 journal titles from over 5000 publishers. Among these, approximately 20,000 are peer-reviewed journals across the scientific, medical, technical and social science disciplines. In comparison with other bibliometric databases, Scopus is better suited to the biomedical field, as it is comprehensive and user-friendly, coupled with the fact that it largely regarded as the world's largest database for abstract and citation information, and is conveniently used in many bibliometric studies.[22,23] We used the remote downloading technique to retrieve articles published from 1997 to 2017 containing the descriptors "*sickle cell*" and "*sickle cell disease*", limited to three fields, namely, title, keyword, and/or abstract. We included all original articles, reviews, editorials, brief reports letters to editors and so forth.

Bibliometric indicators

The bibliometric indicators used in this study are similar to those used in our previous bibliometric studies[19,24] and they include Price's law, duplication time and annual growth rate, Bradford zones, bibliometric coupling and key word analysis.

We employed Price's law[25] as an indicator of productivity, as it is the most common bibliometric indicator for assessing productivity within a specific discipline or country. The Price law uses exponential growth evaluation. To assess if scientific production in sickle cell disease follows Price's law of exponential growth, we modeled our generated data into a linear adjustment, utilizing the equation $y = 50.904x - 101216$, and implemented another adjustment to an exponential curve, using the equation $y = 3E - 46e^{0.0557x}$. The Price law is fulfilled when the coefficient of determination of the exponential curve is greater than that of the linear curve.

The duplication time and annual growth rate were also utilized in this study as bibliometric indicators. The duplication time refers to the time (in years) it takes for a subject to double its production. Conversely, annual growth rate conveys information on the present growth in relation to the preceding year and is denoted in percentage. The duplication time was calculated using the formula:

$$D = Ln^2/b$$

where b represents the constant that relates the growth rate with the already acquired output of the discipline. The annual growth rate was calculated using the formula:

$R = 100 (e^b - 1)$

Bradford's law[26] was utilized to determine the dispersion of scientific literature. Bradford created concentric zones of productivity, referred to as Bradford zones, with decreasing density of information. He hypothesized that each zone contains a similar number of documents, whereas the number of journals in which they are produced increases as one moves from one zone to the next. The division of journals in the different Bradford zones is as follows: 1, n, n^2 … The number of articles are divided into 3 groups of approximately the same size, in which one is the core zone, while the other two are peripheral zones. This stratification aids in identifying the most widely used and highest impact journals in a specific area of interest/evaluation.

The Impact Factor (IF) was used as a measure of the journal's influence and it was originally developed by the Institute for Science Information (Philadelphia, PA, USA) as a bibliometric indicator and was updated annually in the *Journal Citation Report* (JCR) section of Science Citation Index Expanded (SCI). The calculation contemplates the number of times a given journal is cited by SCI journals within the two preceding years. The value is usually a marker of scientific "prestige". We used the JCR 2018 impact factor data for this study.

The National Participation Index (PaI) was evaluated for the overall 1997–2017 scientific publication on sickle cell disease and in the fields of medicine and other medical-cum-health-related-disciplines in the world's ten most productive countries in sickle cell disease research. It is the number of documents on the topic in question (in this case, sickle cell), compared to the global participation index in biomedicine and in a broader scope of sciences and other subareas and medical and health sciences. We further correlated the participation index with health data, such as per capita expenditure on health, as well as the country's gross domestic expenditure on research, with the 2015 data obtained from the World Bank[27] and World Health Organization Department of Health Statistics.[28]

We also used bibliometric coupling to assess the trend of interest of various institutions involved in sickle cell disease research.

Key words analysis was used to evaluate the trend of discussion and research, with respect to disease characteristics, clinical research, pathology and treatment and effect.

Results

Assessment of global publication

A total of 19,921 research publications were recovered using the search criteria within the study period of 1997 to 2017. Of these, 63.72% (n = 12,693) were original articles, while 17.35% (n = 3,457), 5.87% (n = 1,170), 3.21% (n = 639), 2.79% (n = 555), 2.41% (n = 480), 2.15% (n = 429), 1.52% (n = 302), 0.47% (n = 94), 0.36% (n = 72), 0.13% (n = 25) and 0.03% (n = 5) were reviews, letters, notes, conference papers, editorials, book chapters, short surveys, errata, articles in press, books and conference reviews, respectively (Table 1).

As shown in Fig. 1, there has been a remarkable increase in the number of scientific publications in the field of sickle cell disease research over the 20-year period. The linear and exponential adjustments, as per Fig. 1, yielded the correlation coefficients *r* of 0.9721 ($R^2 = 0.9449$) and 0.9751 ($R^2 = 0.9509$), respectively. This shows that the growth of scientific publication on SCD is in the exponential growth stage (as *r* for the exponential curve is >*r* for the linear curve), with an average annual increase of 4.93%. It is worthy of note that only 4.1% of the data is not explained by the equation.

Fig. 2 shows the temporal production of scientific literature. To calculate the duplication time, the trend line was fitted to the equation $y = 1129.2e^{0.152x}$ with the correlation coefficient 0.9590 ($R^2 = 0.9197$) over the 29-year timeframe. Applying the equation for duplication times rendered a duplication time of 4.52 years. This means that the production of scientific publications doubles every 4.52 years.

Fig. 3 shows that the global production of scientific literature on SCD stratified into five-year periods. It was observed that in each 5-year period, there is a gradual increase over the previous one. It was observed that the 2013–2017 period contained the majority of the documents, accounting for 36.41% of the total documents.

Table 2 shows the distribution of the journals in the Bradford zones. A total of 4103 different journals published the articles under study. However, only 13.67% of them were responsible for more than 60% (66.36%) of the published manuscripts. The core Bradford zones (those containing the largest number of articles) consisted of 69 journals; notably

Table 1 – Document type.

Document type	No of documents	%
Article	12,693	63.72
Review	3457	17.35
Letter	1170	5.87
Note	639	3.21
Conference paper	555	2.79
Editorial	480	2.41
Book chapter	429	2.15
Short survey	302	1.52
Erratum	94	0.47
Article in press	72	0.36
Book	25	0.13
Conference Review	5	0.03

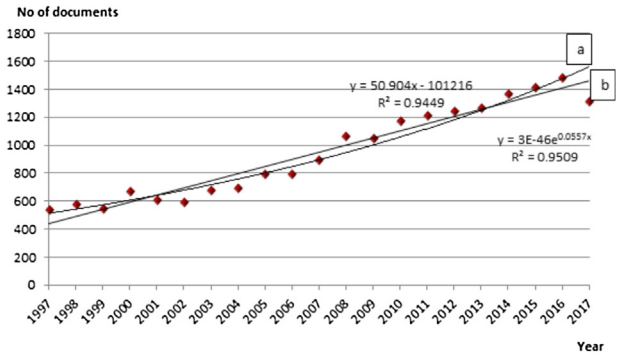

Figure 1 – Chronological distribution of scientific literature on sickle cell disease research within the study period. (a) Exponential trendline. (b) Linear trendline.

Table 2 – Bradford distribution of journals.

	No. of journals	% of journals	No. of articles	% of articles	Bradford multiplier
Core	69	1.68	6672	33.49	
Zone 1	492	11.99	6548	32.87	7.13
Zone 2	3542	86.33	6701	33.64	7.19
Total	4103	100.00	19,921	100.00	7.16

Table 3 – Analysis of sources with the highest number of publications[a].

	No. of documents	Productivity Index	Impact Factor	Country of origin	Abbreviated Journal Title
Blood	642	3.22	15.132	USA	Blood
American Journal of Hematology	525	2.64	5.303	USA	Am. J. Hematol.
British Journal of Haematology	458	2.30	5.128	England	Br. J. Haematol.
Pediatric Blood and Cancer	360	1.81	2.642	USA	Pediatr. Blood Cancer
Journal of Pediatric Hematology/Oncology[b]	243	1.22	1.060	Switzerland	Int. J. Pediatr. Hematol-Oncol.
Hemoglobin	239	1.20	0.462	USA	Hemoglobin
Revista Brasileira de Hematologia e Hemoterapy[c]	193	0.97	0.62	Brasil	Rev. Bras. Hematol. Hemoter.
Transfusion	183	0.92	3.432	USA	Transfusion
Haematologica	182	0.91	9.090	Italy	Haematologica
PLoS ONE	168	0.84	2.766	USA	PLoS One

[a] Data from the Journal Citation Report (2017).
[b] Data from 1999.
[c] Data from 2015.

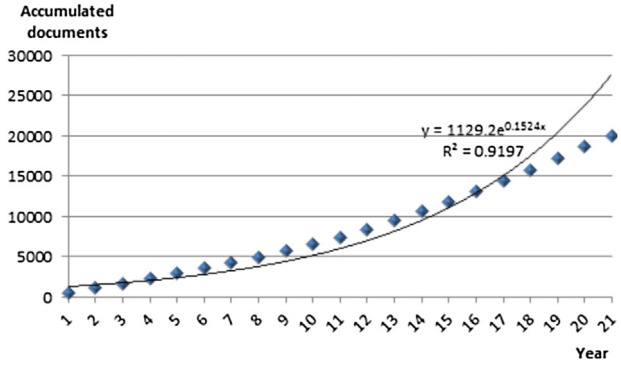

Figure 2 – Temporary evolution of publications on sickle cell disease.

$$D = \frac{Ln2}{b} = \frac{0.68904}{0.1524} = 4.52$$

Production doubles every 4.52 years.

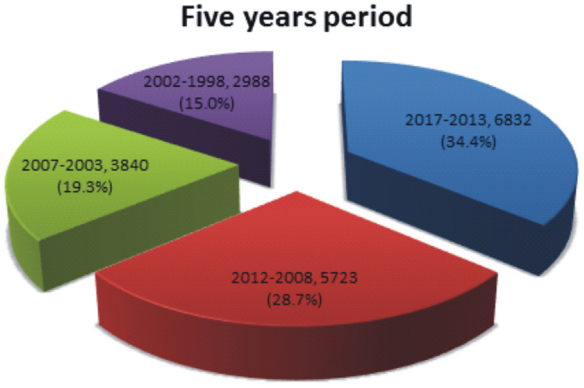

Figure 3 – Cumulative growth in total global sickle cell disease research in each 5-year period.

Blood, *American Journal of Hematology*, *British Journal of Haematology*, and others.

Analysis of sources with highest publication

Table 3 shows the analysis of sources with the largest number of publications on SCD research represented by the top 10 journals on the list, with their corresponding impact factors, according to JCR 2018, and their productivity index in the total database within the study period. Seven (7) and 4 of the journals have impact factors greater than 2 and 5, respectively. The top ten most productive journals were: *Blood*, *American Journal of Hematology*, *British Journal of Haematology*, *Pediatric Blood and Cancer*, *Journal of Pediatric Hematology and Oncology*, *Hemoglobin*, *Revista Brasileira de Hematologia e Hemoterapia*, *Transfusion*, *Haematologica* and *PLoS ONE*.

Table 4 shows the top 20 most productive countries in SCD research, the United States (n = 9167) and the United Kingdom (n = 1869) having the participation index (PI) of 46.02 and 9.38, respectively. Next on the list are France (n = 1379; PI = 6.92) Brazil (n = 933; PI = 4.68), India (n = 660; PI = 3.31), Italy (n = 577; PI = 2.90), Nigeria (n = 574; PI = 2.88), and Canada (n = 522; PI = 2.62). It is pertinent to note the United States alone accounted for nearly half (46.02%) of all publications.

The comparative analysis of the productivity of the top 10 most productive countries in sickle cell research with their overall production in medicine showed that only 7 out of the 10 countries (United Kingdom, USA, France, Brazil, India, Nigeria and Saudi Arabia) devoted a higher proportion of attention to the study of SCD, in relation to medicine in general. The United States, the United Kingdom and France were consis-

Table 4 – Top 20 most productive countries.

Country	No. of documents	%
United States	9167	46.02
United Kingdom	1869	9.38
France	1379	6.92
Brazil	933	4.68
India	660	3.31
Italy	577	2.90
Nigeria	574	2.88
Canada	522	2.62
Germany	429	2.15
Saudi Arabia	418	2.10
Netherlands	375	1.88
Turkey	307	1.54
Jamaica	232	1.16
Greece	216	1.08
Spain	215	1.08
Belgium	205	1.03
Australia	203	1.02
Switzerland	175	0.88
Egypt	150	0.75
Israel	140	0.70

tently leading both in sickle cell disease research and research in medicine in general (Table 5).

Fig. 4 shows the correlation between the production of scientific literature on SCD and current health expenditure (CHE) and gross domestic expenditure on research in the 15 most productive countries in SCD research. In the analysis of the correlation between the participation index and the current health expenditure of each of the top 15 most productive countries in SCD, the trend obtained was inconsistent, except for the United States and France, that maintained their trend. In addition, the correlation between the 15 top producers and the gross domestic expenditure on research also showed an inconsistent pattern, except for France.

Productivity of Institutions

The topmost productive institutions in SCD research are represented in Table 8. The National Institute of Health, Bethesda was the most productive institution (n = 447; 2.24%), followed by INSERM (n = 396; 1.99%), the Children's Hospital of Philadelphia (n = 350; 1.76%), Harvard Medical School (n = 310; 1.56%), St. Jude Children's Research Hospital (n = 306; 1.54%) and others.

Table 6 – Top 20 most productive institutions.

Institution	No. of documents	%
National Institutes of Health, Bethesda	447	2.24
INSERM	396	1.99
The Children's Hospital of Philadelphia	350	1.76
Harvard Medical School	310	1.56
St. Jude Children's Research Hospital	306	1.54
University College London (UCL)	294	1.48
UCSF Benioff Children's Hospital Oakland	290	1.46
Duke University School of Medicine	273	1.37
National Heart, Lung and Blood Institute	268	1.35
The University of North Carolina at Chapel Hill	267	1.34
Albert Einstein College of Medicine of Yeshiva University	259	1.30
AP-HP Assistance Publique - Hopitaux de Paris	257	1.29
Children's Hospital Boston	243	1.22
King's College London	242	1.21
Hopital Henri Mondor	237	1.19
Cincinnati Children's Hospital Medical Center	235	1.18
The Johns Hopkins School of Medicine	220	1.10
Medical College of Wisconsin	219	1.10
University of Illinois at Chicago	217	1.09
University of Oxford	216	1.08

Seventy percent (70%) of the top 20 most productive institutions are located in the United States, whereas the rest are in France (15%), and the UK (15%). Five (25%) of the topmost productive institutions are public universities, while 5 (25%), 4 (20%), 3 (15%), 2 (10%) and 1 (5%) are private universities/medical colleges, not-for-profit hospitals, government agencies, public hospitals and a private hospital, respectively (Table 6).

Citation analysis of the topmost productive institutions showed the highest citation for the National Institute of Health, Bethesda and the National Health, Lung and Blood Institute, while the highest citation per document was recorded at the National Heart, Lung and Blood Institute and Duke University School of Medicine (Table 7).

Table 5 – Comparative analysis of the productivity of the top 10 most productive countries in SCD research, with their overall production in medicine and other areas of biomedical research.

Country	IP Medicine	IP Health Professions	IP Pharmacology, Toxicology and Pharmaceutics	IP Sickle Cells	IP Tuberculosis	IP AIDS
United States	25.51	49.80	15.01	46.02	18.38	33.76
United Kingdom	8.07	14.43	4.14	9.38	8.04	7.43
France	3.84	0.66	1.71	6.92	4.50	3.72
Brazil	1.76	1.22	5.09	4.68	2.00	1.84
India	2.32	0.35	18.08	3.31	5.54	2.51
Italy	3.08	0.74	1.95	2.90	2.84	2.93
Nigeria	0.24	0.09	0.75	2.88	0.43	0.54
Canada	3.64	6.27	1.44	2.62	2.22	3.32
Germany	6.10	1.36	3.17	2.15	3.78	3.81
Saudi Arabia	0.41	0.06	0.62	2.10	0.50	0.15

Table 7 – Citation analysis of the 10 topmost productive institutions.

Institution	No. of documents	%	Citations	Citation/documents
National Institutes of Health, Bethesda	447	2.24	20,253	45.31
INSERM	396	1.99	7306	18.45
The Children's Hospital of Philadelphia	350	1.76	11,584	33.10
Harvard Medical School	310	1.56	14,105	45.50
St. Jude Children's Research Hospital	306	1.54	10,181	33.27
UCL	294	1.48	13,061	44.43
UCSF Benioff Children's Hospital Oakland	290	1.46	12,856	44.33
Duke University School of Medicine	273	1.37	12,499	45.78
National Heart, Lung and Blood Institute	268	1.35	14,187	52.94
The University of North Carolina at Chapel Hill	267	1.34	10,983	41.13

Table 8 – Ten most productive authors in SCD research.

Author	Country	Affiliation	No. of documents	% Documents	Citations	% Citations
Vichinsky, E.	USA	UCSF Benioff Children Hospital	180	0.90	6713	1.91
DeBaun, M.R.	USA	Washington University School of Medicine	164	0.82	3463	0.99
Gladwin, M.T.	USA	Pittsburg Heart, Lung, Blood and Vascular Medical Institute	163	0.82	10,793	3.08
Steinberg, M.H.	USA	Pittsburg Heart, Lung, Blood and Vascular Medical Institute	157	0.79	6062	1.73
Ballas, S.K.	USA	Cardeza Foundation for Hematologic Research	155	0.78	4039	1.15
Galactéros, F.	France	Henri-Mondor Hospital	147	0.74	3106	0.89
Ware, R.E.	USA	Cincinnati Children's Hospital Medical Centre	146	0.73	5556	1.58
Kato, G.J.	USA	Pittsburg Heart, Lung, Blood and Vascular Medical Institute	145	0.73	5239	1.49
Wang, W.C.	USA	St. Jude Children's Research Hospital	138	0.69	6692	1.91
Connes, P.	France	Universite Claude Bernard Lyon 1 Villeubanne; LABEX GR-Ex; Institut universitaire de France	114	0.57	1341	0.38

Fig. 5 shows the bibliometric coupling among the most productive institutions in SCD research.

Productivity of authors

Table 8 shows the analysis of the top 10 most productive authors in SCD research. Vichinsky E, DeBaun MR, Gladwin MT, Steinberg MH, Ballas SK, Galacteros F, Ware RE, Kato GJ, Wang WC and Connes P were the top 10 productive authors. Eight (8) out of the 10 of the most productive authors are resident in the United States and are affiliated with the UCSF Benioff Children's Hospital, Washington School of Medicine, Pittsburg Heart, Lung, Blood and Vascular Medicine Institute, Thomas Jefferson University, Cincinnati Children's Medical Centre and St. Jude Children's Research Hospital. The other two authors are affiliated with the Henri-Mondor Hospital and Institute Universitaire de France/Universite Claude Bernard Lyon 1 Villeubanne/Laboritoire d'Excellence du Globule Rouge in France.

Citation analysis of articles

Table 9 shows the top 10 most cited articles. The most cited article was an update report dedicated on heart disease and stroke, while the second was dedicated to causes of mortality (SCD inclusive). The third top cited article was dedicated to the glutathione metabolism, with mention of how oxidative stress plays a critical role in the pathogenesis of sickle cell disease. Only the eighth top article was dedicated to the treatment of SCD using a mouse model.

Keyword analysis

We identified 160 keywords in the search repertoire. Stratification of the keywords into 4 clusters ("*characteristics*", "*clinical research*", "*pathogenesis*" and "*Treatment and effect*") showed that "*characteristics*" comprised 24.3%, while "*clinical research*", "*pathogenesis*" and "*treatment and effect*" comprised 26.5%, 40.0% and 9.4%, respectively. Under "*characteristics*", "human" was the most commonly used keyword, while "hydroxyurea" and "blood transfusion" were the commonly used keywords under "*treatment and effect*". "Controlled study" was the most commonly used keyword under "*clinical research*", while "anemia" was the most commonly used keyword under "*pathogenesis*" (Fig. 6).

Discussion

The most utilized document type in this study by authors is original article, which accounted for about 63.72% of all article types used. This reflects the fact that the subject matter refers to experiments or clinical research.

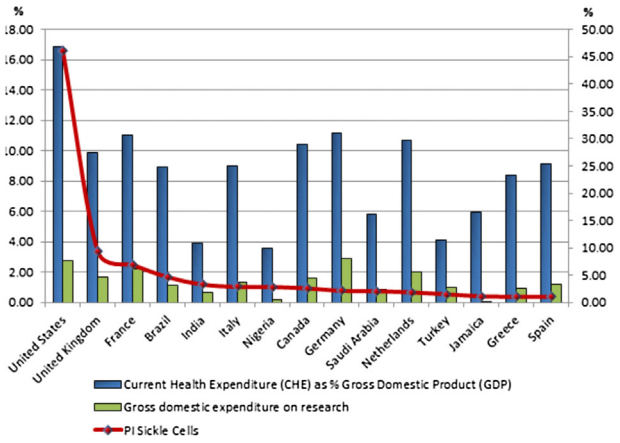

Figure 4 – Relationship between production of scientific literature on SCD and current health expenditure (CHE), as % GDP, and Gross Domestic Expenditure on Research and Development (R&D), in the top 15 most productive countries in SCD research.

We observed an exponential growth trend in publications related to SCD research in the past 20 years, with an average annual increase of 4.93%, without evidence of reaching saturation, as postulated by Price's law, hence fulfilling Price's law. This significant growth in the field of SCD research leads us to the conclusion that the field of SCD is still at the prime of development, from the clinical and basic research perspectives. This immense growth in the research output can be attributed to the continual interest in research geared towards providing curative and disease-modifying agents for SCD. There have been immense efforts made in diverse clinical trials on stem cell replacement/modification, antisickling agents, gene therapy, antioxidant therapy and other anti-adhesive therapies.[29] The observed trend is similar to previous reports in areas of optometry, bipolar disorder and obstetrics and gynecology.[24,30,31] However, the trend is at variance with a linear trend observed in a study on an infectious disease (Lassa fever).[19]

Bradford stratification of the articles showed that only 19 journals (1.68%) were responsible for the production of 33.49% of the published literature. This trend reflects a high concentration of publications by a small group of journals. Individual analysis showed that *Blood* had the highest number of publications, accounting for approximately 3.22% of all publications, followed by *American Journal of Hematology* (2.64%) and *British Journal of Haematology*. All the top ten journals were dedicated to hematology except *PLoS ONE*, that is a multi-disciplinary journal.

Figure 5 – Bibliometric coupling among most productive institutions in SCD research.

Table 9 – Top 10 most cited articles in SCD research.

Article	Authors	Source	Cited	% Citations
Heart disease and stroke statistics-2012 update: A report from the American Heart Association	Roger, V.L., Go, A.S., Lloyd-Jones, D.M., (. . .), Woo, D., Turner, M.B.	*Circulation*	3511	1.00
Global, regional and national and age-sex specific, all-cause and cause-specific mortality for 240 causes of death, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013	Naghavi, M., Wang, H., Lozano, R., (. . .), Sabin, N., Temesgen, A.M.	*The Lancet*	2055	0.59
Glutathione Metabolism and Its Implications for Health	Wu, G., Fang, Y.-Z., Yang, S., Lupton, J.R., Turner, N.D.	*Journal of Nutrition*	1969	0.56
Global, regional and national incidence, prevalence and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013	Vos, T., Barber, R.M., Bell, B., (. . .), Salomon, J.A., Murray, C.J.L.	*The Lancet*	1523	0.43
Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association	Furie, K.L., Kasner, S.E., Adams, R.J., (. . .), Turan, T.N., Wentworth, D.	*Stroke*	1160	0.33
Updated clinical classification of pulmonary hypertension	Simonneau, G., Gatzoulis, M.A., Adatia, I., (. . .), Robbins, I.M., Souza, R.	*Journal of the American College of Cardiology*	1143	0.33
Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association	Kernan, W.N., Ovbiagele, B., Black, H.R., (. . .), Schwamm, L.H., Wilson, J.A.	*Stroke*	1140	0.32
Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin	Hanna, J., Wernig, M., Markoulaki, S., (. . .), Townes, T.M., Jaenisch, R.	*Science*	1097	0.31
Guidelines for the prevention of stroke in patients with ischemic stroke or transient ischemic attack: A statement for healthcare professionals from the American Heart Association/American Stroke Association council on stroke - Co-sponsored by the Council on Cardiovascular Radiology and Intervention. The American Academy of Neurology affirms the value of this guideline	Sacco, R.L., Adams, R., Albers, G., (. . .), Schwamm, L.H., Tomsick, T.	*Stroke*	1086	0.31
Hematopoietic stem-cell transplantation	Copelan, E.A.	*New England Journal of Medicine*	1058	0.30

Country-wise analysis of research output on sickle cell disease showed that the United States, the United Kingdom and France topped the research output in SCD research and accounted for 62.32% of the total research output on sickle cell disease. The United States alone accounted for 46.02% of the total research output. The reason for this increased productivity cannot be far-fetched, as the US, the UK and France housed the most productive institutions, research institutes, hospitals and universities. Moreover, the trio is home to major pharmaceutical companies that manufacture the disease-modifying drug hydroxyurea approved for the management of SCD: *Droxia*®, *Hydrea*®, and *Litalir*® by Bristol-Myers Squibb Co, USA, France, Italy, India, China, England, Belgium and *Siklos*®, by Addmedica, France. India is also home to the brands of hydroxyurea: *Ribore* (Khandelwal Laboratory Pvt Ltd), *Readrox* (Miracalus Pharma Pvt Ltd), *Neodrea* (Vhb Life Science Inc.) and *Myelostat* (Zydus Cardila), while Italy, in addition to Bristol-Myers Squibb Co, houses Teofarma Srl, that manufactures *Oncocarbide*™. In addition, the United States is the home of Emmaus Medical Inc., the pharmaceutical company that manufactures the newly approved disease-modifying drug, *Endari*, for SCD. It is noteworthy that Nigeria, documented as having the highest incidence of sickle cell disease in the world, was the only African country present in the top 20 most productive countries. Hence, the endemicity of the disease could serve as a boost in the interest in studying the disease. Additionally, Nigeria houses the pharmaceutical company Bond Chemical Pvt Ltd, that manufactures the brand of hydroxyurea, *Oxyurea*. While comparing the most productive countries in SCD research to research in general medicine and some other infectious diseases, the striking interest of Brazil, France, Nigeria and Saudi Arabia was remarkable. However, it is noteworthy that Brazil (South America), France (Europe) and Nigeria (Africa) retain the highest sickle cell disease burden in their continents.[17,32,33] This could partly explain the seeming research interest of the duo of Brazil and Nigeria in sickle cell disease research (in relation to other medical research) amidst their limited resources, as compared to other econom-

ically advanced countries on the list, such as France. Moreover, the low comparative participation index of Germany in SCD research, in relation to general research in medicine, was also remarkable.

A comparative analysis between the production in SCD and current health expenditure showed that the higher the current health expenditure is, the greater the productivity in research in SCD becomes, with some exceptions: France, Italy, Canada, Germany, Saudi Arabia, Netherlands, Turkey, Jamaica, Greece and Spain, in which the current health expenditure exceeded their participation index in SDC research. However, Nigeria had the lowest current health expenditure (3.57% of the GDP).

The correlation analysis of the comparison between scientific productivity in SCD and gross domestic expenditure on research and development (R&D) placed Jamaica, Nigeria and India in the last three positions in the evaluated countries. It is noteworthy that only 2 of the most productive countries in SCD research (Germany; 2.88% and the US; 2.79%) had a gross expenditure on R&D above the Organization for Economic Cooperation and Development (OECD) average of 2.3%, while only 4 (Germany; 2.88%, the US; 2.79%, France; 2.23% and Netherlands) had a gross expenditure on R&D above the EU-28 average of 1.9%. The scientific output of a country is a reflection of its earlier investment in research and development in the years preceding the year of analysis and not as a result of a particular economic event in the evaluation period.[30,34]

Institutions in the United States dominated the list of the top 20 most productive institutions, followed by France and the United Kingdom. This further explains why the United States occupied the top in productivity in SCD research. This finding implies that the creation of first-class research institutes is fundamental in the improvement in research and academic output of a country. The National Institute of Health is a part of the United States Department of Health and Human Services that serves as the nation's medical agency. It conducts its own research via its Intramural Research Program, as well as provides major biomedical research funding to external research facilities via its Extramural Research Program.[35] On the other hand, the Institut National de la saite et la Recherche Medicale (INSERM) is the French national institute of health and medical research dedicated to human health, having the objective of promoting health by advancing knowledge about life and disease and treatment innovation in public health research.[36]

Unlike cocitation analysis, which is a measure of the frequency with which two documents are cited together by one document,[37] bibliometric coupling occurs when two different studies reference a common third study in their bibliography.[38,39] Bibliographic coupling shows similarity of the subject matter of the two publications. In this study, we observed the existence of several groups of institutions bibliographically coupled, forming a huge bibliographic network. For instance, the National Heart, Lung and Blood Institute, St. Jude Children's Research Hospital, Children's Hospital Boston and Johns Hopkins School of Medicine can be tagged as premium networks of the American Institutions. Another group of American institutions that are bibliographically coupled are: the Harvard Medical School, Medical College of Wisconsin and Cincinnati Children's Hospital Medical Center. Among the European institutions bibliometrically coupled are: the INSERM, University College London. The citing of papers in common at these Institutions reflects a voluminous bibliometric network showing research focused on related topics.

Vichinsky E, DeBaun MR, Gladwin MT, Steinberg MH, Ballas SK, Galacteros F, Ware RE, Kato GJ, Wang WC and Connes P were the top 10 productive authors. Vichinsky E. focused on treatment, pathogenesis and population-based survey, especially on chronic organ failure in sickle cell disease.[40,41] DeBaun MR focused on pathogenesis and treatment and effect in SCD,[42,43] while Gladwin MT, Steinberg MH, Ballas SK and Galacteros F dedicated most of their studies to the treatment/outcome and pathophysiology of SCD. These authors have published several novel works and are likely to have a tremendous impact on the future development in SCD research.

The core journals utilized in the publication of SCD research were *Blood*, *American Journal of Hematology*, *British Journal of Haematology*, *Pediatric Blood and Cancer*, *Journal of Pediatric Hematology/Oncology*, *Hemoglobin*, *Revista Brazileira de Hematologia e Homoterapia*, *Transfusion*, *Haematologica* and *PLoS ONE*. Subsequently, researchers may pay attention to these journals as future breakthroughs in SCD are more likely to be published in these journals.

The article "Heart disease and stroke statistics-2012 updates", a report from American Heart Association published by *Circulation*, was the most cited article, accounting for 1% of the total citation. It was an article dedicated to statistics, risk factors and economic costs of heart diseases and stroke. The second most cited article was an article on glutathione and its implications in varying health conditions, including sickle cell. The eighth most cited article, "Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin",[44] published by *Science*, was the only article among the top 10 articles dedicated solely to sickle cell disease research. Two of the journals (*New England of Medicine* and *Science*) are delayed open access, while the remaining 8 are hybrid journals. These journals are all well established journals, with impact factors greater than 4.

The analysis of keywords is an important bibliometric tool used in monitoring and discovering directions and popular topics in research.[45,46] In the present study, there is a shift in terms of research focus from "*characteristics*" to "*pathogenesis*" and "*clinical research*". The cluster of treatment and effect was still low. This suggests a non-saturated research in treatment options "begging" for more research. The rule of translational medicine is usually the movement from disease characteristics to treatment.[47] The only disease modifying therapies approved for SCD are hydroxyurea, approved in 1997, and L-glutamate, approved two decades afterward (2017). There have been promising studies on antisickling agents, as well as on gene therapy. Allogenic hematopoietic stem cell transplant and gene therapy are the only curative treatments, showing promising results.[29] The key advantage of gene therapy over hematopoietic stem cell transplant is the option to use autologous stem cells, thereby precluding the need to screen donors. In the cluster of "*characteristics*", "human" was the most commonly used keyword, while "controlled study" was the most commonly used keyword in the cluster of "*clinical research*". "Anemia" was the most commonly used keyword under the

Figure 6 – Keyword analysis among the articles in the studied repertoire.

"*pathogenesis*" cluster, while "hydroxyurea" was the most commonly used keyword under the "*treatment and effect*" cluster.

However, there are some limitations to this study, which are mainly inherent in bibliometric studies. The Scopus database was used for this study, hence, local journals that were not indexed in Scopus during the study period were not included. We might have excluded articles on sickle cell if the authors did not include our search descriptors in the title, abstract or keyword. Moreover, the criteria mapped out by the database themselves determine the subsequent development of the studied material.[48]

Conclusion

Despite the inherent limitations outlined, we believe that this study has provided a significant representation of the global research trend in sickle cell disease research. This study showed that research in SCD is still in the exponential stage. Considering the lag in treatment and effect amidst the exponential growth, it is a pointer that research in SCD will most probably increase in growth in proceeding years, while bearing in mind that the curative approach to SCD is still at the clinical trial stage. A substantial number of the research publications was from high-income countries, including the US, the UK and France.

Author contributions

HUO conceived the study, analyzed data, performed the literature search and prepared the manuscript; FLM performed database analysis and data curation, analyzed data and performed the initial editing of the manuscript; FJP performed database analysis and data curation, analyzed data and performed the initial editing of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Herrick JB. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. JAMA. 1910;312:1063.
2. Pauling L, Itano HA, Singer SJ, Wells IC. Sickle cell anemia, a molecular disease. Science. 1949:543–8.
3. Darrow MC, Zhang Y, Cinquin BP, Smith EA, Boudreau R, Rochat RH. Visualizing red blood cell sickling and the effects of inhibition of sphingosine kinase 1 using soft x-ray tomography. J Cell Sci. 2016;129:3511–7.
4. Hsieh MA, Tisdale JF. Hematopoietic stem cell mobilization with plerixafor in sickle cell disease. Haematologia. 2016;103(5):749–50.
5. Okafor IM, Okoroiwu HU, Ekechi CA. Hemoglobin S and Glucose-6-phosphate dehydrogenase deficiency coinheritance in AS and SS individuals in malaria-endemic region: A study in Calabar, Nigeria. J Global Infect Dis. 2019;11:118–22.
6. Li X, Du E, Dao M, Suresh S, Karniadakis GE. Patient-specific modeling of individual sickle cell behaviour under transient hypoxia. PLOS Comput Biol. 2017;13(3):e1005426.
7. Kaul DK, Fabry ME, Windsch P, Baez S, Nagel RL. Erythrocytes in sickle cell anemia are heterogeneous in their rheological and hemodynamic characteristics. J Clin Invest. 1983;72:22–31.
8. Christopher GW, Hofrichter J, Eaton WA. Understanding the shape of sickle cells. Biophys J. 2005;88:1371–6.
9. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010;376:2018–31.

10. Frenette PS, Atweh GF. Sickle cell disease: old discoveries, new concepts, and future promise. J Clin Invest. 2007;117:850–8.
11. Modell B, Darlison M. Global epidemiology of hemoglobin disorders and derived service indicators. Bull World Health Organ. 2008;86:480–7.
12. World Health Organization Fifty-ninth World Health Assembly: resolutions and decisions, annex 2010. WHA59/2006/REC/1. Geneva: World Health Organization.
13. World Health Organization Sixty-third World Health Assembly: resolutions and decisions annexes. WHA63/2010/REC1. Geneva: World Health Organization.
14. Piel FB Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anemia in children under five, 2010-2050: modeling based on demographics, Excess mortality, and interventions. PLoS Med. 2013;10(7):e1001484.
15. World Health Organization. Regional Committee for Africa; Sickle cell disease in the African Region: fifty-sixth session; 2006. AFR/RC56/17.
16. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemiology of sickle hemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet. 2013;381:142–51.
17. World Atlas World facts; highest number of sickle cell births by country. [Internet] Available from: https://www.worldatlas.com/articles/countries-with-the-highest-number-of-sickle-cell-births-per-year.html. [cited 2019 March 26].
18. López-Muñoz F, Shen WW, Pae CC, Moreno R, Rubio G, Molina JD, et al. Trends on literature on atypical antipsychotics in South Korea: a bibliometric study. Psychiatry Invest. 2013;10:8–16.
19. Okoroiwu HU, López-Muñoz F, Povedano-Montero FJ. Bibliometric analysis of global Lassa fever research (1970-2017): a 47-year study. BMC Infect Dis. 2018;18:639.
20. White HD, McCain KW. Blibliometric. Ann Rev Inf Sci Technol. 1989;24:119–86.
21. López-Muñoz F, Tracy DK, Povedano-Montero FJ, Breedvelt J, Garcia-Pacios J, Fernandez-Martin MP, et al. Trends in the scientific literature on atypical antipsychotic drugs in the United Kingdom: a bibliometric study. Ther Adv Psychol. 2019;9:1–2.
22. Falagas ME, Pitsouni EI, Melietsis GA, Pappas G. Comparison of PubMed, Scopus, web of science and google scholar: strength and weakness. FASEB J. 2008;22(2):338–42.
23. Kulkarni AV, Aziz B, Shams I, Busse JW. Comparisons of citations in web of science Scopus and google scholar for articles published in general medical journals. JAMA. 2009;30(10):1092–6.
24. Povedano-Montero FJ, López-Muñoz F, Cruz FHS. Bibliometric analysis of the scientific production in the area of optometry. Arch Soc Esp Oftamol. 2016;91(4):160–9.
25. Price DJS. Little science, big science. New York: Columbia University Press; 1963.
26. Bradford SC. Documentation. London: Crosby Lockwood; 1948.
27. The World Bank. Available from: https://data.worldbank.org/indicator/GB.XPD.RSDV.GD.25 [cited 2019 March 26].
28. The World Health Organization. Available from: https://apps.who.int/nha/database/select/indicators/en. [cited 2019 March 26].
29. Kapoor S, Little JA, Pecker LH. Advances in the treatment of sickle cell disease. Mayo Clin Proc. 2018;93(12):1810–24.
30. López-Muñoz F, Vieta E, Rubio G, Garcia-Garcia P, Alamo C. Bipolar disorder as an emerging pathology in the scientific literature: a bibliometric approach. J Affect Disosrd. 2006;92:161–70.
31. Garcia-Garcia P, López-Muñoz F, Callejo J, Martin-Agueda B, Alamo C. Evolution of Spanish scientific production in international obstetrics and gynecology journals during the period 1986-2002. Eur J Obstetr Gynecol. 2005;123:150–6.
32. Honsel V, Khimoud D, Ranque B, Offredo L, Joseph L, Pouchout J, et al. Comparison between adult patients with sickle cell disease of sub-Saharan African origin born in metropolitan France and in Sub-Saharan Africa. J Clin Med. 2019;8:2173.
33. Huttle A, Maestre GE, Lantigua R, Green NS. Sickle cell disease in Latin America and the United State. Pediatr Blood Cancer. 2015;62(7):1131–6, http://dx.doi.org/10.1002/pbs.25450.
34. López-Muñoz F, Alamo C, Quintero-Gutiérrez FJ, García-García P. A bibliometric study of international scientific productivity in attention deficit hyperactivity disorder covering the period 1980-2005. Eur Child Adolesc Psychiatry. 2008;17(6):381–91.
35. National Institute of Health. Who we are. Available from: https://www.nih.gov/about_nih/who-we-are. [cited 2019 March 26].
36. Institute national de la santé et la recherché medicale (INSERM). About Inserm. Available from: https://www.inserm.fr/en/about-inserm. [cited 2019 March 26].
37. Small H. Co-citation in the scientific literature a new measure of the relationship between two documents. J Am Soc Inform Sci. 1983;24:265–9.
38. Martyn J. Bibliographic coupling. J Doc. 1964;20:236.
39. Cancino CA, Merigo JM, Caronado FC. A bibliometric analysis of leading universities in innovation research. J Innovation Knowl. 2017;2:106–24.
40. Vichinsky E. Chronic organ failure in adult sickle cell disease. Hematology Am Soc Hematol Educ Program. 2017;2017(1):435–9.
41. Vichinsky E, Tones M, Minniti CP, Barrette S, Habr D, Zhang Y, et al. Efficacy and safety of deferasinox compared with deferoxamine in sickle cell disease: two-year results including pharmacokinetics and concomitant hydroxyurea. Am J Hematol. 2013;88(12):1068–73.
42. Kassim A, DeBaun MR. The case for and against initiating either hydroxyurea therapy, blood transfusion therapy or hematopoietic stem cell transplant in asymptomatic children with sickle cell disease. Expert Opin Pharmacother. 2014;15(3):325–36.
43. DeBaun MR, Kirkham FJ. Central nervous system complications in sickle cell disease. Blood. 2016;127(7):829–38.
44. Hanna J, Wernig M, Markoulaki S, Sun CW, Meissner A, Cassady JP, et al. Treatment of sickle cell anemia mouse model with ips cells generated from autologous skin. Science. 2007;18(5858):1920–3.
45. Gao Y, Wang Y, Zhai X, He Y, Chen RE, Zhou J, et al. Publication trends of research on diabetes mellitus and T cells (1997-2016): a 20-years bibliometric study. PLoS One. 2017;12(9):e0184869.
46. Li T, Ho YS. Bibliometric analysis on global Parkinson's disease research trends during 1991-2006. Neurosci Lett. 2008;441:248–52.
47. Zhao J, Yu G, Cai M, Lei X, Yang Y, Wang Q, et al. Bibliometric analysis of global scientific activity on umbilical cord mesenchymal stem cells: a swiftly expanding shifting focus. Stem Cell Res Ther. 2018;9(1):32.
48. Gómez I, Bordons M. Limitaciones en el uso de los indicadores bibliométricos para la evaluación científica. Política Científica. 1996;46:21–6.