Am J Transl Res 2023;15(3):1569-1589
www.ajtr.org /ISSN:1943-8141/AJTR0148381

*Original Article*

# The research landscape on vascularized composite allografts: a bibliometric analysis (2002-2021)

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Received December 10, 2022; Accepted February 6, 2023; Epub March 15, 2023; Published March 30, 2023

**Abstract:** Objective: Vascularized composite allografts (VCAs) refer to the transplantation of multiple types of tissues during plastic and reconstructive surgery. Several publications have emerged in the field of VCA. However, there are no bibliometric studies on this topic. The aim was to multidimensionally analyze the knowledge base and hotspots in this subject. Methods: We retrieved all publications related to VCA from the Web of Science Core Collection (WoSCC), published from 2002 to 2021. Next, scientometric analysis of different items was performed using various bibliometrics software to explore knowledge base, research hotspots, and advancement trends in this field. Results: We included a total of 3,190 English articles from 2002 to 2021. The number of publications increased steadily annually. The United States produced the highest number of publications, followed by China. Most publications were from Harvard University, followed by Johns Hopkins University. The most authoritative academic journal was Plastic and Reconstructive Surgery. Transplantation occupied the first rank of co-cited journal list. Maria Z Siemionow may have the highest influence in the VCA field with the highest number of citations (n = 88) and co-cited references (n = 1252). Clinical studies on different allografts, immunosuppression, and tissue engineering were both the knowledge base and recent topics in VCA research. Conclusions: The first bibliometric study comprehensively summarized the trends and development of VCA research with steady growth over the past two decades. Currently, the most active topics are the clinical application of multiple allografts, immunosuppression strategies/therapies, and translation of tissue engineering to clinical practice.

**Keywords:** Scientometric, vascularized composite allografts, VOSviewer, CiteSpace, transplantation immunity, tissue engineering

## Introduction

Vascularized composite allografts (VCAs) refer to transplantations that are based on anatomical components, which include multiple types of tissues, such as the skin, tendons, bone joints, muscles, fascial flaps, cartilage, and neurovascular elements among others. Unlike solid organ transplantation, tissue transplantation is not aimed at extending lives but at functional reconstruction [1]. Bumbaširević M [2] reported that annually, approximately 4.66 million Europeans and 2 million Americans may benefit from vascularized composite transplantation related studies. These studies inform on reintegration or embodiment of allografts for surgical amputation of tumors, accident-associated trauma and congenital malformations when standard reconstructive options are exhausted and autologous ingredients are not available. In 1964, the first human full-hand transplantation stimulated subsequent developments in this field [3]. To date, VCA transplantations have been performed on more than 120 extremities, 40 faces and recently, genitouterine transplantations have been done. Morever, various experimental investigations have achieved substantive clinical attention worldwide [4]. Therefore, the development and advancement of this transplantation technology may ease the burden of social welfare, improve the quality of life, and enhance the reintegration of most disabled patients into their family and social environments [5].

Clinically, VCAs have the potential for becoming standard/routine treatment options for patients with large tissue defects who require life quality enhancement and functional reconstruction. The challenges associated with applications of VCAs include: 1) Real risks for complications and chronic rejection [6]; 2) Inconclusive findings with regards to its benefits and risks (medicinal, ethical and finance) [7]; 3) Uncertainty and inconstancy among patients and surgical teams [8]. So far, the advanced technology has impressed scholars a lot, while there remains a lot of frontier keypoints that need attention. Some studies [9, 10] have proposed the concept of precise diagnosis of rejection in VCA, accurately identifying immune pathways, cell types and stages, which shows profound understanding about complex immunobiology in this field and it has emerged as a promising new avenue. Meanwhile, decellularization and recellularization were attempts to retain tissue-specific composition and extracellular matrix architecture, resulting in personalized and precise allografts and reduced immunosuppression [11-13].

Bibliometric methods refer to the process of transforming something intangible into a manageable subject, assessing numerous studies from institutions or countries, and substituting these quantitative estimates with scientific, accurate and definitive statements using mathematical and statistical methods. Compared to meta-analyses and reviews, bibliometric methods can achieve the aim of presenting macro status and demonstrating societal effects of research in multi-dimensions. Scientometric analyses can compensate for their limitations in a complementary fashion [14]. During the past several decades, an increasing number of studies in the field of VCA have been published, revealing the necessity for systematic assessment of these studies. Bibliometric methods can quantitatively assess the influence and development of individual/team studies in a particular field, and reveal various facets as well as research characteristics, providing the directions and potential for further research [15, 16]. Bibliometric analyses can be performed using multiple softwares or online platforms, including VOSviewer [17], CiteSpace [18], HistCite [15], R-bibliometrix [19], and Python [20] among others. Various bibliometric studies in different fields have been published. For instance, Ke [21] reported that the hotspots for drug-induced liver injury (DILI) studies include molecular mechanisms and explorations of new approaches to overcome it. Lu [22] reported the the main research topics on peptide receptor radionuclide therapy (PRRT) are its efficacy and safety, individual doses and advancement of medical imaging techniques. However, currently, there are no systematic bibliometric studies on VCAs. Therefore, we analyzed VCA related studies published in the last two decades to improve on the current knowledge base, establish hot topics, emerging information and to inform on new research directions.

## Materials and methods

### *Sources of bibliometric data and search strategy*

We systematically searched The Web of Science Core Collection (WoSCC) on May 25, 2022 at Xiangya Hospital, Central South University to collate vascularized composite allograft (VCA) related studies published from 2002 to 2021. The database source was set as Science Citation Index Expanded (SCIE) and study types were limited to “articles” or “reviews”. The main search details were: “composite tissue allografts”, “vascularized composite allotransplantation”, “vascularized allograft”, “vascularized composite allografts”, “vascularized allogeneic tissue”, and “vascularized composite tissue transplantation” among others. The detailed search strategies are presented in the **Appendix**. The publication language was restricted to English and two independent examiners (NS and LK) simultaneously downloaded all eligible data in the TXT format. To account for potential bias, only articles and reviews from the WoSCC were subjected to further analyses. Irrelevant literature and duplications were excluded. Any divergent viewpoints between the two authors (NS and LK) were solved by discussions and a third party (JT) was consulted for unresolved agreements.

### *Statistical analysis*

Related data were extracted from the publications to construct a simulated regression model using Microsoft Office Excel 2019 (Microsoft, Redmond, Washington, USA). The regression model ($f(x) = p0x^n + p1x^{n-1} + p2x^{n-2} + p3x^{n-3} + \ldots + pn$) was used to analyze the annual output

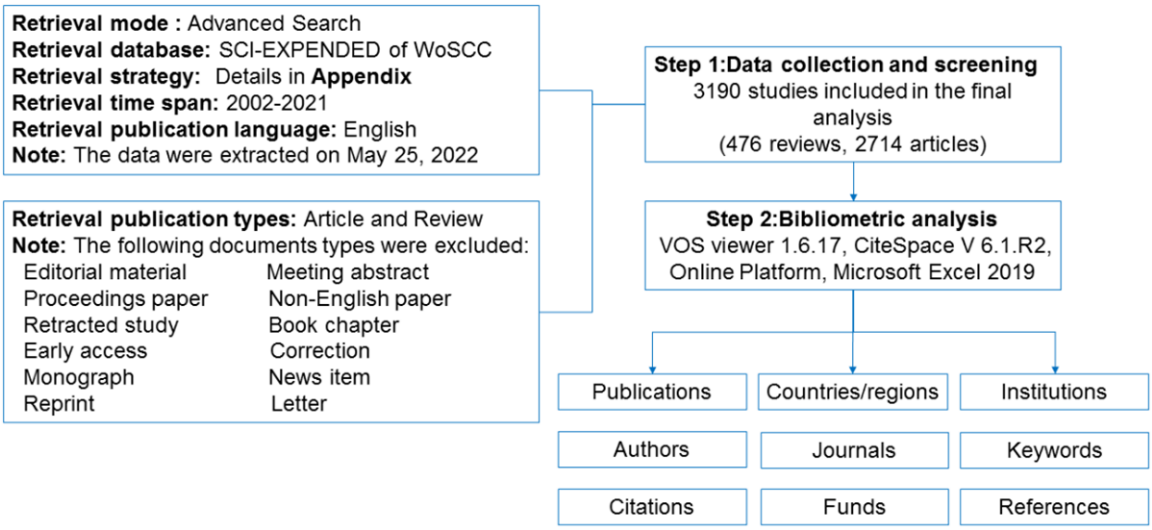


**Figure 1.** Flowchart summarizing the literature search and selection process on VCA. Vascularized composite allograft (VCA).

and to predict the number of publications in 2022. The volume of studies and corresponding year are represented by variables f(x) and x, respectively. Data management and establishment of column charts, bar charts and country distribution maps were performed by Excel. Visualization of VCA research maps was done using VOSviewer (1.6.17): relationship map of co-authorship and co-citation, as well as co-occurrence analysis of keywords [23]. References with strong citation bursts and a dual-map overlay for journals were extracted and contructed by CiteSpace 6.1. R2 64-bit (Pro. Chaomei Chen from Drexel University) to investigate the development trends in a special field. CiteSpace parameters were set as: link retaining factor (LRF = 3), e for top N (e = 1), time interval (2002–2021), years per slice (1), look backyears (LBY = 5), links (strength: cosine, scope: within slices), selection criteria (g-index: k = 10), and minimum duration (MD = 1). Besides, we used the online platform of scientometrics (https://bibliometric.com/) to analyze the frequency of keywords (expanded or not) and academic cooperation networks between countries.

## Results

### *Publication output and trends*

As shown in **Figure 1**, a total of 3,190 VCA studies were identified to have been published between 2002 to 2021, including 2,714 articles and 476 reviews. The annual output of publications on VCA exhibited an increasing trend from 2002 to 2021 (**Figure 2**). There were over 200 published studies in 2017, with 2004 being the year with the least number of publications (n = 69, 2.16%). The average output for the 20 years was about 160. Since 2011, the output exceeded the average publications (n = 192, 6.02%) and were maximum in 2020 (n = 259, 8.12%). To assess the correlations between corresponding years and output, we constructed a curve of best fit (**Figure 2**), which showed that the number of studies will increase to about 265 in 2022. From 2002 to 2021, the average increase in the number of studies was 8.99%.

### *Most prolific countries/regions, funds and institutions analysis*

There were 3,190 co-authored studies published by 2,878 institutions from 75 countries/regions. **Table 1** shows the top 10 prolific countries/regions and institutions based on the number of total publications. The countries were distributed in three continents; 5 in Europe, 3 in Asia and 2 in North America. The United States had the largest number of studies (n = 1459, 45.74%), followed by China (n = 550, 17.24%) and Germany (n = 205, 6.43%), respectively. The rest had less than 200 publications each: France (n = 190); Japan (n = 173); United Kingdom (n = 166); Italy (n = 158); South Korea (n = 120); Austria (n = 108) and Canada

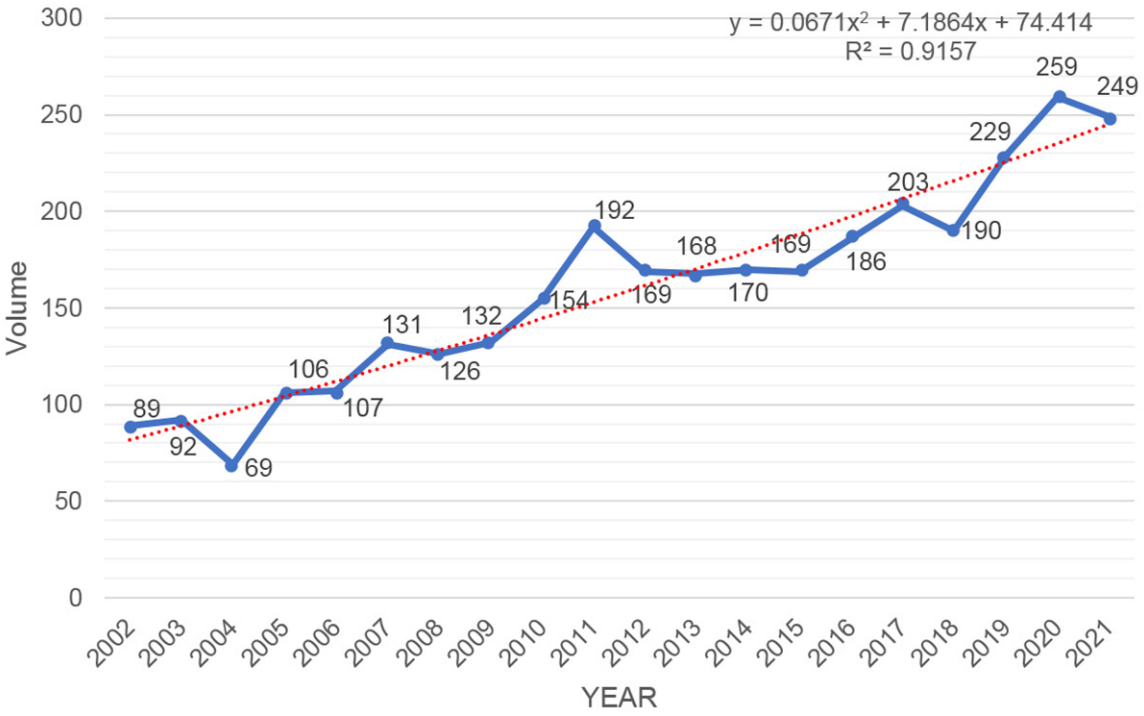


**Figure 2.** The polynomial curve fitting of publication growth in VCA. Vascularized composite allograft (VCA).

**Table 1.** The top 10 countries/regions and institutions involved in VCA research

| RANK | Countries/regions | Publications, n | % of 3190 | Institutions | Publications, n |
|---|---|---|---|---|---|
| 1 | USA (North America) | 1459 | 45.74 | Harvard University (USA) | 287 |
| 2 | China (Asia) | 550 | 17.24 | Johns Hopkins University (USA) | 137 |
| 3 | Germany (Europe) | 205 | 6.43 | Brigham & Women's Hospital (USA) | 136 |
| 4 | France (Europe) | 190 | 5.96 | Cleveland Clinic Foundation (USA) | 121 |
| 5 | Japan (Asia) | 173 | 5.42 | Pennsylvania Commonwealth System of Higher Education (USA) | 118 |
| 6 | UK (Europe) | 166 | 5.20 | League of European Research Universities (LERU, Europe) | 116 |
| 7 | Italy (Europe) | 158 | 4.95 | Massachusetts General Hospital (USA) | 116 |
| 8 | South Korea (Asia) | 120 | 3.76 | University of Pittsburgh (USA) | 111 |
| 9 | Austria (Europe) | 108 | 3.39 | Mayo Clinic (USA) | 85 |
| 10 | Canada (North America) | 96 | 3.01 | #Harvard Medical School (USA) | 81 |
| | | | | #Udice-French Research Universities (France) | 81 |

#: Equal Publications, Rank: according to the number of total publications.

(n = 96). In **Figure 3A**, the sum of outputs from the United States and China markedly exceeded the sum of the rest, which showed that the former two countries represented red and purple color (**Figure 3B**). As shown in **Figure 3C**, we established the co-authorship network map based on countries/regions (35/75, 46.67%) whose publication numbers were set to be ≥ 9 (T ≥ 9). Due to a high number of publications, the United States, China, Germany, and France showed larger sizes of nodes. The network map also revealed active cooperations among countries/regions. Cooperations among the United States, China, Germany, Austria and France were much closer; China exhibited active cooperations with the United States, Japan, United Kingdom, and Germany among others. In addition, as shown in **Figure 3D**, the yellow colors denote the countries/regions that had more emerging studies or rapid developments in the VCA field, including China, India, Turkey, Iran, and South Korea among others. **Figure 3E** shows the top 10 most prolific funding agencies in this field, and eight ranks were occupied by

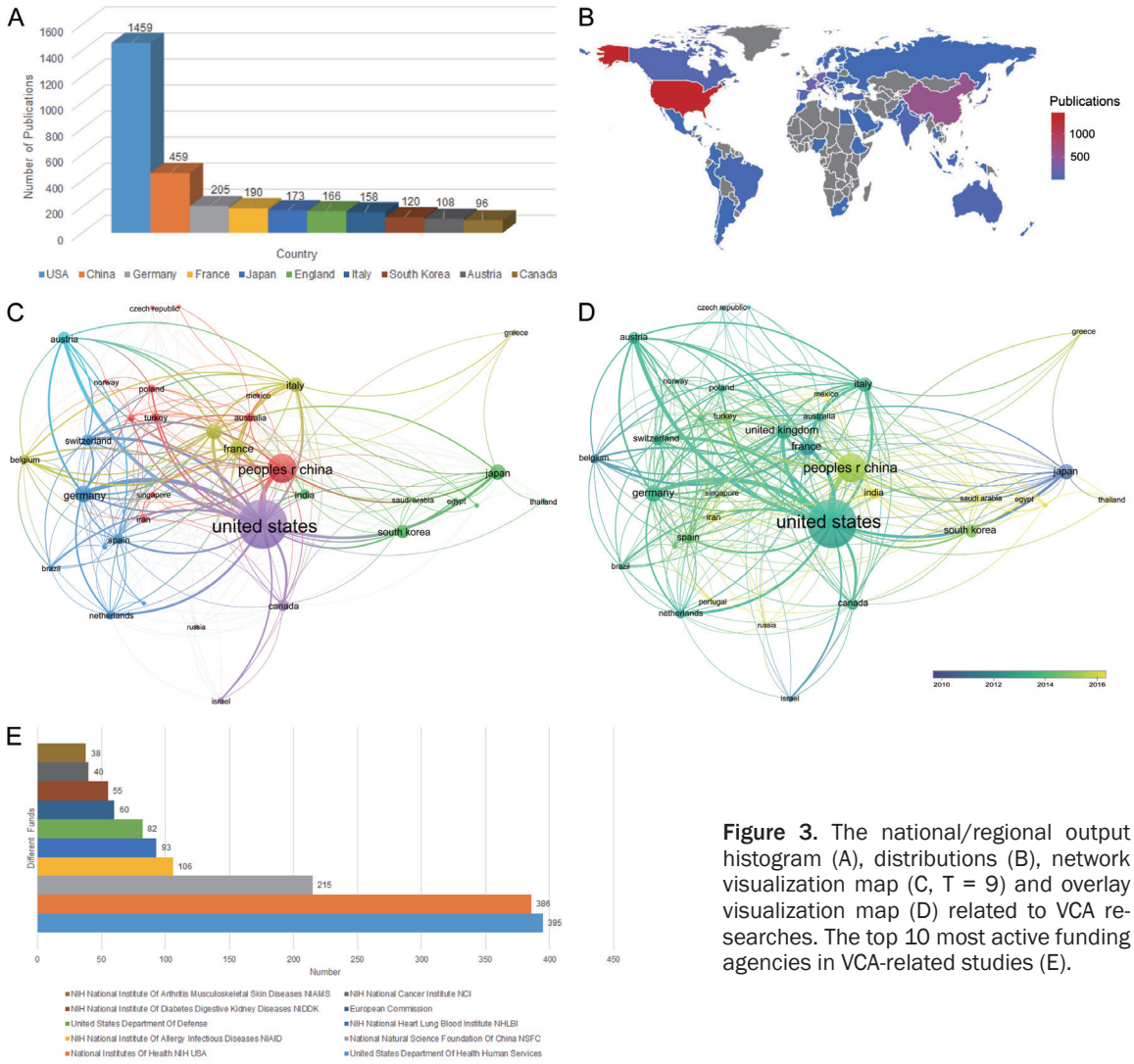


**Figure 3.** The national/regional output histogram (A), distributions (B), network visualization map (C, T = 9) and overlay visualization map (D) related to VCA researches. The top 10 most active funding agencies in VCA-related studies (E).

the United States, one by China, and the remaining one was by the European Commission. **Table 1** shows the top 10 most prolific institutions, all of which are from three countries. Eight of them are from the United States. Harvard University had the largest number of publications (n = 287), followed by Johns Hopkins University (n = 137) and Brigham & Women's Hospital (n = 136). The rest of the institutions had less than 126 publications each (top 10 average output), including Cleveland Clinic Foundation (n = 121), Pennsylvania Commonwealth System of Higher Education (n = 118), League of European Research Universities (n = 116), Massachusetts General Hospital (n = 116), University of Pittsburgh (n = 111), Mayo Clinic (n = 85), Harvard Medical School (n = 81) and Udice-French Research Universities (n = 81). **Figure 4** shows the co-authorship network based on institutions (98/2878, 3.41%) with more than or equal to 11 (T = 11) publications. In **Figure 4A**, Harvard University and Johns Hopkins University are shown to have larger sizes of nodes, denoting a high number of publications. Collaborations among different institutions were also active. For instance, collaborations among Harvard University, Massachusetts General Hospital, Brigham & Women's Hospital and Johns Hopkins University were closer; Johns Hopkins University had active collaborations with the University of Pittsburgh, Medical University of Innsbruck and Johns Hopkins University among others. In addition, as shown in **Figure 4B**, dark yellow colors denote institutions that had more emerging studies or rapid developments in this

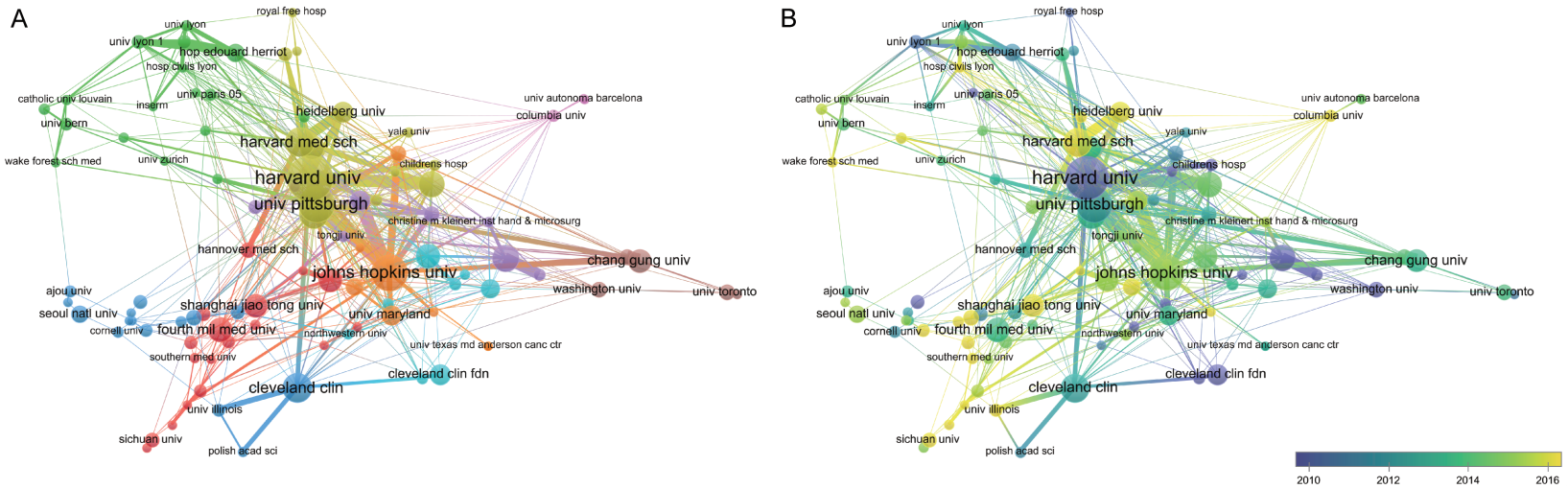


**Figure 4.** Analysis of institutions involved in VCA research. The network visualization map (A, T = 11) and overlay visualization map (B). Vascularized composite allograft (VCA).

field, including Harvard Medical School, Shanghai Jiao Tong University, Sichuan University, Stanford University, Wake Forest University School of Medicine and Chinese Academy of Sciences among others.

*Analysis of journals and co-cited academic journals*

A total of 779 academic journals were found to have been published on VCA, with *Plastic and Reconstructive Surgery* (n = 169, 5.30%, $IF_{2021}$ = 5.169, Q1) ranking first, followed by *Transplantation* (n = 168, 5.27%, $IF_{2021}$ = 5.385, Q1/Q2). Among the top 11 most prolific journals (**Table 2**), 7 (63.63%) were from the United States, 2 (18.18%) were from Denmark, while the remaing two were from the Netherlands and the UK. Among the top 11 journals, *Biomaterials* had the highest impact factor (n = 62, $IF_{2021}$ = 15.304, Q1), followed by *American Journal of Transplantation* (n = 111, $IF_{2021}$ = 9.369, Q1). The above four journals were also the top four most co-cited journals, each of which had more than 3,000 co-citations. *Transplantation* had the highest number of co-citations (n = 7038), followed by *Plastic and Reconstructive Surgery* (n = 6064), *Biomaterials* (n = 5510) and *American Journal of Transplantation* (n = 3744). Over half of the top 10 cited journals were identified in Q1 or Q2. **Table 2** shows the variations with regards to publishers of the top 10 cited and co-cited journals, who included LIPPINCOTT WILLIAMS & WILKINS to ELSEVIER and WILEY.

In **Figure 5**, topic distribution of the journals are presented by dual-map overlay of journals. Citing and cited journals are shown on either side. From left to right, the colors denote cited relationships, for instance, orange, green, red, gray paths, and the different clusters represent different areas. Six main citation ways were discerned, two purple, two orange and two green paths. The orange path shows that the studies published in Molecular/Biology/Genetics journals and Health/Nursing/Medicine journals were frequently cited by studies published in Molecular/Biology/Immunology journals. The purple path shows that studies published in Chemistry/Materials/Physics journals and Molecular/Biology/Genetics journals were frequently cited by studies published in Physics/Materials/Chemistry journals. The green path shows that studies published in Molecular/Biology/Genetics journals and Health/Nursing/Medicine journals were frequently cited by studies published in Medicine/Medical/Clinical journals.

*Authors and co-cited author analysis*

A total of 14,440 researchers have published on VCA. The top four researchers with the most outputs were Maria Z Siemionow (n = 88), Gerald Brandacher (n = 87), W P Andrew Lee (n = 85) and Bohdan Pomahac (n = 85) (**Table 3**). Co-authorship and citation networks among different researchers were analyzed by VOSviewer (**Figure 6**). Consistent with findings in **Table 3**, due to a high number of outputs, nodes of the above four authors were much larger than those of the other authors. The co-occurrence relationship in **Figure 6A** reveals close collaborations among different authors. It is shown that more active authors had more co-occurrence frequencies with other researchers. An overlay visualization map of co-authorship in **Figure 6B** shows several Cenozoic co-authorship clusters, including Bohdan Pomahac, Vijay S Gorantla, Curtis L Cetrulo Jr (not in the top 10 authors list) and Eduardo D Rodriguez related clusters, with a high number of publications in the recent five years.

Two authors were considered as being co-cited when at least one document from each author occurs in the same reference list [22]. According to the top 10 co-cited author list (**Table 3**), Maria Z Siemionow ranked first (n = 1252), followed by Jean-Michel Dubernard (n = 644), and Palmina Petruzzo (n = 615), all of whom had more than 500 co-citations. The other seven researchers had co-citations between 284 and 483. VOSviewer was used to construct the visualization map of co-citations based on authors (22/54,321, 0.04%) with co-citations ≥ 180 (T ≥ 180). In **Figure 6C**, Maria Z Siemionow had the largest sized node for the most co-citations, and also had positive co-cited relationships with Jean-Michel Dubernard, Palmina Petruzzo, Stefan Schneeberger and Chad R Gordon; Jean-Michel Dubernard had strong co-cited relationships with Maria Z Siemionow, Jean-Michel Dubernard, Palmina Petruzzo and Stefan Schneeberger among others.

*Keyword co-occurrence and frequency*

The analysis of keywords and keyword expansion were conducted via the online bibliometric

**Table 2.** The top 10 journals and co-cited journals of VCA research

| RANK | Journal | Publisher | Output | % of 3190 | JIF2021* | Q* | Co-cited Journal | Publisher | Co-citation | JIF2021* | Q* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Plastic and Reconstructive Surgery (United States) | LIPPINCOTT WILLIAMS & WILKINS | 169 | 5.30 | 5.169 | Q1 | Transplantation (United States) | LIPPINCOTT WILLIAMS & WILKINS | 7038 | 5.385 | Q1/Q2 |
| 2 | Transplantation (United States) | LIPPINCOTT WILLIAMS & WILKINS | 168 | 5.27 | 5.385 | Q1/Q2 | Plastic and Reconstructive Surgery (United States) | LIPPINCOTT WILLIAMS & WILKINS | 6064 | 5.169 | Q1 |
| 3 | American Journal of Transplantation (Denmark) | WILEY | 111 | 3.48 | 9.369 | Q1 | Biomaterials (Netherlands) | ELSEVIER SCI LTD | 5510 | 15.304 | Q1 |
| 4 | Annals of Plastic Surgery (United States) | LIPPINCOTT WILLIAMS & WILKINS | 95 | 2.98 | 1.763 | Q3 | American Journal of Transplantation (Denmark) | WILEY | 3744 | 9.369 | Q1 |
| 5 | Transplantation Proceedings (United States) | ELSEVIER SCIENCE INC | 81 | 2.54 | 1.014 | Q4 | Clinical Orthopaedics and Related Research (United States) | LIPPINCOTT WILLIAMS & WILKINS | 2795 | 4.755 | Q1 |
| 6 | Microsurgery (United States) | WILEY | 68 | 2.13 | 2.08 | Q3 | Journal of Bone and Joint Surgery-American Volume (United States) | LIPPINCOTT WILLIAMS & WILKINS | 2341 | 6.558 | Q1 |
| 7 | Biomaterials (Netherlands) | ELSEVIER SCI LTD | 62 | 1.94 | 15.304 | Q1 | Lancet (England) | ELSEVIER SCIENCE INC | 2137 | 202.731 | Q1 |
| 8 | Current Opinion in Organ Transplantation (United States) | LIPPINCOTT WILLIAMS & WILKINS | 57 | 1.79 | 2.269 | Q3 | Journal of Immunology (United States) | AMER ASSOC IMMUNOLOGISTS | 1952 | 5.446 | Q2 |
| 9 | Journal of Plastic Reconstructive and Aesthetic Surgery (UK) | ELSEVIER SCI LTD | 54 | 1.69 | 3.022 | Q2 | Microsurgery (United States) | WILEY | 1630 | 2.08 | Q3 |
| #10 | Journal of Reconstructive Microsurgery (United States) | THIEME MEDICAL PUBL INC | 52 | 1.63 | 2.329 | Q3 | New England Journal of Medicine (United States) | MASSACHUSETTS MEDICAL SOC | 1616 | 176.079 | Q1 |
| #10 | Transplant International (Denmark) | WILEY | 52 | 1.63 | 3.842 | Q1/Q2 | | | | | |

#10: Equal Output, JIF2021*: Journal Impact Factor 2021, Q*: Quartile in Category (2021).

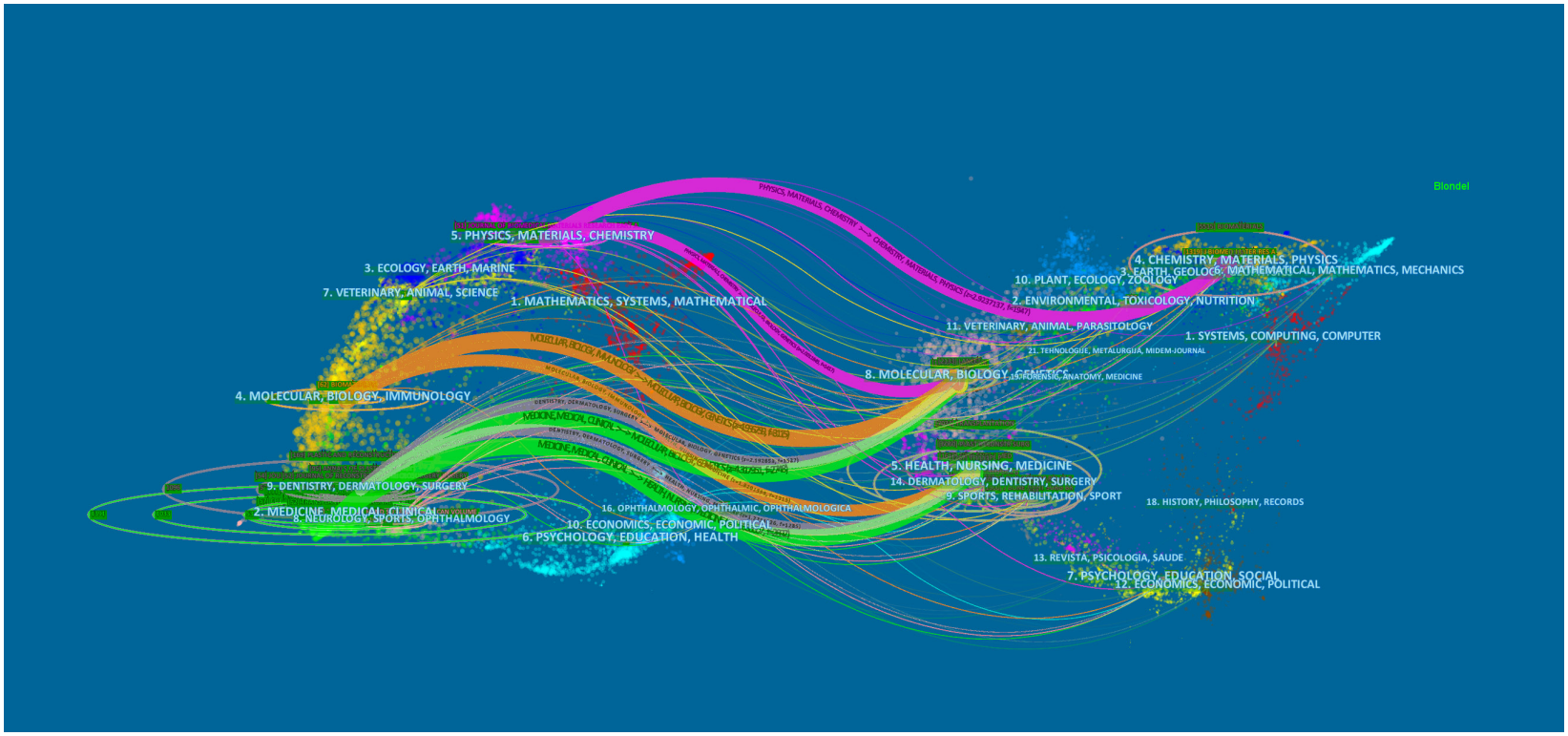


**Figure 5.** A dual-map overlay of journals related to VCA research. Vascularized composite allograft (VCA).

**Table 3.** The top 10 authors and co-cited authors involved in research on VCA research

| RANK | Author | Count | Co-cited Author | Count |
|---|---|---|---|---|
| 1 | Maria Z Siemionow | 88 | Maria Z Siemionow | 1252 |
| 2 | Gerald Brandacher | 87 | Jean-Michel Dubernard | 644 |
| 3 | W P Andrew Lee | 85 | Palmina Petruzzo | 615 |
| 4 | Bohdan Pomahac | 85 | Jean Kanitakis | 483 |
| 5 | Stefan Schneeberger | 62 | Stefan Schneeberger | 450 |
| 6 | Vijay S Gorantla | 57 | W P Andrew Lee | 365 |
| 7 | Eduardo D Rodriguez | 52 | Bohdan Pomahac | 304 |
| 8 | Lawrence Scott Levin | 43 | Linda C Cendales | 352 |
| 9 | Palmina Petruzzo | 38 | Laurent Lantieri | 304 |
| 10 | Emmanuel Morelon | 36 | Marco Lanzetta | 284 |

analysis platform. Keyword expansion is aimed at identifying and extracting a set of related and potential keywords based on a series of given initial keywords, outperforming the conventional statistical methods and enriching the limited initial keywords [52]. The color of the square denotes different keywords, while the height represents the relative frequency of the corresponding keyword. **Figure 7** shows the keywords (**Figure 7A**) and expanded keywords (**Figure 7B**). The following keywords were relatively stable and frequent over the past two decades: tissue engineering, immunosuppression, *in-vitro*, mesenchymal stem-cells and survival among others. The emerging keywords and expanded keywords in the recent five years included bone tissue engineering, regenerative medicine and mesenchymal stem-cells among others.

Keywords with an occurrence of at least 12 times were included in the analysis by VOSviewer. After screening and deleting irrelevant and repetitive keywords, 462 keywords were identified. Different colors represent different research directions, and similar research directions were grouped in the same color. The sizes of nodes represent the frequency of co-occurrence, while lines between points represent connections between different keywords. As shown in **Figure 8A**, four clusters were classified based on keywords: Cluster 1 (tissue engineering related research, red nodes); Cluster 2 (allografts immune rejection & tolerance research, green nodes); Cluster 3 (experimental model research, blue nodes); and Cluster 4 (allografts preclinical & clinical research, golden nodes). **Figure 8B** shows findings from keywords co-occurrence analysis based on an overlay visualization map. Scale color changes contained blue-green-yellow-red, indicating the year span from 2002 to 2021. Among them, Cluster 1 and 3 included many more red nodes, containing keywords like hydrogels, fabrication, hyaluronic-acid, titanium, phosphate, polycarbonate, nanoparticles, 3d printing, osteogenic differentiation, drug-delivery; double jaw, cost-analysis, functional outcomes, and intercalary reconstruction.

*Co-cited references analysis*

Co-cited references refer to studies in which two or more references are cited together by other publications [24]. Among the 3,190 VCA-related studies, there were 84,852 co-cited references. The top 10 co-cited references (≥ 120 times) and the top four references with at least 200 co-citations are shown in **Table 4**. For instance, Dubernard JM [25] published a study entitled "Human hand allograft: report on first 6 months" in *Lancet*, and this publication occupied the first rank due to the high number of co-citations (n = 261), followed by Devauchelle B [26] in *Lancet* (2006, n = 231), Cendales LC [27] in *American Journal of Transplantation* (2008, n = 218) and Petruzzo P [28] in *Transplantation* (2010, n = 201). The other six references had co-citations from 120 to 189. In addition, Dubernard JM had two publications in the top 10 co-cited references and 70% (7/10) of them were in *Lancet* or *The New England Journal of Medicine* journals.

*Burstness of references*

Citation burstness of references refers to the studies that are widely cited in a specific subject at any timespan, which can show the exploration process and predict research directions [15] (**Figure 9**). With regards to citation bursts, the right timeline with blue color or red segments denotes the time span, and each single bar denotes a year, showing the beginning, ending and duration time. From 2005 to 2018, apart from 2014, there were annual citation burst references. Among them, the strength of 25% (5/20) references were more than 30, and

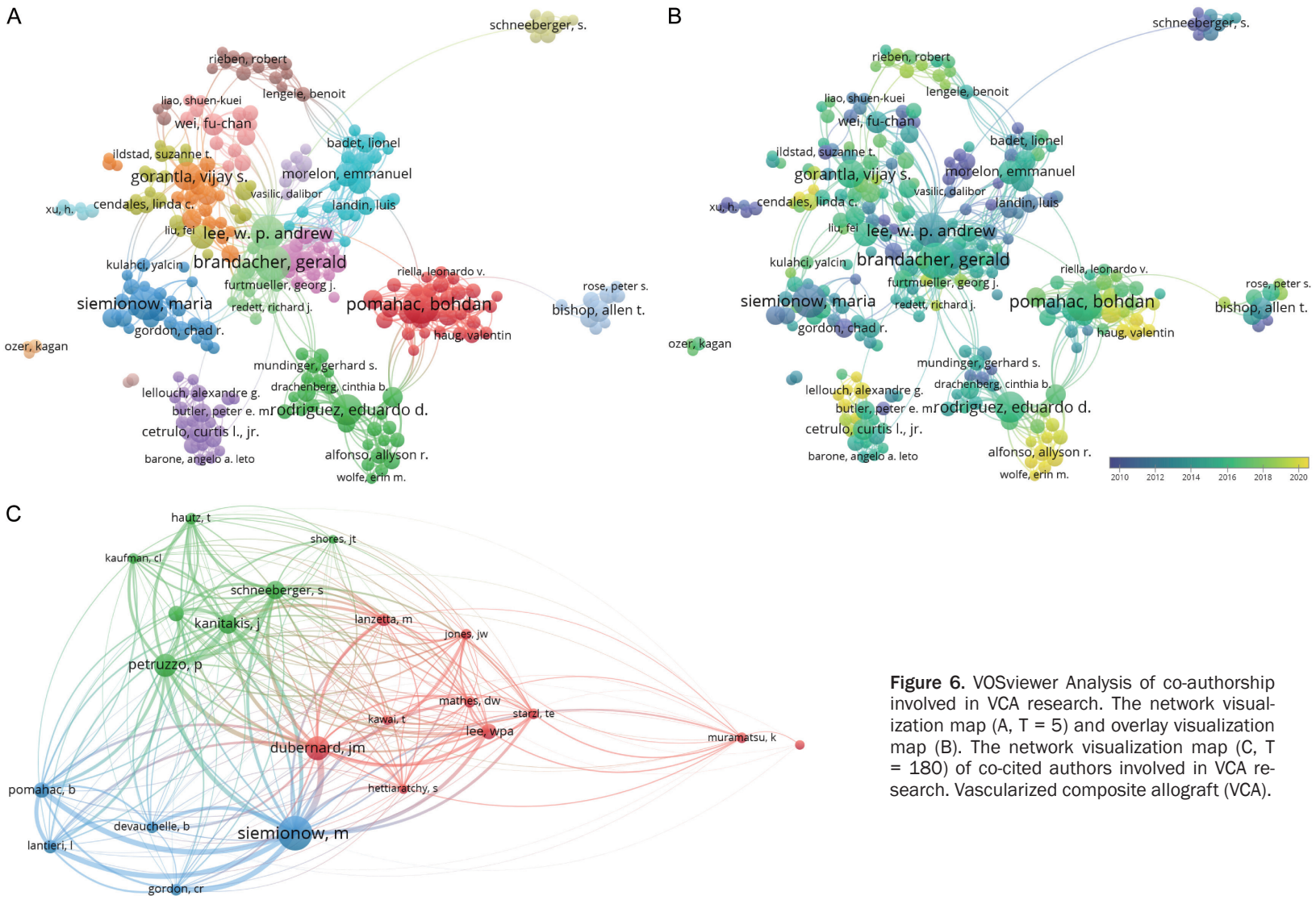


**Figure 6.** VOSviewer Analysis of co-authorship involved in VCA research. The network visualization map (A, T = 5) and overlay visualization map (B). The network visualization map (C, T = 180) of co-cited authors involved in VCA research. Vascularized composite allograft (VCA).

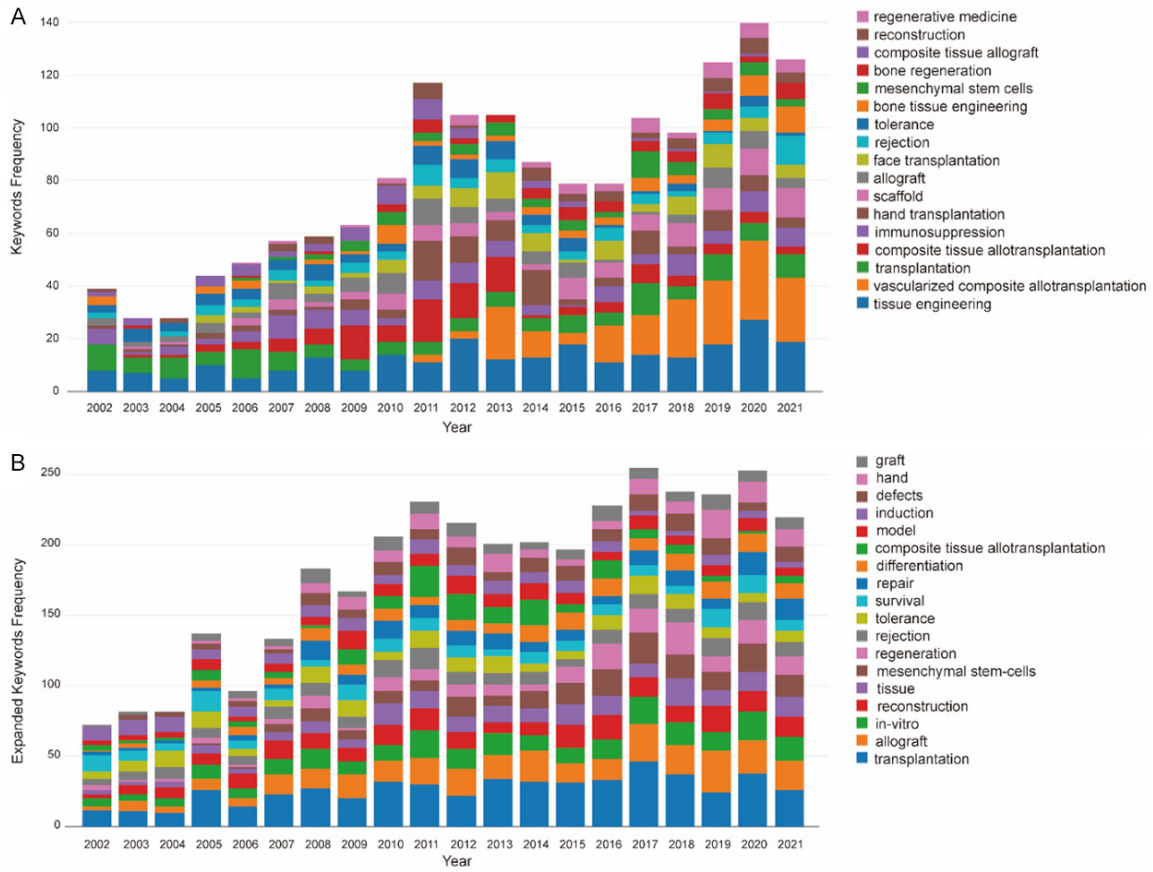


**Figure 7.** Frequency analysis of keywords (A) and expanded keywords (B) from 2002 to 2021.

the strongest burstness (strength = 38.17) was caused by the study entitled "First human face allograft: early report", published by Devauchelle B [26] with citation bursts ranging from 2007 to 2011. Onset years of citation bursts for the rest of the four references were 2008, 2011, 2015 and 2016. The study entitled "The International Registry on Hand and Composite Tissue Transplantation", published by Petruzzo P [28] in *Transplantation* had citation bursts from 2011 to 2015 (strength = 37.51), followed by "Facial transplantation: the first 9 years", published by Khalifian S [29] in *Lancet,* which had citation bursts from 2015 to 2019 (strength = 34.5). "Hand and upper extremity transplantation: an update of outcomes in the worldwide experience", published in *Plastic and Reconstructive Surgery* by Shores JT [30] had citation bursts from 2016 to 2021 (strength = 31.61), while "Outcomes 18 months after the first human partial face transplantation" published by Dubernard JM [31] in *The New England Journal of Medicine* showed citation bursts (strength = 31.18) from 2008 to 2012. Among the references with a cutoff date before 2020, "Upper-extremity transplantation using a cell-based protocol to minimize immunosuppression", published by Schneeberger Sin *Annals of Surgery* had the longest burst duration (5 years). Besides, there were four references [30, 32-34] whose highlight period lasted until the time of analysis. In general, the strengths of the top 20 VCA-related publications ranged from 18.32 to 38.17 with a lasting timespan from 3 to 5 years.

## Discussion

### *General information*

In this bibliometric analysis, based on 2002–2021 studies data from SCI-EXPANDED in the WoSCC, we included 3,190 English-language studies published in 779 academic journals by 2,878 institutions from 75 countries/regions with 84,852 co-cited references. The analysed terms involved the current status, development

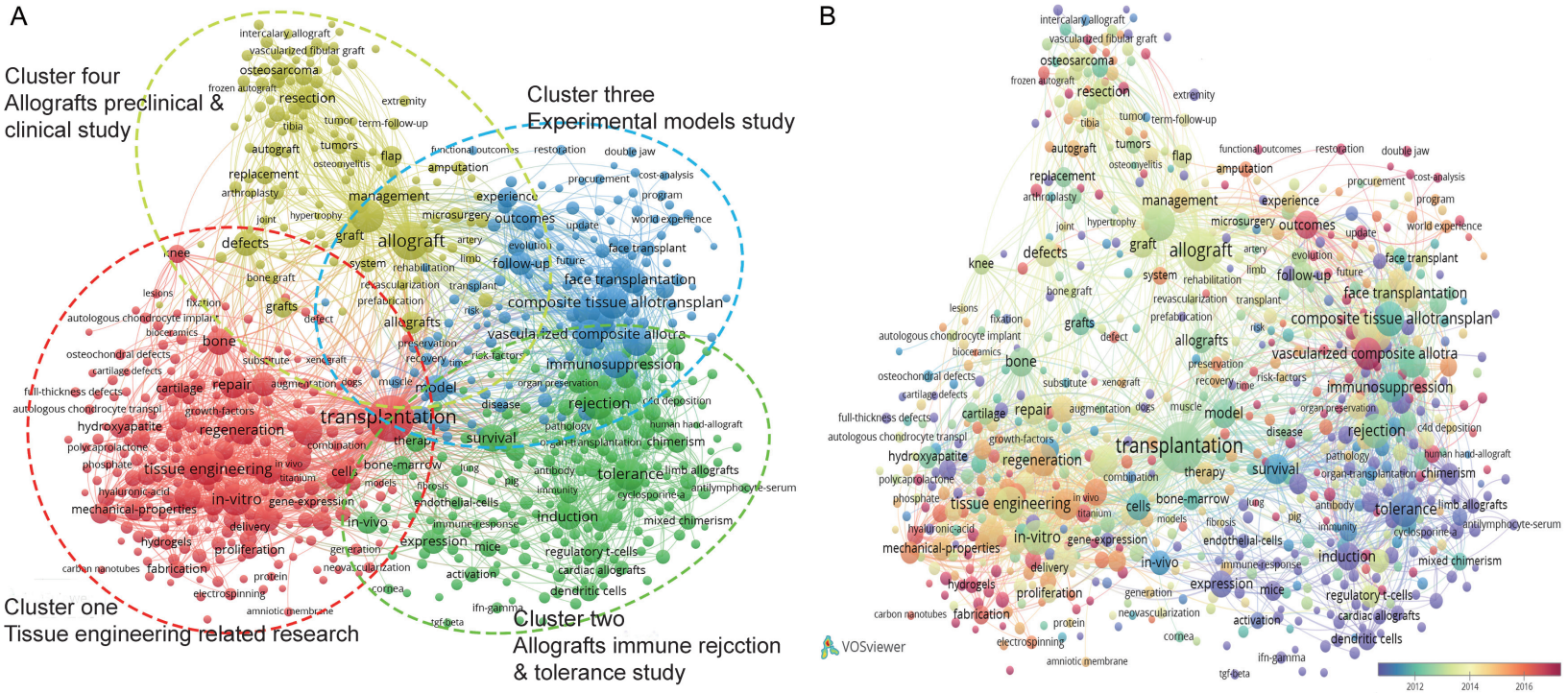


**Figure 8.** A. Network map showing keywords analysis by VOSviewer. B. Overlay visualization map of keywords and corresponding year analysis in the VCA field. Vascularized composite allograft (VCA).

**Table 4.** The top 10 co-cited references involved in research on VCA

| RANK | Co-cited reference | Count | $IF_{2021}$# |
|---|---|---|---|
| 1 | Dubernard JM, 1999, Lancet, V353, P1315 | 261 | 202.731 |
| 2 | Devauchelle B, 2006, Lancet, V368, P203 | 231 | 202.731 |
| 3 | Cendales LC, 2008, Am J Transplant, V8, P1396 | 218 | 9.369 |
| 4 | Petruzzo P, 2010, Transplantation, V90, P1590 | 201 | 5.385 |
| 5 | Lee WPA, 1991, Plast Reconstr Surg, V87, P401 | 189 | 5.169 |
| 6 | Dubernard JM, 2007, New Engl J Med, V357, P2451 | 172 | 176.079 |
| 7 | Jones JW, 2000, New Engl J Med, V343, P468 | 169 | 176.079 |
| 8 | Lantieri L, 2008, Lancet, V372, P639 | 130 | 202.731 |
| 9 | Guo SZ, 2008, Lancet, V372, P631 | 121 | 202.731 |
| 10 | Levi DM, 2003, Lancet, V361, P2173 | 120 | 202.731 |

# $IF_{2021}$: Impact Factor of 2021.

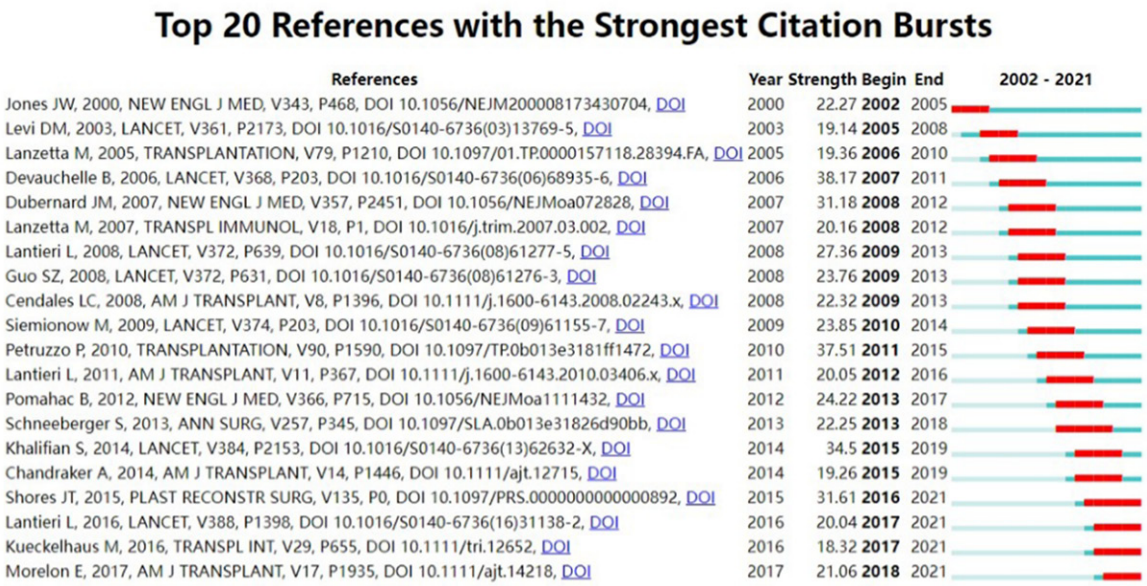


**Figure 9.** Top 20 references with strongest citation bursts.

trend, and future hot topics in this field. The annual publication of VCA-related studies exhibited an increasing trend from 2002 and 2021. According to the constructed curve of best fit, more than 260 studies will be published in 2022, indicating that this field is attracting more attention. The United States, China, and Germany occupied the top three ranks, and only China is the only developing country among the top 10 countries, implying a certain gap with regards to academic abilities on VCA research between developed and developing countries. Among the top 10 most prolific funding agencies, eight ranks were occupied by the United States, one by China, and the remaining one by the European Commission. In addition, eight ranks of the top 10 active institutions were occupied by the United States, demonstrating research advancement leadership of USA institutions in this field. Among them, Harvard University had the highest number of outputs, followed by Johns Hopkins University and Brigham & Women's Hospital, implying higher chances for more collaborations with these institutions. *Plastic and Reconstructive Surgery* and *Transplantation* had the highest number of publications, with *Transplantation* being the first in terms of co-citations. Among the top 10 journals and co-cited journals, 70% were from the United States, showing the important contributions and considerable influence of journals from the United

States. Most of the co-citation journals ranked Q1/Q2 and were defined as high-IF journals, greatly promoting quality advances in the VCA field. A series of these journals may be taken into consideration as our target journals for the sources and submissions. According to dual-map overlay of journal analysis, we discerned interdisciplinary research directions and hotspots. Among the authors, Maria Z Siemionow and Gerald Brandacher had significant contributions on the volume of publications. Maria Z Siemionow ranked first with regards to co-citations. The five authors; Maria Z Siemionow, W P Andrew Lee, Bohdan Pomahac, Stefan Schneeberger, and Palmina Petruzzo were all on the lists of top 10 profilic and co-cited authors, showing their significant influence in the VCA field. Notably, Maria Z Siemionow ranked double first in the above two lists, suggesting that their collaborations performed excellently well. The VOSviewer visualization map showed that these active authors and co-authors had stable and positive collaborations. In the two aforementioned lists of authors, Jean-Michel Dubernard, Linda C Cendales, Palmina Petruzzo, W P Andrew Lee, and Laurent Lantieri occupied five of the co-cited references.

*Knowledge base*

Co-citation relationships are usually evaluated by co-cited references, with the frequency that two or more studies are cited together by other studies, thus may be identified as a knowledge base of a special field [24]. The more times a set of publications are cited, the more meaningful they are in a subject. In this study, the knowledge base of VCA studies were identified by the top 10 co-cited references. The most co-cited study was published by Dubernard JM [25] in 1999, with 261 citations, which demonstrates the milestones of limb transplantation and advanced management in the peri-peration period. The successful feasibility of reimplantation induced multicentre pilot trials in collaboration with other teams. The study published by Devauchelle B [26] in *Lancet* had the 2nd highest number of co-citations. They reported on facial reconstructive surgery, with the immunosuppressive protocol of infusions of donor bone-marrow cells, and provided a novel monitor rejection system on the transplanted oral mucosa. In 2008, Cendales LC [27] published the 3rd co-cited paper in the *American Journal of Transplantation*. The working classification of skin-containing VCA pathology was refined, which proposed a set of standardized criteria for identifying and presenting severity and five grades of acute/chronic rejection in VCA. According to consensus from pathologists, clinicians, and first authors of relevant published studies, a working collective classification system for VCA rejection was established, advancing the understanding of VCA pathology and laying the foundation for clinical and basic investigations. The paper with the 4th highest number of co-citations was published in 2010 by Petruzzo P [28] in *Transplantation*. This study comprehensively analyzed 33 patients (49 hands) with hand transplantations performed from 1998 to 2010, providing a unique chance for interested centers performing VCA. The risks and benefits of the reconstructive transplantation procedures were identified based on multiple indicators, such as recipient/donor characteristics, functional recovery, motor recovery, quality of life (QoL) and all complications. The 5th most co-cited study was published in *Plastic and Reconstructive Surgery* by Lee WPA [35], which suggested a better realization of the immunogenic mechanisms of allografts and presented a wider expansion of applicable means of host immunosuppression. In 2007, Dubernard JM [31] published the 6th most co-cited study, in which long-term follow-up on the first human partial face allograft was conducted, with satisfactory sensitivity, motor recovery, functions and aesthetic results. In 2000, Jones JW [36] published the 7th most co-cited study in *The New England Journal of Medicine*. They developed a protocol for VCA applications and summarized the early successful results with no complications of graft rejection, healing and reintegration into regular social activities. They discussed the significance of adjusting drug doses for immunosuppression on clinical progress. In 2008, Lantieri L [37] published the 8th most co-cited study in *Lancet*. They reported that a patient suffering from congenital deformities/tumours (neurofibromatosis type 1, NF1) who had been subjected to facial transplantation had good functional outcomes, successful sensations and motor reinnervation, excellent psychological recovery and complete social reintegration. Moreover, they proposed three technical challenges associated with this

produce: resection of a disfiguring tumour or removal complexity of plexiform neurofibroma due to its vascularity; arduousness of donor yields; and multiple barriers of transplantation. Guo S [38] analyzed the first partial facial allotransplantation in China and published the 9th most co-cited paper. They showed promising outcomes of long-term follow up after facial allotransplantation, which may be an option for severe facial disfigurement despite three acute rejection episodes. The milestone clinical trial titled "Transplantation of the abdominal wall" published in *Lancet* by Levi DM [39] in 2003 was the 10th study with most co-citations. In their study, allotransplantations of the abdominal wall were proven to facilitate reconstruction of the abdominal compartment during intestinal transplantation. In their initial experience, HLA matching was not of significant clinical significance in this type of transplantation, however, ABO compatibility and matching sizes between the donor and recipient were of much greater importance.

In general, the following topics were in the top 10 co-citations: clinical research (partial or full facial allotransplantations, hand or limb transplantation and abdominal wall); a set of standardized criteria for VCA-related rejection; immunosuppressive protocol; and immunogenic mechanisms, which were the foundations for VCA clinical and basic research. The above results were consistent with the analysis of emerging keywords and expanded keywords in the recent five years.

*Emerging topics*

Usually, researchers show interest in publications with strong citation bursts during a given period [40]. Such studies represent an emerging topic in VCA-related research. The top 20 studies [26-34, 36-39, 41-47] with strong bursts were explored using the Citespace. From 2005 to 2018, except 2014, studies with citation burst appeared annually, accounting for almost all (19/20, 95%) of the top 20 studies with strong strength citations. This indicated that hot topics was not confined to a speficic period, but rather evenly distributed. Notably, 8 of the top 10 co-cited studies [26-28, 31, 36-39] were among the top 20 studies with the strongest citation bursts, and the remaining two were not due to the out-timespan from 2002 to 2021. To some extent, the 8 studies may lay the foundation for the VCA subject and will influence its advancement in the future. Among them, 5 studies with the strongest citation burstness were published by Devauchelle B [26] (2006, *Lancet*, strength = 38.17), Petruzzo P [28] (2010, *Transplantation*, strength = 37.51), Khalifian S [29] (2014, *Lancet*, strength = 34.5), Shores JT [30] (2015, *Plastic and Reconstructive Surgery*, strength = 31.61), and Dubernard JM [31] (2007, *The New England Journal of Medicine*, strength = 31.18). The strengths of these studies were more than 30. The 5 studies discussed the clinical application of VCA in the management of hands/upper extremities and (partial or full) facial allografts transplantation in different centers for the most risk/benefit ratio. The findings from these studies confirmed the technical feasibility of transplantation, discussed the procedure, postoperative side effects, and long-term management of follow-up. For the publications between 2002 and 2015, the main research topics were divided into the following categories: 1) clinical studies on different allografts including clinical trials and the technical feasibility of the surgical procedure in multiple interested centers which was covered by studies by Jones JW [36] in *The New England Journal of Medicine*, Levi DM [39] in *Lancet*, Lanzetta *M* [41] in *Transplantation*, Lanzetta M [42] in *Transplant Immunology*, Lantieri L [37] in *Lancet*, Guo S [38] in *Lancet*, Siemionow M [43] in *Lancet*, Lantieri L [44] in *American Journal of Transplantation* and Pomahac B [45] in *The New England Journal of Medicine*; 2) immunosuppression protocols and tests by Schneeberger S [46] in *Annals of Surgery* and Chandraker, A [47] in *American Journal of Transplantation*; 3) observation and monitor of acute/ chronic rejection by Cendales LC [27] in *American Journal of Transplantation*.

Four studies [30, 32-34] published between early years (2016, 2017, 2018) to 2021 (later) showed the current influences in this field. The first paper published by Shores JT [30] (2015, *Plastic and Reconstructive Surgery*, strength = 31.61) was discussed previously. The study by Morelon E [34] had the second-highest citation burstness (2017, *American Journal of Transplantation*, strength = 21.06) which began in 2018 and has progressed until now. The study was accompanied with an earlier description of the long-term follow-up (10 years) after

transplantation [26], which added the chronic antibody-mediated rejection associated with the evolution of donor-specific antibodies and graft vasculopathy. Lantieri L [33] conducted a single-centre, prospective, open-label study to assess the the long-term risk and benefit of facial allografts. In 2016, a study published in the *Lancet* had the third highest number of citation burstness (strength = 20.04) which began in 2017 and is still on-going. Finally, the study by Kueckelhaus M [32] had the fourth highest number of citation burstness and summarized the multi-step immunosuppressive approaches applied in pre-transplant and post-transplant stages in 2016. In their review, novel methods for reducing rejection response, graft preservation techniques, monitoring methods and therapies were proposed to improve long-term graft outcomes. This review had a burstness strength of 18.32. The citation burstness analysis showed that developments and management of allografts (mainly hand, limb, face abdominal wall, *etc.*) surgery, continuous update reports on short- and long-term follow-up outcomes, novel rejection suppression protocols, grading, and monitoring techniques are the key topics in current research. This was consistent with the results of network map which indicated that cluster three had the second highest number of red nods in **Figure 8B**. In addition, as shown in cluster one in **Figure 8A**, studies [48-50] on tissue engineering are also hotspots in recent years, but the bibliometric analysis timespan is from 2002 to 2021, which may contribute to allografts clinical applications and immunosuppression with much more attentions.

## Strengths and limitations

Our research has several advantages. Firstly, to our knowledge, this is the first bibliometrics study on VCA. Secondly, annual trends were presented in an accurate and objective manner to provide a comprehensive information to guide clinical surgeons and investigators working on the VCA subject. Several bibliometrics softwares were used to explore the relationships among different items including countries, authors, institutions, journals, fund agencies, keywords, citations/co-citations and references in multiple dimensions. This increases the strength of our results. However, the following limitations should be noted. Firstly, only publications in English were retrieved, and therefore some linguistic bias may exist in this study. Secondly, we only included literature from the past two decades (2002-2021), which may not reflect the full landscape of changes in this subject. Moerover, studies published in 2022 were excluded due to insufficient data. This may have affected the strength of our results. Notably, on the one hand, for the accuracy of the analysis and methods, journal classification system, standardization and consistency of publications records, and stronger visualization effect, we selected Web of Science (WoS) databases with more mentioned advantages, on the other hand, this may result in a non exhaustive search of the literature [51].

## Conclusion

The general information, knowledge base, and emerging topics on VCA-related research in the last two decades was analyzed using the VOSviewer, CiteSpace, and biblimetric analysis platform. The United States was the leading country in this field, and most publications were from Harvard University. *Plastic and Reconstructive Surgery* and *Transplantation* were the most authoritative journals in the field of VCA. Maria Z Siemionow was the leading research with the highest number of citations and co-citations demonstrating the significant role of this researcher in the field of VCA. The knowledge base and recent topics in VCA research were dorminated by clinical studies on different allografts, immunosuppression, and tissue engineering. This scientometric analysis may supply some sources on present studies and future topics by a multidimensional overview of VCA-related publications ranging from 2002 to 2021. As researchers continue to identify more information on VCA, high-quality survival of more allografts, new approaches to immunosuppression, and basic translation to clinical practice can become more attractive, promising and interesting.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China (To Dr. Tang, No. 81871557), Science and Health Joint Project of Natural Science Foundation of Hunan Province (To Dr. Tang, No. 2018JJ6056) and Hunan Provience Natural Science Foundation Youth Foundation Project (To Dr. Qing, No. 2019JJ50940).

## Disclosure of conflict of interest

None.

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## Appendix

*Search strategy in Web of Science Core Collection (May 25, 2022)*

((((((((((((((((((((TS = (Composite Tissue Allografts)) OR TS = (Composite Tissue Allograft)) OR TS = (Vascularized Composite Allografts)) OR TS = (Vascularized Composite Allograft)) OR TS = (Vascularized Composite Allotransplantation)) OR TS = (Allotransplantation, Vascularized Composite)) OR TS = (Composite Tissue Allotransplantation)) OR TS = (Allotransplantation, Composite Tissue)) OR TS = (Vascularized Composite Allografting)) OR TS = (Allografting, Vascularized Composite)) OR TS = (Composite Tissue Allografting)) OR TS = (Allografting, Composite Tissue)) OR TS = (vascularized allograft)) OR TS = (composite tissue allotransplant)) OR TS = (composite tissue transplantation)) OR TS = (composite tissue transplant)) OR TS = (vascularized allogeneic tissue)) OR TS = (vascularized composite tissue transplantation)) OR TS = (composite tissue allografting*)) AND DT = (Article OR Review)) AND PY = (2002-2021)).