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Review article

Structural and temporal dynamics analysis on drug-eluting stents: History, research hotspots and emerging trends

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ABSTRACT

Purpose: This review aims to explore the history, research hotspots, and emerging trends of drug-eluting stents (DES)in the last two decades from the perspective of structural and temporal dynamics.
Methods: Publications on DES were retrieved from WoSCC. The bibliometric tools including *CiteSpace* and *HistCite* were used to identify the historical features, the evolution of active topics, and emerging trends on the DES field.
Results: In the last 20 years, the field of DES is still in the hot phase and there is a wide range of extensive scientific collaborations. In addition, active topics emerge in different periods, as evidenced by a total of 41 disciplines, 511 keywords, and 1377 papers with citation bursts. Keyword clustering anchored five emerging research subfields, namely *#0 dual antiplatelet therapy*, *#3 drug-coated balloon*, *#4 bifurcation*, *5# rotational atherectomy*, and *6# quantitative flow ratio*. The keyword alluvial map shows that the most persistent research concepts in this field are *thrombosis*, *restenosis*, etc., and the emerging keywords are *paclitaxel eluting balloon*, *coated balloon*, *drug-eluting balloon*, etc. There are 7 recent research subfields anchored by reference clustering, namely *#2 dual antiplatelet therapy*, *#4 drug-coated balloon*, *#5 peripheral artery disease*, *#8 fractional flow reserve*, *#10 bioresorbable vascular scaffold*, *# 13 intravascular ultrasound*, *#14 biodegradable polymer*.
Conclusion: The findings based on the bibliometric studies provide the current status and trends in DES research and may help researchers to identify hot topics and explore new research directions in this field.

1. Introduction

Since the first clinical trial of drug-eluting stents (DES) was published in 2002, [1], the field of DES has embarked on a 20-year boom. The first-generation DES represented by *Cypher* and *Taxus* was a thicker drug coating on the surface of stainless steel stents, and although the results are better than bare-metal stent(BMS), there was still room for improving in terms of some issues such as chronic inflammation and delayed arterial healing [2–4]. The second-generation DES, represented by *Xience* and *Endeavour*, had thinner struts and coating on the surface of advanced metal platforms, and the drugs also changed from paclitaxel and sirolimus to zotrimoxazole and everolimus [5–7]. These stents performed better; however, there were problems with permanent coating, which remained on the stent surface after the complete drug elution and began to cause problems such as inflammation, and delayed repair of vascular reendothelialization in long-term studies [8–10]. Therefore, so-called the third generation of DES aims to solve the problem of permanent coating by its initially using of biodegradable polymers [11–13] and eventually shifting to polymer-free drug coatings

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Abbreviations

DES	Drug-eluting stents
BMS	Bare metal stent
BRS	Bioresorbable scaffold
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass grafting
WoSCC	Web of science core collection
DAPT	Dual antiplatelet therapy
ISR	In-stent restenosis
ST	Stent thrombosis
LCS	The total local citation score
GCS	Total global citation score
DEB	Drug-eluting balloons
EES	Everolimus-eluting stents
QFR	Quantitative flow ratio
FFR	Fractional flow reserve

[14–16]. But the clinical effectiveness of the third-generation DES needs more time to be validated. In addition, there were novel studies that provide new ideas for the improvement of DES. It was reported that an electrospun core-shell nanofiber coloaded with 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl and rapamycin had the potential to improve the biocompatibility of current DES [17]. Photofunctionalized and drug-loaded TiO_2 nanotubes were demonstrated to improve vascular biocompatibility as a potential material for polymer-free DES [18]. Poly (1,3-trimethylene carbonate) coating for magnesium-based cardiovascular stents, with stable drug release and improved corrosion resistance, could be a good candidate for drug-eluting coating for a magnesium-based stent [19]. Degradable materials are increasingly being employed in the field of DES based on their degradability, but a deeper understanding of the degradation properties of degradable materials in vivo is still required [20,21]. Our team has been working on DES surface modification research, such as antibody coated stent [22–24], endothelial cell planting stent [25], novel zinc-based alloy stent [26], arsenic trioxide coated-stent [27], vascular scaffold with covalent immobilization of biomolecules with mussel adhesive protein [28], and hydrophobic core/hydrophilic shell nano/micro particles coating stent [29] et al., which showed excellent biocompatibility at the level of animal experiments. These studies can provide candidate strategies for the development of novel DES.

Over the past 20 years, more than ten thousand results related to "drug eluting stents" were present when searching in the Web of Science, which were published in thousands of journals and categorized in hundreds of disciplines such as medicine, materials science, and immunology. Reading and analyzing such a large number of publications to understand the history of the DES field and extract research hotspots is a time-consuming and laborious task. Furthermore, being limited by one's own experience, memory, and the adequacy of available literature forces researchers to make subjective judgments about the historical picture of the development of the scientific field. Therefore, different from traditional reviews based on academic viewpoints, bibliometric reviews based on qualitative changes in academic results can provide a more objective and comprehensive description of the historical overview, research hotspots, and development trends in a field [30–32]. Several biometric tools have been applied to scientometrics, including CiteSpace [33], CitNetExplorer [34], VOSviewer [35], and HistCite [36], to assess the profile of an academic field.

In this paper, the program *CiteSpace* (version 5.8 R3), *HistCite Pro* 2.1, and the alluvial generator were used to evaluate the bibliographic catalogs in DES research. The objectives of this study include (1) summarizing the historical features of the DES literature; (2) highlighting articles that have made significant contributions to the field; (3) recognizing the active topics of the research field; (4) revealing emerging trends for future research.

2. Methods

2.1. Data collection and statistics

Thomson Reuters' Web of Science Core Collection (WoSCC) contains over 12,000 influential academic journals that are widely recognized as important by the international academic community. This paper takes WoSCC as the object database and sets "(ALL=(drug eluting stent)) OR ALL=(drug-eluting stent)) OR ALL=(drug eluting stents)) OR ALL=(drug-eluting stents)) OR ALL=(drug elution stent) OR ALL=(drug elution stents)" as the retrieval condition, with a time of 2002–2020, to search for related results about DES. The retrieved literature records were downloaded and saved as a plain text file in the format of "Full Record and Cited References", which was used as the sample of the analysis data in the paper. Finally, 14,931 pieces of literature information were collected and named $DATA_{DES}$. In the meantime, we collected the original data about countries/regions information of publications, so as institutions, journals, authors, and articles type, then used EXCEL (WPS 21019) for data statistics.

2.2. Tools for bibliometric analysis

2.2.1. CiteSpace

The co-occurrence networks. Scientific partnerships are defined as "multiple authors, multiple institutions, or multiple countries/regions appearing in the same paper at the same time." [37] Scientific research requires extensive collaboration and the examination of scientific collaborations can reveal the research status of a specific scientific field, which can be reflected from three dimensions: authorship, institution, and country. When articles from a certain research field are imported into *CiteSpace* software as a dataset, these synergistic relationships and scientific concepts can be visualized as a co-occurrence network. *CiteSpace* uses color-coded nodes and edges to distinguish the merged network, which assigns its color in the dataset each year. The color at the edge of a network indicates the year the co-occurring link was first created. Nodes are composed of different colored "tree rings" whose thickness indicates the number of co-occurrences in a given year. A red ring in a given year indicates a citation explosion, i.e., a surge in citations in that year. The purple ring is used to indicate the degree of inter-node sexual centrality. A node with high intermediate centrality makes sense because it connects one node to another.

Burst detection. According to Jon Kleinberg, a stream of documents such as emails or articles has a specific topic for a certain of time and then fades away over a certain timeline. Such thematic changes over time can be identified using specific text data mining algorithms and represented by "bursts of activity" [38]. Chen et al. defined citation bursts as an indicator of active topics based on Kleinberg's algorithm [39]. Citation bursts are detection of a burst event, which can last for multiple years or one year. *CiteSpace* provides citation burst detection for disciplines, keywords, and references. [40,41] The presence of a citation burst is evidence that a discipline, keyword, or reference is associated with a surge of citations. In other words, the discipline, keyword, or reference has attracted the strong attention of its scientific community.

The cluster analysis. *CiteSpace* provides three clustering algorithms based on title, abstract, and keywords to group publications into conceptual clusters with different research characteristics [41]. According to the settings of slices, the cluster mapping reflects the changes of concept clusters in different periods. In addition, the timeline mapping can also clearly reflect the rise and fall time of a cluster and the nodes connectioned to other clusters.

The detailed steps are as follows, we imported the data $DATA_{DES}$ into *CiteSpace* software(5.8.R3), set "Time Slicing" to "2002–2021″ and "1″

Table 1
Basic information on the distribution of the publications.

Categories	Publications	Research articles	Meeting abstract	Review articles	Authors	institutions	Journals	Subject Categories
Amount	14,931	9713	2645	1440	34,256	8637	1249	127

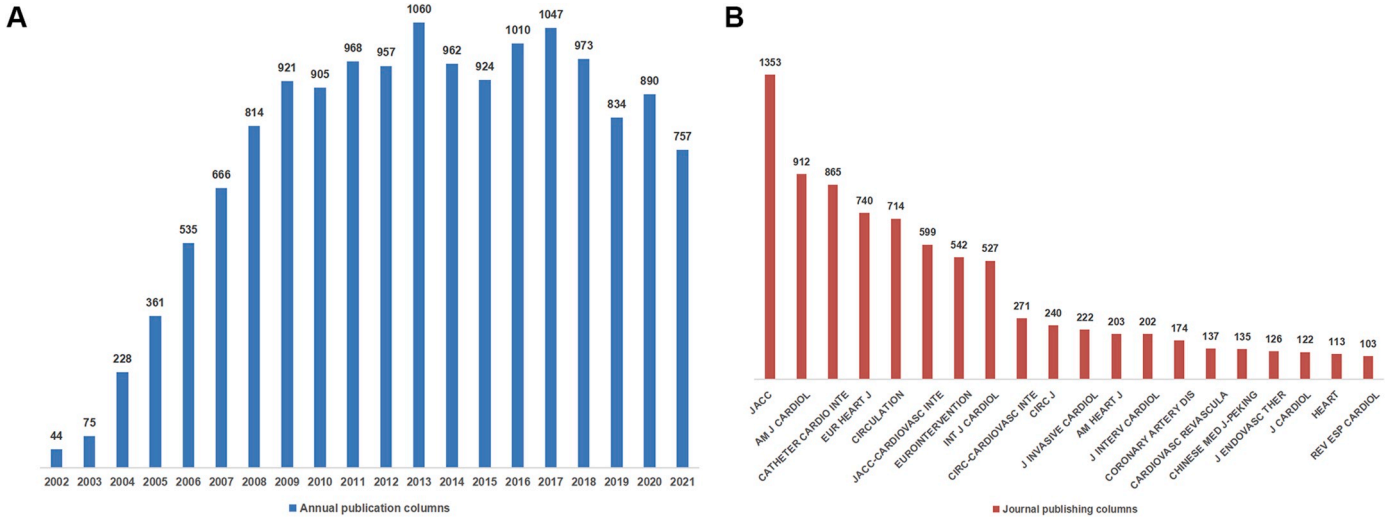

Fig. 1. A: The annual distribution of publications (blue columns). B: The top 20 fruitful journals (Red columns). Y-axis: Publication's quantity.

year per slice, selected the term source "Title", "Abstract", "Author Keywords(DE)" and "KeywordsPlus", selected node type according to requirements, and kept the default value for other settings and automatically generated the country (region) or institution or author collaboration network knowledge map, and finally adjusted the map manually to make it clear and beautiful. In the same way, we depicted keyword clustering maps, the difference was that the node chose "keywords" and time slices were set to 2002–2006, 2007–2011, 2012–2016, 2017–2021. In addition, when selecting "Reference" to generate a co-citation map, we selected the "layout" tab in the "control panel" and continue to select "timeline view" to generate a citation timeline map. Moreover, select the "Burstness" tab was selected in the "control panel" and "view" was clicked to generate a burstness map of keyword, category, or reference.

2.2.2. Hiscite

Each piece of literature is like a lighter in the dark, and each citation is like adding a piece of wood to it. The higher the number of citations, the brighter the literature is, and the more obvious it is at a glance. The *HistCite Pro 2.1* software can plot this numerical relationship, extracting the brightest literature, which allow us to see at a glance which literature is most cited. The *HistCite* use the total local citation score (LCS) and total global citation score (GCS) to score the articles. LCS refers to the citation frequency of a study in the software, and GCS refers to the citation frequency in the WOSCC database. We imported the research articles (9713) from $DATA_{DES}$ into *Hiscite Pro 2.1*, set "Limit" as 30 and kept other settings as their default value, selected "Make graph" to map out the veins of the DES research field and quickly pinpoint the important literature.

2.2.3. The alluvial generator

Alluvial flow diagrams are designed to illuminate temporal patterns in an evolving network [42]. The division and merging of thematic patterns can be viewed as multiple streams that flow smoothly in time. To generate an alluvial map, *CiteSpace* was used in generating a series of individual networks for co-occurring keywords, and these networks were loaded into *the alluvial generator* (http://www.mapequation.org/apps/AlluvialGenerator.html) after being exported from *CiteSpace*. Each keyword will be regarded as a node, and the nodes are clustered on each time slice, and each cluster is considered as a module. Nodes are divided and merged on different time slices to form new modules, while the latest module is formed by the intersection of the previous nodes. The longest-lived nodes in the imported network are highlighted by coloring the flows they form.

3. Results

3.1. The historical features of the DES literature

3.1.1. Distribution of publications

The quantity changes of scientific literature at a given time node can reveal the accumulation of knowledge in a specific research field and provide important parameters for us to grasp the development of this field from a quantitative perspective. A total of 14,391 publications related to DES were retrieved, including 9713 research articles, 2645 meeting abstracts, and 1440 review articles, in which 34,256 authors and 8637 institutions participating, published in 1249 journals in 127 scientific categories (Table 1).

The annual research outputs are illustrated in Fig. 1A. 2002 was the first year that DES entered clinical application, and 44 DES-related paper were published. In 2003, 75 papers were published. However, from 2004 to 2009, the number of publications increased sharply every year. From 2010 to 2018, this high number of publications (around 1000 papers) remained constant, and then had a slight decrease after 2019. Moreover, *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY* ranked the top in the number of published (1353), followed by *AMERICAN JOURNAL OF CARDIOLOGY*(912) and *CATHETERIZATION AND CARDIOVASCULAR INTERVENTIONS*(865). Fig. 1B presents the top 20 most fruitful journals and researchers can refer to this figure when they are considering a submission.

3.1.2. The veins of DES research field

The citation co-citation map shows the relationship of literature in the DES field over the past two decades (Fig. 2). In total, there are 2422

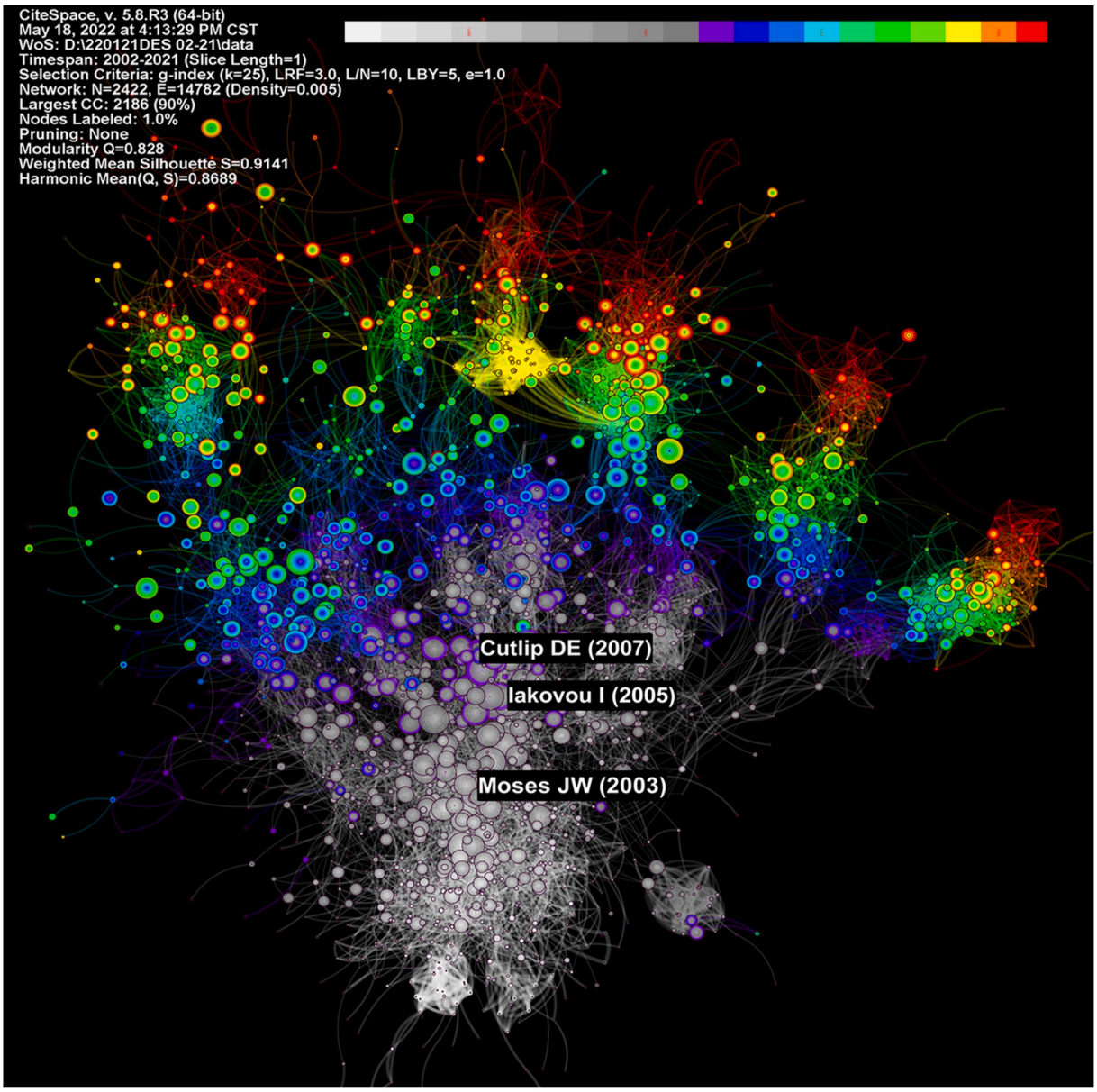

Fig. 2. The citation co-occurrence network. The color bar from left(white) to right(red) indicates the year from 2002 to 2021.

nodes and 14782 links in the network, implying extensive connections between the literature in this research area. Like a large tree, in the early literature (2002–2011), the nodes marked in gray with their dense node density and rich inter-node connectivity, act as the root system of the field, providing nutrients for the sustainable development of the field. In particular, Mose JW (2003) [43], Iakovou I (2005) [44], and Cutlip DE (2007) [45], these three papers occupy an important position in the field of DES research due to their far ahead co-citation frequency of 673, 664, and 630 respectively, and due to their high intermediate centrality (with purple ring). In the mid-term (2012–2015), the nodes marked in blue gradually dispersed, forming the main branches of the research. At a later stage (2016–2021), the nodes develop into twigs and forming tighter clusters, heralding the centralization and differentiation of the research domains. This concentration and differentiation of research clusters will be more clearly shown in subsequent timeline map of reference. Furthermore, we mapped the citation historiography graph of research articles using *HisCite Pro 2.1* (Fig. S1). These landmark articles were highlighted in Table 2 and the top three GCS papers are Cutlip DE (2007), Stone GW (2004), Stone GW (2007). The larger the node, the more important the reference, and the more connected the node is, the higher the mediated centrality of the node. Using these two methods, we not only visualized the citation pulse structure of the literature, but we also focused on the high-contribution literature in this field.

3.1.3. *Scientific cooperation*

As shown in Fig. 4, a large number of nodes and rich links indicate a strong scientific collaboration in three dimensions: country, institution, and author. The national collaboration network has 545 nodes and 2131 links, with node sizes ranging from the United States to Japan, Italy, South Korea, PEOPLES R CHINA (Fig. 4A). The institutional collaboration network appears with 904 nodes and 6533 connecting lines, and the nodes are Cardiovasc Res Fdn, Columbia Univ, Erasmus MC, Yonsei Univ, and Univ Ulsan in order of size, as shown in Fig. 4B. The author collaboration map appears with 1327 nodes and 7161 connecting lines, as shown in Fig. 4C. PATRICK W SERRUYS, GREGG W STONE, SEUNGJUNG PARK, ANTONIO COLOMBO, and RON WAKSMAN lead the number of publications in this field, and the dense linkage represents a large number of scientific collaborations between researchers.

Table 2
The information of the top 30 literature sorted by LCS score.

NO.	Article information	Journal	LCS	GCS
309	Clinical end points in coronary stent trials: a case for standardized definitions [45]	Circulation	1921	4186
100	A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease [46]	N Engl J Med	919	2106
250	Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents [47]	N Engl J Med	663	1274
110	Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? [48]	Circulation	538	1126
313	Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization [49]	Circulation	535	1019
252	Stent thrombosis in randomized clinical trials of drug-eluting stents [50]	N Engl J Med	523	1146
433	Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis [3]	Lancet	523	1124
251	Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden [51]	N Engl J Med	431	953
191	Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy [52]	Lancet	357	1060
2986	Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis [53]	Lancet	331	704
80	Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions [54]	Circulation	301	753
2305	The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents [55]	JACC	293	634
312	Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation [56]	Circulation	284	605
249	A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents [57]	N Engl J Med	282	548
1925	Comparison of zotarolimus-eluting and everolimus-eluting coronary stents [58]	N Engl J Med	268	508
809	Endothelial cell recovery between comparator polymer-based drug-eluting stents [59]	JACC	259	498
4728	Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents [60]	N Engl J Med	247	1186
64	TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions [61]	Circulation	241	621
866	Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study [2]	Circulation	240	457
2349	Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings [9]	Circulation	220	518
1309	Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis [62]	Circulation	215	388
125	Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions [63]	Circulation	206	540
217	Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial [64]	JAMA	192	474
2989	Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial [65]	Circulation	188	522
242	Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation [66]	JACC	181	433
618	Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg [67]	N Engl J Med	180	600
1379	Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis [68]	Circulation	179	361
873	Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study [69]	JACC	178	373
3283	A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation) [70]	JACC	178	457
2811	Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study [71]	Circulation	176	447

LCS: The total local citation score, GCS: The total global citation score. NO: The number of the literature in the database import into *Hiscite pro* 2.1.

Notably, clustering effects are observed among the nodes of authors, such as DUKWOO PARK, SEUNGJUNG PARK, and some nodes clustering into one cluster (Fig. 4C, i), MYEONGKI HONG, YANGSOO JANG, and some nodes clustering into one cluster (Fig. 4C, ii), RON WAKSMAN and some nodes clustering into one cluster (Fig. 4C, iii), ANTONIO COLOMBO and some nodes clustered into one cluster (Fig. 4C, iv).

3.2. Variation of the most active topics

3.2.1. Subject category burst

From 2002 to 2021, a total of 41 of the 127 related disciplines experienced citation bursts. The blue line represents this time interval, and the time span in which a subject category was found to have bursts is depicted as a red line segment with the beginning and end years of the bursts. Fig. 5 depicts the top 30 categories with high burst strength at various times. The burst period of the subject category SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED) has a burst period between 2002 and 2008, with the strongest burst strength of 243.7874. Notable the subject category burstness was becoming diversified over time, like CARDIAC & CARDIOVASCULAR SYSTEMS (2002–2004), NANOSCIENCE & NANOTECHNOLOGY (2015–2016), PHYSICS (2018–2021), SURGERY (2019–2021). The changes in the burst disciplines on the timeline foreshadowed the multidisciplinary nature of the field. Besides, there were 19 burst disciplines from the beginning to 2021 (Table S2), with the top three being *CARDIAC & CARDIOVASCULAR SYSTEMS WE EMERGING SOURCES CITATION INDEX (ESCI)* (2017–2021), *MEDICINE,* and *GENERAL & INTERNAL WE EMERGING SOURCES CITATION INDEX (ESCI)* (2017–2021).

3.2.2. Keywords burst

At a finer level, keyword burst patterns were detected to reveal active contents in the DES field throughout the time span (2002–2021). 551 keywords burst out at different time points, and the top 30 keywords with the strongest burst strength were shown in Fig. 6. Keyword *balloon*

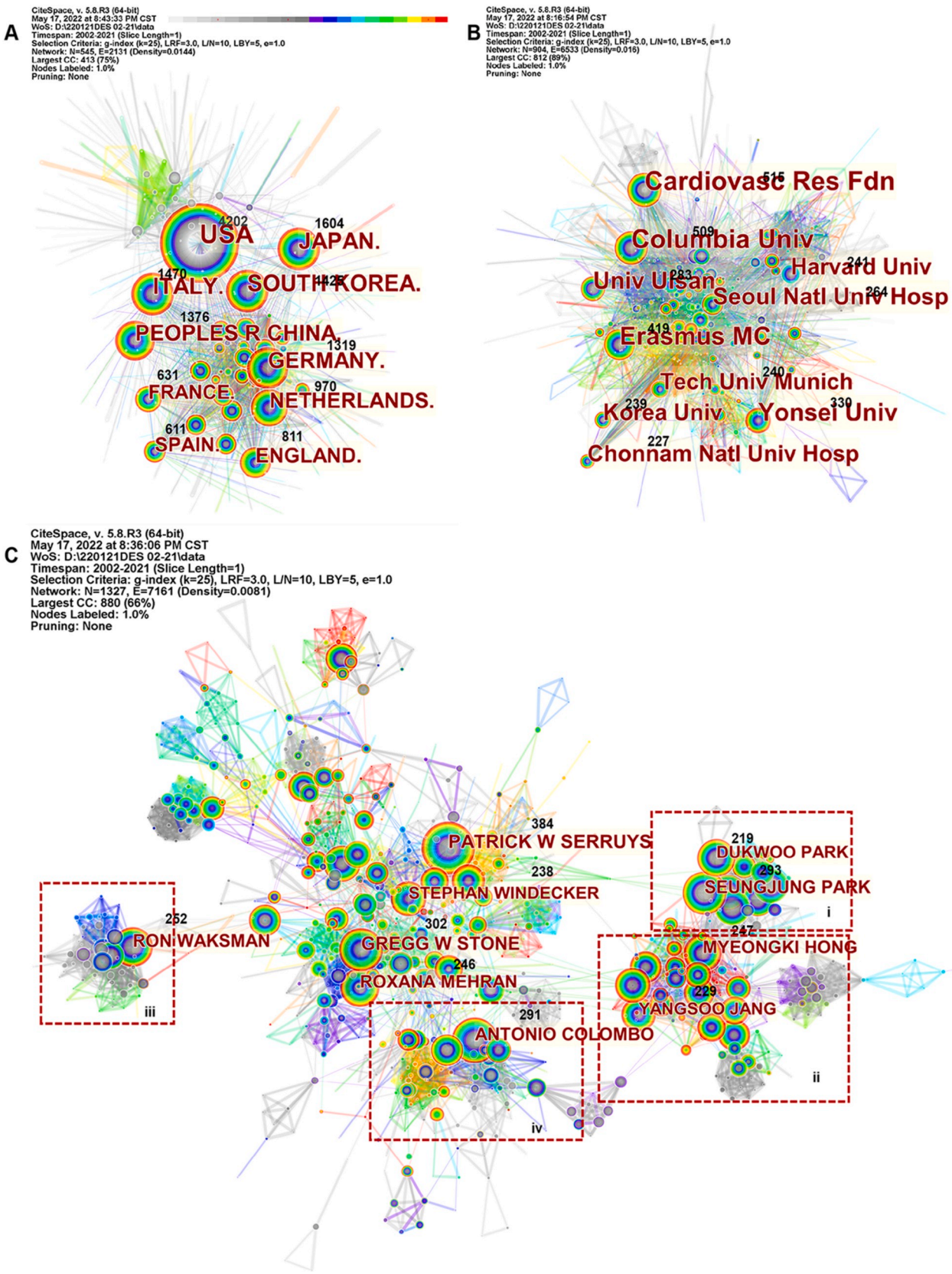

Fig. 4. The scientific cooperation network. A: Country cooperation, B: Institution cooperation, C: Author cooperation, i: Author clustering as represented by DUKWOO PARK; ii: Author clustering as represented by MYEONGKI HONG; iii: Author clustering as represented by RON WAKSMAN; iv: Author clustering as represented by ANTONIO COLOMBO. Number: frequency of co-occurrence.

Subject Categories	Year	Strength	Begin	End	2002 - 2021
SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED)	2002	243.79	2002	2008	
CARDIAC & CARDIOVASCULAR SYSTEMS WE CONFERENCE PROCEEDINGS CITATION INDEX - SCIENCE (CPCI-S)	2002	203.02	2002	2008	
PERIPHERAL VASCULAR DISEASE WE CONFERENCE PROCEEDINGS CITATION INDEX - SCIENCE (CPCI-S)	2002	34.3	2002	2007	
CARDIAC & CARDIOVASCULAR SYSTEMS	2002	18.54	2002	2004	
PERIPHERAL VASCULAR DISEASE WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED)	2002	12.9	2002	2004	
PATHOLOGY WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED)	2002	4.17	2002	2004	
PATHOLOGY	2002	3.99	2002	2004	
ANESTHESIOLOGY WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED)	2002	9.69	2007	2009	
ANESTHESIOLOGY	2002	9.41	2007	2008	
MEDICAL INFORMATICS	2002	3.59	2012	2013	
GERIATRICS & GERONTOLOGY WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED)	2002	4.89	2013	2019	
IMMUNOLOGY WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED)	2002	3.47	2013	2014	
MULTIDISCIPLINARY SCIENCES WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED)	2002	13.94	2014	2021	
MEDICINE, RESEARCH & EXPERIMENTAL WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED)	2002	3.83	2014	2015	
SCIENCE & TECHNOLOGY - OTHER TOPICS	2002	14.05	2015	2021	
RESPIRATORY SYSTEM WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED)	2002	8.47	2015	2017	
NANOSCIENCE & NANOTECHNOLOGY	2002	3.5	2015	2016	
GERIATRICS & GERONTOLOGY	2002	5.88	2016	2019	
ONCOLOGY	2002	5.71	2016	2021	
CARDIAC & CARDIOVASCULAR SYSTEMS WE EMERGING SOURCES CITATION INDEX (ESCI)	2002	171.1	2017	2021	
MEDICINE, GENERAL & INTERNAL WE EMERGING SOURCES CITATION INDEX (ESCI)	2002	41.86	2017	2021	
PERIPHERAL VASCULAR DISEASE WE EMERGING SOURCES CITATION INDEX (ESCI)	2002	10.64	2017	2021	
METALLURGY & METALLURGICAL ENGINEERING	2002	4.02	2017	2021	
MATERIALS SCIENCE, MULTIDISCIPLINARY	2002	7.83	2018	2021	
PHYSICS	2002	7.25	2018	2021	
MEDICINE, RESEARCH & EXPERIMENTAL	2002	6.54	2018	2021	
PEDIATRICS WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED)	2002	3.52	2018	2021	
PHYSICS, APPLIED WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED)	2002	3.46	2018	2021	
SURGERY	2002	7.2	2019	2021	
SURGERY WE EMERGING SOURCES CITATION INDEX (ESCI)	2002	5.13	2019	2021	

Fig. 5. The top 30 subject categories with the strongest citation bursts. Year: Year of the first occurrence, Strength: Burst's strength, Begin: Burst's beginning year, End: Burst's ending year.

angioplasty burst between 2002 and 2007 with the highest burst strength of 83.42, *restenosis* burst between 2002 and 2008 with a burst strength of 79.96, *late thrombosis* burst between 2007 and 2012 with a burst strength of 21.87. Moreover, we pay special attention to the 116 keywords with a burst period until 2021 among all the burstness keywords because they may be the future research hotspots in this field. For example, the keyword *drug-coated balloon* burst with a burst strength of 48.7148 between 2018 and 2021, and the keyword *dual antiplatelet therapy* burst with a burst strength of 44.1586 between 2016 and 2021 (Table S2 in the supplementary materials).

3.2.3. Reference burst

After calculation, 1377 burst articles emerged. Table 3 displayed the top 30 references with the most citation bursts between 2002 and 2021. Morice M (2002) was the article with the first citation burst and it sparked a lot of interest when it was published, [1], which, had a burst strength of 255.15 and lasted for 6 years from 2002 to 2008. It was the first randomized, double-blind trial to show that sirolimus-eluting stents outperformed standard coronary stents in terms of preventing de novo intimal hyperplasia, restenosis, and related clinical events. Grube E (2003) had a burst strength of 93.45 from 2003 to 2008 [61]. This study was the first-in-human experience to evaluate the safety and feasibility of the TAXUS NIRx stent system compared with bare NIR stents for the treatment of coronary lesions. The TAXUS slow-release stent was well tolerated in this feasibility trial and showed promise for the treatment of coronary lesions, significantly reducing restenosis, measured by angiographic and intravascular ultrasound measures of restenosis. From 2004 to 2008, Moses JW2003 had the third burst period, with the strongest burst strength of 314.72 [43]. The authors compared a sirolimus-eluting stents with standard stents in 1058 patients, and showed that using a sirolimus-eluting stents had a consistent treatment effect, reducing restenosis rates and associated clinical events in all subgroups analyzed.

There were 188 burst articles from the beginning to 2021, with the top 20 strength index listed in Table 4. Four of these papers are "Practice Guideline", twelve are "Randomized Controlled Trial", two are "Meta-Analysis", one is "Clinical Trial", and one is "Clinical Trial". All of these articles entered the citation bursts period as soon as they were published in the year or the following year. "Practice Guideline" has a guiding meaning for the clinical application of DES, "Randomized Controlled Trial", "Meta-Analysis", and "Clinical Trial" had a great reference value for stent efficacy. This also reminded the clinical research and basic research workers of DES to pay more attention on these information.

3.3. Emerging trends and new developments

3.3.1. The temporal variation of keyword clusters

There are close internal associations among the keywords, and certain keywords can form different clusters based on their affinity, and the identification of these clusters can more intuitively contour the various hot sub-fields of DES research. The 20 years was divided into four phases per five years and the keyword clusters snapshots in each phase were shown in Fig. 7. In the first snapshot(2002–2006), 1238 papers were included in the calculation, yielding 8 clusters for *#0 outcm*, *#1 smooth muscle*, and *#2 aspirin*, etc. (Fig. 7A) In the second snapshot (2007–2011), 4261 papers were considered, and 8 clusters were generated for *#0 drug delivery*, *#1 clopidogrel*, and *#2 left main coronary artery*, etc. (Fig. 7B) In the third snapshot (2012–2016), 4898 papers were considered, and 7 clusters were created for *0# ciopidogrel*, *#1 optical coherence tomography*, and *#2 in vitro,* etc.(Fig. 7C) In the fourth snapshot (2017–2021), 4296 papers were included and 7 clusters were generated, namely *#0 dual antiplatelet therapy*, *#1 percutaneous coronary intervention*, and *#2 optical coherence tomography*, etc. (Fig. 7D) Compared to the previous 15 years, some classic studies, such as *#1 percutaneous coronary intervention*, and *#2 optical coherence tomography*,

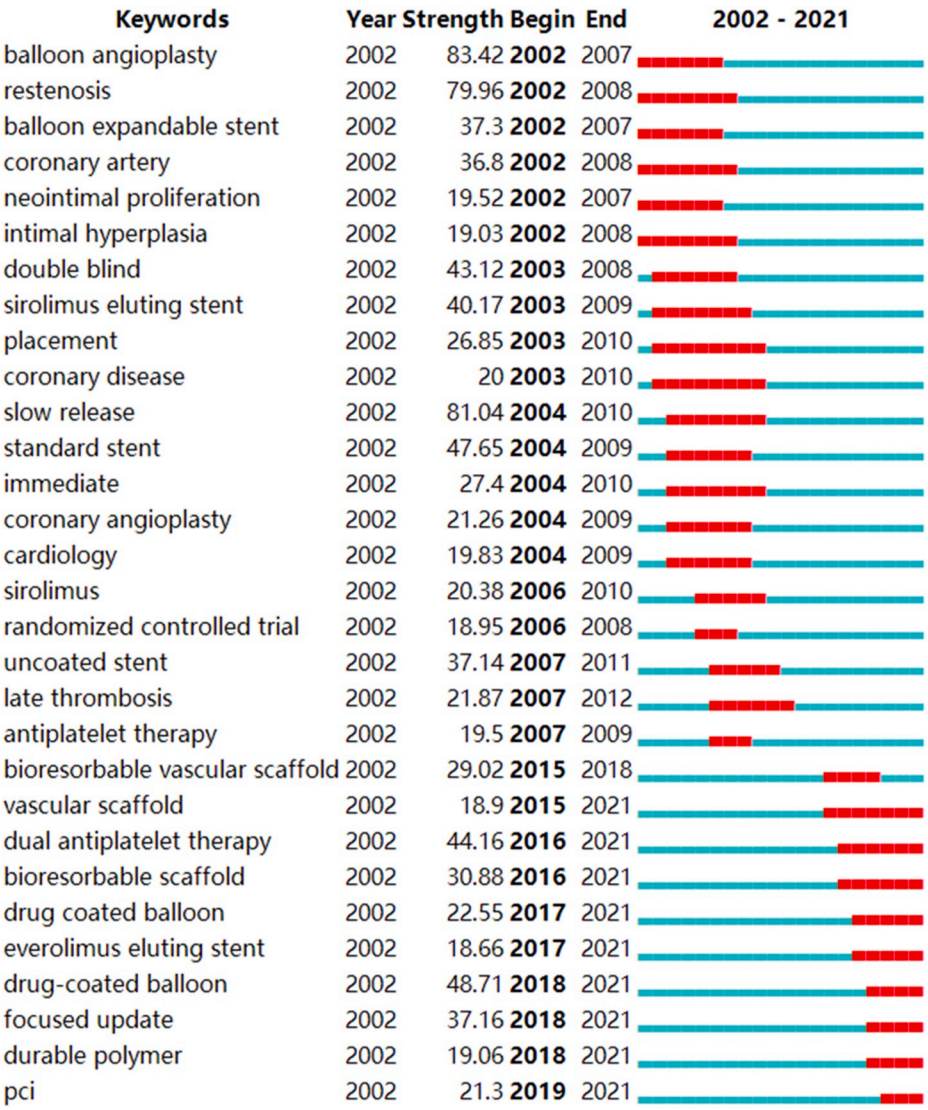

Fig. 6. The top 30 keywords with the strongest citation bursts.

are still hotspots, while the emerging clusters *#0 dual antiplatelet therapy*, *#3 drug-coated balloon*, *#4 bifurcation*, *5# rotational atherectomy*, and *6# quantitative flow ratio* have gained more attention from researchers. Our interpretation of the literature in the emerging clusters revealed that these emerging clusters were aimed at exploring new technologies and approaches to improve the clinical performance of DES. The *#0 dual antiplatelet therapy* gathered 167 articles about exploring better post-stenting antiplatelet therapy options [100,101]. *#3 drug-coated balloon* gathered 105 articles, which are increasingly showing their superiority as an effective complement to stenting [102]. *#4 bifurcation* gathered 83 articles that focused on bifurcation lesions and DES [103]. *5# rotational atherectomy* gathered 62 articles and *6# quantitative flow ratio* gathered 19 articles. Rotational atherectomy and quantitative flow ratio are techniques that can complement DES treatment [104,105]. Table S3 (supplementary materials) showed detailed data for the fourth snapshot (2017–2021), and the "representative keywords within clusters" aid in locating the core research areas of DES for the most recent stage (2017–2021).

3.3.2. The keyword alluvial flow visualization

As shown in Fig. 8, the linked keywords can be assembled to form specific research modules, and as keywords are reassembled, research modules diverge or aggregate to form new modules at different times. Some of the traffic keywords had a strong life span throughout the 20 years, some had become new research trends, and some faded into the long history of the research field. Table S4 (supplementary materials) lists the most trafficked keyword for the top five modules each year. Obviously, the keywords contained in Module 3 in 2021, diverging or converging in this study watershed, formed the largest study tributary (Green marked portion). It heralds Module 3 as the most persistent research module. In addition, we mapped all the keywords of the top 6 modules in 2021 (Fig. 9). Module 1 was named as "*paclitaxel eluting balloon*", gathered 26 keywords like *paclitaxel eluting balloon*, *coated balloon*, and *drug-eluting balloon* (Fig. 9A). Module 2 was named as "aspirin", gathered 27 keywords like *aspirin*, *clopidogrel*, and *dual antiplatelet therapy* (Fig. 9B). Module 3 was named as "drug-coated balloon", gathered 21 keywords like *drug-coated balloon*, *thrombosis*, and *restenosis* (Fig. 9C). Module 4 was named as "antiplatelet drug", gathered 15 keywords like *antiplatelet drug*, *endovascular procedure*, and *intravascular ultrasound* (Fig. 9D). Module 5 was named as "bioresorbable polymer", gathered 16 keywords in the category of new stent materials like *bioresorbable polymer*, *3d printing*, and *target lesion* (Fig. 9E). And Module 6 was named as "bioflow v", gathered 12 like *femoropopliteal lesion*, *calcified coronary lesion*, and *target lesion revascularization* (Fig. 9F). These modules were likely to be the emerging trends in the field of DES in the next 5 years or even longer.

Table 3
The references with citation bursts at different period.

References	Year	Strength	Begin	End	2002–2021
Morice M, 2002, NEW ENGL J MED, V346, P1773, DOI 10.1056/NEJMoa012843 [1]	2002	255.15	2002	2007	
Grube E, 2003, CIRCULATION, V107, P38, DOI 10.1161/01.CIR.0000047700.58683.A1 [61]	2003	93.45	2003	2008	
Moses JW, 2003, NEW ENGL J MED, V349, P1315, DOI 10.1056/NEJMoa035071 [43]	2003	314.72	2004	2008	
Stone GW, 2004, NEW ENGL J MED, V350, P221, DOI 10.1056/NEJMoa032441 [46]	2004	232.4	2004	2009	
Colombo A, 2003, CIRCULATION, V108, P788, DOI 10.1161/01.CIR.0000086926.62288.A6 [54]	2003	130.48	2004	2008	
Schofer J, 2003, LANCET, V362, P1093, DOI 10.1016/S0140-6736(03)14462-5 [72]	2003	111.83	2004	2008	
McFadden EP, 2004, LANCET, V364, P1519, DOI 10.1016/S0140-6736(04)17275-9 [52]	2004	117.89	2005	2009	
Virmani R, 2004, CIRCULATION, V109, P701, DOI 10.1161/01.CIR.0000116202.41966.D4 [48]	2004	99.47	2005	2009	
Iakovou I, 2005, JAMA-J AM MED ASSOC, V293, P2126, DOI 10.1001/jama.293.17.2126 [44]	2005	219.1	2006	2010	
Joner M, 2006, J AM COLL CARDIOL, V48, P193, DOI 10.1016/j.jacc.2006.03.042 [73]	2006	170.75	2007	2011	
Pfisterer M, 2006, J AM COLL CARDIOL, V48, P2584, DOI 10.1016/j.jacc.2006.10.026	2006	136.62	2007	2011	
Kastrati A, 2007, NEW ENGL J MED, V356, P1030, DOI 10.1056/NEJMoa067484 [74]	2007	85.65	2007	2012	
Stone GW, 2007, NEW ENGL J MED, V356, P998, DOI 10.1056/NEJMoa067193 [47]	2007	141.19	2008	2012	
Daemen J, 2007, LANCET, V369, P667, DOI 10.1016/S0140-6736(07)60314-6 [75]	2007	131.26	2008	2012	
Mauri L, 2007, NEW ENGL J MED, V356, P1020, DOI 10.1056/NEJMoa067731 [50]	2007	112.32	2008	2012	
Stettler C, 2007, LANCET, V370, P937, DOI 10.1016/S0140-6736(07)61444-5 [3]	2007	110.15	2008	2012	
Lagerqvist B, 2007, NEW ENGL J MED, V356, P1009, DOI 10.1056/NEJMoa067722 [51]	2007	103.25	2008	2012	
Cutlip DE, 2007, CIRCULATION, V115, P2344, DOI 10.1161/CIRCULATIONAHA.106.685313 [45]	2007	212.78	2009	2012	
Finn AV, 2007, CIRCULATION, V115, P2435, DOI 10.1161/CIRCULATIONAHA.107.693739 [49]	2007	84.82	2009	2012	
Stone GW, 2010, NEW ENGL J MED, V362, P1663, DOI 10.1056/NEJMoa0910496 [76]	2010	96.19	2011	2015	
Kedhi E, 2010, LANCET, V375, P201, DOI 10.1016/S0140-6736(09)62127-9 [77]	2010	83.62	2011	2015	
William Wijns, 2010, Eur Heart J, V31, P2501	2010	100.48	2012	2015	
Levine GN, 2011, J AM COLL CARDIOL, V58, P0, DOI 10.1016/j.jacc.2011.08.007 [78]	2011	92.33	2012	2016	
Nakazawa G, 2011, J AM COLL CARDIOL, V57, P1314, DOI 10.1016/j.jacc.2011.01.011 [55]	2011	83.36	2012	2016	
Palmerini T, 2012, LANCET, V379, P1393, DOI 10.1016/S0140-6736(12)60324-9 [53]	2012	114.29	2013	2017	
Kolh P, 2014, EUR J CARDIO-THORAC, V46, P517 DOI 10.1093/ejcts/ezu366 [79]	2014	220.36	2015	2019	
Mauri L, 2014, NEW ENGL J MED, V371, P2155, DOI 10.1056/NEJMoa1409312 [60]	2014	133.66	2015	2019	
Levine GN, 2016, J AM COLL CARDIOL, V68, P1082, DOI 10.1016/j.jacc.2016.03.513 [80]	2016	83.08	2017	2021	
Valgimigli M, 2018, EUR HEART J, V39, P213, DOI 10.1093/eurheartj/ehx419 [81]	2018	83.34	2018	2021	
Williams B, 2018, J HYPERTENS, V36, P2284, DOI 10.1097/HJH.0000000000001961 [82]	2018	117.6	2019	2021	

3.3.3. *The timeline visualization of references*

A timeline visualization based on the time span of the citations is depicted to predict which topics are emerging, which are classic topics, and which are relatively outdated topics. The timeline map of DES research consisted of 19 clusters in a given time, with clusters arranged top-down according to size (Fig. 10a). Among them, cluster *#0 restenosis*, *#1 everolimus*, *#3 stent thrombosis*, *#6 left main coronary artery*, *#7 optical coherence tomography*, *#9 clopidogrel*, and *#12acute myocardial infarction* were classic topics, which may not be the latest topics but inextricably linked to other clusters. Clusters *#11 bifurcation*, *#15 saphenous vein graft*, *#16 ptca*, *#17longitudinal stent deformation*, *#18 chronic total occlusion*, and *#23prediabetes* were relatively outdated topics, which had few connections to other clusters and no subsequent development on their own timeline. Clusters *#2 dual antiplatelet therapy*, *#4 drug-coated balloon*, *#5 peripheral artery disease*, *#8 fractional flow reserve*, *#10 bioresorbable vascular scaffold*, *#13 intravascular ultrasound*, and *#14 biodegradable polymer* were emerging topics based on the fact that they had been active in the timeline from their emergence to the present, which predicted that these fields will become hotspots for future research. Table S5 (supplementary materials) showed more detail about the emerging clusters. Moreover, some classical papers (big nodes with red ring) played a very important role in advancing the subfield (Fig. 10b). An article published by Mauri L in 2014 [60], belonging to cluster #2 with the co-citation frequency of 319, demonstrated that in

Table 4
The references with citation bursts from beginning to 2021.

Begin	End	Strength	Year	Type	Title
2019	2021	117.5975	2018	Practice Guideline	2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension [82]
2018	2021	83.3399	2018	Practice Guideline	2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS) [81]
2017	2021	83.0799	2016	Practice Guideline	2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [80]
2016	2021	81.0008	2015	Randomized Controlled Trial	Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk [83]
2018	2021	75.5064	2018	Practice Guideline	2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation [84]
2017	2021	70.6003	2016	Randomized Controlled Trial	Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease [85]
2019	2021	70.5712	2018	Meta-Analysis	Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials [86]
2016	2021	68.2418	2015	Randomized Controlled Trial	Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease [87]
2016	2021	64.8417	2015	Meta-Analysis	Long-Term Safety of Drug-Eluting and Bare-Metal Stents: Evidence From a Comprehensive Network Meta-Analysis [88]
2017	2021	61.4687	2016	Randomized Controlled Trial	Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomized, controlled, single-blind, multicentre clinical trial [89]
2017	2021	61.4687	2016	Randomized Controlled Trial	Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease [90]
2017	2021	59.0634	2016	Randomized Controlled Trial	Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention [91]
2015	2021	58.8825	2015	Clinical Trial	A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomized controlled trial [92]
2016	2021	58.0067	2015	Randomized Controlled Trial	Long-term use of ticagrelor in patients with prior myocardial infarction [93]
2018	2021	56.7234	2017	Randomized Controlled Trial	Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularization (BIOFLOW V): a randomized trial [94]
2016	2021	55.9211	2015	Randomized Controlled Trial	Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease [95]
2015	2021	55.4983	2015	Randomized Controlled Trial	ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting [96]
2016	2021	55.3423	2015	Randomized Controlled Trial	A Prospective Randomized Trial of Drug-Eluting Balloons Versus Everolimus-Eluting Stents in Patients With In-Stent Restenosis of Drug-Eluting Stents: The RIBS IV Randomized Clinical Trial [97]
2016	2021	52.949	2015	Review	Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment [98]
2017	2021	51.8875	2017	Randomized Controlled Trial	Bioresorbable Scaffolds versus Metallic Stents in Routine PCI [99]

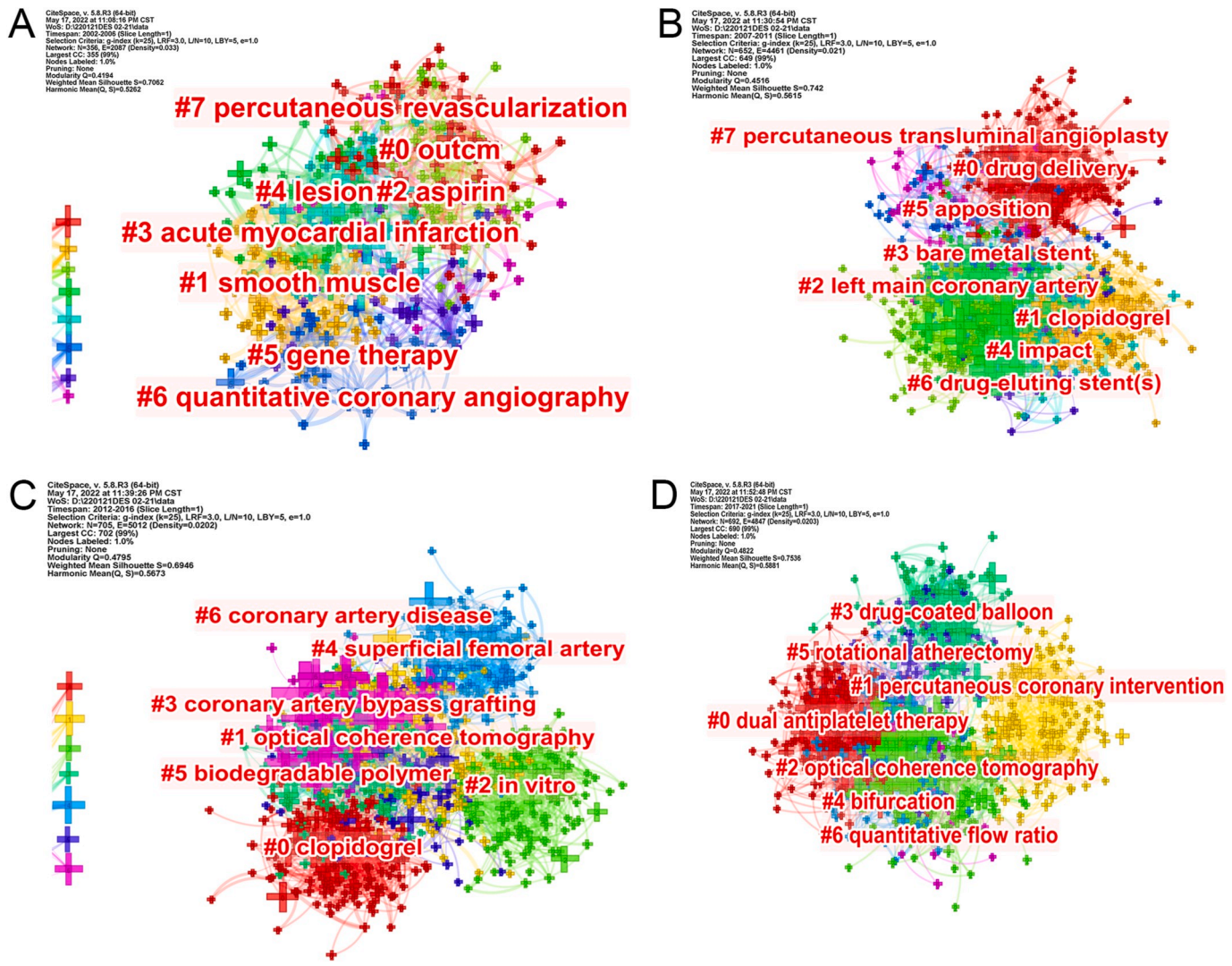

Fig. 7. The keyword clusters snapshots in four periods. A: 2002–2006, B: 2007–2011, C: 2012–2016, D: 2017–2021.

one year after the placement of DES, dual antiplatelet therapy significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events, but was associated with an increased risk of bleeding. Alfonso F (2015, J AM COLL CARDIOL) [97], belonging to cluster #4 with the co-occurrence frequency of 147, evaluated the efficacy of drug-eluting balloons (DEB) and everolimus-eluting stents (EES) in patients with DES in-stent restenosis (DES-ISR) and found that EES provided superior long-term clinical and angiographic outcomes to DEB in patients with DES-ISR. Stone GW(2016, NEW ENGL J MED) [90], belonging to cluster #8 with the co-occurrence frequency of 135, showed that PCI with EES was non-inferior to CABG in terms of the 3-year composite endpoint incidence of death, stroke, or myocardial infarction in patients with left main stem coronary artery disease and a low or moderate SYNTAX score by site assessment. Serruys PW(2015, LANCET) [92], belonging to cluster #10 with the co-occurrence frequency of 157, secondary clinical and surgical outcomes were compared after a 1-year follow-up between everolimus-eluting bioresorbable stents and everolimus-eluting metallic stents and found that everolimus-eluting bioresorbable stents had similar 1-year composite secondary clinical outcomes as everolimus-eluting metallic stents. Von Birgelen C (2016, LANCET) [106], belonging to cluster #14 with the co-occurrence frequency of 108, demonstrated that two very thin strut DES with different biodegradable polymer coatings (eluting everolimus or sirolimus) were not inferior to the durable polymer stent (eluting zotamox) in terms of 1-year safety and efficacy in treating a high proportion of patients with acute coronary syndromes in all patients. We further counted the citation distribution of these five articles in recent years (Fig. 10c) and it can be predicted that these articles may be mentioned again in the coming years.

4. Summary and future perspectives

4.1. Ongoing challenges and emerging themes coexist in the DES field

Based on the scientific maps by scientometrics, this paper reviewed the structural and temporal characteristics of relevant publications in the DES field from 2002 to 2021. There is no doubt that the DES field is still at a hotstage with a dramatic increase in the number of papers, extensive and close scientific collaborations, and the dense citation network. While the active topics in the field change over time, the latest keywords with citation burst, such as *drug-coated balloon*, *dual antiplatelet therapy*, and *bioresorbable scaffold*, have the potential to become hotspots for future research and the latest references with citation burst revolve around these hotspots. These results are also reflected on the keyword cluster map and the reference timeline map. The shift of subject categories burst also reflects the fact that more disciplines are involved in the DES field. Moreover, the results of the keyword timeline visualization indicate that *in stent restenosis* and *thrombosis* are classic themes

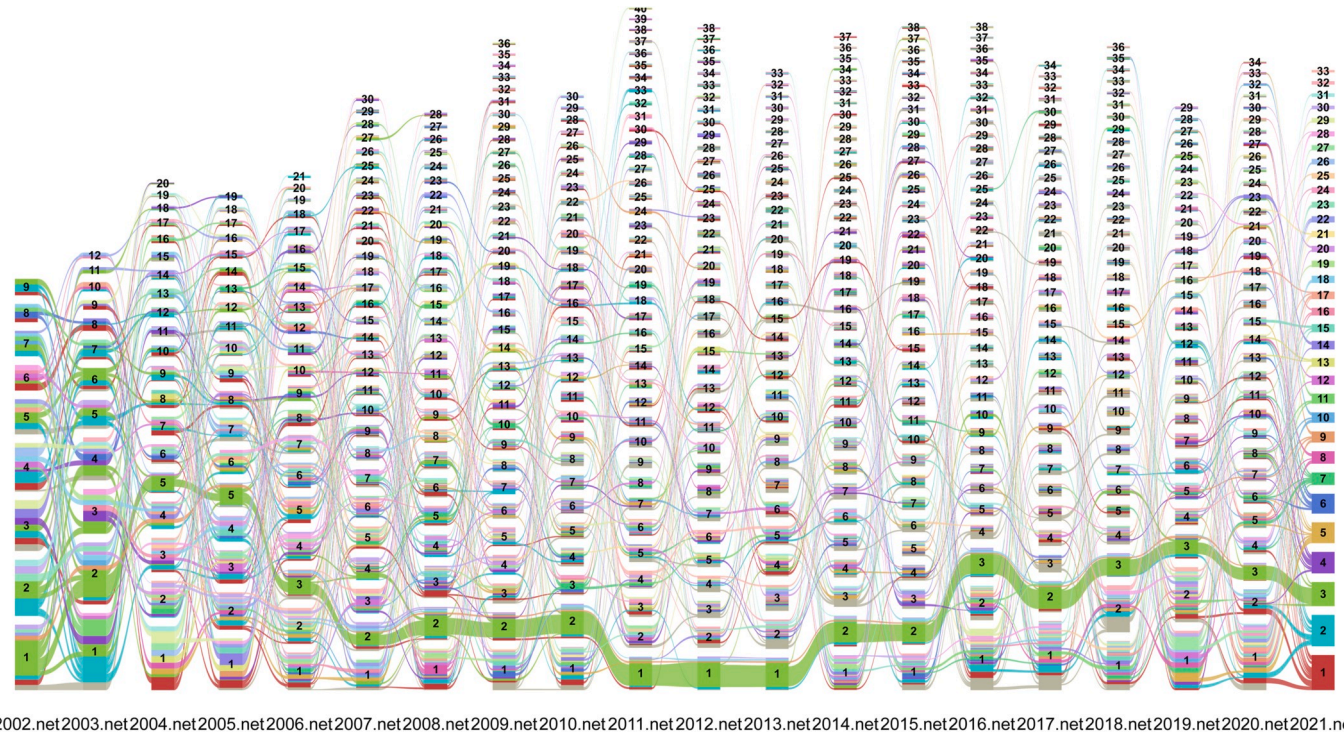

Fig. 8. The keywords alluvial map 2002–2021. X axis: Time slice. Y axis: Counting of modules. Number: Order of modules on each time slice sorted by the number of nodes.

that run throughout the DES research, while keywords such as *dual antiplatelet therapy*, *drug-coated balloon*, *bioresorbable vascular scaffold*, *antiplatelet drug*, *biodegradable polymer*, *3d printing* have become emerging research module. Thus, it can be summarized that ongoing challenges and emerging themes coexist in the DES field.

4.2. Exploration of emerging topics

Drug-coated balloon. It has been found that the vascular stent itself has some insurmountable limitations. These limitations arise from, on the one hand, from the metallic architecture of the stent, which acts as a foreign body and continues to stimulate neointimal hyperplasia, leading to restenosis, and on the other hand, from polymorphic carriers that delay endothelial repair, increasing the incidence of stent thrombosis and prolonging the course of dual antiplatelet therapy [107,108]. Thus, DEB, which combine traditional balloon angioplasty with advanced drug-eluting technology, is increasingly showing its superiority as an effective complement to stenting [109,110]. The unique configuration of DEB avoids the side effects caused by metallic frameworks and polymorphic carriers by applying the drug to a specific area of the vessel wall, allowing local drug concentration there without causing systemic side effects, and can be used to manage restenosis and ISR, as well as for the management of complex lesions such as bifurcation lesions and vascular calcification after rotational atherectomy et al. [111–113] The application of DEB has put forward a new concept of coronary interventions with satisfactory results achieved from preclinical and early clinical studies, but the available data are limited and long-term follow-up data are needed to further determine the efficacy of DEB in large-scale clinical applications.

Dual antiplatelet therapy. Dual antiplatelet therapy (DAPT) with aspirin and P2Y12 receptor inhibitors is the standard of care for preventing stent thrombosis after PCI implantation of DES [81,114]. DAPT was recommended for 12 months or longer after DES stenting in early clinical trials, but this increased the risk of major bleeding [115]. In recent years, several randomized clinical trials testing shorter DAPT durations have demonstrated comparable antithrombotic efficacy due to the availability DES with higher biocompatibility and the potential benefits due to a reduced incidence of major bleeding [114,116]. Furthermore, the use of more potent P2Y12 inhibitors, such as Tegretol and Prasugrel, has been shown to reduce the occurrence of the primary cardiovascular endpoint, but increase the risk of bleeding events is increased [117]. Single antiplatelet therapy with P2Y12 inhibitors is an appealing strategy that may have better antithrombotic efficacy than aspirin and reduces the need for DAPT after DES implantation [118,119]. Given these findings, it remains unknown whether a shorter DAPT regimen and the use of dual antitherapeutic agents following PCI with DES provide adequate protection against ischemic events, and whether the benefit is increased due to reduced major bleeding, which require more future clinical trials to prove.

Bioresorbable scaffold. Long-term inflammation of the coronary artery wall in DES, delayed arterial healing, and the formation of new atherosclerosis are associated with the permanent presence of persistent polymer stent coatings and may lead to late and very late adverse events [120]. Bioresorbable scaffold (BRS) technology provides transient vessel support with drug-delivery capabilities without the long-term limitations of the permanent metallic DES [121,122] But the ideal patient and lesion selection and the best implantation technique should be considered more frequently in future studies.

Quantitative flow ratio. It is a novel method based on angiography, which can quickly calculate fractional blood flow reserve without using pressure line or adenosine. Compared with standard angiographiy guidance, QFR-guided lesion selection strategy has improved the clinical results for one year in patients undergoing PCI [123,124]. The QFR technique, with its reproducibility, simplicity and lack of adenosine side effects, is gradually becoming a new tool for the catheterization laboratory to guide clinicians in the development of interventional treatment strategies.

Biodegradable stent materials. Keyword clustering and literature timeline map visualize the emerging research themes such as *drug-eluting balloons*, *degradable polymers*, and *resorbable stents*, foreshadowing a future in which stent implantation disappears completely in vivo after completing of hemodynamic reconstruction and vascular repair,

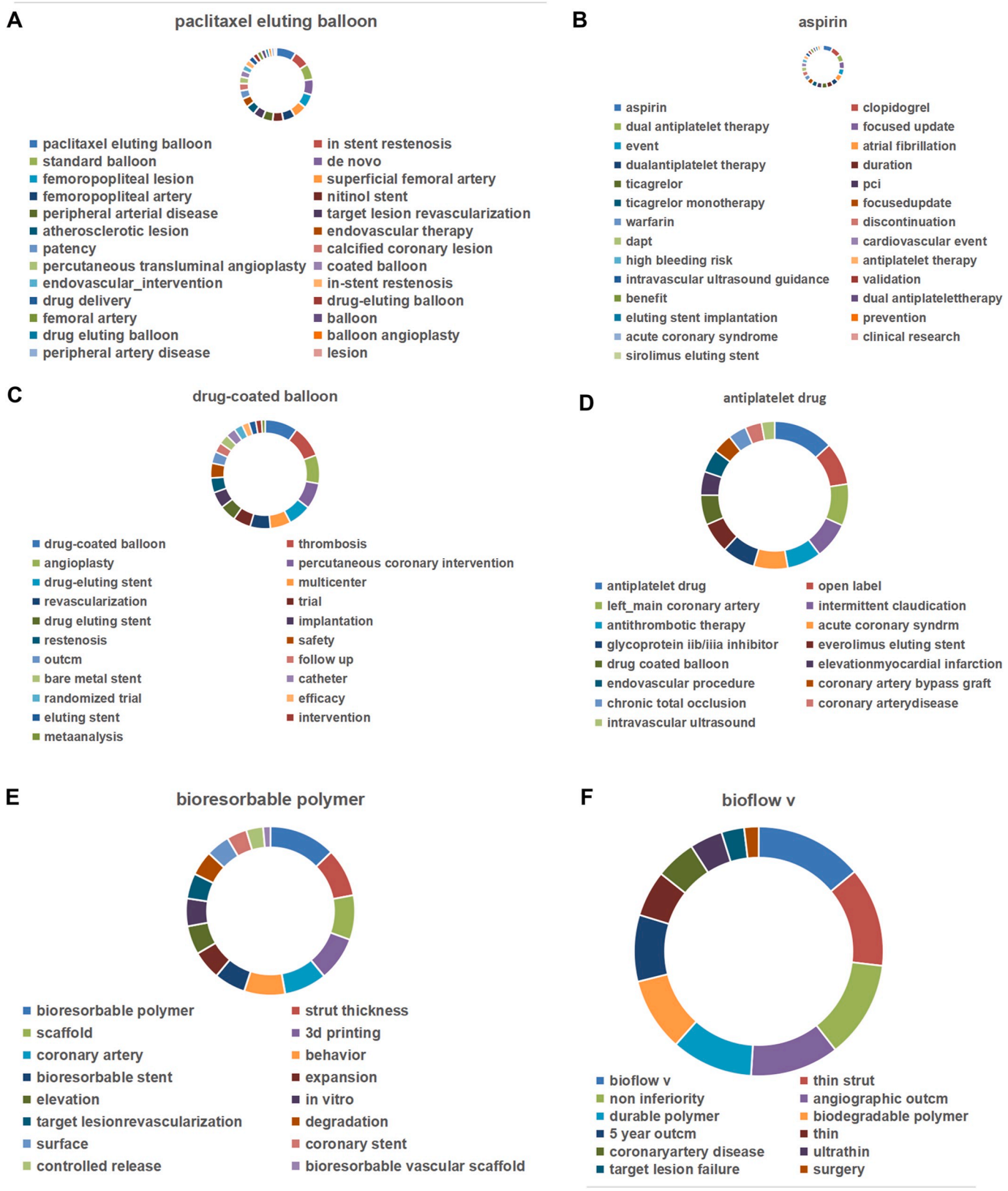

Fig. 9. The keywords of top 5 modules in 2021. A: Module 1. B: Module 2. C: Module 3. D: Module 4. E: Module 5. F: Module 6.

reducing foreign body rejection. The research results of the mechanical properties and degradation characteristics of degradable metallic or polymeric materials provide new ideas for the selection of substrate/coating materials for DES. Mg-based biodegradable metals [125–127], Fe-based biodegradable metals [128,129], and Zn-based biodegradable metals [130–132] are being extensively investigated for the preparation of superior vascular scaffolds.

Collectively, the main reason why these topics have emerged is that

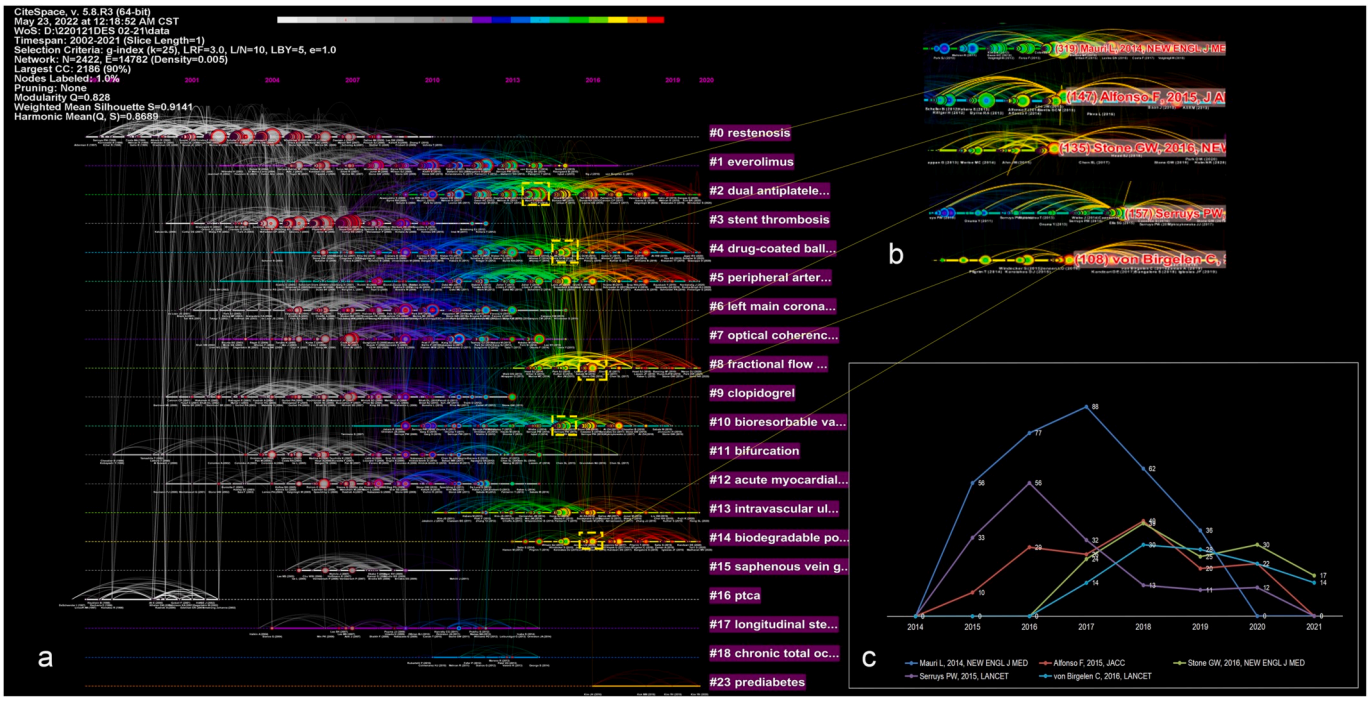

Fig. 10. The reference clusters map. a. the citation timeline visualization, b. The burst citation in #2, #4, #8, #10, and #14, c. citation frequency distribution of the burst citation, X-axis: Year, Y-axis: Cited frequency.

they aim to address or partially address the two challenges that plague long-term clinical outcomes in DES: ISR and LT. And these two challenges still have not been fully solved. Therefore, the authors boldly predict that the future prospects of DES research will continue to revolve around these two challenges and breakthroughs may appear on the emerging topics mentioned earlier.

4.3. Further directions

Big data platform and data mining on DES research. Data mining can reveal the non-trivial process of implied, previously unknown, and potentially valuable information from a large amount of data in a database, which in turn helps decision makers to adjust their strategies, reduce risks and make the right decisions. Cardiovascular disease accounts for nearly 30% of global deaths, and the number of coronary stents implanted worldwide in 2019 alone is approximately 3.4 million, a staggering number, so there is an entirely sufficient sample size to build a big data platform on DES research. Mechanical factors, [133,134], genetic factors, [135,136], biological factors [137,138] and technical factors [139–141] are thought to be involved in clinical outcomes after stent implanting. Whether and how molecular connections exist between these factors can only be more convincingly explained by relying on big data platforms. The NCBI's GEO database has some data on DES (GSE19136, GSE28781, and GSE155793 et al.) that can be used for high-throughput analysis, however, the data is still limited. In addition, imaging data and clinical data are not shared among hospitals around the world on their data platforms, which restricts the use of big data mining in the DES field.

Bionic vascular stent design. As early as 2002, researchers have proposed that stent design such as shape, size, stent struts' width and thickness of stent struts can affect neointimal formation and vascular remodeling [142]. With the advancement of simulation algorithm and processing means [143–146]. In the future, the design of vascular stents will also tend to be more bionic in design, and it is possible to achieve personalized treatment through individualized stent design for different patients and different lesion sites.

Multidrug or multicomponent synergy. With the gradual understanding of the physiological processes at the site of vascular lesions before and after stenting [147–149], researchers have found that multi-drug or multi-component synergy can inhibit ISR and ST more effectively [150,151]. The challenges in this area may come more from drug selection, how the drug is grafted onto the stent, and the effectiveness of the drug.

More scientific postoperative interventions. Although DAPT with aspirin and a P2Y12 receptor inhibitor is the standard of care for preventing ST after DES implantation for PCI [81] The jury is still out on the timing of post-procedure antithrombotic therapy, mono- or dual antiplatelet therapy, in patients undergoing complex percutaneous coronary intervention (PCI) is inconclusive. A study concluded that continuous ticagrelor monotherapy resulted in lower bleeding rates and no increased risk of ischemic events compared with continuous ticagrelor plus aspirin [152]. More clinical data are needed to reveal the final puzzle.

In summary, this study provides an insight into the developing trend of DES research, which may guide new directions for further study.

Statement

This paper does not cover studies in human subjects or animal studies.

Declaration of competing interest

Authors do not have any conflicts of interest to declare.

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Appendix A. Supplementary data

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