Presentation of Chemotherapy Options in Cachexia in the Literature: A Scientometric Evaluation

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Abstract

Background: Cachexia is a multifactorial syndrome characterized by weight loss, muscle wasting, and symptoms such as fatigue and anorexia. The primary aim of this study was to quantitatively and qualitatively examine the research trends and hotspots on chemotherapy options in cachexia.

Methods: A scientometric analysis was carried out according to the Science Citation Index-Expended database in the Web of Science. By utilizing bibliometric software, the performance of the total articles was covered from records, authors and affiliations, journals and research categories, to burst references, citation relationship network, and the keywords co-occurrence overlay visualization.

Results: A total of 1,111 articles were retrieved. The United States occupied the top position both on the total outputs and the cooperation with other countries. *Journal of Cachexia, Sarcopenia and Muscle* had the highest impact factor and the most publications. Eight main groups were clustered by the similarity of the research topic. Ongoing weight loss has been the main bottleneck either in mechanistic research or therapeutic trials. In addition to nutritional supplements, the major options for pharmacological therapy were progestational agents, such as megestrol acetate and corticosteroids. 'Computed tomography' and strategies dealing with 'skeletal muscle mass', 'muscle mass', 'sarcopenia' and 'muscle atrophy' might be the breakthrough for the future diagnosis and treatment of cachexia.

Conclusions: We considered the publication information by summarizing the literature on the pharmacological treatment of cachexia. In summary, this study provides novel and useful data for related scientific research and will help researchers explore cachexia chemotherapy options more intuitively and effectively.

Introduction

Cachexia has long been recognized as a hypercatabolic state which is characterized by an ongoing loss of skeletal muscle (with or without loss of fat mass) that cannot be fully reserved by conventional calorie supplementation[1, 2]. The prominent clinical symptoms associated with cachexia are fatigue and anorexia[3]. It is best described in cancer but is also seen in other advanced chronic inflammatory illnesses such as AIDS, heart failure, end-stage kidney disease, and chronic obstructive pulmonary disease[4]. Although body composition changes are not identical in all of these disease states, the term cachexia is used in all of these disorders.

Between 50% and 80% of patients with advanced cancer develop cachexia[5]. Cancer cachexia is a crucial reason for reduced chemotherapy tolerance, reduced quality of life, reduced physical functioning, and shortened survival[2, 6]. In addition, cancer cachexia can often occur in the presence of comorbidity[7, 8]. Negative protein and energy balance are the principle pathophysiology of cancer cachexia which is driven by a variable combination of decreased oral intake and altered metabolism[9]. Despite the high prevalence of cancer cachexia, there is still no standard of care, and only a few therapeutic options exist[2, 5]. The reason for cancer cachexia is multifactorial, thus, requiring multimodality interventions, including nutrition, exercise, medications[5]. Whereas, an ideal treatment for cachexia would improve anorexia and enhance food intake while also stimulating anabolism, thus overcoming the catabolic drive.

The scientometric analysis could provide powerful support for arranging and clustering the comprehensive and chronological citation network, evaluating and identifying the established and emerging research topics through rigorous algorithmic software tools[10]. Although several available interventions can improve patients' appetite or

increase their bodyweight, the precise benefits of existing drugs are pending further study[11]. Moreover, to the best of our knowledge, no studies have utilized bibliometric software to evaluate cachexia topics and their effects. Herein, we perform this scientometric study to quantitatively describe the current situation and developing trend of publications concerning cachexia chemotherapy based on 1111 articles published in the Science Citation Index Expanded in the past three decades.

Methods

The retrieve in the Science Citation Index-Expended database, Thomson Reuters Web of Science (WoS) Core Collection was completed on 31 July 2020 by two authors independently. In order to equilibrium, both the recall rate and the accuracy rate, medical subject headings, and entry terms were combined through Boolean logic operators. The search criteria were set as: topic = (cachexia) and topic = (drug therap* or chemotherap* or pharmacotherap* or drug treat*), with time span = all years, and excluded non-article document types by refining function. The full records and cited references of all eligible articles were downloaded in both plain text and tab-delimited formats for further software analysis. The citation report of the retrieval results and the journal citation report (JCR) information were obtained from the database as well.

The WoS database provided the annual publication and the distribution in each country. The online software www.bibliometric.com was utilized to calculate the cooperation between various countries and to count the generated inclusive total citation count and average citation count of these indexed articles in each journal. The bibliometric software CiteSpace[12] (5.7.R1), CitNetExplorer[13] (1.0.0), and VOSviewer[14] (1.6.15) based on JAVA were required to obtain the citation burst references, the citation network map, and the keywords co-occurrence visualization.

Opting with a time slice to 1 year, a range between 1991 and 2020, and a selection of all documents, the top 10 references with the highest citation burst scores were tabulated. Setting the resolution parameter to 2.00, and minimizing the article number in each group to 10, the 8 main groups were clustered in which 399 articles were excluded in the citation network map. Merging the abbreviations and acronyms, the plural and singular of the author keywords, the 46 most high-frequency keywords was visualized as the threshold of 10 occurred times.

Results

1. Publication outputs

The retrieval found 1111 articles, with a total citation of 28100, an average citation of 25.29, and an *h*-index of 75 in WoS. Figure 1 shows the total annual publications and the annual publications of the top 6 high yield countries on cachexia. The first article was launched in 1991, and the most productive year was 2019 with 127 records. The top 10 high yield countries and their publication records were: USA (333), Japan (115), Italy (114), Germany (98), Canada (83), Peoples R China (70).

Table 1 depicts the JCR® information and the citations of the top 7 high yield journals. *Journal of Cachexia, Sarcopenia and Muscle* which had the highest impact factor of 9.802 in 2019, ranked top position with 65 publications, accounting for 5.85%. It was cited as high as 195 times among all the eligible 1111 publications. *Clinical Nutrition* had the highest average cited times of 5.47 based on the 30 publications. Both the two journals

were located at the Q1 zone, in the category of Geriatrics & Gerontology (2 of 51) and category of Medicine, General & Internal (9 of 165), and in the category of Nutrition & Dietetics (9 of 89), respectively.

Table 1 The JCR® information and the citations of the top 7 high yield journals.

No	Journals	R	P	Journal Citation Report (JCR®)				Total Citations	Average Citations
				2019 IF	Category	Rank	Quartile		
1	*Journal of Cachexia, Sarcopenia and Muscle*	65	5.85%	9.802	Geriatrics & Gerontology Medicine, General & Internal	2/51 9/165	Q1 Q1	195	3.00
2	*Supportive Care in Cancer*	53	4.77%	2.635	Health Care Sciences & Services Oncology	37/102 163/244	Q2 Q3	135	2.55
3	*Clinical Nutrition*	30	2.70%	6.36	Nutrition & Dietetics	9/89	Q1	164	5.47
4	*PLOS ONE*	26	2.34%	2.74	Multidisciplinary Sciences	27/71	Q2	49	1.88
5	*Nutrition and Cancer an International Journal*	25	2.25%	2.363	Nutrition & Dietetics Oncology	60/89 177/244	Q3 Q3	33	1.32
6	*BMC Cancer*	19	1.71%	3.15	Oncology	129/244	Q3	16	0.84
7	*Anticancer Research*	18	1.62%	1.994	Oncology	203/244	Q4	18	1.00

R: records; P: percentage; IF: impact factor.

2. Cooperation networks

Figure 2 illustrates the cooperation networks among countries on cachexia. As shown in the pie chart, with counting the multinational cooperation articles separately in each country, the U.S has the strongest cooperation with other countries. The U.S actively participated in cooperation with Canada, China, Italy, Australia and other countries. Operational cooperation of nations with neighbouring countries was one of the most important part of academic communication, such as the United Kingdom and Germany, the United States and Canada.

3. Burst references

To detect the core and classical kinds of literature, the reference with citation burst could express it received special concern from the academics in the short time. Table 2 lists the top 20 references with the strongest citation bursts. The strongest burst score of 8.751 was belonged to "Prevalence and clinical implications of sarcopenic obesity in patients with solid tumors of the respiratory and gastrointestinal tracts: a population-based study" on *The Lancet*

Oncology authored by Carla MM Prado, *et al*. in 1990. In the same year, "A controlled trial of megestrol acetate on appetite, caloric intake, nutritional status, and other symptoms in patients with advanced cancer" on *Cancer* by the scholars Eduardo Bruera, *et al*. and “Controlled Trial of Megestrol Acetate for the Treatment of Cancer Anorexia and Cachexia” on *Journal of the National Cancer Institute* by the scholars Charles L. Loprinzi, *et al*. got the earliest citation burst since the year of 1992. The latest article was “ESPEN guidelines on nutrition in cancer patients” on *Clinical Nutrition* by Jann Arends, *et al*. in 2017, while the citation burst started from the next year.

Table 2 Top 20 references with the strongest citation bursts.

References	Strength	Begin	End	1991 - 2020
BRUERA E[15], 1990, *CANCER*	5.4548	1992	1998	
LOPRINZI CL[16], 1990, *JNCI-J NATL CANCER I*	5.1329	1992	1998	
STRASSMANN G[17], 1992, *J CLIN INVEST*	3.8799	1994	1999	
Tisdale MJ, 2002[18], *NAT REV CANCER*	4.3614	2004	2010	
Fearon KCH[19], 2003, *GUT*	5.8464	2005	2011	
Inui A[20], 2002, *CA-CANCER J CLIN*	4.0728	2005	2010	
Moses AWG[21], 2004, *BRIT J CANCER*	4.128	2006	2012	
Fearon KC[22], 2006, *AM J CLIN NUTR*	7.922	2008	2014	
Prado CMM[2], 2008, *LANCET ONCOL*	8.751	2010	2016	
Evans WJ[1], 2008, *CLIN NUTR*	8.5458	2010	2016	
Fearon KCH[23], 2008, *EUR J CANCER*	3.5132	2011	2016	
Tisdale MJ[24], 2009, *PHYSIOL REV*	6.0796	2012	2016	
Mourtzakis M, 2008[25], *APPL PHYSIOL NUTR ME*	5.5382	2012	2016	
McMillan DC, 2009[26], *CURR OPIN CLIN NUTR*	3.4514	2012	2014	
Prado CMM[27], 2009, *CLIN CANCER RES*	7.5148	2013	2017	
Fearon K[28], 2011, *LANCET ONCOL*	5.6964	2013	2017	
Tan BHL[29], 2009, *CLIN CANCER RES*	4.3281	2013	2017	
Fearon K[11], 2013, *NAT REV CLIN ONCOL*	4.4176	2014	2016	
Temel JS[5], 2016, *LANCET ONCOL*	4.5954	2017	2020	
Arends J[30], 2017, *CLIN NUTR*	5.6839	2018	2020	

4. Citation networks

Figure 3 draws the citation network map on cachexia. The blue, green, purple, orange, yellow, brown, pink, and cayan groups represented in turn from 1 to 8 groups, which contains 336 articles, 142 articles, 108 articles, 55 articles, 30 articles, 15 articles, 14 articles, and 12 articles, respectively. The citation score was calculated by the

CitNetExplorer software. Table S1 summarizes the publications with the highest citation score in every eight groups.

5. Co-words

To determine the research hot issues and to track the scientific development, the keywords co-occurrence analysis indicates the relationship of publications. Figure 4 sketches the keywords cooccurrence overlay visualization on cachexia. The top 10 high-frequency keywords were: cachexia (238 times), cancer (131 times), chemotherapy (93 times), cancer cachexia (91 times), sarcopenia (81 times), survival (52 times), weight loss (52 times), quality of life (49 times), anorexia (46 times) and malnutrition (45 times). The most recent appear around 5 years keywords were: skeletal muscle mass and computed tomography (in 2018), muscle mass and sarcopenia (in 2017), and muscle atrophy (in 2016).

Discussion

The alarming increase of cachexia burden needs to pay attention to all policies. While progress in the pharmacological treatment of cachexia has been slow. Contributory factors include the lack of a clear definition for cachexia[1, 2, 18], the multi-factorial nature of the condition[19], the lack of validated biomarkers[23], primitive clinical trial design[31], and a paucity of interest by sponsors of research[23]. Scientific evidence is essential for justify the effectiveness and safety of chemotherapy strategy in the intervention or prevention of disease. Therefore, in this article, scientometrics was used to quantitatively and qualitatively analyze global publication trends and research hotspots of chemotherapy options in cachexia.

The number of total annual publications and the annual publications of the top 10 productive countries were examined regarding chemotherapy options in cachexia. Overall, the number of total annual publications is growing and the increasing trend of annual publications revealed the increasing interest in this area. Besides, the top 10 productive countries issued more than 50% of the total literature (Fig. 1). There was a sudden increase in the number from 2010(27 articles)to 2011 (39 articles). This increase may have occurred for several reasons, including the emergence of a new definition and classification criteria[2].

According to this scientometric analysis, the trend of cachexia publication had a different pattern in the different countries notwithstanding are in the same region, and it is not related to the burden of the syndrome incidence (Fig. 2). Exchange the experiences and transit the knowledge at national and international levels could be useful in the establishment of a collaborative network. The result of the international collaboration analysis demonstrated the view of a joint project between countries. Some regions have strong collaboration in cachexia research, such as North America and western Europe, but some countries such as China and Japan could be more active in scientific collaboration.

The journals that were published most often were *Journal of Cachexia, Sarcopenia and Muscle*; *Supportive Care in Cancer* and *Clinical Nutrition* (Table 1). While most influential journals also included *Lancet Oncology* and *Cancer*. Publications were often categorized into the following subjects: Geriatrics & Gerontology/Medicine, General & Internal, and Nutrition & Dietetics.

Poor physical function in cachexia may be related to many factors, while all of them have been related, at least in part, to the effects of systemic inflammation[22, 25, 32], mediated by abnormally secreted cytokines[17, 26]. In addition, sarcopenic obesity or skeletal muscle depletion is the most important adverse prognostic factor[2, 28, 29,

33], which could be quantified by computed tomography images[24]. Emphasizing the need for evidence-based decision making and the value of review articles in evidence, the pattern of article types showed more than 90% of burst publication state in this category. Significantly, well-designed studies in special conditions such as multimodal intervention for management of cachexia in lung and pancreatic cancer are needed[3]. These studies may shed light on further research in cachexia.

According to the degree of depletion of energy stores, cachexia may be divided into three stages: precachexia, cachexia, and refractory cachexia. Before reaching its refractory phase, cachexia is not completely irreversible. The optimal time to initiate cachexia therapy is early in the disease trajectory, indeed before cachexia has become established: preventing cachexia rather than treating it. In practical terms, this means that cachexia interventions should be given alongside antineoplastic treatment[3, 34].

Ongoing weight loss has been the main criterion either for mechanistic research or therapeutic trials[23]. The major options for pharmacological therapy of cachexia were progestational agents, such as megestrol acetate[15, 16, 35] or corticosteroids[19, 36]. However, knowledge of the mechanisms has led to and continues to lead to, effective therapeutic interventions, including cannabinoids [19, 30], n-3 fatty acids[20, 21], gastroprokinetic agents[19, 30], androgen receptor modulators[11, 30], branch-chain amino acids[30], non-steroidal anti-inflammatory drugs (NSAID)[37] and thalidomide[11, 19] - all of which act on the feeding-regulatory circuitry to increase appetite and inhibit tumor-derived catabolic factors to antagonize tissue wasting and/or cytokine release. Combined treatments such as carnitine plus celecoxib with or without megestrol acetate[38], ghrelin[39–41], and ghrelin receptor agonist anamorelin[5], pentoxifylline[42], l-carnitine-supplementation[43], formoterol[44] also hold promise in offering cachexia patients new options and treatments.

Assess the frequent terms used in related articles about pharmacological treatment of cachexia revealed that the terms of cancer, cancer cachexia, sarcopenia, survival, weight loss, quality of life are frequent terms in the WOS database, highlighting the proportion of cancer cachexia in cachexia and the vital role of lean body mass in the development of cachexia disease. At present, the prognosis of cachexia patients is very poor, even when multimodal treatment strategies are used, which is also clear from the present analyses.

Using wider databases will formulate valid outcomes[45]. Our study was limited since analyses only examined publications indexed in the ISI WOS database. The study also had much strength, including a long study period and its thorough investigation of the impact of publications, countries, and international relationships. Additionally, the inclusion of systematic citation analyses and mapping fields make our findings particularly significant.

Conclusions

This study provides a scientometric analysis of chemotherapy options in cachexia management. Leading scientific issues were determined by examining impact extent and study citation sets of published literature. More specifically, the publication impact, systematic citation search outcomes, mapping fields, and keywords cooccurrence were examined to better understand what policies and management decisions were launched. Our research suggests that cachexia chemotherapy should target reduced oral intake, inflammation-related metabolic alteration, and reduced physical activity. Besides, our results indicate the need for well-designed clinical trials for evidence-based decision-making.

Declarations

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Authors' contributions: All authors listed have approved it for publication. MC and JW contributed equally to this article. They designed the study, analyzed, and interpreted the data, generated the figures and tables, and wrote the manuscript draft. ZZ and RD designed the study and directed the conception process. LW completed data mining in the database and reviewed the manuscript.

Ethics approval: Ethical issues (including plagiarism, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Figures

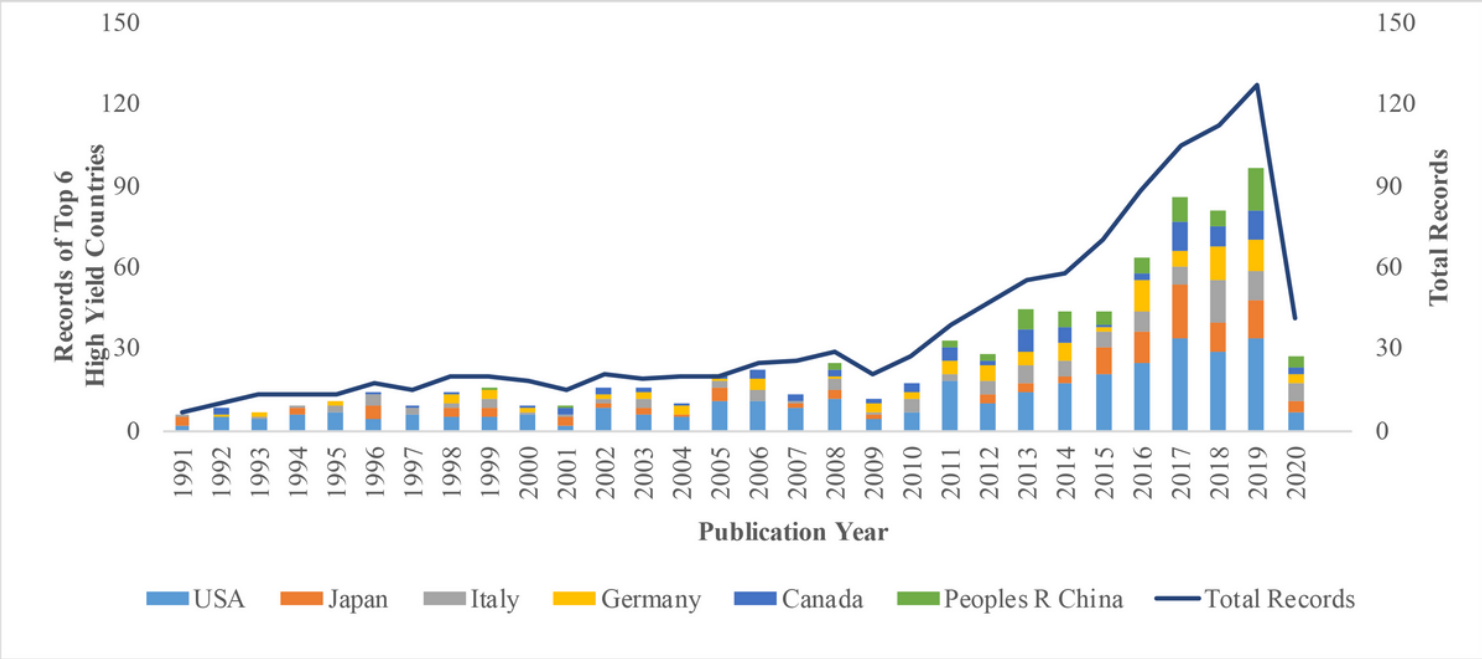

Figure 1

The total annual publications and the annual publications of the top 6 high yield countries on cachexia. The histogram represents the country publications, while the curve line is on behalf of the annual records.

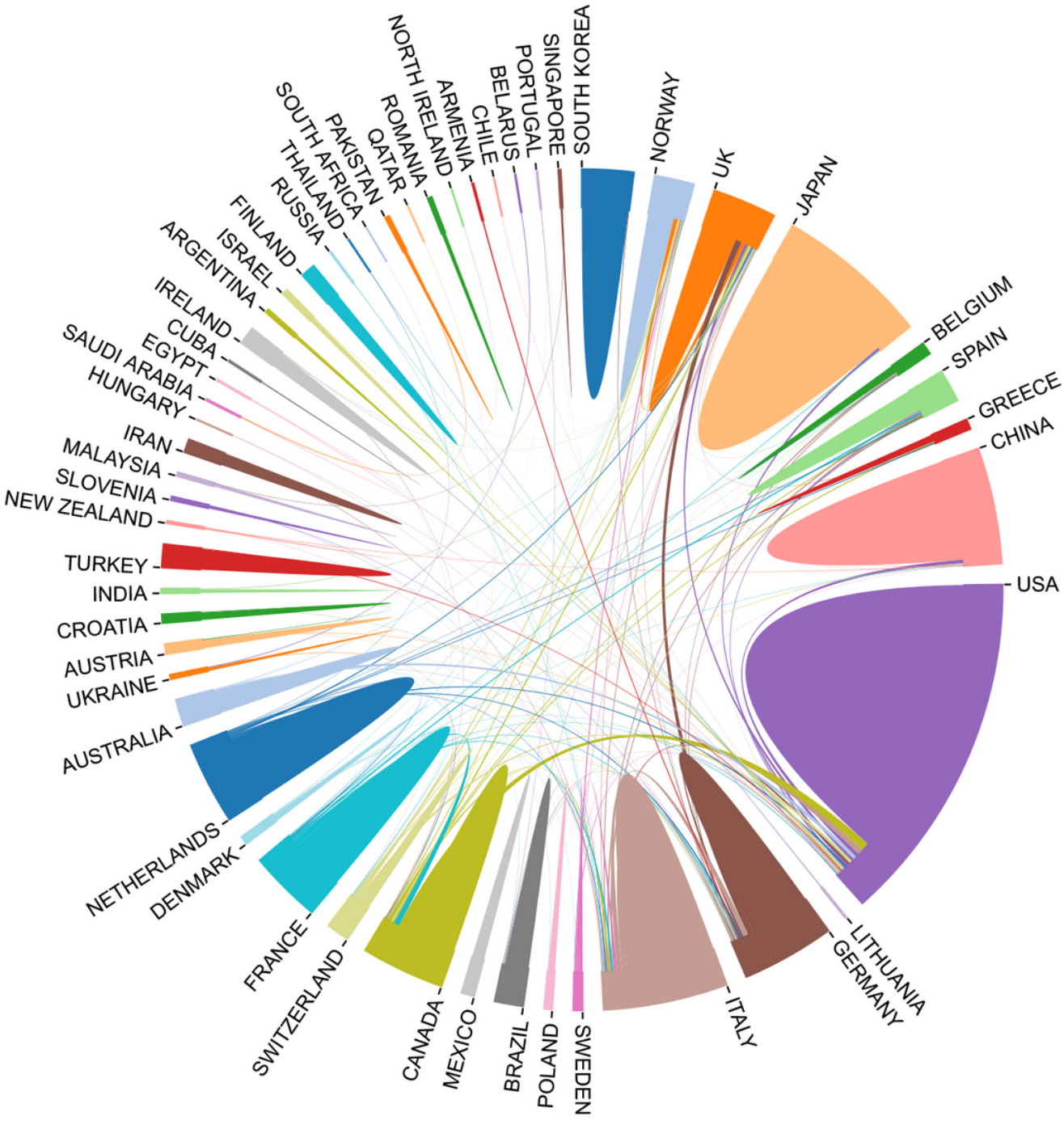

Figure 2

Cooperation networks among countries on cachexia. The area of the pie chart signifies the total publications while the lines delegate the cooperation between countries.

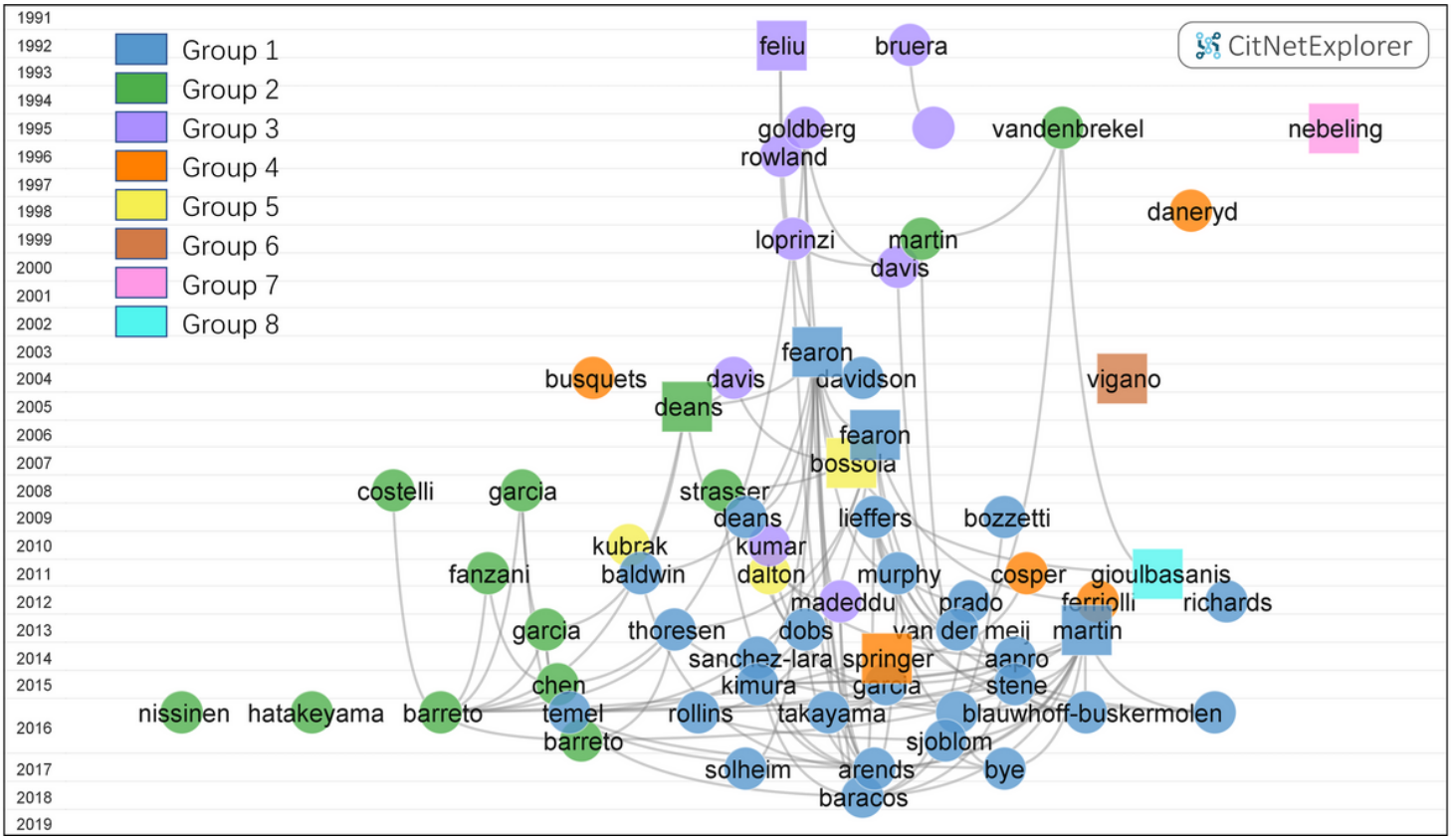

Figure 3

Citation network map on cachexia. Eight groups are colored with different colors. Marked with the first author's last name, dots or tetragons indicates an article, however, the latter represents the articles with the high citation score in each group.

Figure 4

Keywords cooccurrence overlay visualization on cachexia. Each frame notifies a keyword, in which the size and the color are in direct proportion to the occurred times and the average occurred publication year.

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