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Engineering exosomes and their application in cardiovascular field: Bibliometric analysis from 2002 to 2022

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death around the world, warranting an increasing number of studies for its treatment. Among all of its therapeutical strategies, engineered exosomes are attracting growing attention due to their excellent biocompatibility, non-immunogenicity, and favorable plasticity. Despite its increasing popularity, there is yet to be a bibliometric analysis regarding the application of exosomes in CVD treatment. Therefore, the present study assessed the current trends in engineered exosomes in treating CVD by conducting a bibliometric analysis. All associated literatures published between years 2002–2022 were collected, through the Web of Science Core Collection. Our results showed that related studies robustly increased in 2020, followed by a gradual increase from 2020 to 2022, indicating that this field attracted growing attention. Additionally, we described critical network of countries, institutions, authors, top-cited references, and keywords. The present bibliometric study provides systematic observations on engineering exosomes in treating CVD, reveals potential challenges and future direction for additional studies, and may inspire more researchers to commit to investigating treatments for CVD.

1. Introduction

Of all non-communicable diseases, cardiovascular disease (CVD), especially ischemic heart disease, is the leading threat to human health and is responsible for high hospitalization and mortality rates all around the world [1–3]. Though many interventions, such as exercise rehabilitation [4], have alleviated the burdens of CVD, irreversible apoptosis of cardiomyocytes still lacks effective treatment strategy [5]. Despite an increasing number of scientists and studies engaging in the prevention and treatment of CVD, there is still much progress to be made. In order to identify promising treatments, it is necessary to intermittently assess its progress and trends.

Exosomes are nanoparticles released by almost all cell types, which is a great characterization for disease therapy [6,7]. They can

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deliver molecules such as protein, lipid, and nucleic acid through biological barriers and induce cell to cell communication [8,9]. Increasing evidences show that stem-cell derived exosomes attenuate a variety of CVDs including myocardial infarction (MI) [10], aging-associated cardiac dysfunction [11], and pathological cardiac remodeling [12]. Although these are encouraging findings, naturally produced exosomes have insufficient cargo loading potential and are retained in the heart, limiting their usage in the cardiovascular field.

To overcome the shortcomings of naturally generated exosomes, many researchers have begun investigating modifying exosomes with engineering approaches. Modifications optimized exosomes for drug delivery via targeted peptide [7,13] and surface chemical [14] modifications, genetic engineering [15], and ingredients modification [16]. For example, engineered exosomes modified by fusing targeting peptide (CSTSMLKAC) to their membrane protein effectively reduced inflammation and improved cardiac function in ischemic myocardium [17]. Recently, a study found that modified mesenchymal stem cells-derived exosomes via genetic alternation of miR-129-5p attenuated myocardial infarction-induced ventricular remolding in mice [18]. Beyond exosomes, other nanoparticles have also been modified for investigating alternative treatment modalities such as engineered platelet nanovesicles [19] and hybrid cell membrane-coated nanoparticles [20]. Due to the sheer volume and variety of studies regarding engineered exosomes and nanoparticles for treatment of CVD, a systematic overview is warranted for guiding further exploration of CVD treatments.

Bibliometric analysis is gaining traction in all disciplines due to its flexibility and efficiency [21]. However, there is yet to be a bibliometric analysis of research regarding engineered exosomes. To better understand the trends of engineered exosomes in cardiovascular studies, we performed a bibliometric analysis to investigate the past, present, and future of the field. The present study will provide a new horizon for CVD prevention research.

2. Methods

Literatures analyzed in this study were extracted from the Science Citation Index Expanded and Social Science Citation Index of the Web of Science core collection (WOS). A search for "engineering exosomes" from June 30, 2002 to June 30, 2022 returned a total of 1199 results. After excluding editorials, book chapters, early accesses, letters, and meeting abstracts, a total of 673 articles and 472 reviews remained for bibliometric analysis. To further focus the search for engineered exosomes in the cardiovascular field, we then use Topic (Searches title, abstract, author keywords, and Keywords Plus) = ("cardiovascular" or "heart") AND Topic = (engineering exosomes) to filter the literatures in WOS, resulting in 106 records. A total of 37 articles and 62 reviews were selected to build bibliometric maps for analysis (CiteSpace, 5.8.R3) [22,23]. Additional network visualizations of these studies were analyzed through

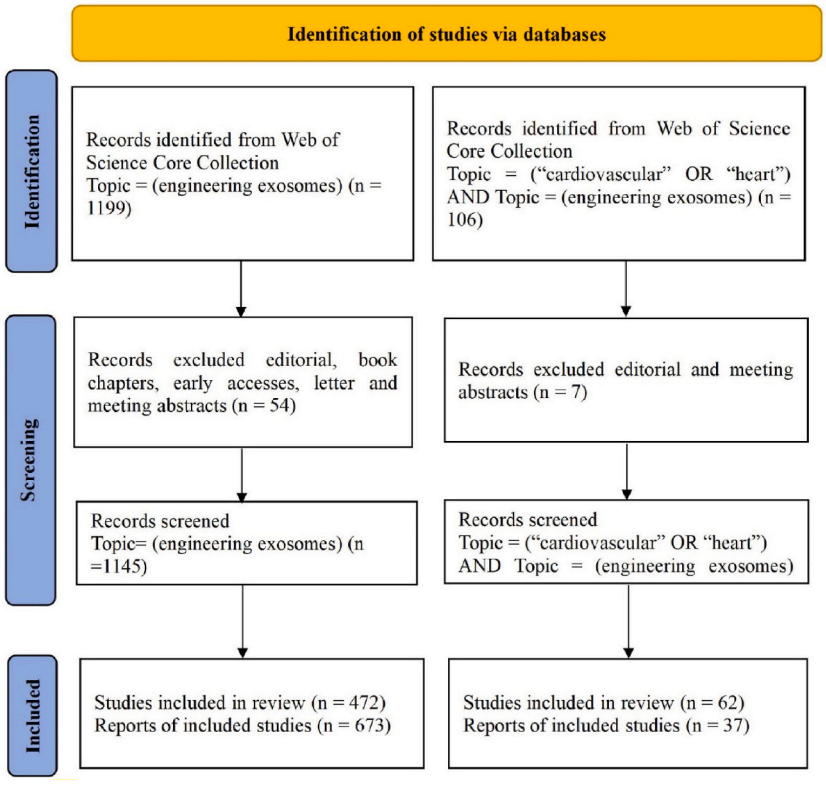

Fig. 1. Flowchart of literature selection All the data were collected from Web of Science Core Collection and underwent analyzing with bibliometrics software CiteSpace and VOSviewer.

VOSviewer (1.6.18), which allowed further assessment of variables such as countries, institutions, and authors. A PRISMA chart, modified based on a public template [24], depicting the literature selection process is shown in Fig. 1.

3. Results

3.1. Analysis of the trend of publications

To better understand the trends of engineering exosomes in the cardiovascular field, we analyzed the selected literatures by their publication years. As shown in Fig. 2, the number of publications regarding engineering exosomes gradually increased between 2002 and 2022, with an especially robust increase in 2020. Notably, only four papers were published before 2010, indicating a cold research field. There was minimal growth between 2010 and 2014. Then, the number of publications dramatically grew from 2015 to 2021, reaching a total output of 360 papers in 2021, indicating that more and more scholars were focusing on engineered exosomes (Fig. 2).

Relative to the field of engineered exosomes, studies in the cardiovascular field emerged later in 2012, during which only one paper was published. As exosome research progressed and after its potential application in the cardiovascular field was identified, there has been gradual increase in studies regarding engineered exosomes in the cardiovascular field since 2012; the present data suggest that while it is still in its infancy, it is expected to grow quickly in the near future.

3.2. Distribution of countries and institutions

60 countries and regions made contribution to the filtered studies on engineered exosomes. To better understand the distribution of authors' countries and institutions, we constructed a map of these articles via CiteSpace and VOSviewer. The node map constituted of 53 nodes and 60 connections in the country distribution map (Fig. 3a) and 327 nodes and 325 connections in the institution distribution map (Fig. 3b). We found that China, USA, and Italy are the top 3 contributing countries in terms of number of publications in the field of engineered exosomes (Fig. 3a). Notably, institutions including Shanghai Jiao Tong University, Huazhong University of Science and Technology, Zhejiang University, and Harvard Medical School were the top contributing institutions in this field (Fig. 3b). To further analyze the node map, we displayed the first published year, the centrality, and the count ratio of the top 10 countries list (Table 1). Data showed that the top three countries with the highest number of engineered exosomes associated publications accounted for 33%, 28%, and 7.5% of the total respectively (Table 1). Respective to institution, Shanghai Jiao Tong University, Huazhong University of Science and Technology, and Zhejiang University had higher centralities compared to other institutes, accounting for 3.06%, 2.10% and 2.01% respectively (Fig. 3b, Table 1).

Subsequently, networks of countries and institutions were constructed in the subfield of CVD associated engineered exosomes. Notably, North Carolina State University (NCSU) in USA was the leading institution. On the other hand, the University of Alabama at Birmingham had publications that were cited a total of 315 times, with an average of 78 times per publication (Table 2), indicating a wide influence in this field. The published numbers from The University of Alabama at Birmingham and Zhejiang University were second only to NCSU in the field of CVD associated engineered exosomes (Table 2). Notably, the institutions from England, South Korea, and Germany also contributed significantly. Among the top countries and institutions, there was active collaboration between China, USA, Italy, and England. Specifically, authors from Zhejiang University and the University of Alabama at Birmingham had a good cooperative relationship.

These data demonstrated that the field of CVD associated engineered exosomes still has room for much progress, additional

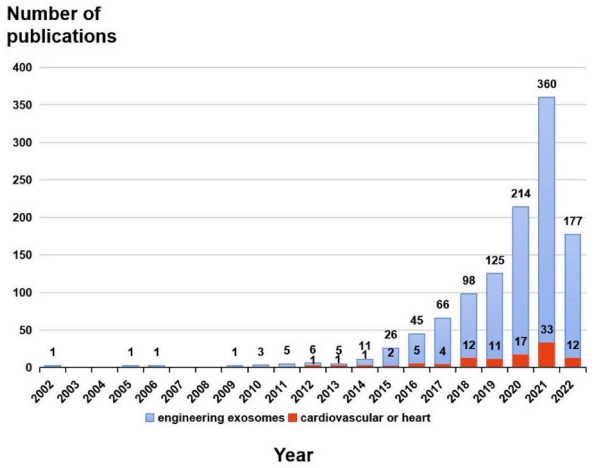

Fig. 2. Trends of engineered exosomes and their related studies in cardiovascular field published over the past 20 years The number of studies on engineered exosomes and their related studies in cardiovascular field were shown as blue and red column respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

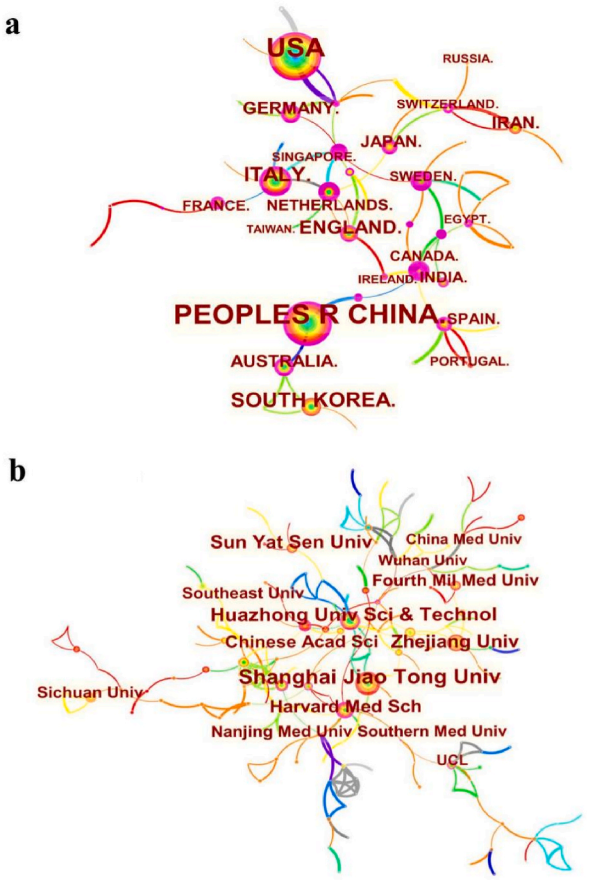

Fig. 3. Network of publications from different countries and institutions about engineered exosomes (a) Distribution of national cooperation of engineered exosomes related literatures, containing 53 nodes and 60 connections in the network. (b) Institutional cooperation network of engineered related studies, including 327 nodes and 325 connections in the network. Especially, the number of documents by different countries and institutions as well as their inter-cooperation were shown as nodes and line respectively. The size of these nodes was positively connected with the number of published literatures.

Table 1
Distribution of publications from different countries and institutions about engineered exosomes.

No.	Country	Year	Centrality	Count (%)	Institution	Year	Centrality	Count (%)
1	Peoples R China	2010	0.27	380 (33.19%)	Shanghai Jiao Tong University	2016	0.03	35 (3.06%)
2	USA	2005	0.14	322 (28.12%)	Huazhong University of Science and Technology	2015	0.13	24 (2.10%)
3	Italy	2012	0.39	86 (7.51%)	Zhejiang University	2018	0.03	23 (2.01%)
4	South Korea	2005	0.07	77 (6.72%)	Sun Yat sen University	2019	0.02	22 (1.92%)
5	England	2010	0.17	51 (4.45%)	Harvard Medical School	2016	0.26	19 (1.66%)
6	Iran	2016	0.07	40 (3.49%)	Chinese Academy of Sciences	2018	0.15	18 (1.57%)
7	Germany	2011	0.33	38 (3.32%)	Fourth Military Medical University	2019	0.03	15 (1.31%)
8	Australia	2014	0.2	34 (2.97%)	Nanjing Medical University	2018	0.12	14 (1.22%)
9	Japan	2013	0.28	29 (2.53%)	Sichuan University	2020	0.01	14 (1.22%)
10	Netherlands	2012	0.44	27 (2.36%)	Southeast University	2018	0.03	14 (1.22%)

researchers, and institutions. Collaboration in this field, although present, must continue to expand.

3.3. Journals and co-cited journals on engineered exosomes

To further explore journal preferences and influence in the field of engineered exosomes, we performed analyses on academic journals and co-cited journals. A total of 1145 articles related to engineered exosomes were published in 401 international journals. Notably, 45 articles were published in the International Journal of Molecular Sciences (3.93%) and more than 20 articles were published in Theranostics (2.27%), Biomaterials (2.18%), Journal of Extracellular Vesicles (2.18%), and Pharmaceutics (2.10%)

Table 2
Distribution of publications from different countries and institutions about engineered exosomes in cardiovascular field.

No.	country	documents	Citations	Average Citation	Institution	documents	Citations	Average Citation
1	USA	43	118	2.74	North Carolina State University	5	200	40.00
2	Peoples R China	32	62	1.94	University of Alabama at Birmingham	4	315	78.75
3	Italy	10	11	1.10	Zhejiang University	3	195	65.00
4	England	6	220	36.67	Zhengzhou University	3	156	52.00
5	South korea	5	595	119.00	Icahn School of Medicine at Mount Sinai	3	128	42.67
6	India	5	10	2.00	Southeast University	3	69	23.00
7	Netherlands	4	66	16.50	Central South University	3	38	12.67
8	Germany	3	215	71.67	Imperial College London	3	55	18.33
9	France	3	31	10.33	University Medical Center Utrecht	3	28	9.33
10	Iran	3	12	4.00				

(Table S1). The top co-cited journal was the Journal of Extracellular Vesicles, whose co-citation reached 2193 times. Other comprehensive journals that were in the top ten co-cited journals list included Molecular Therapy, Nature Communication and Nature (Table S1).

To better understand the core journals in the field of engineered exosome in the cardiovascular field, we performed a cluster analysis. In the field of engineered exosomes associated with CVD, a total of 99 articles were published in 66 journals. The top three journals respective to the number of articles were Cells (7.07%), Frontiers in Cardiovascular Medicine (5.05%), and Circulation Research (4.04%).As shown in Fig. S1, co-cited journals such as Circulation Research/Circulation and the Journal of Extracellular Vesicles/Biomaterials had great influence (Fig. S1). Interestingly, Circulation Research was also one of the top co-cited journal in this field, which may be due to its relevance to the cardiovascular field.

3.4. Authors and co-cited authors in engineered exosomes

Top 10 authors with the most articles were listed to investigate their contributions to the field of engineered exosomes. MAURIZIO FEDERICO contributed the most articles with 14 articles, accounting for 1.22% of all authorships (Table 3). In addition, FLAVIA FERRANTELLI and CHIARA CHIOZZINI followed with 11 and 10 articles respectively. Additionally, the communicable network of all the authors in this field were assessed through analyzing citation rankings of their co-cited author(s) (two or more authors were cited at the same time). Our findings indicated that there were four scientists with more than 200 citations; of those, THERY C and ALVAREZ-ERVITI L were the top two scientists, with 317 citations as co-cited authors (Table 3). Of the authors that contributed to the field of CVD-related engineered exosomes, five scientists (KE CHENG, COSTANZA EMANUELI, SUSMITA SAHOO, and WUQIANG ZHU) had the most significant impact as evidenced by their publication records (Fig. 4a). Respective to co-cited authorships, LUCIO BARILE and RUENN CHAI LAI had the most citations (Fig. 4b).

3.5. The most impact references in the engineered exosomes & cardiovascular field

To better understand the impact of the references, we observed the co-cited references network. References with the greatest influence, as evidenced by cited records, have been listed (Table 4). The top three references had more than 100 co-citations each, demonstrating their significant influence. The most cited reference, "Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer," demonstrated a novel approach to specifically targeting oncogenic KRAS by using engineered exosomes (Table 4). In the Web of Sciences, this article had more than 1000 citations and 140 co-citations.

In the field of CVD associated engineered exosomes, the top three co-cited articles were all related to MI; these indicate that the investigation of treating MI with engineered exosomes has received a lot of attention in recent years. In the top reference, Adam Vandergriff et al. utilized an effective cardiac targeting strategy by binding a specific peptide (CHP) to engineered exosomes to treat

Table 3
Top 10 authors and co-cited authors related to engineered exosomes.

No.	Author	Count (%)	Year	Co-Cited Author	Citation	Year
1	MAURIZIO FEDERICO	14 (1.22%)	2012	THERY C	317	2002
2	FLAVIA FERRANTELLI	11 (0.96%)	2018	ALVAREZ-ERVITI L	317	2012
3	CHIARA CHIOZZINI	10 (0.87%)	2015	RAPOSO G	239	2002
4	FRANCESCO MANFREDI	8 (0.70%)	2018	VALADI H	223	2011
5	GUODONG YANG	6 (0.52%)	2019	TIAN YH	182	2015
6	SRIRAM RAVINDRAN	5 (0.44%)	2016	OHNO S	174	2015
7	CHULHEE CHOI	5 (0.44%)	2021	KOOIJMANS SAA	172	2015
8	ELEONORA OLIVETTA	5 (0.44%)	2018	EL ANDALOUSSI S	172	2015
9	YUJIE LIANG	5 (0.44%)	2021	HANEY MJ	163	2016
10	CLAUDIA ARENACCIO	5 (0.44%)	2018	LAI RC	161	2014

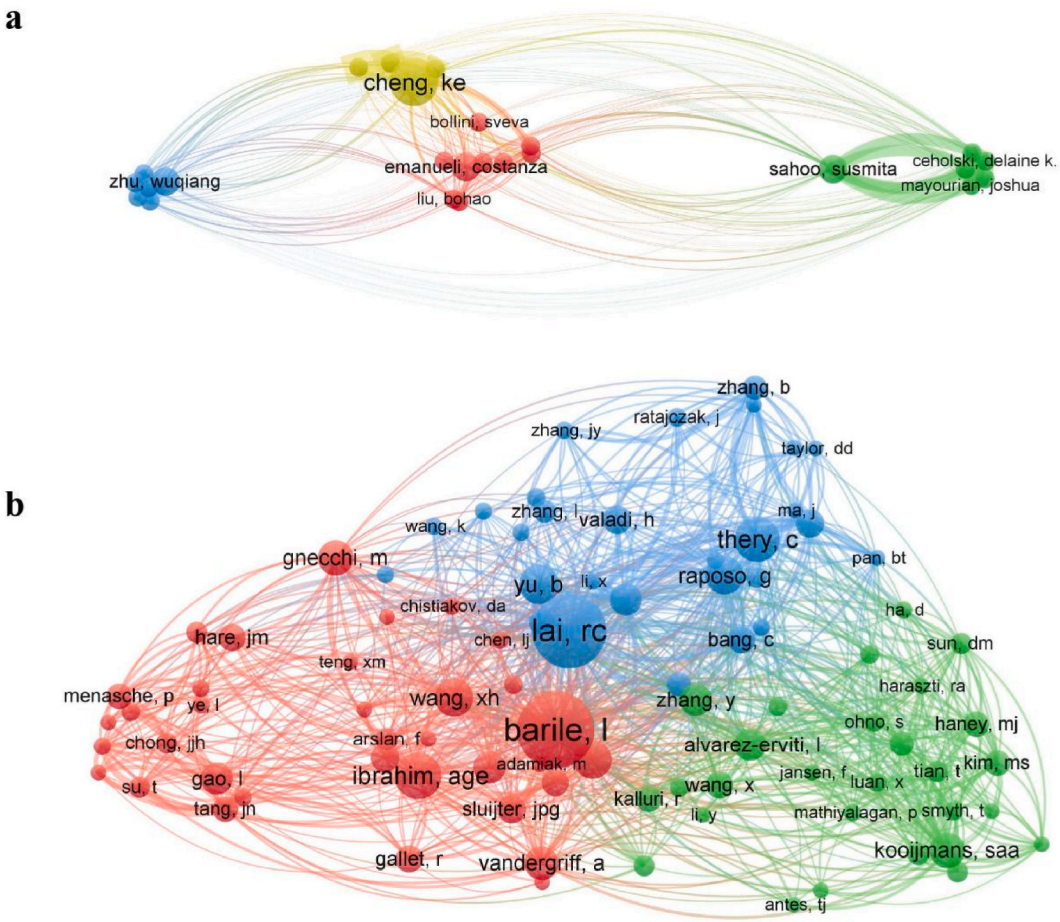

Fig. 4. The visualization map of authors and co-cited authors involved in engineered exosomes & cardiovascular field (a) The cooperative network of authors existed in "engineered exosomes & cardiovascular studies" related articles. (b) The co-citation of authors.

Table 4
Top 10 co-cited references related to engineered exosomes.

No.	Reference	Citation	Year	Centrality
1	Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer	140	2017	0.02
2	Shedding light on the cell biology of extracellular vesicles	125	2018	0.01
3	The biology, function, and biomedical applications of exosomes	114	2020	0
4	Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines	99	2018	0.02
5	Development of exosome-encapsulated paclitaxel to overcome MDR in cancer cells	97	2016	0.06
6	Engineering exosomes as refined biological nanoplatforms for drug delivery	93	2017	0.02
7	A doxorubicin delivery platform using engineered natural membrane vesicle exosomes for targeted tumor therapy	87	2014	0.03
8	Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication	82	2019	0.01
9	Exosomes as drug delivery vehicles for Parkinson's disease therapy	77	2015	0.08
10	Surface functionalized exosomes as targeted drug delivery vehicles for cerebral ischemia therapy	74	2018	0.02

MI. Our previous study has also used the CHP strategy to effectively attenuate ischemia-reperfusion injury in mice and Canis models [7]. In the second most cited reference, Romain Gallet et al. revealed that exosomes released by cardiosphere-derived cells significantly attenuated adverse cardiac modeling in an MI model and provided a possible cell-free strategy for MI treatment.

Notably, three of the articles in the top ten articles for both engineered exosomes and CVD-associated engineered exosomes lists ("The biology, function, and biomedical applications of exosomes", "MISEV2018" and "Engineering exosomes as refined biological nanoplatforms for drug delivery") were overview articles (Tables 4 and 5).

In addition, given the great potential and wide usage of engineered exosomes in different fields, we summarized the application of engineered exosomes in various disease models such as cancer, CVD, cerebrovascular disease, degenerative disease, rheumatic arthritis, diabetes and intervertebral disc degeneration (Table 6), as well as their application in treating various CVD (Table 7).

Table 5
Top 10 co-cited references related to engineered exosomes in cardiovascular field.

No.	Reference	Citation	Year	Centrality
1	Targeting regenerative exosomes to myocardial infarction using cardiac homing peptide	19	2018	0.17
2	Exosomes secreted by cardiosphere-derived cells reduce scarring, attenuate adverse remodeling, and improve function in acute and chronic porcine myocardial infarction	16	2017	0.04
3	Embryonic stem cell-derived exosomes promote endogenous repair mechanisms and enhance cardiac function following myocardial infarction	14	2015	0.08
4	Exosomes as critical agents of cardiac regeneration triggered by cell therapy	13	2014	0.09
5	Exosomal microRNA-21-5p Mediates Mesenchymal Stem Cell Paracrine Effects on Human Cardiac Tissue Contractility	12	2018	0.1
6	The biology, function, and biomedical applications of exosomes	11	2020	0.01
7	Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines	10	2018	0.05
8	Engineering exosomes as refined biological nanoplatforms for drug delivery	10	2017	0.11
9	Targeting extracellular vesicles to injured tissue using membrane cloaking and surface display	9	2018	0.02
10	Cardioprotection by cardiac progenitor cell-secreted exosomes: role of pregnancy-associated plasma protein-A	9	2018	0.1

3.6. Analysis of keywords

The list of top 20 keywords and a visualization map thereof were generated. As shown in Table 8, descriptive names such as "extracellular vesicles", "exosome", "exosomes", "cell-derived exosomes" ,"microvesicles", and "nanoparticle" with a total of 1657 counts, were becoming the most widely used keywords. Furthermore, drug delivery associated keywords including "drug (−) delivery", "delivery" and "therapy" were also used frequently (466 counts). "Stem cell" related keywords were also commonly found in the list of top 20 keywords (Table 8). The relative visualization map of keywords has been shown as Fig. 5. The circles and their labels form an element and the color of these elements identify the cluster it belongs to. There were 3 clusters in red, blue, and green, indicating 3 research directions (Fig. 5). The blue cluster included applications of extracellular vesicles, which included extracellular vesicles, drug delivery, targeted delivery, drug delivery vehicles, siRNA delivery, membrane vesicles, and mediated delivery. The green cluster represented exosomes' functions, which included topics such as exosomes, cells, biomarkers, identification, communication, siRNA, growth, and expression (Fig. 5).

In the field of engineered exosomes for CVDs, one of the cardiovascular diseases, MI, appeared most frequently (Table 9). The visualization map of keywords shows clusters in red, blue, yellow, green, and purple circles, indicating five research directions. The blue cluster represented cell-derived exosomes, which included key words such as extracellular vesicles, mesenchymal stem cell, in vitro, angiogenesis, cancer, endothelial cell, cell-derived exosomes, and miRNAs (Fig. 6). The red cluster represented key words related to MI associated therapeutic studies such as myocardial infarction, stem-cell, therapy, ischemic cardiomyopathy, cardiac regeneration, and cardiomyocytes.

3.7. Top keywords with the strongest citation bursts

To better understand research trends in the field of "engineered exosomes & cardiovascular studies", we performed an outbreak analysis of keywords for engineered exosomes in the cardiovascular field, which generated the top 25 keywords shown in Fig. 7. Four keywords, including "repair", "cardiomyocyte apoptosis", "brain" and "microvesicle" had the strongest citation bursts from 2020 to 2022, indicating that myocardial apoptosis and repair may be a hot topic for engineered exosomes in cardiovascular research in recent

Table 6
The application of engineered exosomes in various diseases models.

Disease models		Effect and Mechanism	Reference
Cancer	Prostatic cancer	E3-aptamer-liagend EVs enclosed SIRT6-siRNA could specifically target prostatic cancer and suppress tumor migration and proliferation	[25]
	Cerebral glioma	Angiopep-2 and TAT modified EVs could enhance the local concentration of drug and suppress the glioma	[26]
	Gastric cancer	EVs-enclosed *anti*-miR-214 could reduce drug resistance	[27]
Cardiovascular diseases	Myocardial infarction	CPCs-derived EVs-enriched miR-322 could protect the heart against myocardial infarction by regulating Nox2	[28]
Cerebrovascular diseases	Cerebral arterial thrombosis	RGD-ligated EVs could load curcumin and suppress inflammation, ultimately improving cerebral arterial thrombosis	[29]
Degenerative disease	Parkinson	Engineering the EVs by the EXOtic to delivery catalase and alleviate the neurotoxicity and neuroinflammation	[30]
Rheumatic arthritis	inflammation	Surface-modified-based engineered exosomes could regulate the reprogramming of macrophages and relieve inflammation	[31]
Diabetes complications	Wound healing	MiR146a-loaded engineered exosomes released from silk fibroin patch promote diabetic wound healing by targeting IRAK1	[32]
Intervertebral Disc Degeneration	Cell apoptosis	Surface-modified exosomes with Cavin-2 could uptake by nucleus pulposus cells under the stimuli of TNFα, which significantly reducing the cell apoptosis and alleviate intervertebral disc degeneration.	[33]

Table 7
The application of engineered exosomes in CVDs.

Disease models	Effect and Mechanism	Reference
Myocardial infarction	CHP-ligated exosomes can target the infarcted heart, reduce fibrosis and cardiomyocyte apoptosis, and improve cardiac function	[34]
	Adipose-derived stem cells-derived EVs containing miR-146a could inhibit AMI-induced apoptosis, inflammation and fibrosis through regulating EGR1	[35]
Myocardial ischemia-reperfusion injury	Exosomes from MSCs overexpressing miRNA-181a alleviated the inflammatory response after myocardial ischemia-reperfusion injury	[36]
Arrhythmia	Extracellular vesicles secreted by immortalized cardiosphere cells exert anti-inflammatory and anti-fibrosis effects and inhibit arrhythmia	[37]
Atherosclerosis	Exosomes derived from M2 macrophages encapsulated with HAL has strong inflammatory tropism and anti-inflammatory ability, and can relieve atherosclerosis	[38]
Diabetes complications	Curcuma polysaccharide and platelet rich plasma exosomes assembled on chitosan/silk hydrogel sponge to enhance wound healing	[39]
	Chitosan wound dressings containing overexpressed miR-126 exosomes can continuously release exosomes and cure full-thickness skin defects	[40]
Heart failure	Extracellular vesicles secreted by iPSC-Pg can effectively improve heart failure by secreting specific miRNAs	[41]
Pulmonary hypertension	MSC EXO may reverse MCT induced pulmonary hypertension through its enclosed miRNA	[42]

Table 8
Top 20 keywords related to engineered exosomes.

No.	Keyword	occurrences	total link strength	No.	Keyword	occurrences	total link strength
1	exosomes	654	2973	11	nanoparticles	105	500
2	extracellular vesicles	500	2611	12	stem-cells	105	555
3	delivery	183	933	13	cancer	103	551
4	exosome	170	830	14	drug delivery	98	608
5	in-vitro	167	976	15	drug-delivery	96	455
6	mesenchymal stem-cells	150	849	16	angiogenesis	92	504
7	microvesicles	145	827	17	therapy	89	459
8	cells	119	531	18	cell-derived exosomes	83	478
9	expression	115	558	19	tissue engineering	75	437
10	stromal cells	112	687	20	sirna	71	369

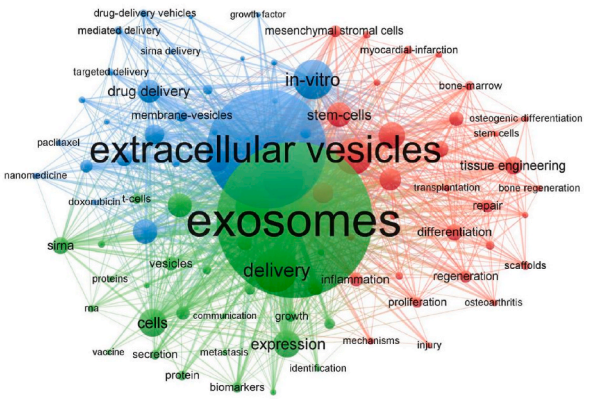

Fig. 5. Visualization map of keywords clustering on engineered exosomes This map constituted by 90 items, including red clusters (32 items), green clusters (30 items) and blue clusters (28 items). Especially, the size of nodes in this map was positively correlated with the frequency of keywords. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

years (Fig. 7). To specifically visualized the progression of research hotspots over time and their clustering connections in the time dimension, the visual map was drawn. As shown in Fig. 8, seven clusters were shown in the timeline diagram. Of these, cluster 0, representing heart failure, was the most active research cluster from 2014 to present, and included key words including heart failure, including myocardial infarction, cardiac patch, cardiomyocyte apoptosis, repair, and injury (Fig. 8). Research between 2012 and 2014 focused on MSCs and exosome delivery, represented by the frequency of the main keywords mesenchymal stem cell (29 times), regenerative medicine, embryonic stem cell, clinical therapy, and delivery (14 times). In the subsequent five years, the studies on diagnosis, tissue repair and regeneration became one of the primary topics, whose keywords included stromal cell (9 times), (acute) myocardial infarction (37 times), stem cell (22 times), ischemic cardiomyopathy, circulating exosome, and cardiac repair. In the past

Table 9
Top 20 keywords related to engineered exosomes in cardiovascular field.

No.	keyword	occurrences	total link strength	No.	keyword	occurrences	total link strength
1	exosomes	56	354	11	heart	14	85
2	extracellular vesicles	42	305	12	myocardial infarction	13	96
3	mesenchymal stem-cells	19	129	13	progenitor cells	13	95
4	in-vitro	18	121	14	microRNAs	12	77
5	myocardial-infarction	18	141	15	microvesicles	12	74
6	stem-cells	17	122	16	tissue engineering	12	99
7	delivery	16	113	17	acute myocardial-infarction	11	82
8	exosome	16	101	18	cardiovascular disease	11	94
9	therapy	15	107	19	nanoparticles	11	53
10	angiogenesis	14	96	20	stromal cells	11	87

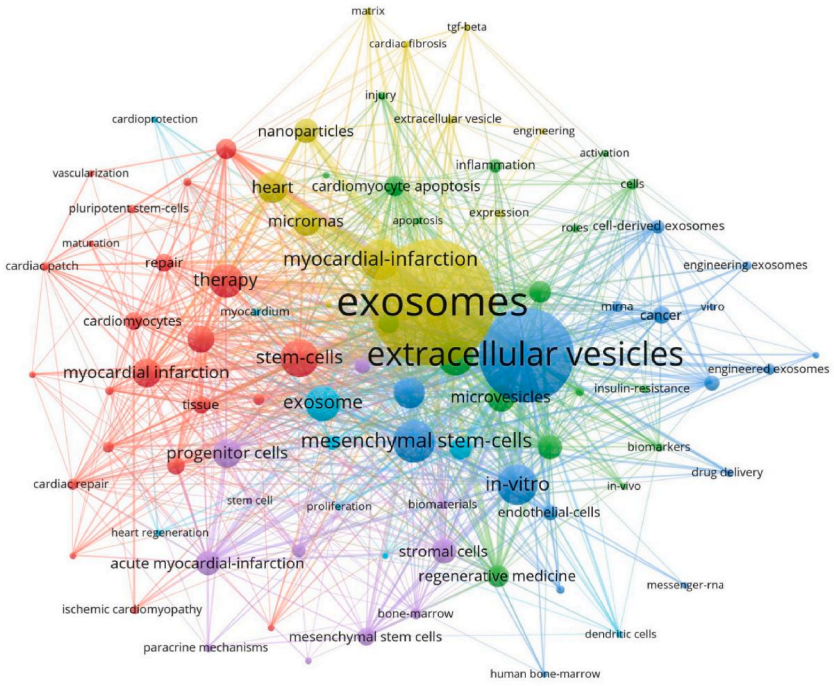

Fig. 6. Keywords clustering map of engineered exosomes & cardiovascular studies 90 items were shown through 6 colors respectively in this visualization map. Especially, 1452 connecting lines occurred and the total connection strength was 2456. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

two years, increasing attention has been paid to the role of engineered exosomes in drug delivery during tissue repair; their associated keywords included nanoparticle, cardiomyocyte apoptosis, dysfunction, engineered cardiac patch, biomimetic drug delivery, drug delivery system and drug carrier. These data showed that stem cell-derived exosomes and drug delivery were important research words in the field of CVD associated engineered exosomes, whose role in treating MI had made great progress.

With the development of biotechnology, cell therapy and cell-free therapy hold great potential to cure various diseases, which are attracting the increasing attention of scientists not only clinicians but also basic researchers. Therefore, an increasing number of studies have been performed to show the power of engineered exosomes in treating diseases. Here we summarize some representative research from clinical trials, animal studies and in vitro application of engineered exosomes (Table 10).

4. Discussion

Exosomes, a subtype of extracellular vesicles (EV), attracted growing interest in the past decade, with more than five thousand publications in recent years. Increasing studies have demonstrated that exosomes and EV are promising biomarkers and drug delivery carriers for treating CVD [56–59]. To better understand the research trends of exosomes and modified exosomes in the treatment of CVD, we performed a bibliometric analysis of exosomes research in the cardiovascular field from 2012 to 2022. Our findings revealed that annual publication in the field of "engineered exosomes" or "engineered exosomes in cardiovascular studies" increased steadily, and dramatically since 2020. Research from America, China, and Italy contributed the most publications. Keywords related to stem

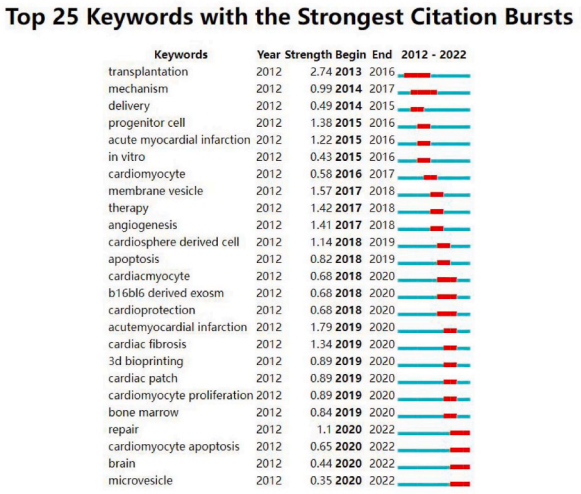

Fig. 7. The top 25 outbreak citation keywords involved in engineered exosomes & cardiovascular studies The burst analysis of keywords in engineered exosomes & cardiovascular related studies showed that four keywords such as repair, myocardial apoptosis, brain, and microcystic vesicles, were in the citation outbreak since 2020.

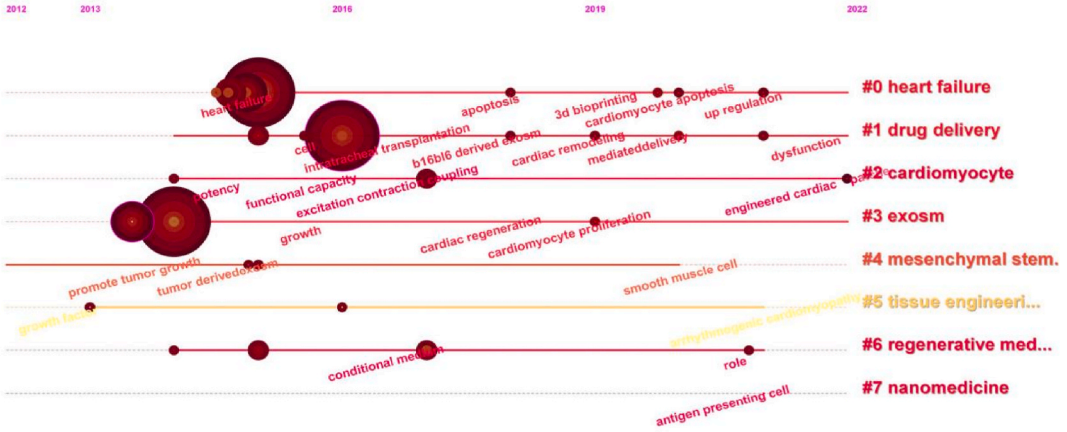

Fig. 8. Visualization timeline map of engineered exosomes & cardiovascular studies In the map, the X-axis was the published year of keywords Y-axis was the cluster number, which could show the time span and research process of each cluster.

cell-derived exosomes were the some of the most common, second only to the keywords related to EV and exosomes, indicating that these are promising therapeutics in protecting against cancer and CVD.

10 papers (6 research articles, 3 reviews and 1 guideline) with highest citations have been listed. Of these, studies on cancer were the most common. The most cited paper by Sushrut Kamerkar et al. from USA discusses how they targeted oncogenic Kras ($KRAS^{G12D}$) in tumors [60]. More specifically, the researchers isolated exosomes from normal fibroblast like mesenchymal cells and modified them with siRNA, which was named iExosomes. The iExosomes had an enhanced efficacy in suppressing the oncogenic gene, which ultimately inhibited pancreatic cancer and increased overall survival in mice models. This article was commented on by three journals and currently has more than one thousand citations. In another paper by Tian T et al., the researchers from China invented a targeting delivery particle by modifying exosomes with a peptide (RGDyK). These engineered exosomes had enhanced targeting capacity and suppressed cerebral ischemia-induced inflammation/cell apoptosis [61]. Of the top 10 articles, three were review articles that summarized the fundamental knowledge of exosomes including their biology, function, and biomedical applications, providing a holistic and detailed introduction to exosomes [62–64]. One of the top articles was the guideline, MISEV2018, which provides supportive information for a minimal guideline for studying EV, which was still a gold standard of studies in the field [65].

To investigate the popular topics in engineering exosomes in CVD, we listed the top 10 cited articles, which included seven research articles, two review articles, and one guideline. Interestingly, the top three research articles were all about myocardial infarction. Adam Vandergriff et al. from USA identified an effective cardiac targeting peptide to modify exosomes, which effectively improved myocardial infarction via increasing the cardiac retention in a rat MI model [34]. In another study, Gallet R et al. from USA assessed the

Table 10
Engineered exosomes in clinical, animal and in vitro systems.

	models		Effect and Mechanism	Reference
Clinical	Cancer		EVs derived from tumor cells containing anti-tumor drugs can reduce drug resistance of tumor cells	[43]
	Critical limb ischemia		MiR-15a and miR-16 may impair the function of human circulating angiogenic cells	[44]
	COVID-19		Exosomes derived from MSC have therapeutic effect on severe COVID-19 by reducing cytokine storm and enhancing immunity	[45]
	Parkinson Disease		Exosome-based biomarkers may be used as objective measures of target engagement in clinical trials using drugs targeting neuronal pathways	[46]
Animal	Mice	Middle cerebral artery occlusion	Exo-cRGD can target cerebral ischemic regions, inhibit inflammatory responses and cell apoptosis in the lesion area	[29]
		Ischemic stroke	SEVs loaded with BDNF could selectively target the infarct region, reduce infarct volume and increase neurogenesis and angiogenesis	[47]
		Gastric cancer	Exosomes encapsulated *anti*-miR-214 enhance the chemotherapy sensitivity and suppress the growth of tumor	[27]
	Swine	Ventricular arrhythmias	Cardiac spheroid-derived EVs can reduce myocardial scarring and suppress ventricular arrhythmias	[48]
		Myocardial infarction	Human myocardial patch can significantly reduce the size of myocardial infarction	[49]
	Rat	Diabetes complications	Curcuma polysaccharide and platelet rich plasma exosomes assembled on chitosan/silk hydrogel sponge to enhance wound healing	[39]
	Canis	Flexor tendon ex vivo model	Tissue engineering purified EVs product (PEP) patch promotes tendon healing in an in vitro canine model	[50]
	Rhesus monkeys	Nonhuman primate stroke model	Glycoprotein-cicSCMH1-EVs promote functional recovery in ischemic stroke	[51]
In vitro	DIPG tumor cell	Diffuse Intrinsic Pontine Gliomas	An extracellular drug delivery system loaded with Panobinostat and PPM1D siRNA can effectively inhibit the survival of DIPG tumors	[52]
	Human Retinoblastoma cell	Retinoblastoma model	Dox loaded extracellular vesicles induce the apoptosis of retinoblastoma in vitro and enhance the anti-tumor effect	[53]
	Neurons	Oxygen glucose deprivation model	Overexpression of CircSCMH1 reduces OGD induced neuronal damage	[51]
	Cardiomyocyte	AngII-induced cardiomyocyte hypertrophic model	Exercise may reduce Ang II-induced cardiomyocyte hypertrophy by releasing CCDC80tide-loaded EVs	[54]
	Renal tubular epithelial cell	LPS induced apoptosis model	Exosomes-miR-93-5p directly regulate TXNIP and affect pyroptosis of renal epithelial cells	[55]

role of exosomes from cardiosphere-derived cell (CDC) in MI and revealed that intracoronary or intramyocardial delivery of CDC exosomes decreased MI-induced scar formation, collagen deposition, and cardiomyocyte hypertrophy in a pig model [66]. In addition, Khan M et al. identified that stem cell-derived exosomes enhanced cardiac function and promoted cardiac repair post MI, which provided a cell-free strategy via utilizing the regenerative capacity of embryonic stem cell with few inflammatory risk [67]. Notably, the MISEV2018 was also one of the top cited articles in the field of CVD associated engineered exosomes, indicating that this article was a widely recognized guideline in exosomes associated studies.

Of all the keywords within our scope, "delivery" and "mesenchymal stem-cells" were the most popular keywords with 183 and 150 occurrences respectively, indicating that mesenchymal stem cell derived exosomes have been studied frequently and possibly has great potential in treating diseases. On the other hand, there is still much progress that must be made before exosomes or engineered exosomes can be utilized for clinical practice.

5. Conclusions

There has been steady growth in the field of engineered exosomes, especially for CVD associated engineered exosomes. Exosomes are a promising drug delivery tool and may be an effective approach to enhancing cardiac targeting capacity, which is much needed not only for MI but also for other cardiovascular diseases. Engineering stem-cell derived exosomes is a popular research topic for exploring treatments for diseases such as CVD. Researchers should be encouraged to continue studying this field to promote discovery of promising treatments.

6. Limitations

We performed a systematic visual analysis of engineered exosomes. However, this study has some limitations. First, we only retrieved the research articles of web of science, excluding book chapters, conference articles and letters, so the comprehensiveness of the papers is limited. Secondly, bibliometrics software also has its own shortcomings, some synonymous keywords can not be completely recognized and combined, although we try to correct, the loss of accuracy is still inevitable. Of note, as the guide of MISEV2018, "extracellular vesicles" is more appropriate to describe the secreted nanoparticles than exosomes when lacking specific characterization. Therefore, it was better for us to distinguish "extracellular vesicles" or "exosomes" when performing the bibliometric

analysis.

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Ethics declarations

Ethical approval This study did not involve humans and/or animals; there is no need for institutional ethics review board approval.

Author contribution statement

Xiao Zhang, Zijiang Yang and Jizong Jiang: Performed the experiments; Analyzed and interpreted the data.
Ming Tang, Longfei Guan and Hangil Lee: Contributed reagents, materials, analysis tools or data.
Hongyun Wang: Conceived and designed the experiments; Wrote the paper.
Jiahong Xu: Conceived and designed the experiments.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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