Fecal microbiota transplantation research output from 2004 to 2017: a bibliometric analysis

Yan Li [1,2], Ziyuan Zou [3], Xiaohui Bian [2], Yushan Huang [2], Yanru Wang [4], Chen Yang [3], Jian Zhao [2], Lang Xie [Corresp. 1]

1 Department of General Surgery, Zhujiang Hospital of Southern Medical University, Guangzhou, Guangdong, China

2 The Second School of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong, China

3 The First School of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong, China

4 Department of Radiation Oncology, Zhujiang Hospital, Southern Medical University, Guangzhou, Guangzhou, China

Corresponding Author: Lang Xie
Email address: langxiezj@hotmail.com

Background: Fecal microbiota transplantation (FMT) is an emerging therapy against *Clostridium difficile* infection (CDI) and inflammatory bowel disease (IBD). Although the therapy has gained prominence, there has been no bibliometric analysis of FMT. **Methods:** Studies published from 2004 to 2017 were extracted from the Science Citation Index Expanded. Bibliometric analysis was used to evaluate the number or cooperation network of publications, countries, citations, references, journals, authors, institutions and keywords. **Results:** A total of 796 items were included, showing an increasing trend annually. Publications mainly came from 10 countries, led by the US (n = 363). In the top 100 articles ranked by the number of citations (range 47-1158), American Journal of Gastroenterology (2017 IF = 10.231) took the top spot. The co-citation network had 7 co-citation clusters headed by 'recurrent *Clostridium difficile* infection'. The top 7 keywords with the strongest citation bursts had three parts, 'microbiota', ' diarrhea ', and 'case series'. All keywords were divided into four domains, 'disease', 'nosogenesis', 'trial', and 'therapy'. **Conclusions:** This study shows the research performance of FMT from 2004 to 2017 and helps investigators master the trend of FMT, which is also an ongoing hotspot of research.

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2 **bibliometric analysis**

4 Yan Li[1,2]*, Ziyuan Zou[3]*, Xiaohui Bian[2], Yushan Huang[2], Yanru Wang[4], Chen Yang[3], Jian Zhao[2],

5 Lang Xie[1]

6 *These authors contributed equally to this work.

8 [1]Department of General Surgery, Zhujiang Hospital,Southern Medical University, Guangzhou

9 510280, Guangdong, China.

10 [2] The Second School of Clinical Medicine, Southern Medical University, Guangzhou 510515,

11 Guangdong, China.

12 [3] The First School of Clinical Medicine, Southern Medical University, Guangzhou 510515,

13 Guangdong, China.

14 [4]Department of Radiation Oncology, Zhujiang Hospital of Southern Medical University,

15 Guangzhou 510280, Guangdong, China.

17 **Correspondence Author**

18 Lang Xie, langxiezj@hotmail.com

ABSTRACT

24 **Background:** Fecal microbiota transplantation (FMT) is an emerging therapy against *Clostridium*

25 *difficile* infection (CDI) and inflammatory bowel disease (IBD). Although the therapy has gained

26 prominence, there has been no bibliometric analysis of FMT.

27 **Methods:** Studies published from 2004 to 2017 were extracted from the Science Citation Index

28 Expanded. Bibliometric analysis was used to evaluate the number or cooperation network of

29 publications, countries, citations, references, journals, authors, institutions and keywords.

30 **Results:** A total of 796 items were included, showing an increasing trend annually. Publications

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34 *Clostridium difficile* infection'. The top 7 keywords with the strongest citation bursts had three

35 parts, 'microbiota', 'diarrhea', and 'case series'. All keywords were divided into four domains,

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38 investigators master the trend of FMT, which is also an ongoing hotspot of research.

INTRODUCTION

41 Fecal microbiota transplantation (FMT) is a therapeutic method by infusing fecal suspensions from

42 a healthy individual into the gastrointestinal tract(Kelly et al., 2016). Zhang et al. noted that GE

43   Hong pioneered the use of feces to treat human diseases in the Eastern Jin Dynasty (300 ~ 400

44   AD) (Zhang et al., 2012). FMT has received public attention over the past decade because of its

45   highly effective treatment of *Clostridium difficile* infection (CDI) and inflammatory bowel disease

46   (IBD) (Khoruts et al., 2016; Khoruts et al., 2015). In 2013, FMT was included in the CDI treatment

47   guidelines which clearly stipulated that FMT should be considered for patients with a third

48   recurrence of CDI (Surawicz et al., 2013). It was pointed out that recurrent CDI was difficult to

49   treat, and the failure rate of antibiotic therapy was relatively high. Moreover, it has been reported

50   that more than 300 cases of recurrent CDI were effectively treated using FMT (van Nood E et al.,

51   2013). FMT not only has a remarkable cure rate, but is also a safe and acceptable treatment option

52   (Brandt et al., 2012a). However, little systematic analysis of FMT has been performed (Hourigan

53   et al., 2015).

54   Systematic reviews and meta-analyses are being increasingly used to summarize medical

55   literature and identify areas in which research is needed (Crowther et al., 2010). Unfortunately,

56   they fail to include all the relevant research, meanwhile, the definition of clinical endpoint for the

57   use in combined statistics is unclear and they have publication bias. Quantitative studies of the

58   literature have been performed for nearly one hundred years, during which bibliometric methods

59   have been developed and matured (Rousseau, 2014). Traditional bibliometric methods had been

60   used to evaluate the variations of particular areas by assessing the productivity of countries,

61   institutions, authors and journals (Keathley-Herring et al., 2016). Nowadays, bibliometric analysis

62   provides a statistical and quantitative analysis of publications and offer a convenient way to visibly

63   measure researchers' efforts in the investigation of a specific field (Ashok et al., 2016; Yao et al.,

64 2018).

65   In the current study, we analyzed those were quoted above and provided additional analysis

66 including keywords of those studies and the clusters of citations(Choi & Kim, 2018; Miao et al.,

67 2017a; Suk et al., 2011). Multiple analytical tools were used to map the trends of FMT research

68 from 2004 to 2017. This analysis will assist researches in understanding the literature regarding

69 FMT, and determining the future directions for future study of FMT.

70 **MATERIALS & METHODS**

71 **Search strategy**

72 Data were acquired from the Science Citation Index Expanded (SCI-E) of the Web of Science

73 Core Collection (WoSCC) of Clarivate Analytics (https://clarivate.com/) on April 22, 2018. The

74 data were downloaded from the WoSCC so that there were no ethical issues. The searching

75 included literature published from 2004 to 2017, and used the following keywords and terms:

76 'Fecal bacteria transplantation$' or 'Intestinal Microbiota Transfer$' or 'Fecal Transplantation$'

77 or 'Fecal Transplant$' or 'Donor Feces Infusion$'. All electronic searches were performed on the

78 same day, April 22, 2018, to avoid changes in citation rates. The year 2018 was excluded because

79 database entries for the year would not be complete at the time of the search. When all data were

80 collected, the results were arranged according to the 'Times cited'.

81

82 **Study selection**

83 Two independent reviewers (Y. Li and Y.S. Huang) collected all the data by reading the titles and

84 abstracts acquired from SCI-E of the WoSCC database. When necessary, the full text was

85   downloaded from PubMed or other databases. Articles were included only if the main topic was

86   FMT, and the language was English. Exclusion criteria were: (1) the main topic of the article was

87   not about FMT; (2) the abstract of the article couldn't be acquired from WoSCC; (3) the article

88   was a duplicate. Any differences between the two reviewers were settled through discussion with

89   a third reviewer.

90

91   **Assessment of the articles and journals**

92   Two researchers (Y.S. Huang and J. Zhao) reviewed the selected articles, and the following data

93   were identified and recorded for analysis: (1) titles, (2) authors, (3) citation number, (4) keywords,

94   (5) publication year, (6) topics (7) funding and (8) countries of origin. Furthermore, the journal

95   names and impact factors (IFs) were also recorded using the 2017 edition of the Journal Citation

96   Reports (JCR).

97

98   **Statistical analysis**

99   Data were converted to txt format and imported into CiteSpaceV, GraphPad Prism 5 , the Online

100   Analysis platform of Literature Metrology (http://bibliometric.com/) and VOSviewer. Data were

101   then analyzed cooperation network of keywords, institutions, cited reference, and authorship

102   quantitatively and qualitatively by CiteSpaceV. GraphPad Prism version 5.0 was used to evaluate

103   the strength and direction of the linear relations between the number of citations in the top 100

104   (T100) cited articles and the number of years since publication, the number of authors, the number

105   of institutions, and the number of countries. It was also used to analyze the correlation of article

106   citations between different databases (WoSCC and Scopus). All probability values were two-

107   tailed, and the threshold for significance was set at $P < 0.05$. Using the Online Analysis platform

108   of Literature Metrology, the number of included articles and the number of articles according to

109   country, published each year were reported.. The analysis also showed the number of the top 17

110   keywords in each year. Exhibiting the relative positions and density of nodes in a network, two

111   dimensional knowledge maps can be produced by VOSviewer which is a computer program

112   primarily intended to be used for mapping, analyzing and exploring different types of networks

113   (Su & Lee, 2010).

114

115   **RESULTS**

116   **Total numbers of published items**

117   It was absolutely necessary to consider the number of published items on FMT as an index of

118   research productivity. From 2004 to 2017, a total of 2,062 publications on FMT were identified

119   through our search strategy in WoSCC, and 824 papers were screened out according to their titles

120   and abstracts, 1,238 publications were excluded because they did not meet our exclusion criteria (

121   titles uncorrelated to FMT in 809 papers, the main contents of 125 articles were irrelevant to FMT,

122   the abstracts were inaccessible for 302 papers, and 2 papers duplicated with other articles).

123   Moreover, 28 articles were excluded because they are non-English language. Thus, 796 articles on

124   FMT from 2004 to 2017 were included in the analysis (Figure 1). One article was published in

125   2004 (n = 1), and it was in 2011 (n = 15) and 2012 (n = 31) when the numbers of published articles

126   each year began to increase dramatically. The yearly number of published articles reached a peak

127   in 2017 (n = 248) (Figure 2(A)).

128

129   **Distribution by countries**

130   The 796 publications on FMT were primarily published by ten countries/regions (n = 722, 90.70%)

131   (Figure 2(B)). The greatest number of publications came from the United States (n = 363, 50.28%),

132   followed by China (72, 9.97%), Canada (69, 9.56%), and Germany (41, 5.68%). The United States

133   was the only country with a dynamic growth in the number of published articles over last five

134   years. An analysis of international cooperation was shown in Figure 2(C); the most frequent

135   collaboration was between the United States and Canada, followed by the US and UK.

136

137   **Distribution by citations**

138   Of the 796 selected articles, the top 100 articles ranked by the number of citations (Table 1,

139   Supplementary Table S1). The median number of citations was 95 (range 47-1158), and three

140   papers were cited over 500 times. The citation index (median 21.17, range 7.18-231.60) was

141   correlated with the number of citations (r^2 = 0.83, P < 0.01) per article in the Web of Science

142   database. In addition, the number of citations and citations index per article was strongly correlated

143   in the Scopus database (Figure 3: r^2 = 0.84, P < 0.01) (Supplementary Figure S1). The T100 articles

144   were published from 2007 to 2016, with the most articles published in 2015 (n = 22), followed by

145   2013 (n = 20; Figure 3). Interestingly, the number of citations in 2013 (n = 4,136) was the highest,

146   followed by 2015 (n = 2774).

147   To identify factors that might influence the number of citations of the T100 articles, we

148 analyzed possible correlations between the number of citations and the number of countries,

149 funding, years since publication, and authors using GraphPad Prism 5 (Figure 3). There was a

150 strong correlation between the number of citations and the number of authors ($r^2 = 0.05$, $P < 0.05$).

151 However, no significant correlations were present between the number of citations and the number

152 of countries ($r^2 = 0.01$, $P = 0.46$), institutions ($r^2 = 0.01$, $P = 0.27$), and years since publication (r^2

153 $= 0.01$, $P = 0.27$).

154

Analysis of references

156 Analysis of cited references is crucial to bibliometric analysis, as the scientific relevance of

157 publications can be evaluated by the map of co-cited references. Using CiteSpaceV, the co-citation

158 network was divided into 7 co-citation clusters (Figure 4(A)). The modularity Q score was 0.54,

159 and the silhouette score was 0.32. These clusters were labeled by index terms from their own citers.

160 The largest cluster was cluster #0 labeled as 'recurrent *Clostridium difficile* infection,' followed

161 by cluster #1, labeled as '*Clostridium difficile* infection.' (Supplementary Table S2)

162

Distribution by journals

164 The 796 articles were published by 294 journals. The top 100 were from 52 journals (Table 2,

165 Supplemental Table 3). According to the Journal Citation Reports (JCR) 2017 standards, the

166 American Journal of Gastroenterology (2017 IF = 10.231) made contributions to the largest

167 number of articles on FMT (10 articles, 10.00%), followed by Gastroenterology (2017 IF = 20.773;

168 8 articles, 8.00%), Journal of Clinical Gastroenterology (2017 IF = 2.968; 8 articles, 8.00%), and

169   Clinical Infectious Diseases (2017 IF = 9.117; 4 articles, 4.00%).

170

171   **Distribution by authors**

172   There were more than 3,000 authors who contributed to the publications on FMT. The network

173   maps of the authors and co-cited authors produced by CitespaceV are shown in Figure 4(B)& (C).

174   Kassam Z had the greatest number of articles (n = 33), followed by Khoruts A (n = 32) and Kelly

175   CR (n = 21). The top five cited authors were Khoruts A (n = 755), by Brandt LJ (n = 720), de Vos

176   WM (n = 557), and Nieuwdorp M (n = 509) (Table 3&4).

177

178   **Distribution by institutions**

179   The publications on FMT were from 933 institutions, and extensive cooperation network analysis

180   was carried out between institutions (Figure 4(D)). The top five institutions ranked by the number

181   of articles published 253 articles, about 31.78 % of the total. The University of Texas MD

182   Anderson Cancer Center (n = 9, 12.44 %) published the greatest number, followed by the

183   University of Washington (n = 58, 7.23%), McMaster University (n = 34, 4.27%), Emory

184   University (n = 32, 4.02%), and the University of Alabama at Birmingham (n = 30, 3.77%) (Table

185   5).

186

187   **Knowledge map of FMT research**

188   Figure 5 illustrates a two-dimensional knowledge map with major keywords as nodes from 2004

189   to 2017. It shows the frequency of keywords and their relative co-occurrence with colors of

190   different intensity to represent it as a heat map. Intense (blue) color indicates the frequency of

191   keywords. A keyword labelled in larger font size turns up in the center of each intense color, which

192   indicates that these keywords appeared more frequently and co-occurred with a higher number of

193   other keywords in the literature. In addition, network visualization of keywords was shown in

194   Figure S2, the distance between two keywords in the visualization approximately indicates the

195   relatedness of the keywords in terms of co-citation links. In general, the closer two keywords are

196   located to each other, the stronger their relatedness. The strongest co-citation links between

197   keywords are also represented by lines.

198

199   **Analysis of kewords**

200   An approximation of research trends was found by analyzing the top 17 keywords (Figure 2(D)).

201   Almost all the keywords appeared rising and falling fluctuations but an ascendant trend. The

202   keywords of 'fecal microbiota transplantation' and '*Clostridium difficile*' were the first and second

203   most frequent in the last five years of the study period. Except for searching keywords which were

204   'fecal microbiota transplantation, 'fecal transplantation', and 'facal transplant', the three most

205   frequent keywords were '*Clostridium difficile*', 'microbiome', and 'inflammatory bowel disease'.

206   These three words are also the main therapeutic directions of all FMT researches in the world.

207   The top 7 keywords with the strongest citation bursts were extracted by CiteSpaceV (Table

208   6). The blue line represents the time interval and the red line represents the duration of a burst

209   keyword, suggesting the beginning and the end of the time interval of each burst. The top keyword

210   was 'flora' (10.56, 2011-2014), followed by 'bacteriotherapy' (7.69, 2009-2013) and 'diarrhea'

211   (7.02, 2011-2013).

212   There were 722 different keywords in the 796 publications. All keywords with the same

213   meaning were merged into one keyword. After data standardization, 481 keywords were selected

214   as core keywords. Among them, 59 keywords appeared more than three times whose frequency of

215   occurrence were 70.24% so that they were selected as core keywords. The classification results in

216   Table 7 are shown in four domains: disease, nosogenesis, trial, and therapy. Among the 59 core

217   keywords, the highest percentage was in the disease domain (40.49%), followed by the therapy

218   domain (41.44%), the nosogenesis domain (14.63%) and the trial domain (3.77%). The

219   transplantation topic in the therapy domain contained the highest percentage (33.30%) of core

220   keywords, which were 'fecal microbiota transplantation' 'microbiome' 'stool transplantation'

221   'bacterial consortium transplantation' 'bacteriotherapy' 'gut microbiome transplantation' and

222   'transplantation'. In the disease domain, infection topics (16.79%) occurred most frequently.

223   Microbiota topics (11.13%) occurred most frequently in the nosogenesis domain. The subject topic

224   in the trial domain accounted for 2.42%.

225

226   **DISCUSSION**

227   **Total number of published items**

228   This was the first bibliometric analysis of FMT. The yearly number of publications rapidly

229   increased from one article in 2004 to 248 articles in 2017, with an average annual increase of

230   17.35% over the last 5 years of the study period. Compared with the total scientific output in the

231   WoSCC database, its average annual growth rate was 3.84% between 2004 and 2017. The

232   increasing incidences of CDI and IBD might explain the increase in the numbers of publication

233   from 2004 to 2017 (Rohlke & Stollman, 2012; Kelly et al., 2012). In addition, the increasing

234   number of output index in the WoSCC database might have also made contribution to the increase

235   in the number of publications. A conclusion can be drawn from the rapid development of FMT,

236   whose research was only in its infancy but promising and potential.

237

Country of origin and institutions

239   The top 10 countries/regions in which FMT studies were performed accounted for for 90.70% of

240   the total number of publications. China was the only developing country among these 10

241   countries/regions, indicating that China has made great progress in the FMT research recently. It

242   is not surprising that developed countries produced the greatest numbers of publications (Van

243   Rossum et al., 2010; Halpenny et al., 2010). The United States, which produced 363 publications

244   (45.60%), demonstrated a leading role in FMT research. This might be related to the high incidence

245   of CDI and IBD in the United States (Orenstein et al., 2013). It might also be related to the financial

246   resources devoted to scientific study in the United States (Zhao et al., 2016). In addition, the United

247   States played a key role in promoting international cooperation, with the strongest international

248   cooperation between the United States and Canada, followed by between the United States and the

249   United Kingdom (Figure 2C). As regard to the cooperation of institution, the top five institutions

250   were ranked by the number of articles, among which 4 institutions subordinated to the United

251   States. This conclusion was consistent with the dominance of the United States. A conclusion

252   could be drawn that the increasing incidence of CDI and IBD has promoted research of FMT in

253   this field.

254

255   **Citation count and possible factors influencing citations**

256   Based on the clarity of network structure and clustering, two indexes were proposed by

257   CitespaceV: the modularity Q score and the mean silhouette score. Modularity and silhouette

258   metrics provided useful quality indicators of clustering and network decomposition. A low

259   modularity means that a network can't be reduced to a cluster with clear boundaries, while a high

260   modularity suggests a well-structured network. The silhouette metric is helpful for estimate the

261   uncertainty involved in identifying the nature of a cluster (Chen et al., 2010). The co-citation

262   network was divided into 7 co-citation clusters with a modularity of 0.54 and a silhouette of 0.32.

263   This result suggested, the inter-cluster connections are considerable, but not overwhelming and

264   are diverse and heterogeneous.

265   Citation counting, a proxy measure of research quality, can help authors understand the

266   characteristics inherent in highly cited studies and provide a new perspective on specific areas

267   (Yan et al., 2011; Fu & Aliferis, 2008). However, there has been no citation analysis of FMT until

268   now. Of 796 selected articles, we focus on the top 100 articles arranged by the number of citations.

269   Interestingly, there was no output in 2017. It's likely that 'older' articles have a longer citable

270   period and attained more citations, and as such accumulative citation frequency will be higher (Liu

271   et al., 2016). To further examine this, we assessed the correlation between years since publication

272   and citation count. However, no obvious correlation was found. In addition, we replaced citation

273   count with citation index to decrease the effect of publication time. Citation counts are quantitative,

274   they can be added, subtracted, normalized, and ploted, satisfactorily, citation index based on these

275   counts abound, the ubiquitous Hirsch or h-index being the most prominent (Will, 2014), and the

276   h-index is an author-level metric that attempts to measure both the productivity and citation impact

277   of the publications of a scientist or scholar (Prathap, 2012). The results indicated that citation count

278   and citation index exhibited a substantial correlation, indicating that publication time has very little

279   influence on citations. In addition, we analyzed the citations of the top 100 publications in Scopus.

280   A strong relationship was found between citation index in WoSCC and citation index in Scopus,

281   so does the relationship between citations and citation index in Scopus, which ruled out the impact

282   of the database on citations.

283

284   **Journals**

285   The IFs of journals were one of the strongest indicators for citations in some way owing to the

286   attraction of high IF journals to the scientific community (Garfield, 2003). The top-cited articles

287   are usually published in high IF journals. The top 100 articles ranked by the number of citation

288   were published in 52 journals, with the exception of one, because its IF was not found in the JCR.

289   The median IF of these publications was 6.96, and the Ifs of 18 (35.29%) publications were greater

290   than 10.00. These results suggested that it was challenging to publish articles on FMT in high IF

291   journals. Meanwhile, it implied the quality of output in this subject area.

292

293   **Authorship**

294   Ranked by the number of articles they owned, the top five authors identified in this analysis

295   published at least 22 articles. They were consequently regarded as 'prolific authors'. The top five

296   authors contributed to at least 472 citations. Surprisingly, there was one author in both analyses

297   where this author not only did well in the number of publications but also the quality of

298   publications. The co-cited authors who had at least 200 co-citation counts, included Van Nood E

299   and Borody TJ. Although neither of them belonged to the category of prolific authors, they played

300   pivotal roles in FMT research; particularly, Van Nood E, who was also the first author of the article

301   with the highest number of citations.

302

303   **Knowledge map of FMT research**

304   A total of 243 items were divided into four clusters, cluster 1, 2, 3, and 4 comprised of 122, 144,

305   9, and 1 items, respectively (Figure 5 & S2). In the item density visualization, each point has a

306   color that indicates the density of items at that point. Colors in the map range from blue to yellow,

307   the larger the number of items (i.e., clostridium difficile infection) in the neighborhood of a point

308   and the higher the weights of the neighboring items, the closer the color of the point is to blue. In

309   the network visualization, items are represented by their label and by default also by a circle. The

310   size of the label and the circle of an item is determined by the weight of the item. The higher the

311   weight of an item, the larger the label and the circle of the item. The color of an item is determined

312   by the cluster to which the item belongs, for example, microbiota in green belong to cluster 2.

313   Lines between items represent links, meanwhile, the distance between two keywords in the

314   visualization approximately indicates the relatedness of the keywords in terms of co-citation links.

315 In general, the closer two keywords are located to each other, the stronger their relatedness. The

316 strongest co-citation links between journals are also represented by lines.

317

318 **Keywords and research fields**

319 In recent years, there has been great interest in the use of FMT for therapy of gastrointestinal and

320 non-gastrointestinal diseases, mainly for CDI and IBD. In most countries/regions, the incidence of

321 IBD is increasing or at a relatively high stable level. Furthermore, IBD patients have a nearly

322 threefold higher risk for CDI compared with the general population (Rodemann et al., 2007).

323 Nevertheless, some patients became refractory to standard therapy and suffered from a poor quality

324 of life. Evidence suggested that FMT was a potential, effective and safe therapy for recurrent,

325 refractory, or severe CDI and IBD, at least when standard treatments had failed (Anderson et al.,

326 2012; Kelly et al., 2014a). The goal of this bibliometric analysis was to provide an overview of

327 FMT's research, and guide future studies.

328 According to the 59 core keywords identified, 4 domains were classified. The disease domain

329 had the highest percentage and the trial domain the lowest. Within the disease domain, the topics

330 of infection and inflammatory have the highest ratio. In this regard, it might relate to the therapy

331 principle of FMT. Evidence has suggested that there is a reduced diversity of luminal microbiota

332 and increased mucosal adherent bacteria in IBD and CDI(Nagalingam & Lynch, 2012). Changes

333 in gut microbiota led to a serious imbalance of host physiology and immune homeostasis, which

334 ultimately results in infection and inflammation. Brandt et al (Brandt et al., 2012b) noted that FMT

335 was a promising therapeutic strategy because it manipulated the microbiota, based on

336   gastrointestinal microbiota's role in driving disorders. Interestingly, the topic of emotion taken up

337   a certain proportion, which was an indication that FMT could be used to treat mental illness.

338   In the therapy domain, the topic of transplantation occupied the largest portion and other

339   major treatments of IBD and CDI were also listed. In general, the standard therapy for CDI and

340   IBD included steroids, amino-salicylates, immunosuppressants, and various biological therapies,

341   most of which are not effective and place a heavy economic burden on patients (Talley et al., 2011;

342   Kappelman et al., 2008). Some patients become refractory to standard management and suffer

343   significant adverse side effects with a poor quality of life (Mcfarland, 2005). Konijeti et al

344   (Konijeti et al., 2014) indicated that FMT was the most cost-effective initial strategy for

345   management of recurrent CDI. FMT can thus reduce the financial burden of patients, and result in

346   a substantial increase in quality of life (Merlo et al., 2016).

347   The domains mentioned above clarified research hotspots clear, and burst keywords can be

348   considered indicators of research frontiers over time (Yin et al., 2016). The blue line represents

349   the time interval and the red line represents the duration of a burst keyword. There were 7 keywords

350   with the strongest citation bursts. After taking similar burst keywords into consideration, they were

351   divided into three categories: (i) Microbiota: The presence of normal, healthy, intestinal microbiota

352   was now considered to offer protection against CDI and IBD. However, the repeated use of

353   immunosuppressants and other therapy with drugs severely disrupted the normal gut microbiota,

354   which always led to the recurrence of CDI and IBD. Instead, FMT allowed the rapid reconstitution

355   of a normal composition of microbial communities. The wonderful effect and desperate need in

356   the patients would drive the development of FMT in the next few years (Hamilton et al., 2012).

357 (ii) Diarrhea: Antibiotic-associated colitis caused by *Clostridium difficile* was the most common

358 cause of hospitalization for diarrhea (Cohen et al., 2015). It was caused by disrupting the normal

359 gut flora and led to dysbiosis that enables *Clostridium difficile* colonization of the patients' gut.

360 Satisfactorily, FMT, a promising therapy for *Clostridium difficile*-associated diarrhea, has the high

361 cure rate of diarrhea (Kelly et al., 2014b; Gough et al., 2011). However, some problems should be

362 further solved and perfected, such as whether FMT should be used as a first-line therapy for the

363 patients with *Clostridium difficile*-associated diarrhea. (iii) Case series: There are many different

364 treatments for CDI and IBD, but none of the treatments are proved to be very useful. In order to

365 find the solution that worked best, it was necessary to analyze representative cases. Rubin et al

366 (Rubin et al., 2013) found the effectiveness of FMT in the therapy of CDI and IBD from a case

367 series of 75 FMT course. This gave the future researchers a clue that case series would be an

368 appropriate way.

369 There are some limitations to the current study. Non-English publications were excluded and

370 as landmark articles published in other languages were not considered. The study only focused on

371 the publications in WoSCC database, and the exclusion of other databases, such as PubMed and

372 Scopus, may have produced slightly different results. Nevertheless, WoSCC is a comprehensive

373 and popular Web database in the field of scientometrics (Miao et al., 2017b).

374

375 **CONCLUSIONS**

376 In conclusion, based on the detailed analysis of the distribution and changes in countries, citations,

377 references, journals, authorship, institutions and keywords, the results of this research and analysis

378   indicate that FMT is an area of very active research. This analysis using bibliometric methods

379   provides a solid overview of current FMT research and may help in providing guidance for further

380   studies.

381

382   **FIGURE LEGENDS**

383   **Figure 1 Overview of article selection process.**

384   **Figure 2 The number of annual publications on FMT from 2004 to 2017(A), growth trends**

385   **of countries on FMT from 2004 to 2017(B), the cooperation of countries/regions contributed**

386   **to publications on FMT from 2004 to 2017(C), growth trend of keywords on FMT from 2004**

387   **to 2017(D).**

388   **Figure 3 Correlations between the number of citations and number of countries (A); the**

389   **number of institutions (B); the number of the years since publication(C); the number of**

390   **authors (D).**

391   **Figure 4 Reference co-citation map of publications (A); Network map of authors**

392   **contributed to publications (B); Network map of co-cited authors contributed to**

393   **publications (C); Network map of institutions contributed to publications (D) on FMT**

394   **from 2004 to 2017.**

395   **Figure 5 Visualization of two-dimensional knowledge map of keywords for the complete**

396   **dataset.**

397

398   **ABBREVIATIONS**

399 FMT   fecal microbiota transplantation

400 CDI   *Clostridium difficile* infection

401 IBD   inflammatory bowel disease

402 SCI-E   the Science Citation Index Expanded

403 WoSCC   the Web of Science Core Collection

404 T100   the top 100

405 JCR   the Journal Citation Reports

406 **ACKNOWLEDGEMENTS**

407 The authors would like to thank editors and the anonymous reviewers for their valuable comments

408 and suggestions to improve the quality of the paper.

409

410

411 **Supplemental Information**

412 **Figure S1**. Correlations between citation index (WoSCC) and time cited (WOSCC) (A); citation

413 index (Scopus) and time cited (Scopus) (B); citation index (Scopus) and citation index (WoSCC)

414 (C).

415 **Figure S2** Network visualization two-dimensional knowledge map of keywords for the complete

416 dataset.

417 **Table S1**. The top 100 most-cited articles ranked by the number of times cited

418 **Table S2.** Major clusters of co-cited references.

419 **Table S3.** Journals with the top 100 articles ranked by the number of citations.

420

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Figure 1

Overview of article selection process.

Identification

Keywords and free words search in Web of Science Core Collection (WoSCC) (n=2062)

Screening

Titles and abstract screened(n=824)

Titles and abstracts of articles excluded (n=1238)
Titles and abstracts unrelated to the study(n=809)
The main content unrelated to the study(n=125)
The abstract inaccessible (n=302)
Duplicates (n=2)

Eligibility

Language of articles assessed for eligibility (n=796)

Language containing non-English (n=28)

Included

Articles included in quantitative synthesis (bibliometric-analysis) (n =796)

Figure 2

The number of annual publications(A), and growth trends of countries(B), the cooperation of countries/regions(C), growth trend of keywords(D) on FMT from 2004 to 2017.

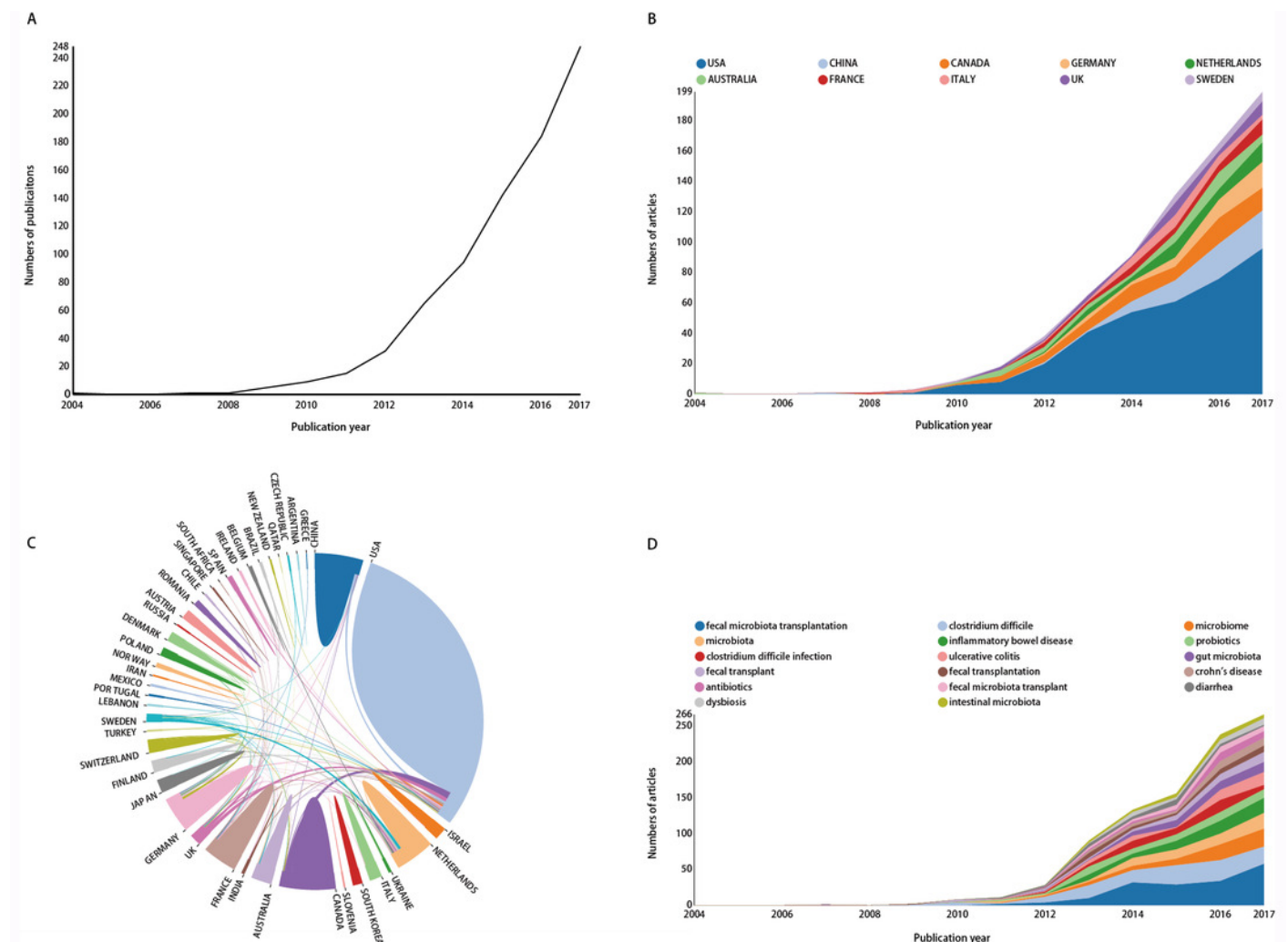



Figure 3

Correlations between the number of citations and countries(A), institutions (B), the years since publication(C), and authors (D).

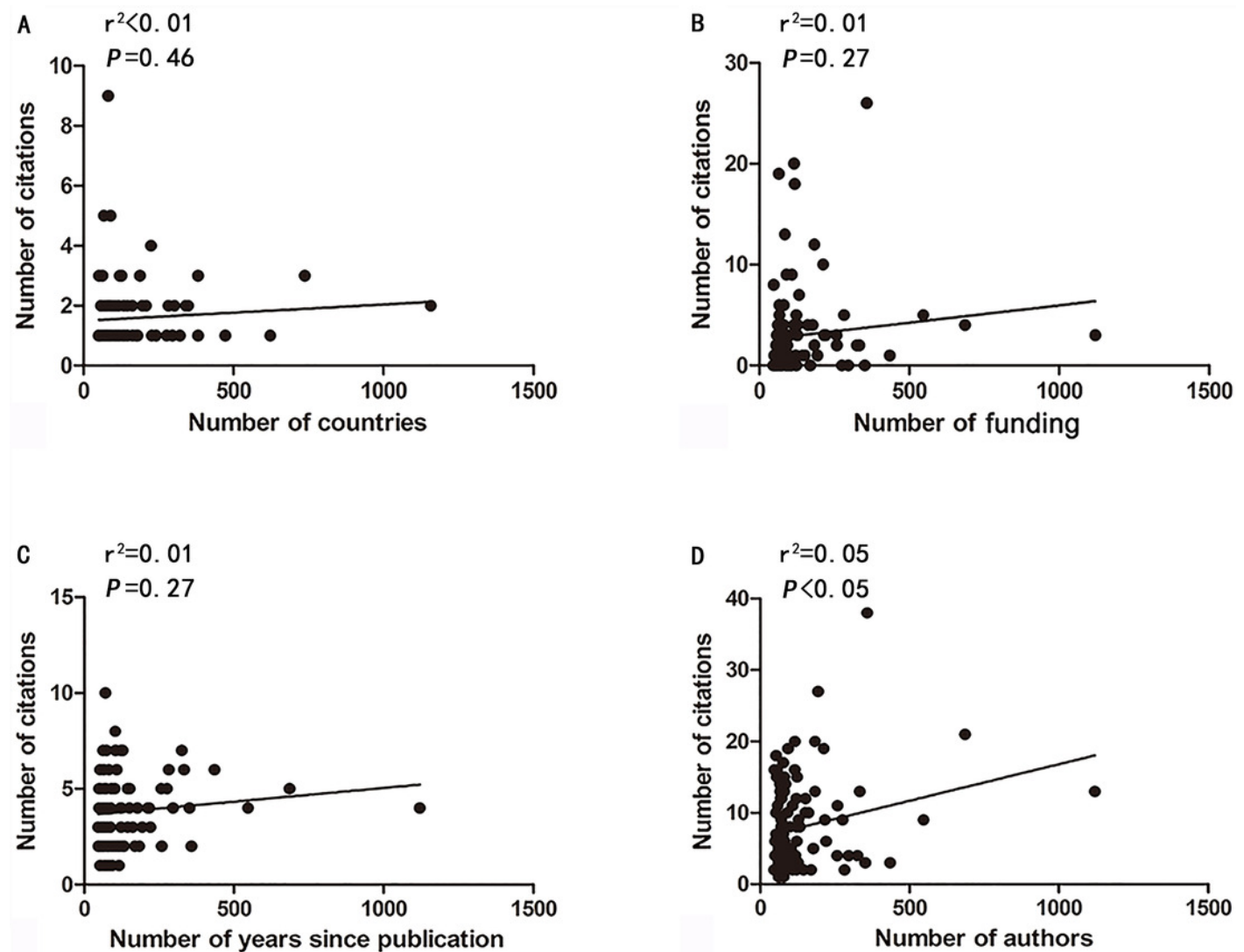



Figure 4

Reference co-citation map(A), Network map of authors (B), Network map of co-cited authors (C) and Network map of institutions (D) contributed to publications on FMT from 2004 to 2017.

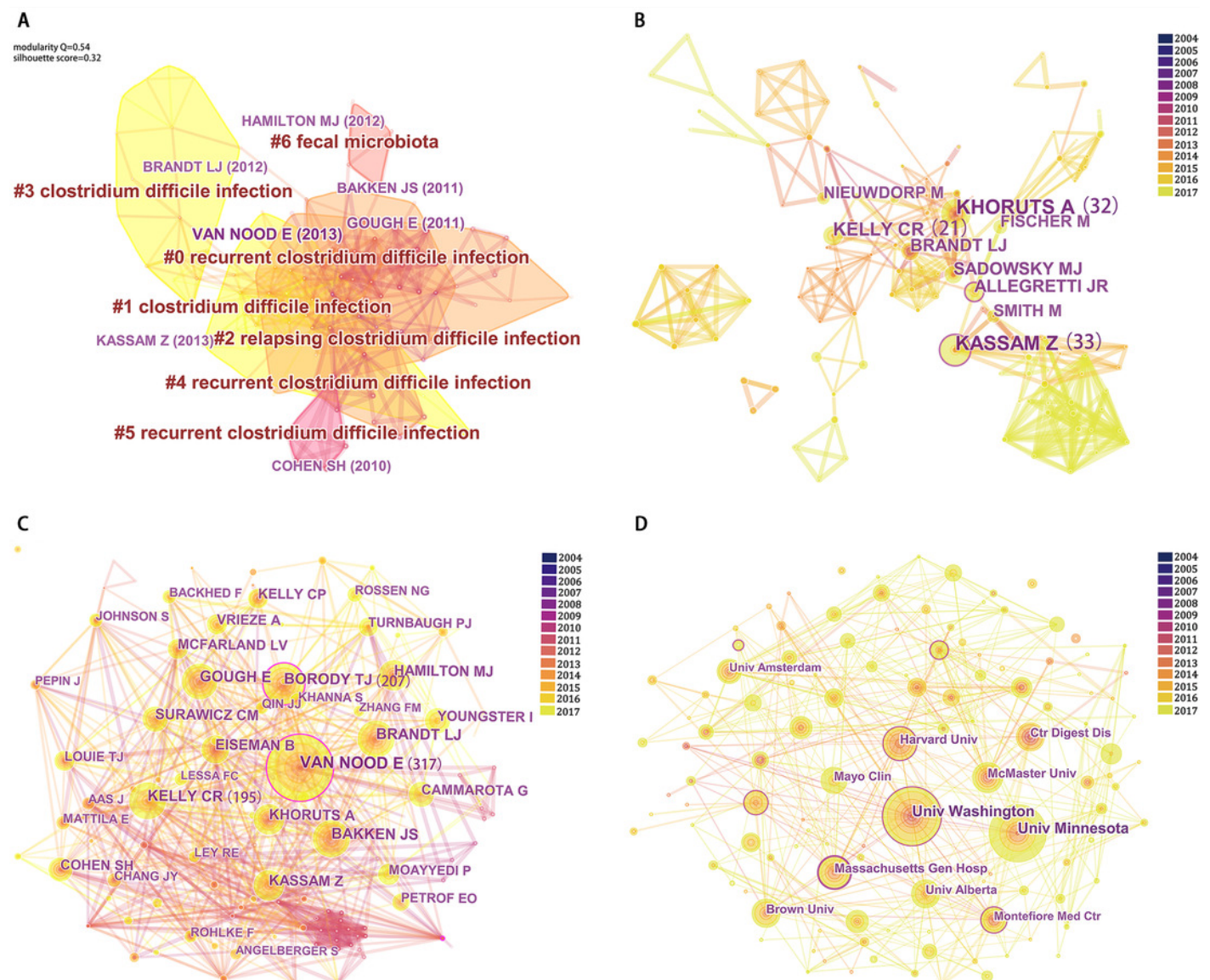



Figure 5

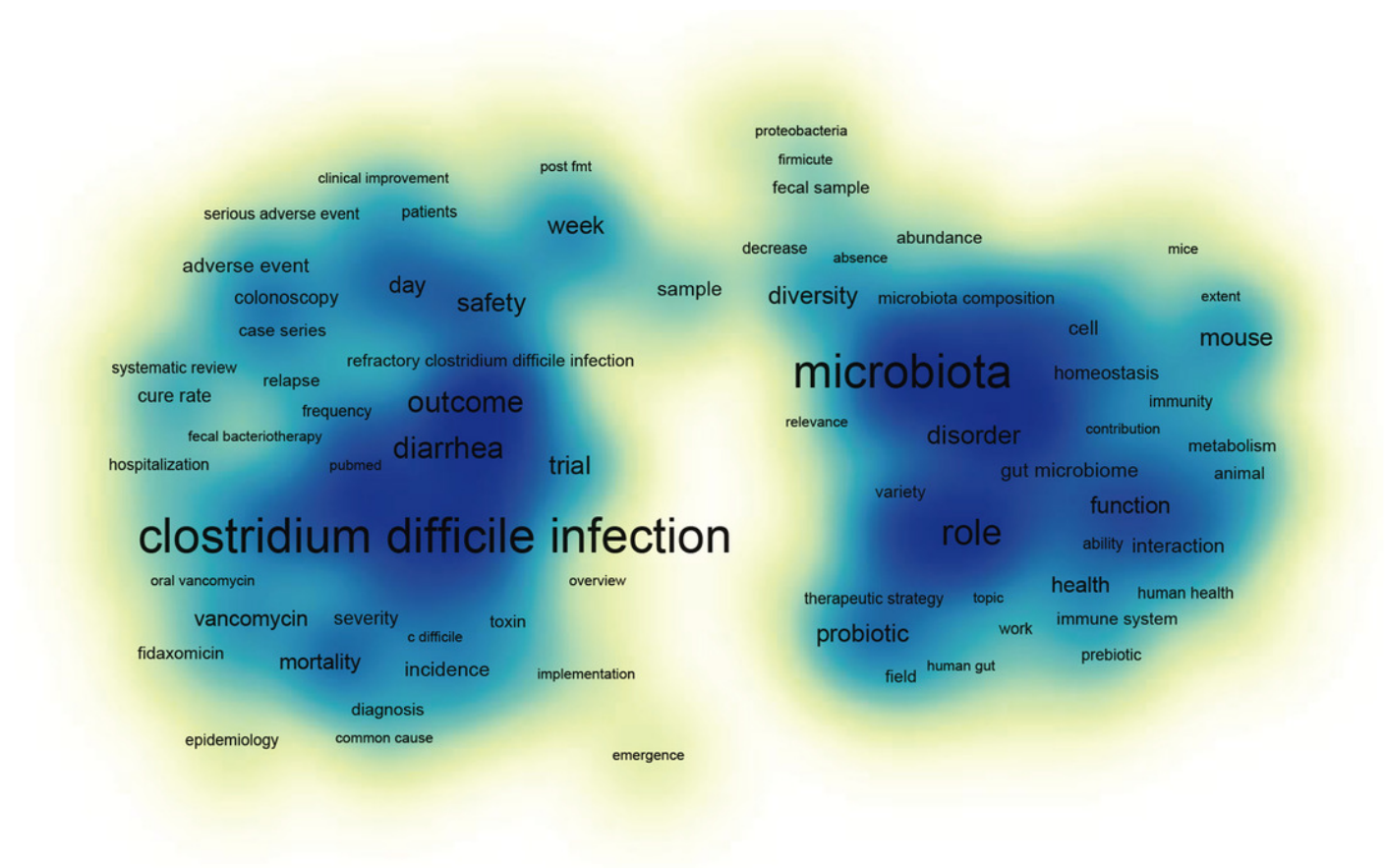
Visualization of two-dimensional knowledge map of keywords for the complete dataset.

Bibliometric information associated with the top 5 of the top 100 cited articles in FMT from 2004 to 2017

Table 1. Bibliometric information associated with the top 5 of the top 100 cited articles in FMT from 2004 to 2017

Rank	Title	Years	Times cited (WoSCC)	Citation index (WoSCC)	Time cited (Scopus)	Citation index (Scopus)
1	Van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile* [J]. N Engl J Med,2013,368(5):407-415.	2013	1158	231.60	1307	261.40
2	Vrieze A, Van N E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome [J]. Gastroenterology, 2012, 143(4):913-916.	2012	738	123.00	800	133.33
3	Surawicz C M, Brandt L J, Binion D G, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections [J]. American Journal of Gastroenterology, 2013, 108(4):478-498.	2013	623	124.60	641	128.20

4	Gough E, Shaikh H, Manges A R. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection [J]. Clinical Infectious Diseases An Official Publication of the Infectious Diseases Society of America, 2011, 53(10):994.	2011	473	67.57	495	70.71
5	Vétizou M, Pitt J M, Daillère R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota [J]. Science, 2015, 350(6264):1079.	2015	382	127.33	391	130.33

The top 5 journals of the top 100 articles ranked by the number of citation contributed to publications on FMT from 2004 to 2017.

Table 2. The top 5 journals of the top 100 articles ranked by the number of citation contributed to publications on FMT from 2004 to 2017.

Rank	Journal	Country	No. of articles	IF 2017
1	AMERICAN JOURNAL OF GASTROENTEROLOGY	the US	10	10.231
2	GASTROENTEROLOGY	the US	8	20.773
3	JOURNAL OF CLINICAL GASTROENTEROLOGY	the US	8	2.975
4	CLINICAL INFECTIOUS DISEASES	the US	4	9.117
5	CELL	the US	3	31.398

The top 5 authors ranked by the number of articles

Table 3. The top 5 authors ranked by the number of articles

Rank	Authors	No. of articles	Total citations	First	Citations of first	Correspond	Citations of correspond
1	Kassam, Z	38	325	4	186	1	7
2	Khoruts, A	33	755	6	153	9	202
3	Kelly, CR	24	375	5	243	8	297
4	Sadowsky, MJ	23	405	2	0	6	148
5	Allegretti, JR	22	22	5	4	1	0

The top 5 authors ranked by the number of citations

Table 4. The top 5 authors ranked by the number of citations

Rank	Authors	No. of articles	Total citations	First	Citations of first	Correspond	Citations of correspond
1	Khoruts, A	33	755	6	153	9	202
2	Brandt, LJ	20	720	8	271	9	342
3	de Vos, WM	8	557	0	0	0	0
4	Nieuwdorp, M	18	509	0	0	9	171
5	Zoetendal, EG	4	472	0	0	0	0

The top 5 institutions ranked by the number of articles contributed to publications on FMT from 2004 to 2017.

Table 5. The top 5 institutions ranked by the number of articles contributed to publications on FMT from 2004 to 2017.

Rank	Institution	No. of articles	No. of citations
1	University of Minnesota, Gemini, Minnesota, the US	99	1999
2	University of washington, Seattle, Washington, the US	58	1136
3	McMaster University, Hamilton, Ontario, Canada	34	1099
4	Emory University, Atlanta, GA, the US	32	119
5	University of Alabama Birmingham, Birmingham, Alabama, the US	30	58

Core Keywords related to FMT from 2004 to 2017.

Table 6. Core Keywords related to FMT from 2004 to 2017.

Domain	Topic	Percentage Within Core Keywords, %	Frequency of Keyword Occurrence (n)
Disease domain (total, 40.49%)	Infection	16.79	Clostridium difficile infection (171), infection (5), bacterial infections (4), refractory clostridium difficile infection (4), fulminant clostridium difficile infection (3)
	Inflammatory	13.73	Inflammatory bowel disease (66), ulcerative colitis (38), crohn's disease (23), colitis (11), inflammation (8), pseudomembranous colitis (7)
	Diarrhea	5.48	Antibiotic-associated diarrhea (26), diarrhea (16), recurrent clostridium difficile infection (16), infectious diarrhea (3)
	Metabolism	2.6	Obesity (12), metabolic syndrome (9), diabetes (4), metabolism (4)
	Functional disease	1.26	Irritable bowel syndrome (11), functional bowel disease (3)
	Emotion	0.63	Depression (4), anxiety (3)

Nosogenesis domain **(total, 14.63%)**	Microbiota	11.13	Gut microbiota (49), microbiota (40), intestinal microbiata (27), bifidobacterium (5), lactobacillus (3)
	Environment	2.69	Dysbiosis (17), gut (4), rain-gut axis (3), gastrointestinal (3), gut permeability (3)
	Immunity	0.81	Immunomodulation (9)
Trial domain **(total, 3.77%)**	Subject	2.42	Children (13), germ-free (5), germ-free animals (3), mathematical modeling (3), mouse models (3)
	Method	1.35	16s rRNA analysis (8), metagenomics (4), clinical trial (3)
Therapy domain **(total, 41.44%)**	Transplantation	33.3	Fecal microbiota transplantation (301), microbiome (41), stool transplantation (9), bacterial consortium transplantation (7), bacteriotherapy (6), gut microbiome transplantation (4), transplantation (3)
	Food	4.13	Probiotics (33), prebiotic (8), diet (5)
	Antibiotics	2.87	Antibiotic therapy (13), fidaxomicin (6), vancomycin (6), metronidazole

(4), infection control (3)

| Fibroptic | 0.81 | Colonoscopy (9) |
| endoscopy | | |

The top 7 Keywords with the Strongest Citation Bursts on FMT from 2004 to 2017

Table 7. The top 7 Keywords with the Strongest Citation Bursts on FMT from 2004 to 2017

Keywords	Year	Strength	Begin	End	2004 - 2017
flora	2004	10.5588	**2011**	2014	
bacteriotherapy	2004	7.6856	**2009**	2013	
diarrhea	2004	7.0221	**2011**	2013	
case series	2004	6.2972	**2011**	2013	
antibiotic associated diarrhea	2004	5.4075	**2010**	2013	
coliti	2004	5.0701	**2010**	2013	

enterocolitis   2004   4.3316   **2010**   2013