



Mapping the intellectual structure of the coronavirus field (2000–2020): a co-word analysis

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Abstract

Over the two last decades, coronaviruses have affected human life in different ways, especially in terms of health and economy. Due to the profound effects of novel coronaviruses, growing tides of research are emerging in various research fields. This paper employs a co-word analysis approach to map the intellectual structure of the coronavirus literature for a better understanding of how coronavirus research and the disease itself have developed during the target timeframe. A strategic diagram has been drawn to depict the coronavirus domain's structure and development. A detailed picture of coronavirus literature has been extracted from a huge number of papers to provide a quick overview of the coronavirus literature. The main themes of past coronavirus-related publications are (a) “Antibody-Virus Interactions,” (b) “Emerging Infectious Diseases,” (c) “Protein Structure-based Drug Design and Antiviral Drug Discovery,” (d) “Coronavirus Detection Methods,” (e) “Viral Pathogenesis and Immunity,” and (f) “Animal Coronaviruses.” The emerging infectious diseases are mostly related to fatal diseases (such as Middle East respiratory syndrome, severe acute respiratory syndrome, and COVID-19) and animal coronaviruses (including porcine, turkey, feline, canine, equine, and bovine coronaviruses and infectious bronchitis virus), which are capable of placing animal-dependent industries such as the swine and poultry industries under strong economic pressure. Although considerable research into coronavirus has been done, this unique field has not yet matured sufficiently. Therefore, “Antibody-virus Interactions,” “Emerging Infectious Diseases,” and “Coronavirus Detection Methods” hold interesting, promising research gaps to be both explored and filled in the future.

Keywords COVID-19 · Coronavirus · Co-word analysis · Text mining · Science mapping · Emerging infectious diseases

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Introduction

Over the last few decades, highly contagious fatal diseases have increased dramatically. Humans and animals alike have been struck down, sometimes resulting in economic crisis. According to the literature, coronavirus fields are recognized as degenerative, incurable diseases causing various health problems. Coronaviruses are highly infectious diseases and may lead to health threats including enteric, respiratory, hepatic, and neurological diseases, so they are extremely demanding to control and even to treat, and they can spread rapidly among communities on a large scale (Gorbalenya et al., 2004). In addition, through adaptive evolution owing to a high mutation rate and genetic recombination, distinct, unique coronaviruses have arisen that have damaging effects on humans and animals. Hence, the adaptive evolution feature has resulted in a novel coronavirus emergence (May et al., 2004).

Coronaviruses have caused primarily enzootic infections in birds and mammals; however, research outputs have recently revealed that the virus can easily affect humans and pass from person to person, leading to a dramatic increase in cases. Generally, coronaviruses have caused respiratory diseases for humans and enteric diseases for animals (Banerjee et al., 2019). In 2002 SARS-CoV infected 8098 Chinese residents, leading to 774 deaths (*CDC. Severe Acute Respiratory Syndrome*, 2018). Besides, 2260 people were affected by MERS-CoV in 2012, resulting in 803 deaths in 27 countries (*WHO. the Middle East Respiratory Syndrome Coronavirus*, 2018). Animal coronaviruses have also contributed substantially to economic problems and animal loss over the last few decades. For instance, infectious bronchitis virus (IBV) took a toll of around \$3,567.40 per 1000 birds in Brazilian poultry farms (Colvero et al., 2015). Furthermore, porcine epidemic diarrhea virus (PEDV) dealt a 3.1% loss to the U.S. pig-farming industry (Schulz & Tonsor, 2015). Coronaviruses have also had a devastating effect on the world economy and human health, which has convinced many researchers to focus on them. Thus, many researchers and practitioners have attempted to either mitigate or overcome the issue using different modern methods reported in a great number of publications on a daily basis, giving rise to a body of work that is extremely complicated to collect and analyze.

Additionally, the novel coronavirus could be interrelated with previous types of coronavirus fields, so a comprehensive analysis of studies in the areas already explored might uncover hidden patterns and useful knowledge that could shed light on the causes of the disease and efficient treatments. Unfortunately, traditional methodologies, such as reviewing and surveying the literature, are neither effective nor efficient means of going about this work; the traditional literature review can neither investigate all material carefully nor provide the researcher with detailed, accurate information on hidden patterns and complex relationships. Furthermore, no work has yet been done to provide researchers with a conceptual map in this critical field of research. Therefore, the co-word analysis approach is utilized here to cope with the problems traditional methods cannot handle and to address the main questions listed below.

- (1) How has the literature of coronavirus fields evolved? What journals actively publish coronavirus-related research?
- (2) What are the main themes and subthemes running throughout coronavirus research?
- (3) How are coronavirus themes related to each other?
- (4) What themes are peripheral and undeveloped?

The key aims of this paper are (a) to provide a comprehensive overview of a huge number of coronavirus papers dating to the period between 2000 and 2020 and indexed in Clarivate Analytics' Web of Science Core Collection (WoS); (b) to examine the current state of the field and promising research directions. The paper is structured into four sections. Following the introduction, the theoretical background and coronavirus-related literature are surveyed and presented, and then the methodology is described. Next, primary data analyses and principal outputs are reported, including the most prolific, reputable journals and themes as well as the relationships among the keywords, and the strategic diagram is presented. Lastly, a discussion and conclusion are provided.

Literature review

Coronaviruses and related diseases

Coronaviruses are important pathogens for humans and other vertebrates. They can infect the hepatic, respiratory, gastrointestinal, and central nervous system of humans, livestock, mice, bats, birds, and other wild animals (Chen & Guo, 2016; Ge et al., 2013; Wang et al., 2006). *Coronaviridae*, with its two main subfamilies *Letovirinae* and *Orthocoronavirinae*, is the largest family in the order *Nidovirales*. *Orthocoronavirinae* consists mainly of four major genera: alpha-coronavirus (α -coronavirus), beta-coronavirus (β -coronavirus), gamma-coronavirus (γ -coronavirus), and delta-coronavirus. Both α -coronavirus and β -coronavirus are found in mammals; γ -coronavirus and delta-coronavirus, however, have evolved to infect birds (Woo et al., 2010).

Until late 2019, only six coronaviruses (CoVs) negatively affecting the respiratory system had been identified as serious threats to public health. Mild upper respiratory disease and, in a few cases, severe infection are associated with HKU1, HCoV-229E, HCoV-NL63, and HCoV-OC43. Additionally, severe respiratory syndrome has often been seen in SARS-CoV- and MERS-CoV-related cases infecting the lower respiratory tract (Fehr & Perlman, 2015; Su et al., 2016). Besides human health issues caused by the virus, some viruses may have influenced livestock, bats, birds, mice, and other families of wild animals (Zhou et al., 2018). Different types of coronaviruses with their groups are briefly illustrated in Fig. 1.

Over the last few months, a novel virus, COVID-19, has emerged from Wuhan, China. The world population has been severely affected by this virus, which has created life-threatening conditions. Due to the highly dangerous nature of the virus for humans, the world economy has been hurt significantly (Maria et al., 2020).

Theoretical background

Bibliometrics has proven itself an inestimable tool for understanding how areas of scientific specialization are organized and how they evolve over time. One of the objectives of bibliometrics is science mapping. Science mapping is a generic process for analyzing and visualizing domains of knowledge, based on extracting and manipulating a certain corpus of scientific literature. The techniques it involves are drawn primarily from computer science, metric studies of science, data and information visualization, visual analytics, and network science. The realm to map may be a scientific discipline, a field of research, topic areas or scientific specialties, or an individual researcher's career. The spatial representations in which science maps consist are created by preprocessing and processing

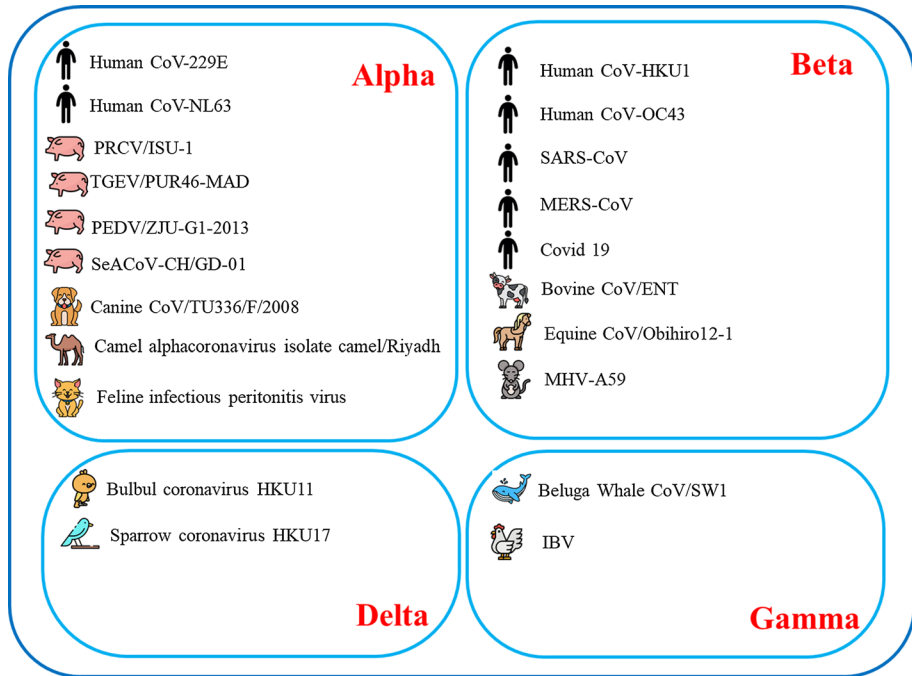


Fig. 1 Coronavirus types

aggregate data containing intellectual contributions retrieved from the literature stored in bibliographic databases like the Web of Science, Scopus, PubMed, Lens, Dimensions, and Microsoft Academic. The bibliographic records contain a number of variables or bibliographic entities, such as publication titles, authors, journals, years, places, institutions, keywords, abstracts, and bibliographic references. By working with these variables and using techniques and methods of citation analysis, concept or topic extraction, bibliometric metrics, algorithms, clustering techniques, visualization techniques, and python libraries or programs, maps of domains of knowledge or science can be designed and built (Thijs, 2019).

The theoretical rationality behind science maps has been addressed by many authors. When a science map is created, it reveals the links between different areas of knowledge, as well as the processes whereby knowledge is disseminated and the direction in which knowledge travels between areas. Science maps afford a means of analyzing the current knowledge within a domain from a bird's-eye view, facilitating the systematic, synthetic review of the literature and sociological or historical analyses. They help to determine the present consensus in regard to a concept, by itself or in combination with other concepts, and to trace variations in research discourse. They are instruments that aid in the detection of potential partners who might be interested in working on related subjects, based on representations of co-authorship maps. One classic subject in this subspecialty is the creation of maps that successfully represent emerging research fronts, or key scientific topics and assets, based on an analysis of the scientific and technological literature (Xu et al., 2020). The most common questions about research fronts and scientific topics include the methodological aspects and techniques involved in their creation (i.e., similarity calculation, clustering). Design and visualization are currently implemented in the form of “global”

maps, “local” maps, or hybrid maps. “Global” maps represent the whole or substantially whole structure of a bibliographic database, while “local” maps select micro-areas of interest or focus on a particular field or specialty. If the research fronts or topics in a given specific subject are projected as a layer of information superimposed on top of a base constructed in the form of a “global” science map, then the product is a hybrid map (Chen, 2019; Boyack & Klavans, 2019).

In this paper, a co-word analysis technique is applied to map the intellectual structure of the “CoronaVirus” field using 13,518 papers collected from a mainstream scholarly database, the Web of Science Core Collection (WoS). The method is recognized as an effective solution for mapping the strength of association between information sections in textual contexts (Viedma-Del-Jesus et al., 2011). In other words, co-word analysis is considered a quantitative method for mapping the relationships and interrelationships among concepts in different textual scientific works (Zhang et al., 2017). The main idea of co-word analysis is to describe documents based on keyword co-occurrence (Callon et al., 1991). Utilizing co-word analysis enables researchers to draw a detailed picture of a specific domain using words’ co-occurrence in different types of bibliometric units, such as book chapters, journal and conference papers, and books (Liu et al., 2012). Co-word analysis is generally used to convert massive networks of keyword information into smaller, more intelligible networks of related concepts with graph theory (Cobo et al., 2011). The co-word network consists of nodes that represent the keywords and links between them. Given a network of keywords, a compound of community detection, network analysis, and strategic diagrams are depicted to detect interesting trends and patterns within a complex keyword interaction network and reveal the conceptual structure of a research field (Callon et al., 1991). The method has been widely utilized in various areas like urbanization (Zhang et al., 2017), supply chain management (Shiau et al., 2015), library and information science (Olmeda-Gómez et al., 2017), the Internet of Things (Yan et al., 2015), marketing (Z. Wang et al., 2015), social media (Gan & Wang, 2015), scientometrics (Ravikumar et al., 2015), non-biomedical modalities (Nguyen, 2019), medical tourism research (Hoz-Correa et al., 2018), child-computer interaction (Giannakos et al., 2020), energy (Wu & Leu, 2014), open data (Corrales-Garay et al., 2019), recommendation systems (Hu & Zhang, 2015), gender differences (Dehdarirad et al., 2014), and epidemiology (Baziyad et al., 2020). Some papers have also utilized co-word analysis in coronavirus research areas.

Bibliometric methods have already been used in regard to some types of coronaviruses, such as COVID-19 (Lou et al., 2020; Pal, 2021; Yang et al., 2020), SARS (Chiu et al., 2004), MERS (Zyoud, 2016) or all three (Haghani & Bliemer, 2020). Papers on COVID-19 have focused on limited features outlining correlations in existing research on the novel COVID-19. However, the latest papers on COVID-19, SARS, and MERS are still restricted to certain areas, and they help practitioners move efficiently forward in a limited direction only. Hence, the scientific work contains major flaws, because the relationships among earlier coronavirus families and other viruses are not sufficiently investigated.

Methodology

Method and data collection

This paper employs the co-word analysis approach for visualizing and analyzing the CoronaVirus-19-related research work published between 2000 and 2020, using the WoS. A

comprehensive framework for designing a co-word-based intellectual map as applied in this paper is shown in Fig. 2.

Data collection

Data collection is categorized into four main stages, namely: (a) database selection, (b) search query, (c) search domain selection, and (d) time duration selection. In this study, the WoS database was set as the key source for data extraction. Although Scopus and the WoS are both among the leading databases researchers use, a wide range of co-word analysis papers has utilized the WoS. In addition, the WoS has a large number of journals indexed and complete and contains consistently formatted citation information for its entries (Khasseh et al., 2017). For these reasons the WoS database was selected.

To identify the keywords to use in the publication search process, the literature on the topic was inspected and experts' advice was taken. This paper mostly concentrates on recent important human coronaviruses, such as COVID-19, MERS, and SARS. The keywords eventually settled on are "coronavirus," "COVID-19," "SARS-CoV," and "MERS-CoV," because COVID-19, SARS-CoV, and MERS-CoV are the main types of coronaviruses causing respiratory diseases in humans and enteric diseases in animals. To find all relevant publications, other combinations and the full names of the acronyms were added, including "severe acute respiratory syndrome," "Middle East respiratory syndrome," and "2019-nCoV." Boolean operators were also used to make the searches more detailed and to target the literature with an appropriate degree of specificity.

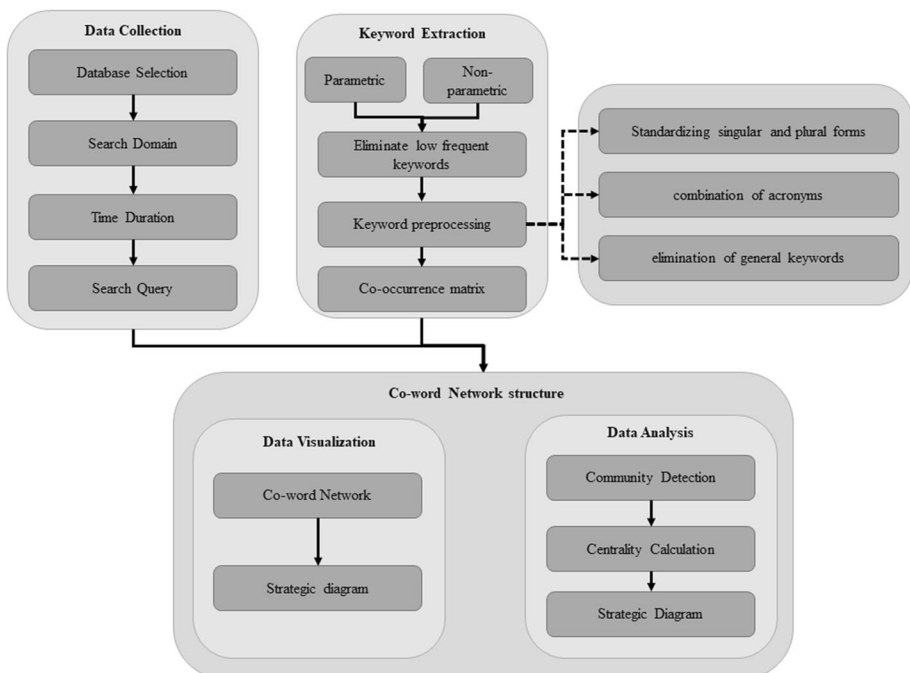


Fig. 2 A comprehensive framework of intellectual structure based on co-word analysis

The search query was performed based on Advanced Search. A careful, structured search for document keywords, titles, and abstracts (Topic search format) was conducted on the WoS. A Topic Search query (TS) searches simultaneously by titles, abstracts, author keywords, and Keywords Plus. Thus, the query strings used in this study are the following:

TS=(("COVID-19" OR "Coronavirus" OR "Corona virus" OR "2019-nCoV" OR "SARS-CoV" OR "MERS-CoV" OR "Severe Acute Respiratory Syndrome" OR "Middle East Respiratory Syndrome")).

All document types (including journal articles, review and conference papers, letters, book chapters, proceedings papers, short surveys, and editorials) were classified as the main input for this study. Other publication types (such as meeting abstracts and news items that do not represent sound publications) were not taken into account. The database contained different languages, including English, Spanish, Russian, Chinese, Japanese, and Korean, but only the search terms in the English language were retrieved. The search query looked for English COVID-19-oriented publications published from January 1, 2000, to January 1, 2020. The search, which was updated on April 1, 2020, returned 13,518 items.

The records were downloaded from the WoS database over the Internet connection provided by the central library at the University of Ottawa. Full records of the dataset were retrieved from the WoS in the CSV Excel format. The databases in which the search was formulated were mostly Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index-Science (CPCI-S), Emerging Sources Citation Index (ESCI), and Arts and Humanities Citation Index (AHCI). The retrieved information included the authors, document type, citation information, publication name, research areas, funding agency, bibliographic information, publication year, title, and keywords. Extracting the dataset posed challenges due to the WoS restriction of a maximum of 500 documents per export. Thus, a strategy was adopted to extract 13,518 documents. The list of selected studies was first sorted by the most recently published, and then 500 items were extracted in one export. This strategy was repeatedly employed until all remaining documents were extracted. Around 28 exports were done to extract all documents in the CSV Excel format from the WoS.

Keyword extraction

Co-word analysis research is based on the keywords extracted from textual data such as papers and blogs. There is, then, a close direct correlation between the quality of the keyword extraction process and the quality of the results. Also, keywords with a frequency of at least 10 were chosen to cooperate in the co-word network according to Hosseini et al. (2021), and the collected keywords were filtered through a number of criteria including (1) standardization of singular and plural keyword forms (e.g., “pig,” “pigs”); (2) combination of acronyms (e.g., “MERS-CoV,” “Middle East respiratory syndrome coronavirus”); (3) elimination of general keywords (e.g., “corona,” “coronavirus”).

After the final list of keywords was found, the co-occurrence matrix (symmetrical matrix) of keywords was calculated using Python 3.6, and the visualization process and community detection were conducted by Gephi 0.9.2 (Bastian et al., 2009).

Co-word network

Co-word analysis generally finds clusters of keywords that appear often in conceptually counterpart papers. The co-word network is calculated based on the normalized

co-occurrence matrix. A co-occurrence matrix is also obtained from keywords in input papers. For example, keywords A and B appeared in 25 papers simultaneously; consequently, the weight of their co-occurrence is equal to 25. Finally, the matrix was normalized depending on the Jaccard index. The Jaccard index is a measurement for analyzing similarities between two objects calculated by the following formulation (Jaccard, 1902):

$$J_{ij} = \frac{C_{ij}}{C_i + C_j - C_{ij}} \quad (1)$$

where C_{ij} is the number of co-occurrences of keywords i and j . Also, C_i and C_j are the numbers of occurrences of keywords i and j , respectively (Jaccard, 1902). The normalized co-occurrence matrix is shown in Table 1 for three selected major keywords.

After the co-occurrence matrix is calculated, the co-word network is presented. Each of the keywords in the co-occurrence matrix plays the role of a node in the co-word network, and each normalized weight of the matrix is considered as an edge weight in the co-word graph. For instance, the importance of 0.4419 is the edge weight between the keywords “COVID-19” and “SARS-CoV-2” in the co-word graph in Table 1.

Identification of themes

Next, a community detection algorithm (a type of clustering method frequently used for graph-based datasets such as co-occurrence data) known as the Louvain method (Blondel et al., 2008) was utilized to map each community. ForceAtlas2 was employed for the layout algorithm (Jacomy et al., 2014). Some manual changes and modifications were also made to node movements to improve coordination. Community detection and the layout algorithm visualization were performed using Gephi 0.9.2. The findings can be seen in the result section. Quantitative validation was done by calculating the modularity values.

The modularity of a network measures the extent to which the network can be broken down into multiple components or modules. This metric provides a reference for the overall clarity of a given decomposition of the network (Newman, 2004).

Usually, a graph with a modularity of between 0.3 and 0.7 is considered a strong cluster in which each community has strong internal relations with its vertices (dense connections within communities or clusters) while having weak relationships with other communities (Xie & Szymanski, 2011). The co-word network’s modularity was measured and found to be 0.378, which lies in the desired range. According to Newman (2004), modularity is found by the following formula:

Table 1 An example of a normalized co-occurrence matrix

	COVID-19	SARS-CoV-2	2019-nCoV	MERS	SARS
COVID-19	1	0.4419	0.1791	0.0039	0.0145
SARS-CoV-2	0.4419	1	0.1731	0.0013	0.0140
2019-nCoV	0.1791	0.1731	1	0.0053	0.0113
MERS	0.0039	0.0013	0.0053	1	0.0433
SARS	0.0145	0.0140	0.0113	0.0433	1

$$Q = \frac{1}{4} \sum_{ij} \left(A_{ij} - \frac{k_i k_j}{2m} \right) s_i s_j \tag{2}$$

$$m = \frac{1}{2} \sum_i k_i$$

where k_i and k_j are the nodes’ degrees and m is the total number of edges. A_{ij} is the number of edges between vertices i and j . The quantities A_{ij} are the elements of the so-called adjacency matrix. $\frac{k_i k_j}{2m}$ is the maximum number of edges being between vertices i and j .

Strategic map

Another analysis method is the strategic diagram of cluster density and centrality. The density of each cluster indicates the internal cohesion of a particular theme, and the centrality of each cluster shows how close each cluster comes to being a component of the central field. Each theme begins at low centrality and density, in the Chaos/Unstructured quadrant. As it gains in centrality, the theme shifts into the Bandwagon quadrant. When the theme’s internal cohesion becomes mature, the theme moves into the Mainstream quadrant. Finally, the theme moves to the Ivory Tower quadrant when it loses its centrality (Giannakos et al., 2020). A schematic strategic diagram is illustrated in Fig. 3.

Many papers in the field of co-word analysis have used keyword clustering and strategic diagramming for data mapping and data analysis. This paper employed keyword clustering and a strategic diagram for CoronaVirus-19-related research. Centrality and density were calculated using Eq. 3 and Eq. 4, respectively (given below). Node centrality equals the total number of direct connections related to a node. Greater centrality for a specific keyword shows that the keyword is used more frequently in research. Also, network density (D) is the proportion between the actual amount of links and the maximum possible number of links that can be obtained from the network.

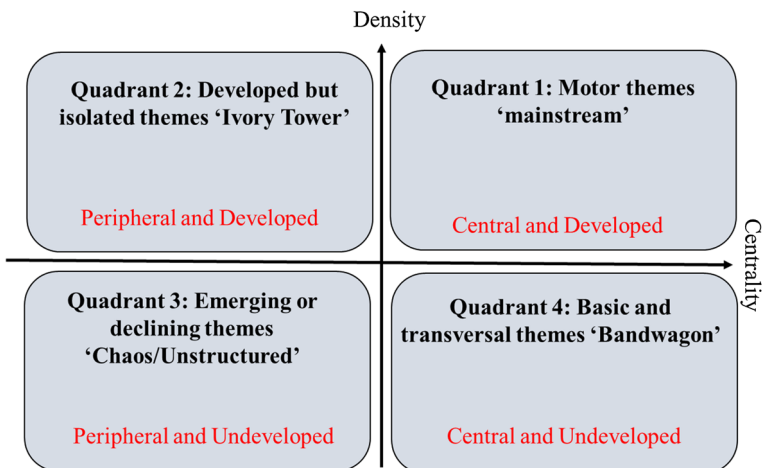


Fig. 3 Strategic diagram of density and centrality

$$c_L = \sum_{i \in L} \sum_{j \in M} w_{ij} \cdot e_{ij} \quad (3)$$

where c_L is the centrality of community L , i denotes nodes in community L , the list of other existing communities except community L is given by M , and j is existing nodes in all M communities. Also, e_{ij} is a binary variable that is equal to 1 if an edge has existed between node i and node j , and otherwise it is equal to 0. Lastly, w_{ij} is considered an edge weight between node i and node j .

$$D_L = \frac{2E}{N(N-1)} \quad (4)$$

where D_L states the density of community L wherein E is the total number of edges in L and N is the total number of nodes in L .

Result

Top keywords and journals

The evolution of the papers published on the topic per year from 2000 to 2020 is illustrated in Fig. 4. Coronavirus research grew significantly between 2003 and 2004 due to the emergence of SARS in 2002 and 2003. The maximum number of coronavirus research publications (1032 publications) was reached in 2004. Between 2004 and 2011, the number of publications gradually declined; nevertheless, academic publications rose steadily once again with the emergence of MERS in 2012. The trend in publications can be expected to continue rising in 2020 because of the COVID-19 pandemic.

After careful examination, 491 keywords were selected for the co-word network. Thirty highly frequent keywords are listed in Table 2.

Table 3 lists the journals that have published more than 100 papers on the topic of coronavirus over the last two decades. *Journal of Virology* accounts for 6.76% of the most

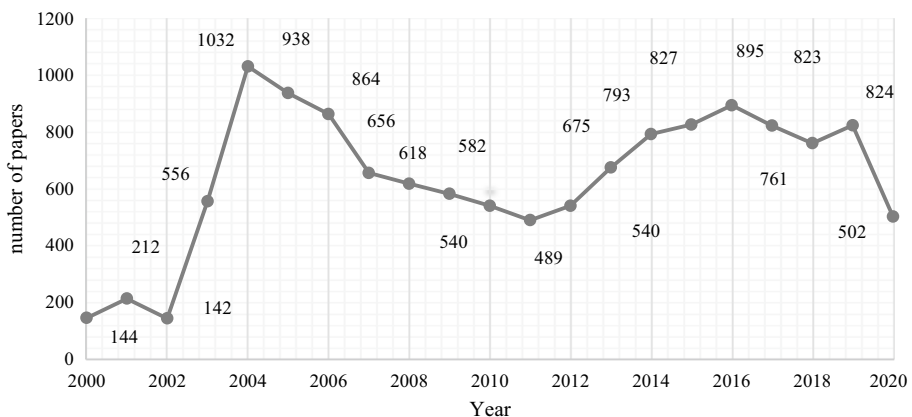


Fig. 4 Quantification of papers on coronavirus topics (between 2000 and 2020, updated on April 1, 2020)

Table 2 Highly frequent keywords in 13,518 papers

No.	Keyword	Occurrences	No	Keyword	Occurrences
1	Respiratory disease	2630	16	Antibody	762
2	Spike	1429	17	Enteritis	733
3	Cats	1349	18	Emerging	706
4	Human	1334	19	AR-PCR	701
5	Pathogen	1329	20	Receptor	695
6	PCR	1238	21	Protease	677
7	RNA	1215	22	Response	661
8	E-protein	1165	23	Pneumonia	619
9	Diarrhea	995	24	Control	606
10	Middle East	920	25	Influenza	598
11	Spike protein	888	26	Replication	596
12	Epidemic	843	27	Vaccines	585
13	Antivirals	830	28	Nucleocapsid	584
14	Epidemiology	791	29	Recombinant	549
15	Respiratory tract	780	30	Diagnosis	526

Table 3 Leading journals in terms of number of coronavirus-related publications (2000–2020)

Journal	# papers	%
Journal of virology	907	6.7621
Emerging infectious diseases	314	2.341
Virology	303	2.259
PLoS ONE	261	1.9459
Virus Research	201	1.4985
Journal of general virology	193	1.4389
Viruses-Basel	177	1.3196
Archives of virology	162	1.2078
Antiviral research	154	1.1481
Journal of virological methods	152	1.1332
Veterinary microbiology	147	1.0960
Journal of medical virology	138	1.0289
Journal of infectious diseases	122	0.9096
Journal of clinical virology	121	0.9021
Vaccine	118	0.8797
Journal of clinical microbiology	117	0.8723
Proceedings of the National Academy of Sciences of the United States of America	117	0.8723
Clinical infectious diseases	113	0.8425
Virology Journal	110	0.8201
Lancet	108	0.8052
Total	13,518	100

Table 4 Modularity measurement of the communities yielded by the community detection algorithm

Id	Cluster	No. sub-communities	Modularity
C1	“Antibody-virus interactions”	–	–
C2	“Emerging infectious diseases”	7	0.421
C3	“Protein structure-based Drug design and antiviral drug discovery”	7	0.436
C4	“Coronavirus Detection methods”	6	0.308
C5	“Viral Pathogenesis and immunity”	–	–
C6	“Animal coronaviruses”	6	0.383

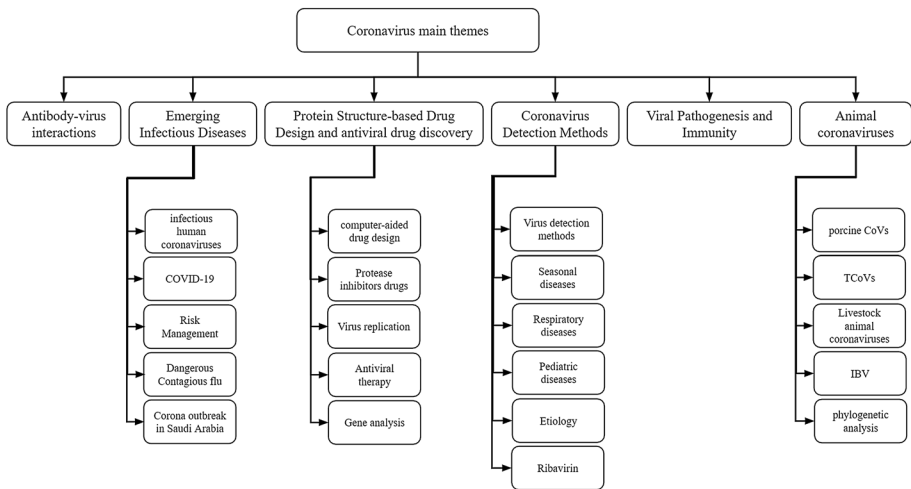


Fig. 6 The main themes of coronavirus

and 0.383, respectively, all within the desired range. The themes of “Antibody-virus Interactions” and “Viral Pathogenesis and Immunity” had smaller scales than the others, so no further detail was required. Community detection was therefore not applied to these themes. The results of the modularity criteria are given in Table 4.

The main themes and sub-themes of coronavirus-related research over the two past decades are depicted in Fig. 6, including six main general themes. The results obtained from the map of each community and the structure of each theme and sub-theme were validated using pathologist’s expert opinions. Additionally, the experts verified both the research findings and future research directions.

Antibody-virus interactions C1

Antibodies play four major roles in connection with pathogenic viruses: antibody-dependent cell-mediated virus inhibition (ADCVI), virus neutralization, phagocytosis, and

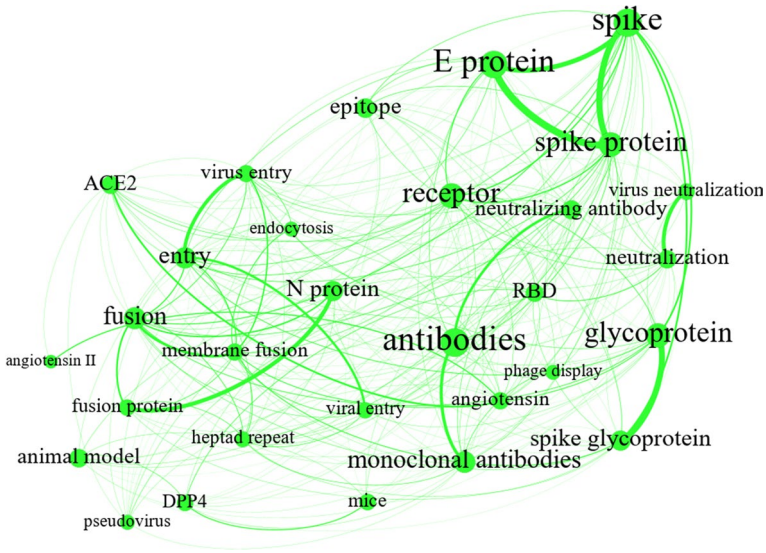
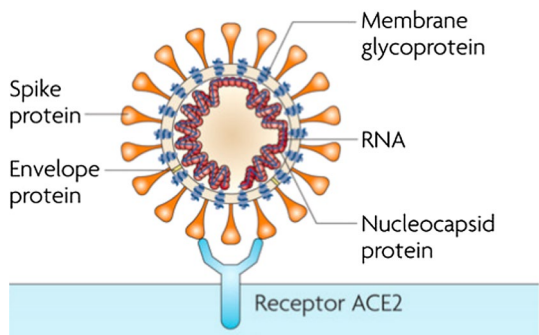


Fig. 7 “Antibody-virus interactions C1”

antibody-dependent cellular cytotoxicity (ADCC) (Forthal & Moog, 2009). The “Antibody” theme, shown in green in Fig. 7, mostly focuses on antibody-virus interactions in a host cell, especially from the perspective of neutralizing antibodies. Neutralizing antibodies are the antibodies that bind to cell-free viruses, thus blocking the viruses; as a result, they eliminate and interrupt virus replication and prevent cell infection (Gorny et al., 2005; Greenspan & Cavacini, 2019; Ringe & Bhattacharya, 2013; Tuen et al., 2005). Furthermore, the theme also covers distinctive virus components associated with viral entry in host cells, including membrane envelope (E) proteins and spike peptides or glycoproteins (S) (David Cavanagh, 1995). Spike protein, a viral membrane protein, plays a vital role in viral entry: It binds to a receptor in the target cell, such as angiotensin-converting enzyme 2 (ACE2) (Hamming et al., 2004), thus providing opportunities for virus-cell fusion (Bosch et al., 2003). A coronavirus structure and the ACE2 viral receptor on the host cell surface are illustrated in Fig. 8 as represented by Oguh et al. (2020). As Fig. 7 shows, the major nodes in the co-occurrence network correspond to neutralizing agents, such as

Fig. 8 Illustration of the coronavirus structure and the ACE2 viral receptor



light blue sub-community, this sub-community can be identified by titling it as highly infectious human coronaviruses, especially MERS and SARS. Also, Fig. 9 shows that the dark blue sub-community can be mapped onto COVID-19 due to its nodes' interrelation in this sub-community (e.g., "SARS-CoV-2," "novel coronavirus," and "2019-ncov").

After the sub-communities were investigated and various components of the community were classified, an explanation of how the map was generated was found. Nodes related to cities and countries appear in Fig. 9, proving that outbreaks of novel human coronaviruses were reported in China (the origin of COVID-19 and the SARS virus outbreak), Saudi Arabia (the origin of the MERS outbreaks), Vietnam, Hong Kong, South Korea, and Singapore. All these countries (except Saudi Arabia) are located near China, so Asian nations, particularly China, are clarified as the main sources of the SARS, MERS, and COVID-19 outbreaks/infections (Peeri et al., 2020). Other nodes, such as "quarantine," "infection control," "prevention," "mathematical modeling," and "risk management," can be helpful for surveying the outputs of community mapping. They will therefore be discussed below.

Risk management, as a leading issue of emerging human coronaviruses, has three primary controversial pillars: risk factors, perception, and communication. A personal intellectual judgment about disease characteristics and risk severity which can instigate behavior designed to prevent the spread of disease is what is considered risk perception (Ferrer & Klein, 2015). When experts who have combatted previous coronavirus outbreaks share information about their experience, making it accessible to the public, they enable researchers and practitioners to make better decisions about how to prevent the disease (Krewski et al., 2011). Furthermore, medical treatment and care can be investigated and then applied by researchers. For example, quarantine, which has been detected as a major effective means of virus transmission prevention, has recently received considerable attention from mathematical modeling standpoints. Indeed, mathematical models are providing managers with useful information for scheduling and planning the quarantine process, leading to outbreak reductions with an efficient use of effort (Mandal et al., 2020). Mathematical modeling not only can promote the optimization of quarantine processes, but also can be utilized for calculating the potential reproduction number of different disease types (Fraser et al., 2004). Mathematical modeling can also reveal the patterns of virus spread and the time when a peak is likely to be reached. Note that in quarantine periods policy-makers are faced with two key factors of outbreaks, namely traveling and gathering.

In general, the historical origins of various virus types and the protective methods used to restrict and immunize humans against infection are connected to emerging infectious diseases through the map (Fig. 9), based on a similarity between emerging novel coronaviruses. This insight uncovers useful hidden knowledge and also helps researchers channel their considerable efforts in the right directions.

Protein structure-based drug design and antiviral drug discovery C3

Some of the nodes in Fig. 10, such as "antiviral," "molecular," "RNA," "protease," "inhibitor," and "interferon," are larger than others due to their centralized position as calculated in the co-occurrence network. Our survey of biological resources has proven that nodes and their links have the utmost importance in antiviral drug development. Based on the given description, this theme can be mapped onto "Protein Structure-based Drug Design and Antiviral Drug Discovery." Nowadays, computer-aided drug design (CADD) plays a key role in how pharmaceutical companies discover drugs (Muegge et al., 2017; Hillisch et al., 2015). Antiviral drugs are classified into two main classes, namely, ligand-based

appears in association with keywords such as “pathogens,” “viral pathogenesis,” “pathology,” and “histopathology.” With the keywords in the community, the concept of immune system response can be mapped onto pathogens. Keywords such as “MHV,” “MuCoV,” and “ER stress” were subsequently investigated further to explore the outputs of the map.

The main studies in the theme concern mouse hepatitis virus (MHV) and murine coronavirus (MuCoV), which provide animal model systems for examining viral tropism and pathogenesis in various tissue organs, including the CNS (for instance, surveying demyelination of the CNS in multiple sclerosis) (Weiss & Leibowitz, 2011), lung, and liver. Other keywords describe immune system responses, including immune-related cells (T-lymphocyte and macrophage), innate immune response, immunology, unfolded protein response, and ER stress. The community is illustrated separately in Fig. 12 to visualize the keyword correlations. By releasing diverse inflammatory mediators such as chemokines, cytokines, and proteases, macrophages recognize and engulf antigens of the pathogens through T lymphocytes (T-cells) (Arango Duque & Descoteaux, 2014; Gordon & Plüddemann, 2013; Kassab et al., 2019). T-cells are stimulated by the antigens presented by macrophages and then release lymphokines to signal other cells. Also, T-cells can react properly to antigens through the recognition of antigens (Filiano et al., 2017; Park & Mitchell, 2012).

Animal coronaviruses C6

The main reason why this community is mapped this way can be outlined by probing its nodes and relationships in Fig. 13. Keywords in this community concentrate on three main animal coronaviruses, namely, a) alpha coronaviruses, such as porcine CoVs, feline coronavirus (FCoVs), and canine coronavirus (CCoV); b) beta coronaviruses, including equine coronaviruses (ECoV) and bovine coronaviruses (BCoV); and c) gamma coronaviruses, like avian infectious bronchitis virus (IBV) and turkey coronavirus (TCoV). The yellow sub-graph displays a phylogenetic analysis of different animal coronavirus types. For further investigation and classification of animal coronaviruses, the Louvain algorithm is employed to survey the sub-communities in Fig. 13. One leading virus group is listed and described below.

The three porcine coronaviruses (light blue in Fig. 13) are transmissible gastroenteritis coronavirus (TGEV), porcine epidemic diarrhea virus (PEDV), which causes enteric infections, and porcine respiratory coronavirus (PRCV), which leads to respiratory disorders. Considering how the porcine CoVs have emerged and re-emerged since 2013, they have been considered a major threat to swine industries the world over (Leyi Wang & Zhang, 2016). FCoV (dark blue in Fig. 13) evolved from the fecal–oral route, resulting in feline infectious peritonitis (FIP), identified as a systematic infectious disease in both domestic cats and their wild peers (Hartmann, 2005). CRCoV (dark blue in Fig. 13) is closely related to feline and porcine strains. It produces gastroenteritis in dogs (de Cássia Nasser Cubel Garcia, 2016). ECoV (dark blue in Fig. 13) is associated with the most common symptoms in equine species (e.g., fever, anorexia, diarrhea, leukopenia, lethargy) (Miszczak et al., 2016). BCoV (green in Fig. 13) is responsible for neonatal calf diarrhea, respiratory disorders, and winter dysentery in cattle (Alfieri et al., 2016). The agent of infectious bronchitis, accompanied by tracheal ciliostasis, nasal discharge, snicking, and rales, is also labeled as “IBV” (red in Fig. 13). Additionally, IBV has harmful effects on kidneys, enteric surfaces, and oviducts, and it impairs egg production and quality (Ambali & Jones, 1990; Cavanagh, 2005; Cook & Mockett, 1995). A highly epidemic enteric disease in turkey peers which

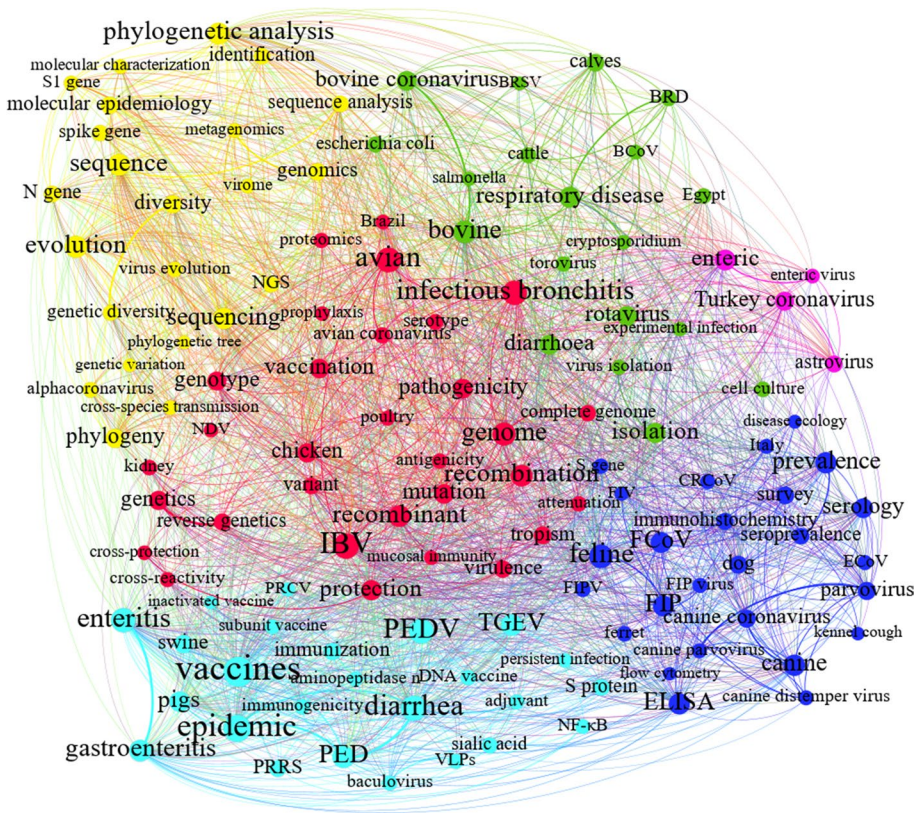


Fig. 13 “Animal coronaviruses C6”

has caused severe damage for turkey-related industries has evolved from TCoV (purple in Fig. 13).

Strategic diagram

The strategic diagram of co-word-related centrality and density is described in this section. The density and centrality of each community are given in Table 5.

For the clustering results, the strategic diagram of the six communities was drawn in Fig. 14 using the centrality and density measures. Moreover, Fig. 14 shows that no motor theme has existed in coronavirus research work.

According to Fig. 9, the two clusters placed in QII (Ivory Towers), “Antibody-virus Interactions C1” and “Viral Pathogenesis and Immunity C5”, are well structured internally but have rather weak external relations. Combining these themes with the other four themes drives them into QI. In other words, a further effort is required to help place this theme in more effective subject areas, shown in Fig. 14.

Also, theme 3 (“Protein Structure-based Drug Design and Antiviral Drug Discovery C3”) falls into the Chaos/Unstructured quadrant, as either an emerging theme or a disappearing theme. Thus, greater concentration on C3 can move it to QII, reflecting greater development as illustrated in Fig. 14.

Table 5 The strategic diagram measurement

Q	ID	Top keywords	Centrality	No. nodes	No. edges	Density
QI: Motor	—	—	—	—	—	—
QII: Ivory towers	C1	Spike, spike protein, E protein, glycoprotein, entry, fusion, spike glycoprotein, membrane fusion, antibodies, and receptor	3321	30	267	0.613793
	C5	Demyelination, immunology, inflammation, response, pathogenesis, immune responses, multiple sclerosis, neuroimmunology, neuroinflammation, and hepatitis	2694	36	324	0.514286
QIII: Emerging/Declining	C3	Replication, protease, inhibitor, docking, antiviral, structure, nucleocapsid, molecular docking, and nucleocapsid protein	6408	83	1036	0.3044
QIV: Basic/Transversal, Bandwagon	C2	Emerging infectious disease, infectious diseases, emerging infectious diseases, emergence, disease, control, Middle East, outbreak, dromedary, and Ebola	7331	107	2013	0.354963
	C4	RTI, respiratory tract, metapneumovirus, human metapneumovirus, rhinovirus, infections, respiratory syncytial virus, respiratory viruses, bocavirus, and human	5355	93	1652	0.386162
	C6	Diarrhea, PED, enteritis, epidemic, infectious bronchitis, canine, gastroenteritis, bovine, phylogenetic analysis, and enteric	6481	128	2274	0.279774

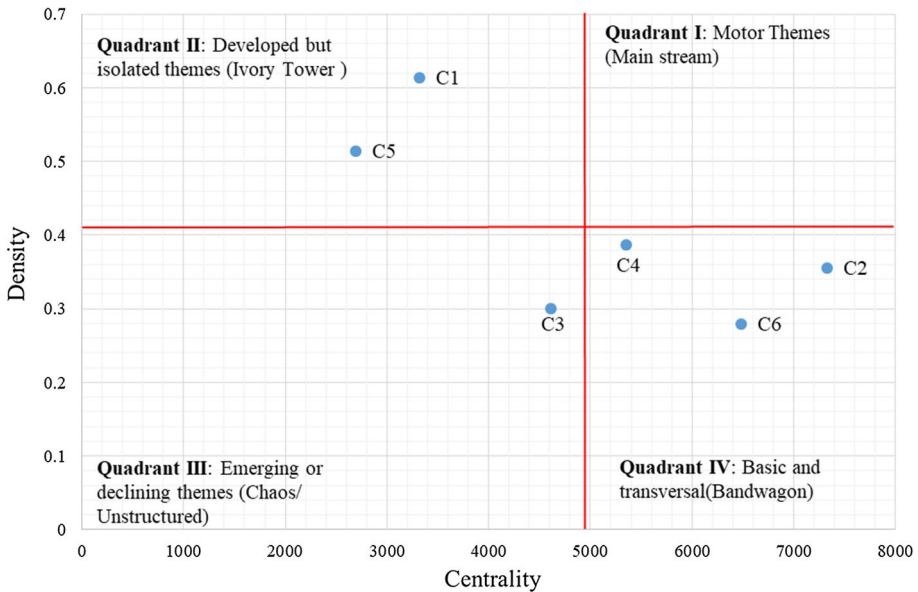


Fig. 14 Strategic diagram

Finally, three main communities (“Emerging Infectious Diseases C2”, “Coronavirus Detection Methods C4” and “Animal Coronaviruses C6”) are in QIV (Bandwagon). They are all central, albeit distinctive from each other. Thus, these themes should be also studied further so they can be moved into QI.

Generally, there remains a paucity of concentration in C2, C4, and C6. Owing to their low density, these areas are more interesting to focus on. Consequently, each of these three areas can be considered a potential subject for further improvement. C1 and C5 are already sufficiently structured, and they have less research potential than the other clusters. Even so, they can be combined with other themes to create novelty values because of the low centrality of the other clusters. Furthermore, due to the diversity and novelty of the coronavirus, no themes lie in QI. Hence, interested researchers have a golden opportunity for further contribution and achievement in that sense.

Discussion

The recent trend in keyword extraction has shown just how important past studies of coronaviruses are. Coronavirus-related research surged with the emergence of SARS and MERS in 2003–2004 and 2012–2016. Therefore, it is predicted that COVID-19 studies will rise noticeably, appearing primarily in *Journal of Virology*, *Emerging Infectious Diseases*, and *PLoS ONE*.

This paper employed a co-word analysis methodology to provide a comprehensive review of coronavirus field research published in the WOS between 2000 and 2020, updated on April 1, 2020. Six main themes emerged from our analysis (Fig. 3). They are named (a) “Antibody-virus Interactions C1,” (b) “Emerging Infectious Diseases C2” (c) “Protein Structure-based Drug Design and Antiviral Drug Discovery C3” (d) “Coronavirus

Detection Methods C4” (e) “Viral Pathogenesis and Immunity C5” and (f) “Animal Coronaviruses C6” Our research findings substantiate the original definition of the coronavirus field summarized below.

Antibody-virus interactions C1

This theme mostly focuses on interactions between antibodies and viruses, particularly in terms of the neutralization process. Also, this theme lies in QII, which indicates strong density and low centrality. In other words, the keywords of this theme are frequently researched and discovered together. On the other hand, it has only weak relationships with the other five themes. Weak relationships indicate golden opportunities for researchers to discover new dimensions of antibody-virus attractions in coronaviruses.

From bioassay perspectives, neutralization assays are not only highly sensitive and quite specific but also time consuming and prohibitively expensive because of their labor-intensive nature and cell culture prerequisites (Atmar, 2014). To bring down time and costs, mathematical modeling and optimization could be applied; mathematical modeling could pave the way for setting arbitrary parameters during neutralization processes to yield the desired results promptly at a lower cost.

Emerging infectious diseases C2

The second theme explains the virology of coronaviruses. It has significant centrality and low density. Accordingly, more work is needed to develop the theme more thoroughly: Coronavirus and non-coronavirus cases in this cluster should be simultaneously subjected to greater investigation and closer examination. Indeed, the body of work done so far has not been integrated well enough to create novelties. Research into HIV, Ebola, dengue fever, Nipah virus, Zika virus, West Nile virus (WNV), HCV, and so on has provided inspiration in the past for non-coronavirus-related achievement and can contribute further to different types of coronavirus-preventive actions. Comparative analysis of non-coronaviruses and coronaviruses is recognized as containing a wide gap; this gap can be closed with multidisciplinary efforts. Utilizing different ideas and methodologies drawn from non-coronavirus work, then, will culminate in an impressive success in the coronavirus research area.

Drug repurposing is also one of the major triggers suggested for devising effective coronavirus drugs. Drug repurposing is an effective strategy, as it involves developing products based on current drugs and thus requires less effort and lower cost than randomized clinical trials and de-novo drug discovery (Cheng, 2019; Cheng et al., 2016). For example, IFN- α , one of the antivirals most widely used against hepatitis, could be useful to inhibit SARS-CoV reproduction in vitro. Furthermore, the HIV medication lopinavir/ritonavir could play a role in SARS-CoV treatment, as could darunavir (a second-generation HIV-1 protease inhibitor) (Lisheng Wang et al., 2020). Consequently, drug-repurposing strategies are crucial for discovering effective drugs and antibodies of coronaviruses.

Protein structure-based drug design and antiviral drug discovery C3

This theme largely concerns protein structure-based drug design, especially using computer-aided drug design methods. According to the strategic diagram, it lies in QIII and has both low density and low centrality. In other words, it is still in its infancy.

As mentioned, computer-aided drug design methods fall into two main classes, namely, ligand-based drug design and protein structure-based drug design. In comparison to the ligand-based drug design methods, the protein structure-based methods account for a major part of computer-aided coronavirus drug design, while Wilson and Lill (2011) state that combining ligand-based and protein-based design methods is essential for promoting the efficiency and reliability of computer drug design. Moreover, ligand-based drug design is employed when limited information about the target protein structure and structure-based methods is available (Wilson & Lill, 2011). Therefore, it can be helpful for detecting drugs to use against emerging coronaviruses, especially those that are in the early stages of outbreak.

Coronavirus detection methods C4

The fifth theme defines coronavirus detection methods that have strong relationships with other coronaviruses; nevertheless, it has not been properly developed in terms of methodologies and technologies. Some advanced technologies, such as the Internet of Things (IoT) and artificial intelligence (AI), and various smart devices can be employed to produce novelties for real-time virus detection. For instance, Mohammed et al. (2020) introduced an IoT-based system for discovering people suspected of being infected by COVID-19. In the proposed system, the suspect zone is scanned by an infrared camera to detect high body temperatures. When high-temperature bodies are found, an optical camera captures the suspected faces of the high-temperature persons, and their location (found via a geographic information system) is sent to health officials. Salman et al. (2020) developed an algorithm based on deep learning methods for detecting COVID-19 from X-ray images.

Viral pathogenesis and immunity C5

This theme investigates pathogenesis and the immunology of coronaviruses. It lies in the Ivory Tower quadrant of the strategic diagram. The theme has high density, which means it could develop well internally. Besides, it has low centrality, which suggests it should be combined with other themes to develop externally and yield novelties. The following viral pathogenesis research questions are proposed (Heise, 2014):

- Which viral infections lead to diseases?
- Does a virus cause disease or not?
- What form of the disease is taken?
- How severe will the disease be?

In short, interactions of coronavirus pathogens and immune system responses are presented in biological terms in this theme. Although pathogenesis studies culminate with a deeper understanding of different types of coronaviruses, investigating effective factors for preventive measures against the emergence of new diseases may significantly prevent novel coronavirus outbreaks even worse than the MERS, SARS, and COVID-19 outbreaks. Methods for finding such effective factors and measuring their effectiveness will come from pathogenesis-related research.

Animal coronaviruses C6

The sixth theme describes the pathology of major animal coronaviruses. While the animal coronavirus community is well connected to other coronavirus fields, the community is not very dense; thus, it can be moved to the Motor Theme quadrant with a little effort. As such, it should be studied more from the viewpoints of pathology and immunology. Additionally, animal coronavirus outbreaks have affected livestock considerably and consequently damaged the economy. Animal health measures can effectively block animal coronavirus outbreaks. Wearable technologies are classified among the leading concepts for improving animal health through time-monitoring systems.

Indeed, biosensors and wearable technologies have become very important in animal health management systems and have been proved to be helpful in poultry farming and dairy cattle raising. One of the main achievements of these technologies is that they provide real-time disease diagnosis, which mitigates profit losses. Sensors can assess and measure different biomedical parameters and provide reliable data that can reduce human error. Also, these technologies can be customized to meet the needs of various types of animals, pets, and livestock (Harrop et al., 2016). Accordingly, designing integrated systems to trace alpha coronavirus symptoms can restrict outbreaks of the virus, eventually resulting in economic recovery.

Conclusions, limitations, and future research

The present research aimed to map the intellectual structure of the coronavirus field from 2000 to 2020 using co-word analysis of publications in the WoS Core Collection database. The results confirmed that research in the coronavirus field is still in its early stage, which consists of a wide range of heterogeneous, interdisciplinary knowledge domains. The study also laid the groundwork for future research in the subject areas. To achieve that goal, this paper explored a knowledge map of the main CoV themes, including six dominant communities, namely (a) “Antibody-virus Interactions C1,” (b) “Emerging Infectious Diseases C2,” (c) “Protein Structure-based Drug Design and Antiviral Drug Discovery C3,” (d) “Coronavirus Detection Methods C4,” (e) “Viral Pathogenesis and Immunity C5,” and (f) “Animal Coronaviruses C6.” Furthermore, a strategic diagram was created showing the communities’ current situation. According to the strategic diagram, none of the communities lie in Quadrant I. This means that there is no domain in the coronavirus field that is both central and mature. As a result, many research gaps still need to be bridged by further research. “Antibody-virus Interactions C1” and “Viral Pathogenesis and Immunity C5” lie in the Ivory Towers quadrant, which means they should be combined with other themes to create novelties in CoV research. “Protein Structure-based Drug Design and Antiviral Drug Discovery C3” is in QIII; this indicates that it needs more concentration before it can develop further. “Emerging Infectious Diseases C2”, “Coronavirus Detection Methods C4” and “Animal Coronaviruses C6” are situated in QIV; they are more central but low in density, traits that mark potential future areas of research.

Although this paper provides a good intellectual structure of the subject, it still has great room for further improvement before it becomes a comprehensive work in the coronavirus field. The major limitations of this study are listed as follows:

Time-consuming

Co-word analysis requires preprocessing and feature selection, which are highly time-consuming tasks, especially when either the number of features (selected words) is large or powerful hardware is not available. Big Data-based co-word analysis could pave the way for both more research papers and better keyword selection, yielding more accurate, comprehensive results.

The future trend

We applied co-word analysis to develop an intellectual map of coronavirus research. However, we did not consider the predictive aspect of research. Consequently, prediction methods, such as link prediction, could be employed to provide a broad overview of future research.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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