From skirmishes to protracted battles: a bibliometric analysis about human beings and coronaviruses from 1991 to 2020

Ling Yue[1], Youjuan Fu[1], Yuanquan LI[1], Jiayi Huang[1], Yifei Wang[1], Ziyi Zhu[1], Zhiyang Wang[1], Jing Li[1], Wei Chen[1], and Chao He[2]

[1]Affiliation not available
[2]Wuhan University

March 30, 2022

Abstract

Background: The coronavirus disease 2019 pandemic (COVID-19) has caused an unprecedented upsurge in the publication of scientific studies as the global community has collaborated to control the spread of the disease. Methods: We conducted a bibliometric analysis to evaluate the research trends and identify the core content based on publication output, the geographic distribution, collaborations and keywords. We searched for articles published from 1900 to June 30, 2020 based on the Science Citation Index Expanded (SCIE) and Social Sciences Citation Index (SSCI) in the Web of Science. Results: Our analysis revealed the following: (1) The number of publications clearly increased after the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) outbreaks and sharply increased during the COVID-19 outbreak. Compared with SARS and MERS, COVID-19 generated a more dramatic and prolonged upsurge in publication. (2) Compared with SARS and MERS, COVID-19 had a more widespread and powerful effect on countries and territories, with a rapid onset. Countries and territories engaged in more international collaboration and communication to cope with the epidemics, and the COVID-19 pandemic led to marked increases in research advancements. (3) Based on the keywords, we found that multiple methods were used to address the COVID-19 pandemic that were based on biology, especially the immune response. Conclusions: Epidemics lead to an extreme acceleration and changes in research.

Introduction

There are seven known coronaviruses that cause diseases in humans. HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 lead to mild upper respiratory infections. Severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are three highly pathogenic coronaviruses that can infect humans and are responsible for the pandemic diseases SARS, MERS and COVID-19 [1].

SARS circulated in 32 countries and territories from November 2002 to August 2003; the cumulative number of infections was 8,422, and the mortality rate reached 10.87%. MERS spread to 27 countries from April 2012 to December 2019; there were 2,496 cases of infections, and the mortality rate was as high as 34.77% [2]. COVID-19 has caused a worldwide pandemic that started in December 2019 and spread with surprising speed. The pattern of the COVID-19 pandemic has changed from the first stage in January and February 2020, in which there was a single epidemic centre (China), to the second stage in March 2020, in which there were multiple epidemic centres (Italy, Iran, and South Korea). By the end of March, the global number of cases was rapidly increasing, with an estimated 50,000 cases confirmed per day [3]. By 26 July 2020, COVID-19 had been reported in 215 countries and territories, and there were 15,785,641 reported cases, with a mortality rate of 4.05% [4].

SARS-CoV, MERS-CoV and SARS-CoV-2 share certain biological, clinical and epidemiological features.

However, according to gene sequencing, the main differences among them are in the open reading frame 1a (ORF1a) gene and the spike coding protein gene [5]. The spike protein of SARS-CoV-2 has the largest sequence divergence, with 380 amino acid sequence substitutions [6], contributing to its affinity. With regard to the clinical characteristics, COVID-19 varied from mild cases to severe cases, and most cases are mild. In contrast, SARS and MERS tend to have an urgent onset and rapidly progress to severe illness [7]. COVID-19 seemingly has a more insidious onset. Due to the abovementioned characteristics, COVID-19, SARS and MERS have different morbidity and mortality rates. COVID-19 has the highest prevalence but lowest fatality rate, while MERS had the highest fatality rate. SARS was characterized by superspreading events, while MERS seemed to be less transmissible, and COVID-19 is unique for its indiscriminate transmission among the general public [5]. Owing to its unique biological, clinical and epidemiological characteristics, SARS-CoV-2 has led to a more prolonged epidemic.

Bibliometrics is an effective tool for evaluating research trends in different scientific fields. Coronaviruses did not attract worldwide attention until the 2003 SARS epidemic, followed by the 2012 MERS outbreak and the recent COVID-19 pandemic. To investigate in more detail the rapid expansion of research stimulated by coronavirus epidemics, we evaluated 25,835 publications to identify the research trends and core contents in the field of coronavirus research between 1991 and 2020. Our article focused on analysing the trends in research on the characteristics of coronavirus infections, which may provide further guidance for present and future studies.

Material and Methods

We obtained publications from the SCIE and SSCI in the Web of Science from 1900 to June 30, 2020. The search terms "Coronavirus*", "SARS", "MERS", "2019-nCoV", "COVID-19", "SARS-CoV*", "MERS-CoV", "HCoV-229E", "HCoV-OC43", "HCoV-NL63", "HCoV-HKU1", "Middle East Respiratory Syndrome*" and "Severe Acute Respiratory Syndrome*" were selected and used to search the titles, abstracts and keywords of publications in journals.

England, Scotland, Northern Ireland, and Wales were considered part of the United Kingdom (UK), while Hong Kong, Macau and Taiwan were considered distinct from mainland China due to differences in their political systems.

We used ArcGIS (10.6) to map the geographical distribution of global publications and reported cases of infections with three human pathogenic coronaviruses. Gephi (0.9.2) was used to visualize core countries and territories in the international collaboration network.

The following aspects were analysed: (a) the characteristics of the publications; (b) the geographical distributions and international collaborations; and (c) keywords indicating hot topics.

Results

Characteristics of publications

There were 25,835 publications on coronaviruses, with 23,058 in only the SCIE (89.25%) 1,111 in only the SSCI (4.30%), and 1,666 publications in both (6.45%). The growth trend in publications on coronavirus in SCIE only coincided with that of all publications on coronaviruses from 1991-2020. The publications in SCIE increased slowly before the outbreak of SARS in 2003, with an average of approximately 134 publications per year. The number of publications in the SCIE clearly increased after the SARS outbreak, reaching a peak (1,089 publications) in 2004, and also rose slowly after the outbreak of MERS in 2012, with a peak (734) in 2016. Unlike the peak during the SARS outbreak, the peak during the MERS outbreak was lower and came later. The number of publications in the SCIE increased dramatically after the COVID-19 outbreak, with 10,221 publications in 2020, which was an unprecedented surge in research. Moreover, the publications in the SSCI and those that were in both the SCIE and SSCI rose slightly from 2003 to 2019 and clearly increased in 2020 (Fig. 1).

Our results indicate that publications in the SCIE played a dominant role in the field of coronavirus infection

research. The outbreaks apparently stimulated research; however, the responses in research during and after the three epidemics were different, and the research field became diversified. Compared with SARS and MERS, COVID-19 generated a more dramatic and prolonged upsurge in publications. In May and June 2020, the volume of studies increased sharply, with studies mainly originating from areas affected by the epidemic (such as China, the United States of America [USA], Italy and the UK).

Geographical distribution and international collaboration

A total of 23,969 publications included the authors' addresses. We plotted a global geographical distribution map of publications during different stages of the epidemic and the reported cases of SARS, MERS and COVID-19 (Fig. 2).

In the period from 1991 to 2002, 49 countries were involved in coronavirus research. The USA produced the most publications (802), followed by the UK (126), the Netherlands (123), Germany (122) and Canada (117); these were the five most productive countries. Research locations were mainly distributed across North America, Europe and Japan. Eighty-three countries participated in coronavirus research from 2003 to 2011. The number of publications from China varied from 4 in the period from 1991 to 2002 to 2,469, at which point China ranked first, followed by the USA (1,907), Canada (517), the UK (378) and Germany (354). Unlike in North America and Europe, the number of publications from Asian countries (particularly China, Singapore and South Korea) and Australia greatly increased, as these countries were affected by SARS. According to World Health Organization (WHO) situation reports, there were reported cases of SARS in 32 countries and territories from November 2002 to July 2003, while Asian countries (especially China, Singapore and Vietnam) and North America (especially Canada and the USA) were affected more severely [8]. In the period from 2012 to 2019, 113 countries issued related publications. The USA ranked first (1,759), followed by China (1,502). Saudi Arabia varied from 11 publications in the period from 2003 to 2011 to 432 publications, ranking 3rd. Moreover, South Korea also devoted more attention to this topic, ranking 6th (346). In addition to North America, Europe, China and Japan, the Middle East (especially Saudi Arabia, Egypt, the United Arab Emirates, Iran and Jordan) and South Korea clearly produced more publications. According to the WHO situation reports, MERS spread to 27 countries from 2012 to 30 June 2018; the Middle East and South Korea were the main epidemic territories, and Saudi Arabia accounted for 83% of cases [9]. In 2020, 144 countries contributed to coronavirus research. The USA ranked first (3,078), followed by China (2,782), Italy (1,518), the UK (1,349) and Canada (588). The number of publications rapidly increased, and the research locations became more diverse following the dramatic and persistent impact of the COVID-19 pandemic.

The proportion of publications that were internationally co-authored varied from 0.45% in 1991-2019 to 10.34% in 2020. Collaborations between countries and territories became more common after the SARS and MERS outbreaks but were clearly enhanced during the COVID-19 outbreak (Fig. 3). In the period from 1991 to 2019, the USA occupied the central position in the collaboration network. The USA collaborated with China and the UK most closely, while most other countries and territories were more likely to produce single-country publications. In 2020, we found that the USA, China, the UK, Italy, Canada, Australia and Germany contributed to more internationally collaborative publications. There was a striking increase in intensive collaborations, with more diversity in the countries and territories participating in the cooperation and communication (Fig. 4).

Our results reveal some interesting findings. First, research locations became more diverse due to the epidemics of SARS, MERS and COVID-19; of the three epidemics, the COVID-19 epidemic had more widespread and powerful effects on countries and territories with scant warning. COVID-19 is a substantial global public health threat, with severe economic implications. The COVID-19 pandemic has stimulated research on traceability analyses, transmission, diagnostic methods, epidemiology, treatments, prevention, and containment of the disease [10]. Patients early in the outbreak provided large sample sizes for studies of the clinical characteristics of COVID-19 and factors that could be used to predict the spread of COVID-19. Second, countries and territories engaged in more international collaborations and communication to cope with the epidemic, and COVID-19 substantially stimulated advancements in research. Scientists from

different countries worldwide have strengthened their collaborative partnerships and launched joint research projects investigating methods of preventing the spread of the disease and controlling the epidemic.

Keywords

There were 11,574 relevant publications with author keywords in the period from 1991 to 2020. To further identify the main research directions and core content in the field of coronavirus research, we classified the author keywords into six categories (Table 1). They were "Epidemiological features", "Biological features", "Immune response features", "Age/sex", "Diseases/symptoms" and "Diagnosis/therapy". China, which was the origin of the outbreak, conducted numerous studies on the clinical characteristics and biochemical markers of COVID-19 and studied the routes of transmission, effective measures to control the spread of the disease (for instance, rapid outbreak responses and lockdowns), epidemiological characteristics, diagnostic methods, treatments (for instance, traditional Chinese medicine) and vaccines. As the COVID-19 epidemic spread worldwide, the areas of focus in various countries and territories ranged from epidemiological characteristics, prevention and control methods, aetiology and antibodies to disease transmission, detection, diagnosis, treatment and prognosis.

Discussion

"Epidemiological features" mainly focused on transmission and surveillance. Although SARS-CoV, MERS-CoV and SARS-CoV-2 mainly induce respiratory infections, understanding the routes of and factors affecting transmission is very important for the prevention and control of epidemics. SARS-CoV and MERS-CoV are transmitted via two routes (respiratory droplets and close contact) [5]. Although the primary modes of transmission of SARS-CoV-2 are also respiratory droplets and contact, fomite transfer and aerosols are possible; furthermore, the faecal-oral route may also be a route of transmission [11]. Transmission by asymptomatic patients has been reported in many countries and territories [11-13], and asymptomatic patients as a source of the spread of the infection have become a key aspect of prevention and control measures. In addition, vertical transmission may be possible [1]. The WHO has indicated that there is a risk of women transmitting SARS-CoV-2 to their babies through breastfeeding [14]. Environmental factors (ambient temperature and humidity) have also been studied in the attempt to elucidate the transmission of SARS-CoV-2 [15]. The routes of transmission of SARS-CoV-2 are complicated and diverse. It has been reported that transmission along cold chains is possible, and transmission along the route by which seafood is transported over long distances may explain the outbreaks in Beijing, Qingdao and Dalian in China. This possibility serves as a reminder of the outbreak at the Huanan seafood market in Wuhan. Traceability analyses have produced uncertain results, and the paths of transmission are complex and confusing. With regard to preventive measures, using face masks, practicing appropriate hand hygiene, maintaining social distance and ensuring adequate ventilation are effective routine methods [16, 17]. Reducing virus variation and adaptation may play important roles in preventing and controlling epidemic situation.

"Biological features" were associated with the pathogenicity of coronaviruses. The latest studies found that the spike protein on the SARS-CoV-2 surface binds to its receptor, angiotensin-converting enzyme 2 (ACE2), to enter host cells, and host transmembrane protease serine 2 (TMPRSS2) is essential for viral entry [18]. Notably, the binding affinity of SARS-CoV-2 for ACE2 is 10- to 20-fold higher than that of SARS-CoV [6], contributing to its virulence. ACE2 expression and the renin-angiotensin system (RAS) are abnormal in patients with hypertension and obesity, and TMPRSS2 is overexpressed when exposed to androgens, indicating that these factors are involved in the pathogenicity of SARS-CoV-2 [19]. With regard to the RAS, abnormal levels of proinflammatory angiotensin II and antiinflammatory angiotensin 1-7 may reflect the severity of COVID-19 [19]. ACE2 and TMPRSS2 expression may modulate the infectivity of SARS-CoV-2 and are therefore promising therapeutic targets for COVID-19.

"Immune response features" included multiple immune-related factors, although most involved immune cells (particularly T lymphocytes, macrophages and B lymphocytes) and cytokines (interferons, interleukins, chemokines, TNF and C-reactive protein). Cytokine storms were a primary focus during the COVID-19 outbreak. Immune responses play essential roles in the interactions between coronaviruses and their hosts,

and cytokine storms are directly correlated with the pathogenesis and disease severity. Evidence indicates that excessive elevations of inflammatory factors are associated with the deterioration of the condition of patients with SARS and MERS, and there is growing evidence that cytokine storms may be involved in the pathogenesis of COVID-19, causing rapid worsening of the condition of the patient [20].

Clinical features, diagnostic methods and therapies are clinical practice issues. Keywords that were included in the category "Age/sex" mainly involved children, pregnant women and older adults. Older adults tend to be more severely affected by infections due to their weakened immunity [1]. Pregnant women and children are unique groups during the COVID-19 outbreak. They pose difficulties with regard to surveillance and diagnosis. Pregnant women are more susceptible to infectious diseases due to immune suppression; moreover, the clinical symptoms are different in pregnant women than in nonpregnant adults. Compared with adults, fewer children are infected by SARS-CoV-2, and their CT images show nonspecific abnormalities (pure ground-glass opacities or consolidation), unlike in adults [21]. There are diverse systemic manifestations included in the category "diseases/symptoms", possibly due to the wide distribution of the receptor and presence of systemic inflammation (cytokine storms). The receptor for SARS-CoV-2 and SARS-CoV, ACE2, is widely distributed among the organs and tissues (mouth, nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain), and the receptor for MERS-CoV, DPP4 (CD26), is expressed on the kidney, small intestine, liver, prostate epithelial cells and activated leukocytes, suggesting that the range of tissue tropism is relatively broader [7]. The nonspecific symptoms and manifestations of COVID-19 may cause difficulties with regard to diagnosis and management. Based on clinical and epidemiological analyses, older age, male sex and preexisting comorbidities were identified as important risk factors for the development of severe or fatal disease in COVID-19 patients, which was similar to the results found in SARS and MERS patients [22-24]. The five most common comorbidities were hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease and tumours, while higher D-dimer levels, higher neutrophil/lymphocyte ratios, higher levels of C-reactive protein, lymphopenia, thrombocytopenia and obesity were independent risk factors for mortality in COVID-19 patients [25-27]. According to epidemiological studies and large-scale data analyses, diabetes is an important risk factor for mortality and progression to acute respiratory distress syndrome (ARDS) in patients hospitalized with COVID-19 [28, 29]. The mortality rate in COVID-19 patients with comorbid diabetes reached 7.3%, which was 2.3% higher than that in nondiabetic patients [30]. Diabetic patients hospitalized with COVID-19 who had poor blood glucose control tended to have a higher risk of mortality and overall poor prognosis due to their preexisting comorbidities, complications and the effects of cytokine storms [29].

It has been confirmed that swab tests (PCR nucleic acid detection) and chest CT scans play important roles in the detection and diagnosis of coronavirus infections [1]. While sequence variation may contribute to false negative results in nucleic acid detection of SARS-CoV-2 for diagnosis of COVID-19. CT scans are very important for screening for COVID-19, especially in patients with highly suspicious, asymptomatic cases with negative nucleic acid test results [13]. With regard to therapies and preventive measures, vaccines, antibody treatments, traditional Chinese medicine and targeted drugs are four methods. Safe and effective vaccines are currently in the clinical trial stage [31]. High-risk groups (for example, medical workers, children, pregnant women, older adults and people with preexisting diseases) will be given priority for vaccination. Widespread availability of vaccines permits eradication of SARS-CoV-2 from endemicity in humans. Early signs indicate that plasma containing anti-SARS-CoV-2 antibodies from patients who have recovered from COVID-19 can reduce mortality in COVID-19 patients [11]. There are a number of therapies undergoing investigation. Hydroxychloroquine, chloroquine, lopinavir/ritonavir and remdesivir have antiviral activities that can control SARS-CoV-2 in vitro [32]; moreover, viral entry inhibitors, ACE2 modulators (angiotensin receptor blockers) and TMPRSS2 inhibitors (camostat mesylate) are promising clinical therapies, and in China, it has been suggested that Shuanghuanglian oral liquid and Lianhuaqingwen are effective treatments in certain patients with COVID-19 [18, 33, 34]. Given the high levels of cytokines in the host, immunosuppressive drugs targeting the interleukin-6 (IL-6) receptor, such as tocilizumab, have been reported to be effective at controlling cytokine storms induced by infection with SARS-CoV-2 [35], and the application

of blood purification technology (plasma exchange, blood/plasma filtration, adsorption, perfusion and continuous renal replacement therapy) is helpful because it removes cytokines and may improve the clinical outcomes in critically ill patients [20].

Conclusion

Our study provides insight into the progress and future directions of global research in the field of coronavirus research. We summarized six categories of the characteristics of coronavirus infections and analysed the implications, identifying the epidemiological and biological properties, clinical features and current therapeutic methods. The reported effective methods of preventing the spread of coronaviruses and treating infected patients can provide important guidance for the prevention and control of coronavirus epidemics worldwide.

Acknowledgments

Fund: This work was supported by a grant from the International Exchange Foundation of Chinese Medical Association "Special Fund for International Diabetes Exchange and Practice" , China (Z-2017-26-1902)

Conflicts of interest: No conflicts of interest, financial or otherwise, are declared by the authors.

Availability of data and material: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable.

Authors' contributions: YJ designed the search strategy with input from YF and CH, and YJ as well as YQ carried out the literature searches and screening, and any discrepancies were discussed with LY and CH, and LY as well as YJ wrote the first draft of the review with input from CH, YQ,YF, ZY, ZY Wang, JL and WC. JY and YJ were responsible for English editing. All authors have read and approved the final manuscript.

Ethics approval: Not applicable.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

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Table 1 The classification of core keywords in 1991-2020

ACE2 angiotensin-converting enzyme 2, *DPP4* dipeptidyl peptidase-4, *TMPRSS2* transmembrane protease serine 2, *SARS*severe acute respiratory syndrome, *ORF* open reading frame,*Nsp* non-structural protein, *ADAM-17* a disintegrin and metalloproteinase 17, *NK cell* Nature Killer cell, *NF-kappa B* nuclear factor kappa-light-china-enhancer of activated B cells,*TNF* tumor necrosis factor, *ARDS* acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disease, *CNS*central nervous system, *rRT-PCR* real-time reverse transcriptase-polymerase chain reaction, *ELISA* enzyme-linked immunosorbent assay

TP total publications, * author keywords mainly presented in 2020

Fig. 1 Global research outputs of Science Citation Index Expanded (SCIE),Social Science Citation Index (SSCI) and publications on coronavirus in 1991-2020

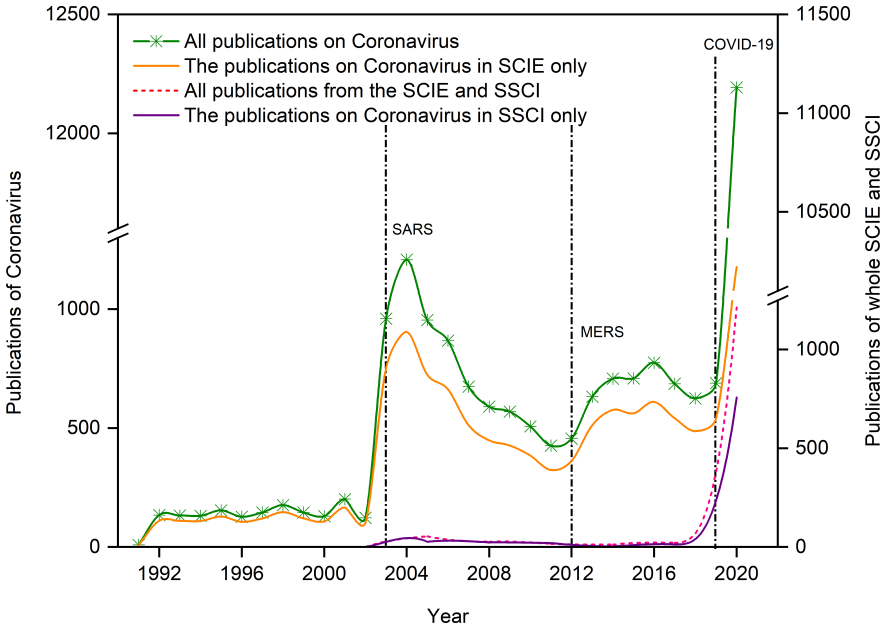
Fig. 2 Distribution changes of global publications in the coronavirus fields and the reported cases during three human coronaviruses outbreaks. (a) Distribution of publications in 1991-2002. (b) Distribution of publications in 2003-2011 and the world reported cases during the SARS outbreak. (c) Distribution of publications in 2012-2019 and the world reported cases during the MERS outbreak. (d) Distribution of publications in 2020 and the world reported cases during the COVID-19 outbreak

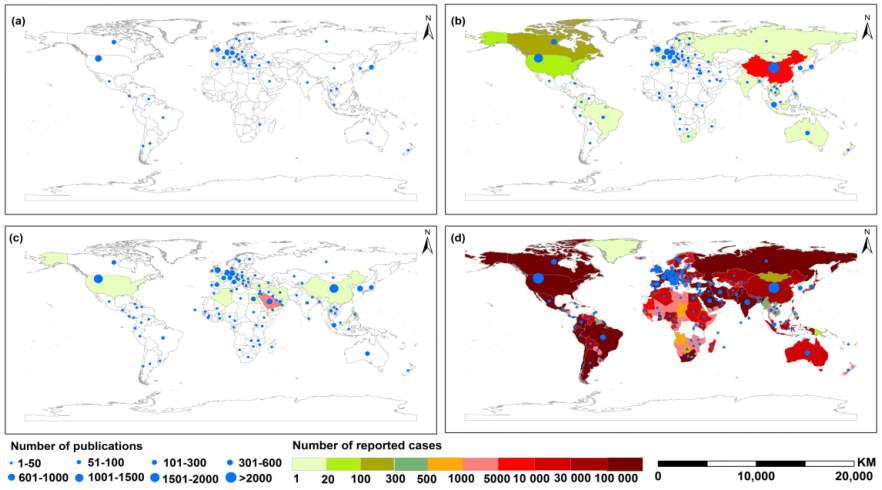
Fig. 3 International-collaborative and independent publications in coronavirus researches

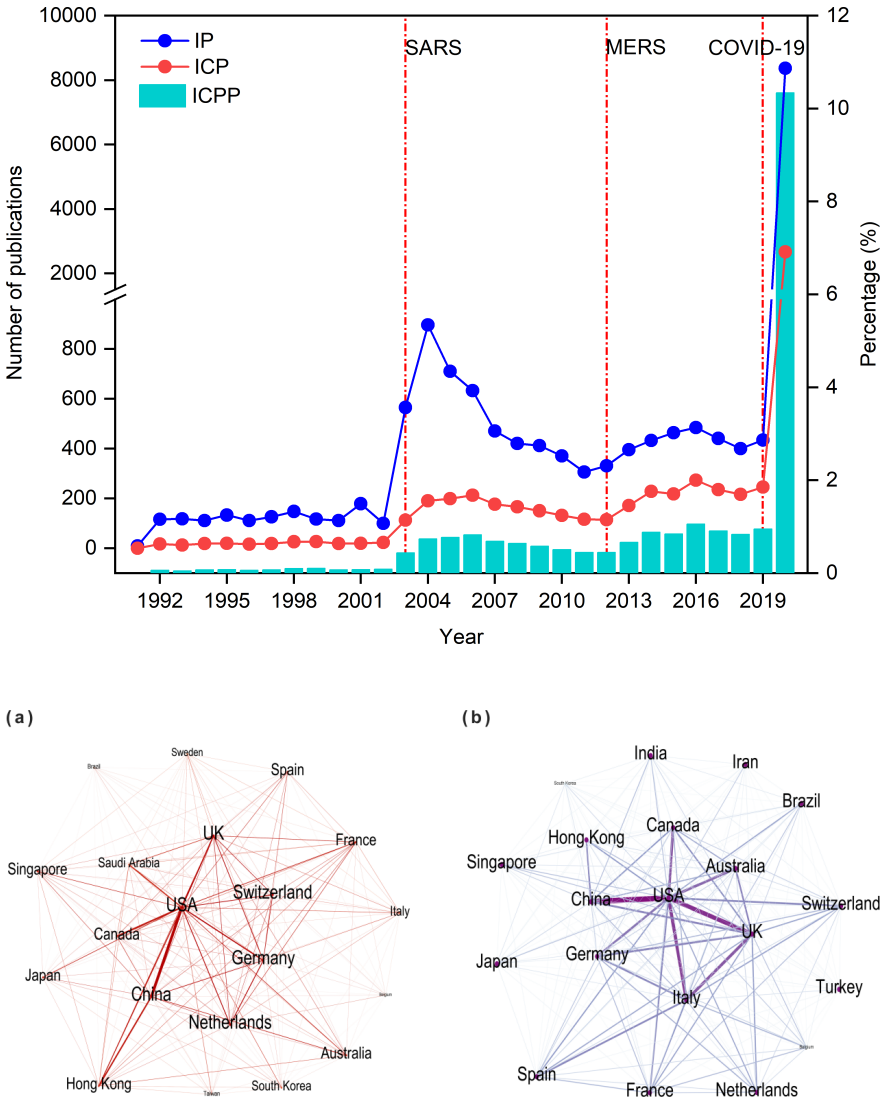
IP independent publications, ICP international-collaborative publications, ICPP the percentage of international-collaborative publications

Fig. 4 Collaboration network of the productive countries or territories

(a) international collaboration in 1991-2019. (b) international collaboration in 2020







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