Original Article

Procalcitonin in infectious diseases: a bibliometric analysis

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Background: Infectious disease is ubiquitous and can represent a major threat to human health. Procalcitonin (PCT) is mainly used to identify the severity of bacterial infections, which can be secondary to many non-bacterial infectious diseases. The purpose of this study was to evaluate current research in the field of infectious diseases and to suggest directions for further investigation.

Methods: The Science Citation Index Expanded (SCI-E) database in the Web of Science Core Collection (WOSCC) was used as the search data source. The search parameters including the search scope were limited to "infectious disease" and the search term was "procalcitonin". The time range of the target literature was 1900 to the final search date of this research (May 7, 2021), and the language was limited to English. The full records of the search results and cited references were exported in plain text format, and Citespace software was used to analyze the documents.

Results: A total of 996 related research documents were found, and the number increased significantly in 2020. The United States, Germany, and the United Kingdom were the main sources of research, and the main research institutions were Aarhus University Hospital and Harvard University. The main journals are publishing material were Clin Infect Dis, Lancet, and Crit Care Med. Analysis of key words showed that the most common current research topics were sepsis and biomarkers of disease monitoring.

Conclusions: Research on infectious disease and the role of PCT is increasing. The main research topics are sepsis and biomarkers for disease monitoring.

Keywords: Procalcitonin; infectious diseases; sepsis; biomarkers

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Introduction

The 2020 COVID-19 pandemic has highlighted the major threat to human health imposed by infectious disease (1-3). Current clinical research on infectious diseases mainly focuses on three areas; the development of specific tests for diagnosis, especially modern molecular diagnostic techniques (4); the identification of co-infections, such as bacterial infections secondary to viral infections (5); and the monitoring of changes of disease during treatment and use of antibiotics (6). Procalcitonin (PCT) is a protein that consists of 116 amino acids and is the peptide precursor of calcitonin (6). PCT is used as a marker indicating the severity of bacterial infections, and increases significantly in the presence of sepsis and severe disease (7). As many bacterial infections can be secondary to non-bacterial infections, it is necessary to clarify the origin of infection in clinical practice so that appropriate antibiotic treatment can be applied and monitored. Many studies have observed the application of PCT in patients with infectious disease, and the 2020 COVID-19 outbreak has increased attention (8). Therefore, in addition to the research on PCT in common

Table 1 Literature type

Literature	Records	Percentage
Article	690	69.3
Review	111	11.1
Letter	97	9.7
Meeting abstract	55	5.5
Editorial material	37	3.7
Proceedings paper	29	2.9
Correction	5	0.5
Early access	5	0.5
Book chapter	1	0.1
Retraction	1	0.1

infections, we should also pay attention to the current research status of PCT in infectious diseases. Different from some meta-analyses about the PCT in infectious diseases, the purpose of this study was to analyze relevant literature in the field of infectious disease to provide a general view on this field and to understand current trends and propose topics for further studies.

Methods

Data source

We used the Science Citation Index Expanded (SCI-E) database in the Web of Science Core Collection (WOSCC) as the data source.

Retrieval method

A subject search strategy was used with the search term "procalcitonin", while at the same time, the search scope was limited to the term "infectious diseases". The time range of the search literature was 1900 to the final search date of this research (May 7th, 2021), and the language of publication was limited to English.

Analysis method

The full record of the search results and cited references was exported in plain text format, and Citespace software was used to analyze the annual publication status, country/institution distribution, journal distribution, author distribution, and keywords of literature related to the application of procalcitonin in infectious diseases.

Statistical analysis

This is a descriptive study and all data were expressed as number and percentage. No statistical comparison was conducted.

Results

Basic results

The search results showed a total of 996 related research documents, of which 690 were original articles, 111 review articles, 97 letters to editors, 55 meeting abstracts, 37 editorial materials, 29 proceedings papers, five early access articles, five corrections, one book, and one retraction (*Tables 1*,*2*, *Figure 1*). The total citation frequency of these documents was 24,895 times, the h-index count was 73, and the average number of citations per item was 24.99 (*Figure 2*). Judging from the results of the annual distribution of the number of papers, the number of related papers published showed a clear increasing trend, especially in 2020 (*Figure 1*). The citation frequency of papers in this field also increased year-by-year (*Figure 2*).

Distribution of countries and institutions

We used CiteSpace V software to draw a national visualization map (*Figure 3*) and an institution visualization map (*Figure 4*), and the results show that the top five countries for the number of papers published were the United States, China, France, Spain, and Germany, and the top five countries in terms of centrality were the United States, Germany, the United Kingdom, France, and the Netherlands (*Tables 3* and *4*). The top five research institutions publishing related papers were the University of Basel, Kantonsspital Aarau, Baylor College of Medicine, Aarhus University Hospital, and Harvard University. However, cooperation between institutions was rare, and the two institutions with the highest centrality were Aarhus University Hospital and Harvard University, each with a centrality score of only 0.03 (*Tables 5* and *6*).

Authors

The author analysis results showed that the distribution of

Table 2 Annual distribution of related papers

Publication year	Records	Percentage (%)
2021	35	3.5
2020	107	10.7
2019	76	7.6
2018	74	7.4
2017	68	6.8
2016	70	7.0
2015	58	5.8
2014	64	6.4
2013	65	6.5
2012	56	5.6
2011	52	5.2
2010	43	4.3
2009	24	2.4
2008	33	3.3
2007	40	4.0
2006	20	2.0
2005	21	2.1
2004	21	2.1
2003	15	1.5
2002	9	0.9
2001	9	0.9
2000	11	1.1
1999	8	0.8
1998	8	0.8
1997	5	0.5
1996	2	0.2
1995	2	0.2

authors in this field was also relatively scattered. There were only two authors with more than 10 publications: Schuetz P and Mueller B, and only three with a centrality score of more than 0.01: Christcrain M, Beishuizen A, and Jong ED, suggesting that there is little cooperation between authors (*Tables 7,8*, *Figure 5*). However, related papers are cited frequently, with those of six authors being cited more than 100 times: Schuetz P, Christ-Crain M, Assicot M, Simon L, Muller B, and Meisner M (*Table 9*). The cited authors were relatively concentrated, and there were three authors with a centrality score greater than 0.1: Bone RC, Becker KI, and Assicot M (*Table 10*, *Figure 6*). The co-citation analysis of the author's literature (*Figure 7*) shows significant chronology and centrality (*Figure 7*).

Distribution of journals

The literature in this study involved 74 journals, of which 17 had published more than 20 papers on this subject. These journals published a total of 739 articles, accounting for 74.2% of the total literature (*Table 11*). The journals cited more than 400 times include *Clin Infect Dis*, *Lancet*, and *Crit Care Med*, all of which are top authoritative journals in this field or comprehensive fields (*Table 12*). Journals with centrality greater than 0.05 were *Ann Intern Med*, *Clin Chem Lab Med*, *Am J Clin Pathol*, *Acta Paediatr*, and *Am J Med* (*Table 13*).

Keywords reflect the research hotspots and frontiers in this field

CiteSpace V software was used to output the keyword co-occurrence map (*Figure 8*) and the top five keywords with frequency were procalcitonin, C-reactive protein, sepsis,

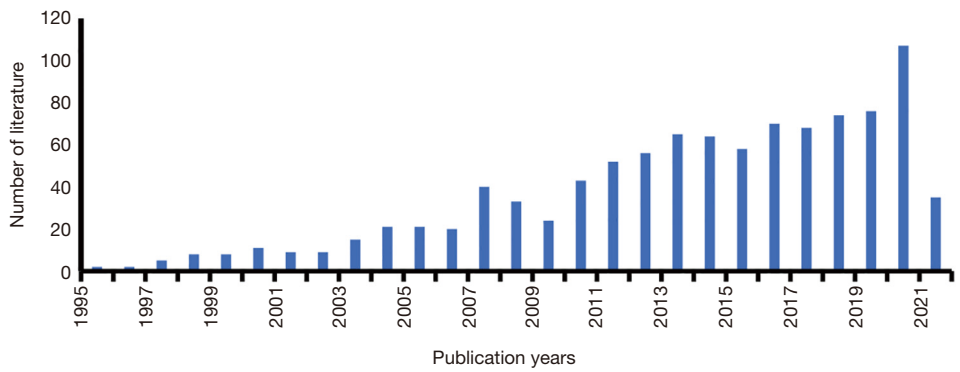

Figure 1 Trends in the number of annual papers published.

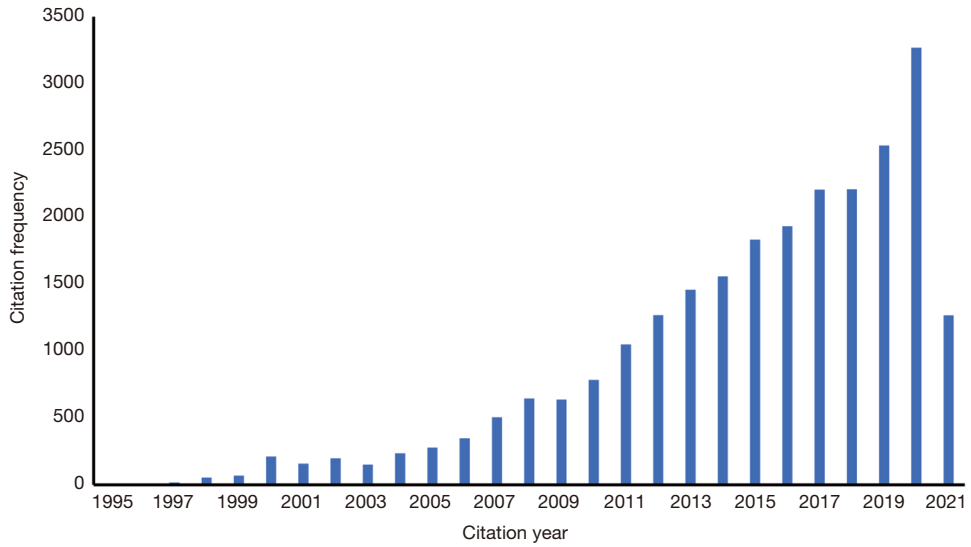

Figure 2 Trends in the frequency of citations of papers in this field each year.

Figure 3 Country visualization map. The knot and connection between countries are few, indicating that the cooperation between countries is rare.

biomarker, and infection (*Table 14*). The top five keywords for centrality were sepsis, c reactive protein, procalcitonin, biomarker, and pneumonia (*Table 15*), and using CiteSpace to perform Burst detection on keywords with high frequency showed high-frequency keywords obviously changed with time (*Figure 9*).

Discussion

PCT is widely used in clinical practice, especially in emergency and critical care medicine, to quickly identify the possibility of bacterial infection. Until February 2019, there were 17 guidelines on the application of PCT, of

Figure 4 Visual map of the organization. There are relatively few knot and connections between knots, suggesting that there is little cooperation between institutions.

Table 3 Top 10 countries for numbers of papers published

Rank	Country	Frequency
1	USA	192
2	China	131
3	France	94
4	Spain	83
5	Germany	77
6	Switzerland	69
7	Netherlands	62
8	Italy	59
9	Japan	45
10	England	44

Table 4 Top 10 countries for centrality

Rank	Country	Centrality
1	USA	0.23
2	Germany	0.20
3	England	0.20
4	France	0.17
5	Netherlands	0.16
6	Italy	0.13
7	Spain	0.10
8	Brazil	0.09
9	Egypt	0.09
10	Slovakia	0.09

which there were 12 recommending the use of PCT for the diagnosis or treatment of bacterial infections, one guideline holding this was not necessary, and four which held that there was insufficient evidence to recommend or not recommend its use (9). However, these studies mainly observed the application of PCT in infection in other fields of clinical medicine (10), and the range and depth of research into the role of PCT specifically in infectious disease is unclear. In response to this, we limited our search scope to the specific field "infectious diseases" and the

Table 5 Top 10 institutions for number of papers published

Rank	Institutions	Frequency
1	University Basel	17
2	Kantonsspital Aarau	14
3	Baylor College of Medicine	11
4	Aarhus University Hospital	10
5	Harvard University	10
6	Erasmus MC	10
7	University Athens	10
8	Capital Medical University	9
9	CHU Nantes	9
10	Univ Rochester	9

Table 6 Top 10 institutions by centrality

Rank	Institutions	Centrality
1	Aarhus University Hospital	0.03
2	Harvard University	0.03
3	Univ Basel	0.01
4	Kantonsspital Aarau	0.01
5	Capital Medical University	0.01
6	Jena University Hospital	0.01
7	University Basel Hospital	0.01
8	Taiwan University Hospital	0.01
9	University Paris 06	0.01
10	Hannover Medical School	0.01

Table 7 Top 10 authors and number of papers published

Rank	Authors	Frequency
1	Schuetz P	22
2	Mueller B	13
3	Julianjimenez A	9
4	Bohuon C	7
5	Christcrain M	6
6	Beishuizen A	4
7	Prat C	4
8	Gendrel D	4
9	Musher Dm	4
10	Gilbert Dn	4

Table 8 Top 3 authors for centrality

Rank	Authors	Centrality
1	Christcrain M	0.02
2	Beishuizen A	0.01
3	Jong ED	0.01

There are only three authors with a centrality score of 0.01.

results showed that there is less study in this than in related fields. The total number of publications was only 996 (as of May 7, 2021, English literature), of which only 690 were original articles. This may be because some infectious diseases are easy to diagnose and have more reasonable indicators for monitoring (11,12), and there is no need for the use of PCT in diagnosis or to guide treatment. However, the substantial increase in related papers in 2020 suggests its increased use as an indicator of infectious disease is not in a small way related to the COVID-19 pandemic, on which more than 20 papers have been published (8,13).

Our results show that most research in this field arises from several institutions in Europe and the United States, and while most researchers in the field also belong to these institutions, there appeared to be little collaboration in terms of authorship between them. This situation is no different in China, which produces many publications, with little evidence of international collaboration. One reason for this may be that there are currently few countries capable of carrying out relevant research in the field of infectious disease (14), which may in turn be due to the high costs in maintaining the strict quality control and biosafety measures required to operate an infectious disease research laboratory (15,16). Despite this, network collaboration is increasing, and has made it easier to carry out multi-center research on many common diseases, rare diseases, and infectious diseases (17). The implementation of networks connecting all parts of the world may also be more conducive to the prevention and control of infectious diseases in poor countries and regions which are unable to establish their own research facilities. In terms of journals, research results in this field are more likely to be published in more detailed professional journals, but high-quality research is more likely to be published in top comprehensive journals and critical care journals. This may be because these studies have more extensive reference value, or the diseases involved are

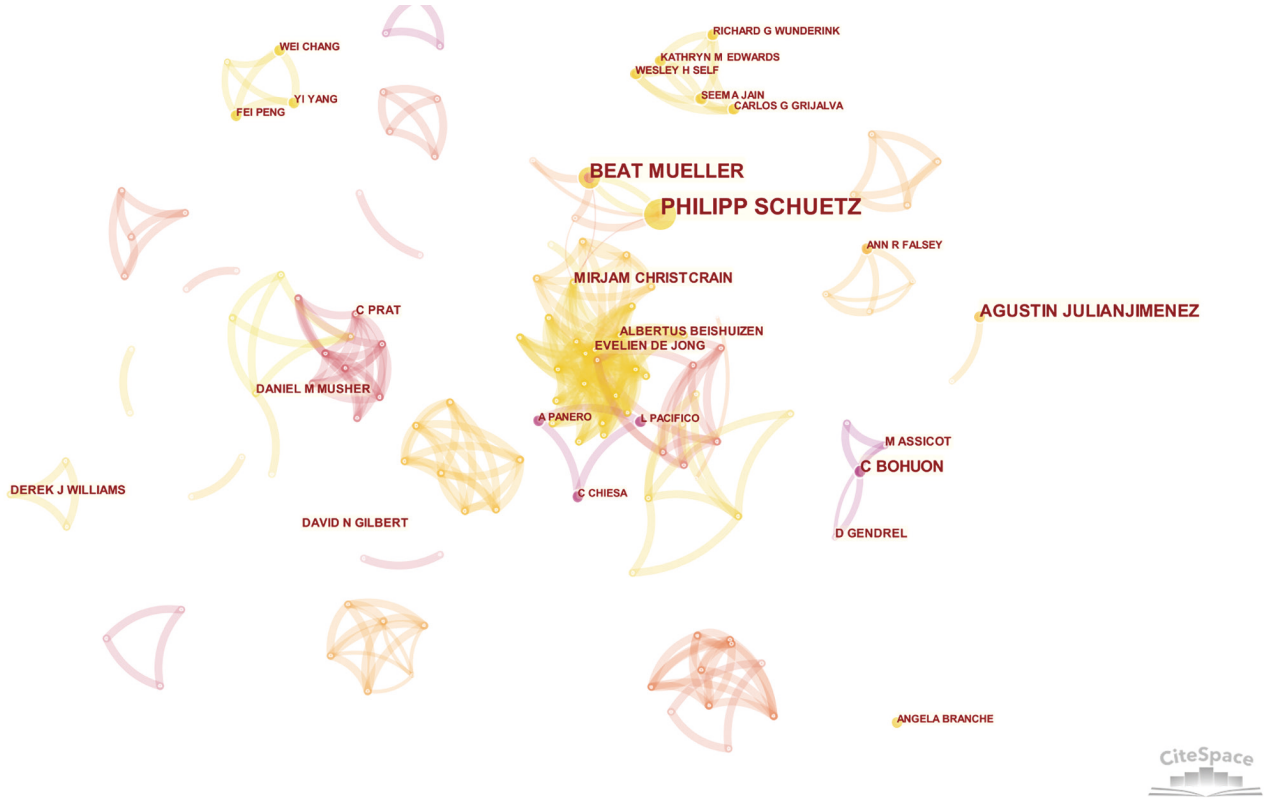

Figure 5 Author co-operation visualization map, which clearly shows that there are few connections between knots.

Table 9 Top 10 authors cited in literature

Rank	Authors	Frequency
1	Schuetz P	231
2	Christ-Crain M	184
3	Assicot M	148
4	Simon L	144
5	Muller B	116
6	Meisner M	101
7	Bouadma L	96
8	[Anonymous]	94
9	Bone RcC	94
10	Gendrel D	90

"Anonymous" often refers to comments from journals.

Table 10 Top 10 co-cited authors of centrality

Rank	Authors	Centrality
1	Bone RC	0.2
2	Becker KI	0.17
3	Assicot M	0.11
4	Meisner M	0.08
5	Giamarellos-Bourboulis EJ	0.07
6	Chiesa C	0.07
7	Dandona P	0.07
8	Gendrel D	0.07
9	Muller B	0.07
10	Simon L	0.07

more serious, and the disease covers more people.

In addition to the term procalcitonin, the most frequently used keywords mainly concerned biomarkers, severe illness, and sepsis, suggesting that many studies are related to post-infection sepsis. Moreover, we have also seen significant changes in the use of keywords over time, suggesting that the focus of research is changing, with the current focus on critical illness-related research, especially sepsis (18,19). Regarding the use of PCT, most

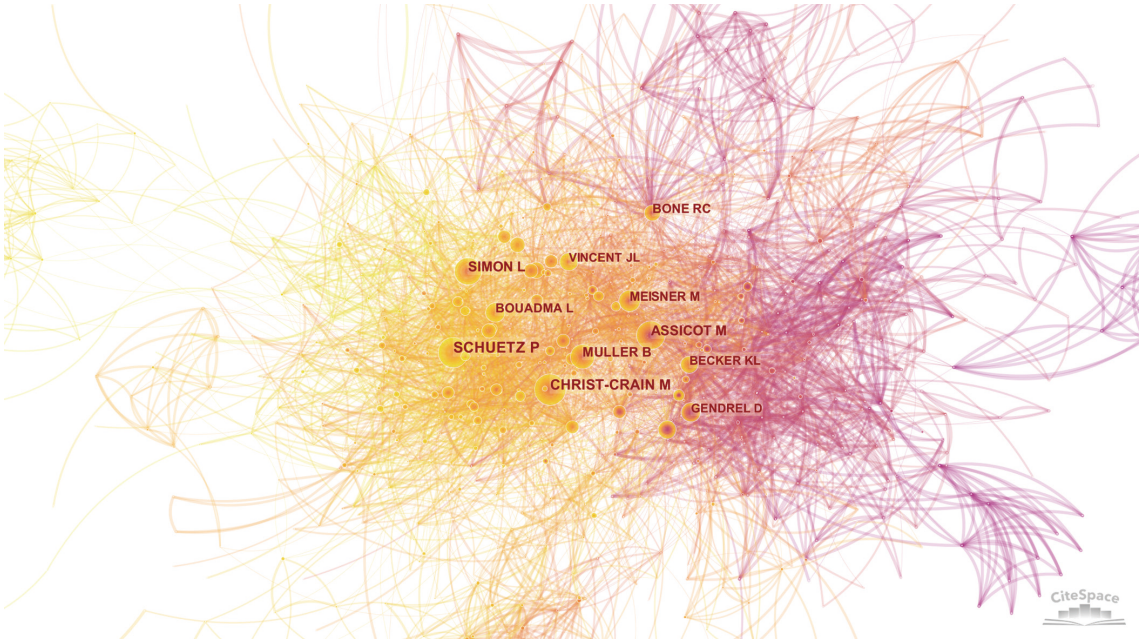

Figure 6 Author's co-cited visualization map.

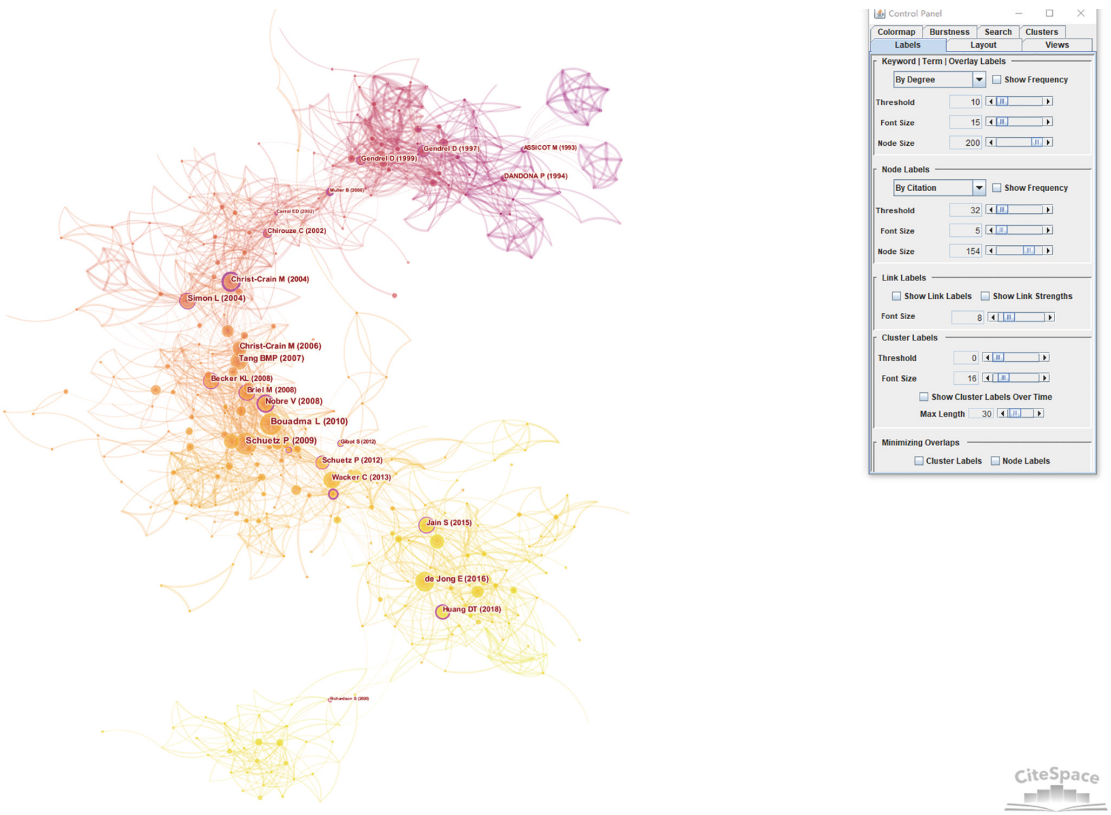

Figure 7 The document co-cited image. The figure clearly shows the chronology and centrality.

Table 11 Top 17 journals by number of published papers

Rank	Journals	Records	Percentage
1	*BMC Infectious Diseases*	90	9.0
2	*Clinical Infectious Diseases*	84	8.4
3	*Infection*	68	6.8
4	*Pediatric Infectious Disease Journal*	65	6.5
5	*European Journal of Clinical Microbiology Infectious Diseases*	59	5.9
6	*Journal of Infection*	54	5.4
7	*International Journal of Infectious Diseases*	41	4.1
8	*International Journal of Antimicrobial Agents*	38	3.8
9	*Clinical Microbiology and Infection*	30	3.0
10	*Lancet Infectious Diseases*	30	3.0
11	*Scandinavian Journal of Infectious Diseases*	30	3.0
12	*Surgical Infections*	30	3.0
13	*Diagnostic Microbiology and Infectious Disease*	27	2.7
14	*Journal of Infection and Chemotherapy*	27	2.7
15	*Expert Review of Anti-Infective Therapy*	24	2.4
16	*Enfermedades Infecciosas Y Microbiologia Clinica*	22	2.2
17	*Current Opinion in Infectious Diseases*	20	2.0

Table 12 Top 10 journals by citation frequency

Rank	Journals	Records
1	*Clin Infect Dis*	613
2	*Lancet*	457
3	*Crit Care Med*	453
4	*Intens Care Med*	388
5	*New Engl J Med*	376
6	*Jama-J Am Med Assoc*	346
7	*Crit Care*	335
8	*Am J Resp Crit Care*	304
9	*Chest*	291
10	*Lancet Infect Dis*	272

Table 13 Top 10 journals cited by centrality

Rank	Journals	Centrality
1	*Ann Intern Med*	0.08
2	*Clin Chem Lab Med*	0.08
3	*Am J Clin Pathol*	0.08
4	*Acta Paediatr*	0.07
5	*Am J Med*	0.07
6	*Brit Med J*	0.05
7	*Am J Trop Med Hyg*	0.05
8	*Brit J Anaesth*	0.05
9	*Clin Chem*	0.04
10	*Antimicrob Agents Ch*	0.04

guidelines currently recommend that bacterial infections are not supported when serum PCT <0.05 μg/L, while serum PCT >2.00 μg/L suggests sepsis, and indicates a serious condition. However, attention should be paid to other clinical manifestations and indicators, and an increase in serum PCT caused by local infection and non-infectious factors should be excluded. Dynamic serum PCT monitoring is very important for disease evaluation and prognostic judgment, especially in critically ill patients, and can guide the use of clinical antibacterial drugs. These

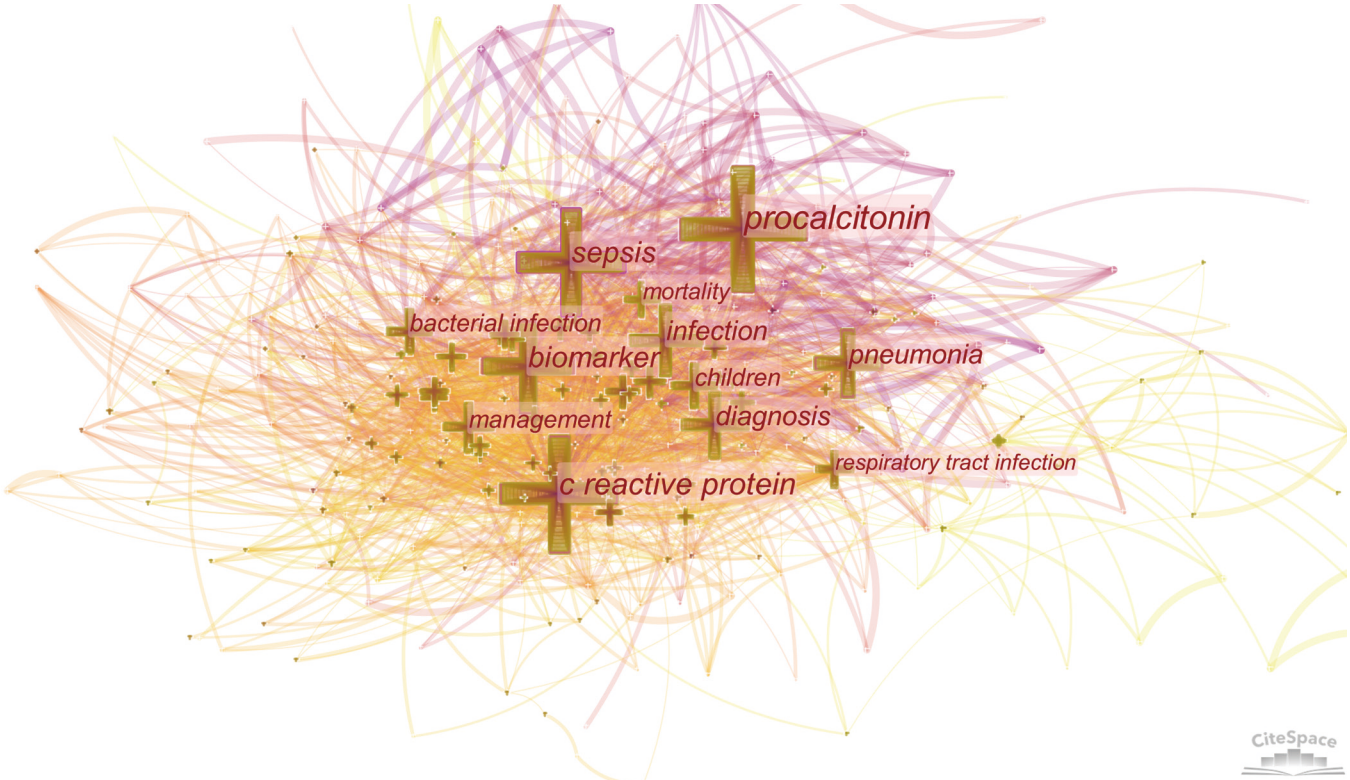

Figure 8 Keyword co-occurrence map. Note: The obvious synonyms were merged when making the keyword map. Such as: sepsis # septic shock, c reactive protein # c-reactive protein, and procalcitonin # serum procalcitonin.

Table 14 Top 10 keywords by frequency

Rank	Key words	Frequency
1	Procalcitonin	566
2	C reactive protein	338
3	Sepsis	295
4	Biomarker	260
5	Infection	182
6	Pneumonia	178
7	Diagnosis	158
8	Management	96
9	Children	93
10	Bacterial infection	92

Table 15 Top 10 keywords for centrality

Rank	Key words	Centrality
1	Sepsis	0.24
2	C reactive protein	0.20
3	Procalcitonin	0.18
4	Biomarker	0.13
5	Pneumonia	0.13
6	COVID-19	0.09
7	Infection	0.08
8	Diagnosis	0.08
9	Children	0.07
10	Interleukin 6	0.06

drugs are not used when serum PCT <0.25 μg/L excludes bacterial infection, and after treatment, when serum PCT is less than 0.50 μg/L or the peak reduction is ≥80%, and if clinical manifestations indicate, discontinuing antibacterial drugs may be considered (20,21).

The chief limitation of this research is that the scope of the document search was limited to "infectious diseases", which may have produced inconsistencies in the

Top 25 keywords with the strongest citation bursts

Keywords	Year	Strength	Begin	End	1995–2021
endotoxin	1995	3.72	1996	2004	
serum	1995	3.44	1996	1997	
interleukin 6	1995	5.16	1997	2009	
c reactive protein	1995	4.65	1997	2005	
sepsis	1995	7.17	1998	2003	
tumor necrosis factor	1995	6.92	1999	2006	
early diagnosis	1995	3.62	2000	2011	
bacterial	1995	5.48	2001	2007	
fever	1995	5.25	2001	2007	
cancer patient	1995	3.78	2005	2011	
critically ill patient	1995	5.86	2007	2013	
intensive care unit	1995	5.29	2008	2013	
low risk	1995	3.34	2008	2012	
pneumonia	1995	5.96	2009	2011	
guidance	1995	5.27	2009	2011	
metaanalysis	1995	4.26	2012	2014	
community-acquired pneumonia	1995	4.15	2013	2017	
febrile neutropenia	1995	3.75	2014	2016	
outcm	1995	3.66	2016	2021	
antibiotic stewardship	1995	4.19	2017	2019	
icu	1995	3.66	2017	2018	
impact	1995	3.49	2017	2019	
adult	1995	5.34	2018	2021	
neonatal sepsis	1995	3.67	2019	2021	
presepsin	1995	3.54	2019	2021	

Figure 9 Top 25 keywords with the strongest citation bursts.

classification of publications, and some may be missed. The results also suggest that the classification of documents should be more accurate to avoid confusion and repetition, which will be conducive to accurate retrieval and results.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1607). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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