Original Article

The application of procalcitonin in respiratory diseases: an evaluation of the current research literature

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Background: Procalcitonin (PCT) can effectively identify bacterial infections and can be used for risk prediction and antimicrobial treatment in patients with unexplained fever and critically ill patients. In this study, statistical analyses of the literature were performed to clarify the application and research status of PCT in respiratory diseases. Future research directions are discussed.

Methods: A literature search was conducted using the Science Citation Index Expanded (SCI-EXPANDED) database in the Web of Science Core Collection (WOSCC). Published literature between 1995 and February 6, 2021 were searched using the following strategies: subject term = procalcitonin; and Web of Science categories = Respiratory System. Using the Citespace software, the literature on the application of PCT in patients with respiratory diseases was analyzed in terms of annual publication status, subject distribution, country/institution distribution, journal distribution, author distribution, and keywords.

Results: A total of 542 related research literatures were identified, with the number of published papers and the number of literature citations increasing yearly. Research was mainly concentrated in the United States, China, Switzerland, and other countries, with countries such as the United Kingdom, the United States, and Canada being involved in international collaborations. Research institutions were mainly universities or hospitals such as the University Hospital of Basel, University of Barcelona, and Northwestern University. In particular, the University Hospital of Basel had extensive inter-hospital collaborations. Stolz *et al.* published many related papers, but the centrality value was low. Authors including Christ-Crain M, Schuetz P, and Stolz D were highly cited. Journals such as the *American Journal of Respiratory and Critical Care Medicine*, *Chest*, and the *European Respiratory Journal* were more influential. Keyword analysis showed that sepsis and pneumonia are the current hot topics.

Conclusions: Related papers mainly focused on respiratory infections, especially sepsis and pneumonia. There were also a small number of studies suggesting that PCT is related to tumors.

Keywords: Procalcitonin (PCT); respiratory system disease; bibliometric analysis

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Introduction

Procalcitonin (PCT) is a highly specific biomarker of infectious inflammatory responses (1). As a sensitive indicator of bacterial infection in the body, its expression increases significantly in the early stages of infections. Often, when PCT levels are elevated, parasitic infections, chronic inflammation, and autoimmune diseases are not yet obvious at clinical examinations. PCT has important clinical significance in identifying the presence of bacterial infections, especially in patients with unexplained fever and critically ill patients, risk prediction, and antimicrobial treatment guidance (2-5). Respiratory tract infections are the most common disease in clinical practice. It is often crucial to identify these bacterial infections as lung infections can easily develop into sepsis. In addition, severely ill patients often have lung infections and PCT is required as a reference for clinical diagnosis and disease monitoring (6-9). Furthermore, some studies have shown that circulating PCT levels are related to lung tumors, chronic obstructive pulmonary diseases (COPDs), asthma, and pulmonary embolisms (10-13). In 2020, PCT was widely used in coronavirus disease 2019 (COVID-19) infection management world-wide (14). This study sought to clarify the application and research status of PCT in respiratory diseases through statistical analysis of the literature and to suggest future research directions.

Methods

Database

A literature search was conducted using the Science Citation Index Expanded (SCI-EXPANDED) database in the Web of Science Core Collection (WOSCC) to analyze the application of PCT in respiratory system diseases.

Search strategy

Literature published between 1995 and February 6, 2021 were included in the search. The following search formulas were applied: (I) subject term = procalcitonin; (II) search scope, Web of science categories = Respiratory System; and (III) the intersection of the results from formulas 1 and 2.

Analysis of data

The full record of the search results and the cited references were exported in text format. The Citespace software was used to analyze the annual publication status, subject distribution, country/institution distribution, journal distribution, author distribution, and keywords of PCT in respiratory diseases.

Table 1 Analysis of the search result document types

Literature type	Record	% of 542
Article	272	50.18
Meeting abstract	160	29.52
Review	47	8.67
Editorial material	31	5.72
Letter	31	5.72
Proceedings paper	11	2.03
Early access	4	0.74
Book chapter	3	0.55
Correction	1	0.18

Results

Literature search results

There were a total of 542 related research documents (18 of which were marked with 2 types of documents, and thus, a total of 560 records were collected at the time of statistical analysis). Of these, 272 were original articles, 160 were conference abstracts, 47 were reviews, and 31 were editorial materials including 13 letters, 11 conference papers, 4 priority publications, 3 books, and 1 correction (*Table 1*). The number of related papers published annually showed an upward trend (*Table 2*, *Figure 1*). The citation frequency was 12,147 in total, the h-index count was 54, and the average number of citations per item was 22.41. The number of citations in the literature also increased yearly (*Figure 2*).

Distribution of countries and institutions

The CiteSpace V software was used to generate national visualization maps (*Figure 3*) where N=75 and E=190 (N represents the number of network nodes and E represents the number of connections) and institutional visualization maps (*Figure 4*) where N=1,000 and E=2,418. The top 5 countries with publication volume were the United States, China, Switzerland, Spain, and Germany. The top 5 centrally ranked countries were the United Kingdom, the United States, Canada, Switzerland, and

Table 2 Science Citation Index (SCI) annual distribution

Year of publication	Record	% of 542
2020	43	7.93
2019	36	6.64
2018	43	7.93
2017	44	8.12
2016	53	9.78
2015	40	7.38
2014	34	6.27
2013	35	6.46
2012	32	5.90
2011	51	9.41
2010	26	4.80
2009	33	6.09
2008	15	2.77
2007	15	2.77
2006	10	1.85
2005	10	1.85
2004	3	0.55
2003	4	0.74
2002	3	0.55
2001	5	0.92
2000	2	0.37
1999	2	0.37
1998	2	0.37
1995	1	0.18

Denmark (*Tables 3*,*4*). Institutions with a large number of publications included universities or hospitals such as the University Hospital of Basel, University of Barcelona, and Northwestern University (*Tables 5*,*6*). Authors with a large number of publications included Stolz, Mueller, and Schuetz (*Table 7*, *Figure 5*). Although author centrality was ranked, the centrality values of the top 10 authors were all lower than 0.001, suggesting that author cooperation was very scattered and not centralized. The analysis showed that Christ-Crain M, Schuetz P, Stolz D, and other authors were cited very frequently, but the centrality value was not high and the top 10 centrality ranking authors were cited relatively less than Christ-Crain M, Schuetz P, and Stolz D (*Tables 8*,*9*, *Figure 6*).

Distribution of journals

There were a total of 542 PCT respiratory-related documents, involving 54 journals, of which 14 journals had more than 10 related articles. These top 14 journals together published a total of 409 respiratory-related articles, accounting for 75.46% of the total literature (*Table 10*). The top 10 journals are listed in *Table 11* by frequency and *Table 12* by centrality of citations. Based on the above results, it can be speculated that journals such as the *American Journal of Respiratory and Critical Care Medicine*, *Chest*, and the *European Respiratory Journal* have greater influence in this field.

Keywords that reflect the research hotspots and frontiers in this field

Using the CiteSpace V software, a keyword co-occurrence

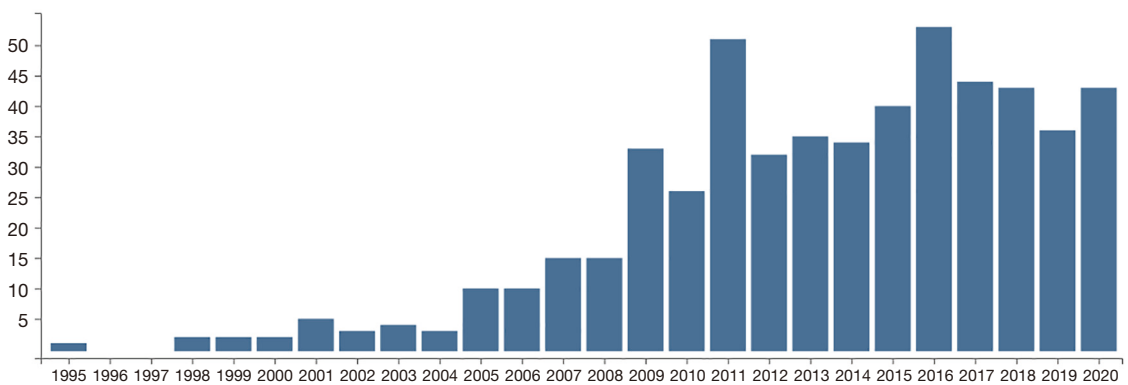

Figure 1 Annual publications. X axis represents the year of publications and Y axis represents the number of publications.

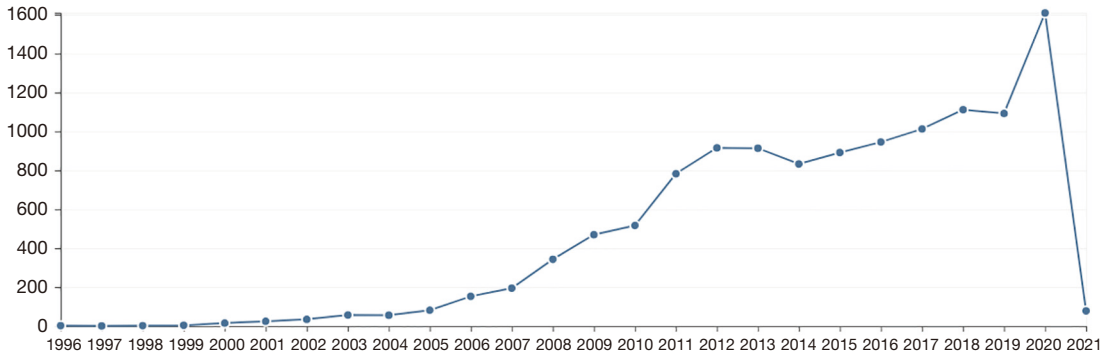

Figure 2 Annual citations. X axis represents the year of citations and Y axis represents the number of citations.

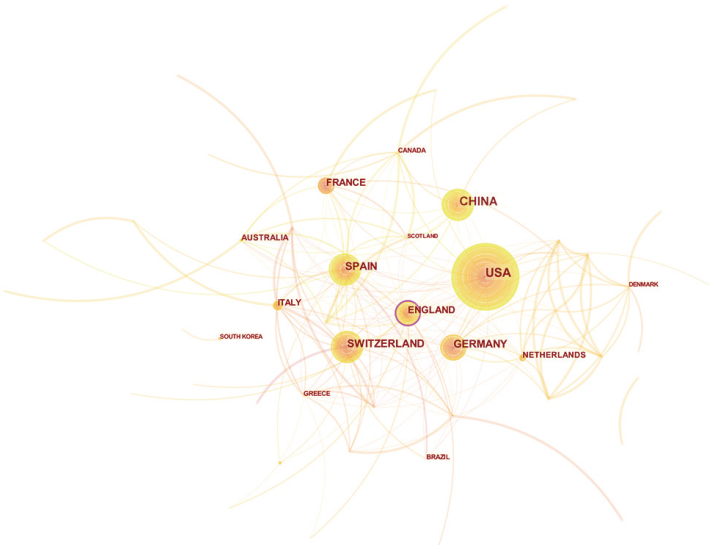

Figure 3 Country visualization map.

map was generated (*Figure* 7, N=574, E=3,327). The top 10 keywords with frequency and centrality are listed in *Tables 13* and *14*. It can be seen that sepsis, pneumonia, and infection are the current research hotspots. CiteSpace was used for burst detection of keywords with higher frequency (*Figure 8*). The results showed that the research hotspots reflected by the keywords gradually changed over time, from the early diagnosis of infection or pneumonia to evidence-based medicine.

Discussion

This study analyzed the relevant literature on the application of PCT in respiratory diseases. The number of relevant publications increases every year, and the research was mainly concentrated in the United States, the United Kingdom, Europe. In addition, a significant number of studies in this field have been conducted in China. However, there have been few international cooperation studies. Moreover, the research has been mainly limited to several research teams in several university research institutions or hospitals. Although these research teams have a large number of publications, they have relatively few international collaborations. The related literature was mainly published in several professional journals. These results suggested that the application of PCT in respiratory diseases has received extensive attention, but research in related fields is still relatively limited worldwide. Biomarkers are an important advancement in modern medicine. There is much evidence supporting classical markers after decades

Figure 4 An institution visualization map.

Table 3 The top 10 countries based on publication

No.	Country	Frequency
1	USA	122
2	China	56
3	Switzerland	55
4	Spain	49
5	Germany	47
6	England	37
7	France	34
8	Italy	21
9	Netherlands	18
10	Australia	17

USA, United State of America.

Table 4 The top 10 countries based on centrality

No.	Country	Centrality
1	England	0.26
2	USA	0.10
3	Canada	0.08
4	Switzerland	0.07
5	Denmark	0.06
6	Germany	0.06
7	Spain	0.06
8	Belgium	0.04
9	Australia	0.04
10	Poland	0.03

of continuous research (15,16). For example, C-reactive protein (CRP) has landmark significance in detecting inflammation (17,18), and troponin has an irreplaceable role in diagnosing myocardial infarction (19,20). Therefore, researchers should carry out more clinical studies, especially multi-center studies, to observe the relationship between PCT and respiratory diseases, in particular, respiratory infectious diseases.

Through the analysis of keywords, the current research hotspots in the field of respiratory diseases appear to be sepsis, pneumonia, and infections. However, according to in-depth analysis of the literature, increasingly, more and more

Table 5 The top 10 institutions based on publication

No.	Institution	Frequency
1	University of Basel Hospital	27
2	University of Barcelona	18
3	University of Basel	13
4	Northwestern University	13
5	Kantonsspital Aarau	10
6	Harvard University	9
7	University of Western Australia	7
8	University Medicine Centre Utrecht	7
9	Hannover Medical School	7
10	University of California San Diego	6

Table 6 The top 10 institutions based on centrality

No.	Institution	Centrality
1	University of Basel Hospital	0.12
2	UMass Memorial Medical Centre	0.08
3	University of Barcelona	0.07
4	Harvard University	0.05
5	University of California San Diego	0.05
6	Northwestern Univ	0.04
7	Massachusetts General Hospital	0.04
8	Kantonsspital Liestal	0.04
9	Johns Hopkins University	0.04
10	Brahms AG	0.04

Table 7 The top 10 authors based on publications

No.	Authors	Number
1	Stolz D	19
2	Mueller B	19
3	Schuetz P	17
4	Tamm M	15
5	Torres A	14
6	Christcrain M	13
7	Menendez R	12
8	Bingisser R	7
9	Welte R	6
10	Pertseva T	6

studies are examining the relationship between PCT and other diseases of the respiratory system, such as the value of PCT in the diagnosis and prognosis of lung cancer patients (10,11,21-24). Studies have shown that even if patients with lung cancer are not co-infected, the average serum PCT levels were higher than that of non-infected patients without lung cancer, and the higher the PCT levels, the worse the prognosis (10,22,23). Other reports have also demonstrated that serum PCT levels can help distinguish between pulmonary embolism and community-acquired pneumonia (25). In contrast, Ateş *et al.* reported that compared with PCT and other indicators, the ratio of neutrophils to lymphocytes to D-dimers is more helpful in distinguishing pulmonary embolism from community-acquired pneumonia (12). Other studies have shown that in children with severe asthma, serum PCT levels were less than 0.5 ng/mL in 75% of children. Further analysis showed that there was no close relationship between the lung infiltration on chest radiograph and the increase in PCT (13). In patients with COPD, elevated PCT levels can help distinguish between acute onset and stable COPD (26,27). However, a literature review suggested that the current available evidence is still relatively weak, and further research is needed. The cut-off value of PCT is yet to be determined to assist in the clinical determination of acute COPD (28). Although these studies have not yet become the mainstream of research, there is an increasing awareness that PCT is not only related to respiratory infections, but may also be related to lung tumors and other airway diseases. Further in-depth research and increased collaboration between institutions and countries/regions will be necessary to develop strong evidence-based medical data.

This study had certain limitations. Due to the methodological limitations of the study, only a basic analysis of the relevant literature could be performed, and thus, individual studies may have been omitted due to different classification methods. Concurrently, due to the large number of included articles, it was not possible to carry out detailed analyses and statistics on each document. Therefore, the present study may only reflect a macroscopic view of the relevant research field. Finally, this research is limited to literature analysis, and it may be more meaningful to add some clinical research results.

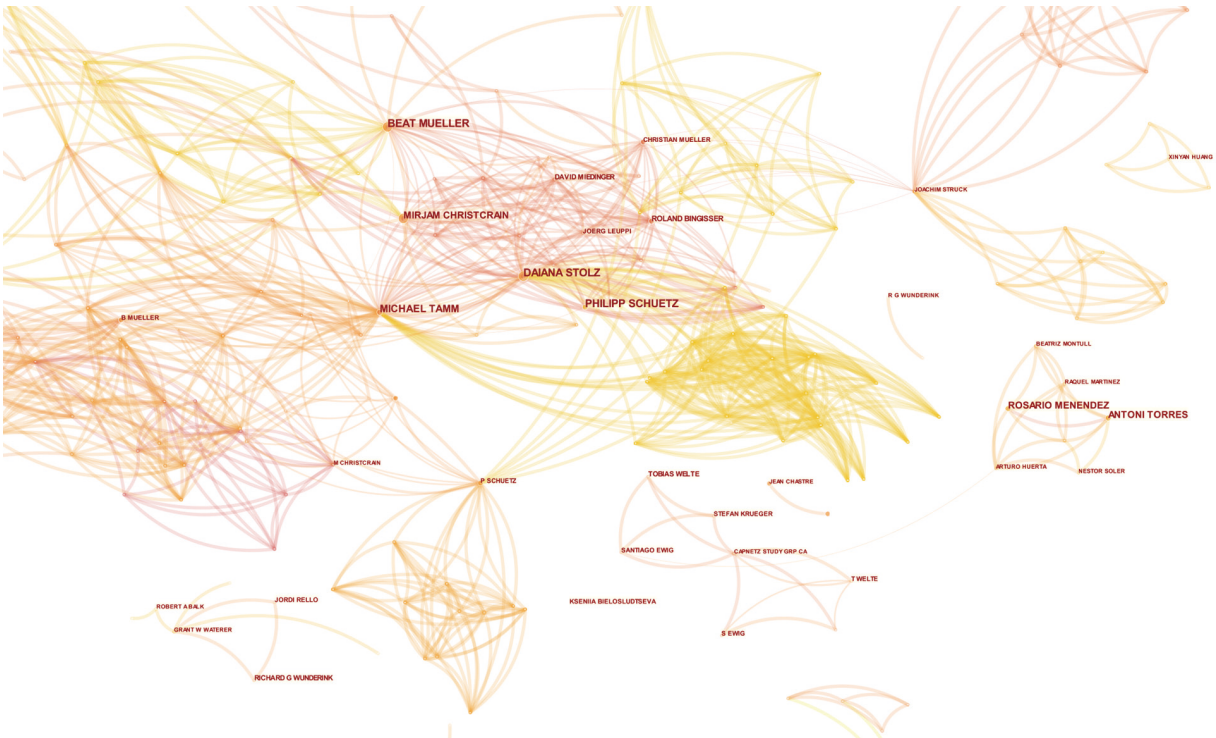

Figure 5 A visualization map of authors.

Table 8 Top 10 co-cited authors based on frequency

No.	Authors	Frequency
1	Christ-Crain M	142
2	Schuetz P	119
3	Stolz D	90
4	Kruger S	60
5	Muller B	57
6	Fine MJ	56
7	Mandell LA	49
8	Menendez R	47
9	Niederman MS	46
10	Luyt CE	43

Table 9 Top 10 co-cited authors based on centrality

No.	Authors	Centrality
1	Assicot M	0.23
2	Bone RC	0.17
3	Anthonisen NR	0.15
4	Aouifi A	0.13
6	Bernard GR	0.13
7	Reith HB	0.11
8	Akgun S	0.11
9	Becker KL	0.1
10	Brunkhorst FM	0.1
11	Gibot S	0.09

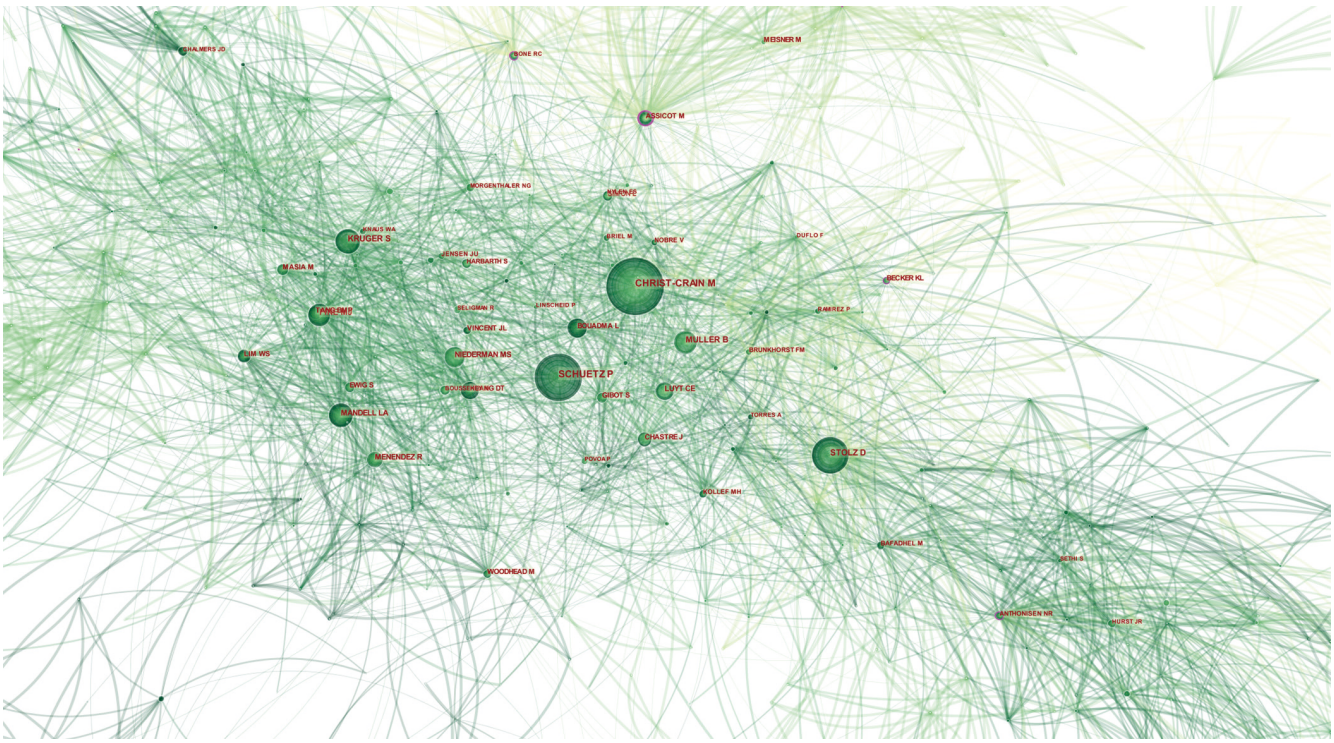

Figure 6 A visualization map of co-cited authors.

Table 10 The top 14 journals in terms of publications

No.	Journals	Record	% of 542
1	*American Journal of Respiratory and Critical Care Medicine*	95	17.53
2	*Chest*	82	15.13
3	*European Respiratory Journal*	71	13.10
4	*Respirology*	40	7.38
5	*Thorax*	21	3.88
6	*Current Opinion in Pulmonary Medicine*	17	3.14
7	*Annals of Thoracic Surgery*	11	2.03
8	*Pediatric Pulmonology*	11	2.03
9	*Respiratory Research*	11	2.03
10	*BMC Pulmonary Medicine*	10	1.85
11	*International Journal of Chronic Obstructive Pulmonary Disease*	10	1.85
12	*Respiratory Care*	10	1.85
13	*Respiratory Medicine*	10	1.85
14	*Revue Des Maladies Respiratoires*	10	1.85

Table 11 The top 10 journals in terms of citation

No.	Journals	Frequency
1	*Chest*	267
2	*Am J Resp Crit Care*	253
3	*Eur Respir J*	216
4	*Lancet*	211
5	*New Engl J Med*	204
6	*Crit Care Med*	197
7	*Clin Infect Dis*	182
8	*Thorax*	170
9	*Intens Care Med*	169
10	*Crit Care*	161

Table 12 The top 10 journals in terms of centrality

No.	Journals	Centrality
1	*Am Rev Respir Dis*	0.14
2	*Acta Paediatr*	0.12
3	*Am J Emerg Med*	0.10
4	*Eur J Clin Microbiol*	0.10
5	*BMJ-Brit Med J*	0.09
6	*Ann Intern Med*	0.07
7	*Am Surgeon*	0.06
8	*Blood*	0.06
9	*Clin Chem Lab Med*	0.06
10	*Am J Med*	0.06

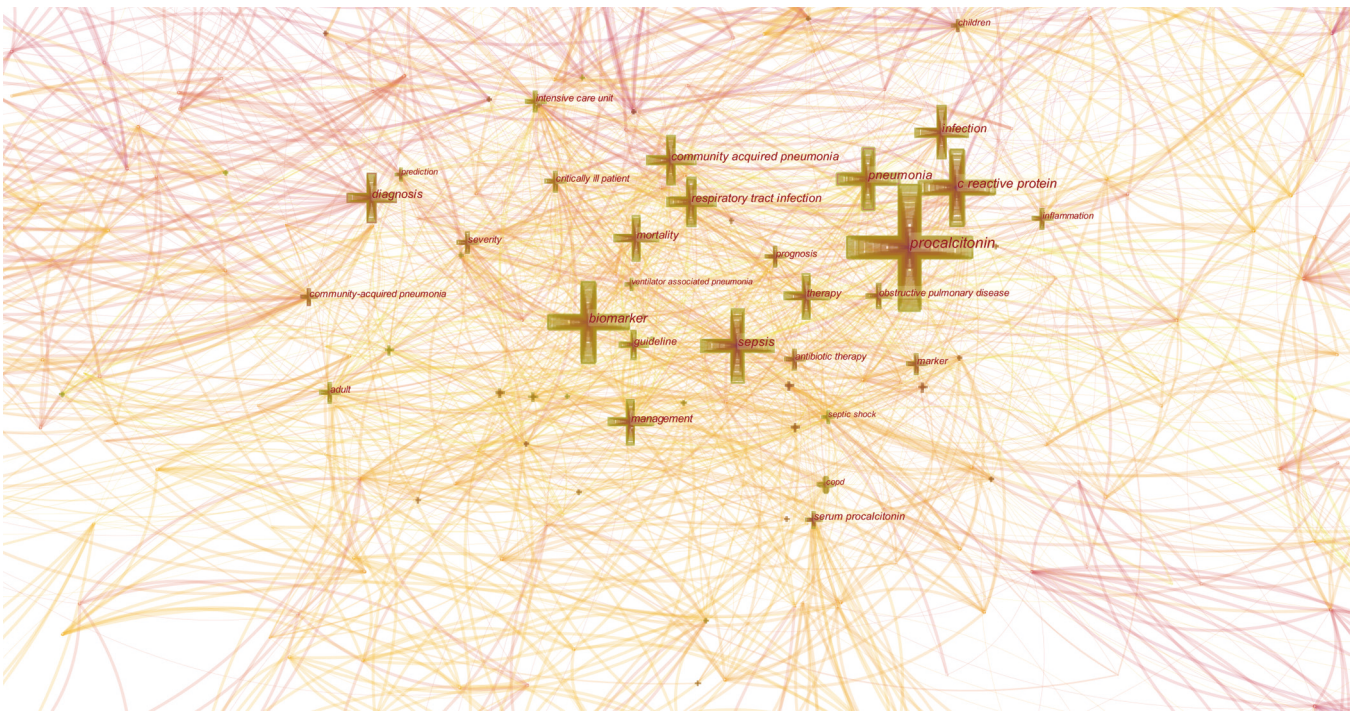

Figure 7 Keyword visualization map generated by the CiteSpace V software.

Table 13 The top 10 keywords in terms of frequency

No.	Keywords	Frequency
1	Procalcitonin	227
2	CRP	112
3	Biomarker	108
4	Sepsis	87
5	Pneumonia	82
6	Infection	68
7	CAP	64
8	Diagnosis	63
9	Respiratory tract infection	62
10	Mortality	55

CAP, community-acquired pneumonia; CRP, C reaction protein.

Table 14 The top 10 keywords in terms of centrality

No.	Keywords	Centrality
1	Diagnosis	0.14
2	Children	0.14
3	Pneumonia	0.11
4	CAP	0.11
5	CRP	0.10
6	Expression	0.10
7	Mechanical ventilation	0.10
8	Serum procalcitonin	0.09
9	Intensive care unit	0.08
10	Inflammation	0.08

CAP, community-acquired pneumonia; CRP, C reaction protein.

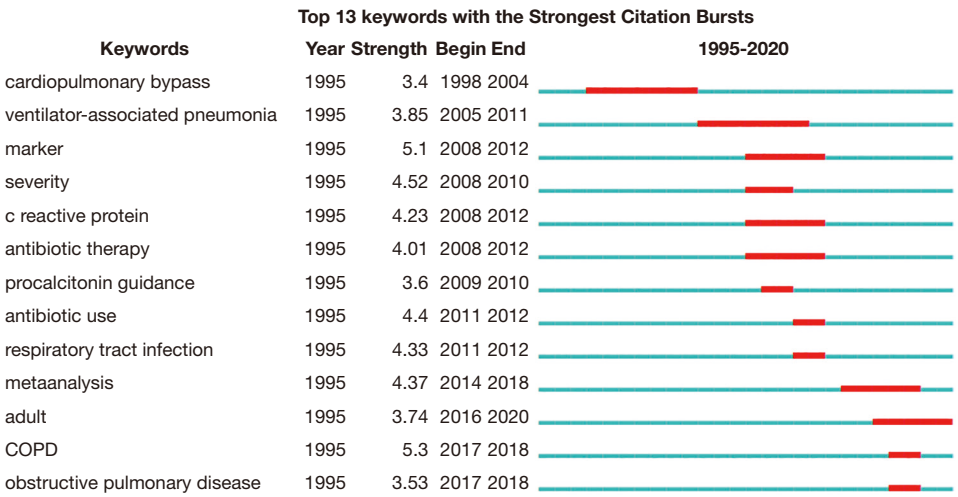

Figure 8 The burst test of keywords using CiteSpace.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-840). 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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