



A bibliometric analysis of the application of procalcitonin in patients in the intensive care unit

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Background: Patients in the intensive care unit (ICU) often have serious infections, and anti-infection treatment is vital for these patients. Procalcitonin (PCT) is often used to identify bacterial infections and monitor the effectiveness of anti-infection treatments. This study aims to analyze the current research hotspots of the application of PCT in ICU patients, and to suggest future research directions.

Methods: The Science Citation Index Expanded (SCI-EXPANDED) database in the Web of Science Core Collection (WOSCC) was used as the data source to search literature from 1995 to February 6, 2021. The search strategy was subject term = procalcitonin AND Web of Science categories = Critical Care Medicine. Using CiteSpace software, literature on the application of PCT in ICU patients was analyzed.

Results: A total of 1,243 papers, including 665 (53.5%) original articles, 87 (7.0%) reviews, 93 (7.5%) letters, 297 (23.9%) conference abstracts, and 101 (8.1%) other articles, were analyzed. The citation frequency was 40,442, the h-index was 96, and the average number of citations per item was 32.54. Research was mainly from the United States, Germany, France, and Spain, amongst others. The research institutions were mainly Univ Basel Hosp, Univ Pittsburgh, and Univ Hosp Geneva. Authors including Schuetz P made more contributions. Critical Care Medicine, Intensive Care Medicine, and Critical Care were important journals in this field of research. The keywords with the highest frequency were PCT, sepsis, and infection, and the more central ones were PCT, inflammation, septic shock, and C-reactive protein. The keywords with the strongest citation bursts were PCT, cytokine, and serum.

Conclusions: Papers are mainly published in critical care medical journals. The countries, institutions, and authors that carry out research are relatively limited. The current hot spots are still inflammation, infection, and shock, especially the management and prognosis prediction of critically ill patients.

Keywords: Procalcitonin (PCT); intensive care; bibliometric analysis

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Introduction

In clinical practice, critically ill patients can be roughly divided into two categories: infectious patients and non-infectious patients. The former includes primary severely infected patients, severely ill patients whose condition is aggravated by infection, and severely ill patients with secondary infections. Infection diagnosis and condition monitoring are important in critical care medicine, especially differential diagnosis and treatment effect monitoring of infected patients. Previously, the indicators commonly used for the diagnosis of infection in critically ill patients included white blood cells, C-reactive protein, and erythrocyte sedimentation rate. In recent years, procalcitonin (PCT) has been widely used in clinical practice, especially in the differential diagnosis of infection and disease monitoring (1-3). In non-infectious severe diseases, the value of PCT is controversial. Studies have found that for trauma patients, the initial peak level of PCT can well predict the risk of sepsis, multiple organ failure, and death (4). It can also predict the risk of acute kidney injury after brain trauma (5), but for patients with acute ST-segment elevation myocardial infarction, PCT cannot predict the risk of death during hospitalization after cardiogenic shock (6). Many guidelines currently recommend the use of PCT to guide clinical diagnosis and disease monitoring, however, some studies believe that the relevant evidence is still relatively weak, and further in-depth research is needed (7). This study is based on the Science Citation Index Expanded (SCI-EXPANDED) database in the Web of Science Core Collection (WOSCC), and analyzes the relevant research literature on the application of PCT in patients in the intensive care unit in recent years. We aim to understand the current research status and provide suggestions for future research.

Methods

Data resource

The SCI-EXPANDED database in the WOSCC was used as the data source for searches.

Search strategy

The search subject terms (TOPIC) were as follows: step 1, use procalcitonin to search in Web of Science categories; step 2, search "Critical Care Medicine" in Web of Science categories; step 3, get the results from the intersection of

Table 1 Analysis of document types from the search results

Literature type	Record	% of 1,243
Article	665	53.50
Meeting abstract	297	23.89
Editorial material	93	7.48
Letter	93	7.48
Review	87	7.00
Proceedings paper	11	0.88
Correction	7	0.56
Early access	1	0.08
News item	1	0.08

step 1 and 2; publication time: 1995 to now (latest update date: 2021-02-06); index: SCI-EXPANDED.

Analysis

The full record of the search results and the cited references were exported in text format, and CiteSpace software was used to analyze the annual publication status, subject distribution, country/institution distribution, journal distribution, author distribution, and keywords listed in the literature regarding critically ill patients.

Statistical analysis

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

Results

Characteristics of the literature

There were a total of 1,243 research documents, including 665 articles, 87 review articles, 93 editorial materials, 93 letters, 297 conference abstracts, 11 conference documents, 7 revisions, 1 priority publication article, 1 news item article, and 1 annotation article (Tables 1,2; Figure 1). The citation frequency was 40,442 times, the h-index was 96, and the average number of citations per item was 32.54 (Figure 2).

The distribution of the research

We used CiteSpace V software to generate a national

Table 2 SCI annual distribution

Year of publication	Record	% of 914
2020	118	12.91
2019	71	7.77
2018	63	6.89
2017	69	7.55
2016	51	5.58
2015	47	5.14
2014	54	5.91
2013	56	6.13
2012	57	6.24
2011	49	5.36
2010	48	5.25
2009	37	4.05
2008	38	4.16
2007	31	3.39
2006	33	3.61
2005	24	2.63
2004	14	1.53
2003	9	0.98
2002	14	1.53
2001	13	1.42
2000	4	0.44
1999	6	0.66
1998	2	0.22
1997	2	0.22
1996	2	0.22
1995	2	0.22

SCI, scientific citation index.

visualization map, as shown in *Figure 3* (N=120, E=343, N represents the number of network nodes, E represents the number of connections). The institutional visualization map is shown in *Figure 4* (N=1,000, E=2,418). The results revealed that the top 5 countries with the highest volume of postings were the United States, Germany, France, Spain, and China. The top 5 centrally ranked countries were the United States, Italy, Spain, Germany, and France (*Tables 3,4, Figure 3*). The institutions with a large number of publications included Univ Basel Hosp, Univ Jena,

Univ Pittsburgh, and other university hospitals, while the organizations that had cooperated more extensively included Univ Basel Hosp, Univ Amsterdam, and Hannover Med Sch (*Tables 5,6, Figure 4*). There were 10 first authors who had published more than 10 papers, especially Schuetz and Mueller. Not only did they have a larger number of papers, their papers were also published in more authoritative journals, such as N Engl J M and Lancet, and their cooperation with other researchers and research institutions was also more extensive (*Tables 7,8, Figure 5*). In terms of reference citations, the research of authors such as Bone, Vincent, and Schuetz were cited more frequently, especially the citations of authors such as Meisner and Becker which were more concentrated (*Tables 9,10, Figure 6*). The above results show that countries such as the United States, Germany, France, and Spain are more advanced in this research field. In particular, research institutions such as Univ Basel Hosp have produced more results. Furthermore, the work of researchers such as Schuetz and Mueller is more influential.

Distribution of journals

There were a total of 1,243 PCT critical illness-related documents, involving 35 journals. Among them, there were 10 journals with more than 20 articles in *Table 11*, and a total of 665 journal articles accounting for 53.5% of the total literature (*Table 11*). The top 10 journals are listed in *Table 8* by centrality and frequency of citations. It can be seen from *Tables 11-13* that *Critical Care Medicine*, *Intensive Care Medicine*, and *Critical Care* were significantly higher than other journals in terms of the number of publications and the number of citations. Based on the above analysis results, it can be inferred that the journals including *Critical Care Medicine*, *Intensive Care Medicine* and *Critical Care* have great influence in this field.

Keywords reflecting the research hotspots and frontiers in this field

With the help of CiteSpace V software, a keyword co-occurrence map was generated (*Figure 7*: N=729, E=5,420). The top 10 keywords by frequency and centrality are listed in *Tables 14* and *15*. It can be seen that PCT, sepsis, and infection were the focus of related research. We further used CiteSpace to detect bursts of keywords with high frequency, as shown in *Figure 8*. Combined with keyword references, hotspots gradually changed over time. In recent

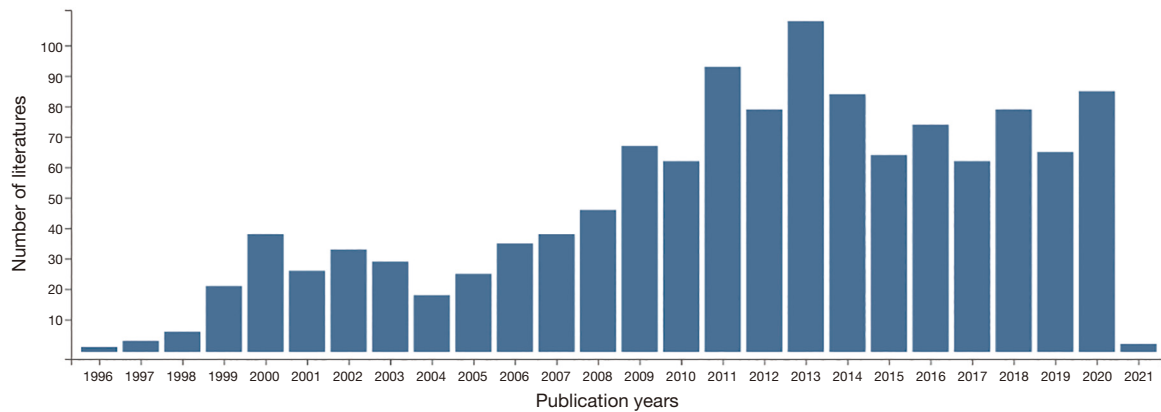


Figure 1 Annual publications.

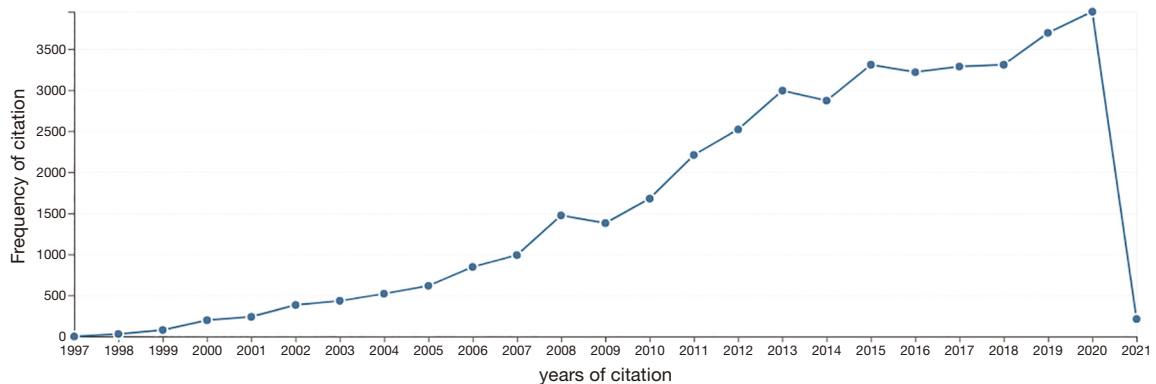


Figure 2 Annual citations.

years, hotspots included biomarkers, disease management, meta-analysis, and presepsin.

Discussion

PCT is a propeptide of calcitonin and a glycoprotein with hormonal activity. It consists of 116 amino acids and has a relative molecular weight of 13,000. Human PCT is regulated by the calcitonin I gene on chromosome 11. It is expressed in a variety of tissues, but the specific location is mainly affected by infection and pathogen types (8). In healthy people or when there is no bacterial infection, PCT is mainly synthesized by the neuroendocrine pathway, that is, the calcitonin I gene expressed by thyroid parafollicular cells and pulmonary neuroendocrine cells is regulated. At this time, the expression level is very low (<0.1 pg/L). Generally, it does not increase during viral infection. The

main reason is that IFN γ released by the human body can directly block the synthesis of PCT. When there is bacterial infection, various tissues outside the thyroid can be induced to express calcitonin I, leading to PCT being released into the blood in large quantities (9). The process is divided into 2 phases: the first is the early phase (2–3 h after infection), which is mainly caused by bacterial infection itself or endotoxin stimulation; and the latter is the delayed phase, which is mainly caused by inflammatory factors (such as TNF- α , IL-1, IL-2, IL-6) which initiate a large amount of synthesis and release of PCT in various tissues outside the thyroid (10). The delayed phase is also an important reason for the peak of PCT within 12–24 h after systemic bacterial infection (11). The biological characteristics of PCT provide an important theoretical basis for the identification of infections and different pathogen infections, especially bacterial and viral infections (12).

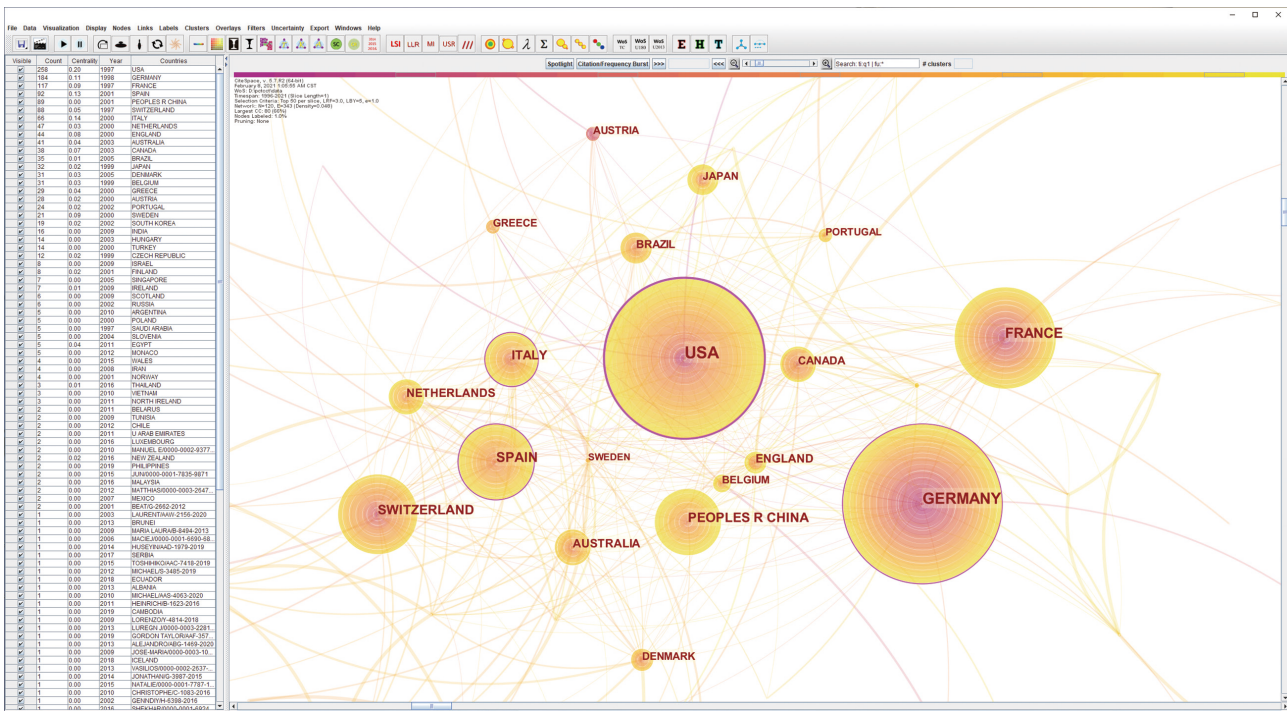


Figure 3 Country visualization map.

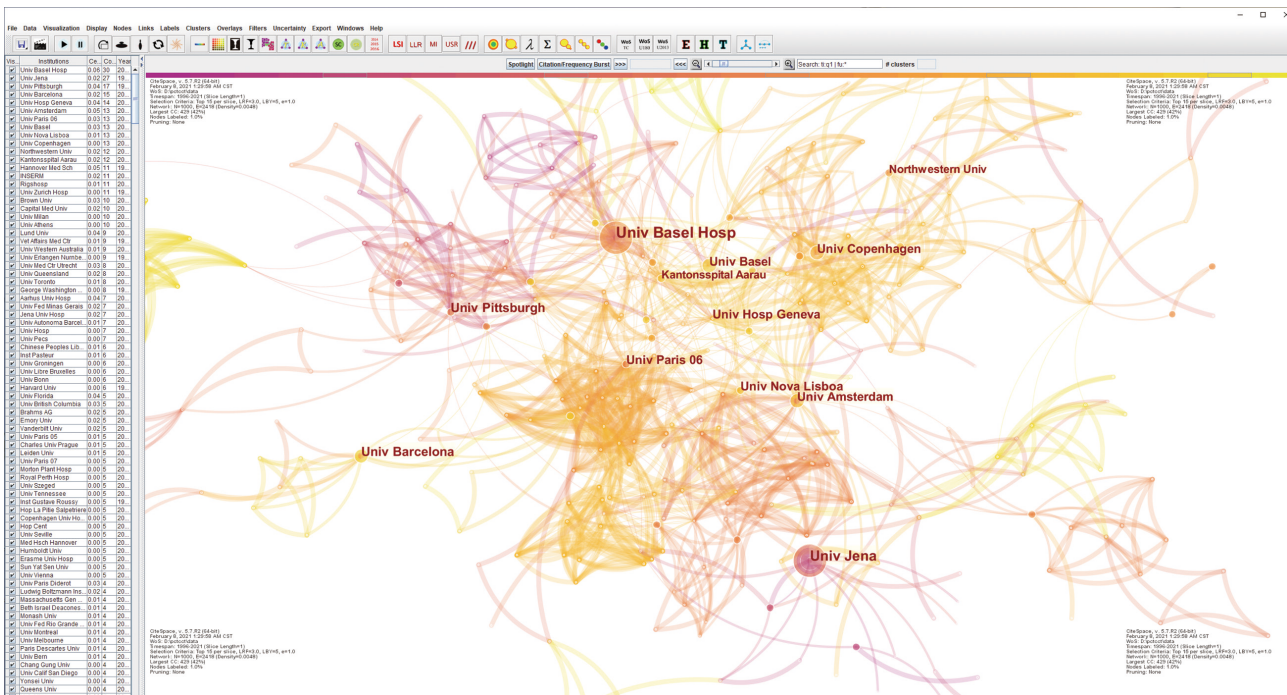


Figure 4 Institution visualization map.

Table 3 Top 10 countries by publication frequency

No.	Country	Frequency
1	USA	258
2	Germany	184
3	France	117
4	Spain	92
5	China	89
6	Switzerland	88
7	Italy	66
8	Netherlands	47
9	England	44
10	Australia	41

USA, United States of America.

Table 4 Top 10 countries by centrality

No.	Country	Centrality
1	USA	0.2
2	Italy	0.14
3	Spain	0.13
4	Germany	0.11
5	France	0.09
6	Sweden	0.09
7	England	0.08
8	Canada	0.07
9	Switzerland	0.05
10	Australia	0.04

USA, United States of America.

Table 5 Top 10 institutions by publication

No.	Institution	Frequency
1	Univ Basel Hosp	30
2	Univ Jena	27
3	Univ Pittsburgh	17
4	Univ Barcelona	15
5	Univ Hosp Geneva	14
6	Univ Paris 06	13
7	Univ Nova Lisboa	13
8	Univ Basel	13
9	Univ Amsterdam	13
10	Univ Copenhagen	13

Table 6 Top 10 institutions by centrality

No.	Institution	Centrality
1	Univ Basel Hosp	0.06
2	Univ Amsterdam	0.05
3	Hannover Med Sch	0.05
4	Univ Pittsburgh	0.04
5	Univ Hosp Geneva	0.04
6	Lund Univ	0.04
7	Aarhus Univ Hosp	0.04
8	Univ Florida	0.04
9	Shanghai Jiao Tong Univ	0.04
10	Univ Klinikum Aachen	0.04

Table 7 Top 10 authors by publication frequency

No.	Authors	Frequency
1	Schuetz P	25
2	Mueller B	23
3	Meisner M	17
4	Reinhart K	16
5	Christcrain M	15
6	Povoa P	14
7	Reinhart K	14
8	Stolz D	13
9	Tamm M	12
10	Torres A	11

Table 8 Top 5 authors by centrality

No.	Authors	Centrality
1	Schuetz P	0.01
2	Mueller B	0.01
3	Nobre V	0.01
4	Struck J	0.01
5	Meierhellmann A	0.01

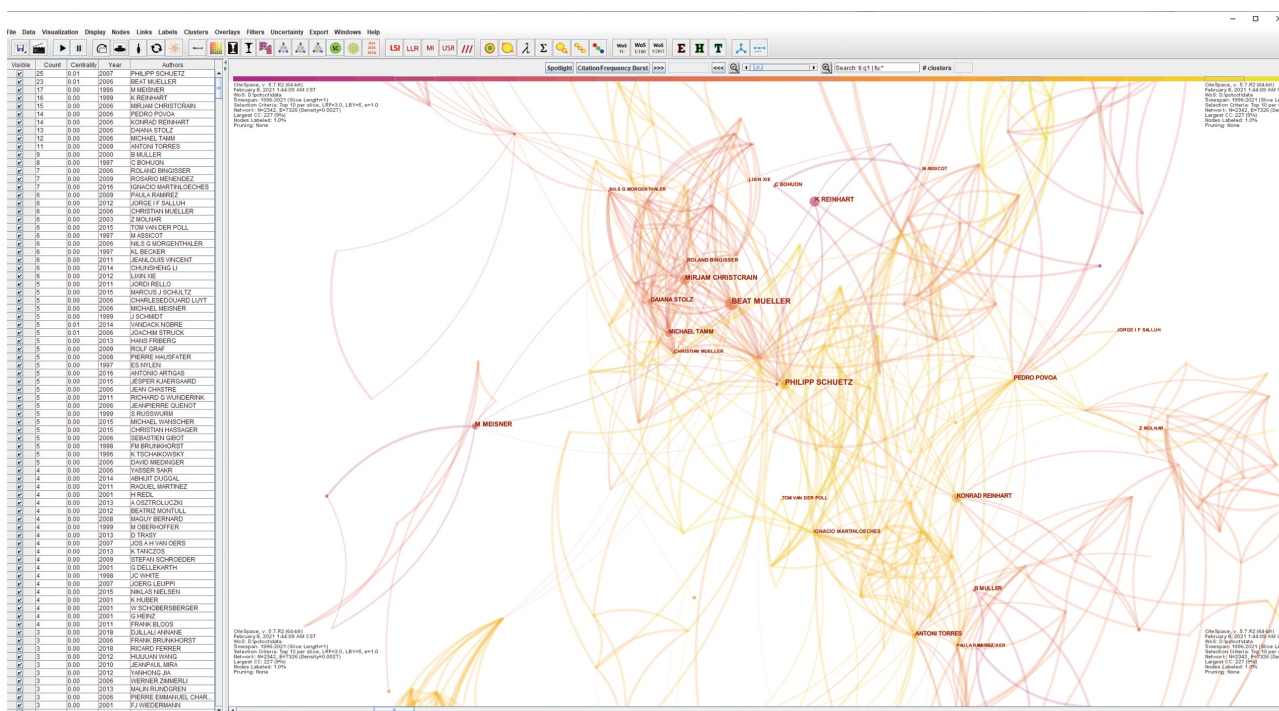


Figure 5 Visualization map of authors.

Table 9 Top 10 co-cited authors by frequency

No.	Authors	Frequency
1	Bone RC	232
2	Vincent JL	230
3	Schuetz P	194
4	Christ-Crain M	173
5	Meisner M	134
6	Muller B	110
7	Dellinger RP	110
8	Assicot M	106
9	Bouadma L	104
10	Levy MM	92

Table 10 Top 10 co-cited authors by centrality

No.	Authors	Centrality
1	Meisner M	0.46
2	Becker KL	0.38
3	Burke DL	0.33
4	Peter B	0.33
5	Assicot M	0.28
6	Davis TME	0.19
7	Bone RC	0.12
8	Christ-Crain M	0.06
9	Vincent JL	0.05
10	Kumar A	0.05

In recent years, researchers have conducted a large number of studies in critically ill patients to observe the significance of PCT on the judgment of the severity of the disease, prognosis, and the use of antibiotics (13-15). The results found that PCT has a good reference value in emergency patients, critically ill patients, and in guiding the use of antibiotics. Many expert consensuses have been

issued (16-19). However, these consensuses mainly focus on the guidance of PCT for the use of antibiotics. Regarding the significance of monitoring PCT in critically ill patients, some large-scale systematic reviews and meta-analyses have been published, further analyzing the application value of PCT from the perspective of evidence-based medicine (20-24). In this study, we found that the clinical application

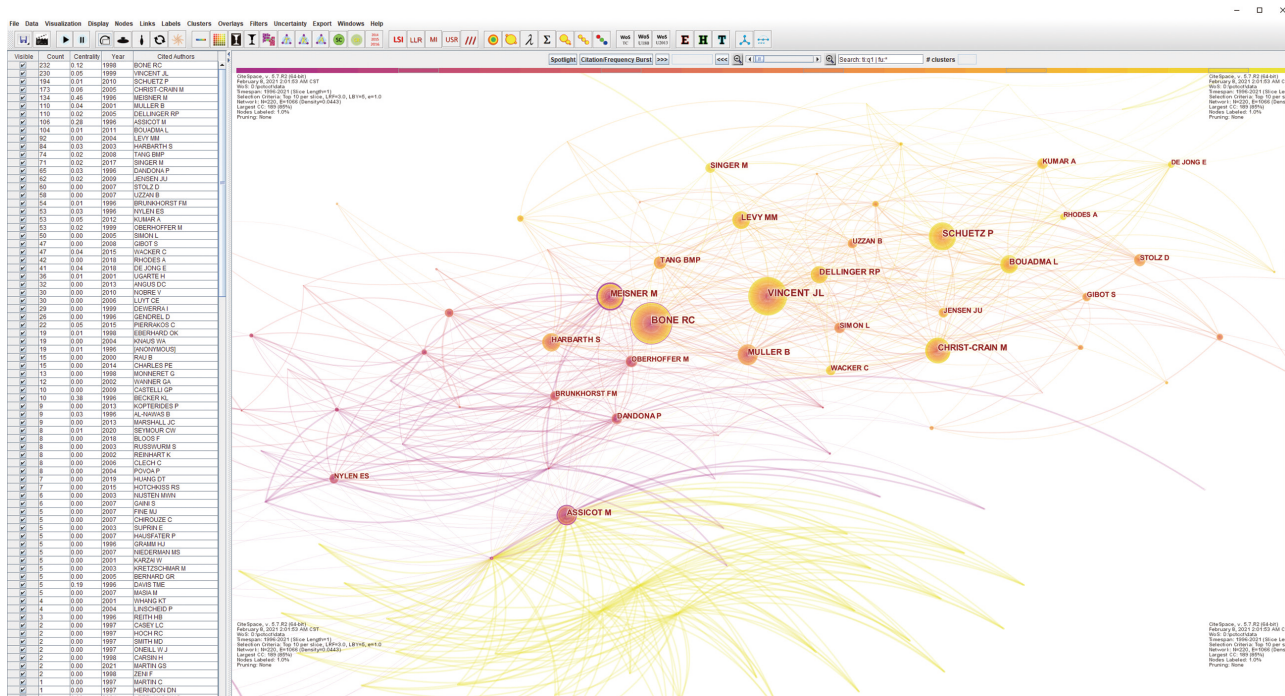


Figure 6 Visualization map of co-cited authors.

Table 11 Top 10 journals by publication

No.	Journals	Record	% of 1,243
1	<i>Critical Care Medicine</i>	248	19.95
2	<i>Intensive Care Medicine</i>	212	17.06
3	<i>Critical Care</i>	189	15.21
4	<i>American Journal of Respiratory and Critical Care Medicine</i>	95	7.64
5	<i>Shock</i>	83	6.68
6	<i>Chest</i>	82	6.60
7	<i>Journal of Critical Care</i>	76	6.11
8	<i>Burns</i>	26	2.09
9	<i>Annals of Intensive Care</i>	25	2.01
10	<i>Pediatric Critical Care Medicine</i>	21	1.69

of PCT has gradually developed from the early diagnosis of bacterial infections to the current diagnosis of disease severity, prognostic indications, and guidance on the use of antibacterial drugs. Furthermore, related research is mainly concentrated in Europe and the United States. In several developed countries, such as the United States, Germany, and France, the institutions and researchers participating

in the research are relatively concentrated. These results reflect that the application of PCT in the intensive care unit is becoming more extensive and in-depth, and the value of its clinical application is also increasing. On the other hand, it also reflects that there is a problem of geographical imbalance in related research, especially in developing regions such as Asia, Africa, and Latin America, which have conducted

Table 12 Top 10 journals by citation

No.	Journals	Frequency
1	<i>Crit Care Med</i>	823
2	<i>Intens Care Med</i>	647
3	<i>Crit Care</i>	579
4	<i>Chest</i>	476
5	<i>Am J Resp Crit Care</i>	474
6	<i>Lancet</i>	438
7	<i>New Engl J Med</i>	409
8	<i>Jama-J Am Med Assoc</i>	402
9	<i>Clin Infect Dis</i>	348
10	<i>Shock</i>	250

Table 13 Top 10 journals by centrality

No.	Journals	Centrality
1	<i>Ann Intern Med</i>	0.21
2	<i>Am J Med</i>	0.18
3	<i>Shock</i>	0.09
4	<i>Anesthesiology</i>	0.09
5	<i>Arch Intern Med</i>	0.08
6	<i>Arch Surg-Chicago</i>	0.08
7	<i>J Infect Dis</i>	0.07
8	<i>Blood</i>	0.07
9	<i>Acta Endocrinol-Cop</i>	0.07
10	<i>Burns</i>	0.06

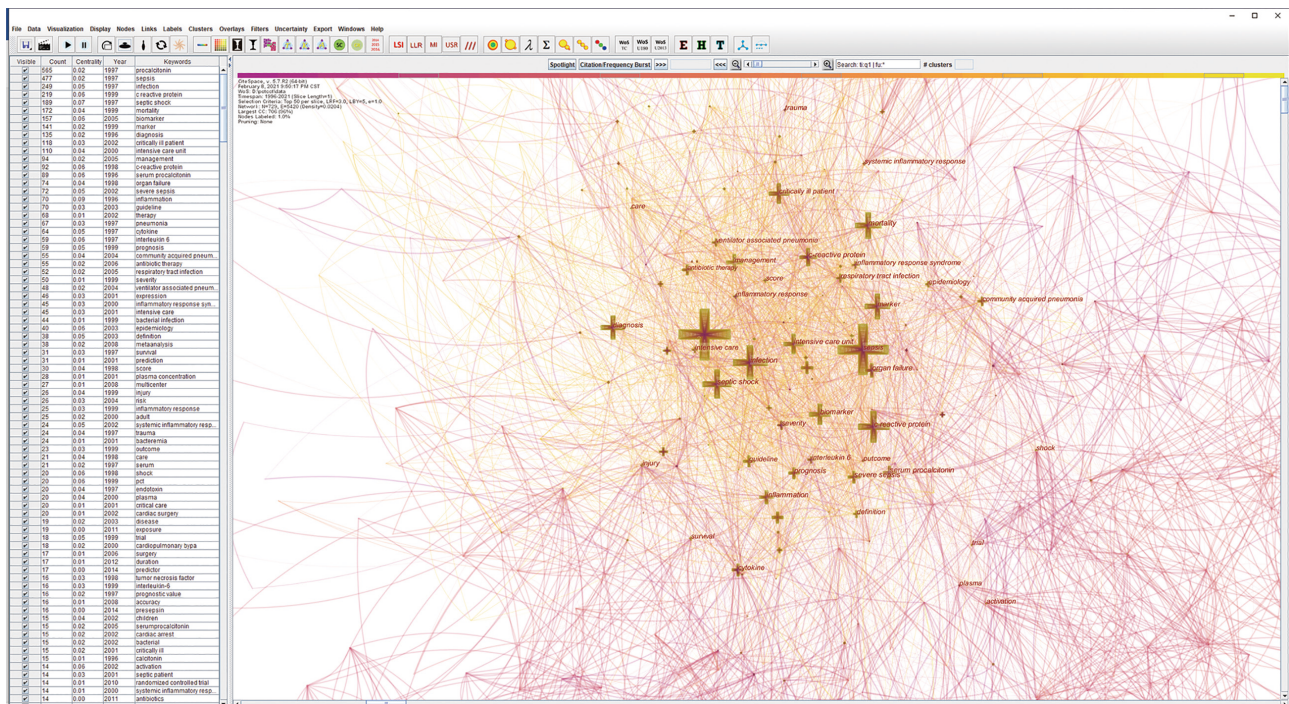


Figure 7 Keyword visualization map generated by CiteSpace V software.

fewer studies. The economic cost of PCT testing is not high, and the medical level of some developing countries around the world is relatively low, and making full use of PCT to guide severe cases, especially the diagnosis and treatment of infected patients, has a good cost-benefit ratio (25,26).

Through our analysis, we also found that not only the countries and regions participating in the research were

relatively concentrated, but also the research institutions and researchers were relatively concentrated, and the centrality value was not very high. That is to say, although there was a certain concentration, it was widely international. International cooperation, inter-agency cooperation, and inter-author cooperation are still insufficient. Therefore, in future research, more cooperation between various levels

Table 14 Top 10 keywords by frequency

No.	Keywords	Frequency
1	Procalcitonin	565
2	Sepsis	477
3	Infection	249
4	C-reactive protein	219
5	Septic shock	189
6	Mortality	172
7	Biomarker	157
8	Marker	141
9	Diagnosis	135
10	Critically ill patient	118

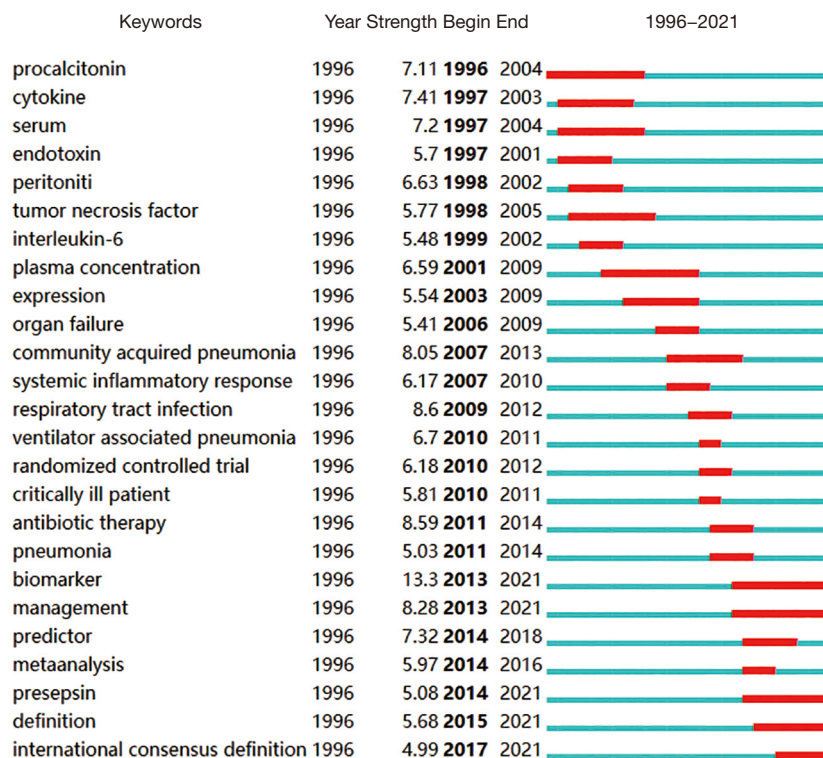
PCT, procalcitonin.

Table 15 Top 10 keywords by centrality

No.	Keywords	Centrality
1	Inflammation	0.09
2	Septic shock	0.07
3	C-reactive protein	0.06
4	Biomarker	0.06
5	C-reactive protein	0.06
6	Serum procalcitonin	0.06
7	Interleukin 6	0.06
8	Epidemiology	0.06
9	Shock	0.06
10	PCT	0.06

PCT, procalcitonin.

Top 25 Keywords with the Strongest Citation Bursts

**Figure 8** Burst test of keywords by CiteSpace.

should be carried out to obtain more valuable evidence-based medical research. In terms of research hotspots, due to the inherent biological characteristics of PCT, it was mainly limited to the clinical application of infected and

critically ill patients, thereby limiting the research field to these patients. However, the future research directions can continue on the basis of the current work. In-depth discussion can also be further analyzed in terms of judging

the early and long-term prognosis of patients.

In summary, PCT has been widely used in critically ill patients, and more and more clinical studies support the use of PCT in the judgment of patients' conditions and to guide the use of antibacterial drugs, but there are also certain controversies. In the future, more multi-center in-depth studies are needed to further provide evidence-based medical research. This study had some shortcomings. This study did not compare the research status of other similar biomarkers horizontally, and there was also a lack of literature analysis on the combined use of PCT and other biomarkers. Increasingly, as more methods currently integrate multiple indicators for diagnosis, risk stratification, and prognostic judgment (22,27), future research should continue to analyze the value of PCT and other biomarkers in comparison and with combined use. And this research is limited to literature analysis, and it may be more meaningful to add some clinical research results which is the future direction.

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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-21-895>). 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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