Original Article

Research status of serum amyloid A in infection: a bibliometric analysis

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Background: Infectious diseases have a significant impact on health. Identifying the pathogenic kind of an infection has important implications for the clinical selection of therapy. Serum amyloid A has been found to have significant changes in expression levels upon infection. The purpose of the present study was to analyze the current status of research on the use of serum amyloid A in infection using a bibliometric approach.

Methods: The Science Citation Index Expanded database in the Web of Science Core Collection (WOSCC) was used as the data source for our search. All search records and cited references were exported in plain text format to form source files for further analysis. Cytoscape software was then used to analyze the source files and generate corresponding visualization graphs.

Results: A total of 1,359 relevant research papers were searched, with a total of 56,607 citations. Core journals included *PLoS One*, *Frontiers in Immunology*, and *Developmental and Comparative Immunology*. The main research countries in this field were the USA, UK, and Denmark. The most cited scholars included JJ Ceron from Spain and MB Pepys from the UK.

Conclusions: There is a limited number of studies on serum amyloid A in infection. More international cooperation and in-depth research are needed.

Keywords: Serum amyloid A; infection; bibliometrics

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Introduction

Infectious diseases have a significant impact on health (1). The pathogens that cause infection are mainly bacteria and viruses, and other important pathogens include fungi, chlamydia, mycoplasma, and parasites (2,3). The most common infectious diseases in clinical practice are viral or bacterial infections of the respiratory, digestive, and urinary tracts, as well as skin and soft tissue (4). The main manifestations of infectious disease are fever, changes in blood counts, and associated signs and symptoms of inflammation at the site of infection (5). In many cases, it is possible to accurately determine whether it is a viral or a bacterial infection based on the patient's clinical manifestations and blood tests. However, at other times, it is difficult to determine the kind of the pathogen that caused the infection (6). If the kind of the pathogen cannot be determined, it is impossible to determine whether to use antibacterial treatment. Overuse of broad spectrum antibiotics could lead to the abuse of antibacterial drugs, resulting in the continuous emergence of drug-resistant bacteria (7). In clinical practice, elevated white blood cell counts (especially neutrophil counts) often indicate bacterial infection. Viral infection often results in a decrease in the number of white blood cells and an increase in the number of lymphocytes. However, the specificity of these

Table 1 Analysis of document type in search results

Document type	Record count	% of 1,359
Articles	1,186	87.27
Review articles	152	11.18
Proceedings	6	0.44
Editorials	8	0.59
Book chapters	6	0.44
Letters to the editor	1	0.07

manifestations is not very high, and they are affected by many coexisting factors, causing great difficulties in clinical differential diagnoses. Recent study has found that procalcitonin is markedly elevated in bacterial infections and not elevated or only slightly elevated in viral infections (8). While C-reactive protein (CRP) is highly sensitive as an inflammatory marker, it has no significant discriminative power for the kind of the pathogen. In recent years, serum amyloid A has been found to have significant changes in expression levels during infection (9). When the body was infected with pathogen, the liver was stimulated to generate serum amyloid A into circulation (9). Serum amyloid A is also an acute reaction protein similar with C-reaction protein. Serum amyloid A can increase and also inhibit the expression level of inflammatory factors (10,11). Serum amyloid A is more sensitive than C-reaction protein when infection occur (10,11). The purpose of the present study was to analyze the current status of research on the use of serum amyloid A in infection using a bibliometric approach.

Methods

Literature search

We used the Science Citation Index Expanded database in the Web of Science Core Collection (WOSCC) as the data source for our search. The database contains English journals and international journals with English abstracts. It reflects the main research content in the scientific field and is currently the main database for bibliometrics. In the literature search, we used "topic" search, and the search terms were "infection (topic)" and "serum amyloid A (topic)". There was no timeframe for the publication of articles.

Analysis method

After completing the search, we exported all search results and cited references in plain text format to form the source file for the next analysis. Cytoscape software was then used to analyze the source files and generate corresponding visualization graphs.

Statistical analysis

The data were imported to Excel, and qualitative data were expressed as percentage.

Results

General information

We retrieved a total of 1,359 related research papers, with a total of 56,607 citations, an average of 41.65 citations per paper, and an h-index of 105. Among all papers (*Table 1* and *Figure 1*), there were 1,186 original articles (87.27%), 152 reviews (11.18%), 6 proceedings (0.44%), 8 editorials (0.59%), 6 book chapters (0.44%), and 1 letter to the editor (0.07%). The number of articles and citations showed a volatile growth trend (*Figure 1*).

Journals

The analysis of journals was done according to the Bradford's law. *PLoS One* was found to have published the highest number of related literature. Some of the journals with a high number of published articles were professional journals in veterinary medicine, accounting for half of the top 20 journals with published articles. The number of articles published in professional journals in human medicine was low (*Figure 2*). Core journals in human medical research in this field included *PLoS One*, *Frontiers in Immunology*, *Developmental* and *Comparative Immunology*, *Infection* and *Immunity*, *Journal of Immunology*, and *Comparative Immunology Microbiology* and *Infectious Diseases* (*Figure 3*).

Countries

According to the analysis of the corresponding author's country, the number of articles published by researchers

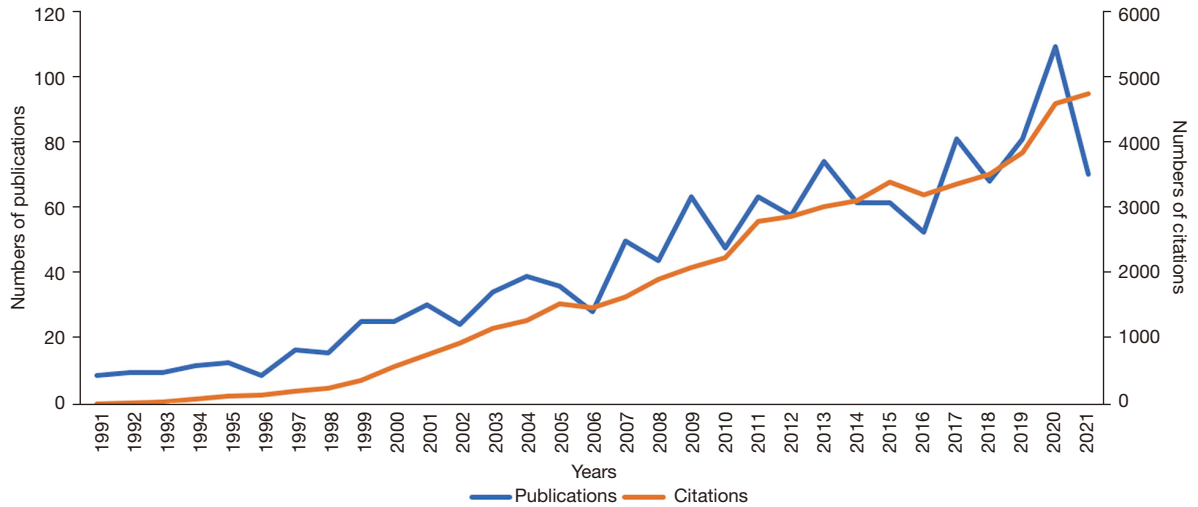

Figure 1 Annual trends in the number of publications and citations.

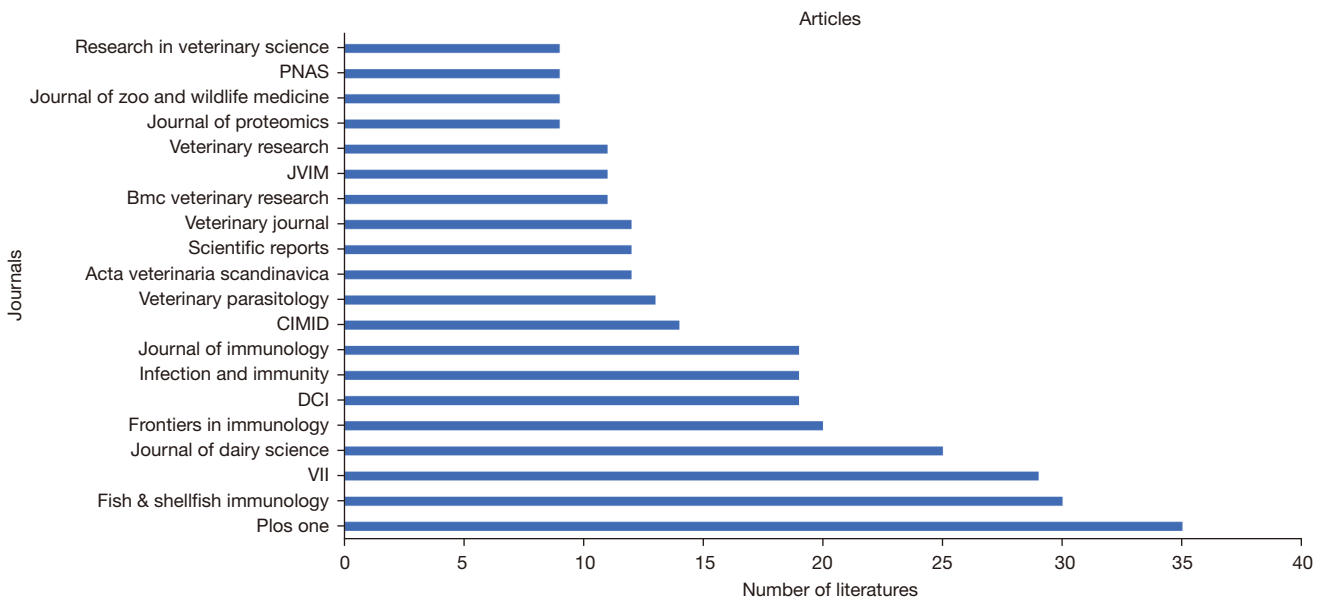

Figure 2 Ranking of journals by number of publications (top 20). *PNAS*, *Proceedings of The National Academy of Sciences; JVIM*, *Journal of Veterinary Internal Medicine; CIMID*, *Comparative Immunology, Microbiology and Infectious Diseases; DCI*, *Developmental and Comparative Immunology; VII*, *Veterinary Immunology and Immunopathology.*

in the USA was the greatest, followed by China, the UK, Japan, and Italy. Countries that had the most cooperation were other countries were the USA, UK, Denmark, China, and Spain (*Figure 4*). The USA cooperated with many countries, particularly the UK and China. China only cooperated with 2 countries: the USA and Australia. Cooperation among other countries was less frequent (*Figure 5*). Based on the number of citations by country, research from the USA, UK, and Denmark was the most cited (*Table 2*).

Institutions

An analysis of the institutions that published the literature

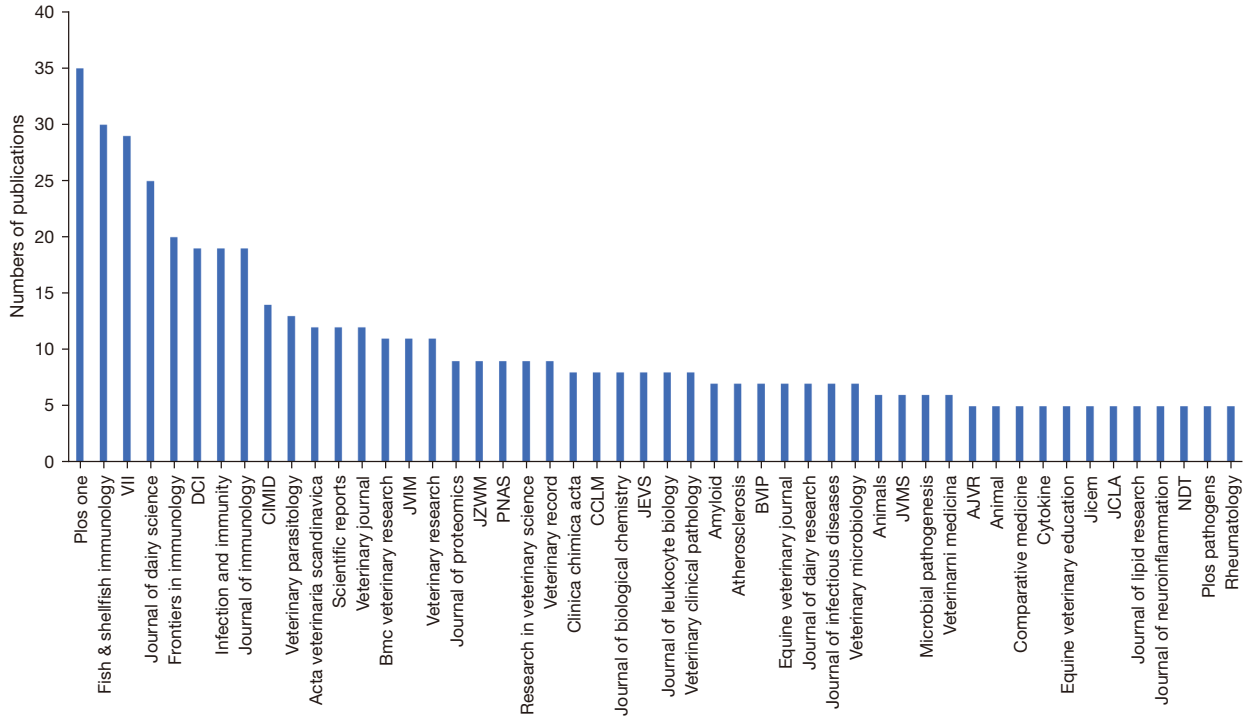

Figure 3 Analysis of core journals according to the Bradford method. *VII*, *Veterinary Immunology and Immunopathology; DCI*, *Developmental and Comparative Immunology; CIMID*, *Comparative Immunology, Microbiology and Infectious Diseases; JVIM*, *Journal of Veterinary Internal Medicine; JZWM*, *Journal of Zoo and Wildlife Medicine; PNAS*, *Proceedings of The National Academy of Sciences; CCLM*, *Clinical Chemistry and Laboratory Medicine*; *JEVS*, *Journal of Equine Veterinary Science; BVIP*, *Bulletin of the Veterinary Institute in Pulawy; JVMS*, *Journal of Veterinary Medical Science; AJVR*, *American Journal of Veterinary Research; JCLA*, *Journal of Clinical Laboratory Analysis; NDT*, *Nephrology Dialysis Transplantation.*

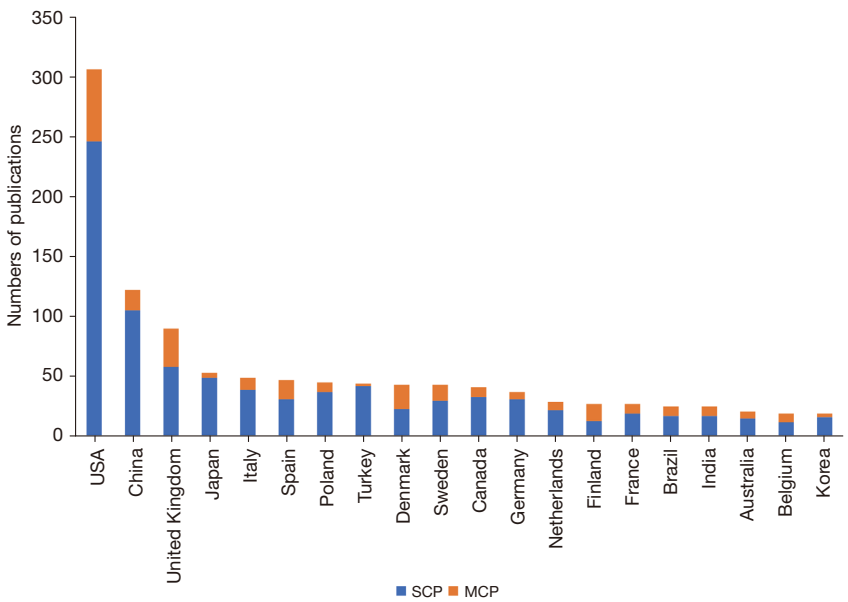

Figure 4 Ranking of countries by number of publications. The country of origin of the literature was determined according to the corresponding author. USA, United State of America; SCP, single country publication; MCP, multiple country publication.

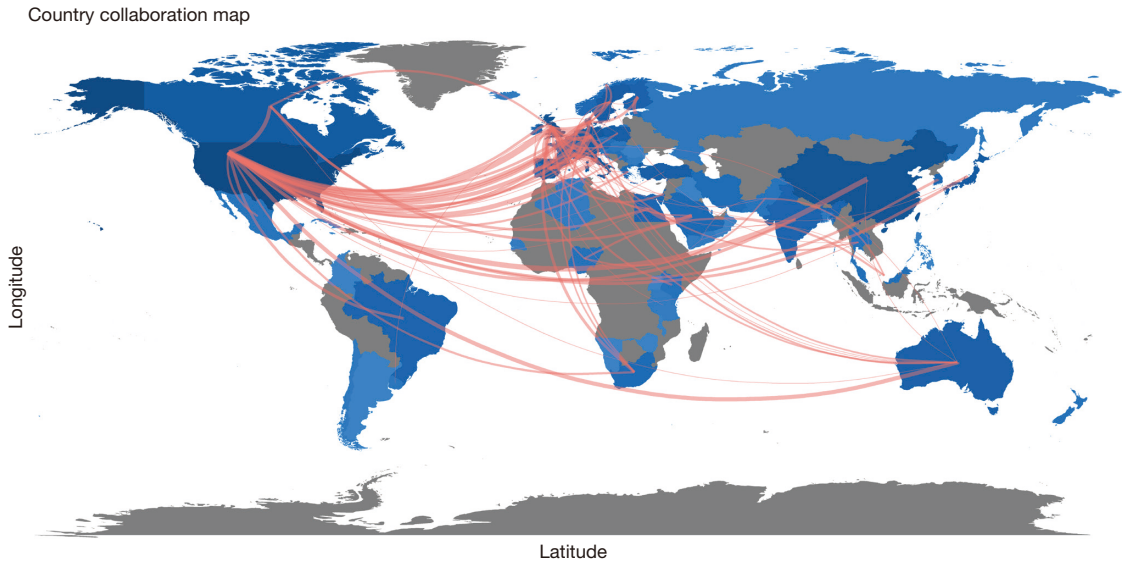

Figure 5 Visualization of national cooperation.

Table 2 Ranking of countries by number of citations (top 10)

Country	Total citations	Average article citations
USA	16,392	53.57
UK	8,557	95.08
Denmark	2,825	65.70
Germany	2,648	71.57
Italy	2,257	46.06
China	2,035	16.68
Japan	1,683	31.75
Spain	1,537	32.70
Ireland	1,473	86.65
Canada	1,420	34.63

Table 3 Ranking of the number of articles published by institutions (top 10)

Institutions	Publications (n)
University of Oxford	441
University of California	302
University of Washington	276
King's College London	256
University of Cambridge	227
University of Bristol	209
Cardiff University	200
Newcastle University	200
Oregon State University	196
The Jackson Laboratory for Genomic Medicine	196

showed that the institutions that published the most literature were mainly in the UK and USA (*Table 3*), and there was extensive cooperation between these institutions (*Figure 6*).

Authors

Authors were ranked according to the number of published articles, and the results showed that PD Eckersall (35 articles) and PMH Heegaard (21 articles) published the most articles (*Table 4*). Further analysis showed that these authors worked in multiple academic institutions. For example, Eckersall worked in Iowa State University in the USA, the Autonomous University of Barcelona in Spain, and the University of Glasgow in the UK, but his research field was mainly in veterinary medicine. Heegaard is a veterinary scholar from the Technical University of Denmark. JJ Ceron, ranked third, is a clinical research scholar from Spain, and MB Pepys is a scholar from the UK

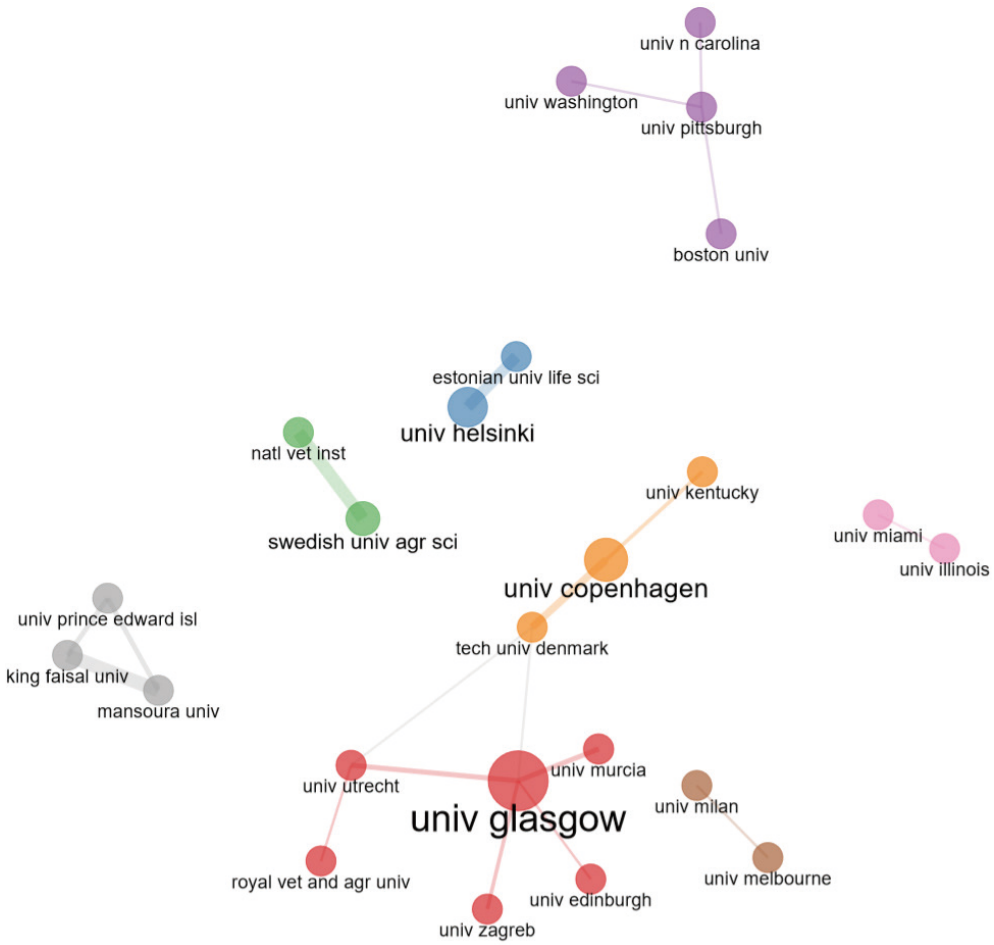

Figure 6 Institutional cooperation. There was close cooperation between multiple agencies.

Table 4 Ranking of the number of articles published by authors

Authors	Articles	Fractionalized articles
PD Eckersall	35	10.70
PMH Heegaard	21	3.36
JJ Ceron	17	2.97
MB Pepys	17	5.00
T Orro	16	2.82
C Cray	14	4.41
A Mantovani	12	1.83
M Pomorska-Mol	12	3.00
I Markowska-Daniel	10	2.52
B Bottazzi	9	1.27

and focuses on amyloidosis and acute phase proteins (acute phase proteins).

Keywords

Analysis of the number of times the keywords were used found that the most frequently used keywords were C-reactive protein (318 times), infection (240 times), and expression (150 times), and these keywords were often used at the same time (*Figures 7*,*8*). This finding indicates that, although serum amyloid A was used as a Topic word in every study, some studies did not use serum amyloid A as a keyword (*Figure 7*), that is, some studies did not focus on serum amyloid A. Further analysis showed that the use of keywords changed over time (*Figure 9*).

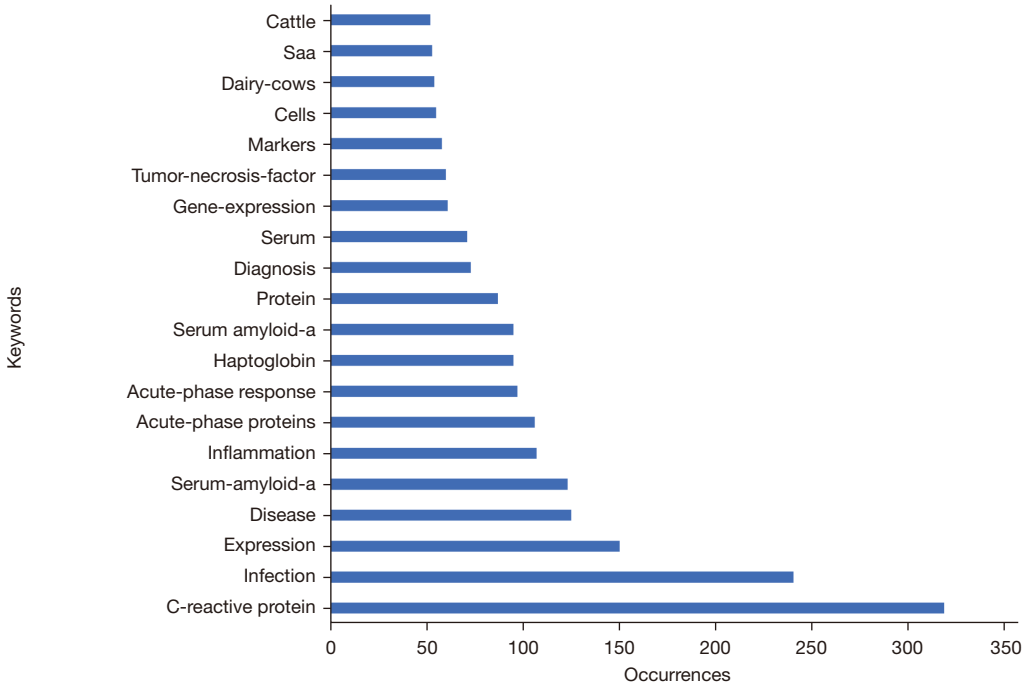

Figure 7 Ranking of keyword usage frequency (top 20). Saa, serum amyloid A.

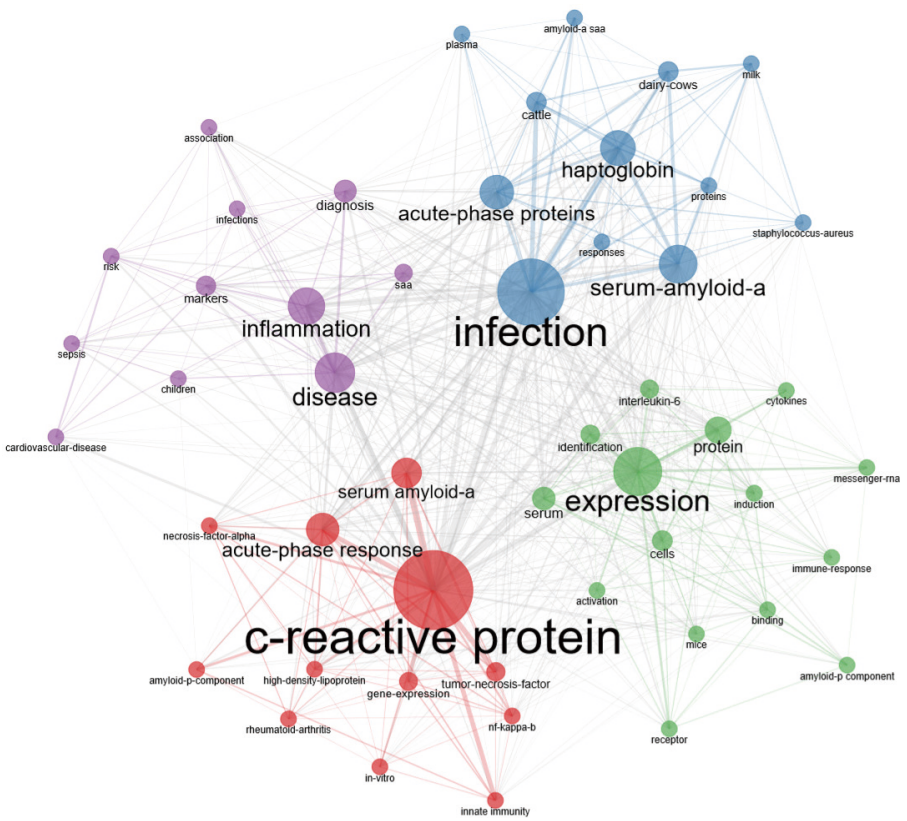

Figure 8 Visualization diagram of keyword combinations.

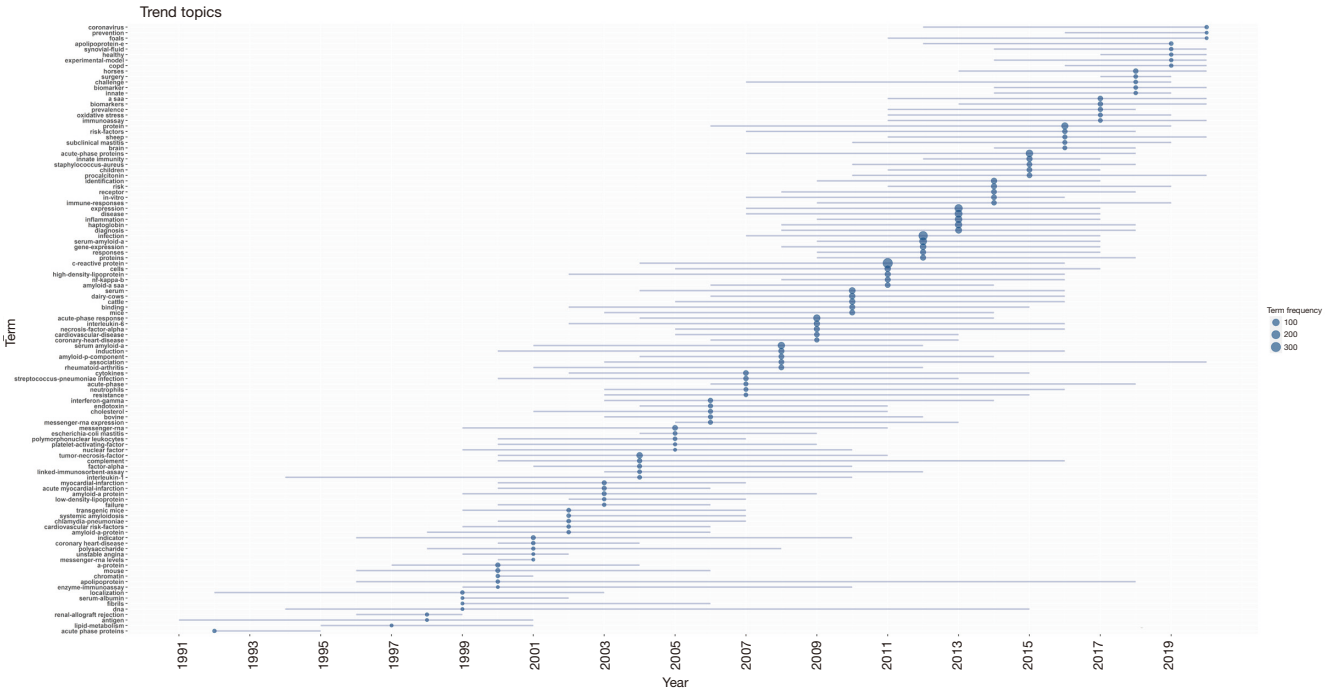

Figure 9 Keyword usage trends.

Discussion

The findings of the present study preliminarily summarize the current research status in this field by analyzing the research literature on serum amyloid A in infection. Most of the literature in this field were original articles (87.27%). In the journal analysis, we found that many of the articles in this field were veterinary research. Of the top 20 journals with the highest number of published articles, half were veterinary and related professional journals. The most important human medicine journal was *PLoS One*. Based on the corresponding author's country, the USA and UK had the most research, cooperation, article citations. Although China had a high number of studies, it had less foreign cooperation. The research institutions were mainly located in the USA and UK, and the research was mainly related to clinical medicine, which is more concentrated in these countries. Ceron and Pepys have done a lot of research in this area. Keyword analysis showed that some studies did not use serum amyloid A as a keyword. Based on the number of studies and related indicators retrieved in this study, we believe that the number of studies on serum amyloid A in infection is relatively low, especially in clinical medicine.

There are many types of biomarkers related to infection commonly used in clinical practice. The most common is the white blood cell count. When bacterial infection occurs in the body, the white blood cell count in the blood increases rapidly, especially the neutrophil count, which is closely related to the degree of infection, disease severity, and prognosis, and in severe cases, sepsis can occur and endanger the patient's life (12). The second is the erythrocyte sedimentation rate, which is often significantly increased when systemic inflammation or local severe infection occurs, and can be used as a preliminary indicator for judging infection (13). Another classic infection-related inflammatory marker is CRP or high-sensitivity C-reactive protein (hs-CRP), which is more conducive to clinical judgment. CRP or hs-CRP is sensitive, but not as specific (14). In the past 20 years, new biomarkers have been used for the judgment and detection of infection. Procalcitonin is a precursor of calcitonin, which can be elevated in the early stage of bacterial infection and can be detected in peripheral blood 2 h later (15,16). Heparin-binding protein has also been shown to be a biomarker of lung infection, urinary tract infection, and intracranial infection, and has been found to be superior to procalcitonin, CRP, and white blood cell count in intracranial infection (17). Other frequently studied biomarkers are interleukin-6, soluble triggering receptor expressed on myeloid cells-1, pro-adrenomedullin, and lipopolysaccharide-binding protein. Serum amyloid A

protein is also an infection-related protein that has been studied more in recent years.

Serum amyloid A is a non-specific acute-phase response protein, and its clinical value as an inflammatory marker has been the focus of increasing attention. Studies have found that the change of serum amyloid A level has certain clinical value for the early diagnosis of infectious diseases, risk assessment, treatment effect monitoring, and judgment of the prognosis of patients (18,19). Serum amyloid A can be significantly increased in both bacterial and viral infections. Using serum amyloid A combined with other indicators, bacterial and viral infections can be distinguished (20,21). A previously published study found that serum amyloid A gradually increases after virus infection. It increases earlier than CRP, and the increase is obvious, reaching a peak on the 3–4 days after infection (22). During disease recovery period, serum amyloid A was found to have continuous decline, which was significantly faster than that of CRP. These characteristics made serum amyloid A beneficial for the judgment of virus infection (22). A previous has compared the expression levels of serum amyloid A in bacterial and viral infections at the same site, and findings indicating that the increase in serum amyloid A is significantly higher in bacterial infection than in viral infection (23). Studies have found that the concentration of serum amyloid A in sepsis patients is significantly increased, especially in neonatal sepsis (24,25). Serum amyloid A has high diagnostic value, and its specificity and sensitivity can reach 95% and 82%, respectively, and can be significantly increased in the early stage of sepsis (24,25).

The findings of the present study indicate that there are relatively few studies on serum amyloid A application. Clinical studies are mainly from the USA, UK, and some European countries. Some studies did not use serum amyloid A protein as a keyword. Research on serum amyloid A in infection is still in its early stages, and its clinical value has not been significantly studied. In addition, although China has published a lot of literature in this field, the analysis results suggest that there is low cooperation with other countries. In future research, international cooperation should be increased to improve the quality of the research. And more studies should be carried out to evaluate the predictive value of serum amyloid A in patients with infection.

Study limitations

In the present study, we identified the country of origin of the literature according to the corresponding author, which could lead to the possibility that some article with multi-country cooperation could be missed in the country cooperation analysis. Another limitation of the present study enrolled some studies on veterinary medicine, therefore, this study fails to analyze the human studies and animal studies respectively and clearly, and only shows the research results of serum amyloid A in the field of infection.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-487/coif). 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.

References

1. Esposito S. Infectious Diseases: Pathophysiology, Diagnostics and Prevention. Int J Mol Sci 2016;17:1464.
2. Standing up to infectious disease. Nat Microbiol 2019;4:1.
3. Casadevall A. Crisis in Infectious Diseases: 2 Decades Later. Clin Infect Dis 2017;64:823-8.
4. Bartlett JG. Update in infectious diseases. Ann Intern Med 2006;144:49-56.
5. Lorber B. Update in infectious diseases. Ann Intern Med 2002;137:974-80.
6. Kaya A, Ergul N, Kaya SY, et al. The management and the diagnosis of fever of unknown origin. Expert Rev Anti

Infect Ther 2013;11:805-15.
7. Wencewicz TA. Crossroads of Antibiotic Resistance and Biosynthesis. J Mol Biol 2019;431:3370-99.
8. Mierzchała-Pasierb M, Lipińska-Gediga M. Sepsis diagnosis and monitoring - procalcitonin as standard, but what next? Anaesthesiol Intensive Ther 2019;51:299-305.
9. Todorov I, Gospodinova M, Bocheva Y, et al. Serum amyloid A protein in the course of infectious mononucleosis. Ther Adv Infect Dis 2019;6:2049936118811208.
10. Sack GH Jr. Serum Amyloid A (SAA) Proteins. Subcell Biochem 2020;94:421-36.
11. Zhang Y, Zhang J, Sheng H, et al. Acute phase reactant serum amyloid A in inflammation and other diseases. Adv Clin Chem 2019;90:25-80.
12. Harris R. Abnormal white blood cell count. Practitioner 1990;234:716-20.
13. Bray C, Bell LN, Liang H, et al. Erythrocyte Sedimentation Rate and C-reactive Protein Measurements and Their Relevance in Clinical Medicine. WMJ 2016;115:317-21.
14. Qian FH, Zhang Q, Zhou LF, et al. High-sensitivity C-reactive protein: a predicative marker in severe asthma. Respirology 2008;13:664-9.
15. Huang DT, Yealy DM, Filbin MR, et al. Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection. N Engl J Med 2018;379:236-49.
16. Tujula B, Hämäläinen S, Kokki H, et al. Review of clinical practice guidelines on the use of procalcitonin in infections. Infect Dis (Lond) 2020;52:227-34.
17. Wu YL, Yo CH, Hsu WT, et al. Accuracy of Heparin-Binding Protein in Diagnosing Sepsis: A Systematic Review and Meta-Analysis. Crit Care Med 2021;49:e80-90.
18. Lannergård A, Larsson A, Kragsbjerg P, et al. Correlations between serum amyloid A protein and C-reactive protein in infectious diseases. Scand J Clin Lab Invest 2003;63:267-72.
19. Qu J, L X, Liu Y, et al. Evaluation of procalcitonin, C-reactive protein, interleukin-6 & serum amyloid A as diagnostic biomarkers of bacterial infection in febrile patients. Indian J Med Res 2015;141:315-21.
20. White MR, Hsieh IN, De Luna X, et al. Effects of serum amyloid protein A on influenza A virus replication and viral interactions with neutrophils. J Leukoc Biol 2021;110:155-66.
21. Gonçalves CA, Sesterheim P. Serum amyloid A protein has been undervalued as a biomarker of COVID-19. Diabetes Metab Res Rev 2021;37:e3376.
22. Liu Q, Dai Y, Feng M, et al. Associations between serum amyloid A, interleukin-6, and COVID-19: A cross-sectional study. J Clin Lab Anal 2020;34:e23527.
23. Urieli-Shoval S, Linke RP, Matzner Y. Expression and function of serum amyloid A, a major acute-phase protein, in normal and disease states. Curr Opin Hematol 2000;7:64-9.
24. Chauhan N, Tiwari S, Jain U. Potential biomarkers for effective screening of neonatal sepsis infections: An overview. Microb Pathog 2017;107:234-42.
25. Bengnér J, Quttineh M, Gäddlin PO, et al. Serum amyloid A - A prime candidate for identification of neonatal sepsis. Clin Immunol 2021;229:108787.

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