

Metrological and Visual Analysis of the Status of Hypotension in Septic Shock

wang qianfei (✉ 1025903923@qq.com)

Hebei University OF TCM <https://orcid.org/0000-0002-6297-3954>

wang chenxi

Hebei Medical University College of Traditional Chinese Medicine

wu lijuan

Hebei PROVINCIAL HOSPITAL OF TCM

MEI jianqiang

HEBEI PROVINCIAL HOSPITAL OF TCM

XU wenzhong

hebei provincial hospital of TCM

CHEN fenqiao

hebei provincial hospital of TCM

Research

Keywords: septic shock, hypotension, research status, Citespace, VOSviewer

Posted Date: December 29th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-136889/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Metrological and visual analysis of the status of hypotension in septic shock

Wang Qianfei ¹, Wang Chenxi ², Wu Lijuan ³, Mei Jianqiang ³, Xu Wenzhong ³, Chen Fenqiao ³

1. Graduate school, Hebei College of Traditional Chinese Medicine, Shijiazhuang, 050091, Hebei Province, China; 2. Basic medical school, Hebei College of Traditional Chinese Medicine, Shijiazhuang, 050020, Hebei, China; 3. Hebei Provincial Hospital of Traditional Chinese Medicine, Shijiazhuang, 050011, Hebei, China

EMAIL: Wang Qianfei:1025903923@qq.com

Abstract

Background: At present, there is a lot of research in the field of septic shock and hypotension, but there is no comprehensive analysis of the current situation, hot spots and frontiers in this field, and many researchers don't know where to start. Therefore, in this study, the research status, research hotspots and frontier trends of septic shock hypotension in the past 30 years were analyzed by knowledge graph, so as to provide a reference basis for further research.

Methods: We collected the literature related to hypotension in septic shock in Web Of Science (WOS) from 1991 to 2020, and made a bibliometric analysis of the literature. At the same time, we use Excel2019 and Adobe Illustrator CC2018 software to analyze the annual volume of articles and draw bar charts and VOSviewer software to draw the relevant maps of countries, authors and institutions to explore the cooperative relationship in this field and CiteSpace software to draw keyword co-occurrence map, cluster timeline map and emergence map of keywords, and analyze the frontiers and hotspots in this field.

Results: A total of 1419 articles were obtained, of which the country with the largest number of

articles was the United States, and the centrality was the highest. Professor Bellomo Rinaldo in Australia has published the largest number of articles, up to 29 articles, which plays an important role in this field. In the organization cooperation graph, Univ sao Paulo cooperates closely with other agencies and publishes a large number of articles. There are high-frequency keywords such as sepsis, septic shock and hypotensio, 11 clusters such as relative adrenal insufficiency, nitric oxide and thromboxane, and high-prominence keywords of endotoxin and tumor necrosis factor.

Conclusion: In the past 30 years, the volume of articles in the field of hypotension in septic shock showed a steady upward trend. Institutions in North America, Australia and Europe have made outstanding contributions to this field, but the degree of inter-country and inter-agency cooperation is worrying. Three major author cooperation groups have been formed, with close ties within the group. In the future, international exchanges and cooperation can be strengthened and the degree of cooperation in this field can be improved. Drugs for the treatment of hypotension, molecular mechanisms including endotoxin and tumor necrosis factor, and physiological and pathological mechanisms of hypotension are the research hotspots and frontiers in recent years.

Keywords: septic shock; hypotension; research status; Citespace; VOSviewer

Sepsis refers to life-threatening organ dysfunction caused by host response disorders caused by infection. Septic shock is sepsis with severe circulatory, cellular and metabolic disorders, and its risk of death is higher than that of simple sepsis^{[1][2]}. Septic shock is caused by persistent hypotension based on sepsis. Vasoactive drugs are still needed to maintain mean arterial pressure (MAP) ≥ 65 mm Hg, and blood lactic acid level > 2 mmol/L after full volume resuscitation. Hypotension in patients with severe sepsis can't be corrected after adequate fluid resuscitation, so fluid resuscitation alone can't accurately increase blood pressure. There are a

variety of causes of hypotension in patients with this disease, and it is particularly important to use vasopressor for the cause. At present, norepinephrine and vasopressin are recommended as the first-line symptomatic pressor drugs in the field of critical medicine^[3], but the fundamental treatment of sepsis is also very important in the process of pressor pressure. including the improvement of adrenocortical function, the improvement of disordered blood coagulation system, the improvement of cardiac function, to achieve the combination of cause and symptom. In the past 30 years, there have been different guidelines for theoretical understanding and clinical treatment of septic shock in the field of hypotension, but some treatments outside the guidelines also depend on people and the times. For example, although norepinephrine is currently a first-line drug for hypotension, the application of m-hydroxylamine is hot in some areas^{[4][5]}. Therefore, it is very important to analyze the development trend and research status in this field.

CiteSpace is an information visualization software developed by Professor Chen Chaomei of Dreisel University in the United States. Based on co-citation analysis theory and routing network algorithm, it calculates the literature and explores the key path and knowledge turning point of the research. A multivariate, time-sharing and dynamic citation analysis visualization language is used to show the research process through the graph^{[6][7]}. VOSviewer is a visualization software developed by professors Van Eck and Wa It-man of Leiden University in the Netherlands, which can draw co-occurrence maps of countries, institutions and authors. the software has unique advantages in drawing maps. At present, although there are a large number of studies in the field of septic shock hypotension, there is a lack of systematic research on the development of this field. This paper analyzes the knowledge graph of the data collected from WOS by using

CiteSpace software and VOSviewer, and draws the relevant charts of countries, authors, institutions and key words, so as to provide a basis for the future research of hypotension in septic shock.

1 Information and methodology

1.1 Data acquisition

The core collection of WOS is searched, and the key word is "Septic AND Hypotension". The search time is from January 1, 1991 to September 15, 2020. The literature type is "Artical" and "Review", and the language is "English". In order to avoid duplication and omission of data, the search and download of data was completed on September 15, 2020. After manual screening and elimination of duplicates, 1419 articles were retrieved including 1282 Artical and 137Review. The study used two independent researchers to review and evaluate the retrieved articles, and different opinions were discussed until a consensus was reached.

1.2 Data conversion

The included literature will be exported in Refworks format and other formats, and the literature information includes title, author, abstract, keyword, year of publication, research institution, journal, volume, starting and ending page number. The data format is converted by CiteSpace and VOSviewer to form the document format corresponding to Citespace and VOSviewer.

1.3 Data processing

Node types are drawn with countries, authors, research institutions, keywords and so on, and visual analysis is carried out.

2 Results

2.1 Number of posts

Fig.1 the number of articles published annually in the field of septic shock and hypotension in WOS from 1991 to 2020

2.2 Country

Each circular node in the picture represents each country or region (the following institutions and authors are the same as above). The size of the node is positively correlated with the number of posts, the connection represents the cooperation among the authors (positive correlation), and the network density represents the degree of cooperation. the lower the country or region, the more scattered the cooperation between countries or regions. At present, a total of 79 countries and regions have contributed to the field of septic shock and hypotension, but most of the papers have been published in a few countries. The top five countries published a total of 948 papers (66.81%), most of which came from North America and Europe. The United States published the most articles (572, 40.31%), followed by Germany (121, 8.52%), France (95, 6.70%), the United Kingdom (82, 5.78%), and Canada (78, 5.50%). The general centrality value > 0.10 is the key node, and there are 5 key nodes in this field, which represent the important structural points and pillar points in the whole research field. The United States (0.96), the United Kingdom (0.30), France (0.13), Canada (0.12), and Germany (0.11) are important pillar countries in the field of septic shock hypotension. The top 5 countries with the highest number of articles are also the five countries with the highest centrality, indicating that the research of these five countries has the most important position in the field of septic shock. Other countries, such as Brazil, Japan, Australia, and so on, have published more than 60 articles, but the centrality is low, so they can improve their influence in this area in the future, and there is room for improvement

both in quantity and quality. The picture shows the label view, the darker the color is, the more cutting-edge the research is. Thailand, New Zealand, Turkey and other countries are currently at the forefront of research, but their publication volume is less and the degree of support in the field is low. The above countries can actively cooperate with countries with more papers to jointly enhance cooperation between countries.

Tab. 1 the number of articles and central top five national information in septic shock and hypotension in WOS from 1991 to 2020

Fig. 2 National or regional cooperation network in the field of septic shock hypotension in WOS from 1991 to 2020

2.3 Author

Fig. 3 collaboration network of authors in the field of septic shock and hypotension in WOS from 1991 to 2020

Among the 908 authors, the author with the largest number of articles is Professor Bellomo Rinaldo, an expert in critical care medicine at the University of Melbourne, Australia, with a total of 29 articles. Table 2 is the top 10 authors. According to Price's law^[8], the core author, according to the formula:

$$M_p = 0.749 \sqrt{N_{pmax}} = 0.749 * \sqrt{29} = 4.03$$

According to the integer number of articles, that is, more than 5 articles (including) published by the core authors, a total of 98 authors, accounting for about 10.79% of the total number of articles, these 98 authors occupy a pivotal position in this field, the discipline influence is very high.

There are three more prominent cooperative teams, which are also formed by the top three scholars. 1 the team with Professor Bellomo Rinaldo as the core is in close contact and publishes

the most articles. The color of the map is the lightest, indicating that the research content is very cutting-edge and hot. The main contents of the study are as follows: animal sepsis hypotension drug trial^{[9][10]}, clinical hypotension drug treatment of septic shock patients^{[11][12][13]}, clinical treatment of bodily organ damage caused by pressor drugs^[14], etc., the quality of the article is very high, and the average influencing factor is more than 20. 2 the team with Professor Martin Westphal as the core, the color of the map is darker, and the frontier and heat of the research are relatively low. The main contents of the study are related to the clinical drug trials of septic shock and hypotension^[15], the combination of the molecular mechanism of pressor drugs with clinical treatment^[16], and the treatment of cardiac function in patients with septic shock^{[17][18]}, and formed the research ideas and systems in this field. Its publication quality is very high, the influence is high.3 the team with Professor Vincent Jean-Louis as the core, the team mainly studies septic shock and blood coagulation^{[19][20]}, clinical drug trials^[21], and other related studies. The research direction of the three teams in the field can represent the development direction of the field, all have their relative attention, and the research level is at the forefront of the field.

Tab. 2 Information of the top 10 authors in the field of septic shock and hypotension in WOS from 1991 to 2020

2.4 Institution

Fig. 4 Network of institutions in the field of septic shock and hypotension in WOS from 1991 to 2020

At present, the top ten institutions in the field of septic shock and hypotension in China are: Univ Sao Paulo (36), Univ Pittsburgh (31), Natl Def Med Ctr (27), Univ Melbourne (26), Harvard Univ (26), Univ Texas (25), Beth Israel Deaconess Med Ctr (24), Monash Univ (23), Univ Libre Bruxelles (20), Univ Toronto (19). There are 155 institutions with more than 5 articles, accounting for 9.14% of the review. As can be seen from the chart, there are fewer connections in the picture,

and the cooperation among various agencies is not good. Only the well-known institutions in Europe and the United States have published more papers, and the cooperation is relatively close. The two institutions of Univ Melbourne and Univ Libre Bruxelles are lighter in color, which means that they are at the forefront of publication. Europe and the United States are mostly areas with good economic development, which can support the consumption of scientific research institutions, and have a good academic atmosphere, can combine basic research, clinical research, and experimental research, with a high level and mature research system.

2.5 The top 10 high-cited papers

The following table shows information about the top 10 citations. The top 10 citations are all very influential articles in this field, and most of them are the key and core contents in the field of septic shock. Among them, Crit. There are 4 articles in Care Med Magazine, which is an authoritative magazine in the field of critical care in the United States with high-quality articles. The influence factor of the top ten articles is more than 7. The first place is the clinical treatment of septic shock published in the New England Journal in 2001, and goal-oriented therapy can improve the prognosis of patients with septic shock; the second is a retrospective analysis in 2001, which comprehensively describes the current epidemiology of sepsis and reintegrates the epidemiological survey in this field; the third is Crit., an authoritative journal in the field of critical medicine. Care Med issued guidelines for septic shock.

Tab. 3 The top 10 high-cited papers in scoliosis research in WOS from 1991 to 2020

2.6 Keyword

Fig. 5 keyword co-occurrence network in septic shock and hypotension in WOS from 1991 to 2020

Fig. 6 Cluster map of key words in septic shock and hypotension in WOS from 1991 to 2020

A co-occurrence graph is generated with keywords as nodes, as shown in figure 3. Among them, there were 2 with frequency > 700, 14 with frequency > 100, and 37 with frequency > 50. The key words of high frequency reflect the overall summary of the research content in this field and the focus of researchers. At present, the focus in the field of septic shock hypotension is still basic research and clinical, animal experiments, molecular mechanism.

Tab. 4 High-frequency keywords in the field of septic shock and hypotension in WOS from 1991 to 2020

On this basis, cluster analysis is carried out to understand the current research hotspots, and the clustering map with a Q value of 0.4005 and M value of 0.4684 is obtained by using logarithmic likelihood algorithm (LLR), as shown in figure 4. Q value is generally in the range of 0-1, Q > 0.3 can be considered to be significant; when M > 0.5, clustering can be considered reasonable, when M > 0.7, clustering is efficient and convincing. The clustering graph structure is significant and the clustering is reasonable (close to 0.5). Eleven clusters appeared in this study, showing the overall knowledge structure of septic shock hypotension, # 0relative adrenal insufficiency, # 1nitric oxide, # 2thromboxane, # 3grade, # 4pentoxifylline, # 5interferon gamma, # 6vasopressin, # 7cachectin, # 8myocardial dysfunction, # 9coagulation, # 10type 2. And draw a time chart (Timeline), to show the relationship and historical span between pattern classes, as shown in figure 5.

To a certain extent, emergent words represent the frontier and development trend of research in the field and explore the high-frequency words in a certain period time. Draw the graph of emergent words, such as figure 6, which shows that there are different research hotspots of septic shock hypotension in different periods. The research hotspots lasting more than 9 years are bacteremia, respiratory distress syndrome, cardiac output, endotoxin, oxygen

consumption, tumor necrosis factor, factor-alpha, antibody, monoclonal antibody, response, catecholamine, escherichia coli, endotoxin shock, and so on.

Fig. 7 emergence map of key words in septic shock and hypotension in WOS from 1991 to 2020

3 Discussion

The scientific knowledge graph shows the relationship between research progress and structure in a certain field through visualization technology, which enables researchers who have not entered the field to understand the research hotspots and frontiers, and authors who have published more papers to understand their research directions. as well as high-quality literature and periodicals, as well as the direction of development in the future. This study uses the WOS core database for literature retrieval, the database literature is comprehensive, high-quality literature, and this study is the first time to analyze the field of septic shock hypotension so that this visual analysis has a certain quality assurance and scientific. In this study, CiteSpace and VOSviewer were used to visually analyze the related studies of hypotension in septic shock.

The number of articles published: a total of 1419 articles about septic shock and hypotension were published from 1991 to 2020, and the publication volume increased year by year, which was in line with the development trend of general emerging fields, especially in the past 4 years. The annual volume of articles is more than 70. In this paper, the knowledge of WOS core collection database for visual analysis, and only contains Artical and Review, other properties of the literature is not included and failed to search PubMed, Embase, CNKI and other databases for retrieval, the data has a certain deviation.

From the national level, the research in the field of septic shock hypotension is mainly concentrated in Europe and the United States, and the top five countries in the world, including

the United States, Germany, France, the United Kingdom, and Canada, account for 66.81% of the total number of articles in the world. and the above five countries are also the five countries with the highest centrality, supporting countries in the field of research. Although there are many articles published in China, the centrality is not high. In the future, China can improve the quality of articles on septic shock and hypotension. The top 10 institutions are all from Europe, the United States, and Australia, the above areas have a large population, economically developed, high disease awareness, so the above situation. The global development is extremely uneven, and there are few studies in Africa, South America, South Asia, and other regions, which are related to a variety of factors in this region. From the perspective of publishing institutions and authors, there are more institutions in Europe, the United States and Australia, most of which are profound medical colleges, strong general hospitals, and research centers. The volume of publication, maturity, and scope of research of the three major teams are at the forefront of the world, and the development of basic theoretical research, molecular mechanism research, clinical and animal experiments are quite perfect. To a certain extent, it can represent the development direction in the field of septic shock and hypotension. Most of the authors who publish most of the articles are clinical experts and basic research professors, who are all researchers and clinical experts in the academic circle. The research direction of the article is relatively comprehensive, and the article has high authority and credibility. The above three factors, the country, the institution, and the author, cause and affect each other, which makes the research level of Europe, the United States, Australia, and other regions and countries advanced. However, there are many connections among hot countries, institutions, and authors, which shows that the degree of cooperation is good; the emergence of a more single node and the single line shows that a

considerable number of institutions have a poor degree of cooperation. It can be seen that there is an obvious regional nature, and the research institutions centered in Europe and the United States are advanced and can represent the development in the field to a certain extent; in addition, there is very little cooperation among other institutions, including Asia, Africa, and South America, and the development situation needs to be improved.

Through the analysis of the co-occurrence map of keywords, this paper reveals the high-frequency keywords and key nodes, including Sepsis and Septic shock.

At present, hot research is still focused on the molecular mechanism of septic shock and hypotension and clinical and animal experiments. Endotoxin, tumor necrosis factor, and antibody research represent the frontier and specific hotspots in this field. Through cluster analysis, 11 clusters appear, and the specific analysis is as follows:

Cluster 0, relative adrenocortical insufficiency (RAI), is one of the main reasons for the occurrence and progression of septic shock. The current incidence of RAI in patients with severe septic shock is 50% Mel 75%^{[22][23]}. Early application of glucocorticoid (GC) is very important. When sepsis progresses to septic shock, there are many phenomena, such as increased exudation of adrenocortical neutrophils, hemorrhage and necrosis of cortical cells, injury of vascular endothelial cells, and so on. High levels of endogenous GC and decreased binding capacity of the endogenous glucocorticoid receptor (GR) to ligand GC can lead to decreased response to exogenous and endogenous GC. However, small doses must be used^{[24][25][26]}, and a prospective, randomized, double-blind, placebo clinical trial ^[27]has shown that high-dose methylprednisolone sodium succinate is not beneficial in the treatment of septic shock. Although the function of the hypothalamus-pituitary-adrenal axis is not affected in the early stage of sepsis, when it reaches

the shock stage of sepsis, it is often associated with adrenocortical insufficiency, resulting in reduced secretion of glucocorticoids and a large number of inflammatory factors such as IL-6, TNF- α , IL-1 and so on^[28]. At present, GC can be used to treat an adrenocortical injury in patients with infection, but its specific dosage and timing, early prevention of RAI is still a difficult problem, and a breakthrough can be made in this direction in the future.

Cluster 1, nitric oxide (NO), plays an important role in relaxing blood vessels, regulating blood pressure, and regulating blood supply. During septic shock, the adrenal medulla increases NO synthase activity, produces a large amount of NO, lowers blood pressure excessively, and maintains hypotension. Among the top ten citations, two are related to the field of nitric oxide. Nitric oxide is formed by L-arginine, a constituent enzyme in vascular endothelial cells. NO synthase induction is involved in the pathogenesis of septic shock. Inhibition of NO synthase may be a new treatment option., Moncada S^[29] has achieved good results by using nitric oxide synthase inhibitors in two patients with septic shock. In addition, a large amount of NO causes changes in gastrointestinal blood supply and aggravates intestinal inflammation, changes in systemic hemodynamics, a decrease of gastrointestinal blood supply, intestinal mucosal ischemic damage, and interaction with neutrophils, resulting in apoptosis of intestinal epithelial cells and decline of intestinal mucosal barrier function.

Cluster 2 and cluster 9, coagulation and thromboxane are the evaluation of patients' blood coagulation function. Coagulation disorder is a common complication in patients with sepsis. According to statistics, sepsis with a coagulation incidence of 50-70% can progress to septic disseminated intravascular coagulation (DIC)^[30], has become a key factor in microcirculation disturbance in septic shock and a key indicator of patient prognosis. During sepsis, inflammatory

mediators IL-6, TNF, IL-1, and leukocytes stimulate vascular endothelial cells to express tissue factors, thus initiating exogenous coagulation pathways, leading to microvascular microthrombosis and microcirculatory disorders. In sepsis, especially in severe sepsis, thrombocytopenia is caused by increased loss or destruction, myelosuppression, and other reasons, accompanied by the weakening of platelet function. therefore, the function of platelets to control the release of vasodilation or contractile substances is significantly weakened, and abnormal coagulation is caused by the decrease of plasma antithrombin level and the inhibition of the fibrinolytic system. Therefore, it is particularly important to control abnormal blood coagulation system in a variety of ways to avoid the occurrence of DIC and reduce the mortality caused by an abnormal blood coagulation.

Cluster 4, pentoxifylline (PTX), is a derivative of methylxanthine and has selective anti-inflammatory effects. Some scholars have found that PTX can inhibit the transcription and production of tumor necrosis factor (TNF), and low-dose PTX can inhibit the expression of bioactive TNF and its mRNA by more than 50%^{[31][32]}. At present^[33], there are two kinds of anti-inflammatory mechanisms: 1^[33]. PTX may inhibit the activity of phosphodiesterase, reduce the degradation of cyclic adenosine monophosphate (cAMP), increase the concentration of intracellular cAMP, reduce the outflow of calcium-dependent potassium ions, change the phosphorylation type of cell membrane proteins and increase the activity of protein kinase, so as to increase the deformability of cell membrane and improve the hemodynamics of microcirculation so as to achieve its anti-inflammatory effect. 2^[34]. PTX can inhibit the expression of β integrin on T lymphocytes, inhibit the expression of CD25, CD69, and CD98, which can promote cell division, inhibit the specific activation of T lymphocyte antigens, and superantigens,

and promote the negative regulation of immune response. 3 inhibit nf-kb pathway. The above mechanisms of pentoxifylline can inhibit the progression of inflammation. However, a piglet trial^[35] showed that pentoxifylline, a TNF inhibitor, attenuated both GBS-induced TNF production and the late GBS effect, but caused a progressive decrease in systemic hypotension. The use of pentoxifylline is controversial at present, and how to avoid hypotension in the future can become a research direction.

Cluster 5, interferon- γ (IFN- γ), has an immunomodulatory effect. Some studies^[36] have shown that interferon can reverse the immune paralysis caused by sepsis. A mouse experiment^[37] showed that IFN- γ at the concentration of 20ng/ml could up-regulate the PRRs related to the activation of inflammatory cells and up-regulate the SR related to the defense of inflammatory cells. And other studies have shown that inflammatory infection understands the abnormal function of cells, especially neutrophils, and interferon can reduce neutrophil count and change granulocyte components to the anti-inflammatory wind. Although there are clinical trials to prove its efficacy, but at present, there are few studies on its molecular mechanism, which can be used as a research direction for in-depth exploration.

Cluster 6, vasopressin or antidiuretic hormone (ADH), is a cyclic peptide hormone secreted by the supraoptic nucleus of the hypothalamus, which can enhance the reabsorption of water by distal tubules and collecting ducts of the kidney, thereby maintaining normal colloidal osmotic pressure in plasma. Persistent hypotension in septic shock seriously affects the secretion of ADH, so ADH is mostly the treatment of the results, how to prevent as soon as possible has become a new direction of exploration. Noradrenaline is generally used for hypotension in patients with septic shock, but it has a great effect on heart rate. M-hydroxylamine has little excitatory effect

on the heart, long-lasting pressor effect and weak use of vasoconstriction. At present, there has been active use of m-hydroxylamine in clinic. A multicenter prospective cohort study^[38] shows that m-hydroxylamine compared with norepinephrine can reduce hospital stay and protect renal function in patients with sepsis.

Cluster 7, tumor necrosis factor or cachexin, is considered to be the primary mediator of septic shock. Various evidences show that the level of TNF- α increases in septic shock, which is positively correlated with the severity and prognosis of septic shock. At present, there are many drugs to show a tendency towards TNF- α , Zhang HF^[39] and so on. In mouse bone marrow macrophages induced by lipopolysaccharide, Fiserol attenuates sepsis-induced multiple organ dysfunction by inhibiting p38MAPK/MK2 signal pathway. Liao FH^[40] et al were treated with anti-endotoxin subnanogold cluster, the key pro-inflammatory factor NF- κ B dependent cytokines, which significantly decreased the concentration of plasma TNF- α after LPS challenge, and significantly prolonged the survival time of LPS-induced sepsis mice. Ultra-small gold nanoclusters can activate endotoxin by compressing the bulk density of LPS and targeting lipid An of LPS, which provides a potential treatment for treatment. Huang w^[41] et al studied that ITK (- / -) BTK (- / -) mast cells showed hyperactive preformation and lipopolysaccharide-induced tumor necrosis factor- α production, when recombined into mast cell deficient SASH mice, it will lead to more severe endotoxin-induced septic hypothermia. The increased activation of kappaB, Akt and p38 in ITK (- / -) Btk (- / -) induced by LPS can significantly inhibit the excessive production of TNF- α and reduce the hypothermia of sepsis.

Cluster 8, cardiac insufficiency, is an important manifestation of multiple organ failure in septic shock. As the most important organ of the circulatory system, the heart is extremely

sensitive to peripheral hemodynamic changes, and cardiac insufficiency occurs in septic shock. Timely treatment of cardiac insufficiency is particularly important, which has further guiding significance for the treatment of hypotension.

Cluster 3 and cluster 10, type 2 and grade, guiding evidence levels are divided into high, medium, low and very low levels according to the GRADE system, RCT as high-quality evidence, clinical future studies can be carried out to control hypotension drugs RCT, but in the process of RCT research. Efforts should be made to minimize the influence of five interference factors, such as the degree of bias, subgroup analysis, indirectness of evidence, inaccuracy of results, and bias of reporting conclusions, so as to ensure high-quality RCT research.

4 Conclusion

Hypotension, as the most important manifestation of septic shock, has been paid more and more attention all over the world, and the level of research in Europe and the United States is relatively high. no matter from countries, institutions and individuals, we should strengthen cooperation with Asia, Africa and South America to promote global treatment and research level of septic shock hypotension. In view of some hot spots and frontiers in the research, we should continue to carry out more in-depth research, but we should also explore some non-hot research to promote the development of the whole discipline.

[1] Cao Yu,Chai Yan-fen,Deng Ying,et al.Emergency treatment guidelines for sepsis/septic shock in China(2018)[J].Journal of Clinical Emergency,2018,19(09):567-588.

[2] Rhodes Andrew,Evans Laura E,Alhazzani Waleed et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016.[J] .Intensive Care Med, 2017, 43: 304-377.

-
- [3] Dellinger R P,Levy Mitchell M,Rhodes Andrew et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012.[J] .Intensive Care Med, 2013, 39: 165-228.
- [4] Hou Li-Chao,Li Shu-Zhi,Xiong Li-Ze et al. Effect of dopamine and metaraminol on the renal function of patients with septic shock.[J] .Chin Med J (Engl), 2007, 120: 680-3.
- [5] Natalini Giuseppe,Schivalocchi Valeria,Rosano Antonio et al. Norepinephrine and metaraminol in septic shock: a comparison of the hemodynamic effects.[J] .Intensive Care Med, 2005, 31: 634-7.
- [6] Li Jie,Chen Chao-Mei.CiteSpace:Text Mining and Visualization in Scientific Literature[M].Beijing:Capital University of Economics and Business Press,2016.
- [7] Chen Yue,Chen Chao-Mei,Hu Zhi-Gang et al.Principle and application of citation space analysis[M].Science press,2014.
- [8] Zhong Wen-Juan.Evaluation about the Core Authors Based on Price Law and Comprehensive Index Method——Take Journal of Library Development as an Example[J].science and technology management research,2012,32(02):57-60.
- [9] Okazaki Nobuki,Iguchi Naoya,Evans Roger G et al. Beneficial Effects of Vasopressin Compared With Norepinephrine on Renal Perfusion, Oxygenation, and Function in Experimental Septic Acute Kidney Injury.[J] .Crit. Care Med., 2020, 48: e951-e958.
- [10] Lankadeva Yugeesh R,Ma Shuai,Iguchi Naoya et al. Dexmedetomidine reduces norepinephrine requirements and preserves renal oxygenation and function in ovine septic acute kidney injury.[J] .Kidney Int., 2019, 96: 1150-1161.
- [11] Cioccarì Luca,Luethi Nora,Duong Thy et al. Cytokine and lipid metabolome effects of

low-dose acetylsalicylic acid in critically ill patients with systemic inflammation: a pilot, feasibility, multicentre, randomised, placebo-controlled trial.[J] .Crit Care Resusc, 2020, 22: 227-236.

[12] Cioccarì Luca, Luethi Nora, Bailey Michael et al. The effect of dexmedetomidine on vasopressor requirements in patients with septic shock: a subgroup analysis of the Sedation Practice in Intensive Care Evaluation [SPICE III] Trial.[J] .Crit Care, 2020, 24: 441.

[13] Hammond Naomi E, Finfer Simon R, Li Qiang et al. Health-related quality of life in survivors of septic shock: 6-month follow-up from the ADRENAL trial.[J] .Intensive Care Med, 2020, 46: 1696-1706.

[14] Leisman Daniel E, Fernandes Tiago D, Bijol Vanesa et al. Impaired angiotensin II type 1 receptor signaling contributes to sepsis induced acute kidney injury.[J] .Kidney Int, 2020, undefined: undefined.

[15] Morelli Andrea, Sanfilippo Filippo, Arnemann Philip et al. The Effect of Propofol and Dexmedetomidine Sedation on Norepinephrine Requirements in Septic Shock Patients: A Crossover Trial.[J] .Crit. Care Med., 2019, 47: e89-e95.

[16] Westphal Martin, van Haren Frank M P, Sepsis and pharmacogenomics: can the VAS(S)T majority of vasopressor treatment be individualized?*[J] .Crit. Care Med., 2014, 42: 1944-5.

[17] Morelli Andrea, Ertmer Christian, Westphal Martin et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial.[J] .JAMA, 2013, 310: 1683-91.

[18] Morelli Andrea, Donati Abele, Ertmer Christian et al. Microvascular effects of heart rate control with esmolol in patients with septic shock: a pilot study.[J] .Crit. Care Med., 2013, 41: 2162-8.

-
- [19] Levi Marcel, Vincent Jean-Louis, Tanaka Kosuke et al. Effect of a Recombinant Human Soluble Thrombomodulin on Baseline Coagulation Biomarker Levels and Mortality Outcome in Patients With Sepsis-Associated Coagulopathy.[J] .Crit. Care Med., 2020, undefined: undefined.
- [20] Vincent Jean-Louis, Francois Bruno, Zabolotskikh Igor et al. Effect of a Recombinant Human Soluble Thrombomodulin on Mortality in Patients With Sepsis-Associated Coagulopathy: The SCARLET Randomized Clinical Trial.[J] .JAMA, 2019, 321: 1993-2002.
- [21] Meresse Zoé, Medam Sophie, Mathieu Calypso et al. Vasopressors to treat refractory septic shock.[J] .Minerva Anesthesiol, 2020, 86: 537-545.
- [22] Zaloga GP, Marik P. Hypothalamic-pituitary-adrenal insufficiency[J]. Crit Care Clin, 2001, 17 (1) :25-41.
- [23] Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock[J]. JAMA, 2002, 288 (7) :862-871.
- [24] Zhuang Y, Chang N, Wang X, et al. Role of low dose corticosteroids in severe sepsis and septic shock: a Meta-analysis[J]. Journal of Southeast University (Medical Science Edition) , 2013, 32 (2) :213-218.
- [25] Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis [J]. Cochrane Database Syst Rev, 2015, (12): CD002243. DOI:10.1002/14651858.CD002243.pub3.
- [26] Yu Wen, Luo Hong-Min. Effect of hydrocortisone treatment on shock progression in patients with severe sepsis: hypress randomized clinical trial[J]. Chinese Critical Care Medicine, 2017, 29(02):116.
- [27] Bone R C, Fisher C J, Clemmer T P et al. A controlled clinical trial of high-dose

methylprednisolone in the treatment of severe sepsis and septic shock.[J] .N Engl J Med, 1987, 317: 653-8.

[28] Venkatesh B, Cohen J. Adrenocortical (dys) function in septic shock—a sick euadrenal state[J]. Best Pract Res Clin Endocrinol Metab, 2011, 25 (5) :719-733.

[29] Taylor Cormac T, Moncada Salvador, Nitric oxide, cytochrome C oxidase, and the cellular response to hypoxia.[J] .Arterioscler Thromb Vasc Biol, 2010, 30: 643-7.

[30] Adamik Barbara, Gozdzik Waldemar, Jakubczyk Dominika et al. Coagulation abnormalities identified by thromboelastometry in patients with severe sepsis: the relationship to endotoxemia and mortality.[J] .Blood Coagul Fibrinolysis, 2017, 28: 163-170.

[31] Strieter R M, Remick D G, Ward P A et al. Cellular and molecular regulation of tumor necrosis factor-alpha production by pentoxifylline.[J] .Biochem. Biophys. Res. Commun., 1988, 155: 1230-6.

[32] Strieber RM, Remick DG, Ward PA et al. Cellular and molecular regulation of tumor necrosis factor-alpha production by pentoxifylline [J] .Biochem Biophys Res Commun, 1988, 155(3) :1230-1236.

[33] Semmler J, Gebert U, Eisenhut T et al. Xanthine derivatives: comparison between suppression of tumour necrosis factor-alpha production and inhibition of cAMP phosphodiesterase activity.[J] .Immunology, 1993, 78: 520-5.

[34] González-Amaro R, Portales-Pérez D, Baranda L et al. Pentoxifylline inhibits adhesion and activation of human T lymphocytes.[J] .J. Immunol., 1998, 161: 65-72.

[35] Gibson R L, Redding G J, Henderson W R et al. Group B streptococcus induces tumor necrosis factor in neonatal piglets. Effect of the tumor necrosis factor inhibitor pentoxifylline on

hemodynamics and gas exchange.[J] .Am. Rev. Respir. Dis., 1991, 143: 598-604.

[36] Leentjens Jenneke,Kox Matthijs,Koch Rebecca M et al. Reversal of immunoparalysis in humans in vivo: a double-blind, placebo-controlled, randomized pilot study.[J] .Am. J. Respir. Crit. Care Med., 2012, 186: 838-45.

[37] Huang Hong,Jiang Jian-Xin,Zhu Pei-Fang et al.The effects of TNF alpha and IFN gamma on the expression of pattern recognition receptors on the surface of mouse alveolar macrophages[J].Chinese Journal of Surgery,2005(11):740-744.

[38] Ma Lin-Qin,Zhang Jia-Qi,Liu Yi et al.Comparison of effects of metaraminol and norepinephrine on elderly patients with septic shock[J].Chinese Journal of Emergency Medicine,2020(04):547-550.

[39] Zhang Hai-Feng,Zhang Hai-Bo,Wu Xue-Ping et al. Fisetin alleviates sepsis-induced multiple organ dysfunction in mice via inhibiting p38 MAPK/MK2 signaling.[J] .Acta Pharmacol. Sin., 2020, undefined: undefined.

[40] Liao Fang-Hsuean,Wu Te-Haw,Huang Yu-Ting et al. Subnanometer Gold Clusters Adhere to Lipid A for Protection against Endotoxin-Induced Sepsis.[J] .Nano Lett., 2018, 18: 2864-2869.

[41] Huang Weishan,Morales J Luis,Gazivoda Victor P et al. Nonreceptor tyrosine kinases ITK and BTK negatively regulate mast cell proinflammatory responses to lipopolysaccharide.[J] .J. Allergy Clin. Immunol., 2016, 137: 1197-1205.

Ethics approval and consent to participate

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. Ethical approval is not required because the research didn't involve human experiments.

Consent for publication

Written informed consent for publication was obtained from each participant enrolled or legal representatives.

Availability of supporting data

The data are accurate and reliable.

Competing interests

The authors have no conflicts of interest to declare.

Funding

Funding: We are grateful to the funds for supporting this study, including Hebei Provincial Government funded the training of excellent Clinical Medical talents and basic Research projects (No.2016034829) .

Authors Contributions

MJ, CF, XW and WL gave guidance to the project; WQ and WC collected data and materials. WQ wrote this article, and all the authors made important contributions to the writing of the manuscript. All authors approved the final version of the manuscript and agreed to be 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. All authors read and approved the final manuscript.

Acknowledgements

I would like to thank all the authors for their contributions to the writing and improvement of English.

Figures

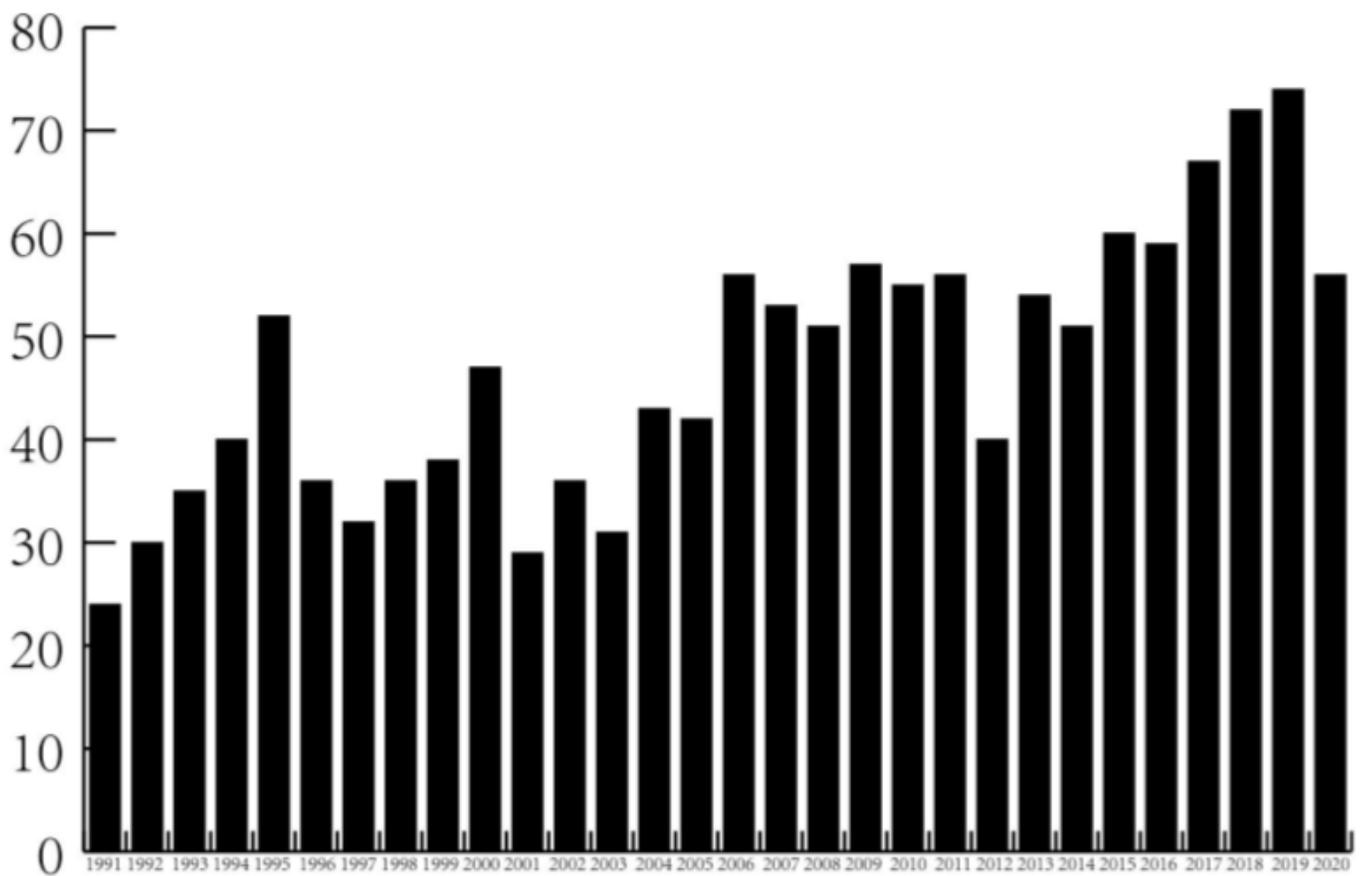


Figure 1

the number of articles published annually in the field of septic shock and hypotension in WOS from 1991 to 2020

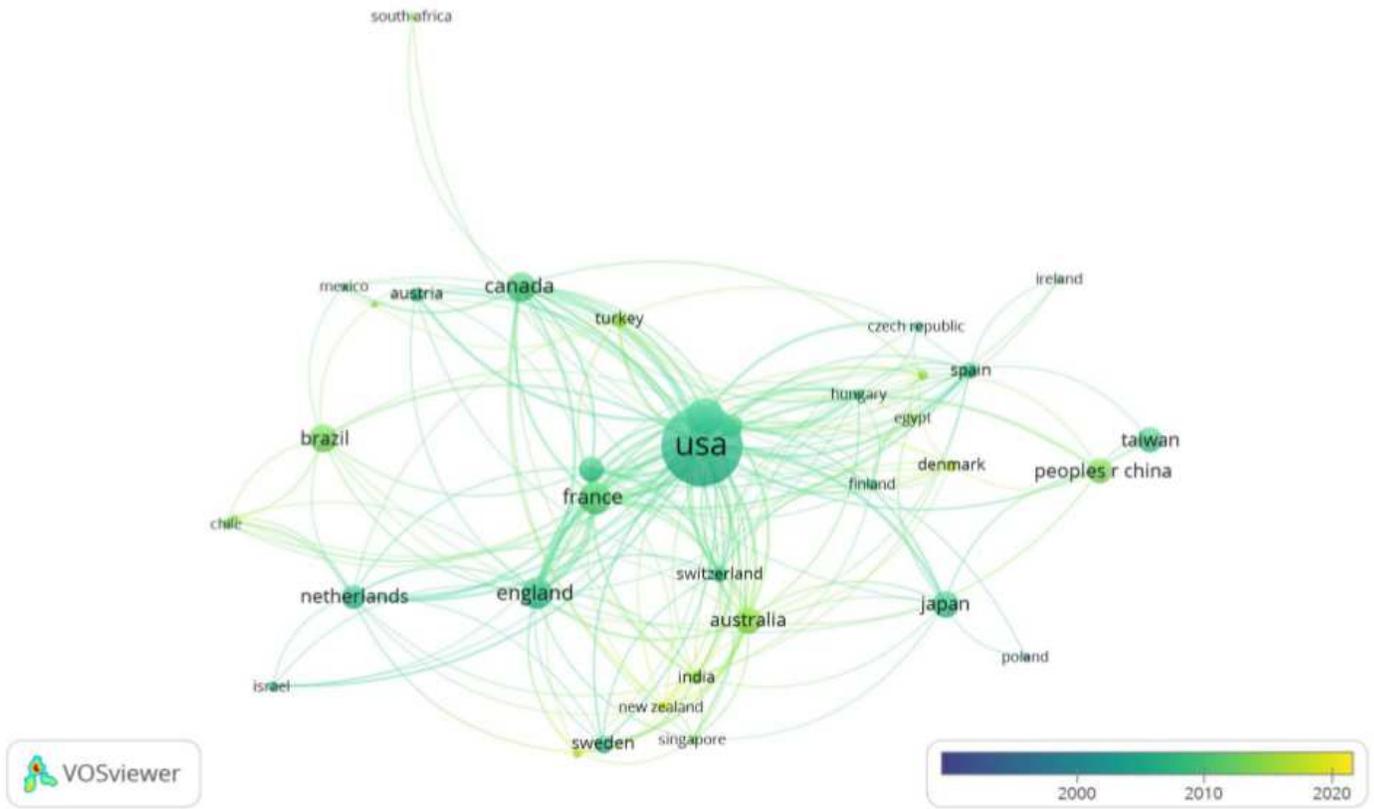


Figure 2

National or regional cooperation network in the field of septic shock hypotension in WOS from 1991 to 2020

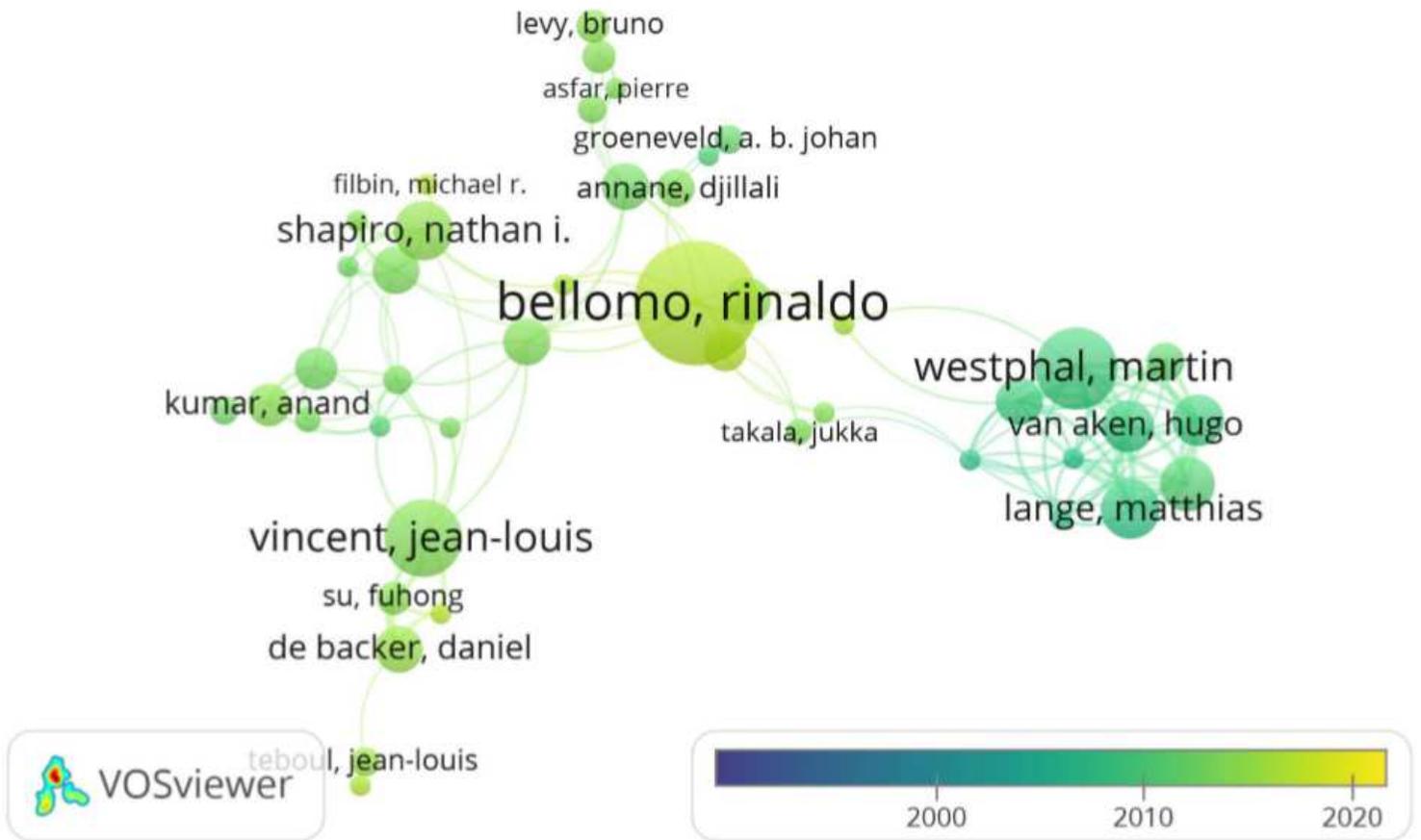


Figure 3

collaboration network of authors in the field of septic shock and hypotension in WOS from 1991 to 2020

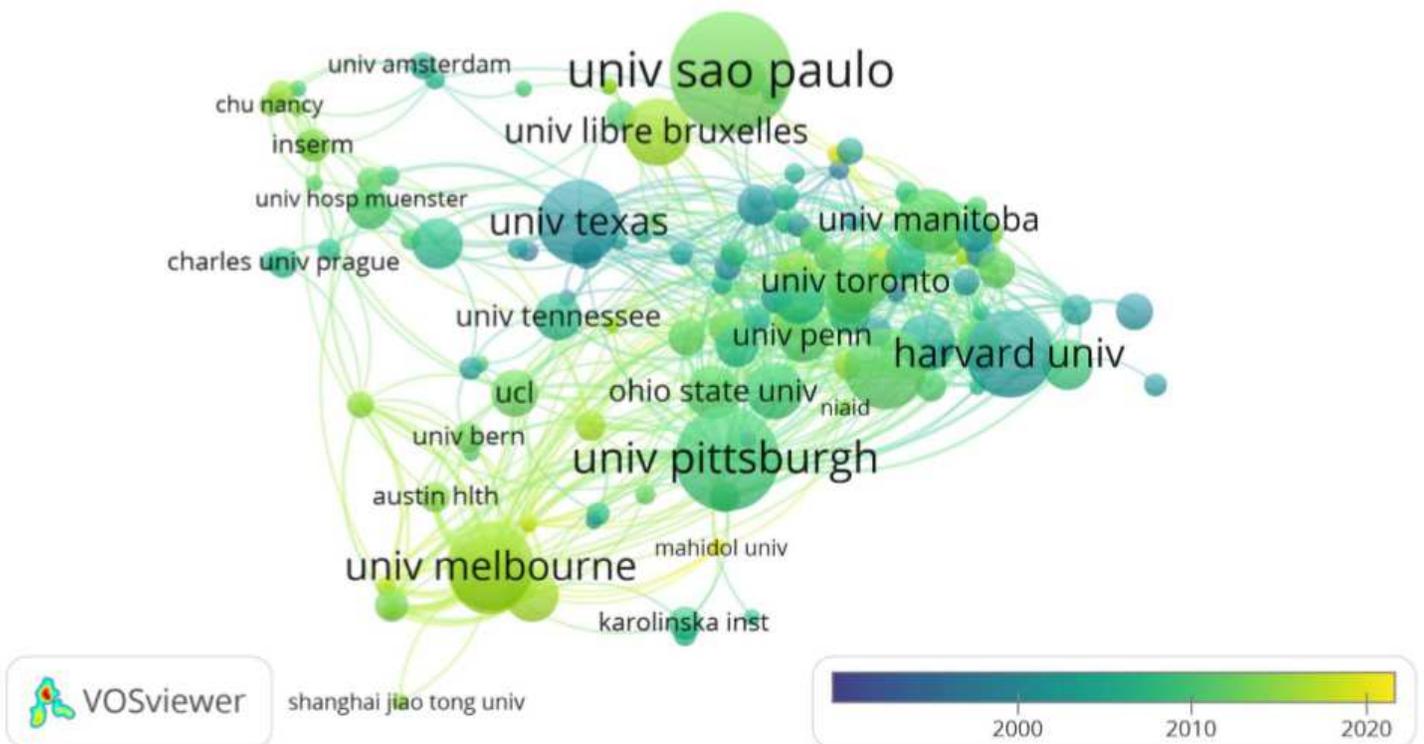


Figure 4

Network of institutions in the field of septic shock and hypotension in WOS from 1991 to 2020

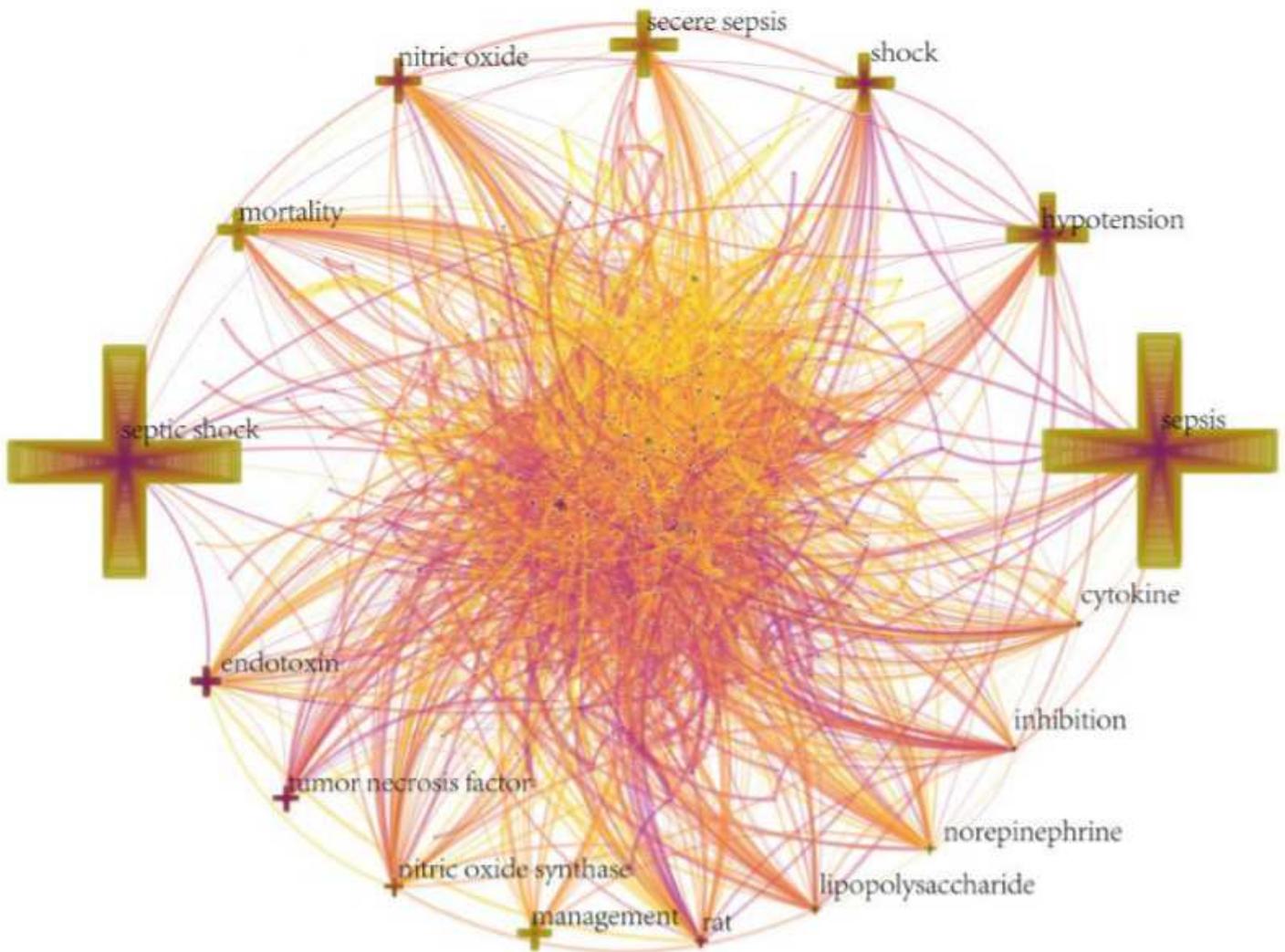


Figure 5

Keyword co-occurrence network in septic shock and hypotension in WOS from 1991 to 2020



Figure 6

Cluster map of key words in sepsis and hypotension in WOS from 1991 to 2020

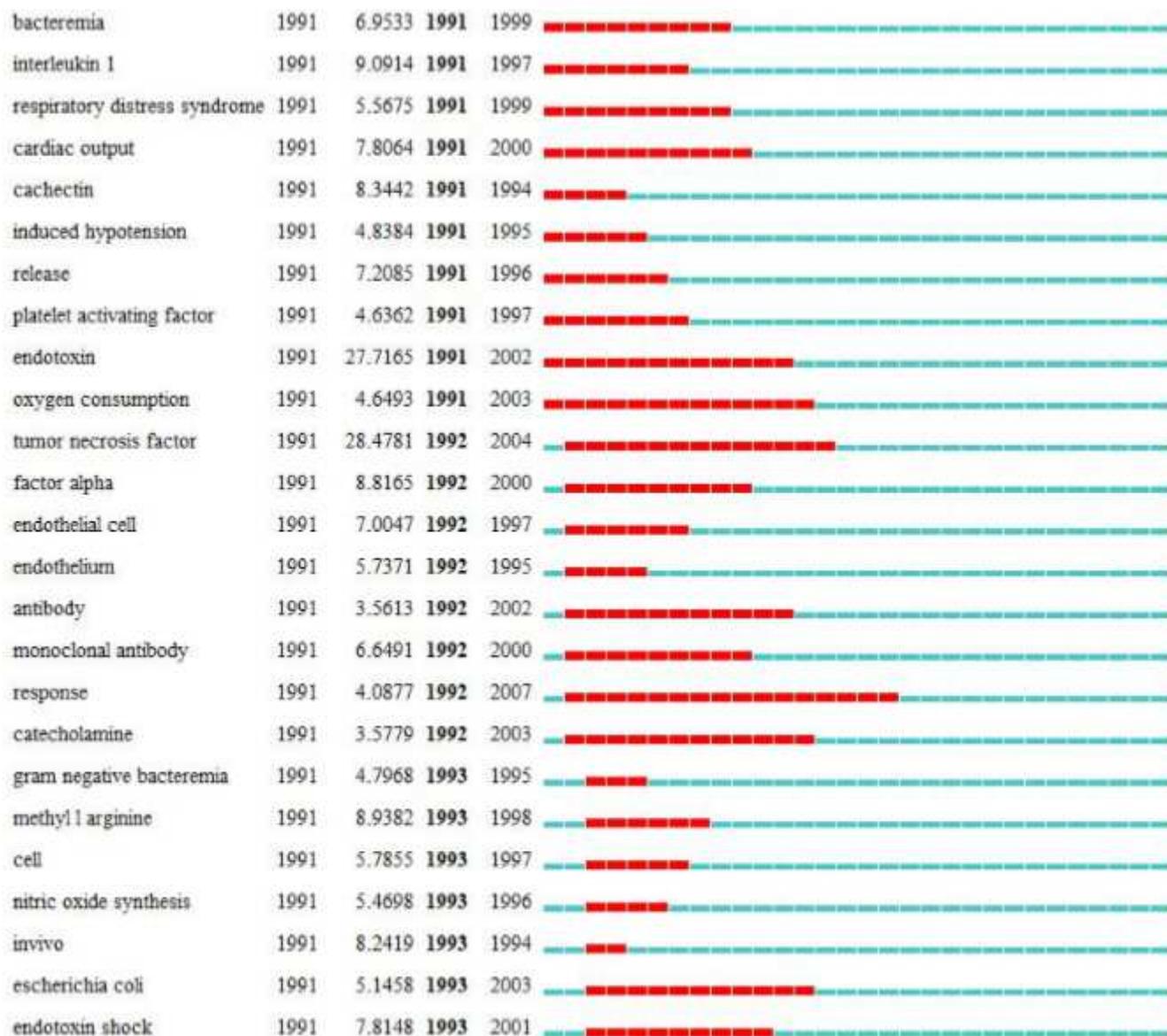


Figure 7

emergence map of key words in septic shock and hypotension in WOS from 1991 to 2020

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TABLE.pdf](#)