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Review Article

Research Status and Trend of Heart Rate Variability in Cancer: A Review and Bibliometric Analysis

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Abstract

Objective: To analyze the hot spots and frontiers of research on heart rate variability in cancer patients via CiteSpace.

Methods: Relevant publications were searched from the Web of Science core collection for the period from January 1, 2000, to October 31, 2022. Network mapping was generated using CiteSpace to identify and analyze countries, institutions, frontier authors, high co-citation authors, keywords, and research hotspots and frontier trends.

Results: A total of 770 relevant publications were searched in this study. This study mainly focused on institutions in Europe and the United States, such as Harvard University, which has a rich history of contributions in this subdomain. A core network of researchers, represented by Shi Bo and Li Guilin, was identified as the primary drivers of research in this area. The United States emerged as the most prolific and influential country in this field, indicating a strong research focus and impact. High-frequency keywords were autonomic nervous system, tumour necrosis factor, inflammation, anxiety, cardiovascular disease, and mortality.

Conclusion: Utilizing the CiteSpace software, this study conducted a comprehensive analysis of the research hotspots and frontiers pertaining to heart rate variability in cancer patients. The results revealed that the neuroimmune regulation of the vagus nerve and the quality of patient survival emerged as significant research foci. Future research should delve into neuroimmune modulation to elucidate its mechanism of action in heart rate variability in cancer patients. And the exploration of supportive care such as yoga and mindfulness therapy in improving the quality of patient survival is encouraged.

Keywords: Cancer, Heart rate variability, Vagus nerve, Quality of survival, Research hotspots, CiteSpace

Introduction

Cancer is a major cause of death and a significant obstacle for countries around the world to improve the life expectancy. In 2020, an estimated 19.5 million new cancer cases were reported globally, and 10 million people died of cancer, which creates a significant social burden [1]. Therefore, in-depth research into the mechanisms of cancer development, early detection and improvement of prognosis is particularly important. Heart Rate Variability (HRV)refers to a permanent fluctuation in the time interval between adjacent heartbeats, produced by the interaction of the autonomic nervous system as well as the cardiovascular system [2]. It includes both time domain analysis and frequency domain analysis, as well as non-linear parametric analysis. Time domain indicators mainly include Standard Deviation of NN intervals (SDNN), Root Mean Square of the difference between adjacent NN intervals (RMSSD), the percentage of the number of beats with a difference between total adjacent beats >50ms to the total number of beats (pNN50), delta index, etc., which are usually recorded by 24-hour ambulatory ECG in clinical practice; frequency domain indicators mainly

include Total Power (TP), Very Low Frequency (VLF), Low Frequency (LF), High Frequency (HF), etc., which are recorded by 5-minute short time course analysis in clinical practice; non-linear analysis method is still in the exploration stage. Due to its sensitivity, convenience, and non-invasive nature [3-7]. HRV has been used in recent years to reflect autonomic nervous system activity and to quantitatively assess cardiac sympathetic and vagus tone and homeostasis [8]. Numerous studies have shown that approximately 80% of patients with advanced cancer patients have autonomic dysfunction [9] and exhibit significantly lower HRV values compared to healthy individuals [10-13]. With the continuous rise in the attention towards cancer, more and more scholars are focusing on the study of HRV in relation to cancer. Due to the variety and complexity of cancer types, it is difficult for researchers to grasp the general direction of this area of research and conduct studies without a priori knowledge. Therefore, it is essential to help researchers analyse the vast literature on the subject. However, a comprehensive and objective presentation of the hot spots and frontiers of research in the field of HRV and cancer-related research has not yet been seen. CiteSpace is a Java-based information visualisation software that can analyse and visualise hotspots and research frontiers in the scientific literature of a particular discipline or field of knowledge over a specific period, and explore the potential knowledge contained in the scientific literature. This study aims to visualize the research hotspots and development trends in HRV and cancer-related English literature through CiteSpace software and provide reference for subsequent scientific research on cancer prevention, treatment, and prognosis improvement.

Material and Methods

Sources of Information

Web of Science (WOS) contains more than 13,000 of the world's most influential academic journals, covering various fields such as natural sciences, engineering, biomedical sciences, social sciences, arts, and humanities. It is an important source of citation information for bibliometric studies and a source of general statistics for bibliometric software. We searched the WOS core collection for relevant articles from January 2001 to October 2022, using the following terms: HRV and cancer (Table 1).

Table 1: Search Strategy.

Set	Search Query
#1	TS = (Heart Rate Variability OR HRV)
#2	TS = (cancer OR tumor OR neoplasm)
#3	Languages=English
#4	Literature Type= original Articles or reviews
#5	(#1) AND (#2) AND (#3) AND (#4)

Inclusion Criteria: Original peer-reviewed original articles or reviews published in English on the relationship between HRV and cancer.

Exclusion Criteria: Conference abstracts or erratum-type literature; unpublished articles; duplicate articles; irrelevant articles.

Research Methodology

Articles retrieved through WOS were exported in 'plain text format' and then imported into CiteSpace 6.1.R3 for further analysis. We followed the main steps of the CiteSpace process to obtain co-citations, keyword co-occurrence, emergent knowledge graphs, etc [14]. The core concepts of CiteSpace include burst detection, mediated centrality, and heterogeneous networks, which help to visualise the current state of research and identify research hotspots and frontiers in a timely manner. Nodes in different graphs represent authors, institutions, countries, or keywords. Node size indicates the frequency of occurrence or citation, number of links between nodes indicates the strength of the collaboration, and node colour indicates the year of occurrence or citation. In addition, nodes with purple cut edges indicate high intermediary centrality and are often identified as hot spots or turning points in a field [15].

Results

Annual Distribution of Research Literature

The number of publications reflects the dynamic process of research, and to a certain extent, the hot spots and development trends of the research field. The initial search of this study yielded 820 publications, and after further screening and deletion of ineligible publications according to the inclusion and exclusion criteria, a total of 770 publications were included. As shown in, the number trend of annual publications related to the relationship between HRV, and cancer fluctuated within a certain range until 2010 and started to show an upward trend after 2010 which indicated that this field was in a phase of continuous development and received increased attention from researchers worldwide (Figure 1).

Distribution Profile of Research

Research Distribution of Countries and Institutions: The distribution of countries and institutions in this area is shown in Table 2. The top four countries with the largest number of publications were the United States (n=252, 32.8%), China (n=98, 12.8%), Germany (n=58, 7.6%), and the United Kingdom (n=54, 7.0%). The volume and centrality of literature published from the United States far exceeds that of other countries, indicating that researches from U.S. play a leading and influential role in this field. Also high in centrality are the United Kingdom, Spain, and Austria, indicating that these countries play a strong bridging role in inter-country cooperation. Although China ranked second in the volume of literature published in this field, its centrality score was only 0.08, significantly lower than that of the United States. it suggests that the depth of Chinese research in this field needs to be improved. The top institution with largest number of publications was Harvard University

in the United States. In addition, five of the top eight institutions were from the United States. As shown in Figure 2(A), the sparse inter-country linkages indicated less cooperation between countries. In Figure 2(B), the most intensive years of inter-institutional cooperation were 2004 to 2012, followed by 2017 to 2019, with the remaining years having less inter-institutional cooperation (Figure 2A,2B).

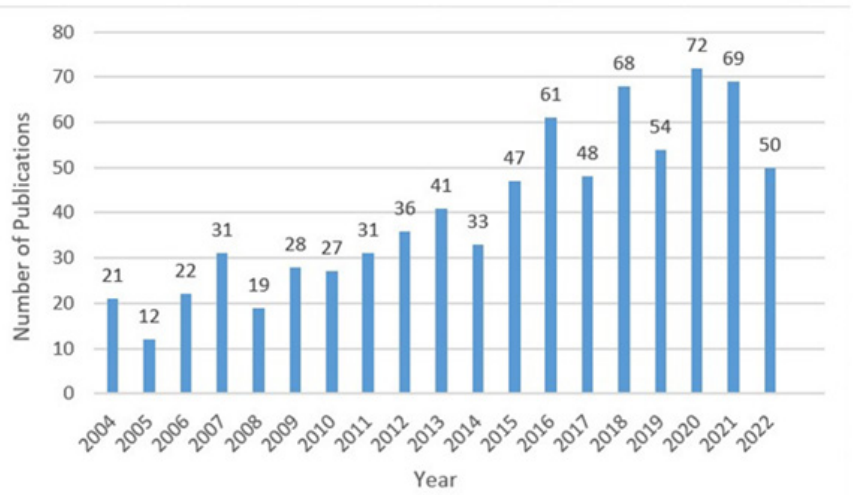

Figure 1: Annual trend of publications.

Table 2: The top 8 countries and institutions.

Rank	Country/Region	Count	Centrality	Year	Institution	Count	Centrality	Year
1	USA	252	0.65	2004	Harvard Univ	13	0.02	2004
2	PEOPLES R CHINA	98	0.08	2004	Natl Yang Ming Univ	11	0.00	2008
3	GERMANY	58	0.09	2004	Bengbu Med Coll	9	0.01	2019
4	ENGLAND	54	0.28	2004	Brigham & Womens Hosp	9	0.00	2005
5	CANADA	41	0.06	2004	Duke Univ	8	0.02	2010
6	NETHERLANDS	39	0.03	2004	Univ Sao Paulo	8	0.00	2014
7	JAPAN	38	0.02	2004	Harvard Med Sch	8	0.00	2017
8	ITALY	37	0.03	2005	Univ Texas MD Anderson Canc Ctr	7	0.01	2010

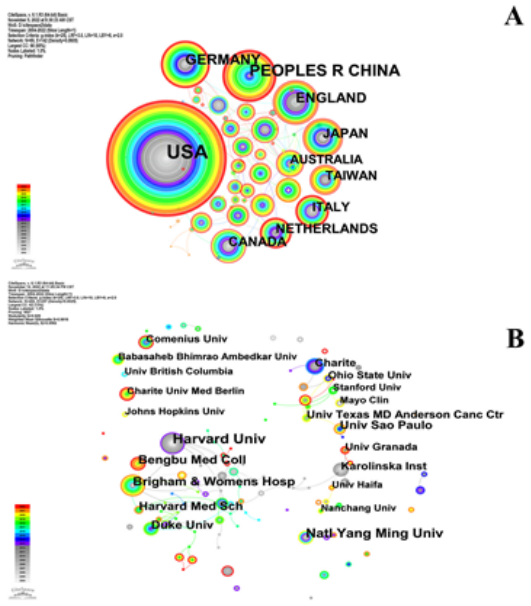

Figure 2: (A) The network of co-country; (B) The network of co-institution.

Authors and Co-Cited Authors: The author co-authorship network shows the collaboration between authors of highly productive articles. As shown in Figure 3(A), the most prolific authors were Shi Bo, Gidron Yori, and Barden Heuer Hubert J, all of whom published 7 articles, followed by Wang Jing Feng with 6 articles. Overall, the collaboration among authors has become more frequent in recent years. A core network of researchers, represented by Shi Bo and Li, Guilin, has been initially formed. In addition, the low centrality of the top 10 authors suggested the need for more high-quality and large-scale collaborations in the future.

Co-cited authors are two or more authors who are cited simultaneously in one or more papers. As shown in Figure 3(B), the top 10 co-cited authors were cited more than 850 times. The most frequently cited authors were CAMM AJ (n=203), followed by TRACERY KJ (n=98), THAYER JF (n=94), and BOROVIKOVA LV (n=71). Four of the top 10 authors had centrality above 0.10, with BOROVIKOVA LV (0.21) being the highest. These higher centrality co-cited authors show purple chronology in the mapping network, indicating that they play an important bridging role (Figure 3A,3B).

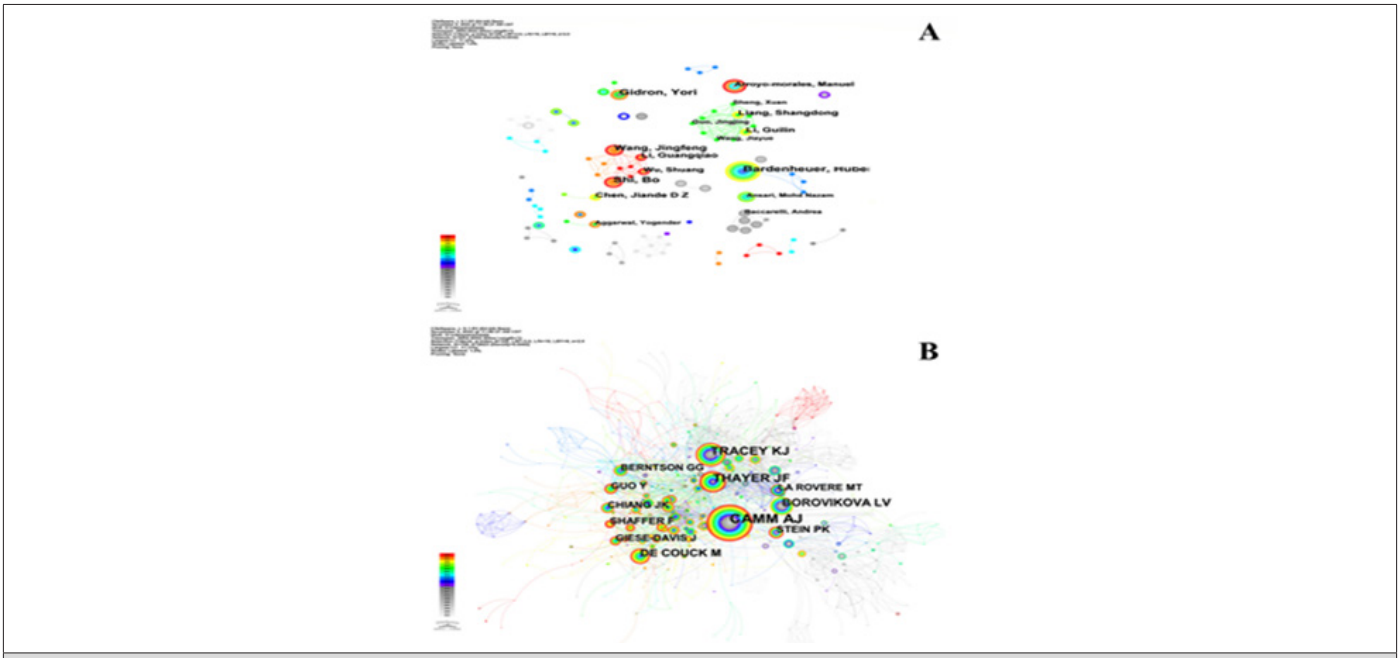

Figure 3: (A) The network of co-authorship; (B)The network of author co-citation.

Research Hotspots and Frontier Analysis

Research Hotspot Analysis: The keywords of the literature are a high summary of the content of the literature, usually reflecting the research hotspots in the field. The higher the mediated centrality of a keyword, the more influential and important it is. We used one year as a time slice, 541 nodes and 1976 connections to form a network of co-cited keywords (Figure 4). (Table 3) showed the top 10 keywords with high frequency and high centrality (excluding those used to conduct the literature search). We summarized the key words in the following five areas:

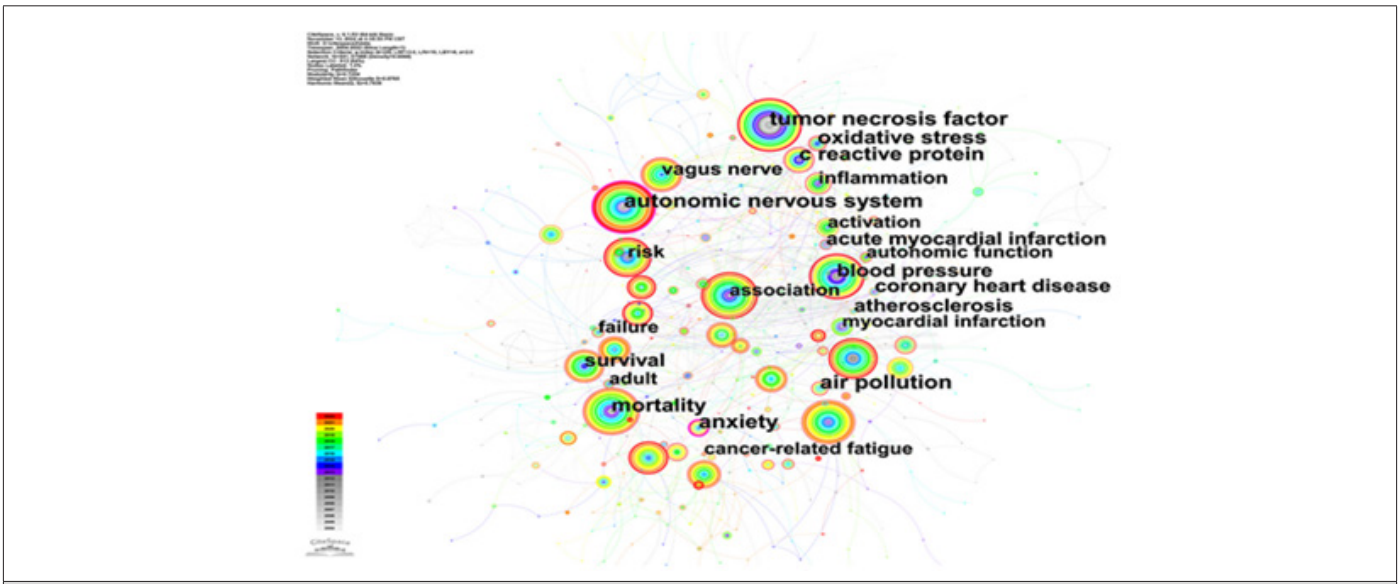

Figure 4: The network of co-occurring keywords.

Table 3: Top 10 keywords in terms of frequency and centrality.

Rank	Frequency	Keywords	Centrality	Keywords
1	76	tumor necrosis factor	0.22	autonomic nervous system
2	76	autonomic nervous system	0.22	anxiety
3	71	mortality	0.18	risk
4	67	association	0.17	c reactive protein
5	66	breast cancer	0.16	mortality
6	63	blood pressure	0.16	blood pressure
7	62	risk	0.15	vagus nerve
8	53	cardiovascular disease	0.15	tumor necrosis factor
9	50	survival	0.15	air pollution
10	50	vagus nerve	0.14	inflammation

i. 'Autonomic nervous system', including vagus nerve, autonomic nerve, cholinergic nerve, etc.

ii. 'Inflammation', including oxidative stress, C-reactive protein, tumour necrosis factor, etc.

iii. 'Negative emotions', including cancer-related fatigue, anxiety, depression, stress, etc.

iv. 'Cardiovascular disease risk', including blood pressure, atherosclerosis, myocardial infarction, etc.

v. 'prognosis', including mortality, survival, quality of survival, etc (Figure 4) (Table 3).

Research Frontier Analysis: Keyword burst detection can reveal emerging or emergent theoretical trends and new topics in a field (Figure 5) [16]. showed the top 18 most explosive keywords. The blue line indicates the time interval, and the red line indicates the time of the keyword outbreaks [15]. The keywords with strong citation outbreaks were 'tumor necrosis factor' and 'myocardial infarction', both in 2004, followed by 'C-reactive protein' and 'fatigue' in 2007 and 2012, respectively. The 'vagus' and 'health' signals continue until 2022, and the signals are still happening, indicating that these areas have received a lot of attention in recent years (Figure 5).

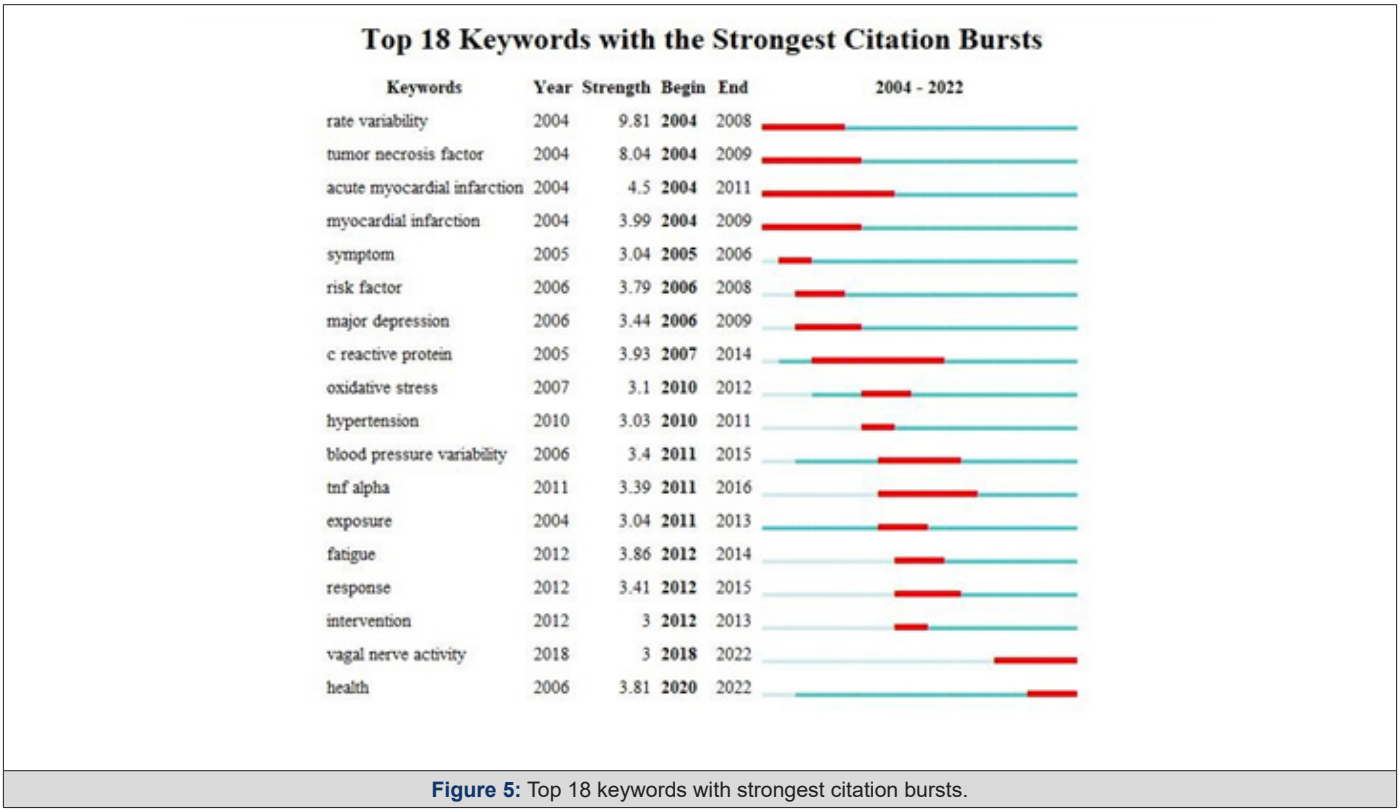

Figure 5: Top 18 keywords with strongest citation bursts.

As can be seen in (Figure 5), the research hotspots were gradually shifting from inflammatory response mechanisms (tumour necrosis factor, oxidative stress, C-reactive protein, etc.) to cardiovascular disease risk and cancer-related fatigue. The keywords that have emerged in recent years were 'Vagus nerve' and 'health' as a proxy for prognosis, quality of life, mortality, etc. This revealed a shift in research emphasis from basic research to the effects of clinical interventions and the benefits of patient care.

Discussion

A total of 770 relevant articles were eventually retrieved because of this study. In recent years, an increasing number of researchers have focused on the abnormal manifestations and pathological mechanisms of HRV in cancer patients, initially forming a core network of investigators represented by Shi Bo and Li Guilin. The United States were the leading country in this area, with Harvard University and Harvard Medical School publishing the most relevant research literature in this field. For keyword analysis, both high frequency and high intermediate centres were autonomic nervous system, tumour necrosis factor, blood pressure (cardiovascular disease), and prognosis. The autonomic nervous system, especially the vagus nerve, was the longest-lasting emergent keyword to date. This suggested that the neuromodulatory mechanisms innervated by the vagus nerve played an important role in bridging the gap between HRV and cancer. The newly emerging keyword 'health' represented by "prognosis", "quality of life" and "mortality" were indicating the research focus shifting to the clinical intervention effects and treatment risks and benefits.

Autonomic Nervous System - A Bridge between HRV and Cancer-Related Factors

Analysis of keyword co-citation bursts showed that the keyword with the most co-citation bursts in 2018 was vagus nerve. The vagus nerve is the main branch of the parasympathetic nervous system, and its innervation is crucial for the healthy functioning of most internal organs [17]. In this paper we argue that the vagus nerve can act as a bridge between HRV and cancer-related factors. Firstly, vagus activity is closely related to HRV parameters. HRV, as a non-invasive test, primarily evaluates the function of the autonomic nerves and reflects their activity and tone [18]. The physiological significance of the various indicators of HRV varies [17]. Specifically, RMSSD, pNN50 and HF are influenced by parasympathetic nerves; SDNN and LF are influenced by both sympathetic and parasympathetic nerves; LF/HF reflects the balance between sympathetic and parasympathetic nerves [19]; and VLF is associated with inflammation, and its reduced level indicates a strong inflammatory response [20]. Overall, HRV is reduced in patients with inflammation, disease, and trauma, suggesting the presence of autonomic dysfunction due to high sympathetic activity and/or low vagus activity. In the case of cancer patients, a study by *Nunan, et al.,* [21] of 21,438 cancer patients showed that RMSSD and SDNN were significantly lower in cancer patients than in healthy individuals. HRV is significantly lower in cancer patients than in normal subjects, indicating an imbalance in autonomic function. This difference is more pronounced in patients with advanced cancer [22]. *Atsunori Kamiya, et al.,* [23] demonstrated through animal experiments that sympathetic innervation of tumors accelerated tumor progression in breast cancer, while parasympathetic innervation of tumors slowed them down. Immunohistochemistry of 29 breast cancer specimens revealed that cancer recurrence was associated with a higher density of tumor sympathetic fibres and a lower density of tumor parasympathetic fibres. This suggests that antagonistic innervation of sympathetic and parasympathetic nerves exists in the breast tumor microenvironment, and that abnormal activation of autonomic nerves may contribute to tumorigenesis or progression. Autonomic nerves can stimulate tumorigenesis, progression, and metastasis by influencing the inflammatory response (particularly pro-inflammatory cytokines and C-reactive proteins) [24,25]. In addition, negative emotions as well as cardiovascular disease are also linked to tumors via the autonomic nerve. See below.

Inflammation-Mediated Tumour-Promoting Mechanisms

Regarding the autonomic nervous system, as reflected by HRV, for inflammation, the vagus nerve has an important neuroimmunological function. It inhibits tumour growth by suppressing the body's inflammatory and tumor-promoting mechanisms through three pathways [26,27]. One is through the Hypothalamic Pituitary-adrenal Axis (HPA) pathway. The inflammatory message causes activation of the vagus afferent fibres and the message is transmitted to the central nervous system. This in turn induces activation of the HPA pathway leading to cortisol secretion, which inhibits the production of pro-inflammatory cytokines (TNF-α, IL-6, etc.), thereby suppressing the systemic inflammatory response; The second is the Cholinergic Anti-Inflammatory Pathway (CAP). The vagus nerve targets the production of the neurotransmitter Acetylcholine (ACh), which binds to the nicotinic alpha 7 receptor expressed by macrophages. This in turn reduces the production and recruitment of inflammatory molecules, leading to a reduction in oxidative stress and an anti-inflammatory effect [28-30]; The third is the splenic sympathetic anti-inflammatory pathway. The celiac ganglion is conveyed via a downstream pathway to stimulate splenic production of ACh and ultimately inhibit the production of the pro-inflammatory cytokine TNF-α [31]. And sympathetic nerves antagonise the vagus nerve. Experiments have shown that the risk of cancer development is reduced after blocking the beta-adrenergic receptors on which sympathetically secreted catecholamines act [32]. In summary, the prevalence of low HRV in tumour patients suggests reduced vagus activity and/or increased sympathetic function, reduced anti-inflammatory function and reduced tumour suppression.

Inflammatory Markers: Theoretical and empirical evidence converge to suggest a negative correlation between HRV indices and inflammatory markers. *Williams, et al.,* [33] reviewed the relationship between 51 inflammatory markers (CRP, IL-6, TNF, etc.) and HRV and found that SDNN-HRV and HF-HRV were negatively correlated with CRP, whereas HF-HRV was negatively correlated with CRP and TNF. *Haarala, et al.,* [34] reported an inverse relationship between LF-HRV and CRP in 1,601 healthy individuals. By analysing 264 middle-aged male twins, *Lambertt, et al.,* [35] found that reduced ULF-HRV and VLF-HRV were associated with increased CRP. This may be due to vagus dysfunction, resulting in abnormalities in the aforementioned anti-inflammatory pathways and consequently a weakened function of the body to inhibit the secretion of inflammatory factors. In contrast, inflammatory markers have been reported to promote tumour development through a variety of pathways.

a) Tumour necrosis factor-α (TNF-α): TNF-α is a serum factor capable of inducing tumour necrosis. It is mainly secreted by activated macrophages when the body develops an inflammatory

response. It acts on the vascular system of the tumour thereby disrupting the blood supply to the tumour cells [36]. However, studies have shown that TNF-α is also capable of inducing cellular carcinogenesis, leading to tumorigenesis. Specifically, TNF-α induces carcinogenesis by the following mechanisms:

i. Induces de novo mutations and inhibits DNA repair mechanisms, resulting in genotoxicity [37].

ii. Direct activation of the NF-κB pathway in tumor cells, and misregulation of NF-κB can directly promote tumour cell survival and proliferation [38].

iii. Activation of immune cells to release other pro-inflammatory cytokines, of which cytokines such as IL-6 have been reported to promote malignancy [39].

iv. Promote the immunosuppressive capacity of myeloid-derived suppressor cells and TREG cells, which in turn promote the escape of tumour cells from immune surveillance [39-41].

v. Promotes Epithelial Mesenchymal Transition (EMT), which causes epithelial cells to lose cell polarity and connectivity to the basement membrane. This results in a higher capacity for migration and invasion, anti-apoptosis, and degradation of the extracellular matrix [42]; Induces the synthesis of Matrix Metalloproteinase (MMP), which degrades various protein components of the extracellular matrix. This disrupts the histological barrier to tissue cell invasion and thus promotes tumour metastasis [43].

b) C-Reactive Protein (CRP): CRP is a non-specific marker of inflammation. At early tumour development, endothelial cells are activated as the tumour grows. CRP in the blood then enters the tissues as part of the normal protective inflammatory response and controls disease progression [44]. In addition, TNF-α can increase the mRNA for CRP, which in turn promotes the translation of CRP; tumour inflammatory signalling is also able to promote the production of hepatic CRP. Studies have shown a positive association between CRP levels and overall cancer, lung cancer, colorectal cancer, head and neck cancer, liver cancer, and kidney cancer45, while the association between CRP and chronic lymphocytic leukaemia is controversial [45-47]. No linear correlation has been found between CRP levels and breast cancer. However, there is a non-linear "increase to decrease" pattern of association between the two, the mechanism of which needs to be further investigated [45,48-50].

Oxidative Stress: OS refers to the imbalance between the production of oxidants (Reactive Oxygen Species) and their elimination through antioxidants. Reactive Oxygen Species (ROS) usually include free radicals with reactive metabolites, which are normal cellular metabolic products. However, the accumulation of ROS can lead to damage to important biomolecules and cells [50]. Numerous studies have shown that ROS accumulation in the paraventricular nucleus of the hypothalamus leads to sympathetic hyperactivity [51-54]. *Anjum, et al*., [55] reported that the production of reactive oxygen species produces oxidative stress on healthy neurons, which further enhances neurodegeneration. HRV analysis, on the other hand, is primarily an evaluation of autonomic function. When inflammation occurs in the body, a large number of mast cells and leukocytes are recruited to the site of injury. At this time, the oxygen consumption of cells increases significantly, and a large amount of ROS is produced and accumulated at the site of injury, which is known as 'respiratory burst' [56,57-59]. Furthermore, the studies have shown that the accumulation of large amounts of ROS can induce carcinogenesis by directly or indirectly damaging DNA and protein products [57,60-63]. In addition, ROS can specifically activate some signalling pathways that regulate cell proliferation and metastasis, and angiogenesis to promote tumour development [64]. However, during cancer development, it is still the early DNA damage stage that is most affected by ROS [65].

We summarize the above mechanisms into a pattern diagram (Figure 6). Besides the main mechanisms described above, low levels of inflammation can provide trophic signals to increase the rate of cell mutation and the proliferation of mutant cells [66]. Chronic inflammation can also promote the tumour process by stimulating the secretion of cytokines and growth factors (e.g., PDGF, TGF-β) that promote rapid cell proliferation [60]. Moreover, tumour cells in the tumour microenvironment can also induce an inflammatory response by promoting the secretion of immune-recruited chemokines and thus positive feedback regulation (Figure 6) [67].

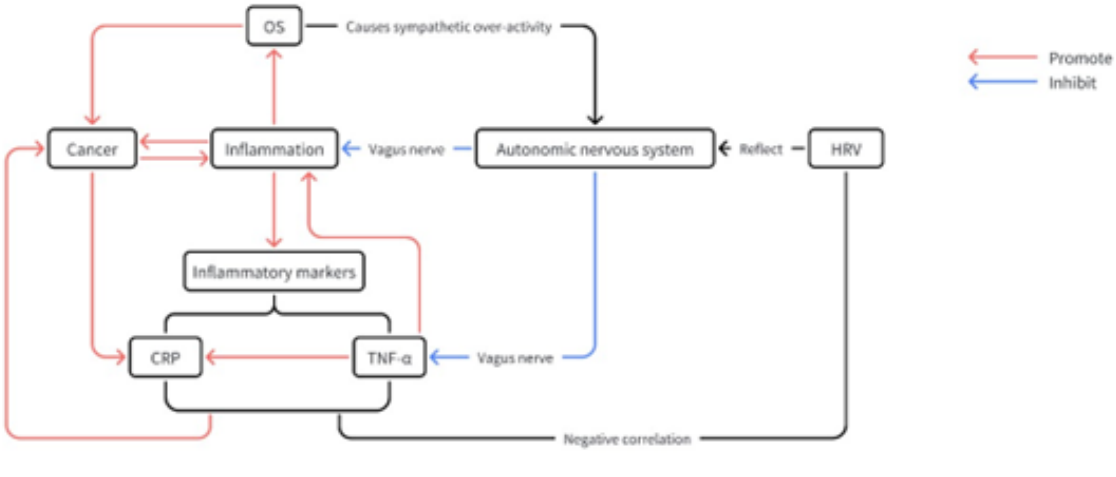

Figure 6: HRV reflects the pattern of inflammation-mediated tumor promotion mechanism.

Negative Emotions Drive the Occurrence or Development of Cancer

Beatrice Bortolato, et al., [68] showed that major depression is common in cancer patients and that the prognosis of cancer patients with comorbid depression is poor. In a study involving 282,203 breast cancer patients, researchers proposed that depression and anxiety were associated with increased recurrence rates and all-cause mortality in breast cancer [69]. This revealing the contributory role of depression and anxiety in breast cancer progression and mortality. A cancer diagnosis may place a significant psychological burden on most cancer patients. They may develop cancer-related exhaustion, mental anxiety or depression, etc., as well as dysfunctional social relationships and abnormal social behavior, ultimately leading to a poor cancer prognosis [69]. We summarize these psychosocial problems as negative emotions. In recent years there has been an increasing interest in the study of negative emotions such as cancer-related fatigue, anxiety and depression, in relation to the triad of vagus nerve and cancer [70]. As already mentioned, many studies have shown that reduced HRV is common in cancer patients, especially in patients with advanced cancer, revealing their vagus nerve dysfunction. Furthermore, a study by *Julian Koenig, et al.,* [71] revealed that states such as depression and anxiety are associated with lower resting-state high-frequency Heart Rate Variability (HF-HRV) levels. Lower HF-HRV levels tend to indicate reduced autonomic activity, especially in the vagus nerve [71]. In other words, lower HRV, or vagus dysfunction, is observed in cancer patients and in patients with negative emotions. Therefore, it is reasonable to believe that there is a relational pathway between negative emotion-vagus nerve-cancer.

In terms of biological mechanisms, depression and anxiety, among others, are associated with abnormalities in the autonomic nervous system and neuroendocrine disorders, contributing to cancer progression and increased mortality [72]. To be specific, depression [73], stress [73] and anxiety [74] may cause specific regions of the prefrontal cortex to become hypoactive, leading to de-inhibition of sympathetic excitatory circuits and energy mobilization and reduced vagus activity [73]. These induces the accumulation of pro-inflammatory cytokines in the tumour microenvironment, promoting inflammation, HPA axis dysregulation and reduced immune surveillance, further affecting tumour metastasis and progression. *Bai Cui, et al.,* [75] found that chronic stress leads to abnormal release and accumulation of hormones such as catecholamines and norepinephrine in the tumour microenvironment by stimulating the HPA axis and Sympathetic Nervous System (SNS). Thereby, it activates the expression of specific receptors for cancer biological processes as well as downstream oncogenes. In addition, negative emotions such as cancer-related fatigue [76], depression and anxiety may also contribute to decreased patient survival by leading to unhealthy and irregular lifestyle behaviours, poor adherence to treatment, and psychiatric disorders. Future research could focus on the role of modulating the body's HRV by intervening in the autonomic nervous system for improving negative emotions in cancer patients as well as cancer prognosis.

Common Risk Factors Exist for Cardiovascular Disease and Cancer

Studies have shown that cancer patients have a higher risk of dying from cardiovascular disease than the general population. Sturgeon. *KM, et al.,* [77] counted the mortality and cause of death of 3,234,256 cancer survivors in the United States and found that 11.3% of patients died from cardiovascular disease. In addition, most cardiovascular disease deaths occur in patients diagnosed with breast, prostate or bladder cancer. Meanwhile, patients with cardiovascular disease have an increased risk of developing cancer [78]. Causes of cardiovascular disease and cancer appearing in the same patient may be complications arising from the use of drugs during treatment [79-82]. For example, anthracyclines are cardiotoxic and alter cardiac autonomic regulation in the treatment of cancer [83]. However, some studies support the hypothesis that cardiotoxicity of anthracyclines can be detected before the onset of left ventricular dysfunction [84, 85]. In addition, there are common risk factors for cardiovascular disease and cancer, such as diabetes, dyslipidaemia, cachexia, and impaired immune response [86,87]. They cause disease mainly through three basic mechanisms, namely oxidative stress and DNA damage, excessive inflammation, and excessive sympathetic nervous system activity. *Maria TLR, et al.,* [88] found that low heart rate variability (SDNN <3 ms) or low-pressure reflex sensitivity (<0.3 ms/mm Hg) significantly increased the risk of multifactorial cardiac death. That is, in similar fashion to cancer, HRV was negatively associated with risk and poor prognosis of cardiovascular disease. It may be due to low HRV suggesting vagus dysfunction, and an important role of the vagus nerve is to reduce the risk of cardiovascular disease by inducing the secretion of vasoactive intestinal peptides, thereby increasing coronary blood flow. Meanwhile, the low vagus activity also reduced its anti-inflammatory and anti-apoptotic effects on the myocardium [89,90]. In addition, in the case of myocardial infarction, necrotic cells enhance the inflammatory response by releasing danger signals such as pro-inflammatory cytokines (e.g., tumour necrosis factor, IL-1) [91]. This in turn promoted the development of cancer. Moreover, inflammatory markers associated with heart failure, such as C-reactive protein, have clear predictive value for cancer [92].

In summary, autonomic imbalance may be a common pathway for increased morbidity and mortality in a range of diseases, including cancer and cardiovascular disease. Cancer increases the risk of cardiovascular disease by suppressing the vagus nerve (the mechanism of which has been described above). Correspondingly, cardiovascular disease can also promote tumorigenesis by promoting an inflammatory response related to the vagus nerve. Future studies may focus on the predictive role of HRV for the development or exacerbation of cardiovascular disease in cancer patients. As well as exploring the role of monitoring HRV and timely intervention of the vagus nerve represented by HRV in reducing cardiovascular disease complications from chemotherapy drug use in cancer patients.

Quality of Survival, Prognosis - Effects and Benefits of Interventions for Cancer

The most frequent keyword outbreak in 2020 was health, in-

cluding quality of survival, prognosis, mortality, and survival, suggesting a shift in research emphasis toward the effectiveness of clinical interventions and the benefits of patient care. In addition to surgery, radiotherapy and targeted tumour therapy, scientists have proposed emerging interventions such as mindfulness therapy, Tai Chi, Qigong and yoga therapy. This provides a new thought of treatment for clinicians. In addition to considering direct killing of cancer cells, aggressive physical and psychological interventions can be used to improve the patient's quality of survival. In a study of 28,790 patients with early-onset colorectal cancer in the United States, results suggested that individual lifestyle behaviours and community patterns may contribute to differences in survival of cancer patients [93]. It also indicates that physical behavior and psychosocial health interventions can affect HRV (i.e., affect autonomic activity).

Physical Behavior Interventions: Physical behavior interventions include a variety of modalities such as exercise training, Tai Chi Qigong, yoga, and HRV-biofeedback. *Kellie Toohey, et al.,* [94] showed that cardiorespiratory fitness (VO2peak) was significantly improved in the high-intensity interval training group compared to the blank control group. They also observed an increase in RMSSD in HRV. It is suggested that exercise improves the vagus nerve function of the body, while reducing the risk of treatment-related side effects and cardiovascular disease [94]. A mete analysis involving 2,166 breast cancer patients showed that yoga was superior to no treatment in terms of improving health-related quality of life, fatigue, and sleep disturbances. Yoga also improved patients' negative emotions such as depression and anxiety during active treatment [95]. HRV-Biofeedback (HRV-B) is a self-activation of the vagus nerve by performing a slow rhythm breathing technique while receiving HRV visual feedback [17]. The method is easy to implement, inexpensive, has few or no side effects, and has been studied in published protocols [96]. In a randomized controlled trial, the HRV-B group increased consistency of HRV [97] and reduced insomnia, fatigue, pain and distress compared to a waitlist control group. In another randomized controlled trial of 34 patients with different cancers, patients who received 4-6 weeks of HRV-B treatment had an increased HRV index along with a significant improvement in sleep quality [97]. There are also behavioral interventions such as Qigong and Tai Chi [98,99] that can improve patients' cardiopulmonary function and improve their quality of survival.

In summary, behavioral interventions such as exercise training can improve HRV, vagus activity and cardiovascular function to some extent, predicting longer survival and better quality of survival [100]. In addition, regular exercise stimulates the immune system, thus increasing the resistance of the body [22, 101,102]. Regular exercise also has been shown to reduce the risk of low-level inflammation and cardiovascular disease [103, 104].

Psychological Interventions: Psychological distress in cancer patients has been a popular issue in recent years. Corresponding psychological intervention therapies have also received increasing attention, especially positive thinking therapy. According to epidemiological analysis, people who suffer from various forms of psychological distress are at high risk of cancer. And cancer patients themselves are often experiencing some form of chronic stress. Both groups typically exhibit a variety of adverse symptoms such as anxiety, depression, sleep disorders, and other mental health disorders [105]. Experiments by *Julienne E. Bower, et al.,* [106] and *Linda Witek Janusek, et al.,* [107] both showed that after treatments such as mindfulness meditation or mindfulness decompression, patients experienced a significant reduction in symptoms such as depression and anxiety, and improvement in sleep disturbances. At the same time the organism has lower production of circulating TNF-α and IL-6 and more production of IFN-γ, showing optimized immune function. That is, intervening in these symptoms and adopting a healthy lifestyle can slow the progression of cancer and improve the quality of survival for patients. *Hye Youn Park, et al.,* [108] administered brief supportive expressive group therapy to 28 patients with metastatic lung cancer. Patients' SDNN increased significantly after treatment, while patients demonstrated significant reductions in pain, perceived stress, anger and sleep disturbances. *Wang, et al.,* [109] found significant differences in patients' SDNN, RMSSD and HF before and after the Mindfulness-Based Stress Reduction (MBSR) intervention. Consistent with the results of a review investigating the association between MBSR and HRV [110], i.e., a significant increase in time-domain-based SDNN and RMSDD and frequency-domain-based HF after 8 weeks of positive thinking training. In addition, there are psychological interventions such as meditation therapy [111,112], music therapy [113,114], and stress management [95], all of which have shown to some extent to be beneficial to patients' physical and mental health and to improve their quality of life. The above results suggest that psychological interventions such as orthomolecular therapy can promote vagus activity in cancer patients. The HRV can also be used as a physiological biofeedback parameter to determine the effect of the intervention.

In summary, psychological intervention can reduce the psychological distress of cancer patients and even improve the immune function of the body, thus improving the quality of survival of cancer patients. However, there are still limitations in the current study, for example, the sample size of the study is small, the observations are mostly limited to psychological scales and there are no clinical indicators such as relapse rate and survival time. Future research is needed to identify effective supportive care programs. Encourage the incorporation of positive thinking therapy, yoga, and psychological interventions into patients' lifestyles to improve quality of life. Also, in order to further clarify the effect of psychological interventions on prognosis, long-term follow-up clinical studies are desired.

Conclusion

This study has analyzed the hot spots and frontiers of research on HRV in cancer patients through CiteSpace. The results of the study indicated that the regulation of the vagus nerve and the quality of survival of patients were hot research areas and trends. Inflammation, negative emotions, and cardiovascular disease risk are important areas of research. Also, the various research areas were inextricably linked, and future research could delve into the interactions between the different factors. Future studies should delve

into the mechanism of the role of autonomic modulation in HRV in cancer patients. And test whether various interventional treatments using HRV as an observational index can clinically improve the prognosis of cancer patients. In addition, exploring the role of supportive care such as positive thinking therapy, yoga and pranayama in improving the quality of patient survival is encouraged. This study is the first to describe the research hotspots and trends systematically and comprehensively in cancer and HRV. However, there are still some limitations in this study. Due to the limitations of the CiteSpace software, we only searched for studies that were included in the WOS Core Collection and published in English. Errors may be caused by the lack of comprehensive literature and the small number of publications. In addition, some newly published high-quality articles may temporarily fall below the classic literature and cause omissions.

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Author Contributions

All authors contributed to the study conception and design Material preparation, data collection and formal analysis were performed by Lishan Ding, Yuepeng Yang and Shichun Jia. The first draft of the manuscript was written by Lishan Ding, Yuepeng Yang and Shichun Jia. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Conceptualization, supervision and review were performed by Chunyan Lin.

Ethics Approval

This is a review study. It does not require any ethical approval or informed consent.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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