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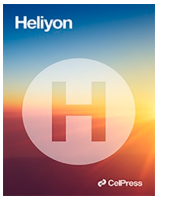

Review article

Research progress of circadian rhythm in cardiovascular disease: A bibliometric study from 2002 to 2022

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ABSTRACT

Background: Given that the circadian rhythm is intricately linked to cardiovascular physiological functions, the objective of this investigation was to employ bibliometric visualization analysis in order to scrutinize the trends, hotspots, and prospects of the circadian rhythm and cardiovascular disease (CVD) over the past two decades.

Methods: A thorough exploration of the literature related to the circadian rhythm and CVD was conducted via the Web of Science Core Collection database spanning the years 2002–2022. Advanced software tools, including citespace and VOSviewer, were employed to carry out a comprehensive analysis of the co-occurrence and collaborative relationships among countries, institutions, journals, references, and keywords found in this literature. Furthermore, correlation mapping was executed to provide a visual representation of the data.

Results: The present study encompassed a total of 3399 published works, comprising of 2691 articles and 708 reviews. The publications under scrutiny were primarily derived from countries such as the United States, Japan, and China. The most prominent research institutions were found to be the University of Vigo, University of Minnesota, and Harvard University. Notably, the journal Chronobiology International, alongside its co-cited publications, had the most substantial contribution to the research in this field. Following an exhaustive analysis, the most frequently observed keywords were identified as circadian rhythm, blood pressure, hypertension, heart rate, heart rate variability, and melatonin. Furthermore, a nascent analysis indicated that future research might gravitate towards topics such as inflammation, metabolism, oxidative stress, and autophagy, thereby indicating new directions for investigation.

Conclusion: This analysis represents the first instance of bibliometric scrutiny pertaining to circadian rhythm and its correlation with cardiovascular disease (CVD) through the use of visualization software. Notably, this study has succeeded in highlighting the recent research frontiers and prominent trajectories in this field, thereby providing a valuable contribution to the literature.

1. Introduction

Cardiovascular disease (CVD) persists as a foremost contributor to mortality and incapacity across the world. Over the preceding three decades, as global socio-economic conditions have improved and populations have swelled, so too has the incidence of CVD risen precipitously. Epidemiological data from both developing and developed nations alike portend an inexorable and rapid increase in the

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number of individuals afflicted with CVD, including ischemic heart disease, heart failure, myocardial infarction, and hypertension [[1–3]]. As a result, researchers hailing from all corners of the globe have endeavored to develop effective and dependable interventions to forestall cardiovascular events.

Various functions and risk factors that pertain to the cardiovascular system, such as blood pressure, heart rate, platelet function, and thrombosis, exhibit significant circadian fluctuations over the course of a 24-h day [[4–7]]. Additionally, numerous clinical studies have demonstrated marked circadian rhythms in CVD, including arrhythmias, myocardial infarction, stroke, and rupture of the abdominal aorta [[8–11]]. In light of these findings, it is conjectured that disorders in circadian rhythm could escalate the risk of CVD. A plethora of researchers have investigated this hypothesis in animal models and have shed light on the physiological and pathological mechanisms [[12–14]]. These circadian rhythms are governed by the suprachiasmatic nucleus (SCN) and the peripheral clock. The SCN can influence cardiovascular function independently or in unison with the peripheral clock [15]. The primary importance of identifying changes in circadian rhythm and episodes of CVD is to provide clues for comprehending the onset and progression of CVD and to offer novel prospects for the treatment and prevention of CVD by further influencing circadian rhythm alterations. As research on circadian rhythms in CVD continues to burgeon and intensify worldwide, it is crucial to collate and summarize all pertinent publications.

Bibliometrics is a multidisciplinary field that employs mathematical and statistical techniques to quantitatively analyze all forms of knowledge. Due to the presence of human factors affecting literature, quantifying literature-related issues remains challenging [16]. Moreover, the high complexity and instability of the literature system make it difficult to obtain sufficient and valid information to reveal macroscopic patterns in literature. The progress of bibliometrics depends on the utilization of advanced mathematical and statistical methods to analyze information in diverse fields [17]. This approach offers an accurate analysis of the geographic

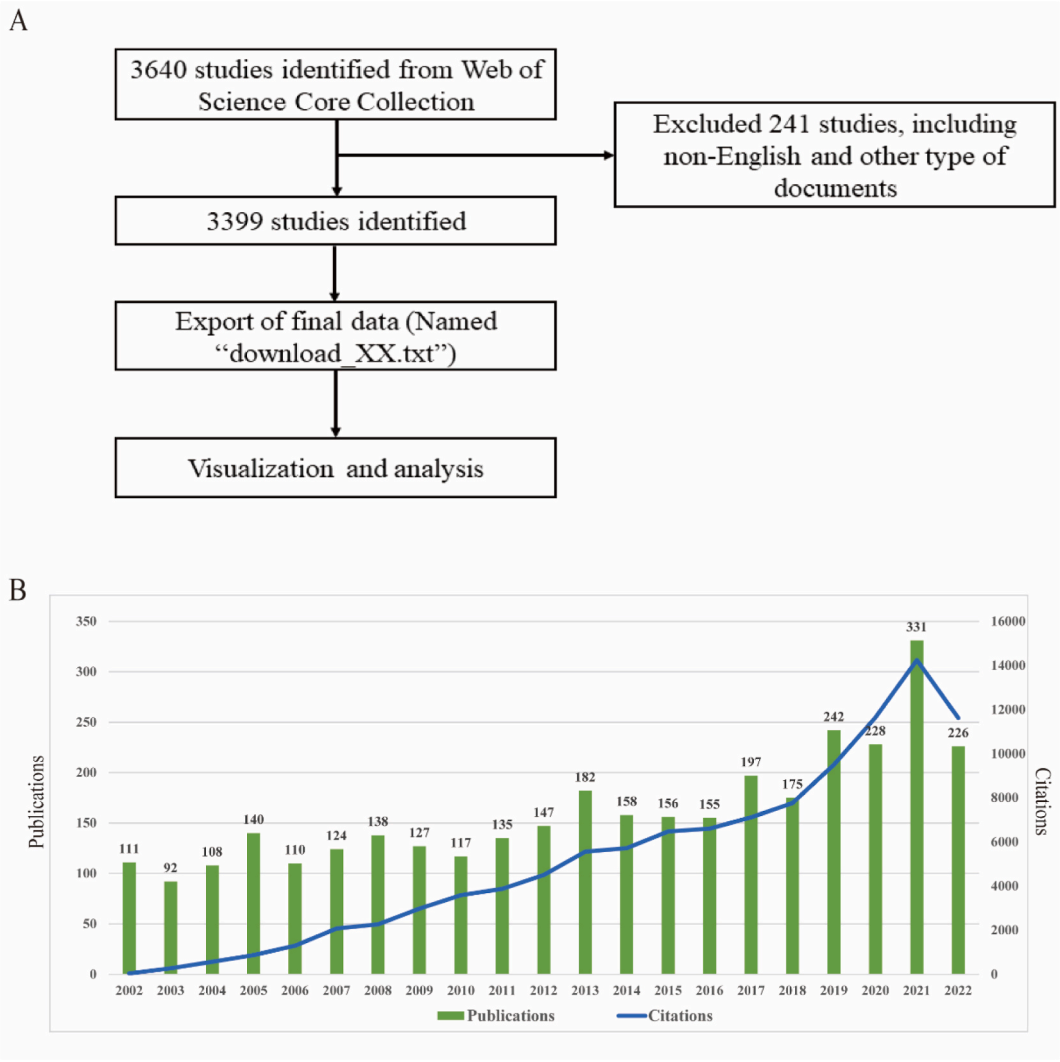

Fig. 1. **(A)** Flowchart illustrating the working strategy and screening process of circadian rhythm in CVD **(B)** Annual trends in publications and citations of circadian rhythms in CVD.

distribution, interrelationships, and clusters of research areas and has become a crucial and popular technique for evaluating the credibility, quality, and impact of academic research. In recent years, this technology has been widely applied in various fields [[18,19]]. However, few systematic reviews and studies have been conducted on literature related to circadian rhythms and CVD, particularly with respect to the quantitative and visual analysis of literature. Therefore, in this study, we gathered relevant literature information from 2002 to 2022 using the Web of Science Core Collection (WoSCC) database and analyzed and visualized the data using application software such as VOSViewer and Citespace. The objective was to investigate the research field's hotspots, thematic trends, and prospective developments.

2. Materials and methods

2.1. Data collection

All bibliographic data published online between 2002 and 2022 were extracted from the Science Citation Index Expanded (SCI-E) of WoSCC, a Clarivate Analytics platform (https://clarivate.com/) on December 2, 2022. The search strategy employed in the WoSCC database was as follows: [(TS=(heart) OR TS=(circulation) OR TS=(cardiovascular)) AND TS=(Circadian rhythm)] AND PY = (2002.01.01–2022.12.01). Subsequently, we narrowed down the publication type to reviews and original articles and limited the language to English. The Endnote software was used to eliminate duplicates, and three individuals independently reviewed the articles obtained from the search for relevance to the topic (Supplementary Table S1). Ultimately, a total of 3399 original articles and reviews fulfilled the inclusion criteria for the analysis, and the retrieved documents were exported in plain text format for complete records and cited references (Fig. 1A).

2.2. Data analysis

In this study, we imported the literature obtained from WoSCC into various analytical tools such as Microsoft Excel 2016, the R package "bibliometrix", VOSViewer and Citespace for visual analysis. Furthermore, we utilized the Web of Science database to scrutinize the impact factor (IF) of relevant journals, Journal Citation Reports (JCR) divisions, and the high citation index (h-index).

VOSviewer is a formidable and renowned bibliometric analysis software that facilitates visual analysis and map creation based on web data [20]. In our study, the VOSviewer software (version 1.6.18) carried out various analyses, including network analysis of countries and institutions cooperation, analysis of journals and co-cited journals, analysis of co-cited references, and keyword co-occurrence analysis. A plethora of bibliometric analysis articles have utilized this software for extensive visual analysis of literary entries [[21,22]].

Citespace is also a practical, classic and citation visualization analysis software developed by Professor Chen Chaomei of Drexel University using Java language [23]. The citespace software is used to find research advances and current research frontiers in a subject area and their corresponding knowledge base. In our present study, the citespace software (version 6.1.R3) accomplished the following analyses: the dual-map overlay of journals; the strongest citation bursts analysis on references and keywords and the timeline view of keywords. Briefly, create a new project in CiteSpace, select the project file folder, select the data folder, give the project a name, select the parameters in the function selection area, Time Slicing is set according to the time range selected when downloading the literature, Years Per Slice is set to 1, Node Types is selected for the content that will be analyzed soon, Pruning is selected in the progression of the pruning sliced networks, and the other parameters are kept at the default settings.

PowerPoint in Microsoft Office (version 2016) was used to create flow charts, and Excel was used to generate pictures of annual publications and citations. Tableau software (version 10.5) combined with excel files for generating visual geographical distribution on publications of circadian rhythm in CVD [24]. What's more, in our study R package "bibliometrix" (version 3.2.1) (https://www.bibliometrix.org) was applied to generate countries collaboration network map, journal publication trends map, word cloud map, keywords evolution analysis and the trend topics analysis of circadian rhythm in CVD [25].

3. Results

3.1. Number and basic features of publications

The quantity of publications often serves as a barometer for the trends in a specific field. Out of the 3399 publications procured from our search strategy, there were 2691 articles and 708 reviews. We observed a general upward trend in the quantity of publications from 2002 to the present, indicating that the investigation of circadian rhythm in the context of CVD is gradually garnering more attention and deserving of further study (Fig. 1B). The quantity of publications related to circadian rhythms and CVD was generally around 100 between 2002 and 2012. However, with advancements in research methodologies, the number of publications in this field has steadily increased from 2012 to 2022. Notably, the highest number of articles on this topic was published in 2021, with 331 articles. In conclusion, our data suggests that more and more researchers are beginning to recognize the potential of circadian rhythms in the field of cardiovascular disease.

3.2. Countries and institutions analysis

The 3399 articles that were scrutinized in this study were produced by 3577 institutions hailing from 86 different countries. Among

these, 372 institutions and 53 countries had produced more than five publications on the subject. As indicated in Fig. 2A and B, the highest number of publications were contributed by the United States (1093, 32.16%), followed by Japan (412, 12.12%) and China (376, 11.06%). It should be noted that Taiwan and the People's Republic of China were amalgamated into China, while England, Scotland, Northern Ireland, and Wales were grouped under the United Kingdom. The University of Vigo was found to be the most prolific institution, having produced 69 publications (2.03%), followed by the University of Minnesota (61, 1.80%) and Harvard University (60, 1.77%) (Table 1).

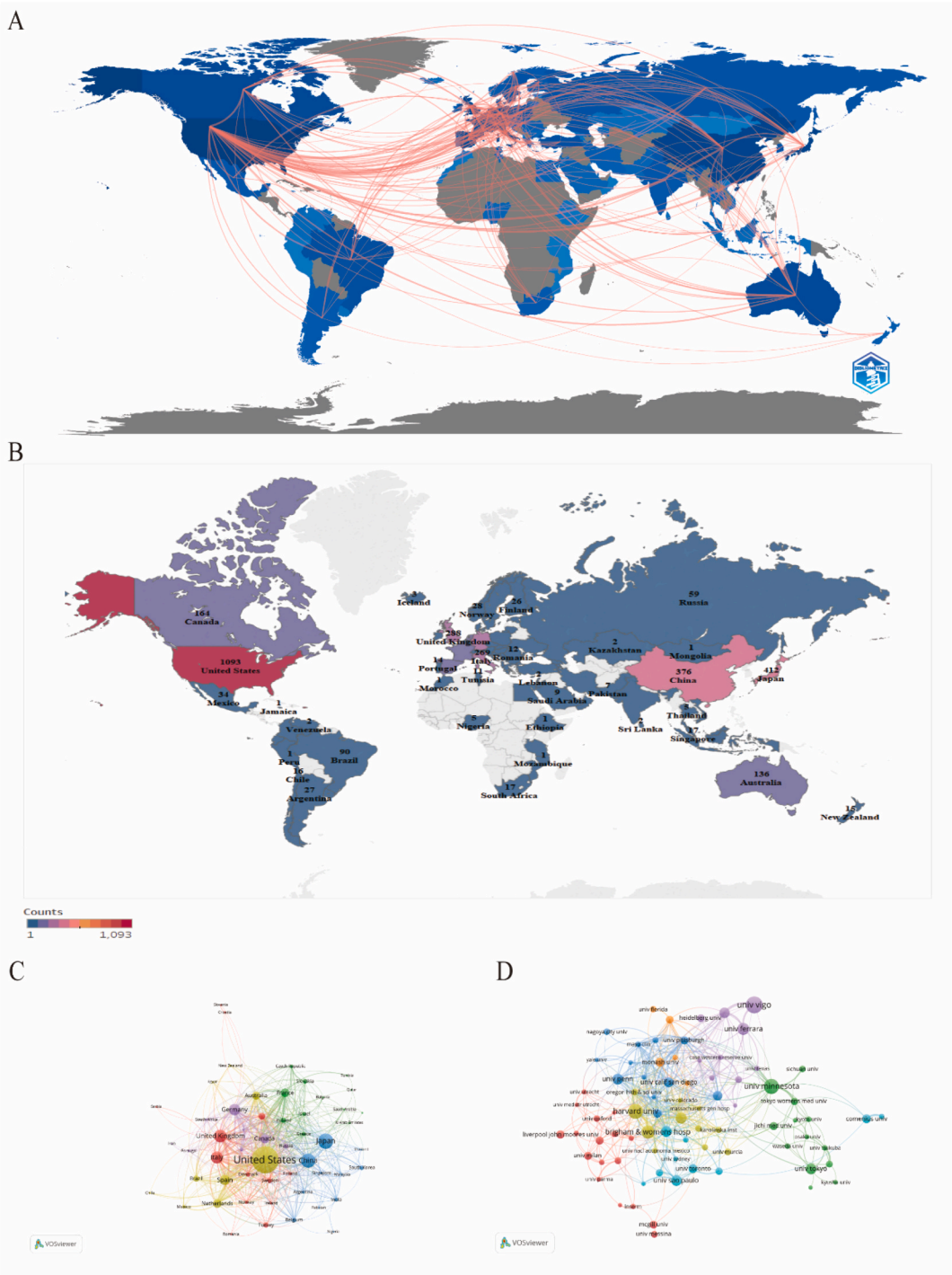

Fig. 2. **(A)** Countries collaboration network map **(B)** The geographical distribution on publications of circadian rhythm in CVD **(C)** Countries cooperation network analysis and **(D)** institutions cooperation network analysis of circadian rhythm in CVD.

Afterward, we applied filters to our data and employed visual techniques to construct distinct collaboration networks among various countries and institutions based on publication numbers and relationships. Each node represents a country or institution, and the size of each node corresponds to the number of published articles. The connecting lines between nodes represent the presence of collaborative relationships between different countries or institutions, with denser lines indicating closer relationships. To maintain brevity in the network, we only visualized the 53 selected countries that published at least 5 documents and the 79 institutions with at least 15 documents. As illustrated in Fig. 2C and D, we observed several fruitful collaborations between different countries and institutions. For instance, China, Japan, India, Korea, Belgium, and Singapore exhibited strong partnerships. Furthermore, the United States, Spain, Australia, Mexico, Netherlands, and Brazil displayed interconnectedness. Notably, the University of Vigo, which boasted the highest number of publications, demonstrated close collaboration with the University of Ferrara, Heidelberg University, Stanford University, Case Western Reserve University, and the University of Texas.

3.3. Journals and co-cited journals analysis

In the previous two decades, research articles concerning CVD and circadian rhythms have been disseminated across 1111 different academic journals. As illustrated by Table 2 and Fig. 3A, among the top ten journals, Chronobiology International (n = 223) and Biological Rhythm Research (n = 67) boasted the highest number of publications, trailed by PloS One (n = 63). According to the JCR partition analysis, four journals are situated in Q1. The journal with the most substantial impact factor (IF) is Hypertension (IF = 9.897). We also observed an escalating number of publications on circadian rhythms and CVD in these top ten journals from 2002 to 2022, with Chronobiology International revealing the most significant upward trend (Fig. 3B). Of the 13787 co-cited journals, 32 were referenced more than 1000 times. As evidenced in Table 3 and Fig. 3C, Chronobiology International (n = 5573) was the most frequently co-cited journal, followed by Circulation (n = 5151). Among the top ten journals, Nature (IF = 69.504) had the highest IF, followed by Cell (IF = 66.85) and Science (IF = 63.832).

The dual cartographic overlay of journals provides a visual representation of the citation relationships between journals and co-citing journals, with clusters of citing journals on the left and clusters of citing journals on the right [26]. Fig. 3D depicts four primary citation routes, including two orange and two green paths. The orange path indicates that research published in Molecular/Biology/Genetics and Health/Nursing/Medicine journals is cited for research in Molecular/Biology/Immunology journals. The green path suggests that research published in Molecular/Biology/Genetics and Health/Nursing/Medicine journals is generally cited by Medicine/Medical/Clinical journals.

3.4. Co-cited references and references burst analysis

The co-cited reference refers to a publication that is cited simultaneously with another publication, indicating a close relationship between them [27]. The higher the number of co-citations between the two publications, the closer their relationship. Among the top ten articles out of 124,746 references in the study of circadian rhythms and CVD presented in Table 4, all have high impact factors, with nine references located in Q1, indicating that they are high-quality papers with significant academic impact in the field. The article published by Muller et al., in 1985 has the highest citation frequency (n = 198), which mainly discussed the circadian rhythmic process in the pathogenesis of acute myocardial infarction [28]. Furthermore, we created a knowledge map of the co-cited references network with citation frequency of no less than 100, as shown in Fig. 4A. “Muller JE, 1985, N Engl J Med” [28], “Millar-Craig MW, 1978, Lancet” [29], “Camm AJ, 1996, Circulation” [30], “Ohkubo T, 2002, J Hypertens” [31] and “Muller JE, 1987, Circulation” [32] exhibited active co-cited connections.

Displayed in Fig. 4B, every bar signifies a year, where the crimson part depicts a robust citation burst. From the 25 references we have compiled, one of the references which exhibited the most powerful citation burst (strength = 28.29) is a review entitled “Circadian rhythms and the molecular clock in cardiovascular biology and disease”, written by Crnko S and published in Nat Rev Cardiol in 2019 [33]. Additionally, another review titled “Role of the circadian system in cardiovascular disease”, penned by Thosar SS and published in J Clin Invest in 2018, has also displayed a substantial citation burst [34].

3.5 Keywords analysis; To scrutinize the hotbeds of research on circadian rhythms in cardiovascular disease (CVD), we extracted author keywords from 3399 publications and analyzed them using co-occurrence analysis on VOSviewer software (Fig. 5A). Similarly, the word cloud plot in Fig. 5B illustrates the keywords frequently utilized in publications on circadian rhythms in CVD. Out of 6441

Table 1
Top 10 countries and institutions on publications of circadian rhythms in CVD.

Rank	Country	Counts (%)	Citations	Institution	Counts (%)	Citations
1	United States	1093 (32.157)	988	University of Vigo (Spain)	69 (2.030)	3137
2	Japan	412 (12.121)	8953	University of Minnesota (USA)	61 (1.795)	1003
3	China	376 (11.062)	2207	Harvard University (USA)	60 (1.765)	7074
4	United Kingdom	288 (8.473)	7979	Brigham & Womens Hospital (USA)	52 (1.530)	3753
5	Italy	269 (7.914)	6063	University of Ferrara (Italy)	47 (1.383)	2490
6	Germany	243 (7.149)	5083	Harvard Medical School (USA)	43 (1.265)	531
7	Spain	203 (5.972)	10783	University of Alabama Birmingham (USA)	42 (1.236)	1174
8	Canada	164 (4.825)	3762	University of Pennsylvania (USA)	42 (1.236)	2319
9	Netherlands	155 (4.560)	9683	University of Sao Paulo (Brazil)	41 (1.206)	981
10	France	151 (4.442)	7044	University of Tokyo (Japan)	41 (1.206)	1100

Table 2
Top 10 journals for research of circadian rhythms in CVD.

Rank	Journal	Counts	IF(2021)	Q
1	Chronobiology international	223	3.749	Q2/Q2
2	Biological rhythm research	67	1.362	Q3/Q4
3	PloS one	63	3.752	Q2
4	Frontiers in physiology	46	4.755	Q1
5	Journal of biological rhythms	41	3.649	Q2/Q2
6	Hypertension	40	9.897	Q1
7	Hypertension research	40	5.525	Q2
8	Physiology & behavior	40	3.742	Q1/Q2
9	Journal of hypertension	38	4.776	Q2
10	American journal of physiology.Heart and circulatory physiology	33	5.125	Q2/Q2/Q1

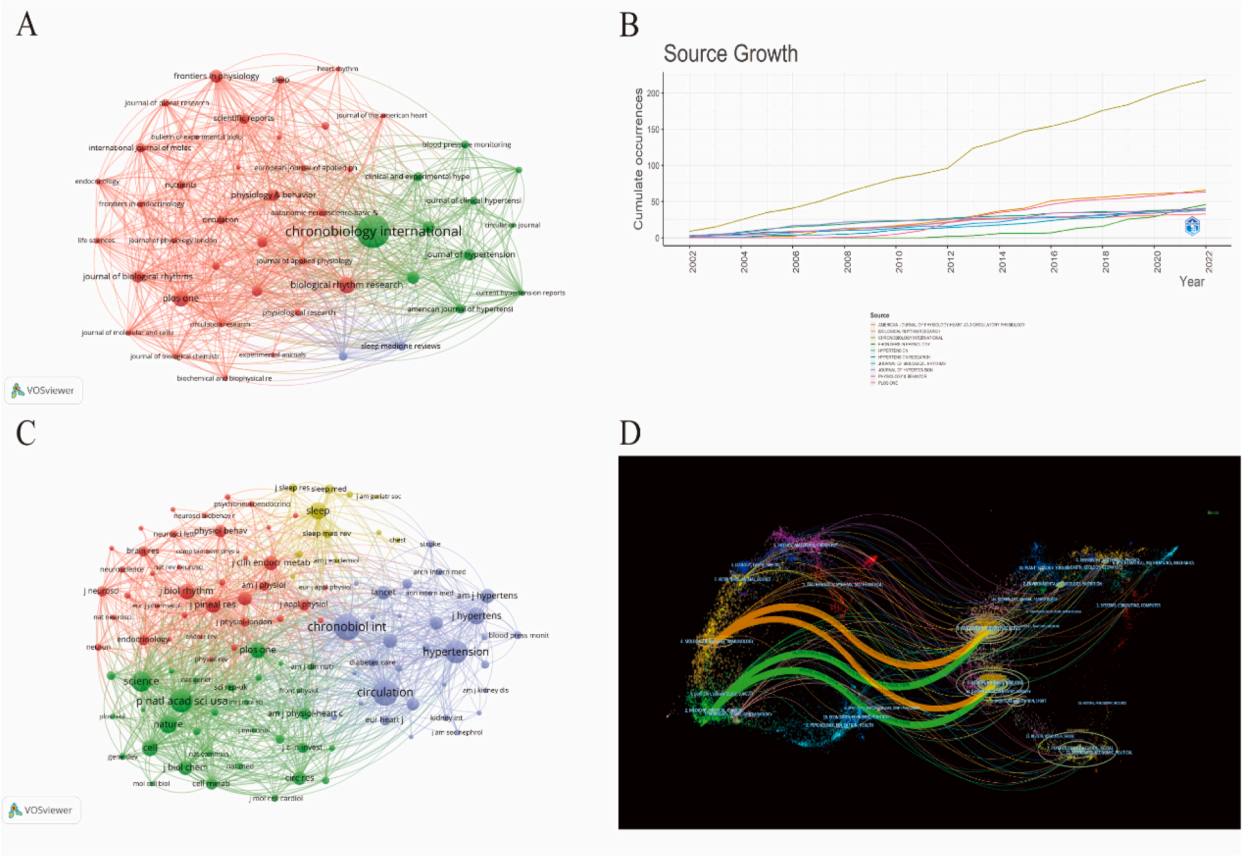

Fig. 3. **(A)** The cooperation relationship between journals and **(C)** co-cited journals of circadian rhythm in CVD **(B)** Graph of journal publication trends and **(D)** the dual-map overlay of journals of circadian rhythm in CVD.

keywords, 446 keywords appeared at least 5 times. After excluding 6 less significant keywords such as "heart," "cardiovascular disease," "circadian," "circadian clock," "circadian rhythm," and "circadian rhythms" (Table 5), we listed the top 20 most frequent keywords. It is noteworthy that the top 3 frequently appearing keywords are "blood pressure" (n = 252), "hypertension" (n = 212), and "heart rate" (n = 206). This is a clear reflection of the fact that blood pressure and heart rate are the most closely linked and well-researched aspects of the cardiovascular system in terms of their relation to circadian rhythms. In the meantime, Fig. 5C illustrates the top 25 keywords that possess the strongest citation bursts. Based on the analysis of the keyword emergence map, it can be inferred that circadian rhythm research in the CVD field has gradually shifted from sudden cardiac death and coronary artery disease to essential hypertension, oxidative stress, chronic kidney disease, and sex differences. Keyword clustering analysis can provide insight into the research directions of keywords in different time periods and select the corresponding keywords as cluster representatives through various algorithms of Citespace. The selected keywords are then used to produce a keyword co-linear timeline chart that dynamically reflects the trend changes of the frontier hotspots (Fig. 5D). Overall, the timeline chart demonstrates that circadian rhythm studies pertaining to the field of CVD focus on 10 topics, including shift work, myocardial infarction, heart failure, heart rate,

Table 3
Top 10 co-cited journals for research of circadian rhythms in CVD.

Rank	Journal	Citations	IF(2021)	Q
1	Chronobiology international	5573	3.749	Q2/Q2
2	Circulation	5151	39.922	Q1/Q1
3	Proceedings of the National Academy of Sciences of the United States of America	4278	12.779	Q1
4	Hypertension	4240	9.897	Q1
5	Science	3550	63.832	Q1
6	Nature	2791	69.504	Q1
7	Sleep	2644	6.313	Q1/Q1
8	Journal of hypertension	2617	4.776	Q2
9	Cell	2420	66.85	Q1/Q1
10	PloS one	2335	3.752	Q2

Table 4
Top 10 co-cited references for research of circadian rhythms in CVD.

Rank	Title	Author and Year	Citations	Journal and IF(2021)	Q
1	Circadian variation in the frequency of onset of acute myocardial infarction	Muller et al. (1985)	198	New England journal of medicine (176.082)	Q1
2	Coordination of circadian timing in mammals	Reppert et al. (2002)	187	Nature (69.504)	Q1
3	Adverse metabolic and cardiovascular consequences of circadian misalignment	Scheer et al. (2009)	178	Proceedings of the National Academy of Sciences of the United States of America (12.779)	Q1
4	Obesity and metabolic syndrome in circadian Clock mutant mice	Turek et al. (2005)	169	Science (63.832)	Q1
5	Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus	Damiola et al. (2000)	163	Genes & development (12.89)	Q1/ Q1/ Q1
6	Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology	Camm et al. (1996)	159	Circulation (39.922)	Q1/ Q1
7	Extensive and divergent circadian gene expression in liver and heart	Storch et al. (2002)	149	Nature (69.504)	Q1
8	Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study	Ohkubo et al. (2002)	129	Journal of hypertension (4.776)	Q2
9	Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension	Verdecchia et al. (1994)	126	Hypertension (9.897)	Q1
10	Circadian variation of blood-pressure	Millar-Craig et al. (1978)	120	Lancet (202.731)	Q1

the circadian clock, chronic kidney disease, and more. Subsequently, we conducted a thematic evolutionary map analysis (Fig. 5E). Our data's time span was evenly divided into three sections, from 2002 to 2016. The nodes within the figure indicate the primary research topics generated from the co-word network analysis during each time slice. The text labels adjacent to the nodes specify the core keywords of the topic and the time slice. The number of keywords contained within each topic is indicated by the size of the corresponding node. Topics from neighboring time slices are linked by streamlines when they share the same keywords. The width of the streamlines is proportionate to the number of keywords shared by related topics and indicates their correlation. Fig. 5E shows that the pattern of research themes gradually transitioned from fragmentation to unity as research progressed. Initially, various keywords such as "circadian rhythm," "circadian clock," and "ambulatory blood pressure monitoring" existed. However, in the recent phase (2017–2022), circadian rhythm theory in CVD has been established, developed, and widely utilized in the research field. Many interdisciplinary studies have emerged under the theme of "hypertension" from isolated topics such as "blood pressure," "atrial fibrillation," and "bedtime hypertension chronotherapy". The research field's comprehensiveness has further improved, with additional disparate themes merging again into new ones from previous time slices. Lastly, we produced a trend graph of author keywords (Fig. 5F), and we discovered that the research hot spots over the last three years were "estrogen," "autophagy," and "oxidative stress," among others.

4. Discussion

The association between circadian rhythm disorders and CVD is robust, and it has been demonstrated that abnormal circadian rhythms, whether resulting from endogenous genetic alterations in the biological clock or exogenous environmental factors, elevate the risk of adverse cardiac events [35]. In today's expansive literature, having an overview of the research field and its future prospects

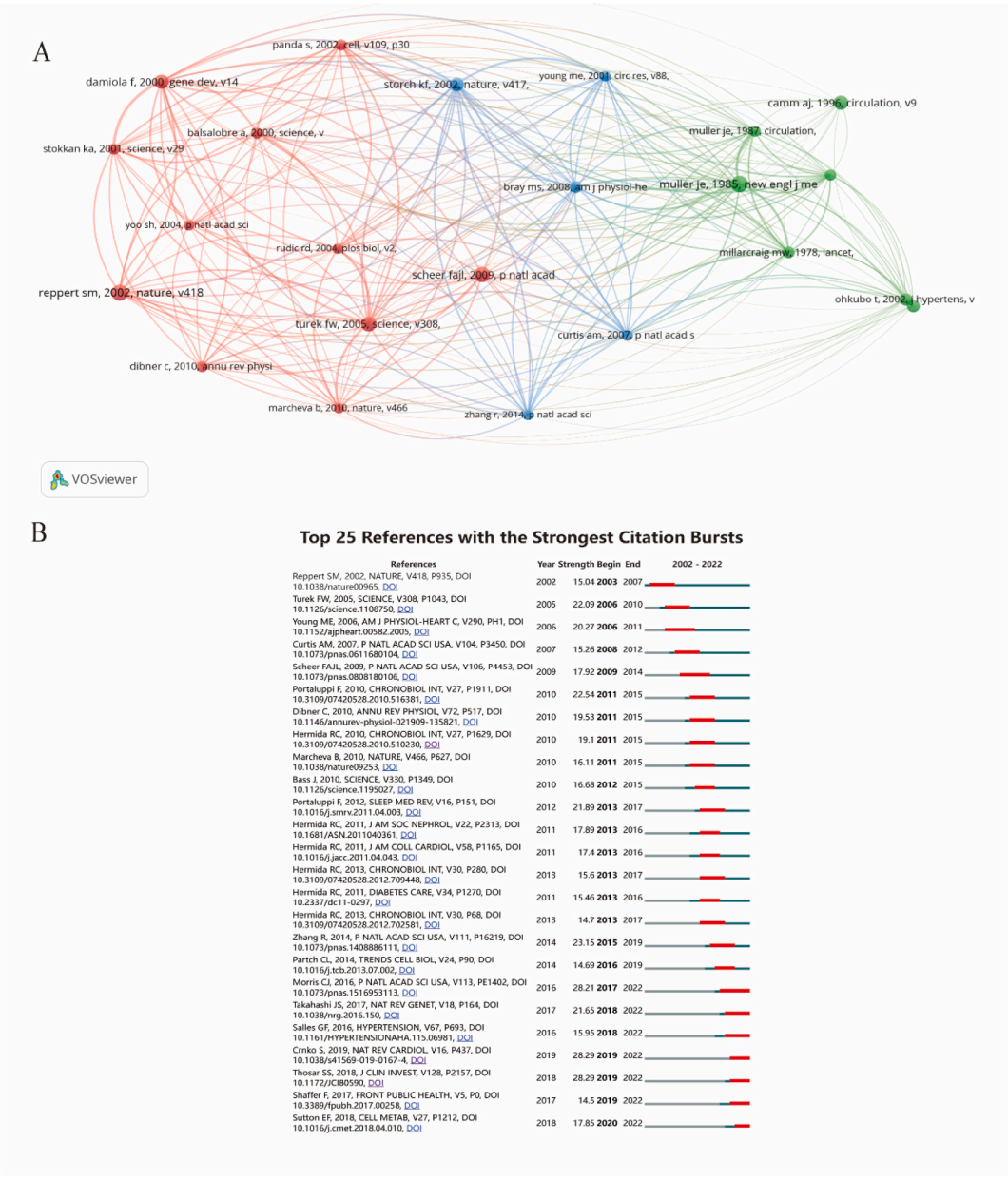

Fig. 4. **(A)** The cooperation relationship between co-cited references and **(B)** top 25 references with the strongest citation bursts of circadian rhythm in CVD.

is crucial, and bibliometrics, which has emerged and evolved, can fulfill this requirement. Prior research has employed bibliometric approaches to study other domains within CVD, but to date, no bibliometric analysis of circadian rhythms and CVD has been conducted [[36–38]].

In this study, we undertook the first statistical analysis of the literature pertaining to circadian rhythms in CVD through the use of bibliometric methods and big data analysis. The identification of high-frequency keywords serves as an indication of the hotspots and development prospects of a research field. In order to determine the main current status and hotspots of circadian rhythm and CVD, we employed a keyword co-occurrence analysis. The resulting timeline graph, formed by a keyword-based clustering analysis, illustrates the top 10 relevant areas. Additionally, through analysis of the top 25 keywords based on the strongest citation bursts, we identified the research hotspots and frontiers in circadian rhythms and CVD. As shown in Table 6, we will now proceed to provide a detailed analysis of the pathophysiology of myocardial injury and common CVD.

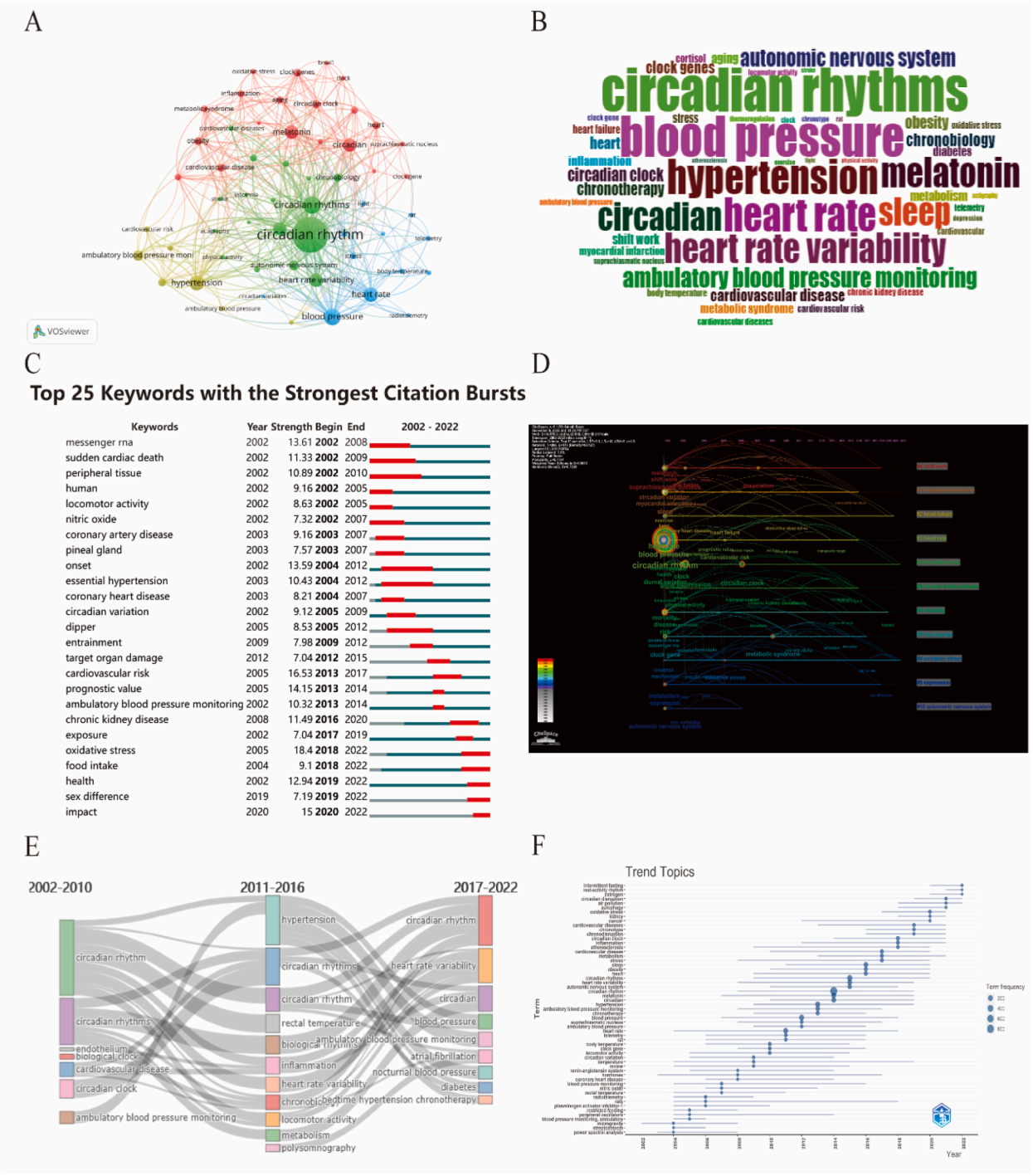

Fig. 5. (A) The keywords clustering analysis (B) Word cloud map regarding the keywords' frequency of occurrence (C) The top 25 keywords with the strongest citation bursts (D) The timeline view of keywords (E) Keywords evolution analysis (F) The trend topics analysis.

4.1. Circadian rhythm and acute myocardial infarction

Research has demonstrated that the onset of acute myocardial infarction displays a significant variation throughout the day, with a noteworthy increase during the early morning hours. This indicates that circadian rhythms may play a crucial role in the development of acute myocardial infarction [[28,74,75]]. Various studies suggest that daylight saving time shifts, winter, Christmas, and Midsummer holidays may pose as risk factors that increase the likelihood of acute myocardial infarction [[76–78]].

Table 5
Top 20 keywords for research of circadian rhythms in CVD.

Rank	Keywords	Counts	Total link strength	Rank	Keywords	Counts	Total link strength
1	blood pressure	252	430	11	obesity	78	136
2	hypertension	212	339	12	clock genes	77	106
3	heart rate	206	296	13	aging	64	106
4	heart rate variability	183	205	14	metabolism	64	95
5	melatonin	183	227	15	shift work	64	97
6	sleep	173	239	16	inflammation	63	100
7	ambulatory blood pressure monitoring	123	192	17	metabolic syndrome	61	123
8	autonomic nervous system	107	155	18	diabetes	59	121
9	chronobiology	82	105	19	stress	55	61
10	chronotherapy	79	138	20	myocardial infarction	53	81

Table 6
Summary of studies on mechanisms related to circadian rhythms in CVD during 2002–2022.

Cardiovascular diseases	Mechanism	PMID	References
Exacerbation of acute myocardial infarction	Elevated PAI-1	24200683	[7]
	Activation of platelets	21931750	[6]
	Activation of the coagulation and fibrinolytic systems	31473402	[39]
	Elevated triglycerides	32519460	[40]
	Elevated plasma endothelin-1	31,070,470	[41]
	PER2 deficiency blunts mobilization and function of EPC	25268972	[42]
	Elevated cTnT	28856443; 24583293	[43,44]
	Rhythm disturbance of macrophages and neutrophils	35,694,249	[45]
	Large numbers of infiltrating neutrophils	27,226,028	[46]
	Genetic variability of the CLOCK gene in women	34,066,863	[47]
	Stimulation of the HPA axis	12,906,367	[48]
Reduction of acute myocardial infarction	Melatonin treatment restores clock gene rhythms affected by NLRP3 activation	35743288	[49]
	Agitated REV-ERBα inhibits inflammation	29232411	[50]
	BMAL1 regulates HSPB1 to reduce oxidative stress damage	34239687	[51]
Exacerbation of myocardial ischemia-reperfusion injury	Deficiency of CLOCK gene leads to impaired mitochondrial autophagy	34085589	[52]
	Disruption of HDAC3-mediated circadian gene expression oscillations induces mitophagy dysfunction	33414413	[53]
Reduction of myocardial ischemia-reperfusion injury	KLF15 promotes the synthesis of NAD	32339045	[54]
	Overexpression of NPAS2 inhibits autophagy	34460437	[55]
	Up-regulation of BMAL1 activates autophagy by targeting HDAC3/SIRT1	33620678	[56]
	Activation of the nuclear melatonin receptor RORα	26797926	[57]
	Activation of PER2 resists inflammatory responses	23977055	[58]
Exacerbation of hypertension	Increased circadian rhythm variability in M-CSF	33604550	[59]
	Knockout PER1 exhibited higher plasma aldosterone levels	36093781	[60]
	Circadian rhythm of intrarenal RAS activation	24728489	[61]
Reduction of hypertension	Deletion of clock genes BMAL1, CLOCK, PER1 and PER2	17360665; 19805330; 27636900; 20053965	[62, 63–65]
	Antioxidant effects of melatonin	25276149	[66]
	SGLT2 decreases blood pressure through natriuresis and decreases sympathetic tone	29349558	[67]
	Empagliflozin decreases blood pressure through increasing urinary sodium excretion	26818652	[68]
	Vascular PPARγ knockdown causes impaired circadian rhythm of blood pressure by targeting BMAL1	19041764	[5]
Exacerbation of arrhythmia	Cardiomyocyte-specific Bmal1 knockout leads to increased vulnerability to arrhythmias	34176211	[69]
	SN local clock-dependent HCN4 rhythm is disrupted	33278629	[70]
	CLOCK-BMAL1 mediates the circadian rhythmogenesis of ventricular arrhythmias via β1-adrenergic receptors	33194018	[71]
Reduction of arrhythmia	BMAL1 affects ventricular repolarization by modulating KCNH2 and altering the expression of K^+ channel genes	25701773	[72]
	Activation of β3-adrenergic receptors reduces ventricular tachycardia and ventricular fibrillation	20661603	[73]

PAI-1: plasminogen activator inhibitor-1; EPC: endothelial progenitor cells; cTnT: cardiac troponin T; HPA: hypothalamic-pituitary-adrenal; NAD: nicotinamide adenine dinucleotide; M-CSF: macrophage colony-stimulating factor; SN: sinus node.

It is widely recognized that intracoronary plaque rupture, platelet aggregation, coagulation system activation, and thrombosis are the primary factors involved in the pathology of acute myocardial infarction. During the intercircadian period, dynamic changes in platelet activation and fibrinolysis may be linked with an augmented risk of thrombotic occlusion in the morning [[7,39]].

Additionally, the circadian system affects platelet activation, including platelet surface activated glycoproteins (GP) IIb-IIIa, GPIb, and P-selectin [6]. Elevated platelet aggregation and hindered fibrinolytic activity lead to heightened blood viscosity, the creation of a hypercoagulable state of blood, and a considerably greater risk of thrombosis in the morning, which aligns with the observed early morning morbidity peak phenomenon, leading to an increased possibility of acute myocardial infarction occurrence.

Furthermore, higher plasma triglyceride concentrations have been associated with an elevated risk of myocardial infarction. Yuan et al. discovered that fasting blood triglyceride concentrations exhibit circadian rhythms in both young and older adults, peaking in the early morning in both groups. Elevated levels of triglycerides in the early morning promote a hypercoagulable state of blood, leading to decreased fibrinolysis and causing endothelial cell dysfunction, which can contribute to the development of acute myocardial infarction [40]. In addition, plasma endothelin-1 concentration is found to increase in the morning, peaking around noon. Endothelin has a detrimental effect on coronary arteries, leading to coronary artery spasm, which could be a triggering risk factor for acute myocardial infarction [41].

Ischemic tissue neovascularization necessitates not only angiogenesis but also the presence of circulating endothelial progenitor cells (EPC) during angiogenesis [79]. The clock gene PER2 has been demonstrated to regulate EPC mobilization and function after myocardial infarction, and a deficiency of PER2 can restrict recovery after myocardial infarction [42].

Vascular inflammation is a significant contributor to the development of acute myocardial infarction, and the clock gene CLOCK/BMAL1 is a central element of the circadian mechanism that plays a role in regulating vascular inflammation and metabolism [80]. Recently, it was discovered that NLRP3 inflammatory vesicles and melatonin affect heart clock gene expression, and continuous melatonin treatment was successful in reducing inflammation and restoring circadian rhythms in the myocardium [49]. In addition, it enhances cardiac function by modulating the inflammatory and remodeling processes, thereby inhibiting myocardial infarction through agonizing the clock gene Rev-erbα [50].

Reactive oxygen species (ROS) are crucial for maintaining physiological functions of the body. The production and clearance of ROS are biorhythmic, and the circadian rhythm coordinates mitochondrial physiology to regulate the biological rhythm of ROS [81]. Oxidative stress is a major cause of acute myocardial infarction, and studies have demonstrated that the clock gene BMAL1 regulates the redox status of HSPB1 to counteract oxidative stress damage in cardiac myocytes [51].

Cardiac troponin T (cTnT) is a clinically specific indicator of myocardial infarction. Several recent clinical studies have found statistically significant circadian biological variation in troponin blood concentrations by blood sampling in multiple volunteers without cardiac disease [[43,44]]. Interestingly, a large cohort study of patients with chest pain symptoms only justified elevated troponin levels, with no evidence of diurnal variation in cardiac troponin T concentrations [82]. In addition, another indicator of myocardial injury, troponin I, was also shown to have no correlation with circadian rhythm [83]. Therefore future circadian rhythm definitions regarding markers of myocardial injury need to be explored in numerous studies.

Circadian oscillations in immune system components have the potential to influence disease onset and treatment. Recent studies have shown that periodic recruitment of immune cells to tissues can affect disease [[84,85]]. The immune system plays a crucial role in the pathophysiology after myocardial infarction [86]. It has been found that T cells and their different subpopulations' responses during myocardial infarction follow circadian rhythmic oscillations similar to those observed in the normal heart, with higher numbers during resting periods and a sharp decrease upon entering active periods. However, these oscillatory patterns are disturbed in macrophages and neutrophils after myocardial infarction [45]. Although large numbers of infiltrating neutrophils are often thought to be detrimental to post-infarction outcomes, studies have found a stable circadian rhythm in cardiac neutrophil recruitment, and anti-inflammatory therapy during the active phase can significantly reduce infarct size and improve cardiac function [46].

Many of the physiological processes regulated by circadian rhythms differ between women and men. Nocturnal systolic, diastolic blood pressure and heart rate are higher in women than in men [[87,88]], so there are significant differences in circadian rhythms based on gender for CVD [33]. One study found evidence of differences between men and women in a recessive genotype model of the CLOCK gene rs11932595 in a large sample of patients with myocardial infarction. In addition, the prevalence of dyslipidemia was significantly higher in women than in men [47].

The hypothalamic-pituitary-adrenal (HPA) axis has circadian rhythmicity [89]. It was found that the occurrence of myocardial infarction at different times could lead to different levels of stimulation of the HPA axis [48].

4.2. Circadian rhythm and myocardial ischemia-reperfusion injury

In recent years, owing to the continuous advancements in reperfusion therapy such as percutaneous coronary intervention (PCI), the mortality rate of myocardial infarction has witnessed a significant decline. However, myocardial ischemia-reperfusion injury following reperfusion still cannot be disregarded. Recently, tolerance to myocardial ischemia-reperfusion injury has been demonstrated in mice, which is contingent upon the timing of coronary artery occlusion. Moreover, Ronald et al. have also exhibited in humans that myocardial infarct size and left ventricular function after STEMI have a circadian rhythm dependence on the time of day of the ischemic episode [[90,91]].

Nicotinamide adenine dinucleotide (NAD) protects the heart from ischemia-reperfusion injury [92]. A study shows that KLF15 controls circadian rhythmicity of Nampt expression in the heart and promotes NAD synthesis at specific times of the day to reduce myocardial ischemia-reperfusion injury [54].

Autophagy is a highly conserved evolutionary process that primarily regulates protein degradation and organelle turnover during cellular stress. Autophagy plays a crucial role in the cardiovascular system and contributes to the maintenance of normal cardiac function. Loss of clock gene CLOCK activity in vitro and in vivo was found to lead to increased myocardial ischemia-reperfusion injury, which may be associated with restricted activation of mitochondrial autophagy [52]. In contrast, HDAC3-mediated disruption of

circadian rhythm gene expression oscillations induces mitochondrial autophagy dysfunction and exacerbates myocardial ischemia-reperfusion injury [53]. In addition, overexpression of Neuronal PAS Domain Protein 2 (NPAS2) ameliorates myocardial ischemia-reperfusion injury by inhibiting autophagy through interaction with the clock gene Cry 2 [55]. Our recent study discovered that autophagy, mediated by activation of the clock gene BMAL1, could mitigate myocardial ischemia-reperfusion injury [56].

It has been established that melatonin receptor RORα, an endogenous protective receptor against ischemia-reperfusion injury, is a pivotal mediator of cardioprotection and plays an indispensable role in the prevention of ischemic heart injury [57]. PER2 is a crucial component of the circadian clockwork and a significant regulator of circadian amplitude. Research has demonstrated that PER2 activation can resist the potent inflammatory response during reperfusion, thus reducing myocardial ischemia-reperfusion injury [58].

Clock genes still play a vital regulatory role in the process of revascularization in patients with ischemic heart disease. Consequently, further research on clock genes may provide a critical theoretical foundation for the prevention and treatment of myocardial ischemia-reperfusion injury.

4.3. Circadian rhythm and hypertension

The diurnal blood pressure rhythm is characterized by an increase upon awakening in the morning, a plateau during the day, and a decrease at night. Nevertheless, it is particularly crucial for hypertensive patients to have this 24-h dynamic alteration in blood pressure interrupted. Previous studies have demonstrated that peripheral tissues, such as smooth muscle, liver, adrenal glands, and kidneys, all contribute to regulating blood pressure rhythms [93]. However, the precise mechanism still necessitates elucidation.

The systemic deletion of BMAL1 in mice abolished the circadian rhythm of blood pressure and concurrently induced hypotension, probably via reduced catecholamine production [62]. Several other fundamental clock genes have also been reported to regulate blood pressure in different ways [[94,95]]. The arterial pressure of CLOCK knockout mice is reduced, and the mean arterial pressure, systolic blood pressure, and diastolic blood pressure are approximately 10 mmHg lower than those of wild-type mice [63]. Likewise, mice lacking PER1 and PER2 also display reduced blood pressure [[64,65]].

Melatonin, a circadian hormone secreted from the pineal gland in darkness, has been studied to demonstrate its hypotensive effect on blood pressure in hypertensive patients [96]. Additionally, melatonin may play a role in the circadian rhythm of blood pressure in nocturnal hypertensive patients through its scavenging and antioxidant effects [66].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been widely developed as antidiabetic agents, and in addition to their hypoglycemic effects, strong evidence suggests that SGLT2 inhibitors also have beneficial effects on hypertension [67]. The study found that empagliflozin prevented the development of blood pressure elevation with normalization of its circadian rhythm to a dipper profile, which was associated with increased urinary sodium excretion [68].

Recent studies have highlighted the importance of circadian rhythms in relation to the body's immune function and its impact on the development of cardiovascular disease [97]. Studies have demonstrated higher levels of macrophage colony-stimulating factor (M-CSF) in peripheral blood serum of patients with essential hypertension and increased circadian variability of M-CSF levels in blood compared to normal subjects [59].

Peroxisome proliferator-activated receptor γ (PPARγ) is a member of the nuclear receptor ligand-activated transcription factor superfamily. Studies have demonstrated that the rhythmic expression of vascular PPARγ is light sensitive and that PPARγ regulates circadian rhythms of blood pressure and heart rate through direct interaction with the BMAL1 gene [5].

Notably, the analysis of our present study also delved into the interplay between circadian rhythms and chronic kidney disease. The disturbance of the circadian rhythm of renal function is closely linked to the pathogenesis of hypertension, chronic kidney disease, and renal fibrosis [98]. Investigations have shown an abnormal circadian rhythm of urinary sodium excretion in association with hypertension arising from chronic kidney disease [99]. Deletion of the clock gene PER1 causes higher plasma aldosterone levels, leading to salt-sensitive hypertension [60]. Moreover, the circadian pattern of renin-angiotensin system activation in the kidney may lead to renal injury and hypertension, which is related to rhythmic alterations in blood pressure [61]. Taken together, renal salt handling is deemed a critical determinant of blood pressure, and renal insufficiency is seldom absent in hypertensive patients. Thus, salt sensitivity of blood pressure and excess salt intake have important roles in the genesis of the cardiorenal connection. These findings suggest a significant correlation between renal physiology and the circadian pattern of blood pressure.

4.4. Circadian rhythm and arrhythmia

Arrhythmias are the predominant cause of mortality among patients with cardiovascular disease. Life-threatening arrhythmias, such as ventricular tachycardia and ventricular fibrillation, are generally believed to have a higher likelihood of occurrence in the morning. The circadian rhythm of the arrhythmia was also observed to be regular, with values decreasing at night, increasing during the day, and reaching a peak in the morning. The distribution of rhythms is dependent on the pattern of arrhythmias and heart disease [100]. Consistent with the onset of paroxysmal AF in community patients, new-onset AF in patients in the intensive care unit exhibits classical circadian rhythm changes [101]. In addition, patients with frequent premature atrial contractions (PACs) exhibit circadian rhythms [102].

Furthermore, disturbances in the circadian rhythm can elevate the susceptibility to arrhythmias [69]. It is now widely accepted that the supraoptic nucleus of the hypothalamus regulates the circadian rhythm of heart rate through circadian changes in autonomic tone to the sinus node, particularly the increase in vagal tone at night [103].

A long and short abnormal QT interval is associated with an increased risk of fatal ventricular arrhythmias (94). It was found that the QT interval exhibited circadian rhythmicity in the mouse heart, while cardiomyocyte-specific Bmal1 knockout mice had a longer

QT interval [69]. Arrhythmia vulnerability appears to be increased when the cardiac clock is disrupted.

Diurnal differences in intrinsic sinus node activity and diurnal differences in mRNA and protein of hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 (HCN4) were shown to accompany diurnal variations in heart rate and intrinsic sinus node pacing rate [70].

Expression of certain specific K+ channel genes in the myocardium exhibits unique circadian rhythmicity [104]. BMAL1 in the heart alters K+ channel gene expression by regulating circadian rhythm expression of KCNH2, which is critical for the diurnal variation of normal ventricular repolarization [72].

However, drugs that affect circadian rhythms, such as the circadian hormone melatonin, have also demonstrated pleiotropic effects and have shown potential as antiarrhythmic agents [105].

The research highlighted that the suprachiasmatic nucleus governs the circadian rhythms of neurohumoral factors, particularly the autonomic nervous system, which exerts a modifying effect on ion conduction and acts as a triggering factor for cardiac arrhythmia [103]. CLOCK/BMAL1 also regulates the transcriptional expression of β1-β3-adrenergic receptors, and thereby regulates the circadian rhythmicity of ventricular arrhythmias in chronic heart failure [71]. Additionally, a different study observed that activation of β3-adrenergic receptors reduced the incidence of ventricular tachycardia and ventricular fibrillation in rats with acute or healed myocardial infarction [73].

Nevertheless, this study does bear witness to several limitations. Firstly, this study retrieved data only from WoSCC, and ignored other databases, so some articles may have been missed. Second, almost all articles were published in English, which may have led to selection bias in terms of language of publication.

5. Conclusion

In conclusion, the pivotal role of circadian rhythms in cardiovascular disease has garnered significant attention, with a marked increase in research over the last decade. Relevant cardiovascular diseases by modulating myocardial circadian rhythms may become a new research hotspot for clinical translation. Notably, certain institutions in the United States and Spain have produced a higher volume of outputs and results in this area, indicating their earnest investment. However, enhanced collaboration between countries and institutions is also imperative. This study evaluated fundamental information in this field, encompassing countries, institutions, journals, references, and keywords. Analysis of prospective thematic trends suggested that inflammation, metabolism, oxidative stress, and autophagy might hold promising potential as emerging hotspots.

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Data availability

The original data associated with this study has not been deposited into any publicly available repository, as the data used to support the results of this study are provided by the Web of Science Core Collection with permission. Additional data will be made available on request to the corresponding authors.

CRediT authorship contribution statement

Hao Tian: Writing – original draft, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Xiaoshuai Zhao:** Visualization, Validation. **Yuxi Zhang:** Writing – review & editing. **Zhongyuan Xia:** Writing – review & editing, Writing – original draft, Visualization, Validation, Funding acquisition.

Declaration of competing 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28738.

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