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REVIEW / *DERLEME*

Which Measures and Parameters of Heart Rate Variability Analysis may be Useful for Early Detection and Predicting Prognosis of Sepsis? A Systematic Review

Sepsisin Erken Teşhisi ve Prognoz Tahmininde Hangi Kalp Atım Hızı Analiz Ölçümleri ve Parametreleri Kullanışlı Olabilir? Bir Sistematik Derleme

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ABSTRACT

Sepsis causes a series of pathological changes, such as cardiovascular, respiratory, and thermoregulation. These changes alter heart rate variability (HRV). Even without any changes in the vital signs or clinical presentation of the disease, HRV may still be altered due to sympathetic nervous system activation caused by infection. Our aim in this review was to present sepsis-related HRV measures and parameters by examining the literature and their possible role in predicting the severity and mortality of sepsis. Databases were searched for original research articles reporting on human HRV-related sepsis published in the English language between April 1996 and May 2023. After completion of the article search, a total of 79 articles were selected for further evaluation where the full text of the articles was reviewed and 13 of the articles met the criteria for inclusion. The mean values of each HRV parameter were corrected to the sample size of each study, and the overall means were calculated accordingly. Statistical comparisons were performed after correcting for sample size using the Willcoxon signed-rank test. After the final evaluation, with a total of 1453 patients, 9 studies on sepsis in humans were included. The weighted mean age was 64.24 years, and 53.9% were male. Of the studies included, all underwent frequency domain analysis, and four underwent non-linear analysis. Seven of the nine studies were conducted in the emergency departments, and two were conducted in the intensive care units. 6 studies compared parameters between survivors and non-survivors, and 3 studies compared parameters between different severity levels of sepsis. SDNN, RMSSD, SDNN, HTI, LFnu, HFnu, LF/HF ratio, SD1, SD2, detrended fluctuation analysis (DFA)α_1, and DFAα_2 appear to be related to mortality in patients with sepsis outcome. Therefore, monitoring these parameters for the early detection of sepsis may be beneficial.

Keywords: Sepsis, variability in heart rate, time domain parameters, frequency domain parameters, non-linear analysis

ÖZ

Sepsis, kardiyovasküler, solunum ve termoregülasyon gibi sistemlerde patolojik değişikliklere neden olur. Bu değişiklikler de kalp hızı değişkenliğinde (HRV) alterasyonlara neden olur. Vital bulgularda veya hastalığın klinik sunumunda herhangi bir değişiklik olmasa bile, enfeksiyona bağlı olarak sempatik sinir sistemi aktivasyonu nedeniyle HRV parametreleri değişebilir. Bu sistematik derlemedeki amacımız, literatürü inceleyerek sepsise ilişkin HRV ölçümlerini ve parametrelerini sunmak ve bunların sepsisin şiddetini ve ölüm riskini tahmin etmedeki olası rolünü araştırmaktır. Veritabanları, Nisan 1996 - Mayıs 2023 tarihleri arasında İngilizce dilinde yayınlanmış sepsis üzerine HRV analizlerini insan çalışmalarını bildiren orijinal araştırma makaleleri için tarandı. Makale araması tamamlandıktan sonra, 79 makale daha ayrıntılı bir değerlendirmeye tabi tutulmak üzere seçildi ve bu makalelerin tam metinleri incelendikten sonra 13 makale kriterlere uygun olarak sınıflandırıldı. Her HRV parametrelerinin ortalama değerleri her çalışmanın örnek büyüklüğüne göre düzeltildi ve genel ortalamalar hesaplandı. İstatistiksel karşılaştırmalar Wilcoxon eşleştirilmiş diziler testi ile yapıldı. Toplam 1453 hastanın yer aldığı dokuz çalışma dahil edildi, ortalama yaş 64,24 yıl ve tüm katılımcıların %53,9'u erkekti. Dahil edilen çalışmaların hepsi zaman, frekans domain analizi gerçekleştirdi ve dört tanesi bu analizlere ek olarak doğrusal olmayan analizler gerçekleştirdi. Dokuz çalışmanın yedisini acil serviste ve ikisini hastanelerin yoğun bakım ünitelerinde gerçekleştirildi. Altı çalışma sağ kalanlar ile hayatını kaybedenler arasındaki parametreleri, üç çalışma ise sepsisin farklı şiddet seviyeleri arasındaki parametreleri karşılaştırdı. SDNN, RMSSD, SDNN, HTI, LFnu, HFnu, LF/HF oranı, SD1, SD2, eğilimsiz dalgalanma analizi (DFA)α_1 ve DFAα_2, sepsis sonucuyla ilişkili gibi görünmektedir. Bu nedenle, sepsisin erken teşhisi için bu parametrelerin izlenmesinin faydalı olabilir.

Anahtar Kelimeler: Sepsis, kalp atım hızı değişkenliği, zaman tabanlı parametreler, frekans tabanlı parametreler, doğrusal olmayan analizler

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Introduction

Sepsis is a disorder characterized by the presence of infectious organisms in regions of the body that should ordinarily be devoid of bacteria or viruses, such as blood or tissues, due to a bacterial or viral infection. Sepsis can cause a heightened inflammatory response throughout the body. And, as a result of the body's overreaction, some organs may receive less oxygen and/or blood perfusion, a condition known as septic shock (1). The sympathetic nervous system (SNS) is integral to the development and progression of septic shock. Research has shown that dysfunction within the sympathetic branch of the autonomic nervous system (ANS) disrupts heart and vascular regulation, contributing to circulatory collapse in septic shock (2). This condition involves an inadequate response to low blood pressure and inflammatory stress, leading to compromised SNS function (3). In the early stages of septic shock, elevated levels of catecholamines are present; however, the sympathetic regulation of the heart and blood vessels remains impaired, suggesting that central autonomic dysregulation plays a significant role in the resulting circulatory failure (2). Therefore, monitoring the activity of the ANS in patients with sepsis or septicemia is important. Various methods are available for assessing ANS function, but heart rate variability (HRV) analysis has gained popularity in recent years due to its ease of use, non-invasive nature, and low cost. Both electrocardiography (ECG) and photoplethysmography (PPG) can be used to assess HRV, namely autonomic nervous function. The RR interval time series, which consists of the time intervals between consecutive R waves of the QRS complexes in ECG or PPG signals, is used to assess HRV (3).

HRV analysis includes several methods, with the most common being the time-domain analysis. The proposed method involves extracting numerical data through a basic mathematical examination of the time intervals between successive heartbeats. These figures quantify the extent of HRV across different time scales, whether extensive recordings spanning 24 hours or brief recordings lasting only a few minutes (3). The most commonly examined parameters were the standard deviation of normal heartbeats (SDNN), the root mean square of successive heartbeat intervals (RMSSD), and the number of normal heartbeats occurring within intervals less than 50 milliseconds (NN50) (4). The second most common method is frequency domain analysis. Frequency domain analysis is an intricate analytical method that reveals the distribution of signals across specific frequency bands. High-frequency power (HF) denotes activity within the 0.15-0.40 Hz range, while low-frequency power (LF) represents activity within the 0.04 - 0.15 Hz range (5). The LF/HF ratio, a comparison of low-frequency to high-frequency frequencies, is sometimes interpreted as indicative of sympathovagal balance, although this interpretation is subject to controversy (6,7). On the other hand, non-linear methods differ from the above mentioned "classical" HRV analysis methods because they do not assess the variability of the heart rate but rather the quality, scaling, and correlation characteristics of the signal (8).

Although rare, sepsis patients who require admission to an intensive care unit (ICU) may experience a turbulent course because of a pathological inflammatory reaction called "Cytokine Storm". Increases in inflammatory markers, such as C-reactive protein (CRP), follow the initiation of a cytokine storm. Because it is crucial to start early pharmacological therapies to achieve better results, these factors help clinicians determine when to implement them (9). However, one disadvantage of these laboratory tests is that they may not sufficiently alert clinicians to start treatment promptly enough (10).

Sepsis triggers a range of pathological changes across various systems, including cardiovascular, respiratory, and thermoregulatory systems. These changes can lead to fluctuations in HRV. HRV may be affected even in the absence of noticeable changes in vital signs or clinical symptoms because infection-induced activation of the SNS can still influence HRV (11). This may enable us to begin pharmacological interventions at very early phases even 12-24 hours before clinical changes (such as fever, tachycardia or positive culture results) (11). As a new and promising tool, continuous monitoring of HRV and even complexity in ICU settings may also provide useful information regarding the overall health of patients. A predictive model for sepsis severity that combines HRV with laboratory values has shown superior performance compared with models based on single domains (such as clinical data, laboratory values, or HRV alone). This combined model achieves better discrimination and provides a more balanced sensitivity and specificity than individual domain-based models (12).

To date, apart from sepsis, which is a pathological condition caused by a positive feedback mechanism triggered by infection, changes in HRV parameters have been associated with cardiomyopathies (13), arterial hypertension (14), myocardial infarction (15), and kidney failure (16). However, HRV analysis involves several components that represent different dynamics of the ANS. There are more than 25 different parameters of HRV analysis, and these parameters belong to different HRV measures, such as time and frequency domain analysis and non-linear methods (4). Regarding the mechanism of pathology, HRV parameters may be affected differently (3). Thus, it is crucial to select the most sensitive HRV measures and parameters corresponding to the underlying pathology and physiopathological mechanism to interpret the HRV analysis results as accurately as possible. In this review, we aimed to explore HRV measures and parameters related to sepsis by analyzing the existing literature and evaluating their potential role in predicting the severity and mortality of sepsis. We hypothesized which specific HRV parameters may serve as valuable indicators for identifying sepsis patients and forecasting disease progression and outcomes.

Methods

The EBSCO, PubMed, and Web of Science databases were searched for original research articles published in the English language between April 1996 and May 2023, focusing on research examining the relationship between sepsis and HRV in humans. This period was selected because "Task Force of The European Society of Cardiology" published the "Guidelines for HRV Measurement, Interpretation, and Clinical Use" in 1996 (5).

Both authors independently screened the titles, abstracts, and methods of the articles to assess their relevance according to the inclusion criteria. The articles deemed relevant by both authors were further reviewed. Other article types, such as reviews, meta-analyses, letters to the editor, and conference abstracts, were excluded. If no consensus on relevance was not initially reached, the full text of the article was reviewed. Any disagreements were resolved through discussion until consensus was reached in all cases.

Search Terminology

The search approach for this systematic review incorporated keywords such as "autonomic nervous system", "ANS", "heart rate variability", "HRV", "heart rate dynamics", "heart rate characteristics", "heart rate complexity", "heart rate fluctuations", and "spectral analysis". These terms were combined with terms related to sepsis, such as "sepsis", "septic shock", "septicemia", "infection", "endotoxemia", and "inflammation". The filters included studies focused on "human" subjects and settings like "ICU", "intensive care", "emergency department", "ER", and "hospital".

Selection Criteria and Data Extraction

Studies that met the following criteria were selected after the final review: (i) were published between April 1996 and May 2023; (ii) examined the ANS activity of human subjects in hospital settings (iii) analyzed ANS activity via time domain and/or frequency domain and/or non-linear analysis. We followed the guidelines for precise and reliable HRV measurement as outlined by "Task Force of the European Society of Cardiology". These guidelines ensure consistency and precision in data collection, facilitating valid assessments of HRV in clinical and research settings and provide frequency domain analysis results in normalized units because interstudy comparisons are not recommended with absolute powers (5).

All selected papers were imported into Mendeley (version 1.19.4, London, UK), from which all duplicates were removed. After completion of the article search, a total of 79 articles were selected for further evaluation where full text of the articles was reviewed and 13 of the articles met the criteria for inclusion.

Risk of Bias Assessment

The Cochrane Collaboration's Risk of Bias tool was used to evaluate the bias in randomized controlled trials (RCTs), while the ROBINS-I tool was applied for observational studies. Each study was independently reviewed by two assessors, and any differing opinions were resolved through discussion.

Statistical Analysis

Due to limited data in the studies, a meta-analysis could not be conducted; thus, a descriptive analysis was performed instead. In cases of significant clinical or statistical heterogeneity, descriptive analysis was performed, whereas subgroup analysis was performed to separate studies based on quality or the interventions used. The mean values of HRV parameters, including LFnu, HFnu, LF/HF, RMSSD, SDNN, HRV triangular index (HTI), SD1, SD2, detrended fluctuation analysis (DFA)α_1, and DFAα_2, were adjusted according to the sample size of each study, and overall means were calculated accordingly. The combined results are presented as means standard deviations (SDs). Statistical comparisons, adjusted for sample size, were conducted using the Wilcoxon signed-rank test.

HRV Measures Used in Included Studies with Sepsis

HRV analysis can be conducted using various measures, each providing distinct insights. The most commonly used methods for HRV analysis are time-domain, frequency-domain, and non-linear techniques. This section will outline the basic concepts behind these methods, followed by a discussion of their potential roles in the early detection, severity assessment, and prognosis of sepsis.

Time-domain Analysis

HRV, which is measured over monitoring periods ranging from 1 minute to more than 24 hours, is quantified using time-domain indices that evaluate the degree of HRV during these intervals (6). Common time-domain indices include the standard deviation of normal-to-normal intervals (SDNN), the root mean square of successive differences (RMSSD), the number of pairs of successive normal-to-normal intervals that differ by more than 50 milliseconds (NN50), the percentage of pairs of successive normal-to-normal intervals that differ by more than 50 milliseconds (pNN50), the HTI, and the triangular interpolation of the NN interval (TINN) (5,6).

SDNN, which refers to the standard deviation of the intervals between consecutive normal sinus beats, is typically measured in milliseconds. Although 5 min is the standard duration for short-term HRV recordings, some studies have proposed using shorter periods, ranging from 1 to 4 min. In these short-term recordings, respiratory sinus arrhythmia (RSA), driven by parasympathetic activity, is the dominant factor contributing to HRV, particularly during slow, regulated breathing. When measured over a full 24-hour period, SDNN is widely regarded as the "gold standard" for assessing cardiac risk because it has strong predictive value for both morbidity and mortality (6).

The parasympathetic nervous system's (PNS) activity is intimately linked to the percentage of successive NN intervals that differ by more than 50 ms, which is known as pNN50. However, for RSA assessment, RMSSD is frequently chosen over pNN50, particularly in older individuals. Finding the time difference between each pulse in milliseconds, squaring each difference, averaging them, and taking the square root yields the root mean square of consecutive differences between normal beats or RMSSD. The key time-domain metric for evaluating vagal tone is RMSSD, which represents beat-to-beat HRV and is strongly associated with the non-linear metric SD1. RMSSD also exhibits a strong correlation with pNN50 and HF power over a 24-hour period. HTI is a geometric measure that estimates the integral of the RR interval histogram density divided by its height, while TINN represents the base width of the NN interval histogram (6).

Frequency Domain Analysis

The frequency-domain analysis of HRV evaluates the proportion of a signal falling within the frequency bands. Researchers have identified several frequency bands that correlate with different physiological phenomena. The most studied bands in human HRV analysis are ultra-low frequency (ULF), very-low frequency (VLF), LF, HF, and the LF/HF ratio. The ULF band requires at least 24 hours of recording, which is often difficult to obtain (17). Although there is no consensus on the exact mechanisms generating ULF power, experimental evidence suggests that slow-acting biological mechanisms, such as circadian rhythms, may primarily drive ULF activity (18). The VLF band is thought to be generated by the activation of afferent sensory neurons in the heart and may be influenced by stress responses (19,20). This activation triggers feedback and feed-forward reflex mechanisms within the heart's intrinsic nervous system, as well as extrinsic cardiac ganglia in the thoracic cavity and spinal cord (21). The LF band, previously referred to as the baroreceptor range due to its strong correlation with baroreceptor activity, is influenced by both the parasympathetic (PNS) and SNS, along with baroreceptor function (5,6,22-24). In contrast, the HF band is primarily linked to parasympathetic or vagal activity, earning the label "respiratory band" due to its association with heart rate fluctuations during respiration (6). The LF/HF ratio is commonly used as an indicator of sympathetic and parasympathetic balance, as the LF component reflects both sympathetic and parasympathetic influences, whereas the HF component predominantly represents parasympathetic control (24).

Normalized HRV parameters, like LFnu and HFnu, are determined by dividing the raw values of LF or HF by the total spectral power, which is generally the sum of LF and HF. These values are expressed as percentages (5). Normalized HRV parameters are particularly helpful for comparing studies because they enhance the consistency and clarity of the results. By normalizing, the proportional changes in the frequency bands can be represented in a similar way, regardless of the spectral method used (5). However, this approach has certain limitations. A significant issue is the inherent relationship between LFnu and HFnu, where LFnu = 1 HFnu. The two values are mathematically interchangeable and do not provide distinct information. Including both LFnu and HFnu does not yield extra insights, as variations in one directly correspond to those in the other (25).

Non-linear Analysis Methods

The cardiovascular system, like all biological systems, exhibits complex dynamics. Goldberger proposed that reductions in variability and complexity could indicate the presence of pathological conditions (27). The heart rate, one of the most significant dynamic parameters, is influenced by neural, hormonal, and hemodynamic changes originating from various systems and organs.

Non-linearity refers to relationships between variables that do not follow a direct, proportional pattern and cannot be represented with a straight line. Non-linear metrics are valuable for capturing the underlying variability within a time series, highlighting the complex processes involved in heart rate regulation.

Some pathologies like myocardial infarction (MI), diabetes, and mood disorders, may decrease complexity (17,27,28). In this section, we review the most investigated non-linear measurements; Poincaré Plot parameters SD1, SD2, SD2/SD1, and DFA exponents DFAα_1 and DFAα_2.

Poincaré Plot

To analyze the Poincaré plot, an ellipse is fitted to the plotted points. The ellipse's width is determined by the standard deviation (SD1) of each point's distance from the y = x axis, and its length is determined by the standard deviation of each point's distance from the line y = x + average R-R gap (SD2) (4). It is believed that SD1 correlates with variations in blood pressure, power in the LF and HF bands, and the overall power of brief recordings (e.g., 5 minutes) (29,30). SD2 reflects LF band power and baroreflex sensitivity. The ratio of SD2 to SD1 (SD2/SD1) is considered analogous to the LF/HF ratio from frequency domain HRV analysis (31).

Detrended Fluctuation Analysis

DFA was used to extract the self-similarity (correlations) between consecutive RR intervals. The DFA calculates the scaling exponents (short-term, DFAα_1 and long-term, DFAα_2) from the time series and reflects the fractal correlation characteristics of complex dynamic heart rate series (6). DFAα_1 is suggested to reflect baroreceptor reflex activity, while DFAα_2 is thought to represent regulatory mechanisms that stabilize fluctuations in the cardiac cycle (32,33).

Results

The analysis included nine studies with a total of 1,453 patients. The mean age of the participants was 64.24 years, and 53.9% were male (34-42). Table 1 presents the main characteristics of all studies, such as sample size, mean age, study settings, and significant HRV findings ($p \leq 0.05$).

The included studies assessed various HRV parameters across different domains. In the time domain, the following parameters were evaluated: RMSSD, SDNN, NN50, pNN50, and TINN. In the frequency domain, the parameters included the normalized low-frequency power (LFnu), normalized high-frequency power (HFnu), the ratio of LFnu to HFnu (LFnu/HFnu), and the total power (TP). The non-linear methods assessed included Poincare Plot standard deviation 1 (SD1), Poincare Plot standard deviation 2 (SD2), the ratio of SD1 to SD2 (SD1/SD2), and short-term (α_1) and long-term (α_2) fractal scaling coefficients derived from (DFA). The significant HRV findings are summarized in Table 1.

Of the studies included, all performed frequency domain analysis, and four also performed non-linear analysis (Table 1). Seven of the nine studies were conducted in the emergency departments, and two were conducted in the intensive care units. 6 studies compared parameters between survivors and non-survivors (34-39), and 3 studies compared parameters between different severity levels of sepsis (40-42).

Table 2 shows the combined results of LFnu, HFnu, LF/HF, RMSSD, SDNN, HTI, SD1, SD2, DFAα_1, and DFAα_2 parameters of the selected studies, comparing the parameters between survivors and non-survivors of the sepsis (36,38-40). LFnu, LF/HF, SD2, DFAα_1, and DFAα_2 were lower in the non-survivor group, whereas HFnu, RMSSD, SDNN, HTI, and SD1 were higher in the non-survivor group.

Discussion

In this review, we found that non-surviving patients with sepsis had lower LFnu, LF/HF ratio, SD2, DFAα_1, and DFAα_2, while survivors exhibited higher HFnu, RMSSD, SDNN, HTI, and SD1. This suggests that HRV parameter monitoring can help predict mortality in patients with sepsis. However, the relationship between HRV and sepsis severity remains unclear, likely due to the limited number of studies that examined HRV parameters in relation to sepsis severity.

The role of the ANS in the pathophysiology of sepsis has gained attention, with vagus nerve stimulation known to influence cortisol release. Acetylcholine, the main neurotransmitter of the vagus nerve, has anti-inflammatory effects, (43) including reducing cytokine release (TNF, IL-1beta, IL-6, and IL-18) and mitigating the cytokine storm seen in septic shock (44).

Our findings align with those of studies that suggest HRV analysis, a non-invasive method for assessing autonomic function, may be helpful for predicting outcomes in patients with septic arthritis. Combining HRV monitoring with widely used clinical scoring systems, such as SOFA, qSOFA, mSOFA, and APACHE II, can improve prognosis prediction. HRV analysis is convenient, with smartwatches offering accessible, non-invasive monitoring options. Therefore, HRV is an ideal tool for use in emergency departments, general wards, and ICU settings.

Table 1. Summary of studies investigating heart rate variability (HRV) in sepsis and critical care patients

First author (year)	Sample size (n)	Sex (% of male)	Mean age (overall)	Study setting	Study groups	Significant HRV findings
Arbo et al. (34)	72	61.1	60.4±20.3	Emergency department	1. Sepsis 2. Severe sepsis 3. Septic shock	Decreased LFnu, Increased HFnu, Decreased LF/HF ratio correlate with the severity of the sepsis.
Bonjorno et al. (35)	60	58.3	50.3±13.0	Intensive care unit	1. Survivor 2. Non-survivor	Higher HTI and SD1 in surviving group.
Chen et al. (36)	132	47.0	66.7±10.2	Emergency department	1. Survivor 2. Non-survivor	Lower SDNN, Total Power (nu), LFnu/HFnu in non-survivors and higher HFnu in survivors.
Kim et al. (37)	189	56.1	57.517.6±	Emergency department	1. Severe sepsis patients admitted to ICU 2. Sepsis patients admitted to general ward, 3. Sepsis patients discharged within 24 hours 4. Healthy volunteers.	Total Power and LFnu were decreased in all groups compared to healthy individuals. HFnu was decreased in severe sepsis and sepsis patients admitted to general ward groups compared to healthy individuals.
Papaioannou et al. (38)	45	57.8	57.8	Intensive care unit	1. Survivor 2. Non-survivor	CRP negatively correlates with SDNN, LFnu, LF/HF and positively with HFnu and SD1/SD2 ratio. SDNN and HF are independent predictors of severity of sepsis.
Pong et al. (39)	364	49.2	67.1±16.1	Emergency department	1. No 30 day in-hospital mortality 2. 30 day in-hospital mortality	Increased SDNN, RMSSD, NN50, pNN50, TINN, HFnu, SD1, and decreased LFnu in 30 day in-hospital mortality group.
Prabhakar et al. (40)	343	50.7	67.5±15.6	Emergency department	1. Survivor 2. Non-survivor	Increased SDNN, RMSSD, TINN, HFnu, SD1 and decreased LF/HF, DFAα_1, DFAα_2, LF nu in non-survivors group.
Samsudin et al. (41)	214	50.5	66.9±15.6	Emergency department	1. Survivor 2. Non-survivor	Increased SDNN, RMSSD, TINN HFnu, SD1 and decreased DFAα_1, DFAα_2 and LF (nu) in non-survivors.
Tang et al. (42)	34	Not provided	52.9	Emergency department	1. Systemic inflammatory response syndrome 2. Severe sepsis 3. Healthy volunteers.	LFnu was decreased in severe sepsis patients.

HF: high-frequency, LF: low-frequency, RMSSD: root mean square of successive heartbeat intervals, SDNN: standard deviation of normal heartbeats, HTI: HRV triangular index, DFA: detrended fluctuation analysis

Table 2. Comparison of heart rate variability (HRV) parameters between survivors and non-survivors in sepsis and critical care patients

	Survivors			Non-survivors			
	Mean	**SD**	**n**	**Mean**	**SD**	**n**	**p-value**
LFnu	43.2864	24.63906	847	33.09029	24.7233	206	**0.02443**
HFnu	45.20782	24.23509	847	63.38981	24.4311	206	**0.02402**
LF/HF	2.762645	3.785706	673	1.521084	4.33735	166	**0.01041**
RMSSD	24.3383	33.82116	847	43.07961	49.0573	206	**0.02492**
SDNN	21.38553	22.22373	847	32.16214	32.9631	206	**0.02048**
HTI	4.8	2.7	21	6.5	3.15714	39	**0.01142**
SD1	19.34021	27.3337	746	27.45447	30.9277	235	**0.02506**
SD2	25.7	26.7	174	9.287356	37.1	40	**0.00154**
DFAα_1	0.683993	0.389328	551	0.517949	0.28654	156	**0.00561**
DFAα_2	0.955724	0.40811	725	0.683163	0.40357	196	**0.03295**

SD: standard deviation, HF: high-frequency, LF: low-frequency, RMSSD: root mean square of successive heartbeat intervals, SDNN: standard deviation of normal heartbeats, HTI: HRV triangular index, DFA: detrended fluctuation analysis

In this review, we found that non-survivors had significantly lower LFnu, LF/HF ratio, SD2, DFAα_1, and higher DFAα_2 and HFnu, RMSSD, SDNN, HTI, and SD1. Several studies support this, including a study by Chao et al. (10) that determined whether decreases in SDNN predict elevations in CRP in COVID-19 patients. With a 90.9% positive predictive value, significant declines in SDNN predicted increases in CRP levels in the following 72 hours. Natarajan et al. (45) found that RMSSD was significantly decreased before the onset of COVID-19 symptoms. Aragón-Benedí et al. (46) found that lower SDNN and HFnu are associated with a poor prognosis, higher mortality, and higher IL-6 levels in COVID-19 patients. Similarly, Krishnan et al. (47) found that SDNN, RMSSD, LF, HF, and DFA parameters were associated with Sepsis-related acute respiratory failure patients. Kenig and Ilan (48) proposed a predictive model for severe sepsis that included the mean RR interval and DFAα_2 alongside other clinical parameters. This model aimed to enhance the efficacy of sepsis treatment by incorporating DFA analysis as a predictive component. Furthermore, a case report monitoring HRV in a patient with late-stage sepsis observed a reduction in LF and HF prior to death, indicating HRV alterations in the progression of sepsis (49). Although studies involving experimental animals are not included in this review, trends of decreasing SDNN and RMSSD are consistent with findings observed in a peritonitis-induced sepsis model in pigs (50).

HRV is a promising indicator of sepsis development. According to Brown et al. (51), changes in HRV, such as loss of complexity or changes in sympathovagal balance, can anticipate the development of shock and organ dysfunction and signal the onset of sepsis. Additionally, continuous monitoring of HRV in adult patients has been associated with reduced HRV, which coincides with the onset of sepsis (52).

Several HRV parameters have been found to be lower in non-surviving septic patients compared to survivors, among all the HRV measures studied for predicting mortality risk of sepsis. However, further research is necessary to identify which specific HRV parameters are most effective in predicting sepsis mortality, as well as to establish appropriate cutoff values for each parameter. In some studies investigating the predictive value of HRV analysis in sepsis, SDNN, RMSSD, and HFnu were particularly notable.

Sepsis can be predicted using longitudinal HRV data collected from regularly used commercial wearable devices, such as Apple Watch, FitBit, and Polar. Significant changes in HRV parameters, especially RMSSD, SDNN, HTI, LFnu, HFnu, LF/HF ratio, SD1, SD2, DFAα_1, and DFAα_2 are candidate parameters for the identification of sepsis. More studies are needed to evaluate the predictive power of these parameters by confirming the cases with laboratory tests.

Study Limitations

The low quantity and quality of the included papers are the primary limitations of this systematic review. Thus, although it may be concluded that monitoring the reduction of HRV and that these stood out parameters may be linked to sepsis detection and severity, more studies are needed to determine the best methodology and cutoff points that can be used.

Conclusion

In the studies included in this review, several HRV values were altered in non-surviving septic patients. SDNN, RMSSD, SDNN, HTI, LFnu, HFnu, LF/HF ratio, SD1, SD2, DFAα_1, and DFAα_2 appear to be related to mortality in patients with sepsis outcome. Therefore, monitoring these parameters for the early detection of sepsis may be beneficial. Larger and better-designed research is needed to support these conclusions.

Ethics

Authorship Contributions

Concept: H.K., Data Collection and Process: H.K., Analysis or Interpretation: H.K., H.F.Ö., Literature Search: H.K., H.F.Ö., Writing: H.K., H.F.Ö.

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