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Heart Rate Variability as a Prognostic Tool for Palliative Patients : a Literature Review

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ABSTRACT

Background: Heart rate variability (HRV) is the fluctuation in interval between two heartbeats. Decreased HRV indicates diminished flexibility of the autonomic nervous system (ANS) to physiological changes and is associated with poorer disease progression and mortality in several diseases. We reviewed conditions in which HRV can be utilized as a prognostic tool for palliative patients. **Methods** We performed a comprehensive search in PubMed, ScienceDirect, and Google Scholar to find articles published up to January 2023 related to HRV and prognosis for cancer-related disorders, cardiovascular disease, and sepsis. 41 relevant articles were selected and reviewed. **Results:** ANS changes due to chronic cancer pain and metastastic bone cancer can be detected by HRV analysis and increased vagal activity is related with longer overall survival on advanced cancer patients. Lower HF is a risk factor for shorter life expectancy of metastatic or recurrent breast cancer. SDNN and RMSSD reduction correlates with poorer survival in NSCLC and metastatic brain cancer. Increased risk of stroke was observed in patients with lower RMSSD and SDNN. Reductions of LF were associated with two times increased risk myocardial infarction and higher mortality one year after stroke. *A decrease in HRV is related to mortality, but are not specific to cardiovascular disease.* SDNN and HF are HRV parameters that are most consistently correlated with sepsis *and can predict mortality within 30 days of hospitalization. HRV analysis helps in assessing the* prognosis of diseases. Typically, reduced HRV is linked to worse outcomes and increased mortality rates in conditions such as cancer, cardiovascular disease, and sepsis. HRV can be used as an adjunct for disease prognosis, but not as a standalone parameter.

Keywords: Heart rate variability, prognosis, mortality

INTRODUCTION

Heart rate variability (HRV) is defined as the fluctuation in interval duration between two heartbeats.[1,2] HRV reflects the function between the brain, heart, and autonomic nervous system (ANS).[2] Heart rate variability can be calculated by the time-domain method, by assessing the time between R-R waves, and the frequency-domain method, which calculates the frequency, as described in Table 1.[3] Currently, many HRV monitoring devices are sold commercially with high accuracy and can be used on a daily basis.[4] In recent years, HRV use has been increasing significantly. Its popularity is perhaps due to its ease of use, noninvasive, relatively los cost, and utility across a wide range of discipline. This includes physiology, psychology, sports medicine, and palliative care. [5]

HRV analysis is useful for determining disease prognosis. Decreased HRV indicates less flexibility of the autonomic system to respond to physiological changes in the body and is associated with diseases such as infection, cardiovascular disease, depression, anxiety, psychosocial stress, cancer and predict mortality.[6,7,8,9] Lower HRV was found in adult cancer patients as well as in recovered cancer patients. Decreased HRV was also found in pediatric leukemia patients.[10,11] Degree of reduction in HRV can also predict the occurrence of cancer-related fatigue and chronic pain in cancer.[9] Other chronic condition such as cardiovascular disease and chronic kidney disease also presents with ANS instability could be assessed with HRV.

MATERIAL AND METHODS

We conducted a literature search for papers published up to January 2023 on PubMed, Google Scholar, and ScienceDirect. The topic was heart rate variability for prognosis of cancer, cardiovascular disease, sepsis, and chronic kidney disease. Study selection was based from a search strategy using Medical Subject Heading, MeSH: "heart rate variability","sepsis/prognosis, "cancer/prognosis", "cardiovascular diseases/prognosis", "chronic kidney disease". 41 relevant articles were selected, reviewed and analyzed.

Table 1. HRV domain measures[2]

Parameter	Unit	Description
VLF	ms^2	Very low frequency: Absolute power of the very-low-frequency band (0.0033–0.04 Hz)
LF	ms^2	Low frequency: Absolute power of the low-frequency band (0.04–0.15 Hz)
HF	ms^2	High frequency: Absolute power of the high-frequency band (0.15–0.4 Hz)
SDNN	ms	Standard deviation of normal to normal intervals
RMSSD	ms	Root mean square of successive R-to-R interval differences

DISCUSSIONS

Use of HRV in Cancer-Related Pain

Pain is defined as an unpleasant sensory and emotional experience caused by an injury. Pain intensity is usually reported on a numerical scale that ranges from 0 to 10. This numerical scale can be used for acute pain as well as chronic pain. Anatomically, parts of the brain responsible for pain perception (the insula cortex, the anterior cingulate cortex, the amygdala, the prefrontal cortex, and the nucleus tractus solitarius) are also related to the regulation of ANS, in which HRV can be used as a marker of ANS reactivity to nociceptive stimulation.[12] Several studies focusing on pain sensitivity have used HRV to assess autonomic response. A systematic review on this topic was carried out by Koenig et al. that identified 20 studies demonstrating increased sympathetic baroreflex activity and decreased vagal parasympathetic activity, and found changes in HRV frequency domain.[12] Pain-related HRV changes are associated with ANS fluctuation and instability which can be detected in palliative care patients with advanced cancer. Current evidence suggests longer survival in cancer patients who have increased vagal nerve activity.[13] In addition, the effect of chronic pain on HRV is also influenced by depression. A study examining the relationship between bone metastatic cancer pain with pain scale above 4, adjusted for depression scores on the Hospital Anxiety and Depression Scale (HADS) found a

significant association with HRV, as measured by the LF/HF ratio (p=0.03) and were influenced by the patient's emotional state.[14]

Use of HRV on Cancer-Related Stress

Cancer and its treatment often cause physical and psychological distress. Previous studies have shown that the influence of the cancer itself, the effects of surgery or cancer treatments, and psychological distress can also influence cardiac autonomic function and modulate ANS in patients with cancer. ANS changes and dysfunction have been reported in cancer patients, with lower HRV than healthy controls.[15] Fatigue and depression have marked impact on impaired vagal function in patients with breast cancer, but there has been few investigation into the relationship between HRV and more specific psychological dimensions.[16] Besides the influence of depression, a decrease in anger emotions is also followed by an increase in HRV, especially on HF domain.

In one study, HRV was compared between two groups, namely breast cancer survivors undergoing aggressive treatment in the first year vs. healthy woman. Cardiovascular imbalances were observed in breast cancer survivors with significantly higher resting heart rates, and HF domain.[17] On the other side, low HF domain is a risk factor for shorter life expectancy in women diagnosed with metastatic or recurrent breast cancer.[18] HRV can also be used as a substitute for plasma cortisol and a marker of increased inflammation to detect surgery-related stress and autonomic dysfunction in patients undergoing radical gastrectomy for gastric cancer.[19,20]

Use of HRV as a Prognostic Tool for Cancer Patients

HRV may be a useful noninvasive tool for evaluating the prognosis of cancer patients. However, some studies still found that HRV is an imprecise prognostic tool, especially in patients with advanced cancer.[21–23] Prognostic function of HRV, especially for patients with metastatic cancer, has been discussed in several studies. The main hypothesis is that lower HRV is associated with tumor growth through three pathways, namely inflammation, oxidative stress, and ANS activation, especially the sympathetic nervous system. In the early stages of cancer, conventional treatments such as surgery and radiotherapy reduce the tumor, perhaps leaving less margin for vagal nerve activity to contribute to the process.[21] The effects of chemotherapy and radiotherapy that decrease HRV appear to be reversible with discontinuation of treatment. Therefore, this effect may not be relevant for patient prognosis.

In a recent study, HRV index was compared with other clinical variables to describe overall survival in patients with advanced non-small cell lung carcinoma (NSCLC).[24] SDNN significantly correlated with poor survival. Therefore, HRV may be a useful tool for monitoring patient's general well-being, rather than predicting overall survival. A 2010 study examined the relationship between HRV and patient survival with metastatic brain cancer. HRV analysis used SDNN and RMSSD with a limit value of 10 milliseconds and 7 milliseconds respectively in healthy populations. In patients with metastatic brain cancer, the median SDNN and RMSSD were 15 milliseconds and 10.5 milliseconds. These results indicate that HRV in cancer patients is slower than the healthy population.[25] Kim et al also investigated the relationship between HRV and survival of cancer patients in palliative care. The data analysis included the Karnofsky Scale, HRV, and anorexia. The HRV parameter used was SDNN, with a median of 21.3 milliseconds indicating significantly lower duration of survival.[26] Therefore, HRV can be used as a prognostic tool in terminal cancer patients.

Use of HRV in Stroke Patients and Cardiovascular Disease

Chen et al found an association between decreased HRV and the vascular system involved in stroke. Significantly lower HRV was found in patients with small vascular occlusive stroke compared with large vessel atherosclerosis. In addition, in small vessel occlusion, the VLF, LF, and HF scores were lower while the LF/HF ratio was higher compared to healthy controls.[27] Decreased SDNN and RMSSD scores also correlates with an increased risk of stroke, especially in patients with diabetes, in which HRV could be used as a predictor of stroke occurrence in this population.[28] Zeynep et al found a correlation between decreased SDNN at night (using a 48-hour Holter monitoring recording) and an increased risk of stroke.[29] Stroke patients are also at high risk of stroke recurrence and other diseases, this can have a long-term impact on quality of life and mortality. In an analysis by Krause et al., reductions in SDNN, RMSSD, and LF were associated with increased mortality in 12 months after stroke. Decreased HF and LF/HF ratio were also associated with an increase in myocardial infarction after stroke within 365 days.[30]

Because HRV is reflects cardiac ANS function, it can be assumed that HRV can be used to identify certain cardiovascular disease. This hypothesis is also stated from several studies that low HRV is associated with coronary heart disease, a predictor of mortality from cardiovascular disease, and sudden cardiac death.[31,32] Low HRV is also associated with two times increased risk of myocardial ischemia, and can also increase the sensitivity and specificity of stress testing to detect myocardial ischemia if used concurrently.[31] An increase in HRV has also been shown to reduce the lifetime risk of cardiovascular disease, especially in the SDNN, LF, LF/HF parameters, while a decrease HRV indicates an increased risk.[33] However, the use of HRV as a predictor of mortality is less specific. The results of a study by Vuoti et al showed that a decrease in HRV is related to mortality, but these deaths are not specific to cardiovascular disease, but also correlates with other causes of death.[34]

Use of HRV in Sepsis Patients

Sepsis is defined as a life-threatening condition of organ dysfunction and is caused by dysregulation of body response to infection.[35] Sepsis and septic shock are the leading causes of death in critically ill patients, with mortality rate up to 50%. Serological assays and inflammatory biomarkers such as C-reactive protein (CRP), lactate, and procalcitonin can aid in the diagnosis of sepsis, but their use is sometimes difficult due to the time consuming results.[36,37] Therefore, the use of HRV can be considered because the results appear in real-time.

When there is systemic injury and inflammation, there will be a response that is regulated by the brain to eliminate pathogens and reduce inflammation, called the cholinergic anti-inflammatory pathway. This reflex is regulated primarily by the parasympathetic system, and is useful in keeping inflammatory cytokines from rising too high in the circulation. A meta-analysis by Williams et al found that was a negative correlation between HRV and inflammatory markers. SDNN and HF are HRV parameters that are most consistently correlated with inflammatory markers. CRP and leukocyte count are inflammatory markers most strongly associated with HRV.[38] HRV can also be used as a marker of septic shock. Septic shock patients were found to have higher RMSSD and HF values, also lower LF and LF/HF compared to sepsis without shock.[39,40]

Furthermore, HRV can also be used as a predictor of mortality in septic patients. A systematic review by Castilho et al concluded that SDNN, VLF, LF, and LF/HF decreased in sepsis patients who died, and SDNN was the most accurate parameter with a cutoff value of 17 ms.[41] A scoring system for Singapore Emergency Department Sepsis (SEDS) also uses several HRV parameters, such as mean NN

and detrended fluctuation analysis (DFA) to identify and predict sepsis emergency patients and mortality within 30 days of hospitalization.[39,42]

Use of HRV in Chronic Kidney Disease Patients

In patients with chronic kidney disease (CKD), an ANS imbalance occurs due to decreased kidney function. Changes that occur include a decrease in parasympathetic function compared to sympathetic, thereby affecting the hemodynamics of the kidney.[43] Decreased parasympathetic function is represented by lower HF values in the morning compared to healthy people.[44] The relationship between HRV and CKD is similar to other diseases that have been discussed, namely a decrease in SDNN parameter is related to lower Glomerular Filtration Rate (GFR) and is not affected by age, diabetes mellitus and hypertension. However, other HRV parameters such as RMSSD, HF, LF and LF/HF did not show a significant relationship. This suggests that a low HRV does not cause CKD but may occur together.[43] Keiko et al found that SDNN values less than 75 milliseconds were associated with an increased incidence of CKD patient mortality on hemodialysis.[45] However, other studies stated that changes from SDNN and RMSSD, whether decreasing or increasing, are associated with significantly increased mortality in patients with kidney disease and other diseases such as coronary heart disease and diabetes, so their use in predicting mortality for CKD patients is less specific.[46]

CONCLUSIONS

HRV reflects the interaction between the brain, heart, and ANS. Analyzing HRV can help assess disease prognosis, with reduced HRV indicating diminished flexibility of the autonomic system to adapt to physiological changes. HRV can serve as an indicator of ANS responsiveness to nociceptive stimuli in advanced cancer patients receiving palliative care. Additionally, the ANS is influenced by the patient's psychological state; for instance, depression can lead to reduced vagal function, which in turn can increase HRV. Research has demonstrated that HRV values are influenced by cancer treatments, making HRV a potential prognostic marker for terminal cancer patients.
A low HRV indicates a disturbance in cardiovascular function (myocardial infarction, ischemia, stroke), although it can't be used as a specific predictor of mortality. In addition, ANS also regulates parasympathetic reflexes in the cholinergic antiinflammatory pathway so that in systemic infection conditions such as sepsis, HRV can be a marker of septic shock and a predictor of patient mortality. In chronic kidney disease (CKD), where there is an imbalance of ANS, HRV parameter decreases along with a decrease in the glomerular filtration rate (GFR). Although related to parasympathetic function, HRV cannot be used as a specific predictor of mortality in CKD.

HRV analysis appears to be versatile in its applications, but current studies do not support its use as a standalone prognostic tool for palliative patients. It is advisable to use HRV alongside other prognostic tools, such as performance scores and various assessment methods. Additional research is needed to compare HRV with other disease prognosis assessment techniques. The authors aim for this review to provide a summary and direction for future research in this expanding field.

CONFLICT OF INTEREST

Competing interests: No relevant disclosures.

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CONTRIBUTORS

HJ and YA wrote, and edited the manuscript. HS supervised the final version of the manuscript.

REFERENCES

1. McCraty R, Shaffer F. Heart Rate Variability: New Perspectives on Physiological Mechanisms, Assessment of Self-regulatory Capacity, and Health Risk. *http://dx.doi.org/107453/gahmj2014073*. 2015;4(1):46-61. doi:10.7453/GAHMJ.2014.073

2. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. *Front Public Health*. 2017;5:258. doi:10.3389/FPUBH.2017.00258

3. Singh N, Moneghetti KJ, Christle JW, Hadley D, Plews D, Froelicher V. Heart Rate Variability: An Old Metric with New Meaning in the Era of using mHealth Technologies for Health and Exercise Training Guidance. Part One: Physiology and Methods. *Arrhythm Electrophysiol Rev*. 2018;7(3):193. doi:10.15420/AER.2018.27.2

4. Stephenson MD, Thompson AG, Merrigan JJ, Stone JD, Hagen JA. Applying Heart Rate Variability to Monitor Health and Performance in Tactical Personnel: A Narrative Review. *Int J Environ Res Public Health*. 2021;18(15). doi:10.3390/IJERPH18158143

5. Laborde S, Mosley E, Bellenger C, Thayer J. Editorial: Horizon 2030: Innovative Applications of Heart Rate Variability. *Front Neurosci*. 2022;16:937086. doi:10.3389/FNINS.2022.937086

6. Johnston BW, Barrett-Jolley R, Krige A, Welters ID. Heart rate variability: Measurement and emerging use in critical care medicine. *J Intensive Care Soc*. 2020;21(2):148-157. doi:10.1177/1751143719853744

7. Koenig J, Kemp AH, Beauchaine TP, Thayer JF, Kaess M. Depression and resting state heart rate variability in children and adolescents - A systematic review and meta-analysis. *Clin Psychol Rev*. 2016;46:136-150. doi:10.1016/J.CPR.2016.04.013

8. Billman GE, Huikuri H v., Sacha J, Trimmel K. An introduction to heart rate variability: Methodological considerations and clinical applications. *Front Physiol*. 2015;6(FEB):55. doi:10.3389/FPHYS.2015.00055/BIBTEX

9. Taylor MR, Garrison MM, Rosenberg AR. Heart rate variability and psychosocial symptoms in adolescents and young adults with cancer. *PLoS One*. 2021;16(11). doi:10.1371/JOURNAL.PONE.0259385

10. de Couck M, Gidron Y. Norms of vagal nerve activity, indexed by Heart Rate Variability, in cancer patients. *Cancer Epidemiol*. 2013;37(5):737-741. doi:10.1016/J.CANEP.2013.04.016

11. Kirizawa JM, Garner DM, Arab C, Valenti VE. Is heart rate variability a valuable method to investigate cardiac autonomic dysfunction in subjects with leukemia? A systematic review to evaluate its importance in clinical practice. *Support Care Cancer*. 2020;28(1):35-42. doi:10.1007/S00520-019-05047-X

12. Forte G, Troisi G, Pazzaglia M, de Pascalis V, Casagrande M. Heart Rate Variability and Pain: A Systematic Review. *Brain Sciences 2022, Vol 12, Page 153*. 2022;12(2):153. doi:10.3390/BRAINSCI12020153

13. Masel EK, Huber P, Engler T, Watzke HH. Heart rate variability during treatment of breakthrough pain in patients with advanced cancer: a pilot study. *J Pain Res.* 2016;9:1215. doi:10.2147/JPR.S120343

14. Murofushi K, Murofushi W, Komazawa M, et al. Preliminary Study on Establishing a Heart Rate Variability–Based Method for Objectively Evaluating Bone Metastasis Pain. *International Journal of Radiation Oncology*Biology*Physics*. 2022;114(3):e447. doi:10.1016/J.IJROBP.2022.07.1673

15. Park HY, Oh S, Noh Y, Kim JY, Kim JH. Heart Rate Variability as a Marker of Distress and Recovery: The Effect of Brief Supportive Expressive Group Therapy With Mindfulness in Cancer Patients. *https://doi.org/101177/1534735418756192*. 2018;17(3):825-831. doi:10.1177/1534735418756192

16. Arab C, Dias DPM, Barbosa RT de A, et al. Heart rate variability measure in breast cancer patients and survivors: A systematic review. *Psychoneuroendocrinology*. 2016;68:57-68. doi:10.1016/J.PSYNEUEN.2016.02.018

17. Wang SJ, Chang YC, Hu WY, Chang YM, Lo C. The Comparative Effect of Reduced Mindfulness-Based Stress on Heart Rate Variability among Patients with Breast Cancer. *International Journal of Environmental Research and Public Health 2022, Vol 19, Page 6537*. 2022;19(11):6537. doi:10.3390/IJERPH19116537

18. Giese-Davis J, Wilhelm FH, Tamagawa R, et al. Higher Vagal Activity as Related to Survival in Patients with Advanced Breast Cancer: An Analysis of Autonomic Dysregulation. *Psychosom Med.* 2015;77(4):346. doi:10.1097/PSY.0000000000000167

19. Hu S, Lou J, Zhang Y, Chen P. Low heart rate variability relates to the progression of gastric cancer. *World J Surg Oncol*. 2018;16(1):1-5. doi:10.1186/S12957-018-1348-Z/TABLES/4

20. Cheng W, Liu J, Zhi M, et al. Stress and autonomic nerve dysfunction monitoring in perioperative gastric cancer patients using a smart device. *Ann Noninvasive Electrocardiol*. 2022;27(1). doi:10.1111/ANEC.12903

21. Mouton C, Ronson A, Razavi D, et al. The relationship between heart rate variability and time-course of carcinoembryonic antigen in colorectal cancer. *Auton Neurosci*. 2012;166(1-2):96-99. doi:10.1016/J.AUTNEU.2011.10.002

22. Kim DH, Kim JA, Choi YS, Kim SH, Lee JY, Kim YE. Heart rate variability and length of survival in hospice cancer patients. *J Korean Med Sci*. 2010;25(8):1140-1145. doi:10.3346/JKMS.2010.25.8.1140

23. Fadul N, Strasser F, Palmer JL, et al. The association between autonomic dysfunction and survival in male patients with advanced cancer: a preliminary report. *J Pain Symptom Manage*. 2010;39(2):283-290. doi:10.1016/J.JPAINSYMMAN.2009.06.014

24. Kim K, Chae J, Lee S. The Role of Heart Rate Variability in Advanced Non-Small-Cell Lung Cancer Patients. *J Palliat Care*. 2015;31(2):103-108. doi:10.1177/082585971503100206

25. Wang YM, Wu HT, Huang EY, Kou YR, Hseu SS. Heart rate variability is associated with survival in patients with brain metastasis: A preliminary report. *Biomed Res Int*. 2013;2013. doi:10.1155/2013/503421

26. Kim DH, Kim JA, Choi YS, Kim SH, Lee JY, Kim YE. Heart Rate Variability and Length of Survival in Hospice Cancer Patients. *J Korean Med Sci*. 2010;25(8):1140-1145. doi:10.3346/JKMS.2010.25.8.1140

27. Chen CF, Lai CL, Lin HF, Liou LM, Lin RT. Reappraisal of heart rate variability in acute ischemic stroke. *Kaohsiung J Med Sci*. 2011;27(6):215-221. doi:10.1016/J.KJMS.2010.12.014

28. Fyfe-Johnson AL, Muller CJ, Alonso A, et al. Heart Rate Variability and Incident Stroke: The Atherosclerosis Risk in Communities Study. *Stroke*. 2016;47(6):1452-1458. doi:10.1161/STROKEAHA.116.012662

29. Binici Z, Mouridsen MR, Køber L, Sajadieh A. Decreased nighttime heart rate variability is associated with increased stroke risk. *Stroke*. 2011;42(11):3196-3201. doi:10.1161/STROKEAHA.110.607697

30. von Rennenberg R, Krause T, Herm J, et al. Heart Rate Variability and Recurrent Stroke and Myocardial Infarction in Patients With Acute Mild to Moderate Stroke. *Front Neurol*. 2021;12. doi:10.3389/FNEUR.2021.772674/FULL

31. Goldenberg I, Goldkorn R, Shlomo N, et al. Heart rate variability for risk assessment of myocardial ischemia in patients without known coronary artery disease: The hrv-detect (heart rate variability for the detection of myocardial ischemia) study. *J Am Heart Assoc*. 2019;8(24). doi:10.1161/JAHA.119.014540

32. Fang SC, Wu YL, Tsai PS. Heart Rate Variability and Risk of All-Cause Death and Cardiovascular Events in Patients With Cardiovascular Disease: A Meta-Analysis of Cohort Studies. *Biol Res Nurs*. 2020;22(1):45-56. doi:10.1177/1099800419877442/ASSET/IMAGES/LARGE/10.1177_1099800419877442-FIG2.JPEG

33. Kubota Y, Chen LY, Whitsel EA, Folsom AR. Heart Rate Variability and Lifetime Risk of Cardiovascular Disease: the Atherosclerosis Risk in Communities Study. *Ann Epidemiol*. 2017;27(10):619. doi:10.1016/J.ANNEPIDEM.2017.08.024

34. Vuoti AO, Tulppo MP, Ukkola OH, et al. Prognostic value of heart rate variability in patients with coronary artery disease in the current treatment era. *PLoS One*. 2021;16(7):e0254107. doi:10.1371/JOURNAL.PONE.0254107

35. Singer M, Deutschman CS, Seymour C, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801. doi:10.1001/JAMA.2016.0287

36. Barichello T, Generoso JS, Singer M, Dal-Pizzol F. Biomarkers for sepsis: more than just fever and leukocytosis—a narrative review. *Crit Care*. 2022;26(1):1-31. doi:10.1186/S13054-021-03862-5/TABLES/1

37. Ahmad S, Tejuja A, Newman KD, Zarychanski R, Seely AJE. Clinical review: A review and analysis of heart rate variability and the diagnosis and prognosis of infection. *Crit Care*. 2009;13(6):1-7. doi:10.1186/CC8132/METRICS

38. Williams DWP, Koenig J, Carnevali L, et al. Heart rate variability and inflammation: A meta-analysis of human studies. *Brain Behav Immun*. 2019;80:219-226. doi:10.1016/J.BBI.2019.03.009

39. Samsudin MI, Liu N, Prabhakar SM, et al. A novel heart rate variability based risk prediction model for septic patients presenting to the emergency department. *Medicine*. 2018;97(23). doi:10.1097/MD.0000000000010866

40. Chen WL, Kuo CD. Characteristics of Heart Rate Variability Can Predict Impending Septic Shock in Emergency Department Patients with Sepsis. *Academic Emergency Medicine*. 2007;14(5):392-397. doi:10.1111/J.1553-2712.2007.TB01796.X

41. de Castilho FM, Ribeiro ALP, Nobre V, Barros G, de Sousa MR. Heart rate variability as predictor of mortality in sepsis: A systematic review. *PLoS One*. 2018;13(9). doi:10.1371/JOURNAL.PONE.0203487

42. Chiew CJ, Liu N, Tagami T, et al. Heart rate variability based machine learning models for risk prediction of suspected sepsis patients in the emergency department. *Medicine*. 2019;98(6). doi:10.1097/MD.0000000000014197

43. Thio CHL, van Roon AM, Lefrandt JD, Gansevoort RT, Snieder H. Heart Rate Variability and Its Relation to Chronic Kidney Disease: Results From the PREVEND Study. *Psychosom Med*. 2018;80(3):307. doi:10.1097/PSY.0000000000000556

44. Makimoto H, Fujiu K, Shimizu K, et al. Impaired heart rate variability in patients with non-diabetic chronic kidney disease — Prominent disruption of vagal control and daily fluctuation. *IJC Metab Endocr*. 2015;9:22-27. doi:10.1016/J.IJCME.2015.10.003

45. Oikawa K, Ishihara R, Maeda T, et al. Prognostic value of heart rate variability in patients with renal failure on hemodialysis. *Int J Cardiol*. 2009;131(3):370-377. doi:10.1016/J.IJCARD.2007.10.033

46. Drawz PE, Babineau DC, Brecklin C, et al. Heart Rate Variability Is a Predictor of Mortality in Chronic Kidney Disease: A Report from the CRIC Study. *Am J Nephrol*. 2013;38(6):517-528. doi:10.1159/000357200