Original Paper

The Assessment of Heart Rate Variability in Patients with Pancreatic Cancer

MIHAI PETRESCU[1], ION UDRIȘTOIU[1], FELICIA MILITARU[1], ALEXANDRA-ROXANA PETRESCU[2], GEORGICĂ TÂRTEA[3], VICTOR RAICEA[4], ANA-MARIA CIUREA[5], ANA-MARIA PETRESCU[6], CRISTIN CONSTANTIN VERE[7]

[1]*Department of Psychiatry, University of Medicine and Pharmacy of Craiova, Romania*

[2]*Department of Pathology, University of Medicine and Pharmacy of Craiova, Romania*

[3]*Department of Physiology, University of Medicine and Pharmacy of Craiova, Romania*

[4]*Department of Cardiovascular Surgery, University of Medicine and Pharmacy of Craiova, Romania*

[5]*Department of Oncology, University of Medicine and Pharmacy of Craiova, Romania*

[6]*Department of Obstretics and Gynecology, University of Medicine and Pharmacy of Craiova, Romania*

[7]*Department of Gastroenterology, University of Medicine and Pharmacy of Craiova, Romania*

ABSTRACT: The aim of our study is to provide an assessment of heart rate variability (HRV) as a predictor for the survival of patients with pancreatic cancer (PCa). We conducted a retrospective, descriptive study. 53 consecutive patients who were newly diagnosed with pancreatic cancer (PCa), were included. In the end, 41 patients were included in the analysis, out of which 14 patients survived at least until the 24-month follow-up, while 27 patients died within 24 months from the diagnosis. These patients were monitored with 24-hour Holter electrocardiogram (ECG) prior to the initiation of any therapy for determining heart rate variability. To establish the cut-off values of HRV, 24-hour Holter ECG recordings of 20 healthy subjects were analyzed. In addition to heart rate analysis, HRV indices were also analyzed: SDNN, rMSSD, ULF and VLF. Median survival in patients with low value of SDNN was 9 months, compared to patients with hight SDNN where median survival was 15 months (Hazard ratio 2.301, 95% CI of ratio 0.9080 to 5.833, p= 0.034). Although low values of the HRV indices in the frequency domain were associated with reduced survival, no statistically significant differences were recorded. The reduction of heart rate variability indices is a negative prognostic factor in patients newly diagnosed with pancreatic cancer.

KEYWORDS: *Pancreatic cancer, heart rate variability, predictor.*

Introduction

Pancreatic cancer (PCa) is one of the most aggressive and lethal malignancies worldwide, characterized by a poor prognosis and a low survival rate (the 5-year survival rate between 15-25%) [1-3].

Despite advancements in diagnostic techniques and treatment modalities, the life expectancy of patients with PCa remains discouraging [3].

Therefore, there is a critical need for the identification of reliable prognostic markers to aid predicting patient outcomes and tailoring individualized treatment strategies.

Heart rate variability (HRV) is a well-established marker of autonomic nervous system activity and cardiovascular health [4].

It reflects the natural variability in the time intervals between consecutive heartbeats and it is influenced by various physiological and pathological factors [5].

HRV analysis has been extensively studied in cardiovascular diseases and has shown promising applications in predicting clinical outcomes [6].

Lately, there has been a growing interest in exploring the potential role of HRV as a predictor for the survival of patients with cancer [6].

The rationale behind this interest is that the autonomic nervous system plays a crucial role in modulating various physiological processes, such as tumor growth, invasion, or metastasis [6].

Therefore, it is hypothesized that altered HRV patterns may directly or indirectly reflect the tumor's aggressive behavior and overall the patient prognosis [6].

Several studies have investigated the correlation between HRV parameters and survival outcomes in patients with pancreatic cancer [7-9].

These studies have utilized various HRV analysis techniques, including time-domain, frequency-domain, and nonlinear analysis [4].

The aim of our study is to provide an assessment of HRV as a predictor for the survival

10.12865/CHSJ.49.02.05

of patients with pancreatic cancer. This assessment will contribute to the understanding of the prognostic role of HRV in pancreatic cancer.

Material and Methods

This study was approved by the Local Ethics Committee (number 225/20.12.2021) and was performed in accordance with the international regulations in the field, including the Helsinki Declaration.

Each patient was informed about data collection for this study and provided written consent for data collection from their medical records.

Data that could lead to patient identification were excluded and a code was assigned to each patient.

Study design and patient selection

We conducted a retrospective, descriptive study, which included fifty-three consecutive patients, newly diagnosed with pancreatic cancer (PCa) at the Emergency County Hospital of Craiova (October 2017- June 2020).

Patients were subjected to a 24-hour Holter electrocardiogram (ECG) follow-up prior to the initiation of any therapy.

From the study were excluded patients younger than 18 years, patients with active infections, or those who had received medications with beta-blockers or other anti-arrhythmic drug that can modify HRV.

24-hour Holter ECG recordings of 20 healthy subjects were analyzed, maintaining the gender and age proportions consistent with the patients included in the study, in order to establish the cut-off values of the HRV.

Out of the 53 patients that were evaluated for eligibility, 12 were excluded. In the end, 41 PCa patients were included in the analysis, out of which 14 patients survived at least until the 24-month follow-up, while 27 patients died within 24 months from the diagnosis.

Figure 1 depicts the study design.

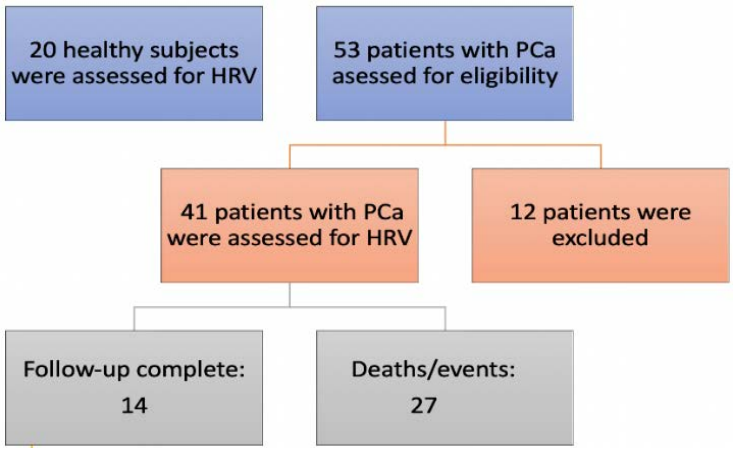

Figure 1. Study design.

Follow-up of the patients and Heart rate variability assessment

Among the types of pancreatic cancer, we only included patients with pancreatic ductal adenocarcinoma in our study.

HRV assessment was conducted for each patient using Holter ECG monitoring for 20-30 hours. This action was performed using a TLC5000 Holter ECG system (Contec Medical Systems, Hebei Province, China), which allowed for time and frequency domain analysis of HRV.

Patients who were later diagnosed with PCa were eligible for the study. Meanwhile those whose diagnosis was not confirmed were not included.

The main indices analyzed in the time domain were the standard deviation of all normal-to-normal (NN) intervals (SDNN) and the root mean square of successive differences between normal heartbeats (rMSSD) [4].

In the frequency domain, the following indices were analyzed: the ultra-low-frequency (ULF) band and the power of the very low-frequency band of the HRV spectrum (VLF). Figure 2 depicts the images with HRV indices determined automatically by the Holter ECG.

All HRV indices included in our study were analyzed for the entire monitoring period (20-30 hours for each patient).

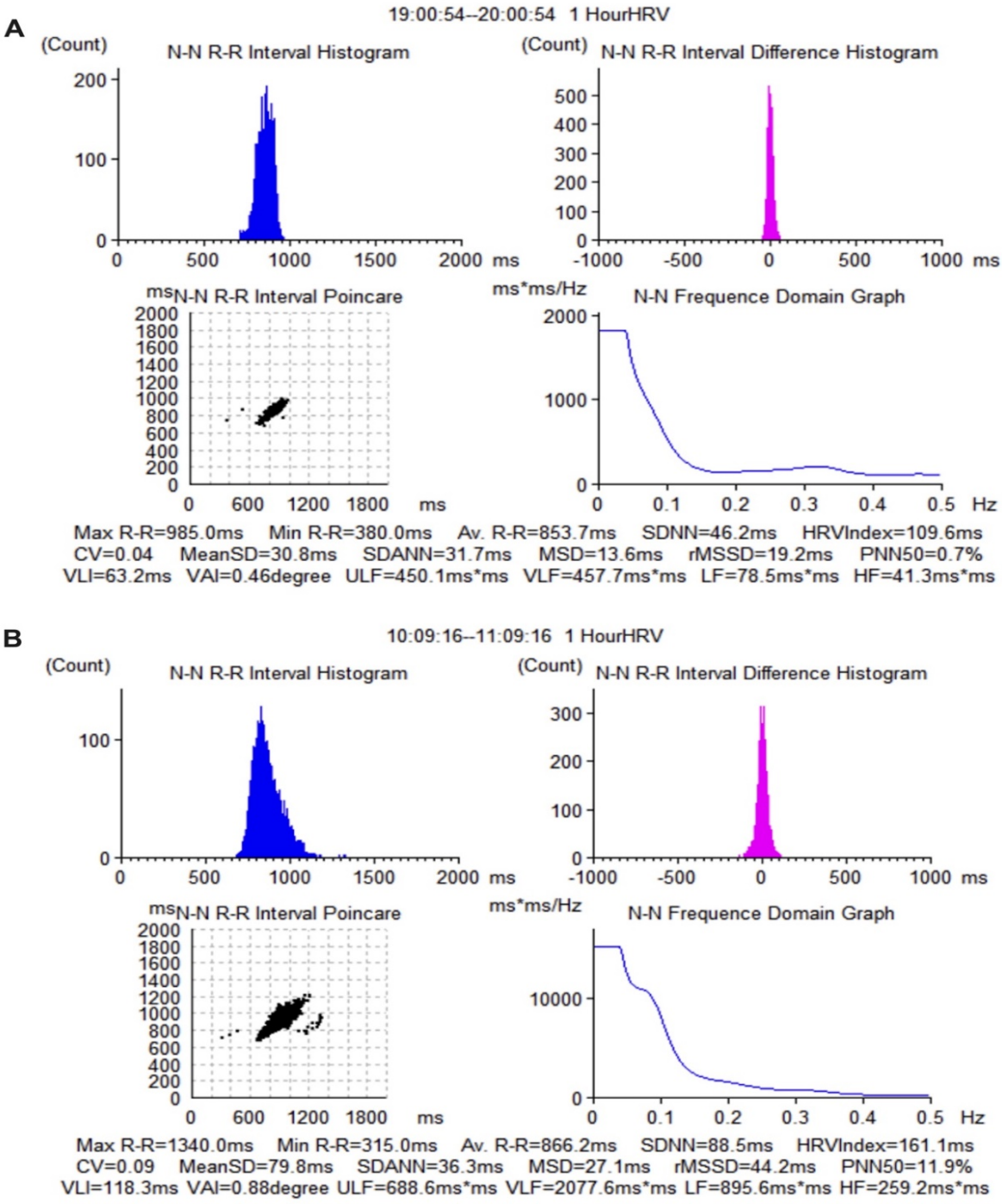

Figure 2. Representative images with HRV indices determined over one hour in patients with pancreatic cancer (A) and in the control group (B).

Statistical analysis

Statistical analysis was performed using GraphPad software (San Diego, CA, USA).

The results were expressed as mean and standard deviation. Student's t-test and ANOVA, as appropriate, were used to compare means between groups.

Receiver operating characteristic (ROC) curves were used to determine the cut-off value for each HRV index.

Kaplan-Meier curves were then generated to analyze patient survival based on clinical and biological characteristics, and the log-rank test was used to determine if the differences between the groups were statistically significant.

A significance level of $P < 0.05$ was chosen to represent a statistically significant difference between the compared groups in our study.

10.12865/CHSJ.49.02.05

Results

The 24-hour heart rate analysis recorded values of 70.5±9.9 beats per minute (bpm) in subjects from the control group compared to patients with pancreatic cancer (PCa) where the values were higher, with an average of 75.8±6.6bpm, but without registering a statistically significant difference (p=0.062).

During the day, the heart rate values in the control group were 79.5±12.5bpm and in the group of patients with PCa they were 80±12.4bpm (p=0.766), while during the night there were recorded statistically significant differences (59.5±8.7bpm in the control group vs. 72.4±10.1 bpm in the PCa group, p=0.031).

These results are shown in Figure 3A. In addition to heart rate analysis, HRV indices were also analyzed: SDNN, rMSSD, ULF and VLF.

In the time domain for SDNN, a value was recorded in the Control group of 126.1±22.6ms vs. 62.8±20.3ms in the PCa group (p=0.004) and for rMSSD a value of 81.0±24.5ms in the Control group compared to 51.7±18.2ms in the PCa group (p=0.009, Figure 3B).

The same trend of decreasing HRV indices was also observed in the frequency field.

Thus, for ULF, a value of 1129.3±252.4ms*ms was recorded in the Control group vs. 478.3±249.7ms*ms in the PCa group (p=0.002) and for VLF a value of 841.6±204.8ms*ms in the Control group compared to 441.7±262.5ms*ms in the PCa group (p=0.013, Figure 3C).

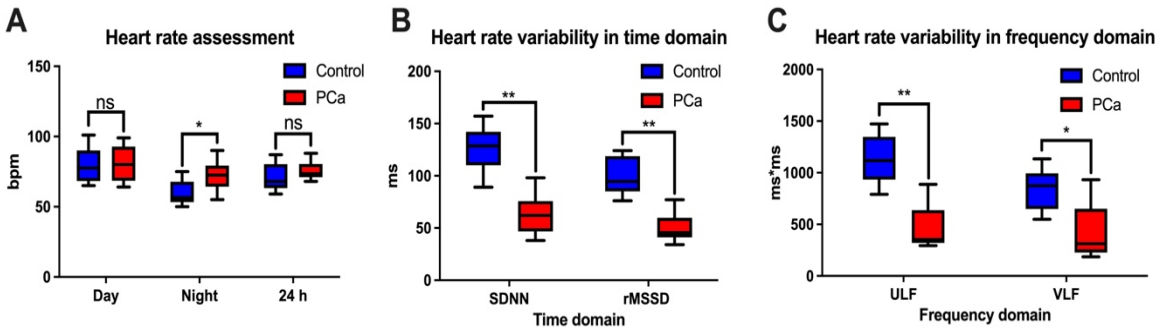

Figure 3. A-Heart rate assessment for 24 h, day and night. B-Heart rate variability in time domain. C-Heart rate variability in frequency domain. PCa-pancratic cancer.

Another interesting observation was on the heart rate curves.

We found that in patients with pancreatic cancer, the 24-hour heart rate variability is much reduced compared to the control group.

As it can be seen in Figure 4, in patients with pancreatic cancer the differences are reduced in terms of the frequency curve during the day compared to the night.

In the control group, higher frequencies predominate during the day, compared to night, which represents a normal, physiological curve of heart frequencies.

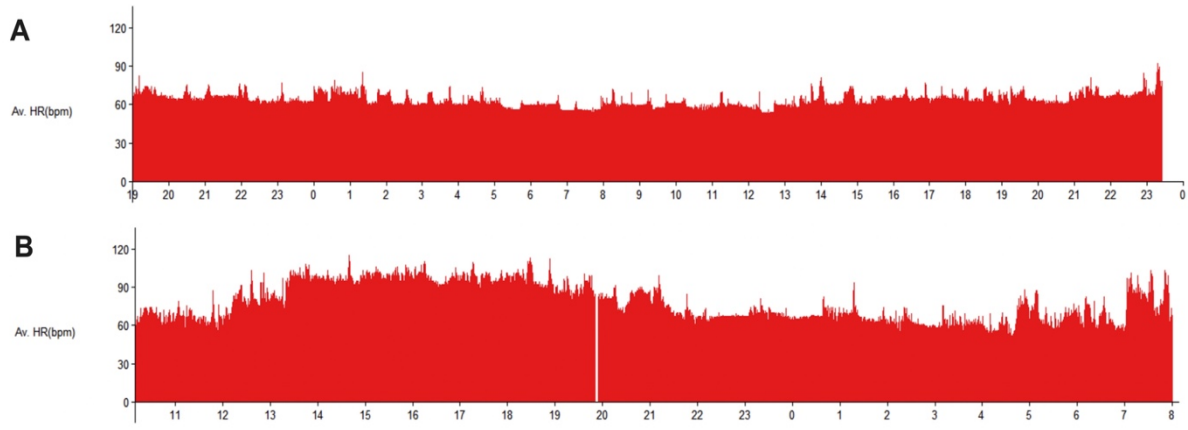

Figure 4. Representative images of 24-hour heart rate curves in a pancreatic cancer patient (A) and a control patient (B).

To establish the cut-off value according to which we analyzed the survival of patients with pancreatic cancer, we analyzed the ROC curves.

Thus, for SDNN we set a value of 116ms (area under curve-AUC= 0.8049), for rMSSD we set a value of 53 ms (AUC= 0.9323), for VLF we set a value of 278ms*ms (AUC= 0.8970) and for ULF we established a value of 265ms*ms (AUC=0.9079).

These results are presented in Figure 5.

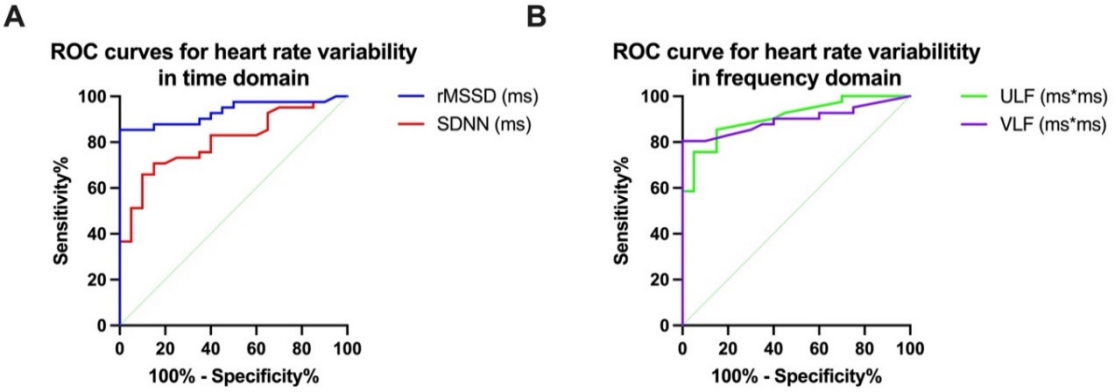

Figure 5. Receiver operating characteristic (ROC) curves to determine the cut-off value for each HRV index in time domain (A) and in frequency domani (B).

We analyzed patient survival according to SDNN, rMSSD, ULF and VLF, taking into account the cut-off values determined earlier. Median survival in patients with SDNN <116ms was 9 months, compared to patients with SDNN >116ms where median survival was 15 months (Hazard ratio 2.301, 95% CI of ratio 0.9080 to 5.833, p=0.034, Figure 6A).

Regarding rMSSD, a median survival of 11 months was recorded for rMSSD (ms) <53vs. 15 months at rMSSD (ms) >53 but without statistical significance (Hazard ratio 1.343, 95% CI of ratio 0.606 to 2.971, p=0.446, Figure 6B).

Although low values of the HRV indices in the frequency domain were associated with reduced survival, no statistically significant differences were recorded.

Thus, in the frequency domain median survival for VLF (ms*ms) <278 was 9 months vs. 15.5 months for VLF (ms*ms) >278 (Hazard ratio 1.395, 95% CI of ratio 0.6310 to 3.083, p=0.410, Figure 6C).

Last but not least, for ULF (ms*ms) <265, a median survival of 9 months was recorded vs. 15 months for ULF (ms*ms) >265, but still without statistical significance (Hazard ratio 1.292, 95% CI of ratio 0.5885 to 2.837, p=0.523, Figure 6D).

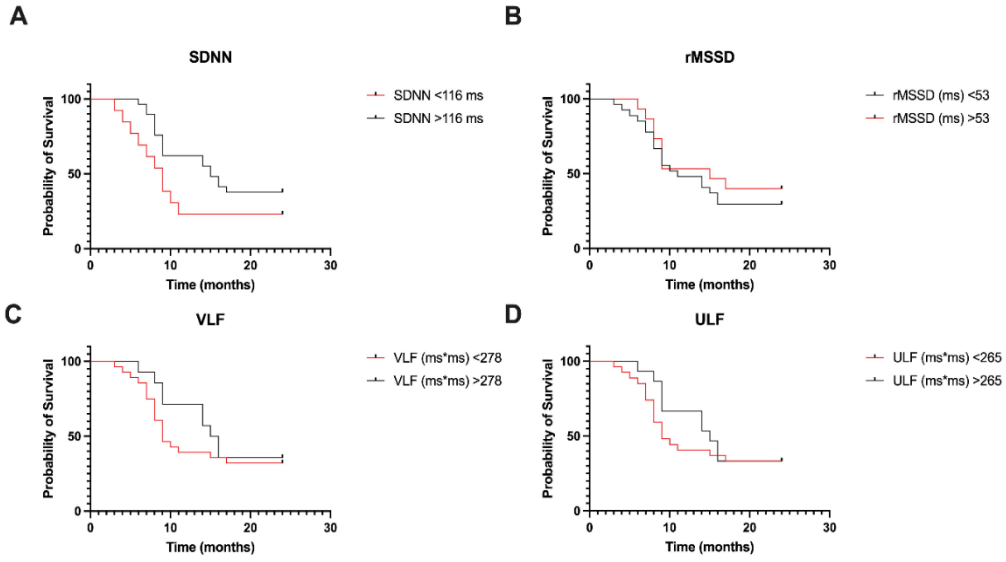

Figure 6. Survival curves depending on SNDD (A), rMSSD (B), VLF (C) and ULF (D).

10.12865/CHSJ.49.02.05

Discussion

HRV refers to the variability in the time intervals between heartbeats, and it's often used as a biomarker for autonomic nervous system activity [10-13].

While HRV has been widely used as a prognostic factor in cardiovascular diseases, recent research has suggested its potential prognostic value in different types of cancer as well [14].

In our study, the reduction of HRV indices was associated with a decrease in the survival rate.

Autonomic regulation of the cardiovascular system and its connection to cancer prognosis has been increasingly recognized.

Cancer patients often show changes in autonomic nervous system functioning, with studies revealing that low HRV is associated with higher stress levels, inflammation, and metabolic syndromes-all factors that may play a role in cancer development and progression [15].

Cancer-related fatigue, sleep disturbances, and distress, which often accompany a cancer diagnosis, may induce autonomic dysfunction, which can negatively affect HRV.

Therefore, observing changes in HRV may provide useful prognostic information for individuals who have cancer [15-16].

Clinical trials have begun to evaluate HRV in cancer contexts.

Research has shown that lower pretreatment HRV in cancer patients is associated with inferior survival outcomes.

HRV has been examined in several cancer types including breast, lung, gastric, colorectal, and ovarian cancers.

For instance, decreased HRV was considered as a negative prognostic factor for survival in hepatocellular carcinoma [17].

However, while these findings are promising, there's still a need for more extensive research to clarify the exact role HRV can play as a prognostic tool.

This includes understanding how HRV measurements can be incorporated into standard cancer care, understanding the precise mechanisms by which changes in HRV could link to cancer progression, and assessing whether interventions that improve HRV can improve cancer outcomes [17-18].

It should be mentioned that an additional activation of the sympathetic autonomic nervous system appears through the reduction in HRV indices.

The sympathetic nervous system (SNS), part of the autonomic nervous system, plays fundamental roles in the body's stress responses, cardiovascular functions, glucose metabolism, and inflammation, among others.

Recent research has suggested that the SNS also plays a significant role in cancer development, metastasis, and responses to therapeutic interventions [19].

The pancreas, in particular, is extensively innervated by sympathetic neuronal fibers. Hence, it has been hypothesized that the SNS may significantly impact pancreatic cancer physiology [20].

The SNS utilizes neurotransmitters, including norepinephrine (NE) and epinephrine (E), to relay its signals. In the context of cancer biology, these neurotransmitters appear to modulate different aspects of tumor development and progression [19].

They can stimulate cancer cell proliferation, possibly by influencing cell-cycle regulation and growth factor release [19].

In pancreatic cancer specifically, sympathetic neuronal stimulation can exacerbate the disease by promoting a pro-tumorigenic microenvironment [22].

Given its multi-faceted role in pancreatic cancer pathophysiology, the sympathetic nervous system is being recognized as an important player and potential therapeutic target for this deadly disease.

Targeting the signaling pathways controlled by the SNS could open new avenues for improving the treatment options and management of pancreatic cancer patients.

However, this field is still in its early research stage, and more studies are required to fully understand these intricate interconnections.

Conclusion

The reduction of heart rate variability indices is a negative prognostic factor in patients newly diagnosed with pancreatic cancer.

Conflict of interests

None to declare

Refferences

1. Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nat Rev Gastroenterol Hepatol, 2021, 18(7):493-502.
2. Cai J, Chen H, Lu M, Zhang Y, Lu B, You L, Zhang T, Dai M, Zhao Y. Advances in the epidemiology of pancreatic cancer: Trends, risk factors, screening, and prognosis. Cancer Lett, 2021, 520:1-11.

3. Hu JX, Zhao CF, Chen WB, Liu QC, Li QW, Lin YY, Gao F. Pancreatic cancer: A review of epidemiology, trend, and risk factors. World J Gastroenterol, 2021, 27(27):4298-4321.
4. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health, 2017, 5:258.
5. Tiwari R, Kumar R, Malik S, Raj T, Kumar P. Analysis of Heart Rate Variability and Implication of Different Factors on Heart Rate Variability. Curr Cardiol Rev, 2021, 17(5):e160721189770.
6. Zhou X, Ma Z, Zhang L, Zhou S, Wang J, Wang B, Fu W. Heart rate variability in the prediction of survival in patients with cancer: A systematic review and meta-analysis. J Psychosom Res, 2016, 89:20-25.
7. Anker MS, Ebner N, Hildebrandt B, Springer J, Sinn M, Riess H, Anker SD, Landmesser U, Haverkamp W, von Haehling S. Resting heart rate is an independent predictor of death in patients with colorectal, pancreatic, and non-small cell lung cancer: results of a prospective cardiovascular long-term study. Eur J Heart Fail, 2016, 18(12):1524-1534.
8. De Couck M, Maréchal R, Moorthamers S, Van Laethem JL, Gidron Y. Vagal nerve activity predicts overall survival in metastatic pancreatic cancer, mediated by inflammation. Cancer Epidemiol, 2016, 40:47-51.
9. Arai YC, Morimoto A, Sakurai H, Ohmichi Y, Aono S, Nishihara M, Sato J, Ushida T, Inoue S, Kurisuno M, Kobayashi Y. The effect of celiac plexus block on heart rate variability. J Anesth, 2013, 27(1):62-65.
10. Kim Y, Yoon HY, Kwon IK, Youn I, Han S. Heart Rate Variability as a Potential Indicator of Cancer Pain in a Mouse Model of Peritoneal Metastasis. Sensors (Basel), 2022, 22(6):2152.
11. 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):49.
12. Shukla RS, Aggarwal Y. Time-domain heart rate variability-based computer-aided prognosis of lung cancer. Indian J Cancer, 2018, 55(1):61-65.
13. Guo Y, Koshy S, Hui D, Palmer JL, Shin K, Bozkurt M, Yusuf SW. Prognostic Value of Heart Rate Variability in Patients With Cancer. J Clin Neurophysiol, 2015, 32(6):516-520.
14. Palma S, Keilani M, Hasenoehrl T, Crevenna R. Impact of supportive therapy modalities on heart rate variability in cancer patients - a systematic review. Disabil Rehabil, 2020, 42(1):36-43.
15. Shi B, Wang L, Yan C, Chen D, Liu M, Li P. Nonlinear heart rate variability biomarkers for gastric cancer severity: A pilot study. Sci Rep, 2019, 9(1):13833.
16. Ciurea AM, Gheonea DI, Schenker M, Mehedințeanu AM, Târtea GC, Vere CC. The Prognostic Correlation of Heart Rate Variability at Diagnosis with Survival of Patients with Hepatocellular Carcinoma. Diagnostics (Basel), 2021,11(5):890.
17. Mehedințeanu AM, Sfredel V, Stovicek PO, Schenker M, Târtea GC, Istrătoaie O, Ciurea AM, Vere CC. Assessment of Epinephrine and Norepinephrine in Gastric Carcinoma. Int J Mol Sci, 2021, 22(4):2042.
18. Kamiya A, Hiyama T, Fujimura A, Yoshikawa S. Sympathetic and parasympathetic innervation in cancer: therapeutic implications. Clin Auton Res, 2021, 31(2):165-178.
19. Guillot J, Dominici C, Lucchesi A, Nguyen HTT, Puget A, Hocine M, Rangel-Sosa MM, Simic M, Nigri J, Guillaumond F, Bigonnet M, Dusetti N, Perrot J, Lopez J, Etzerodt A, Lawrence T, Pudlo P, Hubert F, Scoazec JY, van de Pavert SA, Tomasini R, Chauvet S, Mann F. Sympathetic axonal sprouting induces changes in macrophage populations and protects against pancreatic cancer. Nat Commun, 2022, 13(1):1985.
20. Guo K, Ma Q, Li J, Wang Z, Shan T, Li W, Xu Q, Xie K. Interaction of the sympathetic nerve with pancreatic cancer cells promotes perineural invasion through the activation of STAT3 signaling. Mol Cancer Ther, 2013, 12(3):264-273.
21. Kim-Fuchs C, Le CP, Pimentel MA, Shackleford D, Ferrari D, Angst E, Hollande F, Sloan EK. Chronic stress accelerates pancreatic cancer growth and invasion: a critical role for beta-adrenergic signaling in the pancreatic microenvironment. Brain Behav Immun, 2014, 40:40-57.
22. Boehm K, Duckheim M, Mizera L, Groga-Bada P, Malek N, Kreth F, Gawaz M, Zuern CS, Eick C. Heart rate variability for rapid risk stratification of emergency patients with malignant disease. Support Care Cancer, 2018, 26(9):3289-3296.

Corresponding Author: Victor Raicea, Department of Cardiovascular Surgery, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania, e-mail: dr.raicea.victor@gmail.com

 10.12865/CHSJ.49.02.05