INFLUENCE OF CANCER SEVERITY AND FUNCTIONAL STATUS OF CANCER ON CARDIAC PARASYMPATHETIC INDICATORS

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INTRODUCTION
The autonomic nervous system (ANS) not only plays a major role in physiological situations but also in various pathological conditions such as diabetic neuropathy, myocardial infarction [1,2]. ANS controls most of the viscera, and many solid cancers are formed in the same viscera [3,4]. Consequently, recent studies have revealed autonomic dysfunction in cancer patients [5]. In support of this view our previous study on association between ANS and cancer reduced cardiac vagal function was observed in cancer patients compared to healthy individuals [6]. Further, in a relatively small sample size, we also observed that vagal function declines with severity of cancer [7]. These study findings, warrants confirming the same in a larger sample size. At present, cancer research is looking into the possibility of heart rate variability (HRV) parameters as a prognostic indicator of cancer.

HRV is a simple non-invasive tool for assessing ANS function [8]. HRV parameters are commonly used in both normal subjects and in various clinical conditions [9,10]. Among the HRV parameters, root mean square of successive N-N interval difference (r-MSSD) and expiratory:inspiratory ratio (E:I ratio) are the two known indicators of cardiac parasympathetic function [11]. At present, severity of cancer is evaluated based on the findings of histopathological report and patients are staged as per American Joint Committee on Cancer (AJCC) staging [12]. In oncology, Eastern Cooperative Oncology Group (ECOG) performance score and the Faces Pain Scale score (FPS) was noted. Two indicators of vagal function, E:I ratio and root mean square of successive N-N interval difference (r-MSSD) were included. E:I ratio during deep breathing at six respiratory cycles/minute and r-MSSD at rest was obtained from 1 minute lead II electrocardiogram. Data were analyzed by applying suitable statistical tests. p≤0.05 was considered significant.

METHODS
This was a hospital based cross-sectional study conducted in Kasturba Medical College and Hospital, Mangalore, India. This study was conducted after obtaining Institutional Ethics Committee approval (Ref: IEC KMC MLR 03-14/77 dated 19th March 2014) and informed consent from study participants. All procedures were undertaken according to the Declaration of Helsinki.

Study subjects
This study involved 267 patients with a solid malignant tumor who were freshly diagnosed with head and neck cancer (n=104), gastrointestinal (n=82), and gynecological cancer (n=81). Among the study subjects recruited, based on the American Joint Committee of Cancer staging [12]: 22 were with Stage I, 62 with Stage II, 96 with Stage...
III, and 87 were with Stage IV. Stage I and II were combined together to form the early stage and Stage III and IV were considered the advanced stage of cancer. Control group was comprised 250 healthy subjects who were matched for age and sex of study subjects.

Inclusion and exclusion criteria
Cancer patients either with head and neck or gastrointestinal or gynecological cancer alone and who were not yet put on any treatment were included. Exclusion criteria included patients with cardiovascular disease, implanted pacemaker, ectopic beats and patients on cardiac medication (anti-arrhythmic drugs, b-blockers), history of diabetes, hypertension, thyroid diseases, abnormal breathing and chronic obstructive pulmonary disease. Patients in whom tumor extended up to the cervical sympathetic chain or any other conditions known to alter vagal function or influence inflammation such as arthritis or inflammatory diseases were excluded.

Study protocol and procedure
All the test procedures were explained to the study participants before starting the study. All the subjects in the study and control groups underwent clinical examination. However, study subjects alone were subjected to a detailed physical examination.

Clinical measurements
Information on functional status and intensity of pain endured by an individual was assessed by the ECOG performance status and FPS in study subjects alone. The ECOG performance status is widely used as a clinical indicator for general functional condition, and it is defined as follows: 0 meant for normal function, 1 used for bare minimal functional impairment, 2 used for spending time in bed for ≤50%, 3 for impairment amounting to spending more than 50% of time in bed, and 4 used for completely bed ridden and 5 accounts for death [17]. In this study, ECOG score was noted from the case sheet of the patients as evaluated and documented by the oncologist. FPS measures the intensity of the pain endured by the subjects: 0 - Very happy no pain, 2 - Hurts little bit, 4 - Hurts more than a little, 6 - Hurts to greater extent, 8 - Hurts a whole lot, and 10 - Hurts more than imagined (don’t have to be crying to feel this much pain) [13].

FPS chart:

Each patient was asked to state the pain endured by them according to the FPS chart provided to them and then FPS was noted. Stage of cancer was noted from the oncologists’ report which is based on histopathological report and defined by AJCC criteria followed for staging of cancer [12].

In addition, to routine general examination in both study and control subjects, the body mass index (BMI), blood pressure (BP), and Heart rate (HR) were recorded. For calculating BMI, first, the height and weight of all the subjects were measured. BMI was calculated using the formula: Weight in kilograms (kg) divided by height in meters (m) squared [23]. BP was measured using sphygmomanometer in sitting position. Both systolic and diastolic pressure was measured in all the subjects and mean of two readings was taken as BP. HR was obtained from counting the total number of R-R intervals in 1-minute lead II electrocardiogram (ECG) recorded in supine position in subjects after giving them sufficient rest of 5 minutes.

Vagal nerve activity assessment
In study and control subjects, vagal nerve function was assessed by quantifying the following parameters, namely, expiratory:inspiratory ratio (E:I ratio) and r-MSSD. In this study for assessing vagal nerve function in subjects, 1-minute lead II ECG was used. In all the subjects, 1-minute lead II ECG was recorded at a speed of 25 mm/s for 60 seconds using Cardiart 1087/MKVII, BPL Ltd. Bengaluru, Karnataka, India. ECG recordings were carried out in the supine position after subjects were given sufficient rest of 15 minutes.

Assessment of E:I ratio in response to deep breathing
Deep breathing test was conducted in the morning after the subjects were given complete rest. Each subject was taught to breathe at six breaths per minute. That is 5 seconds for each inhalation and 5 seconds for each exhalation. Once the subjects were comfortable enough to breathe at 6 respiratory cycles per minute, study procedure was conducted. Subjects were instructed to follow the commands of the examiner. Then, the examiner raised his hand to signal the start of each inhalation and lowered his hand to signal the start of each exhalation. Simultaneously lead II ECG was recorded at the speed of 25 mm/s for 60 seconds while the subject breathed as instructed (Cardiart 1087/MKVII, BPL Ltd. Bangalore, Karnataka, India). After the recording of ECG, each R-R intervals were measured accurately. The longest R-R interval during expiration and the shortest R-R interval during inspiration was expressed as E:I ratio [24].

Assessment of r-MSSD
r-MSSD was estimated from 1 minute resting lead II ECG tracing. ECG recording was obtained after the subject was lying in a supine position in completely relaxed state. Each of the R-R intervals were measured accurately and computed. Then, r-MSSD was estimated by applying suitable statistical procedures using Microsoft Windows XP Professional (Microsoft Corporation, Redmond, WA, USA) [25,26].

Statistical analysis
Unpaired t-test/Mann-Whitney U statistic was used to compare between two different groups. One-way ANOVA/Kruskal-Wallis (KW) test followed by multiple comparisons was used to compare when the groups were more than two. The Pearson correlation coefficient test was used to find the correlation between two groups. The level of significance was determined by a two-tailed test. p<0.05 was taken as significant.

RESULTS

Baseline characteristics in study and control subjects
In a total of 267 study subjects, 136 were females, and 131 were males. Among, these study subjects 209 had squamous cell carcinoma, 56 were with adenocarcinoma, and 2 were with mucopidermoid carcinoma. The study subjects were with three primary sites of malignant tumor: Gynecological (n=81); gastrointestinal (n=82); head and neck (n=104). The mean age of the study subjects among these three sites of the primary tumor was comparable (gynecological: 52.06±8.26 years; gastrointestinal: 53.59±9.49 years; head and neck: 53.01±10.52 years; one-way ANOVA F=0.5365, p=0.05853). In study subjects mean ECOG score was 1.38±0.60 and mean FPS score was 3.51±2.62.

The data on comparison of baseline characteristics between study and control groups is presented in Table 1. BMI was significantly lower in the study group compared to controls (Mann–Whitney U-statistic=19916.0; p≤0.0001, Table 1). HR was significantly higher in the study group compared to controls (Mann–Whitney U-statistic=25472.0, p≤0.0001, Table 1). Age, systolic BP, and diastolic BP did not differ significantly between study and control group (Table 1).

Vagal nerve functions in early stage and advanced stage of cancer compared to control group
Data on vagal nerve function in early stage and advanced stage of cancer compared to control group are presented in Table 2. r-MSSD and E:I ratio was significantly different among control, early and advanced stage of cancer (KW=178.13, p<0.001; 329.16, p<0.0001, respectively). r-MSSD and E:I ratio was significantly lower in the early stage and advanced stage of cancer compared to control group (p<0.0001, Table 2).

Table 1: Age, systolic BP, and diastolic BP did not differ significantly between study and control group

Table 2: r-MSSD and E:I ratio was significantly different among control, early and advanced stage of cancer (KW=178.13, p<0.001; 329.16, p<0.0001, respectively). r-MSSD and E:I ratio was significantly lower in the early stage and advanced stage of cancer compared to control group (p<0.0001, Table 2).
Comparison of vagal nerve functions between early and advanced stage of cancer in study subjects

Data on comparison between early stage and advanced stage of cancer are presented in Figs. 1 and 2. r-MSSD and E:I ratio was significantly lower in the advanced stage of cancer compared to early stage (p≤0.0001, Figs. 1 and 2, respectively).

Vagal nerve functions in different stages of cancer in study group compared to control group

Data on vagal nerve function parameters in different stages of cancer and control are presented in Table 3. r-MSSD and E:I ratio was significantly different in subgroups of stages of cancer and control group (KW test=185.47, 331.89; p≤0.0001, Table 3). E:I ratio was significantly less in Stage I, Stage II, Stage III, and IV compared to control group (Table 3). r-MSSD was significantly different in Stage II, Stage III, and IV compared to control group (Table 3). There was no significant difference in r-MSSD between Stage I and control group (Table 3). In study subjects, there was no significant difference in E:I ratio and r-MSSD between Stage I and II (Table 3). There was no significant difference in E:I ratio and r-MSSD between Stage III and IV (Table 3).

Correlation between r-MSSD and ECOG and FPS score in study group

Data on the correlation between r-MSSD and ECOG score and FPS score in the study group are presented in Figs. 3 and 4, respectively. Significant negative correlation was observed between r-MSSD and ECOG score (r=−0.1346, p≤0.0278; Fig. 3). Significant negative correlation was observed between r-MSSD and FPS score (r=−0.1575, p≤0.0100; Fig. 4).

Correlation between E:I ratio and ECOG and FPS score in study group

ECOG score and FPS score were not significantly correlating with E:I ratio (r=0.0813, p≤0.1853; r=−0.0634, p≤0.3017, respectively).

DISCUSSION

This study investigated the association between vagal nerve function and severity of cancer. This study also sought its correlation with the functional status of these cancer patients (as assessed by ECOG score and FPS).

In this study, r-MSSD and E:I ratio, the two indicators of vagal function were significantly reduced in the early and advanced stage of cancer compared to healthy subjects (Table 2). Further, in study subjects, patients in advanced stage of cancer had a lower vagal function (E:I ratio and r-MSSD) compared to the early stage of cancer (Figs. 1 and 2). This finding confirms our previous study findings (with the smaller sample size) were in it was observed that E:I ratio and r-MSSD declines with severity of cancer [7]. Early stages of cancer had lesser tumor burden and are with comparatively smaller tumor size and lesser nodal metastasis. Whereas, advanced stage of cancer patients are generally with greater tumor size, greater lymph node metastasis and were with metastasis to distant organs than the primary site of the tumor [27]. Therefore, these findings suggest that in cancer patients, vagal function deteriorates as the tumor burden increases. De Couck et al. also observed low vagal function in advanced stage compared to the early stage of cancer but involving only r-MSSD as an indicator for vagal function whereas our study involved both E:I ratio and r-MSSD [4]. Their study population included comorbid conditions such as cardiovascular disease and diabetes which are known to influence vagal function indicators whereas our study populations were only with cancer.

To further elucidate our study findings, we compared two indicators of vagal function, namely, r-MSSD and E:I ratio between different stages of cancer and control subjects (Table 3). Both r-MSSD and E:I ratio

![Fig. 1: Comparison of root mean square of successive N-N interval difference (r-MSSD) between early and advanced stage of cancer in the study group. ***p≤0.001 compared to the early stage of cancer. Sample size n=84 for early stage, n=183 for the advanced stage of cancer. Values are expressed as mean±standard deviation](image)

![Fig. 2: Comparison of expiratory:inspiratory ratio (E:I ratio) between early and advanced stage of cancer in the study group. ***p≤0.001 compared to the early stage of cancer. Sample size n=84 for early stage, n=183 for advanced stage of cancer. Values are expressed as mean±standard deviation](image)

### Table 1: Baseline characteristics of study and control group

| Variables                   | Control group (n=250) | Study group (n=267) |
|-----------------------------|-----------------------|---------------------|
| Age (years)                 | 53.4±9.63             | 52.9±9.55**         |
| Body mass index (kg/m²)     | 21.5±5.26             | 19.5±3.46***        |
| Heart rate (beats/min)      | 71.6±5.10             | 74.1±7.39**         |
| Systolic blood pressure (mmHg) | 116.0±13.13         | 119.5±10.37**       |
| Diastolic blood pressure (mmHg) | 79.7±10.95           | 77.5±6.79**         |

**Statistically significant at p≤0.001 compared to control group;***Non-significant compared to control group, n=Sample size. Values are expressed as mean±SD. SD: Standard deviation.

### Table 2: Vagal nerve functions in early stage and advanced stage of cancer in study group compared to control group

| Vagal function parameters | Control (n=250) | Early stage (n=84) | Advanced stage (n=183) |
|---------------------------|-----------------|---------------------|-------------------------|
| r-MSSD                    | 39.3±12.64      | 32.3±9.14***        | 26.4±9.61***            |
| E:I ratio                 | 1.34±0.08       | 1.18±0.14***        | 1.14±0.06***            |

**Statistically significant at p≤0.001 compared to control group; n=Sample size, values are expressed as mean±SD. SD: Standard deviation, E:I: Expiratory:inspiratory ratio, r-MSSD: Root mean square of successive N-N interval difference.
were significantly different in subgroups of stages of cancer and control subjects. Among, the two indicators of vagal functions E.I ratio alone were decreased in as early as Stage I of cancer compared to control group. Whereas, r-MSSD started declining from only Stage II of cancer. Therefore, this study finding suggests that vagal function and the onset of cancer are interlinked. Thus, this study provides sufficient evidence of an association between cancer pathogenesis and vagal function and suggests the possibility of considering vagal function as a prognostic factor in relation to cancer and its severity.

Among, the two vagal indicators taken into account, r-MSSD was negatively correlated with ECOG score (Fig. 3). ECOG score gives information regarding physical performance state and is a simple measure composed of total six categories which range from being in normal activity, at a score of 0, to death, at a score of 5, respectively, which remains important in decision-making in terms of cancer staging and its prognosis [17]. ECOG score has been well explored in terms of its prognostic role in survival values of the advanced stage of cancer [18]. However, only one study reported observing a significant correlation between ECOG score and HRV parameters. However, their study was restricted only to lung cancer patients [26]. In this study, we observed vagal function reduced as ECOG score increased in cancer patients. A higher ECOG score clinically represents greater tumor burden or progressive stage of tumor [17]. In our study, we have observed that vagal function deteriorated as stage of cancer advanced or tumor burden increased. Moreover, this suggests that vagal function and severity of cancer are inversely related. Hence, we could imply that low vagal function is associated with poor performance status in addition to the consequence of tumor burden in cancer.

In this study, r-MSSD was negatively correlating with FPS in cancer patients (Fig. 4). FPS is a visual analog pain scale which measures the pain endured by an individual with pathological conditions [29]. Pain is a complex mechanism and it involves several structures of central nervous system, and one among them is ANS [30]. Pain is reportedly associated with changes in autonomic dysfunction such as sweating, BP variations, and giddiness [31]. Moreover, greater HRV is associated with decreased pain sensitivity in normal subjects as assessed by FPS [13]. However, no literature dealt with pain and its association with vagal function in cancer patients. In this study, we observed FPS score increased while vagal function reduced. Pain normally accompanies disease and the intensity of pain coincides with the disease progression and rise in sympathetic activity and a decrease in vagal activity is typically associated with pain [32,33]. Thus, negative correlation observed between r-MSSD with FPS score suggests that in cancer patient, decrease in vagal function is linked to the intensity of pain endured by the patients due to increased tumor burden. Therefore, it could be proposed that low vagal function is associated with poor performance status (ECOG) and higher perceived pain (FPS) in addition to tumor burden. Findings from this study highlight the important role of r-MSSD in quantifying the association of vagal function with tumor burden and functional status (ECOG and FPS score) in cancer patients. In oncology, cancer stage plays an important part in revealing the prognosis of the patient. And our study findings strongly support the view that pathogenesis of cancer and vagal function are interlinked. Thus, this study provides ample support to consider assessment of vagal function as a new prognostic factor in clinical set up in relation to cancer patients for screening and monitoring its progression. This study is with certain limitations. In our study three sites of cancer, namely, head and neck gastrointestinal cancer, and gynecological cancer were pooled together, and data were analyzed. Second, we did not quantify standard deviation of NN intervals (SDNN) which gives a combined effect of both sympathetic and parasympathetic activity. It is well-known that in autonomic dysfunction patients vagal nerve is reported to be affected at the earliest than sympathetic activity [34], therefore, we did not consider SDNN in this study.

### Table 3: Vagal nerve functions in four different stages of cancer in study group compared to control group

| Vagal function parameters | Control (n=250) | Stage I (n=22) | Stage II (n=62) | Stage III (n=96) | Stage IV (n=87) |
|--------------------------|----------------|---------------|----------------|-----------------|----------------|
| r-MSSD                   | 39.31±12.64    | 36.45±0.30    | 30.80±8.62     | 26.08±4.59      | 26.08±4.59     |
| E.I ratio                | 1.34±0.08      | 1.22±0.08**   | 1.17±0.15**    | 1.14±0.07**     | 1.14±0.06**    |

**Non-significant compared to control group Stage I; and control; †††NSa Statistical significant at p≤0.001 compared to control; †††NSb Statistical significant at p<0.001 compared to control; †††NSc Statistical significant at p≤0.001 compared to control; NSa Statistical significant at p≤0.05 compared to control; NSb Statistical significant at p≤0.05 compared to control. n=Sample size, values are expressed as means±SD, SD: Standard deviation, E.I: Expiratory:inspiratory ratio, r-MSSD: Root mean square of successive N-N interval difference
CONCLUSION
Severity of cancer affects vagal nerve functions. Among, the two indicators of vagal nerve function, E/I ratio quantifies vagal dysfunction at the early stage of cancer. In addition, to this, r-MSSD alone was associated with the functional status of cancer (ECOG and FPS). E/I ratio and r-MSSD could be considered as a new prognostic factor in cancer patients for screening and monitoring its progression.

REFERENCES
1. Malpas SC, Maling TJ. Heart-rate variability and cardiac autonomic function in diabetes. Diabetes 1996;39(10):1177-81.
2. Pipilis A, Flather M, Ormerod O, Sleight P. Heart rate variability in acute myocardial infarction and its association with infarct size and clinical course. Am J Cardiol 1991;67(13):1137-9.
3. Gidron Y, Perry H, Glennie M. Does the vagus nerve inform the brain about preclinical tumours and modulate them? Lancet Oncol 2005;6(4):245-8.
4. DeCouck M, Mravec B, Gidron Y. You may need the vagus nerve to understand pathophysiology and to treat diseases. Clin Sci (Lond) 2012;122(7):323-8.
5. Stone CA, Kenny RA, Nolan B, Lawlor PG. Autonomic dysfunction in patients with advanced cancer; prevalence, clinical correlates and challenges in assessment. BMC Palliat Care 2012;11:3.
6. Bijoor SN, Subbalakshmi NK, Bankerje S. Cardiac autonomic modulation in cancer patients as assessed by time domain measures of heart rate variability. Int J Health Sci Res 2015;5(2):194-8.
7. Bijoor SN, Subbalakshmi NK, Banerjee S. Influence of cancer and its severity on vagal nerve activity assessed by time domain measures of heart rate variability. Res J Pharm Biol Chem Sci 2016;7:1215-20.
8. Sztajzel J. Heart rate variability: A noninvasive electrocardiographic method to measure the autonomic nervous system. Swiss Med Wkly 2004;134(35-36):514-22.
9. Urooj M, Pillai KK, Monika T, Venkatesh SN, Nilanjan S. Reference ranges for time domain parameters of heart rate variability in Indian population and validation in hypertensive subjects and smokers. Int J Pharm Pharm Sci 2011;3(1):36-9.
10. Urooj M, Shilpi G, Venkateshan SP, Monika T. Reference range of heart rate variability and validation in subjects with asymptomatic elevated liver function enzymes. Int J Curr Pharm Res 2014;6(4):49-52.
11. Fouad FM, Tarazi RC, Ferrario CM, Fighaly S, Alicantzi C. Assessment of parasympathetic control of heart rate by a non-invasive method. Am J Physiol 2004;134(35-36):514-22.
12. Edge SB, Byrd DR, Compton CC, Fritz Ag, Greene FL, Trotti A, editors. AJCC Cancer Staging Manual. 7th ed. New York: Springer Publishers; 2010.
13. Warden V, Hurley AC, Voicer L. Development and psychometric evaluation of the pain assessment in advanced dementia (PAINAD) scale. J Am Med Dir Assoc 2003;4:9-15.
14. Abhishe S, Mubeen K. Biology of head and neck cancer pain. Asian J Pharm Clin Res 2012;5(1):7-9.
15. Lavigne DJ, Zuccotti M, Castronovo V, Manzini C, Veglia F, Smirne S, et al. Heart rate changes during sleep in response to experimental thermal (Noceceptive) stimulations in healthy subjects. Clin Neurophysiol 2001;112:532-5.
16. Appelhans BM, Lueckcn LJ. Heart rate variability and pain: Associations of two interrelated homeostatic processes. Biol Psychol 2005;71:174-82.
17. Oken MM, Creech RH, Torney DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-55.
18. Jang RW, Caniasco VB, Swann N, Banerjee S, Mak E, Kaya E, et al. Simple prognostic model for patients with advanced cancer based on performance status. J Oncol Pract 2014;10:335-9.
19. Ahmad S, Tejuja A, Newman KD, Zarychanski R, Seely AJ. Clinical review: A review and analysis of heart rate variability and diagnosis and prognosis of infection. Crit Care 2009;13(6):1-7.
20. Almoznino-Sarafian D, Sarafian G, Zysman I, Shteinshnader M, Tzur I, Kaplan BZ, et al. Application of HRV-CD for estimation of life expectancy in various clinical disorders. Eur J Intern Med 2009;20(8):779-83.
21. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, et al. Effects of cardiac autonomic dysfunction on mortality risk in the action to control cardiovascular risk in diabetes (ACCORD) trial. Diabetes Care 2010;33(7):1578-84.
22. Yien HW, Hsu SS, Lee LC, Kuo TB, Lee TY, Chan SH. Spectral analysis of systemic arterial pressure and heart rate signals as a prognostic tool for the prediction of patient outcome in the intensive care unit. Crit Care Med 1997;25(2):258-66.
23. Physical status: The use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser 1995;854:1-452.
24. Subbalakshmi NK, Adhikari PM, Sathyanarayana R, Jeganathan PS. Deterioration of cardiac autonomic function over a period of one year in relation to cardiovascular and somatic neuropathy complications in Type 2 diabetes mellitus. Diabetes Res Clin Pract 2012;97:313-21.
25. Wheeler T, Watkins PJ. Cardiac denervation in diabetes. Br Med J 1973;4:584-6.
26. Kleiger RE, Stein PK, Bosner MS, Rotman JN. Time domain measurements of heart rate variability. Cardiol Clin 1992;10:487-98.
27. Minakshi G, Dahiya J, Rakesh KM, Harish D. Therapies in cancer pain Scale. J Am Med Dir Assoc 2003;4:9.
28. Park-Kim S, Singer J, Wachter-Shikura N, Levine RL. Nociceptive) stimulations in healthy subjects. Clin Neurophysiol 2001;112:532-5.