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Research Article

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

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ABSTRACT

Objective: To investigate the influence of cancer severity and functional status of cancer patients on cardiac parasympathetic indicators.

Methods: A total of 267 patients with a fresh clinical diagnosis of solid malignant tumor not yet put on cancer therapy and 250 controls matched for age, sex of study subjects were included. Severity of cancer was defined based on the American Joint Committee on Cancer staging. Accordingly, study subjects were subdivided into early stage (Stage I and II combined) and advanced stage (Stage III and IV combined). In cancer patients, the Eastern Cooperative Oncology Group (ECOG) performance score and the Faces Pain Scale score (FPS) was noted. Two indicators of vagal function, expiratory:inspiratory ratio (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. $p \leq 0.05$ was considered significant.

Results: R-MSSD and E:I ratio was significantly reduced in the early and advanced stage of cancer compared to controls ($p \leq 0.0001$). r-MSSD and E:I ratio was significantly reduced in advanced stage compared to the early stage of cancer ($p \leq 0.0001$). r-MSSD and E:I ratio was significantly different in subgroups of stages of cancer and controls ($p \leq 0.0001$). In cancer patients, r-MSSD was negatively correlated with ECOG and FPS score ($p \leq 0.0278$, $p \leq 0.0100$).

Conclusion: Severity of cancer affects vagal function. However, r-MSSD alone was associated with functional status (ECOG, FPS) of cancer patients.

Keywords: Cancer, Eastern Cooperative Oncology Group score, Faces pain scale score, Vagal function.

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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 prognosticator 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, Faces Pain Scale (FPS) and the Eastern Cooperative Oncology Group score (ECOG) have been applied extensively to assess the functional status of cancer patients. FPS is a visual analog tool to measure intensity of pain endured by an individual [13,14]. Studies have revealed an association between experimental pain and ANS in healthy individuals [15,16]. Nonetheless, studies on association between autonomic function and pain in cancer are not documented. ECOG performance status score has been widely used in clinical set up to assess general functional condition in cancer patients [17]. In cancer patients, ECOG score was widely applied for survival analysis in an advanced stage of cancer [18]. Indices of parasympathetic function are considered to be independent predictors of mortality in health and disease conditions including cancer [19-22]. However, no data are available on the relationship between cardiac vagal function and ECOG score in cancer patients. Therefore, based on the need for a novel prognostic factor in solid malignant tumor patients, and to further elucidate the association between cardiac parasympathetic function and pathogenesis of cancer this study aimed at investigating the influence of tumor burden (severity) and functional status of cancer patients on cardiac parasympathetic indicators.

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.

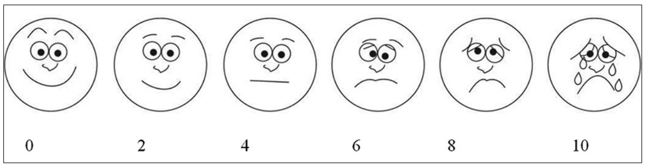
Study protocol and procedure

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 minimum 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 108T/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 breath 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 108T/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 functions 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 mucoepidermoid 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 $F=0.5365$, $p\leq0.5855$). In study subjects mean ECOG score was 1.38±0.60 and mean FPS score was 3.51±2.26.

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; $p\leq0.0001$, Table 1). HR was significantly higher in the study group compared to controls (Mann–Whitney U-statistic=25472.0, $p\leq0.0001$, 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). (KW=178.13 $p<0.0001$; 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 ($p\leq0.0001$, 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 ($p\leq 0.0001$, 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; $p\leq 0.0001$, Table 3). E:I ratio was significantly less in Stage 1, 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 ($r=-0.1346$, $p\leq 0.0278$; Fig. 3). Significant negative correlation was observed between r-MSSD and FPS score ($r=-0.1575$, $p\leq 0.0100$; 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 ($r=0.0813$, $p\leq 0.1853$; $r=-0.0634$, $p\leq 0.3017$, 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

Table 1: Baseline characteristics of study and control group

Variables	Control group (n=250)	Study group (n=267)
Age (years)	53.40±9.63	52.90±9.55[NS]
Body mass index (kg/m^2)	21.55±2.56	19.56±3.46***
Heart rate (beats/min)	71.66±5.10	74.41±7.39***
Systolic blood pressure (mmHg)	116.03±13.13	119.59±10.37[NS]
Diastolic blood pressure (mmHg)	79.74±10.95	77.54±6.79[NS]

***Statistical significant at $p\leq 0.001$ compared to control group; [NS]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	39.31±12.64	32.31±9.14***	26.49±4.61***
E:I ratio	1.34±0.08	1.18±0.14***	1.14±0.06***

***Statistical significant at $p\leq 0.001$ 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

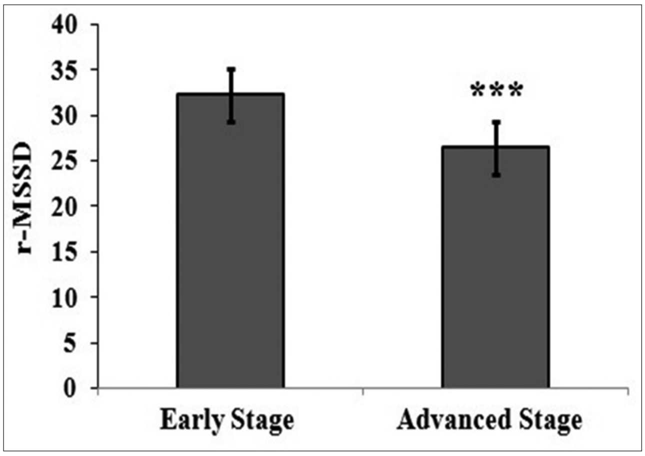


Fig. 1: Comparison of root mean square of successive N-N interval difference (r-MSSD) between early and advanced stage of cancer in the study group. ***$p\leq 0.001$ compared to the early stage of cancer. Sample size n=84 for early stage, n=183 for the advanced stage of cancer. Values are expressed as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

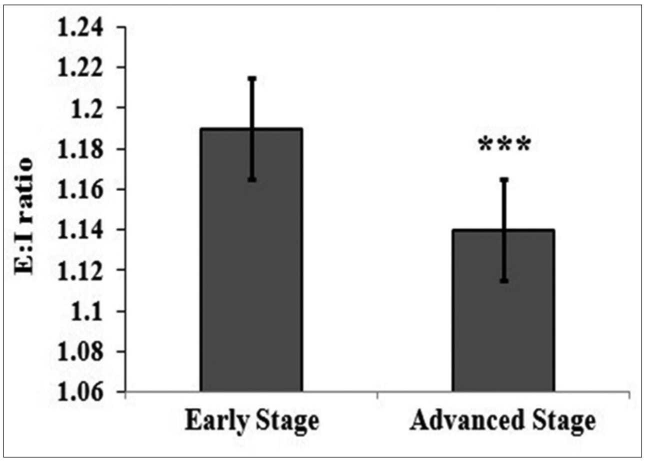


Fig. 2: Comparison of expiratory:inspiratory ratio (E:I ratio) between early and advanced stage of cancer in the study group. ***$p\leq 0.001$ compared to the early stage of cancer. Sample size n=84 for early stage, n=183 for advanced stage of cancer. Values are expressed as mean±standard deviation

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[NSa]	30.80±8.62[†††NSb]	26.85±4.65[†††]	26.08±4.59[†††NSc]
E:I ratio	1.34±0.08	1.22±0.08***	1.17±0.15***[NSb]	1.14±0.07***	1.14±0.06[NSc]

[NSa]Non significant compared to control group Stage I, and control; [NSb]Non-significant compared to Stage I; [†††]Statistical significant at p≤0.001 compared to control; ***Statistical significant at p≤0.001 compared to control; [†††]: p ≤ 0.001 compared to control. 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

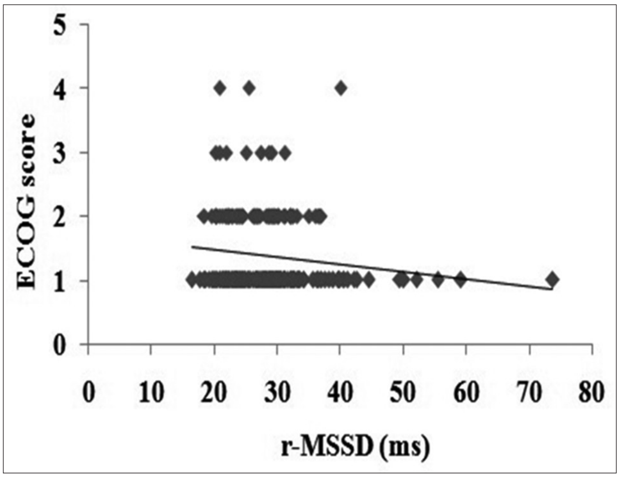


Fig. 3: Correlation between root mean square of successive N-N interval difference (r-MSSD) and the Eastern Cooperative Oncology Group (ECOG) score in study subjects. Sample size n=267. Significant negative correlation noted with r=−0.1346 and p=0.0278, where Y-axis=ECOG score and X-axis=r-MSSD

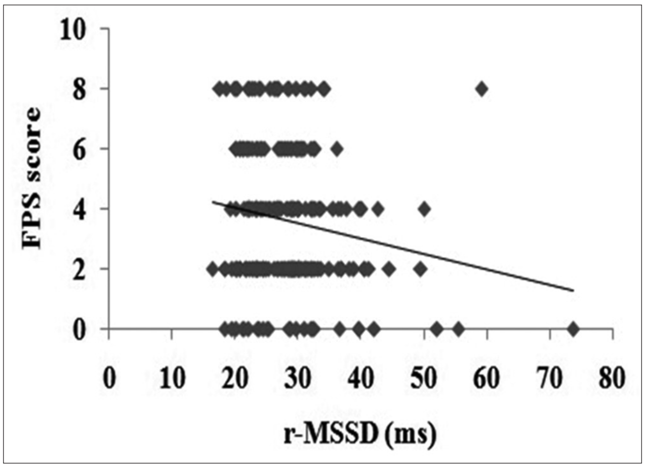


Fig. 4: Correlation between root mean square of successive N-N interval difference (r-MSSD) and Faces Pain Scale (FPS) score in study subjects. Sample size n=267. Significant negative correlation noted with r=−0.1575 and p=0.0100, where Y-axis=FPS score and X-axis=r-MSSD

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 [28]. 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.

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.

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