Association of Heart Rate Variability with Patient Reported Outcomes in Adolescents and Young Adults with Cancer

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Abstract

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Background: Psychological distress is prevalent during adolescent development, and adolescents and young adults (AYAs) with serious illness like cancer experience even higher rates of depression, post-traumatic stress, and suicide. Recent large meta-analyses link depression and stress with cancer incidence and survival across a variety of malignancies. Identifying the mechanisms underlying these biobehavioral connections is a growing focus of epidemiologic and laboratory investigation, and evidence points to autonomic nervous system (ANS) dysregulation as an important component of this relationship. Heart rate variability (HRV), which is the fluctuation between successive heartbeats, is a measure of ANS regulation and has been widely applied in both social science and biomedical settings. The objective of this study was to examine associations between HRV and patient-reported psychosocial outcomes in AYAs with cancer.

Methods: This was a secondary analysis of a completed randomized controlled trial (RCT) testing a resilience intervention in AYAs with cancer. Heart rate variability was our predictor of

interest, and patient-reported psychosocial measures served as our outcomes. HRV was derived from baseline electrocardiograms (ECGs) found in the medical record. Eligible patients were English speaking, aged 12-25 years, and diagnosed with a new cancer within 10 weeks of enrollment, or diagnosed with relapsed or refractory cancer. To test associations between HRV and PRO scores, we performed linear regression. In our adjusted models, we controlled for factors known or hypothesized to affect both ANS regulation (and thus HRV) and psychological constructs represented by our PROs.

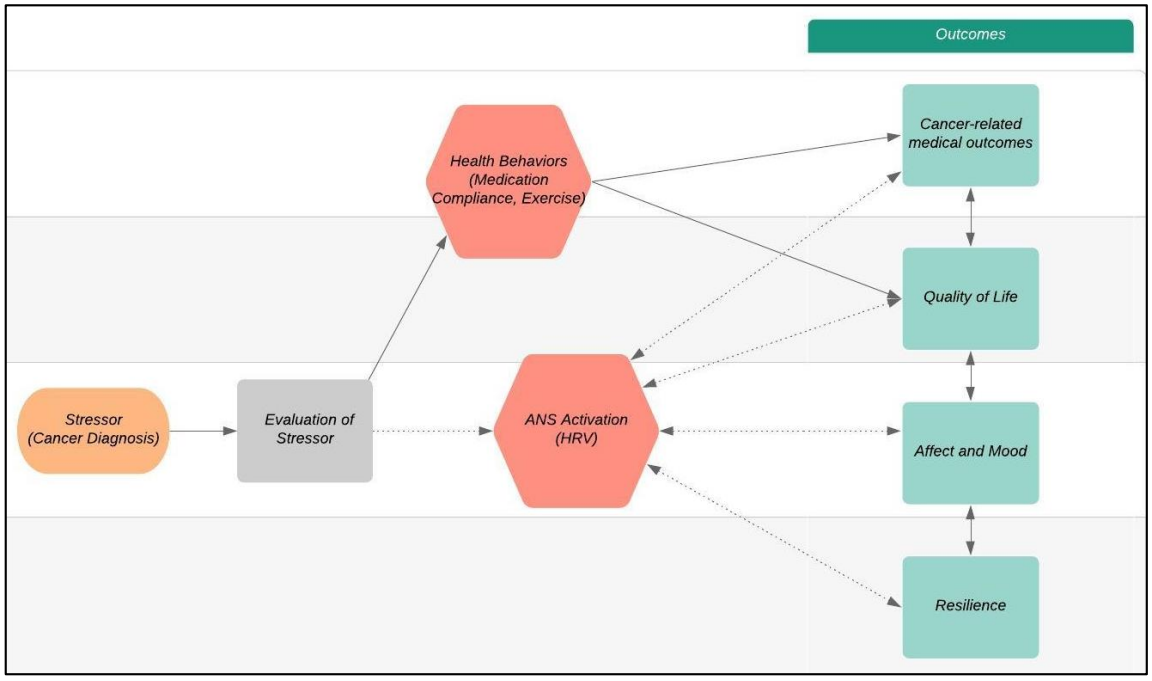
Results: There were a total of n=76 patients with both ECGs and surveys at baseline. Just under half of participants were female, and the mean age at study entry was 16 years with a range of 12 to 25 years. The most common cancer diagnosis was leukemia or lymphoma, and most participants self-identified as White. The median values (IQR) for SDNN and RMSSD were 30.9 (12.7-50.3) and 31.2 (20.4-38.6), respectively. Newly-diagnosed patients had higher median HRV values [SDNN=33.0 (13.2-50.4), RMSSD = 29.5 (11.6-47.6)] compared to those patients who enrolled in the trial at the time of relapse [SDNN = 23.6 (10.2-50.2), RMSSD = 20.8 (10.0-43.1)]. There was no statistically significant association between PRO measures and SDNN or RMSSD in either an unadjusted or adjusted linear regression model.

Conclusion: In this secondary analysis, we did not find evidence of an association between HRV measures and patient-reported psychosocial outcomes. However, this study is the first to report normative values for two commonly-used measures of HRV in AYA patients with cancer. This baseline data provides an important framework for future study in this field.

INTRODUCTION

Psychological distress is prevalent during adolescent development, and adolescents and young adults (AYAs) with serious illness like cancer experience even higher rates of depression, post-traumatic stress, and suicide.[1-3] Poor mental health directly translates to inferior cancer-related health outcomes. Recent large meta-analyses link depression and stress with cancer incidence and survival across a variety of malignancies.[4-7] In contrast, positive psychological well-being has been associated with protective health effects, including lower risk of relapse and cancer-related mortality.[8] Identifying the mechanisms underlying these biobehavioral connections is a growing focus of epidemiologic and laboratory investigation, and evidence points to autonomic nervous system (ANS) dysregulation as an important component of this relationship **(Figure 1)**. Heart rate variability (HRV), which is the fluctuation between successive heartbeats, is a measure of ANS regulation and has been widely applied in both social science and biomedical settings.[9-12] Here, we will review the measurement and interpretation of HRV in the research setting and then present a cross-sectional post-hoc analysis of HRV and psychosocial outcomes from a randomized trial of a resilience intervention in AYAS with cancer.

Figure 1. Conceptual Model



HRV Physiology

HRV serves as a proxy measure for ANS status. It is primarily determined by the two branches of the ANS: the sympathetic nervous system and parasympathetic nervous system. Sympathetic activation releases catecholamines into circulation, which causes an increase in heart rate and cardiac contractility about 5 seconds following the stimulus.[13] In contrast, parasympathetic activation leads to the release of acetylcholine, which slows the heart rate almost instantaneously. Thus, the interplay of sympathetic/parasympathetic activity is the main driver of HRV, but there are additional factors that contribute to HRV to a lesser degree. The renin-angiotensin-aldosterone system, intrinsic cardiac muscle responsiveness, respiratory sinus arrhythmia, and circadian rhythm can exert some influence on HRV as well.[14,15]

Measuring and Interpreting HRV

Standards for measuring and interpreting HRV have been published by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[16] Although the gold standard for HRV measurement is a 24-hour recording, components of HRV can reliably be determined from 5 minute, 1 minute, and even 10 second electrocardiogram (ECG) monitoring.[17,62,63]

The simplest approach to measuring HRV uses time domain methods, which determine the intervals between normal heart beats to derive a number of HRV variables.[16] These include the standard deviation of normal to normal beats (SDNN), the standard deviation of the average of normal to normal beats (SDANN), and the root mean square of standard deviations (RMSSD). Time domain metrics are among the most common HRV data reported, as they are relatively easy to calculate and do not require sophisticated equipment to capture.

All of the above HRV variables can be measured as a passive basal “vital sign”, or as a more active response to an intervention. Passive HRV is captured during rest or normal activity, and there are published normative values for both adults[18] and children[19], as well as for healthy and diseased populations.[20,21] Active HRV reflects the short term changes in HRV in response

to a stimulus. For example, biofeedback therapy measures real time changes in HRV as participants receive specific breathing maneuver coaching.[22]

HRV in Research

Generally, lower HRV signifies decreased 'autonomic flexibility', with the inverse being true for higher HRV. Although there are some established thresholds that are associated with adverse outcomes,[23] comparing changes in HRV within individuals may be more informative. Given the critical role the ANS plays in a number of physiologic and psychologic processes, HRV as a measure of ANS status has emerged as a helpful prognostic tool in many biomedical and social science studies.

Medical Studies: A growing number of clinical studies indicate ANS dysregulation (indexed by HRV) is an important component of physical disease processes.[24] For example, alterations in HRV are associated with a five-fold increase in mortality following myocardial infarction.[25] Reduced SDNN was predictive of in-hospital mortality in patients with sepsis,[26] and utilizing HRV to detect early deterioration in the neonatal intensive care unit was associated with a 22% reduced risk of mortality in very low birthweight infants.[27] HRV has also been correlated with a number of inflammatory markers in the blood, including IL-6[28], CRP, and IL-10.[29] In patients with cancer, autonomic dysfunction indexed by HRV is associated with disease progression and poorer overall survival,[30,31] as well as late effects such as cancer-related fatigue and chronic pain.[32,33] This relationship between medical conditions and HRV signal impaired ANS function, which could also have implications for psychological health.

Psychosocial Studies: Low basal HRV has been independently linked to adverse psychosocial outcomes in a number of different populations. Individuals with depression have lower HRV, and a recent meta-analysis showed a significant negative correlation between depression severity and HRV.[34] Anxiety disorders, including panic disorder, post-traumatic stress disorder (PTSD), and social anxiety disorder, are also associated with reduced HRV measures.[35] As in adults, alterations in HRV have been associated with depression, anxiety, and emotion regulation in

adolescents.[36-38] In addition to anxiety and depression, altered HRV has been associated with bereavement,[39] negative social interactions,[40] and general psychosocial stress.[41]

HRV in AYAs with Cancer

As we have gained a deeper understanding of HRV physiology and measurement, there have been a growing number of studies investigating its use as a diagnostic and prognostic tool in clinical settings. Given the significant physical and psychosocial stress associated with cancer diagnosis and treatment, HRV measurement may be particularly helpful as a simple, non-invasive assessment of several indices of patient wellbeing **(Figure 1)**. It is important to note that the relationship between ANS dysregulation indexed by HRV may be bi-directional depending on the circumstance (i.e. generalized anxiety causing sympathetic activation vs inappropriate sympathetic activation leading to decreased quality of life).[59] Using this conceptual model as a framework, we are interested in understanding how ANS dysregulation, using HRV as a proxy measure, may influence downstream biopsychosocial outcomes.

Thus far, nearly all oncology research using HRV has focused on adult patients, leaving a gap in our understanding of this landscape in children and AYAs with cancer. Identifying biomarkers associated with distress could identify at-risk patients and facilitate the development and dissemination of targeted psychosocial interventions in this vulnerable population.

METHODS

This was a secondary analysis of a completed randomized controlled trial (RCT) testing a resilience intervention in AYAs with cancer. Specifically, we conducted a cross-sectional analysis of available baseline data prior to receipt of the intervention. Heart rate variability was our predictor of interest, and patient-reported psychosocial measures served as our outcomes of interest. We hypothesized that adverse psychosocial states (higher anxiety, depression, distress and lower quality of life and resilience) would be associated with lower HRV.

Participants and Setting: The Phase II Promoting Resilience in Stress Management (PRISM) Randomized Trial was conducted at a single institution (Seattle Children's Hospital, SCH) from

January 2015 to October 2016. Eligible patients were English speaking, aged 12-25 years, and diagnosed with a new cancer requiring treatment within 10 weeks of enrollment, or diagnosed with relapsed or refractory cancer any time before enrollment. Demographic and disease-related variables were requested in surveys and collected from the medical record. Of the n=92 AYAs with baseline patient reported psychosocial measures, n=76 also had available electrocardiograms (ECGs) to derive HRV. These 76 patients were included in the present analysis.

Measures (Table 1)

Heart Rate Variability: HRV was determined using 10 second ECGs obtained at the time of cancer diagnosis. As part of standard clinical care at SCH, patients undergo routine screening ECGs regardless of cancer type prior to beginning therapy. These ECGs were extracted from the medical record and digitized using previously described methods.[44] Using an open-source R software (RHRV), we analyzed ECG recordings to derive the two most widely used time domain parameters: standard deviation of normal to normal beats (SDNN) and root mean square of successive differences (RMSSD) per published guidelines.[16,45]

Psychological Variables: All participants were invited to complete a survey consisting of AYA age–validated instruments upon enrollment, and received a $25 gift card upon survey completion.

Pediatric Quality of Life (PedsQL) Generic and Cancer Module Teen Reports. The PedsQL 4.0 Generic and 3.0 Cancer Modules include a combined total of 50 items evaluating QOL of AYAs with cancer. Subscales assess physical, emotional, social, and school well-being, plus cancer-related domains such as pain and hurt, nausea, procedural or treatment anxiety, and perceived physical appearance. Items are rated on a 5-point Likert scale and total scores transformed to a 0-100 scale with higher scores representing higher QOL. In healthy populations, a score of <70 is considered at risk for poor QOL.[64] In patients with cancer, mean

scores for the Generic and Cancer PedsQL Modules are reported at 70.9 (SD 17.2)[60] and Mean 65.3 (SD 16.3)[43], respectively. Internal consistency is excellent and ranges from 0.75 to 0.92.[46]

Hospital Anxiety and Depression Scale (HADS). The HADS assesses depressive and anxious symptoms in patients with serious illness.[47] It has been validated in AYAs with chronic illness[48] as well as AYA cancer survivors.[49] The scale consists of 7 questions for anxiety and 7 for depression. Each is scored from 0-3, for a total range of 0-21 points per subscale. The mean score for adolescents with cancer is 11 (SD 6.2).[43] "Caseness" of anxiety and depression is defined as ≥8 points, with sensitivity/specificity of 0.8/0.9 for anxiety and 0.8/0.8 for depression.[47] It has very good reliability (α=0.83-0.82).[47]

Connor-Davidson Resilience Scale (CD-RISC). The CD-RISC is a reliable and widely used instrument to measure inherent resiliency.[50] The 10-item instrument has high internal consistency (Cronbach's alpha = 0.85), and has been used in diverse populations including adolescents, parents and cancer patients.[50,51] Each item consists of a 5-point Likert scale (scored from 0-4) for a total of 40 points, with higher scores reflecting greater resilience. The mean score among healthy US adults is 31.8 (SD 5.4),[51] and 28 (SD 5.8) in adolescents with cancer.[43]

Kessler-6 General Psychological Distress Scale (K6). This 6-item scale measures level of psychological distress experienced in the past month. The instrument has been extensively cross-validated, including among adolescents.[52] Responses are scored on 5-point Likert scale, generating a range of zero to 24 points. The average score for healthy adolescents is 5.8 (SD 4.7)[61], and 7 (SD 4.7)[43] for adolescents with cancer. Previous studies have shown that scores ≥ 7 are consistent with "high" distress and those ≥ 13 meet criteria for serious, or debilitating psychological distress.[53]

Table 1. Study Measures			
Outcome Measure	Construct	Population Norms	Population Type
Biomarkers			
Heart Rate Variability*			
SDNN (ms)	ANS regulation	Median 66.4 (IQR 46-86.8)[19]	Healthy Adolescents
RMSSD (ms)	ANS regulation	Median 69 (IQR 49-99.6)[19]	Healthy Adolescents
Patient-Reported Outcomes			
PedsQL			
Generic	Quality of Life	Mean 70.9 (SD 17.2); MCID 4.4[60]	Children/Adolescents with Advanced Cancer
Cancer-Specific	Quality of Life	Mean 65.3 (SD 16.3)[43]	Adolescents with Cancer
HADS	Anxiety	Mean 11 (SD 6.2); MCID 3.1[43]	Adolescents with Cancer
CD-RISC	Resilience	Mean 28 (SD 5.8)[43]	Adolescents with Cancer
K6	Distress	Mean 7 (SD 4.7)[43]	Adolescents with Cancer
***** Data reported for females for simplicity; published normative data available for both males and females MCID = Minimum Clinically Important Difference			

Data Analysis

In this secondary analysis, we used baseline ECGs and survey data to examine the relationship between HRV parameters and patient-reported quality of life and resilience, as well as symptoms of anxiety, depression, and distress (**Figure 1**). We included data from patients who at baseline had both interpretable ECGs and completed surveys. We summarized baseline measures using means/medians, standard deviations, frequencies and proportions. All variables were reported as continuous, with some variables converted to ordinal or dichotomous when appropriate using clinically relevant cut points (e.g. a HADS depression subscale score of ≥ 8). To test associations between HRV and PRO scores, we kept both variables in their continuous forms, and therefore performed linear regression. In our adjusted models, we controlled for factors known or hypothesized to affect both ANS regulation (and thus HRV) and psychological constructs represented by our PROs (anxiety, depression, distress, and quality of life): age, gender, cancer type, and cancer status (relapsed vs newly diagnosed). The 'cancer type' variable was grouped into three categories common to oncology research: Leukemia/Lymphoma (hematologic malignancies), Non-central nervous system (CNS) Solid Tumors, and CNS Solid Tumors. CNS and non-CNS solid tumors were ultimately combined for

analytic purposes, as there was a very small number of CNS solid tumor patients. Patient age was transformed into an ordinal variable based on age groups thought to be the most similar developmentally and physiologically. Exploratory stratified analyses were also performed to assess the HRV-PRO relationship in the context of differing age categories, gender, cancer type, and cancer relapse status.

RESULTS

There were a total of 76 patients with both ECGs and surveys at baseline. Just under half of participants were female, and the mean age at study entry was 16 years with a range of 12 to 25 years (**Table 2)**. The most common cancer diagnosis was leukemia or lymphoma, and most participants self-identified as White.

Psychological Instrument Results (Table 2): Baseline surveys revealed an average HADS score of 11.1 (SD 6.3), with nearly one-third of participants meeting criteria for clinically relevant anxiety or depression at the time of cancer diagnosis with a subscale score of $\geq$ 8. Average resilience, measured by the CD-RISC, was slightly below healthy adult population norms at 28.9 (SD 6). Self-reported distress was higher than in non-ill adolescents, with an average score just below the cutoff of 8 for "high" levels of distress. General and cancer-specific QOL was 60.3 (19.1) and 65.6 (SD 16.8), respectively.

HRV Results: Descriptive summaries of the two measures of HRV (SDNN and RMSSD) are shown below. The median values (IQR) for SDNN and RMSSD were 30.9 (12.7-50.3) and 31.2 (20.4-38.6), respectively (**Table 3)**. Newly-diagnosed patients had higher median HRV values [SDNN=33.0 (13.2-50.4), RMSSD = 29.5 (11.6-47.6)] compared to those patients who enrolled in the trial at the time of relapse [SDNN = 23.6 (10.2-50.2), RMSSD = 20.8 (10.0-43.1)]. **Figure 2** illustrates HRV measures stratified by age, gender, cancer type, and cancer relapse status. **Figure 3** shows the distribution of HRV measures across the study population. Values for both SDNN and RMSSD demonstrated a right skew, with a higher proportion of patients falling on the

lower end of the HRV spectrum. Vertical red lines demonstrate normal median values in the healthy adolescent population.[19]

Associations between HRV and PROs: Scatterplots representing the relationship between RMSSD**,** SDNN and baseline patient reported outcomes are shown in **Figures 4 and 5**. Based on these visual representations, there did not appear to be a linear relationship between either measure of HRV and baseline anxiety, depression, distress, quality of life, or resilience. **Table 4** confirms there was no statistically significant association between PRO measures and SDNN or RMSSD in either an unadjusted or adjusted linear regression model. In exploratory stratified analyses of patient-reported anxiety and depression scores **(Table 5)** there were no statistically significant relationships among other subgroups. However, the association between depression and RMSSD approached statistical significance in females, as did the association between depression and SDNN in patients aged 20-25 years.

DISCUSSION

In this cross-sectional post-hoc analysis, we did not find a statistically significant association between heart rate variability and patient reported outcomes in AYAs with cancer. However, results of this study did provide baseline normative values for two of the most commonly used HRV measures, SDNN and RMSSD, which have yet to be published in this population. Our results indicate baseline HRV in AYAs with cancer is much lower than in healthy adolescents, with this discrepancy more striking in relapsed compared to newly-diagnosed patients. This raises the question of a treatment effect in addition to likely compounded psychosocial stress of multiple cancer diagnoses. This finding of autonomic dysfunction indexed by HRV has also been reported in the childhood cancer survivor population.[58] Given the growing interest in using HRV as a measure of ANS function in psychosocial and biomedical research, documenting the normal values and distribution is an important first step in building a larger program of research in biobehavioral AYA oncology.

There are several possibilities for why we did not find a relationship between HRV and psychological states when this has been reported in other adolescent populations.[12,54] First, as a secondary analysis of a larger dataset, our study was not powered to detect our associations of interest. It is also possible that factors related to patients' underlying disease and developmental stage may obfuscate any more subtle correlations between ANS dysregulation and HRV measured at a single time point. We also utilized standard 10 second ECGs to derive HRV in this study, which may have contributed to the lack of significant findings. Although using ultra-short ECG recording is a reliable measure for determining RMSSD and SDNN,[17,62,63] 24-hour monitoring is still the gold standard.[16] Additionally, ECGs were collected at different times during the day and night, and HRV is known to have significant diurnal variation.[57] Nonetheless, the use of baseline ECGs in this study provided an opportunity to utilize available data from a time point that minimized potential confounders, as ECGs were largely obtained prior to central line placement, chemotherapy initiation, and not for a cardiac-related clinical indication.

Most HRV studies to date, including ours, have been observational in nature, and thus it is somewhat unclear what direction the relationship between ANS activation and psychological state actually is – does the adverse psychosocial state come before decreased HRV, or vice versa? Given what we know from other psychoneuroimmunology principles,[56] it is likely this relationship can be bi-directional and should be studied in a controlled, longitudinal fashion when considering interventional targets. However, given the known physiologic sequelae of dysregulated ANS function,[9-11,13] exploring associations (or lack thereof) between markers of ANS status and psychosocial conditions is important. Prior work has shown associations between HRV and medical outcomes in adult patients with cancer,[20,32] but very few studies have explored the relationships between HRV and psychological outcomes.[55] In this study, we chose to use the psychosocial measures as our outcome as normative values and meaningful clinical cutoffs exist, whereas this is yet unpublished for HRV in the AYA oncology population.

Participants in this study were enrolled on a larger randomized trial testing the resilience intervention, PRISM. Primary results from this trial indicated the intervention was associated with improved resilience and cancer-specific quality of life, as well as decreased distress.[43] Because we did not have consistent ECG recordings beyond baseline in our patient cohort, we were unable to evaluate possible effects of the PRISM intervention on HRV. However, understanding the physiologic correlates of improved psychosocial outcomes is an important area of investigation for future research.

This study has several important limitations. We had a relatively small, demographically homogeneous sample, and thus our results may not be generalizable to other populations. Given the nature of multiple comparisons in our analysis, there was also an increased risk for bias in our results. Additionally, there are other variables known to contribute to baseline HRV, such as physical fitness level,[19] that were not collected as part of this study and thus could not be accounted for in the analysis. However, despite these limitations, this is the first study to report baseline HRV data in the adolescent cancer population. This provides a useful framework to develop larger prospective studies in biobehavioral pediatric/AYA oncology. Future research should include longer, more dynamic HRV measures, as well as testing psychosocial interventions using HRV as a physiologic marker.

Conclusions

In this secondary analysis, we did not find evidence of an association between HRV measures and patient-reported psychosocial outcomes. However, this study is the first to report normative values for two commonly-used measures of HRV in AYA patients with cancer. This baseline data provides an important framework for future study in this field.

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Appendix: Tables and Figures

Table 2. Patient Characteristics	
	Total N=76
Sex	
Female	43%
Age Range	12-25y
Mean (SD)	16y (3y)
12-15y	43%
16-19y	43%
20-25y	13%
Race	
White	63%
Black/African American	3%
Asian	7%
Other*	28%
Cancer Diagnosis	
Leukemia/Lymphoma	75%
CNS Tumor	3%
Non-CNS Solid Tumor	22%
Psychological Instrument Score	**Mean (SD)**
HADS Total	11.1 (6.3)
HADS Depression	5.1 (3.4)
Above clinical cutoff on HADS Depression	29%
HADS Anxiety	6.0 (3.6)
Above clinical cutoff on HADS Anxiety	28%
CD-RISC	28.9 (6.0)
Kessler-6	6.9 (4.8)
Quality of Life (PedsQL)	60.3 (19.1)
Cancer Specific QOL	65.6 (16.8)
*Other = mixed race, missing, or other	

Table 3. Heart Rate Variability Measures		
	SDNN median (IQR)	**RMSSD median (IQR)**
All patients (n=76)	30.9 (12.7-50.3)	31.2 (20.4-38.6)
Age		
12-15 (n=33)	25.7 (12.8-52.9)	23.0 (10.6-40.7)
16-19 (n=33)	39.5 (8.8-49.0)	27.9 (8.1-47.7)
20-25 (n=10)	34.3(17.4-47.9)	30.9 (15.8-56.9)
Sex		
M (n=43)	29.9 (11.5-47.9)	27.9 (8.6-48.6)
F (n=33)	31.9 (12.8-50.7)	28.2(11.1-45.5)
Cancer Status		
Newly-diagnosed (n=58)	33.0 (13.2-50.4)	29.5 (11.6-47.6)
Relapsed (n=18)	23.6 (10.2-50.2)	20.8 (10.0-43.1)
*** All results reported in msec**		

Figure 2. HRV Measures by Age, Gender and Cancer Type

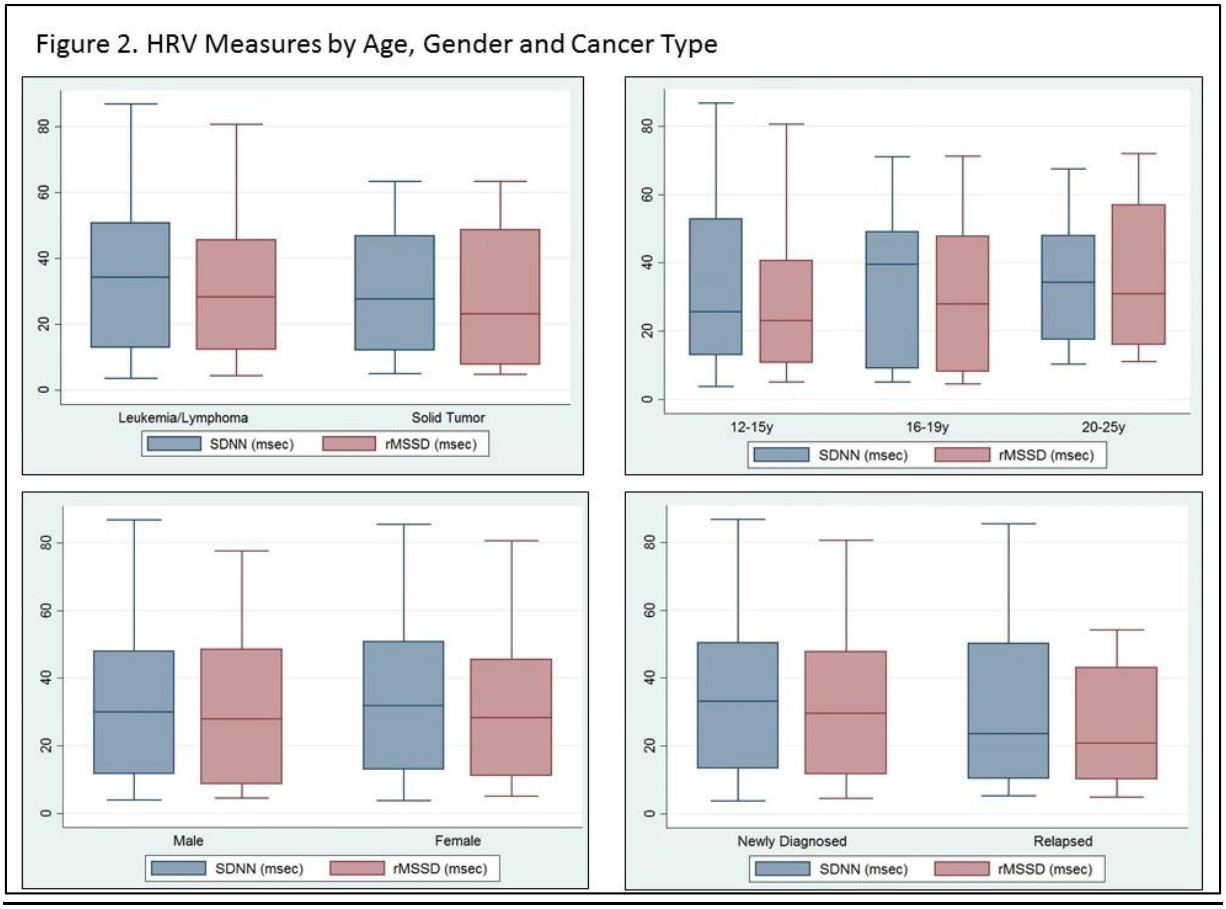
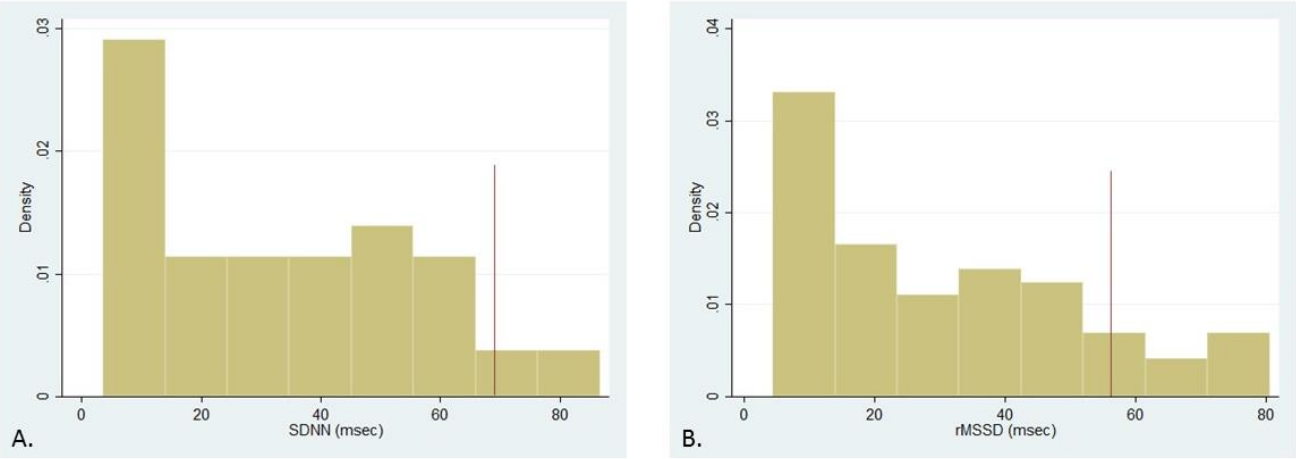
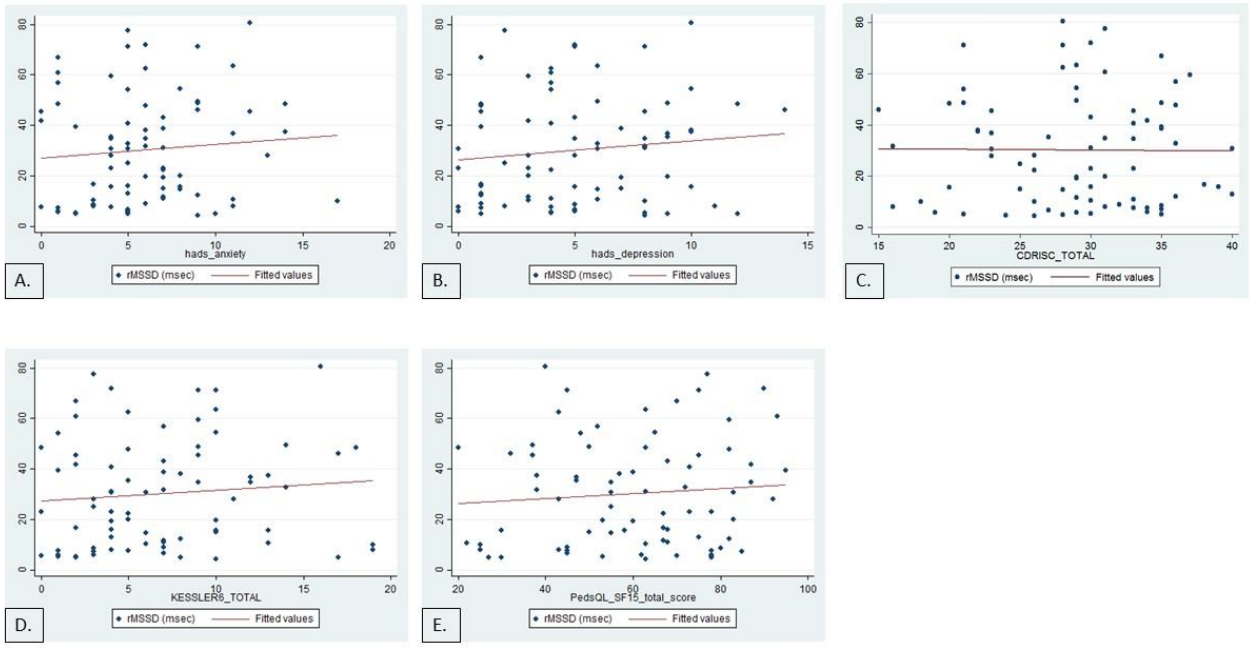


Figure 3. Distribution of HRV Measures



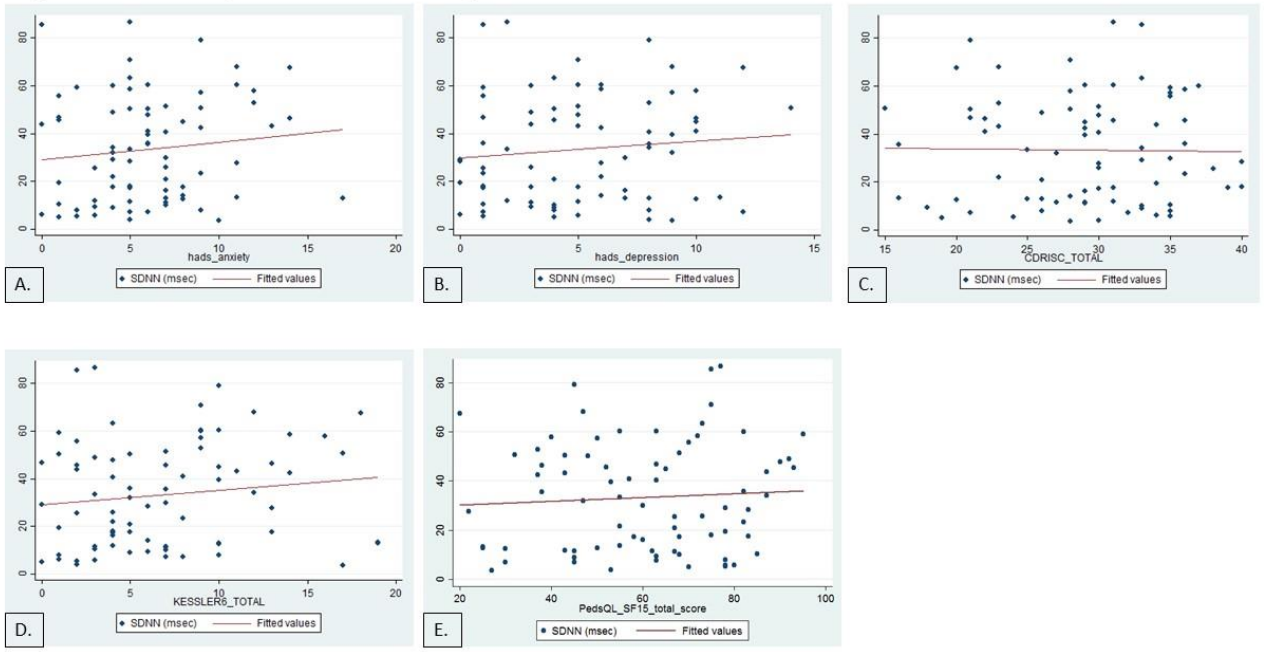
Histograms showing the distribution of (A) SDNN and (B) rMSSD for the entire sample of n=76 patients. Vertical red lines indicate normal values for healthy adolescents.

Figure 4. Relationship of rMSSD to Patient Reported Outcomes



Scatterplots showing unadjusted relationship between rMSSD and (A) Anxiety, (B) Depression, (C) Resilience, (D) Distress, and (E) Quality of Life

Figure 5. Relationship of SDNN to Patient Reported Outcomes



Scatterplots showing unadjusted relationship between SDNN and (A) Anxiety, (B) Depression, (C) Resilience, (D) Distress, and (E) Quality of Life

Table 4. Association of Heart Rate Variability with Patient Reported Outcomes

	SDNN			RMSSD		
Model 1	β coefficient	95% CI	p-value	β coefficient	95% CI	p-value
Anxiety	0.02	[-0.02 -0.06]	0.3	0.01	[-0.02 - 0.05]	0.46
Depression	0.16	[-0.02 - 0.05]	0.36	0.02	[-0.02 - 0.06]	0.32
Distress	0.03	[-0.02 - 0.08]	0.25	0.02	[-0.03 - 0.07]	0.42
Resilience	-0.005	[-0.07- 0.06]	0.89	-0.003	[-0.07 - 0.06]	0.93
General QOL	0.06	[-0.14 - 0.26]	0.57	0.08	[-0.13 - 0.28]	0.45
Cancer-specific QOL	-0.06	[-0.24 - 0.11]	0.48	-0.002	[-0.18 - 0.18]	0.99
Model 2						
Anxiety	0.16	[-0.02 - 0.05]	0.35	0.01	[-0.02 - 0.05]	0.42
Depression	0.01	[-0.02 - 0.05]	0.44	0.02	[-0.02 - 0.05]	0.3
Distress	0.02	[-0.02 - 0.07]	0.3	0.02	[-0.03 - 0.07]	0.4
Resilience	-0.002	[-0.06 - 0.05]	0.94	-0.01	[-0.07 - 0.05]	0.71
General QOL	0.07	[-0.1 - 0.25]	0.42	0.06	[-0.12 - 0.24]	0.5
Cancer-specific QOL	-0.04	[-0.18 - 0.09]	0.51	-0.02	[-0.15 - 0.12]	0.86

*Linear regression models with patient reported outcomes as primary outcome of interest, and SDNN or RMSSD as the predictor of interest. Model 1 = unadjusted model, Model 2 = adjusted for Age, Gender, and Cancer Relapse Status

Table 5. Association of Heart Rate Variability with Depression and Anxiety Stratified by Gender, Cancer Type and Age

	SDNN			RMSSD		
	β coefficient	95% CI	p-value	β coefficient	95% CI	p-value
Anxiety						
Males	0.11	[-0.30 - 0.52]	0.59	0.02	[-0.39 - 0.43]	0.93
Females	0.29	[-0.37 - 0.95]	0.37	0.48	[-0.25 - 1.21]	0.19
Leukemia/Lymphoma	0.08	[-0.33 - 0.49]	0.69	0.06	[-0.38 - 0.50]	0.79
Solid Tumor	0.51	[-0.37 - 1.38]	0.24	0.51	[-0.29 - 1.31]	0.19
12-15y	-0.03	[-0.55 - 0.49]	0.91	0.17	[-0.41 - 0.74]	0.56
16-19y	0.35	[-0.25 - 0.95]	0.24	0.22	[-0.39 - 0.84]	0.47
20-25y	0.82	[-0.73 - 2.38]	0.24	0.24	[-1.32 - 1.81]	0.72
Depression						
Males	-0.02	[-0.47 - 0.43]	0.92	0.03	[-0.42 - 0.47]	0.9
Females	0.37	[-0.20 - 0.93]	0.19	0.54	[-0.08 - 1.15]	0.09
Leukemia/Lymphoma	0.18	[-0.18 - 0.55]	0.32	0.25	[-0.14 - 0.65]	0.2
Solid Tumor	0.02	[-0.90 - 0.93]	0.97	-0.006	[-0.85 - 0.84]	0.99
12-15y	0.05	[-0.40 - 0.49]	0.84	0.29	[-0.19 - 0.78]	0.23
16-19y	0.17	[-0.43 - 0.78]	0.56	0.06	[-0.56 - 0.67]	0.85
20-25y	1.06	[-0.21 - 2.33]	0.09	0.53	[-0.86 - 1.92]	0.38

*Association of patient reported anxiety and depression with HRV measures stratified by gender, cancer type, and age using linear regression models. Models adjusted for age and cancer type when not the stratum of interest. Coefficients interpreted as change in PRO score for every 10msec change in HRV. CNS and non-CNS solid tumor categories collapsed for analysis.