Heart Rate Variability as an objective measure of cancer related fatigue.

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ABSTRACT

Aim: To systematically identify and synthesise evidence examining heart rate variability (HRV) as an objective measure of cancer related fatigue (CRF).
Background: Cancer related fatigue can be a significant symptom burden, often impacting people for many years . Assessment of CRF is universally recommended and is commonly quantified using subjective assessment tools . Cancer related fatigue is underreported and often undiagnosed, with the severity and scale of the problem for survivors ill defined. Identifying a viable objective measurement of CRF would provide data on the prevalence and impact of CRF on the cancer survivor.
Method: Searches were conducted in the electronic databases CINAHL, MEDLINE, Cochrane Reviews, Scopus, and PubMed. Search terms included 'heart rate variability' and 'cancer related fatigue.' Search results were screened for inclusion into the review.
Results: The search strategy identified 172 studies and a limited number of studies that identified a correlation between HRF and CRF, ranged in strength from weak to strong. Two studies, one by Crosswell at al (19) and Fagundes et al (20) demonstrated strong p-values that low HRV was positively correlated with reported high fatigue scores. The third study by Shih et al (21) demonstrated a weaker association and p-value, however this study also confirmed low HRV was corelated high reported fatigue scores.
Conclusion: Further research in this area is warranted.

INTRODUCTION

- Cancer-related fatigue (CRF) is a debilitating symptom affecting cancer survivors.
- CRF is prevalent in over half of all cancer survivors.
- The exact pathophysiology of CRF is not well understood.
- Identifying and assessing CRF is challenging as survivors may not report or underreport fatigue.
- Heart rate variability (HRV) is a potential physiological marker for measuring CRF.
- HRV reflects the cardiac system's ability to adjust to physiological and environmental changes.
- HRV is considered a measure of autonomic nervous system (ANS) regulation.
- High sympathetic activation and low parasympathetic activation in CRF release pro-inflammatory markers.
- Low HRV indicates low adaptation of the ANS to stress and stimuli, indicating increased inflammation.
- HRV could assist in accurately assessing, measuring, and monitoring CRF as an objective physiological measure of ANS dysregulation.

METHODS AND MATERIALS

- The systematic review conforms to the PRISMA 2020 reporting guideline.
- Searches were conducted in May 2022 using the electronic databases of CINAHL, MEDLINE, Cochrane Reviews, Scopus, and PubMed.
- Initial searches returned a broad range of literature, which was refined to specific search terms of "heart rate variability" AND "cancer related fatigue."
- Only studies written in English, full text, peer-reviewed, and dated from 2011 to May 2022 were included.
- The author extracted the data and collated it into an Excel spreadsheet.
- The quality of the data was assessed using the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies.

RESULTS

Selection
The search identified 172 studies, 63 were removed as duplicates, and a further 96 were excluded after abstract and title screening. The full text of 13 studies were assessed and three studies were included in the review. All three were observational studies. All studies were critically appraised and all three were included in this review.
Demographics and disease characteristics
Two studies focused on survivors of breast cancer (19,20), the third study (21) focused on late stage lung cancer.
HRV as a measure of CRF
Two studies (20,21) used wearable technology to measure HRV and all three used standard subjective fatigue measures. The third study (19) used ECG to measure HRV in addition to blood sampling to measure inflammatory markers as a marker of fatigue. One study (20) measured norepinephrine as a measure of fatigue in breast cancer survivors.

Table 5: Characteristics included studies

	Criteria to assess HRV	Criteria to assess CRF	Hypotheses	Clinical findings
Crosswell et al (2014)	ECG recordings - measuring R-R over time.	Fatigue Inventory (FSI)	Lower levels of HRV associated with higher CRF	-Lower RMSSD scores correlated with higher average levels of fatigue and correlated with greater fatigue severity. -Low RMSSD correlated positively with FSI (p=0.043) after adjusted for BMI and age -Low RMSSD correlated weakly with FSI average when controlled only physical activity (p=0.084)
Fagundes et al (2011)	PPG- - No continuous collection of data, data collected one set time period	MFS1-SF and RAND SF-36	CRF would indicate higher norepinephrine and lower HRV in BC survivors	Correlation between higher reported CRF and higher norepinephrine and lower HRV. Higher MFS1-SF and low HRV (p=0.005) Higher SF-36 and low HRV (p=0.013)
Shih et al (2021)	PPG developed frequency-domain parameters to measure HRV - LF-HF. Data collected continuously over a 7-day period.	BFI	Develop an objective CRF fatigue criteria based on HRV.	Correlation between LF-HF and CRF in study population. Positive correlation between BFI and HRV sleep (p=0.86) Weak negative correlation between BFI and HRV active state (p=0.47)

Table 6- Summary of Analysis and Consideration of Confounding Factors

STUDY	CRF MEASURE	HRV MEASURE	OTHER MEASURES	STATISTICAL ANALYSIS	CONFOUNDING FACTORS CONSIDERED
FAGUNDES ET AL	MFS1-SF and RAND SF-36	Using PPG wrist watch, R-R intervals processed through software*to produce value for RMSSD*	Blood samples of norepinephrine	Mixed regression analysis	Age, BMI, physical activity adjustments were made in analysis
CROSSWELL ET AL	Fatigue Inventory (FSI)	Stationery ECG recording to analyse R-R to calculate RMSSD	Blood samples of IL-6 and CRP*	Regression analyses	Physical activity and smoking were considered.
SHIH ET AL	BFI (Brief fatigue Inventory)	PPG wearable technology using LF-HF ratio from HRV data collected. Data divided into sleep and active states as wearable worn continuously	N/A	Multivariate regression analysis to understand BFI to LF-HF.	Nil factors adjusted such as use of hypnotics and ability to ambulate during test period.

DISCUSSION

There is currently limited evidence demonstrating a strong association between CRF and HRV, limiting the ability to use HRV as an objective and feasible measure of CRF. While ANS dysfunction, which would manifest as low HRV, is one possible contributor to CRF , Crosswell et al (19) found a strong positive association between inflammatory markers and CRF was not present. However, Fagundes et al (20) did show a positive association between levels of norepinephrine and higher levels of reported fatigue. The two studies that have used technology to assess HRV, focused only on BC survivors (19,20) and the technology used differed, making a comparison of results difficult. The study by Shih et al (21) suggested that when fatigue is tracked over both active and sleep states, fatigue could change over time. The use of HRV as an objective measure of CRF is an area that warrants further research. The evidence presented in this review should be considered cautiously as the most recent study is that of Shih et al (21) published in 2021. This is surprising as in recent years, with the advent of more sophisticated technology able to assess HRV and other biomarkers, for example the explosion in wearables such as smart watches and fitness trackers (24), no recent studies have researched how this technology may be effective in assessing and measuring HRV as it relates to CRF.

CONCLUSIONS

This systematic literature review found that there is a lack of evidence that would confirm conclusively that HRV is an objective measure of cancer related fatigue. Only two studies, both of them older studies, provided convincing evidence that low HRV correlated with higher reported subjective measurement of fatigue. The evidence from these studies is limited, as two cancer types were included and results cannot be generalised to other cancer types and demographics.

REFERENCES

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