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Original Research

Heart rate variability as a digital biomarker for frailty in cardiovascular patients

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ABSTRACT

Background: Frailty is a syndrome associated with age-related impairments in multiple organ systems, of which the autonomic nervous system plays a fundamental role. Measurement of heart rate variability (HRV) is a non-invasive method to evaluate the autonomic activity and gain insights into cardiovascular health and potentially, frailty. A few small studies have explored the relationship between HRV and frailty, with promising but conflicting results.

Objective: To investigate the relationship between HRV and frailty among adult patients with cardiovascular disease.

Design: A cross-sectional study was conducted using clinical data.

Setting: Data were collected from an ambulatory cardiology clinic.

Participants: The cohort comprised 155 patients with a mean age of 67 years (44 % female).

Measurements: HRV was assessed seated at rest for 2.5 min using a finger-based photoplethysmography (PPG) device. Frailty was assessed using the Clinical Frailty Scale (CFS), with a score ≥5 considered frail. Associations between HRV and frailty were examined using a Spearman correlation matrix and multivariable ordinal regression model. The LF/HF ratio (a frequency-domain measure reflecting imbalances between sympathetic and parasympathetic activity) was the primary HRV measure analyzed.

Results: The prevalence of frailty was 15 %. Among all HRV measures, the LF/HF ratio was most closely correlated with frailty ($p < 0.001$). In the multivariable model, each 1 standard deviation decrease in LF/HF ratio was associated with a 1.1-point increase in CFS (95 % CI 0.7–1.6, $p < 0.001$). The optimal ROC cutoff at which the LF/HF ratio was associated with frailty is ≤ 0.37.

Conclusions: The LF/HF ratio is inversely correlated with the CFS and independently associated with frailty. Measurement of HRV is a promising technique to enrich existing frailty scales and assist in frailty assessments in an ambulatory cardiology clinic.

1. Introduction

Frailty is a geriatric syndrome that is highly prevalent in cardiovascular patients and characterized by age-related impairments in multiple organ systems [1]. These impairments collectively limit the individual's physiological reserves and ability to maintain homeostasis in the face of stressors, predisposing them to adverse health outcomes such as mortality and major cardiovascular or non-cardiovascular morbidity [2]. One of the key impairments is reduced responsiveness of the autonomic nervous system [3], with a recent systematic review highlighting the association between frailty and autonomic dysfunction as reflected by exaggerated orthostatic heart rate change and diminished HRV [4].

Heart rate variability (HRV) refers to the time interval variation between consecutive heartbeats, influenced by a complex interplay of the sympathetic (SNS) and parasympathetic (PNS) branches of the nervous system [5]. Accordingly, HRV has garnered attention as a candidate biomarker of frailty [6].

Biomarkers derived from HRV signals have the potential to enrich established frailty scales derived from questionnaires and physical tests, or to screen for patients who could benefit from frailty assessments. The potential for screening is exciting because HRV can be measured opportunistically in large numbers of patients who are already equipped with wearable sensors (e.g., smartwatches) or undergoing in-hospital or ambulatory cardiac monitoring (e.g., Holter tests). Identifying mark-

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Table 1
Heart rate variability metrics in the time and frequency domains.

HRV time domain measures		
RMSSD	ms	Root mean square of successive RR interval differences
SDNN	ms	Standard deviation of NN intervals
Ln (RMSSD)	ms	Natural log of root mean square of successive RR interval differences
pNN50	%	Percentage of successive RR intervals that differ by more than 50 ms
Mean RR	ms	Average RR interval duration
HRV frequency domain measures		
LF peak	Hz	Peak frequency of the low-frequency band
LF power	ms^2	Absolute power of the low-frequency band
HF peak	Hz	Peak frequency of the high-frequency band
HF power	ms^2	Absolute power of the high-frequency band
TP	Hz	Total Power: sum of ULF, VLF, LF, and HF bands
LF/HF	-	Ratio of LF-to-HF power

* *Abbreviations*: HRV, heart rate variability; ms, milliseconds

ers of frailty is useful for risk stratification and treatment guidance; one proven use case being prediction of operative risk and need for (pre)rehabilitation in older patients set to undergo cardiac surgery [7]. Applications in cardiac patients are promising given the known associations, at both the epidemiological and pathophysiological levels, between cardiovascular disease and diminished HRV [8]. Accordingly, this study sought to determine the feasibility and accuracy of using HRV measured by a portable plethysmography device to detect frailty in a real-world cohort of ambulatory patients with prevalent or suspected cardiovascular disease.

2. Methods

2.1. Study population and design

This cross-sectional study was conducted at the Jewish General Hospital, McGill University (Montreal, Quebec) between August 2022 and February 2023. The study cohort consisted of consecutive adult patients who attended their ambulatory appointments at the cardiovascular medicine clinic. All patients underwent clinical assessments of their medical history, medications, signs and symptoms of heart disease, vital signs, and frailty. The device used to measure heart rate had the functionality of recording pulse signals and deriving HRV measures using validated algorithms. The Research Ethics Board approved the analysis of clinical data for research on opportunistic biomarkers of frailty with waived individual-level consent.

2.2. Heart rate variability analysis

HRV was collected at rest in a seated position from the right or left index finger for 2 min and 30 s using the Elite HRV CorSense device. The CorSense device employs photoplethysmography (PPG), a non-invasive technique that illuminates the skin with light, typically on a finger or earlobe. This light is then absorbed and reflected, allowing for the detection of changes in blood volume. PPG provides insights into blood flow dynamics and pulse rate by capturing these changes. The CorSense device captures the PPG signal, enabling the extraction of HRV measures in both the time and frequency domains. Captured measures of HRV in the time and frequency domains are listed in Table 1. HRV measures were disregarded in cases of active arrhythmia, pacing, or poor-quality recordings (those with paroxysmal atrial fibrillation or backup pacemakers who were in sinus rhythm were not disregarded).

2.3. Frailty assessment

Frailty was assessed using the Clinical Frailty Scale (CFS) with the standardized classification tree for reliability [9], and a score ≥ 5 was considered frail. Duplicate observers graded the CFS to arrive at a consensus. CFS is a validated tool used to assess the frailty of older adults in clinical settings. It provides a quick and standardized way to evaluate a person's overall health status, functional abilities, and resilience to stressors. The CFS is typically used by healthcare professionals, particularly geriatricians, to guide treatment decisions and care planning for older adults. The scale consists of a series of pictorial representations and descriptors that depict different levels of frailty, ranging from very fit (level 1) to severely frail (level 9). The assessments are based on the individual's overall health, mobility, activities of daily living, cognition, and comorbidities, among other factors. CFS > 5, indicates dependence in at least one Independent Activity of Daily Living (IADL), while CFS > 6, depicts dependence in at least 1 Basic Activity of Daily Living (BADL) or multiple IADLs. The CFS assumes that individuals with a CFS of 4 or higher are not engaging in moderate to vigorous physical activity.

2.4. Statistical analysis

Summary statistics and distributional histograms were inspected. Data were presented as medians and interquartile ranges for continuous variables and as the number of individuals and percentage [n, (%)] for categorical variables. The patients were divided into two groups: frail patients with CFS ≥5 and non-frail patients with CFS < 5. The Wilcoxon rank-sum test was used to test for differences in HRV measures, non-parametrically, between the frail and non-frail groups. A Spearman correlation matrix was used to test for correlations between various HRV metrics non-parametrically. Ordered logistic regression was used to determine the association between HRV metrics and CFS grade after adjusting for patient demographics and comorbidities. The coefficients from this model represent the associated change in CFS grade per unit increase in each variable. Receiver Operating Characteristics (ROC) analyses were used to determine the optimal cut-off for HRV metrics to discriminate between frail and non-frail patients. These statistical analyses were performed using Stata software (version 18; College Station, Texas). Finally, machine learning analyses were performed using H2O Driverless AI software (version 1.10.5) to determine the optimal model for correlation between CFS < 5 and clinical variables with 3-fold cross-validation using their engine for model selection, feature selection, and hyperparameter tuning.

3. Results

Of 238 patients with HRV data, 83 were excluded due to arrhythmias or poor-quality readings; these patients were otherwise similar to those with good-quality readings in terms of age, sex, and comorbidities. Thus, 155 patients were included in the final analysis. The mean age was 67 years, with 31 % being ≥75 years and 44 % being females. The mean CFS score was 3, with 15 % being frail. Frail older patients had a similar heart rate, lower diastolic blood pressure, a higher proportion of diabetes, and heart failure. The most prevalent comorbidities were hypertension

Table 2
Patient characteristics and heart rate variability stratified by frailty status.

	All (N=155)	Non-frail (N=131)	Frail (N=24)	*P*-value
Age, years	67 (59, 77)	65 (57, 74)	80 (75, 87)	<0.001
Age ≥75	48 (31 %)	30 (23 %)	18 (75 %)	<0.001
Female	68 (44 %)	56 (43 %)	12 (50 %)	0.51
Clinical frailty scale	3 (2, 4)	3 (2, 3)	5 (5, 6)	<0.001
Heart rate	71 (62, 79)	71 (62, 79)	71 (62, 82)	0.99
Systolic blood pressure	129 (119, 139)	127 (119, 136)	137 (121,145)	0.17
Diastolic blood pressure	72 (66, 81)	73 (66,81)	66 (58, 75)	0.007
Hypertension	97 (63 %)	81 (62 %)	16 (67 %)	0.65
Coronary artery disease	74 (48 %)	59 (45 %)	15 (63 %)	0.12
Diabetes	36 (23 %)	27 (21 %)	9 (38 %)	0.07
Heart failure	18 (12 %)	12 (9 %)	6 (25 %)	0.03
Atrial fibrillation	18 (12 %)	14 (11 %)	4 (17 %)	0.40
Beta-blocker use	66 (43 %)	56 (43 %)	10 (42 %)	0.92
Time domain				
RMSSD	32.9 (21.4, 50.0)	32.9 (21.4, 50.0)	36.8 (20.8, 70.5)	0.40
SDNN	33.5 (24.3, 49.7)	33.7 (25.8, 49.7)	29.3 (16.4, 48.7)	0.29
ln(RMSSD)	3.5 (3.1, 3.9)	3.5 (3.1, 3.9)	3.7 (3, 4.3)	0.29
pNN50	7.0 (.01, 19.0)	6.0 (1.0, 17.0)	12.5 (1.5, 27.5)	0.23
Mean RR	854.6 (756.9, 959.5)	854.6 (759.6, 959.0)	848.9 (742.5, 975.1)	0.87
Frequency domain				
TP, ms^2	467.8 (222.5, 1138.4)	504.5 (241.6, 1154.8)	353.1 (59.4, 945.1)	0.21
LF power	219 (69.9, 472)	231.9 (77.2, 554.2)	78.3 (20.1, 267.1)	0.01
HF power	259.1 (98.3, 576.3)	259.1 (99.6, 571.9)	259.2 (43.8, 626.2)	0.95
LF peak	0.06 (0.05, 0.09)	0.06 (0.05, 0.09)	0.07 (0.05, 0.11)	0.24
HF peak	0.28 (0.22, 0.34)	0.28 (0.21, 0.34)	0.34 (0.28, 0.39)	0.002
LF/HF	0.78 (0.42, 1.47)	1.01 (0.46, 1.69)	0.37 (0.23, 0.67)	<0.001

* Values presented as median (25^{th} percentile, 75^{th} percentile) or N (%). Non-frail and frail defined as Clinical Frailty Scale ≤4 or ≥5 out of 9. Abbreviations: refer to Table 1.

Table 3
Ordinal logistic regression model for association between clinical variables and frailty.

	Coefficient	95 % CI	*P*-value
Age	0.050	0.018, 0.082	0.002
Female	−0.355	−1.112, 0.402	0.36
Systolic blood pressure	0.032	0.007, 0.056	0.01
Diastolic blood pressure	−0.070	−0.115, −0.024	0.003
Heart rate	0.030	−0.023, 0.083	0.27
Hypertension	−0.704	−1.484, 0.077	0.08
Coronary artery disease	0.601	−0.223, 1.426	0.15
Diabetes	0.268	−0.563, 1.099	0.53
Heart failure	0.576	−0.412, 1.563	0.25
Atrial fibrillation	0.611	−0.497, 1.719	0.28
Pacemaker	0.996	−0.686, 2.678	0.25
Beta-blocker use	−0.325	−1.203, 0.553	0.47
RMSSD	0.032	−0.031, 0.096	0.31
SDNN	−0.025	−0.067, 0.018	0.26
ln(RMSSD)	−0.895	−2.395, 0.606	0.24
PNN50	−0.008	−0.057, 0.040	0.74
Mean RR	−0.001	−0.006, 0.005	0.83
Total Power	−0.003	−0.014, 0.007	0.53
LF Power	0.004	−0.007, 0.014	0.50
HF Power	0.003	−0.007, 0.014	0.52
LF Peak	4.260	−6.865, 15.384	0.45
HF Peak	1.425	−3.083, 5.934	0.54
LF/HF	−1.144	−1.612, −0.677	<0.001

*Coefficients represent the change in Clinical Frailty Scale per 1-unit increase in that variable. Abbreviations: refer to table 1.

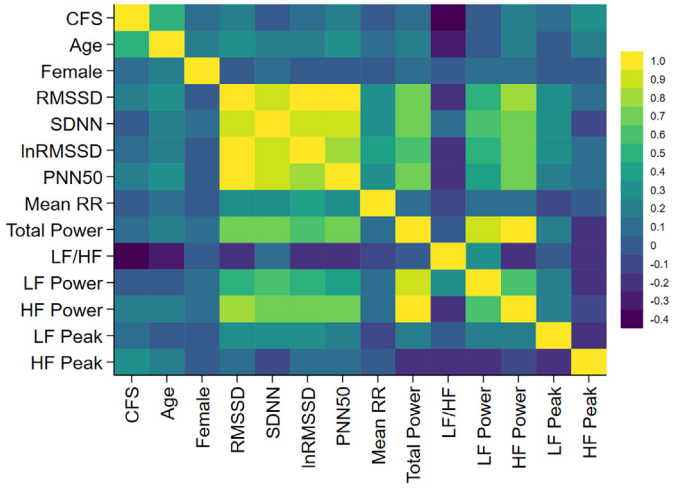

Fig. 1. Spearman correlation heatmap.

(63 %), coronary artery disease (48 %), diabetes (23 %), and heart failure (12 %) (Table 2).

No HRV metrics in the time domain and three in the frequency domain were associated with frailty expressed as a dichotomous variable: LF/HF ratio ($P < 0.001$), LF power ($P = 0.01$), HF peak ($P = 0.002$). The LF/HF ratio was lower (0.37) in frail compared to non-frail (1.01) patients. LF power was lower in frail (78.3 ms^2) compared to non-frail (231.9 ms^2) patients. HF peak was higher in frail (0.34 Hz) compared to non-frail (0.28 Hz) patients (Table 3). The linear regression showed that one HRV metric in the time domain and four in the frequency domain were correlated with frailty expressed as an ordinal variable: SDNN (P = 0.0391), LF/HF (P < 0.001), LF power (P = 0.0002), HF peak (P = 0.0123), Total Power (P = 0.0207). There were variable correlations between the different HRV metrics (Fig. 1). In a sub-group analysis of 68 patients with pre-frailty defined as CFS 3 or 4, there were no statistically significant correlations between pre-frailly and HRV metrics.

As shown in Table 3, multivariable ordinal logistic regression revealed that the LF/HF ratio was the only HRV metric associated with frailty (expressed as an ordinal variable) after adjusting for covariates. Each unit decrease in LF/HF ratio translated to a 1.14 (95 % CI −1.61, −0.68) unit increase in CFS grade. ROC analysis showed that the specificity-optimized cutoff for LF/HF ratio associated with frailty (expressed as a dichotomous variable) was 0.37, with a sensitivity of 54 % and a specificity of 82 %. The balanced cutoff for the LF/HF ratio associ-

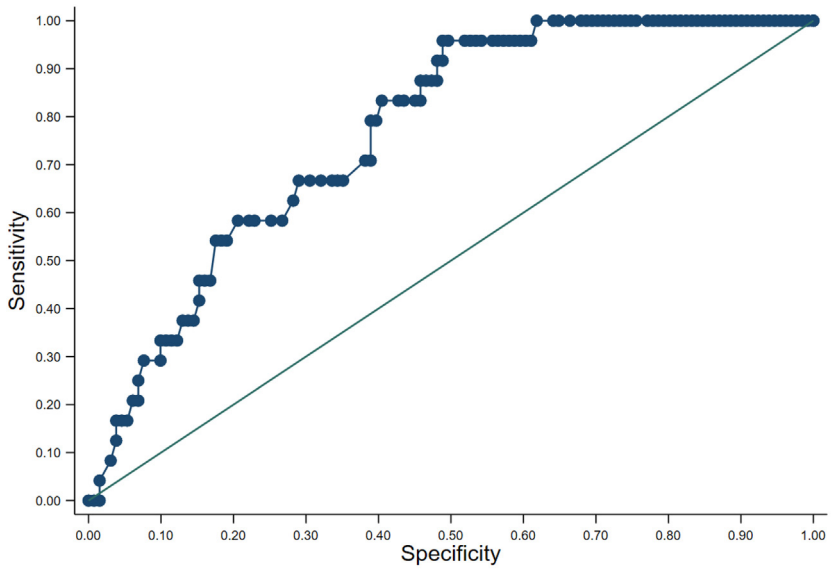

Fig. 2. ROC Curve of LF/HF in association with frailty.

ated with frailty was 0.94, with a sensitivity of 96 % and a specificity of 51 %. Other risk factors for increased CFS grade were older age, higher systolic blood pressure, and lower diastolic blood pressure.

The HRV measures were entered into the Driverless AI autoML software engine in addition to comorbidities, vital signs, age and sex (24 variables considered). The optimal model for correlation between CFS < 5 and clinical variables was found to be a LightGBM architecture with 4 variables retained, in descending order of feature importance (as indicated by Shapley coefficients): higher age (0.39), lower LF/HF (0.25), lower diastolic blood pressure (0.18), lower LF power (0.17). Comorbidities were not significantly associative. This model achieved an area under the ROC curve of 0.911, area under the precision-recall curve of 0.758, true positive rate of 83 %, false positive rate of 7 %, and accuracy of 92 % to identify frailty (Fig. 2).

4. Discussion

The study's primary purpose was to determine whether HRV measures were associated with frailty in middle to older-aged cardiovascular patients. The study findings were threefold: first, feasibility of measurements was variable using a portable finger-based PPG sensor, with one-third of patients not reliably assessed due to arrhythmia or poor signal quality. Second, HRV measures in the frequency domain were generally more closely correlated with the CFS score than those in the time domain. Third, the LF/HF ratio, a frequency domain measure, showed the strongest correlation with frailty, independent of age and other confounders, with an optimal cut-off of ≤ 0.37 for excluding frailty. However, to reliably identify frailty in this population, additional clinical testing may be required.

Heart rate is not a metronome, but rather a dynamic process influenced by a multitude of physiological functions operating at various time scales, even in a stable physiological state. This phenomenon is commonly referred to as physiological complexity. Short-term HRV primarily reflects the influence of the SNS and PNS, while longer-term HRV takes into consideration factors such as pharmacological agents, circulating hormones, and circadian rhythms. Aging is generally associated with a decline in HRV, also known as a loss of physiological complexity, although it can be mitigated by maintaining physiological wellbeing.

One hypothesis proposes that the loss of physiological complexity diminishes adaptability to stressors, resulting in the geriatric syndrome of frailty. In the cardiovascular system, the decline in HRV is mediated by age-related dysfunction of the autonomic nervous system, namely: sinus node dysfunction, B-adrenoceptor hypo-responsiveness, and decreased parasympathetic tone [10]. Both HRV and frailty are inversely associated with oxidative stress and inflammatory markers [11,12] representing a shared mechanistic pathway and potential causal link towards the development of cardiovascular disease, a leading cause of death in older adults.

There are only three studies examining the relationship between frailty and HRV, all conducted in community-dwelling older women. The first two studies from the Women's Health and Aging Study I (WHAS I) measured HRV using ambulatory electrocardiography during a variety of physical tasks over 2–3 h and found that LF power, LF/HF ratio, and SDNN were inversely associated with Fried's frailty scale [13,14]. Contrastingly, the third study from a small cohort of 23 women measured HRV using chest heart rate monitors during supine rest over ≤5 minutes and found that LF power and LF/HF ratio were positively associated with frailty [15]. Our results are consistent with the WHAS I cohort, broadening the generalizability to men and women including patients with active cardiovascular disease, affirming the conclusion that frail individuals are more likely to have low LF/HF ratios due to low LF power (and preserved HF power).

Historically, attempts to understand the LF/HF ratio assumed that LF power was driven by SNS activity while HF power was driven by PNS activity, a simplistic sympathovagal balance [16,17]. Many have since challenged this belief, suggesting that drivers of LF and HF power were more complex [5,18–22]. LF power is roughly driven by 50 % PNS, 25 % SNS, and 25 % other factors [23]. Aging affects LF power by increasing sympathetic tone (SNS), reducing baroreceptor sensitivity (PNS), reducing respiratory variation (PNS), and reducing autonomic adaptability (SNS-PNS). HF power remains predominantly driven by 90 % PNS, and 10 % SNS [18]. SNS and PNS activation are not mutually exclusive, as one branch can override the other even during maximum activation. For instance, in the mammalian dive reflex, the PNS decreases heart rate despite maximal sympathetic activation [24]. In addition to the physiological determinants, HRV measures are significantly impacted by testing conditions, comorbidities, and medications.

Cardiovascular disease, diabetes, and hypertension are associated with reduced LF power and HRV. Medications such as beta-blockers block sympathetic activity and, theoretically, may reduce LF power [25–27]. As nearly half (43 %) of the patients in our study were receiving beta-blockers, it raises the question of whether part of the reduction in LF power and association with frailty may be explained by the sympatholytic effect of beta-blockers. This is unlikely as beta-blocker use was not correlated with the LF/HF ratio and it was evenly distributed between non-frail and frail patients. Most of the patients were diagnosed

with cardiovascular diseases or risk factors, but this unlikely to be confounding the association between LF/HF ratio and frailty since it persisted after adjusting for comorbidities and beta-blocker use in the multivariable model.

Autonomic imbalance and HRV, particularly diminished vagal tone, has been linked to increased mortality [28–30] and the presence of hypertension, a cardiovascular risk factor [31,32]. In the Framingham Heart Study, a one standard deviation decrease in log-transformed LF power was associated with a 1.7-fold increase in all-cause mortality [33]. Our findings suggest that part of this association may be mediated by frailty, which has consistently been shown to be associated with all-cause mortality and cardiovascular events in epidemiological studies of older adults [34].

Given the possibility of measuring HRV opportunistically using available cardiac monitors and wearable devices, it is attractive to integrate in clinical care. One such use-case of HRV testing may be as an early indicator of patients who could benefit from comprehensive frailty assessments. Another use-case may be as a surrogate parameter to track changes in frailty level over time. HRV measured by non-contact PPG has previously been used as a surrogate parameter to gauge the impact of geriatric rehabilitation in frail and non-frail older adults [35]. Future studies with larger, more diverse populations and comprehensive assessments of comorbidities and physical activity are necessary to validate and expand upon these findings. This research serves as an initial step, paving the way for more robust studies in the field.

4.1. Limitations

The first limitation is the potential for contamination of HRV outputs by uncontrolled conditions in a clinical setting. For ideal assessment of HRV, it is advisable to instruct participants to abstain from sympatholytic or sympathomimetic medications and diuretics for 48 h. Participants should also refrain from consuming food and coffee for at least 3 h, empty their bladder, and avoid vigorous exercise on the test day. While physical activity is a key determinant of autonomic balance [36], the lack of a comprehensive exercise history beyond the CFS limits the ability to fully assess its impact in frailty. The second limitation is PPG-based methodology for acquiring HRV signals. ECG-based methodologies are generally preferred for their accuracy and reliability. PPG and ECG have demonstrated a high degree of correlation under controlled conditions, suggesting PPG can be a practical alternative [37,38]. The third limitation is the 2.5 min collection timeframe; longer timeframes are preferred, especially for HRV measures in the frequency domain. The shorter PPG approach was chosen in this study because it is more pragmatic and realistic to acquire in a busy outpatient clinic workflow. Lastly, while our study provides valuable insights into the relationship between HRV and frailty in an ambulatory cardiovascular population, it is important to note the mean age of the cohort was 67 years. Thus, these findings may not be fully generalizable to older populations with a higher prevalence of comorbid conditions.

5. Conclusions

This study has demonstrated an inverse relationship between HRV and frailty, clarifying conflicting results from prior small studies and extending generalizability to both sexes and patients with cardiovascular diseases or comorbidities. Specifically, the frequency-domain measure of LF/HF ratio ≤ 0.37 was found to be associated with frailty as measured by the CFS. While the LF/HF ratio remains a complex and incompletely understood parameter, its clinical application may be to assist healthcare professionals with flagging patients for further comprehensive frailty assessment and longitudinal monitoring of frailty in middle to older age patients. This knowledge, acquired with little additional cost or effort through existing cardiac monitors and wearables, may facilitate early frailty interventions and personalized care to improve outcomes in the context of frailty.

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Conflict Of Interest

The authors have no conflicts of interest to report.

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M.S. led the writing of the manuscript and data collection. S.G.A co-led the writing of the manuscript and was involved in data collection. J.A. led the conceptualization, methodology, funding acquisition, supervision, and editing of the manuscript. M.S. and J.A. were responsible for the data analysis.

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