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Revisiting Left Ventricular Ejection Fraction Levels: A Circadian Heart Rate Variability-Based Approach

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ABSTRACT Analysis of heart failure is important in clinical practice to ensure coronary artery disease (CAD) patients will be provided with appropriate timely treatment. The current gold-standard, echocardiography, although reliable, provides a once-off left ventricular ejection fraction (LVEF) measurement and does not provide information about heart function disturbances during day/night cardiac cycles. Additionally, the discrimination between heart failure with preserved and mid-range ejection fraction remains challenging in echocardiography tests. In this vein, this study was sought to investigate the ability of heart rate variability (HRV) in categorizing CAD patients into multiple LVEF groups throughout the 24-hour circadian cycle and checking its agreement with established gold-standard echocardiography-based guidelines. A total of 92 CAD patients who have suffered from heart failure were included in this study. The newly introduced index, HRV ejection fraction (HRVEF), was based on optimizing indices extracted from HRV data, which are correlated with the sympathetic and parasympathetic nervous systems, to form group membership of the preserved (HFpEF), mid-range (HFmEF), and reduced (HFrEF) LVEF categories. HRVEF groups optimized on hourly basis through Jenks natural breaks algorithm exhibited a consistent pattern with a goodness of variance fit (GVF) of more than 70% accuracy during the late-night to early-morning (01:00-08:00) and evening (17:00-23:00) time periods. At these hours, several HRV indices were found significant (p-value $\leq$ 0.05) in differentiating between HRVEF groups using statistical analysis of variance (ANOVA) test. These features include the successive differences between normal heartbeats (RMSSD), low and high frequency (LF, HF) power, standard deviation of normal heartbeats (SD2), short-term scaling exponent (alpha1), and percentage of normal heartbeats in alternation segments (PAS). The findings of this study suggest HRV as a promising supplementary tool to the once-off echocardiography for timely LVEF measurements and heart failure prognosis. It paves the way towards multi-time HRV-based estimations for LVEF according to the association between LVEF and HRV indices to better demonstrate the circadian cardiac function at different LVEF levels in CAD patients.

INDEX TERMS Heart failure, coronary artery disease, left ventricular ejection fraction, cardiac circadian rhythm, heart rate variability, Jenks natural breaks.

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I. INTRODUCTION

Heart failure is a chronic condition that is characterized by a damaged or weakened heart muscle that often leads to a

reduction in the overall cardiac output [1]. Worldwide, it is estimated that more than 26 million people are suffering from heart failure [2]. Early diagnosis as well as timely medication help people to live a relatively normal life [3]. Left ventricular ejection fraction (LVEF) is the main clinical indicator used in the early diagnosis of heart failure. It represents the ratio of the stroke volume to the end-diastolic volume, i.e., percentage of blood pumped from the left ventricle [3], [4].

The American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) [5] classify heart failure based on LVEF into three main groups; namely heart failure with preserved EF (HFpEF, EF$>$ 50%), heart failure with reduced EF (HFrEF, EF$<$ 40%), and heart failure with mid-range EF (HFmEF, 40% $\leq$EF$\leq$ 50%). In contrast, the American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) [6] define HFpEF as $>$ 55%, HFrEF to $<$ 50%, and HFmEF ranging between (50% $\leq$EF$\leq$ 55%). Clinically, the current gold-standard for measuring LVEF is echocardiography [7]. Despite being an efficient technique in determining LVEF, it is considered expensive and not often available in public healthcare services [8]. In addition, it is a once-off measurement for the cardiac output, therefore, it is not able to provide time variant measurements as well as an overall representation of the heart rhythm with respect to cardiac output throughout the day/night cycles. Additionally, although the current ACCF/AHA and ASE/EACVI guidelines provide classifications for patients based on LVEF levels measured using echocardiography, there is disagreement between cut-off values for preserved, mid-range, and reduced patient groups. Patients from these groups may exhibit similar heart functionality at the time of the echocardiography test. This usually occurs for the HFmEF patients group that, despite of their lower LVEF, a normal heart function can still be observed and hence, this group is usually considered ambiguous. Therefore, a progression of heart failure may arise in patients classified with normal or close to normal heart function.

Developing supplementary indicators for heart failure associated with left ventricular systolic dysfunction is an important clinical aim. One such option is the use of electrocardiography (ECG) and the corresponding heart rate variability (HRV) features [9]. HRV represents the changes in cardiac interbeat (RR) intervals that may be associated with endocrine, autonomic nervous system (ANS), or intrinsic modulation of cardiac rhythm [10]. In coronary artery disease (CAD) patients, changes in the autonomic regulatory balance involves both the sympathetic and parasympathetic branches depending on the underlying cause and disease progression [11]. Despite the wide usage of HRV in cardiovascular disease analysis, a deep understanding of the relationship between LVEF and HRV is still lacking and is not well defined. Further investigations on the mechanistic functionality of the heart as observed by HRV features is required in the analysis of heart failure progression in CAD patients. A promising supplementary tool to the current gold-standard (echocardiography) is ECG and its corresponding HRV, which provides a more extensive perspective about the functionality of the heart at different LVEF levels [12]–[14].

Several studies have observed a strong association between HRV and cardiovascular diseases including CAD [15]–[21]. Specific cardiac function characteristics observed using different HRV features at certain times of the day/night cycle could suggest changes in cardiac function associated with heart failure progression in parallel with circadian rhythm changes. Thus, HRV ejection fraction (HRVEF) levels can be considered as multi-time measurements as opposed to the once-off measurements provided by echocardiography. Thus, a combination of HRV, which has been shown to be a strong indicator for sudden cardiac death, with LVEF may provide a more powerful assessment tool for treatment and medication options for patients with established heart failure. Additionally, in literature, it was found that there is an association between HRV indices with the severity of heart failure [22], [23]. Furthermore, it was suggested that HRV attributes proved its ability in providing information complementary to LVEF traditional clinical indices [24].

Motivated by the aforementioned, the current study (Fig. 1) aimed to investigate the ability of HRV and its corresponding features in classifying a total of 92 CAD patients into LVEF groups as defined by ACCF/AHA and ASE/EACVI. Unlike the current gold-standard, the new proposed index, HRVEF, is based on optimizing group membership into HFpEF, HFmEF, and HFrEF using HRV derived time-domain, frequency-domain, non-linear, and fragmentation indices. The optimization was based on Jenks natural breaks algorithm to determine which HRV features and cut-off values provide the best fit into HFpEF, HFmEF, and HFrEF classes. The advantage of using this approach lies in segmenting LVEF data in 1-dimension (1D) based on the values of features obtained from every patient at every hour over the 24-hour circadian cardiac rhythm. Therefore, in addition to the current ACCF/AHA and ASE/EACVI LVEF classification guidelines, the HRVEF grouping may provide a more comprehensive per-hour categorizations that combines LVEF and HRV features. Furthermore, this approach provides hourly categorization for patients based on the correlation between HRV indices and the cardiac function.

II. MATERIALS AND METHODS

A. DATASET AND PATIENTS ENROLLMENT

The selected CAD patients dataset was obtained from the Intercity Digital ECG Alliance (IDEAL) study of the University of Rochester Medical Center Telemetric and Holter ECG Warehouse (THEW) archives [25]. An informed consent was obtained from all participants prior to enrolling in the study. The database measurements were conducted according to Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects (Revised November 13, 2001 - effective December 13, 2001) and in accordance with the Declaration of Helsinki. Furthermore, the Research Subject

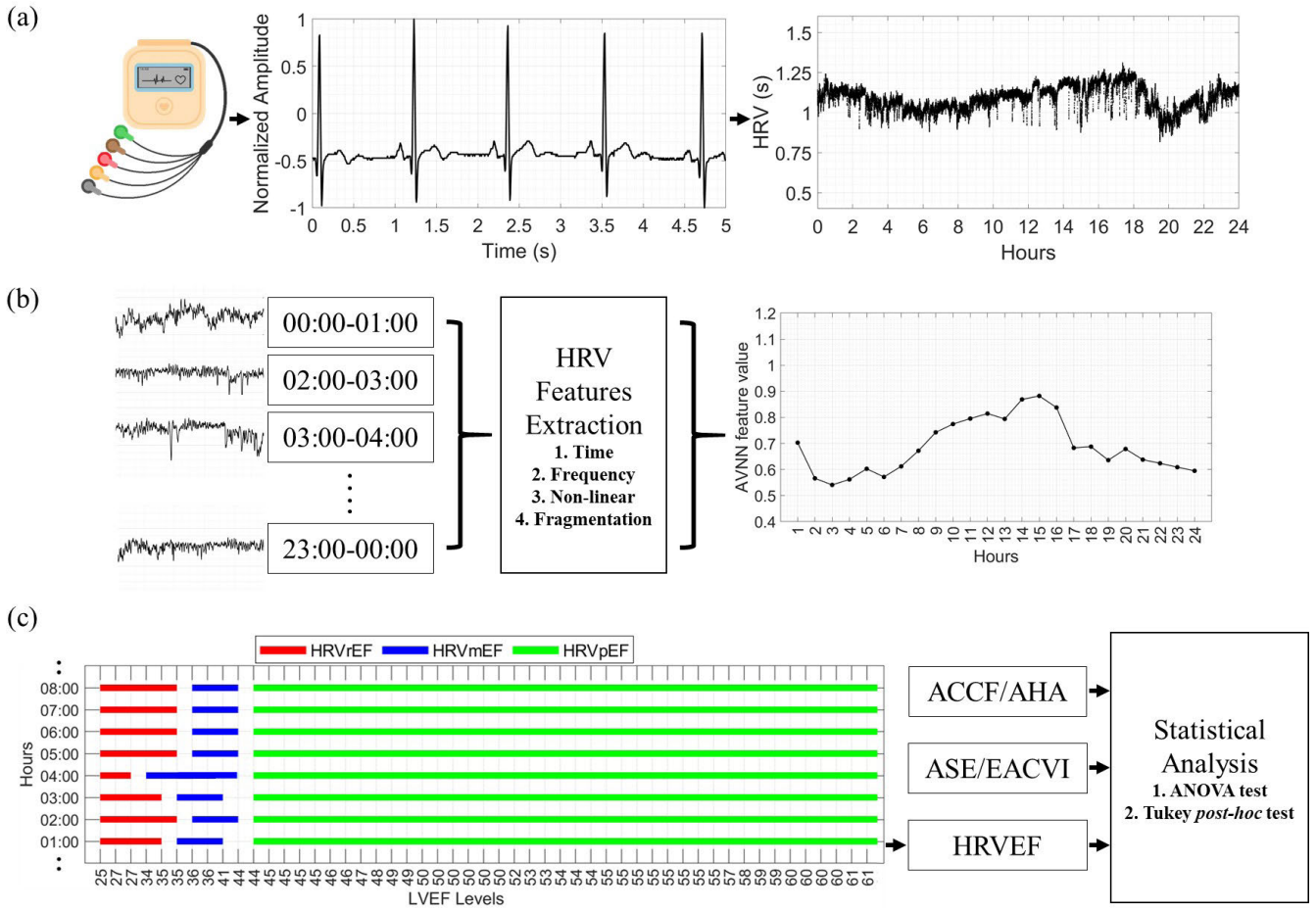


FIGURE 1. Flowchart for the generation of per-hour heart rate variability ejection fraction (HRVEF) index. (a) HRV acquisition from 24-hour Holter ECG recordings of coronary artery disease (CAD) patients. (b) Per-hour extraction of HRV features from time, frequency, non-linear, and fragmentation metrics (showing average normal-to-normal feature (AVNN)). (c) Utilizing Jenks natural breaks algorithm to categorize patients with respect to their left ventricular ejection fraction (LVEF) levels and statistically comparing them with current gold-standard guidelines.

Review Board of the University of Rochester approved the IDEAL protocol [26], [27].

The original dataset included 271 patients that were in a stable condition after 2+ months since their latest cardiac event. All patients passed the eligibility criteria that included having exercise-induced ischemia, a record of myocardial infarction (MI), at least one vessel narrowing >75%, stable ischemic heart disease, and sinus rhythm. Furthermore, these patients did not suffer from dilated cardiomyopathy, unstable angina, congestive heart failure (CHF), previous coronary artery bypass surgery (CABG), and cerebral/renal vascular diseases.

All patients had a 24-hour Holter ECG recorded using a three pseudo-orthogonal lead configuration (X, Y, Z) that correspond to limb lead I, augmented limb lead aVF, and precordial lead V3, respectively. In addition. an echocardiography test was performed to measure their LVEF percentage at the time of the enrollment. In the current study, patients with hypertension (110), diabetes (9), or both (27) were excluded from any further analysis, as these comorbidities have a strong effect on HRV. This resulted in including 92 patients in the finalized dataset after additionally removing patients with missing ECG or HRV annotations. The complete demographic information of patients within each LVEF group following both LVEF guidelines is provided in Table 1. In the table, most information are illustrated by the range (mininum to maximum) and the mean±standard deviation (std) values. All Holter ECG recordings were initially pre-processed to remove noise and ectopic beats using the signal-dependent rank order mean (SD-ROM) [28] and adaptive filtering [29], [30] techniques to decrease abnormalities in the data.

B. CIRCADIAN HRV FEATURES

The database does not provide the starting time of each recording, therefore, the starting point for analysis of the 24-hour circadian rhythm was initially fixed prior to any further analysis. Cosinor fitting analysis [12], [31] was performed to ensure that all HRV data starts from 12:00AM. It is a commonly used algorithm in literature that is capable of handling unorganized data in terms of recordings starting

TABLE 1. Demographic information of patients within each LVEF group according to the ACCF/AHA and ASE/EACVI gold-standard guidelines.

LVEF Guidelines		Patients (n)	Sex (M/F)	Age (Mean±Std) (yrs)	BMI (Mean±Std) (kg/m^2)	BPS (Mean±Std) (mmHg)	BPD (Mean±Std) (mmHg)	LVDS (Mean±Std) (mm)	LVDD (Mean±Std) (mm)	Smoking (Yes/No)	Syncope (n)	VT (n)
ACCF/AHA	*pEF*	65	57/8	35-84 (56.42±11.27)	17.99-36.33 (25.83±3.77)	100-160 (121.77±12.51)	50-90 (76.39±7.29)	22-55 (33.87±7.53)	33-68 (51.02±6.49)	50/15	7	5
	mEF	19	19/0	40-80 (59.22±11.42)	22.55-31.26 (27.13±2.51)	90-150 (123.47±15.12)	60-95 (75.21±10.07)	31-57 (42.14±7.52)	37-71 (54.72±10.91)	14/5	1	2
	rEF	8	8/0	41-70 (54.25±9.74)	21.55-36.85 (26.75±5.25)	90-130 (116.25±13.30)	60-80 (70.13±6.11)	33-66 (46.21±12.73)	28-75 (55.71±16.32)	7/1	1	4
ASE/EACVI	*pEF*	51	44/7	35-79 (55.98±11.11)	19.72-36.33 (25.56±3.67)	100-160 (121.75±12.96)	60-90 (75.53±6.44)	22-55 (33.37±6.78)	33-59 (50.53±4.98)	40/11	3	6
	mEF	20	19/1	40-84 (58.68±11.57)	17.99-33.96 (26.66±3.71)	100-140 (122.30±11.13)	50-90 (78.15±9.72)	26-45 (37.23±4.48)	40-68 (54.08±7.03)	13/7	5	0
	rEF	21	21/0	40-80 (57.00±11.15)	21.55-36.85 (27.21±3.63)	90-150 (120.76±15.62)	60-95 (73.33±9.13)	31-66 (44.56±9.03)	28-75 (55.02±11.79)	19/2	1	5
Overall (per-guideline)		**92**	**84/8**	**35-84 (56.79±11.14)**	**17.99-36.85 (26.18±3.70)**	**90-160 (121.64±13.12)**	**50-95 (75.60±7.96)**	**22-66 (36.80±9.24)**	**28-75 (52.21±8.84)**	**71/21**	**9**	**11**

BMI: Body mass index (kg/m^2), BPS: Systolic blood pressure (mmHg), BPD: Diastolic blood pressure (mmHg), LVDS: Left ventricular end-systolic dimension (mm), LVDD: Left ventricular end-diastolic dimension (mm), VT: Ventricular tachycardia

time [32]–[34]. In this analysis, a cosine function is used to fit each HRV data by calculating the midline estimating statistic of rhythm (MESOR-M), amplitude (Amp), and acrophase (AC). The reference angle was chosen to be 0°, referring to 12:00AM, with an increase of 15° for every hour obtained after converting the 24-hour AC into angle data using (360/24). For example, if an AC of 65.30° was obtained for a patient's HRV data, it is converted to the corresponding hour of 04:00AM. After obtaining the time-fixed dataset for all patients, several per-hour HRV features were extracted from time- and frequency-domain metrics [35], non-linear metrics including Poincare plot, detrended fluctuation analysis (DFA), and multi-scale entropy (MSE) [36], [37]. Furthermore. the newly introduced fragmentation metrics [38] were also included. All features used in the current study are listed and briefly defined in Table 2.

TABLE 2. Definitions of heart rate variability (HRV) features.

Feature	Definition
Time domain	
AVNN (ms)	Average N-N interval
SDNN (ms)	Standard deviation of N-N intervals
RMSSD (ms)	Square root of the mean of the sum of squares of differences between adjacent N-N intervals
pNN50 (%)	Percentage of N-N intervals $>$ 50ms
SEM (ms)	Standard error of the average N-N interval
Frequency domain	
BETA	Slope of the linear interpolation of the spectrum for frequencies less than VLF band upper bound
HF Norm (%)	Normalized high frequency (HF) power
HF Peak (Hz)	Peak frequency in the HF band
HF Power (ms^2)	Power in the HF band
LF Norm (%)	Normalized low frequency (LF) power
LF Peak (Hz)	Peak frequency in the LF band
LF Power (ms^2)	Power in the LF band
LF/HF	Ratio between LF power and the HF power
Total Power (ms^2)	Total power in both frequency bands
VLF Norm (%)	Normalized very-low frequency (VLF) power
VLF Power (ms^2)	Power in the VLF band
Non-linear	
SD1 (ms)	Standard deviation of N-N intervals along the perpendicular to the line-of-identity
SD2 (ms)	Standard deviation of N-N intervals along the line-of-identity
Alpha1	Detrended fluctuation analysis with low-scale slope
Alpha2	Detrended fluctuation analysis with high-scale slope
Sample Entropy	Complexity of physiological time-series signals
Fragmentation	
PIP (%)	Percentage of inflection points in the N-N interval
IALS	Acceleration/deceleration segments inverse average length
PSS (%)	Percentage of short segments
PAS (%)	Percentage of alternation segments

C. MISSING DATA IMPUTATION

Data imputation is an essential technique to ensure having a complete dataset. It is defined as the process in which missing data are replaced with new data values learned through different algorithms [39]. Data imputation techniques are widely implemented in literature to address missing values issue often found in medical data [40]–[42]. In addition, it is essential to carefully correct and replace missing values to provide complete analysis of clinical data, especially those who rely on 24-hour measurements (as in this study). In this work, data imputation was applied on the extracted HRV features dataset, as many patients had missing recordings at certain hours, thus, they had no values for HRV features extracted at these hours.

1) MOVING MEAN

In this basic data imputation approach, each missing value for each feature is replaced by a moving mean value with a pre-defined window length. In this work, the window size is determined to be 5.

2) K-NEAREST NEIGHBOUR (kNN)

In kNN, missing values are filled based on the information taken from other available values obtained from

neighbours [43]. If the targeted missing value is expected to be numerical, which is the case in current data, the missing value is filled with a value obtained from the k nearest neighbours. In this work, the number of k neighbours was selected to be 5.

3) MULTIPLE IMPUTATION BY CHAINED EQUATIONS (MICE)

The MICE algorithm suggests the use of multiple imputations in addressing missing values as opposed to single imputation methods. In multiple imputations, missing values are imputed multiple times iteratively with values drawn from a posterior predictive distribution of the missing values conditional on the available values [44]. An advantage of the MICE algorithm is the ability to impute data on a variable-by-variable basis [45].

4) NEURAL NETWORKS

The selected neural network architecture is based on Datawig framework [46], which provides deep learning models to impute missing values. In this approach, features are learned through a symbolic API of Apache MXNET. The advantage of utilizing this technique, as in any deep learning trained model [47], is the ability to learn from all other features prior to any prediction of missing features values. In this work, each missing value is initially replaced by the average value of its variable across patients. The encoder and featurizer were selected to be numerical corresponding to the type of data imputed.

5) RANDOM FOREST (RF)

RF is machine learning algorithm that utilizes ensembles of decision trees through bootstrap aggregation to make decisions [48]. In the context of data imputation, all missing values were initially replaced by their corresponding variable average. Then, for each LVEF group, the model was trained using patients HRV features dataset as the input data. On the other hand, the response (regression value/label) for every patient was the target feature value. The training and prediction was allowed to run for three iterations to keep updating the missing value (that was initially set as the average value) and optimize it further. The training/prediction of missing values was performed iteratively as a regression problem, where on each iteration, missing values of every feature were updated based on all other learned features. The iterative approach resembles an optimization problem, where the dataset is updated on each iteration to reach an optimized HRV features dataset with no missing values. The imputation process is performed as a prediction provided after learning from all other features. In this work, the total number of decision trees used for training was specified to be 50.

D. JENKS NATURAL BREAKS OPTIMIZATION

Jenks natural breaks is a 1D clustering technique used to arrange data values into different classes based on within-classes variance calculations. The natural ranges in a dataset of values refer to the most optimal class ranges found naturally in the data that form natural groups of values with similar characteristics [49]. To optimize natural classes, the algorithm seeks minimizing the deviation of values in each class from the class mean. In addition, it tries to maximize the deviation of values from the mean of other classes. In other words, it reduces the within-class variance and increases the between-classes variance [49], [50].

This technique performs three major steps iteratively to optimize natural breaks. These steps are:

1) Find the sum of squared deviations from the current array mean (SDAM) as follows,

$$SDAM = \sum_{i=1}^{n} (x_i - \bar{x})^2, \tag{1}$$

where i denotes the array value, n is the total number of values in the array, and $\bar{x}$ is the mean of values within the array.

2) Find the sum of squared deviations from each class mean (SDCM) by,

$$SDCM = \sum_{k=1}^{m} \sum_{i=1}^{n} (x_{ik} - \bar{x}_k)^2, \tag{2}$$

where k is the class number, m is the total number of classes, x_{ik} is the i^{th} value in the class array, and $\bar{x}_k$ is the mean of values within the class.

3) Decide if a move of one unit from the class with a larger SDCM to an adjacent class with a lower SDCM is needed. This step is needed to ensure that the within-class deviations are minimized.

A goodness of variance fit (GVF) parameter is measured at the end of the clustering process to evaluate the variance fitting performance. GVF ranges between 1 (perfect fit) and 0 (worst fit) and is calculated as follows:

$$GVF = \frac{SDAM - SDCM}{SDAM}. \tag{3}$$

To ensure the best possible clustering process of the data, the GVF value was obtained when for three clustering scenarios; namely 2, 3, and 4 classes. The best class clustering scenario was selected at each hour and for every HRV feature once the GVF reaches a value of more than or equal to 0.70. In the case of 2-class, HRVEF groups were named as HRV with reduced EF (HRVrEF) and HRV with preserved EF (HRVpEF). For 3-class scenario, an additional group was included between the two aforementioned groups as HRV with mid-range EF (HRVmEF). Finally, the 4-class scenario included an additional HRVmEF named as HRV with mid-range 2 EF (HRVm2EF).

It is worth noting that the calculations of GVF were not affected by the imbalance found in the current dataset. GVF is a measure of how each category differ from other categories as well as how each category's samples are close to each other, thus, the total number of samples does not affect one class over the other.

E. STATISTICAL ANALYSIS OF FEATURES

To evaluate HRV features on an hourly basis, the average feature value was calculated for each of ACCF/AHA and ASE/EACVI LVEF classification guidelines as well as the HRVEF groups obtained by the Jenks algorithm. An one-way analysis of variance (ANOVA) test was carried out to compare the mean values of each feature across LVEF groups with significant difference between groups at ($p < 0.05$) [51]. Furthermore, a multiple comparison post-hoc analysis (Tukey *post-hoc* test) [52] was applied.

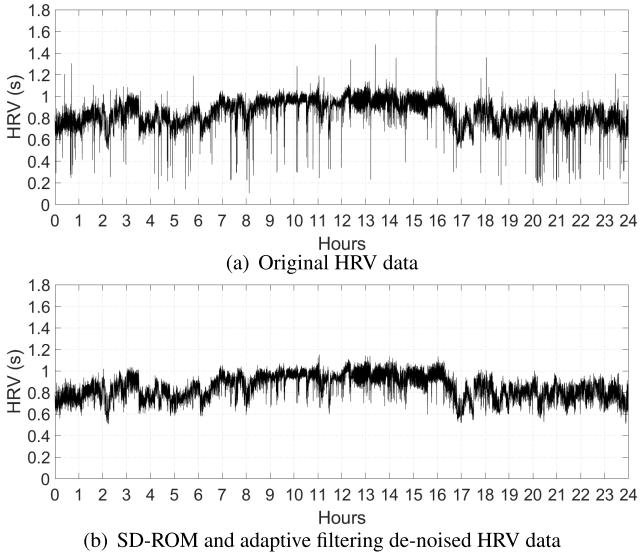


FIGURE 2. An example of the signal-dependent rank order mean (SD-ROM) and adaptive filtering applied to 24-hour HRV data. (a) Original HRV data; (b) SD-ROM and adaptive filtering [28], [29] de-noised HRV data.

III. RESULTS

A. HRV PRE-PROCESSING

Fig. 2 shows the denoising process of HRV abnormalities using SD-ROM and adaptive filters. From the figure part (a), the original HRV data had few peaks above and below the normal range of HRV. Such peaks are considered abnormal (noise) and may affect the observations and analysis of LVEF. These abnormalities could rise due to ectopic beats, arrhythmias, or miss-detection of the peaks in the ECG signal by the annotator. Part (b) shows the filter effect in successfully obtaining the real HRV data of normal beats (normal-to-normal) without any abnormalities. All HRV data were pre-processing and denoised for every hour segment in the 24-hour cardiac cycle prior to feature extraction and further analysis.

B. MISSING HRV FEATURES IMPUTATION

Initially, missing HRV features, as a result of a corrupted recording or an unrecorded hour, on each hour were imputed for the three LVEF groups. An example to show missing values percentages was taken from the dataset for the three LVEF groups based on ACCF/AHA guidelines (Fig. 3(a)). This example roughly shows three ranges for the missing values, namely 5%, 10%, and 20% across the three groups. These missing values were considered to be missing completely at random (MCAR), which means that there are no relationships (dependency) between features across each patient. It is worth noting that the reduced LVEF group had the least number of patients data (8), therefore, missing values percentage was often higher than other groups. For example, 40 missing values in reduced group represent 20% missing values defect, while 40 missing values in the preserved group represent only 2.5%. Therefore, a missing value weighed more in this category compared to the other LVEF categories due to the small sample size. In addition, hour 9:00 AM had a complete dataset for the three groups with no missing values, thus, it was selected as the hour to be used for evaluating imputation techniques.

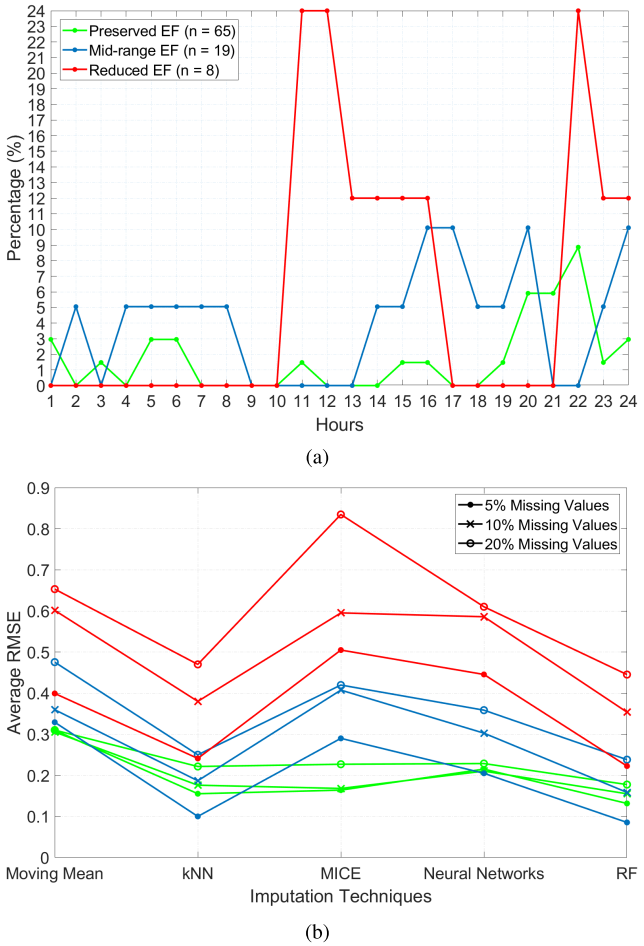
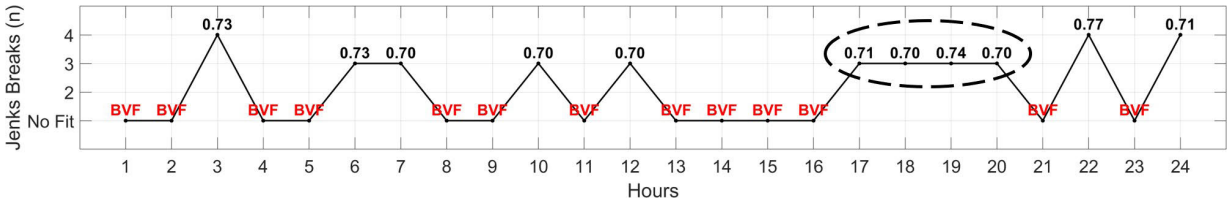
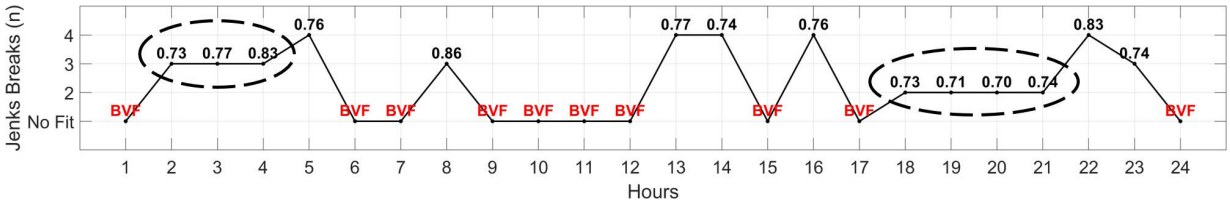


FIGURE 3. HRV feature imputation process to ensure a complete features dataset with no missing values. (a) Percentage of missing values across the 24-hour HRV data for each LVEF patient groups. (b) Average root mean square error (RMSE) for the five data imputation techniques. Three missing values scenarios (Dot: 5%, Cross: 10%, and Circle: 20%) were applied on the preserved (green), mid-range (blue), and reduced (red) LVEF groups to evaluate each technique.

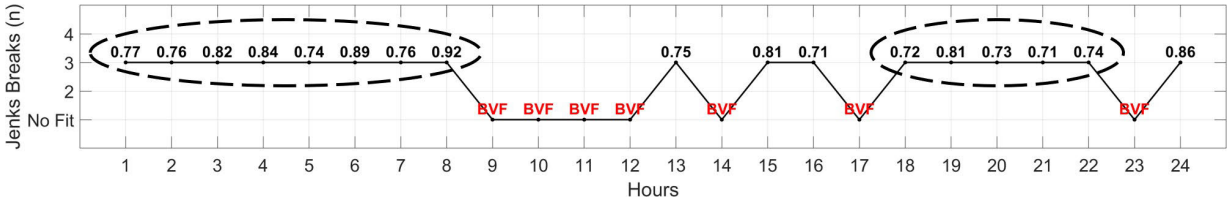
To adjust the dataset to include complete 24-hour HRV features data, several data imputation techniques were applied



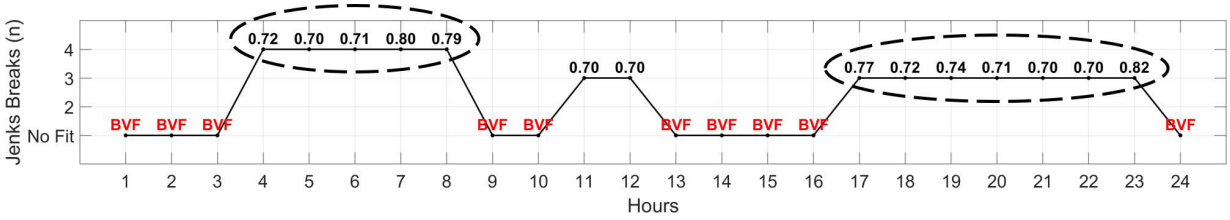
(a) Time-domain: RMSSD



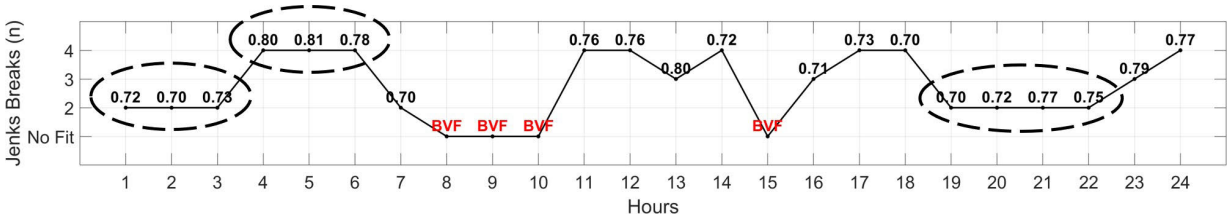
(b) Frequency-domain: HF Peak



(c) Frequency-domain: LF Power



(d) Non-linear: SD2



(e) Fragmentation: PAS

FIGURE 4. **Heart rate variability ejection fraction (HRVEF) grouping using Jenks for selected HRV features. The figure shows the number of Jenks breaks whenever the goodness of variance fit (GVF) have reached ≥ 0.70 for (a) time-domain: RMSSD. (b) Frequency-domain: HF Peak. (c) Frequency-domain: LF Power. (d) Non-linear: SD2. (e) Fragmentation: PAS. Bad variance fit (BVF) was assigned for GVF < 0.70. The dashed circles denote having three or more consecutive ≥ 0.70 GVF.**

(discussed in Section II-C) based on conventional or sophisticated methods. Among these techniques are the moving mean filling, k-nearest neighbour (kNN), multiple imputation by chained equation (MICE), neural networks, and random forest (RF). To decide on which technique to use for HRV missing data imputation, a systematic approach was followed. Initially, an amount of 5%, 10%, and 20% of missing values was introduced to per-hour patients' data from each LVEF group. Then, missing values were imputed using each technique and evaluated through the root mean squared error (RMSE) between the original and the newly imputed dataset. Lastly, the average RMSE value across all HRV features for all patients in every LVEF category was calculated to elaborate on the performance of each technique.

The performance of the data imputation techniques is depicted in Fig. 3(b) for the preserved (green), mid-range (blue), and reduced (red) LVEF groups classified based on the ACCF/AHA guidelines. The figure shows the average

RMSE value using each imputation technique with 5%, 10%, and 20% missing values scenarios. Based on the figure, kNN and RF methods had the lowest error among the three LVEF groups. For the 5% missing values scenario, kNN had error values of 0.16, 0.10, and 0.24 for the preserved, mid-range, and reduced LVEF groups, respectively. On the other hand, the error for these three groups was slightly lower using RF with 0.13, 0.08, and 0.22. For the 10% missing values scenario, the error increased to 0.18, 0.19, and 0.38 using kNN and 0.15, 0.15, and 0.35 using RF for the three groups, respectively. The highest error values were observed for the 20% missing values scenario with 0.22, 0.25, and 0.47 for kNN and 0.17, 0.23, and 0.44 for RF. The highest RMSE values were observed for the reduced LVEF group across all imputation techniques. This is due to the small number of samples (8) in the reduced group as compared to the preserved (65) and mid-range (19) groups.

Based on the observation obtained from the average RMSE of the five data imputation techniques, RF was selected to impute the HRV dataset. The average error values across the three missing values scenarios for preserved, mid-range, and reduced groups were 0.15, 0.15, and 0.34, respectively. These values were less than kNN which had values of 0.19, 0.18, and 0.36 for preserved, mid-range, and reduced groups, respectively. The selection was not only based on the best average RMSE values, but also was due to the ability of RF as a machine learning method to learn from all other features prior to predicting the missing value in the dataset.

C. GENERATING HRVEF GROUPS

1) NATURAL BREAKS OPTIMIZATION

The outcomes of the Jenks natural break optimization algorithm in generating HRVEF groups is shown in Fig. 4 for a feature from every HRV metric including RMSSD, HF Peak, SD2, and PAS features. These features have exhibited a unique pattern in the number of Jenks breaks at specific time periods more than other features. These time periods were mostly during the late-night to early-morning (01:00-08:00) and evening (17:00-23:00) hours, where three or more consecutive GVF values of more than 0.70 were observed. The complete Jenks natural breaks optimization for every HRV features is provided in Supplementary Fig. S1.

From the time-domain, RMSSD had GVF values ranging between 0.70 to 0.74 with three natural breaks during the evening hours. The HF Peak feature from the frequency-domain had close pattern during the evening but with two natural breaks. In addition, three breaks had a better fitting performance during the late-night hours with values in the range of [0.73-0.83]. Furthermore, LF Power returned three natural breaks during the late-night to morning and evening hours with GVF values of more than 0.70. For the non-linear metrics, SD2 had the most continuous pattern with four natural breaks during the early-morning hours and three natural breaks during the evening hours. For the fragmentation metrics, PAS had the best performance with two breaks during the late-night and evening hours and four groups during the early-morning hours. A GVF of more than 0.80 was observed mainly when using four natural breaks.

2) HRVEF GROUPS DISTRIBUTION

The distribution of HRVEF groups based on Jenks natural breaks is depicted in Fig. 5 and 6 for the late-night to early-morning (01:00-08:00) and evening (17:00-23:00) hours, respectively. The complete 24-hour spectrum for every HRV features is provided in Supplementary Fig. S2.

During the late-night to early-morning hours, RMSSD had a close pattern for groups distribution. The HRVpEF group was always determined to be more than 44% LVEF. Furthermore, HRVmEF group ranged between 36% and 44% LVEF percent levels except for hours 01:00, 03:00, and 04:00 where an additional HRVm2EF group was observed. The HRVrEF group ranged between 25% and 35% LVEF levels for almost all the hours. The HF Peak feature had more variability in the decision for groups limits across the hours. The late-night hours (01:00-04:00) suggested three groups with varying HRVmEF group limits of more than 48% LVEF. On the other hand, the early morning hours (05:00-06:00) had four and two groups, respectively. The HRVpEF had a wider range across most hours. Similarly to RMSSD, LF Power had three groups estimation during most of the hours with the HRVmEF group ranging between 36% to 44% except for two early-morning hours where the majority of patients were considered in the HRVrEF group. SD2 feature showed a unique pattern for the HRVmEF groups. The late-night hours had three groups scenario with HRVmEF limits between 35% and 41% LVEF levels. The early-morning hours had four groups with an additional HRVm1EF at high LVEF levels ranging between 73% and 74%. However, the majority of patients had similar HRV characteristics, thus, they were included in the HRVmEF group ranging between 34% and 73%. The last HRV feature, PAS, suggested a two group scenario during the late-night hours with a LVEF range between 25% and 54% for HRVrEF and 54% to 82% for HRVpEF. In addition, early-morning hours had four grouping scenario with the HRVmEF group ranging between 44% and 70% and HRVm1EF ranging between 70% and 71%.

During the evening hours, the distribution of HRFEV groups had close patterns to the one in the late-night to early morning hours using the RMSSD feature. The range of the HRVmEF group was between 34% to 41% for most hours except for hour 22:00-23:00 where an additional HRVm2EF group was needed for patients with 35% to 41% LVEF levels. The HRVpEF had patients with LVEF levels of more than 41% while the HRVrEF had patients with levels of less than 34%. For the HF Peak feature, two groups were essential to divide patients during most hours without exhibiting a unique pattern. Most patients were considered as HRVrEF with levels of less than 55%, while HRVpEF patients were suggested to have more than 55% except for hours 16:00-17:00 and 18:00-19:00. A pattern close to RMSSD was observed for the LF Power feature with three groups at most hours. The range

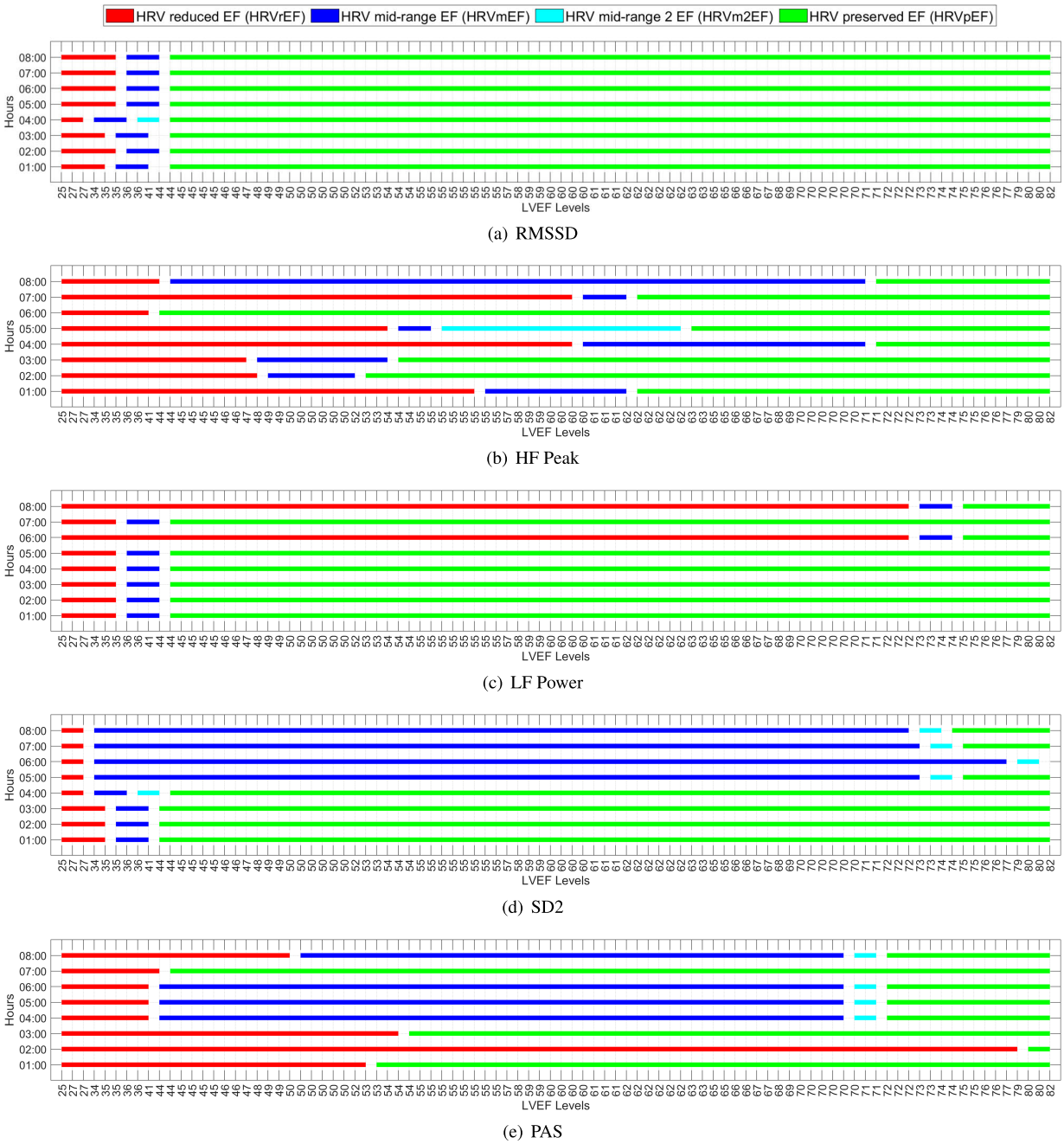


FIGURE 5. **The late-night (01:00-03:00) to early-morning (04:00-08:00) hours distribution of heart rate variability ejection fraction (HRVEF) groups across patients based on Jenks natural breaks.**

for HRVmEF group was between 35% and 44% with values less than 35% for the HRVrEF group and more than 44% for the HRVpEF group. The SD2 feature had three groups scenario across all hours with varying HRVmEF limits. However, it is worth noting that hours 22:00-23:00 covered a wider range of patients within these groups with LVEF values between 55% and 79%. The last feature, PAS, suggested four groups scenario during the 16:00-18:00 time window with HRVm1EF of more than 65% and less than 71%. However, most hour intervals had two group scenarios with HRVpEF patients presenting with LVEF levels of more than 53%.

It is worth noting that the GVF measure was not affected by the total number of samples included in each category, which was shown in Figures 4, 5, and 6. Taking SD2 as an example, in Figure 4d, SD2 had bad variance fitting (BVF) in hours 1-3 even though these hours had widespread of the preserved LVEF group (as in 5d). On the other hand, hours 4-8 had high GVF accuracies of 70-80% in 4d with the widespread being

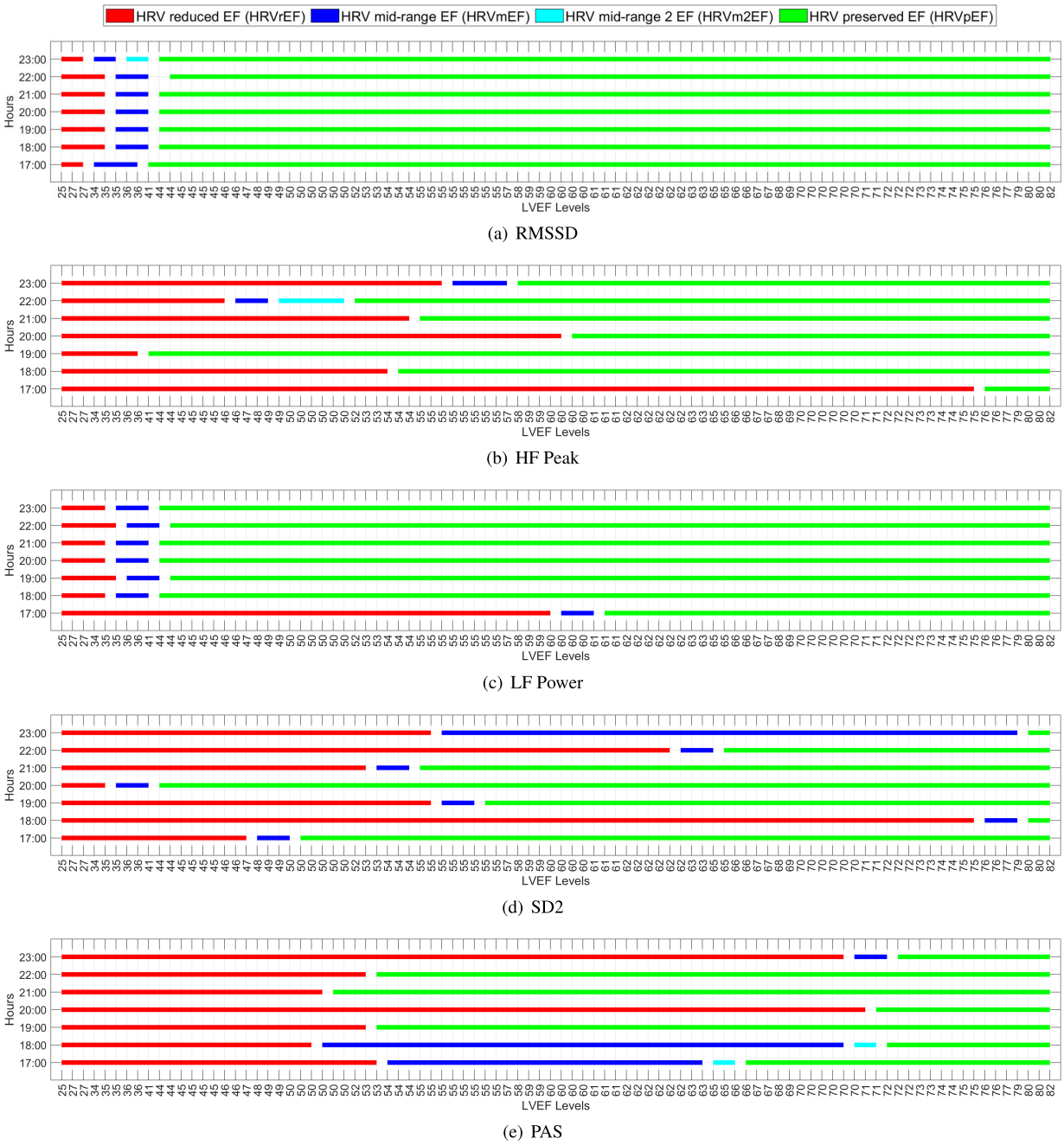


FIGURE 6. The evening (17:00-23:00) hours distribution of heart rate variability ejection fraction (HRVEF) groups across patients based on Jenks natural breaks.

in favor of the mid-range LVEF group as shown in 5d. Therefore, GVF is a measure of clustering separability between the two, three, or four HRVEF categories.

D. STATISTICALLY DISCRIMINATIVE FEATURES

Table 3 shows the values of features during two time periods, early-morning (03:00-04:00) and evening (18:00-19:00), where most significant differences occurred across features. The table shows feature values (Mean ± STD) for ACCF/AHA, ASE/EACVI, and HRV/Jenks guidelines.

Based on ACCF/AHA guidelines, RMSSD showed significant differences between the groups during the late-night (02:00-03:00) and evening (17:00-22:00). In addition, HF Power and LF Power showed similar patterns during the same time periods. However, Alpha1 was only significantly different between 05:00-06:00. On the other hand, following the ASE/EACVI guidelines, RMSSD was significant during the late-night period (02:00-04:00) and bewtwwen 21:00-22:00. Similarly to ACCF/AHA guidelines, HF Power had a similar pattern in the distribution

TABLE 3. HRV features values (Mean±STD) at the most significantly different hours along with the *p*-value for one-way ANOVA test. The table shows features based on the ACCF/AHA, ASE/EACVI, and HRVEF/Jenks categories.

HRV Features		RMSSD		HF Peak		HF Power		LF Power		SD2		Alpha1		PAS	
Significant Hours		03:00-04:00	18:00-19:00	03:00-04:00	18:00-19:00	03:00-04:00	18:00-19:00	03:00-04:00	18:00-19:00	03:00-04:00	18:00-19:00	03:00-04:00	18:00-19:00	03:00-04:00	18:00-19:00
ACCF/AHA															
Mean ± STD	*pEF*	0.03±0.01‡	0.02±0.01‡‡	0.26±0.07	0.25±0.05	154.25±143.27‡‡	140.34±112.04‡‡	565.40±541.06	511.66±374.38‡‡	0.11±0.04	0.11±0.04**	1.37±0.16**‡‡	1.38±0.17*	9.78±11.28	8.50±8.84
	mEF	0.02±0.02¶¶	0.02±0.01¶¶	0.27±0.06	0.28±0.08¶¶	193.48±327.17¶	128.56±162.71¶¶	390.90±393.10¶¶	302.63±305.87¶	0.09±0.04	0.09±0.04**	1.20±0.23*	1.19±0.25*	11.16±6.88	12.74±9.32
	rEF	0.04±0.04¶¶‡	0.05±0.03¶¶‡‡	0.25±0.06	0.21±0.07¶¶	586.81±1003.10¶¶‡	601.83±718.28¶¶‡‡	1260.70±2206.90¶¶	1034.10±1380.70¶‡‡	0.11±0.06	0.11±0.05	1.20±0.20‡‡	1.21±0.12	16.06±7.02	11.18±7.47
ANOVA *p*-value		**0.017**	**8.293x10^{-5}**	0.922	**0.039**	**0.004**	**4.010x10^{-6}**	**0.034**	**0.005**	0.228	**0.060**	**3.741x10^{-4}**	**4.680x10^{-4}**	0.258	0.166
ASE/EACVI															
Mean ± STD	*pEF*	0.03±0.01‡‡	0.02±0.01	0.27±0.07	0.25±0.06	151.19±150.00‡‡	143.16±99.96‡‡	590.07±594.88	533.95±372.42	0.10±0.04	0.11±0.04	1.38±0.16‡	1.36±0.18‡	9.43±11.90	8.80±9.55
	mEF	0.02±0.01¶¶	0.02±0.01¶¶	0.26±0.06	0.26±0.07	140.22±125.11	111.27±136.44¶¶	392.06±263.53	364.32±366.61	0.10±0.05	0.12±0.05	1.32±0.15¶¶	1.38±0.18¶	10.08±7.84	9.80±8.37
	rEF	0.04±0.03¶¶‡‡	0.03±0.03¶¶	0.28±0.07	0.24±0.08	389.33±684.46‡‡	331.55±503.13¶‡‡	790.24±1421.00	602.14±931.27	0.11±0.05	0.10±0.05	1.17±0.23¶¶‡	1.18±0.23¶‡	14.28±7.27	11.45±7.78
ANOVA *p*-value		**0.019**	**0.020**	0.767	0.708	**0.024**	**0.010**	0.301	0.355	0.926	0.338	**9.490x10^{-5}**	**7.180x10^{-4}**	0.186	0.519
HRVEF/Jenks															
Mean ± STD	*pEF*	0.03±0.01$^{\chi}$	0.02±0.01*	0.23±0.07**	0.25±0.06	163.12±198.28‡	137.67±124.28‡	525.93±514.43**	464.38±368.92**	0.10±0.04	0.11±0.04**	1.36±0.16*‡	1.25±0.23	8.47±6.36$^{\chi}$	8.36±8.84‡‡
	mEF	0.04±0.02^{o}	0.06±0.07*¶	0.29±0.07**	NA	1906.80±1498.70¶	1175.40±936.91¶	3627.50±4211.30**¶¶	2345.20±2545.90**¶¶	0.12±0.04	0.19±0.06**¶¶	0.99±0.38*	0.94±0.45^{o}	8.92±7.57^{o}	NA
	m2EF	0.14±0.01$^{\chi o+}$	NA	NA	NA	NA	NA	NA	NA	0.11±0.10	NA	NA	1.38±0.16^{o+}	40.45±30.11$^{\chi o+}$	NA
	rEF	0.02±0.01^{+}	0.03±0.01¶	0.27±0.06	0.21±0.07	146.84±174.36¶‡	257.67±262.94¶‡	471.80±532.76¶¶	597.08±675.13¶¶	0.06±0.02	0.10±0.04¶¶	1.18±0.20‡	1.19±0.20^{+}	16.50±6.70^{+}	12.46±8.59‡‡
ANOVA *p*-value		**1.971x10^{-10}**	**0.017**	**0.027**	0.120	**1.275x10^{-14}**	**1.201x10^{-13}**	**4.978x10^{-8}**	**1.765x10^{-6}**	**0.018**	**3.800x10^{-4}**	**2.860x10^{-5}**	**3.102x10^{-5}**	**6.469x10^{8}**	**0.042**

*: Significant difference between pEF and mEF groups (p-value $<$ 0.01), **: Significant difference between pEF and mEF groups (p-value $<$ 0.05).
¶: Significant difference between rEF and mEF groups (p-value $<$ 0.01), ¶¶: Significant difference between rEF and mEF groups (p-value $<$ 0.05).
‡: Significant difference between pEF and rEF groups (p-value $<$ 0.01), ‡‡: Significant difference between pEF and rEF groups (p-value $<$ 0.05).
$^{\chi}$: Significant difference between pEF and m2EF groups (p-value $<$ 0.01), $^{\chi\chi}$: Significant difference between pEF and m2EF groups (p-value $<$ 0.05).
^{o}: Significant difference between mEF and m2EF groups (p-value $<$ 0.01), ^{oo}: Significant difference between mEF and m2EF groups (p-value $<$ 0.05).
$^{+}$: Significant difference between rEF and m2EF groups (p-value $<$ 0.01), $^{++}$: Significant difference between rEF and m2EF groups (p-value $<$ 0.05).
HRVm2EF: HRV with mid-range 2 EF group (second stage mid-range category).
NA: Not Applicable (only 3 HRVEF categories were determined).

of significant differences across the 24 hours. However, LF Power showed significant differences during the early-morning period (03:00-06:00 and 10:00-11:00 and evening (18:00-19:00). For Alpha1, a significant difference occurred across all hours due to the drop in the values in the HFrEF group.

Compared to ACCF/AHA and ASE/EACVI, using HRVEF groups, RMSSD, HF Power, LF Power, and Alpha1 have exhibited close patterns in their significant differences across hours. This pattern was mostly focused on the late-night (00:00-03:00) to early-morning (04:00-11:00) and evening (17:00-23:00) hours. However, LF Power had a significant difference between the groups during the afternoon hours (13:00-16:00). In contrast to ACCF/AHA and ASE/EACVI, RMSSD showed a high difference between values for HRVm2EF and other groups during the time periods 01:00-04:00 and 22:00-00:00. In addition, Alpha1 exhibited significant differences between HRVm2EF and other groups during the same aforementioned time periods. Additional features were also represented in the figure such as HF Norm, HF Peak, SD2, and PAS. Among these feature, SD2 have showed significant differences during the afternoon (12:00) along with the PAS (12:00-13:00 and 15:00-16:00).

Relative to Jenks clustering, it is worth noting that the significant p-value measures shown in the table reflect the statistical significance between each group separately. On the other hand, Jenks natural break clustering took into account the dataset as a whole in a 1D feature space when iteratively evaluating clusters and reporting GVF results. Therefore, a GVF can be high if the category in between was essential in discriminating between it and the other two groups. For example, HFmEF and HFpEF as well as HFmEF and HFrEF in RMSDD at hour 18:00-19:00 had significant differences as shown in Table 3, however, no significance was observed between HFpEF and HFrEF. Thus, a high GVF was observed using the 1D Jenks clustering algorithm due to the separation ability of HFmEF between it and the other two groups, which matches with the statistical analysis results.

IV. DISCUSSION

This study demonstrated a strong association between LVEF and HRV during specific time periods in the circadian cardiac rhythm. The new index, HRVEF, allowed for multi-time estimations of LVEF throughout the day and night based on the functionality of the heart as represented by HRV features. The results suggest HRV as a promising automated and accurate supplementary tool to the once-off echocardiography test for timely LVEF measurements and heart failure prognosis. Clinically, despite of the reliability of echocardiography in providing accurate LVEF measurements, it is essential to be able of providing an estimation for LVEF levels throughout the day/night cardiac cycles. Thus, a patient may require echocardiography tests as an initial evaluation of his/her LVEF level, then, takes a 24-hour ECG test. This allows to observe cardiac functionality variations throughout the hours correlated with LVEF levels. In addition, in this study, we recommended best time-periods (late-night, early morning, evening) for ECG measurements to categorize and predict LVEF levels with the highest possible accuracy.

Although the Jenks algorithm is most commonly used in choropleth maps clustering, it is interesting to observe its ability in segmenting data for medical applications. Jenks natural breaks and HRV allowed for an expanded view on the distribution of LVEF among CAD patients. Unlike the current LVEF guidelines where a patient is classified based on their echocardiography LVEF level, the Jenks breaks optimization for certain HRV features helped in assigning patients into LVEF groups on an hourly basis. In addition, the optimization was not only based on a three groups scenario, but also indicated that for certain HRV features and time

intervals the patients could be divided into two and four LVEF groups.

The variations in the number of group scenarios across the 24 hours show that a single feature may be observed very similarly across patients with different LVEF levels, thus, resulting in fewer LVEF groups. Taking HF Peak feature as an example, which is a good indicator for the cardiac parasympathetic nerve activity [53], a two groups scenario of HRVrEF and HRVpEF was suggested during the evening time periods (18:00-21:00). Therefore, at these hours, the need for an additional mid-range group was not required. This indicates that there is a greater effect of parasympathetic system modulation of cardiac rhythm in the evening hours and hence a greater difference between postulated groups with less intragroup variance.

However, at other time periods, a wider distribution of patients based on LVEF was observed, leading to higher number of LVEF groups (three or four). An example of this was the LF Power results, that mainly represents the sympathetic branch of the ANS [53], where a three groups scenario was suggested with a $\geq$ 0.70 GVF during the late-night to early-morning (01:00-08:00) and evening (18:00-22:00) hours. Furthermore, features such as SD2 which reflects sympathetic activation [54] and PAS that mainly represents changes in the heart rate acceleration [55] suggested an additional HRVm2EF group due to a greater variability in these HRV features between patients during the early-morning time periods. This indicates that the early morning sympathetic surge affects patients with similar LVEF differently due to some difference in heart mechanics or rhythm generator which is identified by the more sensitive HRV feature.

The analysis of HRV provides information about the overall status of ANS modulation of cardiac rhythm. Although the use of HRV features for estimating LVEF is effective when investigating the effect of the ANS on cardiac rhythm, the relationship between HRV indices and LVEF has not been well defined in CAD patients in the literature. One of the reasons could be that HRV analysis is affected by the presence of cardiac arrhythmias and oscillatory modulations due to sources other than intrinsic cardiac regulation (e.g. SA node) [56]. The observations found in this study highlight the role of the ANS in cardiac rhythm and progression of cardiovascular diseases including heart failure. Our analysis is of interest as it extends findings in [57] which showed that reduced HRV was associated with New York Heart Association (NYHA) functional class, left ventricular end diastolic dimension, reduced left ventricular ejection fraction, and peak exercise oxygen consumption (p-value $<$ 0.05) in all patients. More recently, [58] showed that HRV differentiated patients with symptomatic heart failure and impaired LVEF and patients without heart failure symptoms and normal LVEF. The significance of the findings remained following adjustment for clinical variables including age, sex, creatinine, fasting glucose, CAD, hypertension, diabetes mellitus (DM), dyslipidemia, and the use of beta blockers, calcium channel blockers (CCBs) and angiotensin II receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs) in five different logistic regression models, where medication has been shown not to highly influence the results. Additionally, [59] reported similar findings of noninvasive autonomic features identifying patients with increased risk of hospitalization due to heart failure among clinically stable patients with left ventricular systolic dysfunction, even when adjusting for other clinical parameters including medication. The utility or association of HRV with heart failure is further highlighted by [21], who reported that the mortality risk in post-acute myocardial infarction patients with low LVEF is predicted by indices reflecting decreased HRV or heart rate responsiveness and cardiac parasympathetic dysfunction, whereas in patients without low LVEF, the risk is predicted by a combination of indices that reflect decreased HRV or heart rate responsiveness and indicator that reflects abrupt large heart rate changes suggesting sympathetic involvement [59]. The high accuracy obtained in the current work ($>$ 70% GVF) for categorization of heart failure as well as the statistically significant differences between heart failure categories at known time periods (late-night to early morning and evening) for increased risk of heart attack indicate the importance of this approach.

In the current study, pre-processing of the ECG ensured removal of heart rate artifacts and led to significant findings. High-frequency HRV features (HF Peak, HF Power), SD2, and Alpha1, which are associated with parasympathetic nervous system activities correlated with the degree of LVEF. This was especially the case during the late-night to early-morning (00:00-06:00) and evening (19:00-23:00) time periods, which are high-risk times for cardiac arrest. These findings match the previous observations reported in the literature that suggested time intervals such as 6 pm to 12 am as times of higher mortality due to cardiac infarction [60]. The current findings could open up the possibility of cardiovascular chronopharmacology where HRV provides additional information during specific hourly (diurnal and nocturnal) intervals. In addition, several studies in literature have elaborated on the variability of the cardiac function throughout the 24-hours of the day [12], [60]–[62], thus, specific time-periods (as observed in this study) are usually more preferred for heart failure, CAD, and LVEF assessment.

Relative to the current ACCF/AHA and ASE/EACVI guidelines for heart failure classification based on LVEF, results for HRVEF indicated some changes in the range of accepted heart failure classes based on LVEF classifications. Features such as RMSSD and pNN50 suggested a range for HRVmEF group between 35% $\geq$ EF $\geq$ 44%. This agrees to some extent with the ACCF/AHA guidelines for patients with more than 40% LVEF, however, based on the ACCF/AHA guidelines, few HFrEF patients were assigned to the mid-range group. On the other hand, more patients were in the mid-range category based on ASE/EACVI but these guidelines recommend a range of 50% to 55% for mid-range LVEF, which is significantly different to the HRVEF estimations shown herein. The aforementioned findings show

patients with EF $\geq$ 44% at normal heart functionality during the late-night to early-morning and evening time periods. However, these patients become at-risk of developing cardiac abnormalities leading to heart failure by moving from being HRVpEF to HRVmEF or HRVrEF during the afternoon as seen in the full spectrum of the RMSSD and pNN50 features (Supplementary Figure S2). Both of these features reflect the modulation of the parasympathetic activity and their variations are usually linked to heart failure. For example, lower RMSSD has been shown to be associate with an increase in all-cause mortality [63]. Furthermore, RMSSD variations are mainly due to the fast frequency modulation of the SA-node via the parasympathetic input at about 1-4 beats coupled with a slower sympathetic input between 4-10 beats. Additionally to these features, HF Power and SD1 showed similar results suggesting less activation in the parasympathetic branch at the aforementioned time periods.

In contrast to the ACCF/AHA and ASE/EACVI guidelines where the upper cut-off value for the mid-range group was set at 50% and 55%, respectively, a wider distribution for the HRVmEF group was observed with the SD2 feature during the early-morning (05:00-08:00) time periods. Furthermore, an additional HRVm2EF group was suggested due to the higher variability between patients at higher LVEF levels (EF $\geq$ 70%). The additional group with a LVEF range between 73% to 75% suggests greater force of the heart activity for patients at those levels during early-morning hours and distinguished them from the preserved and mid-range LVEF groups. However, most of the HRVmEF patients (EF $\geq$ 44%) were considered earlier as preserved patients during the late-night (01:00-04:00) hours, which matches the range for the ACCF/AHA guidelines of EF $\geq$ 50%, before they start dividing up in the early-morning. This shows that these patients were possibly not at-risk of a cardiac event associate with heart failure during these time periods as seen from the SD2 feature that reflects sympathetic branch activation, as sympathetic activation usually implies greater risk of a cardiac event. Looking at the overall 24-hour spectrum of this feature, patients started to divide into two groups with the majority being considered as HRVrEF patients before they start returning back during the late-night hours. Knowledge about the at-risk time periods allows for optimal medications to prevent any further development of a cardiac event in the future. Although the PAS HRV feature showed no clear grouping of patients throughout the 24-hour cycle, it had a similar pattern during the early-morning time periods as seen in Supplementary Figure S2, which supports the claim that the early morning is a high-risk time periods for cardiac arrest associated with heart failure.

Comparing the significant differences across LVEF groups based on ACCF/AHA, ASE/EACVI, and HRVEF, the statistical discrimination ability was higher between the HRVEF groups as seen in Table 3. The mid-range group (blue) had a wider difference in values compared to other groups for features such as RMSSD, HF Power, and LF Power, which was not clearly shown in the observations associated with the ACCF/AHA and ASE/EACVI guidelines. In the proposed HRVEF guidelines, greater differences in values were observed for the reduced patients, whereas the patients with rEF had closer values to the preserved group. However, patients in the rEF with very low LVEF values as discussed earlier showed severe symptoms of heart failure that distinguished them from the preserved patients. The more discrimination ability of mid-range patients, the less ambiguity there is in the classification of such patients and the better the treatment and medication process. In addition, the newly introduced HRVm2EF group was found to be significantly different at certain time periods, in contrast to the ACCF/AHA an ASE/EACVI guidelines for LVEF. This may indicate additional information about high functionality of the heart at specific time periods for specific patients [64]. Lastly, to elaborate on the findings of the ANOVA test relative to Jenks natural breaks, for example, the RMSSD feature showed significant difference at hour 19:00 (as shown in Table 3) between HFmEF and the other two categories. Therefore, due to the high variability in this category, it resulted in observing high GVF when clustering the groups using Jenks natural breaks algorithm.

It is worth noting that most of the patients included in this study were male patients from the elderly group who were smokers in general, however, sex and age discrepancies disappeared in an extensive study in [65], and is also less apparent during sleep periods and rather more dependent on type of HRV feature. In addition, smoking mainly influences high frequency (HF-HRV) portion of HRV, but not the LF/HF balance and more within a short time frame (10 minutes) following smoking [66], [67].

V. STUDY LIMITATIONS

Although this study shows strong association between LVEF categories and HRV features at certain time periods, it has a number of shortcomings. The majority of the subjects included in this study were male with mean age of 56 years old. Therefore, future studies may apply additional investigations on the efficacy of HRV categorization of LVEF groups on a more evenly distributed dataset between male and female subjects, as older male subjects were often found more prone to sleep apnea that slightly affects HRV parameters [68]. In addition, while the algorithm was efficient in identifying two, three, and four LVEF categories using hourly HRV features, it should be noted that most of the patients may have taken medications, including beta blockers, anti-arrhythmics, and diuretics, which may affect the autonomic control system. Thus, even though medications may influence HRV and LVEF, further analysis are still required for future studies to address the effect of medications on the distribution of LVEF categories using HRV features. Furthermore, the proposed approach to categorize patients with accordance to their LVEF levels showed high levels of performance (accuracy $\geq$ 0.70) at specific hours in the day/night cycles, however, the predictive accuracy of these estimations needs to be validated on a larger cohort of patients under a longitudinal

follow up study. On the technical part, despite of the successfulness of the imputation techniques used in this study, especially RF, further analysis on actual HRV feature values are required to strengthen the observations. In addition, even though Jenks algorithm was simple, yet efficient, future studies may consider the use of other clustering techniques when applied on HRV features to form HRVEF groups. Thus, providing a wider insight on the usefulness of HRV indices in providing multi-time estimations of LVEF through computerized algorithms. Lastly, future works may also consider providing a complete study over the expenses related to ECG Holter tests to compare with echocardiography for frequent clinical tests. It is usually estimated that a Holter test ranges from 299 USD to 355 USD and an echocardiogram varied from 210 USD to 1830 USD, which may or may not include the cost for the interpretation by the cardiologist [69].

VI. CONCLUSION

This study demonstrated the strong association between LVEF and HRV features by using Jenks natural breaks. It suggests HRV as a promising multi-time tool or framework in estimating LVEF levels in CAD patients as well as as a supplementary tool to current echocardiography-based measurements.

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DECLARATION OF COMPETING INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Mohanad Alkhodari, Herbert F. Jelinek, Leontios J. Hadjileontiadis, and Ahsan H. Khandoker designed research idea. Mohanad Alkhodari performed research, developed data imputation, and provided Jenks natural breaks clustering. Shiza Saleem developed the de-noising approach. Mohanad Alkhodari, Herbert F. Jelinek, Leontios J. Hadjileontiadis, and Ahsan H. Khandoker analyzed data and results. Mohanad Alkhodari wrote the paper. Mohanad Alkhodari, Herbert F. Jelinek, Leontios J. Hadjileontiadis, and Ahsan H. Khandoker edited the paper. All authors agreed on the manuscript.

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