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Association of non-linear dynamics of heart rate variability with all-cause mortality in patients with sarcoidosis

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Abstract. *Background and aim:* Sarcoidosis (Sarc) is linked to increased morbidity and mortality. While 24-hour ambulatory ECG recording is essential for evaluating patients with cardiac symptoms, the complementary role of heart rate variability (HRV) for risk stratification in Sarc patients remains undefined. The aim of this observational study was the assessment of non-linear indices of HRV as independent predictors of mortality in Sarc. *Methods:* 317 patients with confirmed diagnosis of Sarc, underwent comprehensive conventional cardiac testing, including Cardiac Magnetic Resonance (CMR) with late gadolinium enhancement (LGE). These patients were followed up for all-cause mortality as endpoint. Each patient underwent twenty-four-hour Holter monitoring, from which approximate entropy (APEN), short and long-term detrended fluctuation analysis (DFAα1 and DFAα2, respectively), as well as other HRV parameters, were calculated. *Results:* The study recruited 317 patients (137 men, 180 women) with a mean age of 48.22 ± 11.88 years. Over a median follow-up period of approximately 48 months, 17 deaths were recorded. Competing risk analysis revealed that decreased DFAα1 was a robust prognostic indicator for increased total mortality. ROC analysis demonstrated that the area under the curve (AUC) of DFAα1 (< 0.95) for predicting mortality was 0.761 (95% confidence interval (CI) = 0.617–0.905). DFAα1 ≥ 0.95 was associated with total mortality (HR = 0.109, 95% CI = 0.033–0.362, P= 0.0003). *Conclusion:* Evaluation of cardiac autonomic dysfunction by DFAα1 serves as an independent predictor for all-cause mortality in patients with Sarc.

Key words: prediction, all-cause mortality, sarcoidosis

Introduction

Sarcoidosis (Sarc) presents as a systemic disease with a variable course, ranging from benign involvement of a single organ to multi-organ failure and mortality (1). In advanced pulmonary or multiorgan Sarc, ten-year mortality rates can surge up to 9% (2).

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Historically, pulmonary fibrosis, pulmonary hypertension, and involvement of the cardiac, hepatic, or neurological systems have been commonly regarded as the main causes of mortality in Sarc patients. However, the advent of advanced cardiac imaging modalities, such as cardiac magnetic resonance (CMR), has highlighted cardiac causes as significant contributors to mortality, more prevalent than previously reported (3). Previous predictive models for mortality in Sarc primarily focused on respiratory complications, including pulmonary fibrosis and pulmonary hypertension (2,4). These studies consistently indicated that several variables, predominantly respiratory, independently predicted mortality. These variables included pulmonary fibrosis, pulmonary hypertension, age, race, and composite scores employed in other fibrotic diseases. A recent study by Kirkil et al1 on a large cohort of Sarc patients underscored that advanced age, combined with extensive pulmonary fibrosis or pulmonary hypertension, independently predicted mortality. The authors emphasized the unlikelihood of a single variable identifying all patients who would succumb to pulmonary Sarc. Heart rate variability (HRV) indices have emerged as valuable parameters for predicting morbidity and mortality across various diseases (5-8). HRV reflects the interplay between parasympathetic and sympathetic activity and has been used as a simple, noninvasive measure to assess autonomic nervous function (9). Decreased HRV derived from linear analysis of RR intervals indicates subclinical autonomic neuropathy, which can predict the risk of mortality in different diseases (10). Recent research has indicated that methods based on nonlinear dynamics, specifically short and long-term detrended fluctuation analysis (DFAα1 and DFAα2), yield more robust predictive outcomes than classical linear methods of HRV (11,12,13). DFA fractal exponents of heart rate time series have been observed to correlate with autonomic tone. It is noteworthy that HRV tends to decrease with age, primarily due to reduced vagal tone (14-15). Considering that age is one of the variables associated with an increased risk of death in Sarc and that cardiac Sarc is a significant cause of mortality in these patients, we tested the hypothesis that HRV is also associated with outcomes in patients with Sarc. To discern the independent effects of cardiac involvement from those of advanced age on disease outcomes, we analyzed a substantial cohort of patients who underwent comprehensive cardiac assessments, including cardiac CMR.

Methods

Subjects

This observational study included 345 consecutive patients diagnosed with Sarc, based on the consensus statement of the American Thoracic Society, European Respiratory Society (ERS), and World Association of Sarc and Other Granulomatous Disorders (16). These patients were referred to the General Hospital of Chest Diseases "Sotiria," the University Hospital of Alexandroupoli, Attiko, and "Laiko" Hospital between October 2006 and June 2014. The diagnosis was confirmed within 6 months before the initial evaluation. Exclusion criteria comprised known collagen vascular disease, implanted cardiac devices, cardiac dysfunction related to congenital heart disease, heart failure, or coronary artery disease. Patients were excluded from the study either due to the exclusion criteria (n=20) or failure to complete the baseline assessment (n=8).

Data collection

All patients had experienced symptoms for a minimum duration of 6 months; they underwent baseline assessments, including clinical evaluation, 12-lead electrocardiogram, standard exercise test, 24-hou---r ambulatory ECG recording (Holter), and standard transthoracic echocardiography with left ventricular (LV) analysis (17). Cardiac magnetic resonance imaging (CMR) was additionally performed in patients suspected of possible cardiac involvement, following previously described methodology (18). Chest radiographs were evaluated to determine disease stage using Scadding's standard radiographic criteria. Serum levels of serum angiotensin-converting enzyme, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured in the preceding month and were available for all patients. The presence of arterial hypertension, diabetes mellitus, hyperlipidemia, and smoking habits were noted. Each participant's weight and height were measured, and blood pressure was recorded using a standard protocol. The study protocol was approved by the institutional ethics committee of the three hospitals, and informed consent was obtained from all patients, following the principles of the Declaration of Helsinki.

Echocardiography

Echocardiography was performed using a Phillips iE33- Cardiovascular machine and reviewed by experienced operators blinded to the ECG results and clinical status of patients. Standard apical four- and two-chamber and long-axis views were utilized for measurements, including baseline left ventricular end-diastolic diameter (LVEDd), left ventricular end-systolic diameter, left atrial diameter, interventricular septum thickness, left ventricular posterior wall thickness, and left ventricular ejection fraction (LVEF), according to the guidelines of the American Society of Echocardiography.

Holter recordings and analysis

Holter ECG was obtained using a high-resolution (1000 Hz) digital 3-lead monitoring system (Synescope, ELA Medica, France). All ECG recordings were transferred to a computer for analysis, with patient characteristics and outcome data concealed. Each beat was first automatically labeled as normal or aberrant by the Holter analysis software, and then carefully edited by an expert analyst. Annotated RR time series were transferred to a personal computer using dedicated software (ELA Medical Syneflash) and processed based on previously described criteria. ECGs were analyzed only if recordings were eligible for at least 18 hours. The number of premature ventricular complexes (PVC) and the presence of Non-Sustained Ventricular Tachycardia (NSVT) during the 24-hour recording were noted. NSVT was defined as more than three consecutive beats of ventricular premature contractions.

HRV

Long-term HRV (typically 24 h) measurements were conducted according to international guidelines, using the freely available Kubios HRV software (Version 2.2) (19). Time and frequency domain as well as nonlinear HRV components were analyzed, based on the series of normal-to-normal RR intervals. Five time-domain indices were measured, including the standard deviation of all normal-to-normal RR intervals in the entire recording (SDNN), the mean of the standard deviations of the normal RR intervals in all 5-min segments in the entire 24-hour recording (SDNN index), and the mean of the standard deviation of the averaged normal-to-normal RR intervals in all 5-min segments of the 24-hour recording (SDANN index) to represent autonomic function. Additionally, the root mean square of successive differences in normal RR intervals and the percentage of differences between adjacent normal-to-normal intervals >50 ms (pNN50) were considered to be markers of parasympathetic tone. Frequency-domain HRV analysis was based on the estimation of power spectral density, and the ratio of the 24-hour low-frequency ([LF] 0.04–0.15 Hz) to the high-frequency power ([HF] 0.16–0.40 Hz) was calculated to represent the sympathovagal balance. The nonlinear properties of HRV were analyzed by entropy and DFA. Approximate entropy (ApEn) reflected the logarithmic likelihood that two sequences that were similar (within a tolerance r) for m points remained similar on incremental comparisons (20). In the DFA method, long-range correlations between interbeat intervals separated by several beats were detected by investigating the scaling behavior of the heartbeat fluctuations on different time scales, disregarding trends and non-stationarities in the data18. The fractal structure of the heart rate was quantified by estimating a short-term ($\alpha 1$, short-term fluctuations, obtained from the range $4 \leq n \leq 16$) and a long-term ($\alpha 2$, long-term fluctuations, obtained from the range $16 \leq n \leq 64$) scaling exponent by DFA, as previously (13).

Follow-up and endpoints

Follow-up occurred every 6 months through contacting by telephone and/or was verified by accessing medical records. The endpoint was all-cause mortality.

Statistics

Baseline dichotomous demographic, clinical, and laboratory characteristics were compared between survivors and non-survivors using the chi-square or Fisher's exact test, as appropriate. The normality of continuous numerical data in each group was assessed using the Kolmogorov-Smirnov test. Continuous variables were compared using the t-test or Mann-Whitney test, when the assumption of normal distribution was rejected. Each continuous variable was subsequently converted into a binary categorical variable by splitting the values into two

groups based on a well-established cutoff point or median value when the cutoff point was not clearly defined in the existing literature. The association of ECG findings with all-cause mortality was assessed by Kaplan–Meier survival analysis and log-rank test. Further analysis of the A1index values and A1 expressed dichotomously (> or< 0.95 as used elsewhere) was done with stepwise backward logistic regression versus survival and with Receiver Operation Characteristic (ROC). The observation period began when an individual with Sarc was first referred to our outpatient cardiology clinic for further investigation. Survival time (in months) from the initial date of observation to the occurrence of death, loss of follow-up, or the end of the study period was recorded for each patient. Survival time was censored on December 31st, 2018, or at the time a patient was lost to follow-up. Additional univariate Cox proportional-hazards models for each potential prognostic factor were constructed to calculate the unadjusted 5-year mortality risk. Multivariate analysis was not feasible due to the relatively small number of deaths observed during the follow-up period. Results were considered statistically significant if the p-values were less than 0.05.

Results

In this observational prospective cohort study of consecutive individuals with Sarc, the five-year all-cause mortality was nearly 6% (17/317). The main causes of death were severe cardiac manifestations in 40% and revere respiratory failure due to fibrosis in 20% of patients, pulmonary infections in 20% and the rest died due to cancer. A comparison of demographic, imaging, clinical, and laboratory characteristics revealed that patients who did not survive the follow-up period were older (median age 66 vs. 49 years), had a longer disease duration (median duration 4.5 vs. 1.5 years), were more likely to show a gadolinium enhanced pattern in CMR (LGE), were treated with oral steroids, presented with more comorbidities like diabetes mellitus (DM) and dyslipidemia compared to those who survived. Clinical and echocardiographic screening for possible cardiac Sarc revealed elevated serum B-type natriuretic peptide (BNP) levels, left atrial (LA) size, interventricular septum (IVS) and posterior wall (PW) thickness, pulmonary artery systolic pressure (PASP, through tricuspid valve regurgitation, indicative of possible Pulmonary Hypertension) (all p-values < 0.01), and left ventricular end-systolic volume (LVESV) (p=0.022) among the non-survivors compared to survivors. Regarding 24-hour Holter ECG monitoring parameters, lower values of SD2, Lmax, DET, A1, D2, SD24, LF24PER (all p-values < 0.01), and LFHF24 (p=0.012) and a higher SD1/SD2 ratio (p < 0.001) were associated with mortality. Furthermore, a higher proportion of non-survivors presented paroxysmal atrial fibrillation (PAF) or more severe ventricular arrhythmias (Lown categories 4A and 4B) during baseline 24-hour Holter ECG monitoring compared to survivors (all p-values < 0.01) (Table 1). Competing risk analysis revealed that decreased DFAα1 was a robust prognostic indicator for increased total mortality. ROC analysis demonstrated that the area under the curve (AUC) of DFAα1 (< 0.95) for predicting mortality was 0.761 (95% confidence interval (CI) = 0.617–0.905). DFAα1 ≥ 0.95 was associated with total mortality (HR = 0.109, 95% CI = 0.033–0.362, P = 0.0003).

Statistical analysis revealed higher mortality for patients with an elevated SD1 to SD2 ratio (≥ 0.11 (units)), low Lmax (< 705 (units)), low DET (< 99.4 (units)), low A1 (< 1.28 (units)), or the presence of serious ventricular arrhythmias (Lown Category > 3) in 24-hour Holter ECG monitoring, or those with an elevated echocardiographically-measured PASP (≥ 40 mmHg) (all p-values < 0.05). Logistic Regression among the aforementioned prognostic factors, low A1 and increased PASP were associated with higher unadjusted hazard ratios for death, estimated by univariate Cox proportional hazards regression analysis [HR (95% CI): 64.76 (1.16-3608.4) for A1 < 1.28, and 28.73 (9.95-82.94) for PASP ≥ 40 mmHg]. This result collectively shows that increased systolic pulmonary artery pressure contributes to the fatal outcome along with autonomic dysfunction.

Discussion

This study assessed non-linear heart rate variability (HRV) measures, especially the short-term fractal scaling exponent (DFAα1) in patients with Sarc. The latter emerged as a powerful predictor of mortality, surpassing conventional HRV assessments. This finding accompanies the evidence on a possible intricate relationship between pulmonary involvement, cardiac manifestations, and mortality in Sarc.

Table 1. Descriptive characteristics of all patients (n=317), alive (n=300) and deceased (n=17) Group

Parameters	Total Population (n=317)	Alive Group (n=300)	Deceased Group (n=17)	Significance
Sex (F/M)	180/137	169/131	11/6	0.618
Age (years)	48.78±12.4	47.9±11.66	64.06±15.69	**0.001**
BMI (kg/m^2)	28.1±5.05	27.92±5.02	31.93±4.51	**0.021**
Disease Duration (years)	3.79±5.77	3.76±5.76	4.51±6.16	0.689
Arterial Hypertension	71	63	8	**0.013**
Diabetes Mellitus	38	29	9	**0.0001**
Hyperlipidemia	90	81	9	**0.012**
Current Smoking Habit	69	67	2	0.546
Current Cortisol Treatment	123	112	11	0.066
Gadolinium (+) in Cardiac MRI (LGE)	134	123	11	**0.05**
SACE (Serum Angiotensin Converting Enzyme)	54.41±33.24	55.47±33.12	18.43±7.84	**0.028**
Ejection Fraction (%)	60.18±3.65	60.39±3.67	56.57±6.32	**0.042**
Systolic Arterial Pressure (mmHg)	122.91±12.23	122.92±11.91	125.5±17.07	0.512
Diastolic Arterial Pressure (mmHg)	78.68±6.84	78.83±6.74	77.00±7.15	0.446
Heart Rate Variability				
Mean Heart Rate (BPM)	78.03±9.58	77.99±9.28	83.5±14.06	0.052
pNN50	7.25±8.61	7.19±8.62	9.09±9.33	0.476
RMSSD	29.6±17.69	29.35±17.67	34.79±19.68	0.321
SDNN	124.17±37.88	126.41±36.88	78.31±31.00	**0.0001**
LF/HF	4.25±2.82	4.35±2.84	2.18±1.8	**0.002**
ApEN	1.07±0.12	1.07±0.12	1.05±0.12	0.416
DFA_1	1.24±0.22	1.26±0.20	0.87±0.21	**0.0001**
DFA_2	1.05±0.12	1.05±0.11	1.04±0.16	0.711

Abbreviations: SACE: Serum Angiotensin Converting Enzyme, SDNN: Standard deviation of the NN (R-R) intervals, NN50: number of pairs of successive NN (R-R) intervals that differ by more than 50 ms, PNN50: proportion of NN50 divided by the total number of NN (R-R) intervals, LF: low frequency, HF: high frequency, ApEN: Approximate entropy, DFA: Detrended Fluctuation Analysis, RMSSD: Root Mean Square of Successive Differences.

The research involved a substantial cohort of biopsy-proven Sarc patients, who underwent comprehensive HRV assessment at the initial visit and were closely followed for a period of 5 years. Notably, the findings not only confirm the previous data linking impaired pulmonary function with the long-term prognosis of Sarc but also expand our understanding by delineating an association between specific non-linear dynamics derived from heart rate variability (SD1/SD2 ratio, Lmax, DET and A1) and all-cause mortality in Sarc patients. The study reveals the possible clinical significance of identifying certain arrhythmias, such as premature atrial contractions (PAF) or ventricular arrhythmias (Lown categories >3), during the baseline 24-hour Holter electrocardiogram (ECG) monitoring, as these were found to be associated with an increased risk of mortality. Consistent with earlier research, the study underscores the perturbed nature of HRV in Sarc patients, independent of the disease severity or the chosen treatment modality (22-24). By focusing on a sizeable group of asymptomatic Sarc patients, the study provides valuable prognostic insights into the role of heart rate analysis in identifying individuals at a heightened risk of mortality, beyond the traditional clinical and imaging parameters. Of particular significance is the finding that the

reduced short-term scaling exponent, DFAα1, can predict mortality even in patients with Sarc who do not exhibit any signs of myocardial involvement or clinically overt neurosarcoidosis. The advancements in modern computerized techniques have enabled a more accurate estimation of beat-to-beat variability in heart rate, spanning from seconds to even 24 hours, allowing for the derivation of both linear (time and frequency domain) and non-linear HRV indices. This technological development has facilitated the non-invasive evaluation of autonomic nervous system (ANS) function through the assessment of sympathetic and parasympathetic integrity (25-27). The pivotal role of the autonomic nervous system in regulating the intricate interplay between respiration and circulation is well recognized. Dysregulation of the ANS has been documented in various pathological conditions, including autoimmune diseases like diabetes (28,29), multiple sclerosis (31,28), rheumatoid arthritis (32-34), systemic lupus erythematosus (35), and scleroderma (36). This dysregulation is linked to an increased risk of mortality in patients with comorbidities such as diabetes mellitus, hypertension, congestive heart failure, and coronary artery disease, primarily due to the propensity of autonomic imbalance to predispose individuals to cardiac arrhythmias (37-40). Several studies have also highlighted the connection between ANS dysfunction, as indicated by heart rate variability behavior, and inflammation (41,42), potentially providing a plausible explanation for the association of HRV indices in Sarc patients with mortality, independent of the chosen therapy and the duration of the disease. The findings from this study are consistent with earlier research that has reported an association between Sarc and ANS dysfunction (22-24). For instance, Tiran et al (24), in their comparative study of 12 Sarc patients and controls, reported a decrease in the high-frequency component of the power spectrum in HRV, possibly indicating reduced parasympathetic tone or a blunted cardiac response to vagal modulation. Similarly, Uslu et al (23) suggested a reduction in HRV in patients with systemic Sarc compared to the control group, with more pronounced changes observed in patients with cardiac Sarc. Aktop et al (22) also demonstrated the presence of diurnal fluctuations in HRV in Sarc patients, particularly the night-time LF/HF values, suggesting heightened sympathetic activation in these patients. However, the existing literature does not definitively clarify whether the observed HRV abnormalities are solely related to autonomic dysfunction in Sarc or are indicative of myocardial involvement in the disease process. The incorporation of cardiac magnetic resonance (CMR) scans in this study showed that patients presented with the presence gadolinium enhanced pattern in CMR (LGE), during the long follow up had a fatal outcome (Table 1). It is well known the correlation of LGE uptake as a surrogate marker of fibrosis with mortality in heart failure, in myocarditis and in sarcoidosis (3). Despite the advancements, none of the previous studies had explicitly aimed to demonstrate the predictive role of heart rate variability indices concerning all-cause mortality, nor did they delve into the examination of non-linear parameters, such as detrended fluctuation analysis. The detrended fluctuation analysis method, which assesses the qualitative characteristics and correlation features of heart rate behavior, has been shown to offer valuable insights into the fractal scaling properties through HRV analysis, particularly with regard to mortality prediction (43) Notably, a growing body of evidence has emerged, highlighting the prognostic power of short-term fractal scaling properties, analyzed using the DFA technique. In line with this, the current study's findings reveal that the fractal analysis of HRV, especially the short-term fractal scaling exponent (DFAα1), which captures the qualitative fluctuation patterns of the heart rate, can effectively predict both cardiac-specific and all-cause mortality. These findings are in agreement with prior studies that have indicated an increased risk of mortality and life-threatening arrhythmias in patients, both with and without structural heart disease, based on DFA1 (44-49). Furthermore, in non-cardiac populations, the DFA1 value has been proposed as a specific risk marker for cardiac death and has shown a significant association with overall mortality (42,43). A noteworthy limitation of this study is the relatively small number of deaths, which may have affected the statistical power of the analyses. Additionally, the potential influence of diabetes, either directly or as a consequence of treatment with steroids in severe cases of Sarc, may have contributed to the observed mortality rates in the study population. Factors such as diabetic cardiovascular autonomic neuropathy and micro-macrovascular complications of diabetes mellitus could have influenced the mortality outcomes, although the lack of comprehensive data on the degree of glycemic control precludes further detailed

analysis in this context. Moreover, another limiting factor arising from the small number of deaths was the inability to calculate the median survival time; means were calculated instead, as recommended in the relevant literature (50). Finally, multivariate analysis was not feasible due to the relatively small number of deaths observed during the follow-up period. Univariate analysis showed that increased pulmonary artery systolic pressure and autonomic dysfunction were among the most important factors for a fatal outcome. Nevertheless, it is elusive if there is a relationship between these two factors and further studies are needed to address this query. In conclusion, this study contributes to our understanding of the complex interplay between impaired pulmonary function, cardiac implications, and mortality in Sarc. By highlighting the predictive significance of nonlinear heart rate variability measures, particularly the short-term fractal scaling exponent (DFAα1), this study provides valuable insights into the prognostic assessment and risk stratification in Sarc patients. Furthermore, the study sheds light on the role of the autonomic nervous system in various pathological conditions, including Sarc, underscoring the potential link between HRV indices and mortality, independent of the therapeutic approach and the duration of the disease. The inclusion of detrended fluctuation analysis further strengthens the prognostic value of HRV analysis in identifying patients at a higher risk of adverse outcomes. While the study's limitations call for caution in the interpretation of the findings, they also warrant further investigations to comprehensively unravel the intricate associations and potential clinical implications for the management of Sarc patients.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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