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Research Article

# Decoding the Risk: Heart Rate Variability as a Powerful Predictor of Sudden Cardiac Death in Chronic Hemodialysis Patients—A 36-Month Prospective Study

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## Abstract

**Introduction:** This study aimed to estimate the impact of the C-reactive protein (CRP), serum albumin, lipids, and heart rate variability (HRV) on sudden cardiac death (SCD) in chronic hemodialysis patients (CHPs) to derive the strongest predictor for SCD.

**Methods:** In this prospective study, 90 CHPs, average age 59.2 ± 11.4 years, were observed over a three-year follow-up period to detect SCD. HRV, with a focus on standard deviation of normal-to-normal intervals (SDNN), was measured using a 12-channel ECG. Peripheral blood samples were obtained from all participants, followed by routine blood tests: urea, creatinine, lipid status, hemoglobin, hs-CRP, albumin, and calcium - phosphorus product.

**Key Findings:** The mean SDNN was 107.97 ± 24.51 ms. Among CHPs, SDNN was significantly lower in deceased patients (79.20 ± 14.84 ms) compared to survivors (106.91 ± 23.09 ms, P = 0.0097). The mean survival time for SCD was 34.8 ± 5.3 months. Cox regression coefficients b (-0.1146, 0.1224, 0.0781, and 0.0934), hazard ratio (HR) (0.8917, 1.1303, 1.0812, and 1.0979), and *p*-value (0.042, 0.203, 0.680 and 0.378) for SDNN, hs-CRP, albumin and hemodialysis (HD) duration, respectively, showed strongest predictive impact for SCD of HRV (SDNN) covariate, with hazard rate rising by 1.12145 (12.45%) for every single unit decrease of SDNN. Receiver operating characteristics (ROC) analyses for SDNN were as follows: area under the curve (AUC) = 0.835 (P < 0.001), with a cut-off value of ≤84 ms (sensitivity 80.0%, specificity = 83.53%). AUC results for covariate albumin (AUC = 0.542, P = 0.766), CRP (AUC = 682, P = 0.204), and HD duration (AUC = 0.558, P = 0.717) did not reach significance in predicting the risk for SCD.

**Conclusion:** HRV proved to be a robust and independent predictor of sudden SCD in CHPs, with HR increasing by 11.48% for each unit decrease in SDNN (ms). In contrast, hs-CRP, serum albumin, lipids, and HD did not demonstrate a statistically significant effect on SCD risk prediction in CHPs.

**Keywords:** heart rhythm variability, standard deviation of normal-to-normal intervals, sudden cardiac death, chronic hemodialysis patients, Holter electrocardiography

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## 1. Introduction

Patients in the advanced stage of chronic kidney disease (CKD), particularly those in the terminal stage (ESRD), face four- to 20 times the risk of sudden cardiac death (SCD) compared to the general population (GP) [1]. SCD is responsible for one in four deaths and is the leading cause of overall mortality [2]. Hemodialysis (HD) patients experience an annual mortality rate of approximately 20%, and cardiovascular (CV) disease is the leading contributor to these deaths [2, 3].

Although traditional factors like high blood pressure, hypercholesterolemia, diabetes, smoking, excess weight, and a sedentary lifestyle contribute to atherosclerosis and are linked to the risk of SCD in the GP, they do not explain the markedly elevated risk observed in patients undergoing chronic HD [4].

The conventional understanding of disease pathophysiology based on established cardiac risk factors seems insufficient to account for the extent of SCD risk in chronic hemodialysis patients (CHPs). Instead, various unique cofactors and exposures seem to play a role in determining risk in this population [5].

Patients suffering from ESRD are characterized by elevated sympathetic activity and disturbances in cardiac autonomic function, measurable through changes in heart rate variability (HRV) [6, 7]. HRV refers to the measurement of variations in the interval between successive heartbeats, and its value is obtained by determining the value of standard deviation (SD) of the intervals between nodes (SDNN) [8, 9]. SDNN captures the full range of cyclical elements contributing to fluctuations during the recorded period, thus indicating overall variability [9]. Calculating SDNN over a 24-hour period provides more accurate results compared to shorter monitoring durations, such as 5-minute (short-term) or < 5-minute (ultra-short-term) intervals often used in biofeedback sessions [10-13].

Moreover, patients undergoing chronic HD face a higher risk of persistent inflammation caused by the artificial nature of the dialysis membrane and procedure, vascular access complications, infections, and various coexisting health conditions. C-reactive protein (CRP), an acute-phase inflammation marker, and serum albumin, an indicator of nutritional status, are valuable factors predicting morbidity and mortality in CHPs [14, 15].

Inflammation, either independently or by exacerbating autonomic dysfunction and sympathetic reactivity, may serve as a trigger in cases of abnormal myocardium, potentially leading to arrhythmias and resulting in sudden death [15, 16]. Inflammation, oxidative stress, disrupted calcium or phosphate balance, lipid metabolism abnormalities (such as the LDL/HDL cholesterol ratio), and hypertriglyceridemia, which are common in HD patients, may contribute to coronary artery atherosclerosis and SCD [16, 17].

The aim of this prospective study was to achieve three primary aims: 1. to assess correlation between demographic and laboratory biomarkers with HRV, 2. to assess the impact of CRP, serum albumin, lipids, and HRV on SCD in CHPs over a 36-month observation period and to derive the strongest predictor for the SCD by Cox proportional hazards model, and 3. to calculate the critical cut-off level of the strongest predictor which would be the most suitable for the risk stratification of SCD.

## 2. Patients and Methods

### 2.1. Patients

In this prospective and observational study, we examined 90 CHPs (59 male and 31 female) from two dialysis centers, during a 36-month follow-up period from March 2016 to February 2019, with an average age of 59.2 ± 11.4 years, and an average body mass index (BMI) of 23.93 ± 3.55 kg/m$^2$. Out of the sample, 21 patients (23.3%) were smokers, 40 (44.4%) had hypertension, and 18 (20%) had diabetes.

The median duration on chronic dialysis therapy was 4.25 (2.0 to 6.0) years with tailored HD sessions of 4-5 hours, three times a week. A low-flux synthetic membrane was utilized, and bicarbonate dialysate was administered at a flow rate of 500 mL/min, to achieve a Kt/V ≥1.2 (1.273 ± 0.346). Participants had to be over 18 years of age and have undergone HD for a minimum of 6 months to meet the inclusion requirements. Exclusion criteria included a HD frequency other than three times per week, diagnosed malignancies, severe hematological disorders, cirrhosis, degenerative conditions, severe psychiatric disorders, signs of CV events (such as stroke, heart attack, or peripheral artery disease), and confirmed malignant arrhythmias occurring within 6 months prior to the initiation of the study. Informed written consent was obtained from all participants, and the study received approval from our institution's ethics committee. We extracted disease and demographic details from patient charts, including age, weight, height, hypertension, diabetes, smoking status, and other conditions that may impact HRV and the cardiovascular system.

Holter electrocardiography (ECG) measurements of SDNN and laboratory tests were conducted at baseline and subsequently at 6-month intervals over the course of 3 years. The mean of the repeated measurements was used for analysis. In this way, we provided more recent results for the patients with SCDs which occurred at the end of the study. Each patient was observed from baseline over a period of 3 years for any occurrence of a lethal event diagnosed as SCD. It is typically characterized as a sudden, natural, and unexpected fatal cardiac incident that happens within an hour from the appearance of symptoms. This definition also includes cases of death with no clear non-cardiac origin in patients who were clinically stable within the 24 hours prior to the event [18-20].

### 2.2. Assessing HRV

We used Contec TLC5000 Holter 12 channels 24h ECG monitor for personal computer software analyzer FDA&CE (Shenzhen Senshao Technology Co., Ltd. Guangdong, China). We evaluated HRV parameter at about the same time of the day, due to circadian variation in autonomic cardiac function. We performed a detailed evaluation of HRV, ensuring adequate data quality by examining the highest and lowest heart rates, as well as circadian HRV derived from hourly average heart rate values. To assess HRV, we reviewed the histogram of heart rate intervals and the time series plot of inter-beat interval variation. We used time domain HRV as a less sensitive method to scan errors [19], calculation that included the mean node to

node (N-N) interval, average heart frequency, the gap between the longest and shortest NN interval, and the difference in heart rate observed during night and day [19, 21]. We presented the results for HRV as SDNN in milliseconds (ms). The measurement was performed between hemodialysis sessions.

### 2.3. Clinical and Biochemical Parameters

Peripheral blood samples were taken from all patients, and routine blood tests, including hemoglobin, urea, creatinine, lipid panel, serum albumin, calcium-phosphorus product (Ca x P), and high-sensitivity CRP (hs-CRP), were analyzed with routine laboratory procedures and equipment.

### 2.4. Statistical Analysis

Data analysis was performed using MedCalc for Windows version 19.1.3 (MedCalc Statistical Software, MedCalc Software Ltd, Belgium). The data are provided as mean ± SD, interquartile range (percentiles) with median, frequency, or percentage. An unpaired *t*-test was used for normally distributed variables, and the Mann-Whitney U test for non-normally distributed variables between survivors and non-survivors. To examine the associations between HRV and demographic as well as clinical variables, point-biserial correlation was used for binary and continuous variables, and bivariate Pearson's/Spearman's correlation was applied for continuous variables, depending on the data distribution. Kaplan-Meier survival analysis was used to calculate survival rates. To identify independent determinants and predictors of SCD, Cox regression hazard analysis was utilized. To determine cut-off values and classify patients as survivors or non-survivors of SCD, receiver operating characteristic (ROC) curve analysis was carried out. A *p*-value below 0.05 was regarded as statistically significant.

## 3. Results

### 3.1. Demographic and Clinical Parameters

We enrolled 90 CHPs (59 male, or 65.6%, and 31 females, or 34.4%) with mean age 59.2 ± 11.4 years, average BMI of 23.93 ± 3.55 kg/m$^2$, and a median HD of 4.25 years. Twenty-one patients (23.3%) were smokers, 40 patients (44.4%) had hypertension, and 18 patients (20%) had diabetes. The maximum and mean follow-up period was 36 and 30.3 ± 10.2 months, respectively, with five (5.5%) SCD deceased patients, or 24 deaths (26.6%) from all-cause mortality. The survival period of survived CHPs was 4–36 months or 34.8 ± 5.3 months.

A 24-hour Holter monitoring ECG analysis and biochemical laboratory test were successfully conducted on all 90 CHPs. The mean SDNN was 107.97 ± 24.51 ms in CHPs ≥40 years but 105.37 ± 23.54 ms in patients <50 years. In CHPs ≥50 years it was 98.82 ± 20.06 ms, and in CHPs ≥60 years it was 90.02

± 14.19 ms (P <0.0001). The mean SDNN in diabetic CHPs was 106.11 ± 23.75 ms, compared to 102.18 ± 23.03 ms in non-diabetic patients (P = 0.529). The median HD duration in survived CHPs was 4 years, compared to 5 years in deceased patients (P = 0.664). The study group was predominantly male, with normal (i.e., healthy) BMI of 23.93 ± 3.55 kg/m$^2$. The median hemoglobin level of 113 g/L was within the target range for maintenance hemoglobin (100–115 g/L) for CHPs, following the Kidney Disease Improving Global Outcomes (KDIGO) criteria [21]. A median LDL to HDL cholesterol ratio value of 1.9 indicates an average risk of CV disease. The median, mean, and standard deviation (SD), numbers (N), percent (%), range (min – max), and 25$^{th}$ to 75$^{th}$ percentiles for other demographic and laboratory parameters are shown in Table **1**.

**Table 1**: Demographic and clinical parameters and their correlations with HRV in studied patients.

| **Variables** | **Mean ± SD** | **Min - Max** | **Correlation with HRV (SDNN)** | |
|---|---|---|---|---|
| | **Median** | **25$^{th}$ to 75$^{th}$ P** | **r (ρ)** | **P** |
| Age, yr | 59.2 ± 11.4 | 29 - 84 | -0.708 | < **0.0001** |
| BMI, kg/m$^2$ | 23.93 ± 3.55 | 16.8 - 35.4 | -0.005 | 0.966 |
| Hypertension, N (%) | 40 (44.4) | | -0.212 | **0.045** |
| Diabetes, N (%) | 18 (20) | | 0.034 | 0.749 |
| Smokers, N (%) | 21 (23.3) | | -0.309 | **0.003** |
| Sex, male N (%) | 59 (65.6) | | 0.005 | 0.963 |
| Hemodialysis duration, yr | 4.25 | 2.0 to 6.0 | -0.313 | **0.003** |
| Hemoglobin, g/L | 113 | 99.0 to 121.0 | -0.129 | 0.224 |
| Urea, mmol/L | 20.0 | 17.6 to 24.5 | -0.040 | 0.706 |
| Creatinine, μmol/L | 732.6 ± 203.4 | 90.4 - 1268.0 | 0.134 | 0.207 |
| Cholesterol, mmol/L | 4.0 | 3.4 to 5.0 | -0.004 | 0.968 |
| HDL -cholesterol, mmol/L | 1.15 | 3.47 to 4.21 | -0.105 | 0.326 |
| LDL -cholesterol, mmol/L | 2.2 | 1.5 to 2.8 | 0.039 | 0.712 |
| Triglycerides, mmol/L | 1.43 ± 0.61 | 0.4 - 3.9 | -0.092 | 0.390 |
| LDL/HDL cholesterol ratio | 1.9 | 1.4 to 2.8 | 0.140 | 0.187 |
| hs - CRP, mg/L | 6.0 | 6.0 to 12.0 | -0.373 | **0.0003** |
| Albumin, g/L | 38.72 ± 5.08 | 20.0 - 49.9 | 0.219 | **0.038** |
| Ca x P, mmol/L | 2.995 | 1.82 to 4.10 | -0.012 | 0.913 |
| HRV (SDNN), ms | 107.97 ± 24.51 | 58.7 - 178.0 | / | / |
| Survival (months) | 34.8 ± 5.3 | 4.0 - 36 | 0.298 | **0.004** |

The results are expressed as: mean ± SD (standard deviation), median, min - max, 25th to 75th P (percentiles), N (number) and % (percent). SDNN: Standard deviation of node-to-node intervals, HRV: Heart rate variability, yr: year, BMI: Body mass index, HDL: High - density lipoprotein, LDL: Low - density lipoprotein, hs-CRP: high – sensitivity C - reactive protein, Ca x P: Calcium - Phosphorus product.

## 3.2. Unpaired *t*-Test of SDNN Intervals

Comparing the results from the SDNN intervals between the two subgroups (the group with or without SCD) we found statistically significant difference between them (P = 0.0097, test statistic t = -2.643). The value of SDNN in the deceased CHPs is significantly lower compared to the survivors (79.20 ± 14.84 ms, vs. 106.91 ± 23.09). The interval with 95% confidence (CI) for the mean SDNN in surviving CHPs ranged from 101.925 to 111.887 ms, while the 95% CI for the mean SDNN in CHPs who died from SCD was lower, ranging from 60.775 to 97.625 ms.

## 3.3. Unpaired *t*-Test and Mann-Whitney U Test of Demographic and Clinical Variables

In Table **2**, we present a comparative analysis of demographic and clinical variables between survivors and non-survivors. Our findings indicate a statistically significant difference in LDL-cholesterol levels and SDNN between the two groups. No statistically significant differences were observed for other demographic variables, including age, BMI, hypertension, diabetes, smoking status, and gender, or clinical variables such as urea, creatinine, total cholesterol, HDL-cholesterol, LDL/HDL ratio, hs-CRP, albumin, and calcium-phosphate (Ca x P) product. The *p*-values indicating statistical significance, as well as the mean, median, and interquartile range ($25^{th}$ to $75^{th}$ percentiles), are detailed in Table **2**. This comprehensive comparison highlights key differences in LDL-cholesterol and SDNN while confirming the absence of significant variation in other measured parameters across the two groups.

**Table 2**: Comparison of demographic and clinical variables between survivors and non-survivors.

| Variables | Survivors (N = 85) | Non-survivors (N = 5) | P |
|---|---|---|---|
| Age, yr | 60.52 ± 11.96 | 58.87 ± 12.37 | 0.765 |
| BMI, kg/m$^2$ | 23.78 ± 3.67 | 21.39 ± 4.34 | 0.164 |
| Hypertension, N (%) | 37 (43.52) | 3 (60) | 0.474 |
| Diabetes, N (%) | 16 (18.82) | 2 (40) | 0.252 |
| Smokers, N (%) | 20 (23.53) | 1 (20) | 0.857 |
| Sex, male N (%) | 56 (65.88) | 3 (60) | 0.789 |
| Hemodialysis duration, yr | 4 (2 - 6) | 5 (1.75 - 11) | 0.664 |
| Hemoglobin, g/L | 113 (99 - 121) | 101 (83 to 117.25) | 0.286 |
| Urea, mmol/L | 20.0 (17.07 - 24.55) | 22.5 (19.57 - 24.3) | 0.413 |
| Creatinine, µmol/L | 709.97 ± 212.69 | 793.4 ± 97.76 | 0.388 |
| Cholesterol, mmol/L | 4.1 (3.37 - 5.12) | 3.6 (2.95 - 3.77) | 0.072 |
| HDL - cholesterol, mmol/L | 1.2 (0.8 - 1.63) | 1.0 (0.85 - 1.1) | 0.463 |
| LDL - cholesterol, mmol/L | 2.3 (1.67 - 2.9) | 1.6 (1.17 - 1.9) | **0.035** |

**Table 2**: Continued.

| Variables | Survivors (N = 85) | Non-survivors (N = 5) | P |
|---|---|---|---|
| Triglycerides, mmol/L | 1.41 ± 0.57 | 1.84 ± 1.19 | 0.130 |
| LDL/HDL cholesterol ratio | 1.88 (1.5 - 3.03) | 1.9 (1.19 - 1.99) | 0.428 |
| hs - CRP, mg/L | 6.0 (6 - 12) | 12 (6 - 24) | 0.099 |
| Albumin, g/L | 38.29 ± 4.85 | 37.02 ± 4.37 | 0.569 |
| Ca x P, mmol/L | 2.62 (2.28 - 4.08) | 4.8 (3.7 - 5.2) | 0.127 |
| HRV (SDNN), ms | 106.91 ± 23.09 | 79.20 ± 14.84 | **0.0097** |
| Survival (months) | 36 ± 0.0 | 16 ± 12.06 | <**0.0001** |

The results are expressed as: mean ± SD (standard deviation), median, 25th to 75th P (percentiles), N (number) and % (percent). yr: year, BMI: Body mass index, HDL: High - density lipoprotein, LDL: Low - density lipoprotein, hs-CRP: high - sensitivity C - reactive protein, Ca x P: Calcium - phosphorus product, HRV: Heart rate variability, SDNN: Standard deviation of node to node intervals.

A notched box and whisker diagram of SDNN interval values in two subgroups presents: mean, range, 25$^{th}$ and 75$^{th}$ percentiles, and 95% CI for the mean and outside value. The results of *t*-test of unpaired data (test statistic *t* and *p*-value) are shown in Figure **1**.

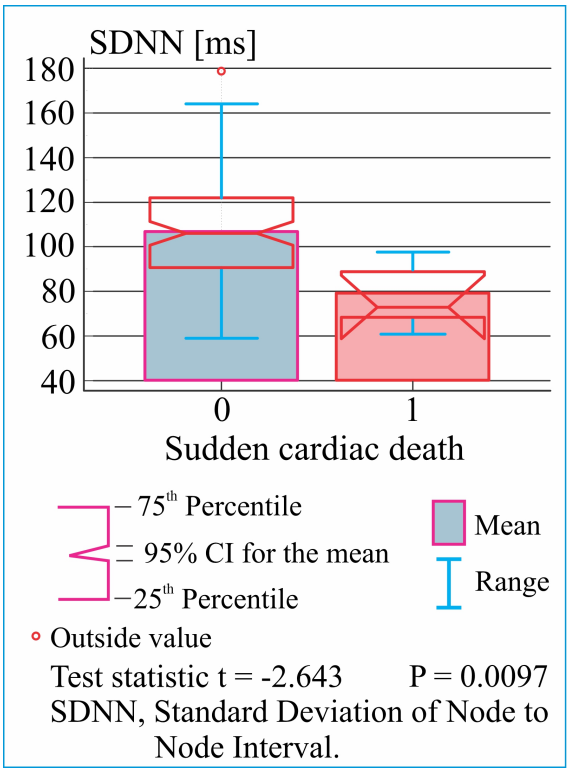


**Figure 1**: A notched box plots of the SDNN intervals in two subgroups according to the SCD (*t*-test for unpaired data).

## 3.4. Point-Biserial and Bivariate Pearson's/Spearman's Correlation Analysis

The strength of association between the variables listed in Table **1** and the direction of their relationship with HRV is calculated by point-biserial and Pearson or Spearman correlation analysis. The results obtained are represented as *r*, *ρ*-values. The statistical significance of these associative connections is represented by *p*-value. There was a statistically significant and inverse relationship between HRV and age ($r = -0.708$, $P < 0.0001$), HRV and hypertension ($\rho = -0.212$, $P = 0.045$), HRV and smoking status ($\rho = -0.309$, $P = 0.003$), HRV and HD duration ($r = 0.313$, $P = 0.003$), and between HRV and hs-CRP ($r = -0.373$, $P = 0.0003$). Statistically significant, but positive correlation, was found between HRV and albumin levels ($r = 0.219$, $P = 0.038$), HRV and low albumin levels (albumin < 38 g/L, N = 39 CHPs, $r = 0.412$, $P = 0.010$), and between HRV and survival ($r = 0.298$, $P = 0.004$).

## 3.5. Outcomes and Survival Analysis

Over the span of 36 months, 24 deaths due to all-cause mortality were reported: four (16.6%) from myocardial infarction, two (8.3%) from pulmonary edema, three (12.5%) from heart failure with fluid retention, three (12.5%) from stroke, two (8.3%) from arrhythmia, and a total of five (20.83%) from arrhythmia, sepsis, ketoacidosis, carcinoma of the urinary bladder, and diabetic coma (one case each). Additionally, five (20.83%) deaths were attributed to SCD, accounting for the largest proportion of deaths in this cohort.

The mean survival period in survived CHPs in Kaplan-Meier all-cause mortality estimator was 30.28 ± 10.18 months, but the mean survival period in survived CHPs in the same estimator for SCD mortality was 34.8 ± 5.3 months. A statistically significant variation ($P = 0.0002$) was noted in the survival periods of surviving CHPs, based on the cause of death (all-cause vs. SCD). The time continuum of lethal events (SCD) occurred in the following order from baseline to 36 months: $4^{th}$, $8^{th}$, $14^{th}$, $19^{th}$, and $35^{th}$ months. The solid red line in Figure **2** shows a Kaplan-Meier survival curve, depicted as a series of horizontal steps, each representing a decline in survival probability corresponding to the occurrence of five SCD in CHPs, gradually approaching the true survival function. The 95% CI is displayed with two thinner orange dashed lines. The number of CHPs at risk for each 5-month interval is shown below the horizontal (x-axis) of the time. The percentage of survival probability is shown on the vertical (y-axis) of the coordinate system.

## 3.6. Cox Proportional-Hazards Model

In the Cox regression model, we carefully selected variables based on statistical significance to avoid multicollinearity. Due to the strong correlation between age and SDNN ($r = -0.708$, $P < 0.0001$), age was excluded from the final model to ensure stability and prevent model overfitting. Alternative models with both variables included were tested, but the final model focused on SDNN and other relevant predictors, given its more stable contribution to the outcome.

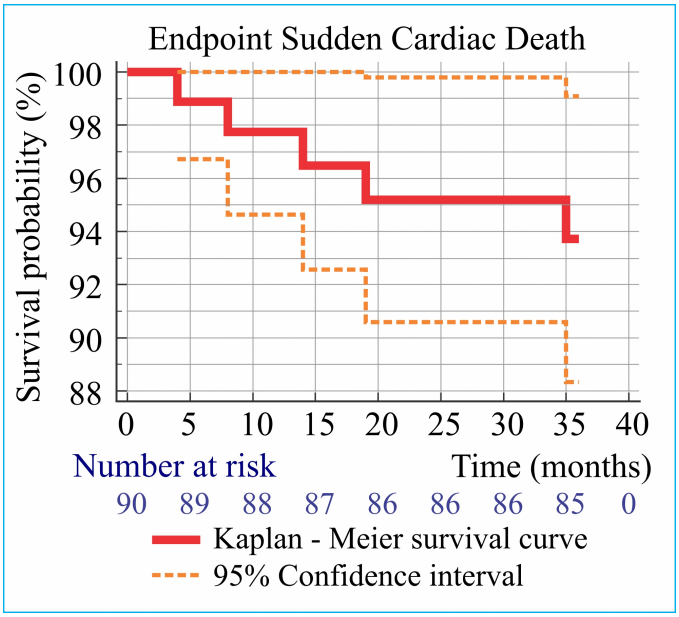


**Figure 2**: Kaplan - Meier estimates of SCD survival in CHPs.

Following the Cox regression analysis, the covariates that remained in the model after applying backward stepwise selection were HRV (SDNN), CRP, albumin, and HD duration. Based on the exclusion criterion of P > 0.7, the remaining variables were not included in the regression model for analysis. Table **3** displays the findings from the Cox regression analysis, including the regression coefficient (b), standard error (SE), Wald statistic, hazard ratio (HR), and 95% CI of HR for independent predictors of SCD outcome.

**Table 3**: Cox proportional - hazards regression model in detection of predictors for sudden cardiac death in CHPs.

| **Cox proportional - hazards regression** | | | | | | |
|---|---|---|---|---|---|---|
| Method | | Backward | | Number of events | | 5 |
| Enter variable if P < | | 0.05 | | Total numbers | | 90 |
| Remove variable if P > | | 0.7 | | | | |
| **Overall model fit** | | | | | | |
| Null model -2Log Likelihood | | | | | 23,249 | |
| Full model -2Log Likelihood | | | | | 13,192 | |
| Chi - squared | | | | | 10,057 | |
| Significance level | | | | | **P = 0.039** | |
| **Coefficients and standard errors** | | | | | | |
| Covariate | b | SE | Wald | P | HR | 95% CI of HR |
| SDNN | -0.1146 | 0.0564 | 4.1344 | **0.042** | 0.8917 | 0.7985 to 0.9959 |
| CRP | 0.1224 | 0.0961 | 1.6227 | 0.203 | 1.1303 | 0.9362 to 1.3646 |
| Albumin | 0.0781 | 0.1894 | 0.1698 | 0.680 | 1.0812 | 0.7458 to 1.5673 |
| HD Duration | 0.0934 | 0.1059 | 0.7777 | 0.378 | 1.0979 | 0.8921 to 1.3512 |

Variables with P > 0.7 were not included in the model: hemoglobin, urea, creatinine, low - density lipoprotein/high - density lipoprotein cholesterol ratio, and calcium - phosphorus product. HR: Hazard ratio, SDNN: Standard deviation of node-to-node intervals, CRP: C - reactive protein, HD: hemodialysis, SE: Standard error, CI: Confidence interval.

A negative regression coefficient (b = -0.1146) for SDNN as a covariate indicates a decreased hazard (HR = 0.8917), meaning that an increase in SDNN is associated with a reduced risk of SCD and an increase in survival time. The HR coefficient for HRV (SDNN) is 0.8917, indicating a decrease in risk with increasing SDNN. However, when interpreting the reciprocal (1/0.8917), the risk increases by 1.12145 (12.145%) for every single unit decrease in SDNN (ms), as shown in Table **3**. We confirm this statement with a probability of 99.958% (P = 0.042). The SCD risk prediction on a larger CHP mass reaches 1.0041 to 1.2523 (CI). The impact of CRP, albumin, and HD in prediction of SCD risk has no statistical significance ($P \geq 0.05$). The highest Wald value (4.13, or $b^2/SE^2$) for SDNN covariate confirms its strongest predictive impact for SCD.

In Cox regression analysis, the covariates hypertension, BMI, and smoking status did not show statistically significant value in predicting the risk of SCD. Their negative "b" regression coefficients (-1.9049, -0.3358, and -0.4090) showed that by increasing the value of covariates (hypertension, BMI, and smoking), the value of SDNN decreases with survival time, and thus the risk for SCD increases, but statistically insignificant (0.152, 0.059, and 0.726), respectively. Of all demographic variables, diabetes is the only covariate with statistically significant value in predicting the survival time and SCD in our cohort of CHPs (P = 0.020, b = -2.9634, Wald = 5.4066, and HR = 0.05164). Nevertheless, the verified Cox-model showed no statistically significant difference between demographic variables (covariates) hypertension, BMI, smoking, and diabetes in predicting survival and SCD (Overall Model Fit: Chi-squared = 9.263, P = 0.055).

## 3.7. Estimation of Cut-off Point

We evaluated all 90 CHPs to differentiate between those with and without SCD (SCD = 1, N = 5 and SCD = 0, N = 95) using ROC curves, a diagnostic test tool, to determine the sensitivity and specificity of potential predictors such as SDNN, serum albumin, CRP, and HD in assessing SCD risk. The results of ROC curve analysis for HRV (SDNN) in prediction of SCD were as follows: area beneath the curve (AUC) = 0.835, 95%CI = 0.742 to 0.905, z statistic = 3.836, standard error = 0.0874, $P < 0.001$, Youden index = 0.6353, associated criterion $\leq$ 84 ms, sensitivity 80.00%, and specificity = 83.53%.

The ROC curve for HRV (SDNN) as an indicator of SCD risk is shown in Figure **3**.

Each data point on the ROC curve represents a specific sensitivity and specificity pair for a given HRV (SDNN) threshold in detecting SCD. The SDNN cut-off value was $\leq$84 ms. Youden Index (J) = 0.6353 defines the maximum potential effectiveness of a biomarker (SDNN). The potential effect of the biomarkers serum albumin, CRP, and HD in prognosis for SCD risk is shown by J index: $J_{albumin}$ = 0.2706, $J_{CRP}$ = 0.3412, and $J_{HD}$ = 0.2824. The composite image, depicting three ROC independent curves for serum albumin, CRP, and HD as prognostic markers for the event, is presented in Figure **4**.

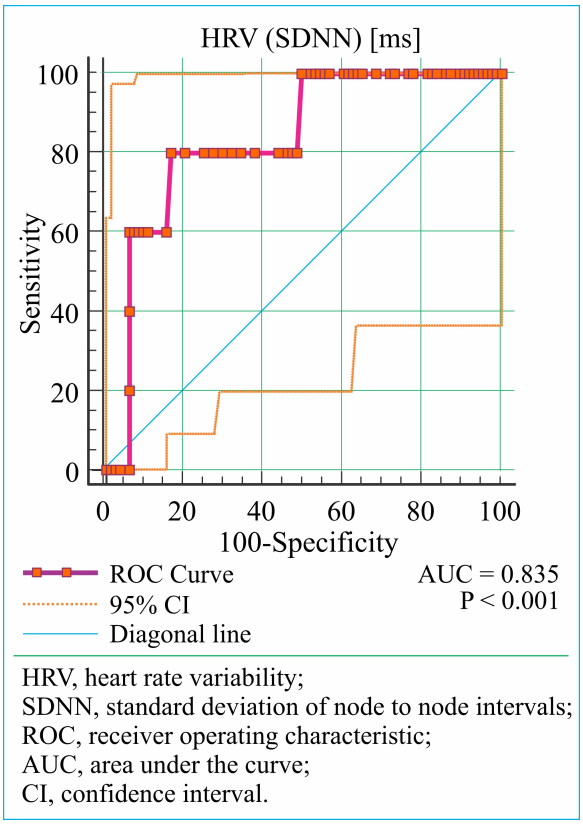


**Figure 3**: Receiver operating characteristics curve for HRV (SDNN) as predictor of SCD.

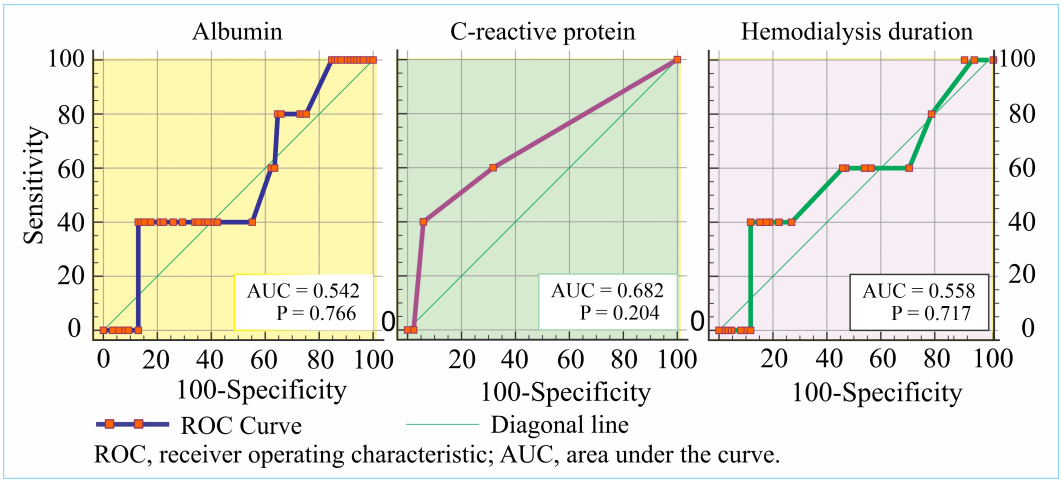


**Figure 4**: Receiver operating characteristics curve for albumin, CRP, and HD duration as predictor of SCD.

The higher the AUC coefficient, the greater the area above the diagonal line, which indicates a stronger predictive value for the SCD event. The results of pairwise comparisons of the three ROC curves revealed no important difference between the serum albumin and CRP curves (P = 0.268, difference between areas = 0.140), between serum albumin and HD (P = 0.855, difference between areas = 0.016), and between CRP and HD (P = 0.376, difference between areas = 0.124). However, a significant difference was found between SDNN and HD (P = 0.038, difference between areas = 0.277). The associated criterion (ac) with

sensitivity/specificity (s/sp) results for albumin, CRP, and HD were: ac ≤ 32.4 g/L, s/sp = 40.0/87.06%; ac > 12 mg/L, s/sp = 40.0/94.12%, and ac > 10 years, s/sp = 40.0/88.24%, respectively.

Considering the value of P for statistical significance, the covariates serum albumin (P = 0.766), CRP (P = 0.204), and HD (P = 0.717), did not show statistical significance (P ≥ 0.05) in predicting the risk for SCD, in contrast to the statistically significant prediction (P < 0.001) of strong independent predictor HRV (SDNN).

## 4. Discussion

Most of the noninvasive risk assessment studies in CHPs explored the outcome by different diagnostic approach. Some predicted the SCD based on left ventricular hypertrophy (LVH) as a predictor [22, 23], others of SCD predicted by two independent predictors, HRV and LVH [24], or of all-cause [25] and CV mortality [8] predicted by HRV, or of SCD by prediction of signal-averaged ECG [26], others by outcome measure of all-cause mortality and SCD by prediction of baroreflex effectiveness index [27, 28], and some by outcome measure of SCD predicted by prolonged QT interval [28].

Our study is one of the rarest (if not the only) that examines the predictive impact of HRV (SDNN) and some traditional and non-traditional risk factors on SCD in CHPs. The aim of this prospective observational study was to evaluate the impact of CRP, serum albumin, lipids, and HRV on SCD in CHPs and determine the strongest predictor and its critical cut-off level for optimal risk stratification over a 36-month period.

### 4.1. Basic and Comparative Results for HRV (SDNN)

The results of Kida et al. [13] for the mean HRV (SDNN) as a predictor of death in survived and deceased HD patients after major adverse cardiac and cerebrovascular event (MACCE) are very close to the results of our study, which are 78.3 ± 31.2 ms vs. 79.20 ± 14.84 ms for deceased CHPs after MACCE and SCD, and 102.1 ± 31.7 ms vs. 106.91 ± 23.09 ms in survived patients from Kida et al. and our study, respectively. Due to the lack of other relevant studies examining HRV (SDNN) as a predictor in SCD, the comparison of SDNN value was made with a lethal outcome from another study, but still with cardiac etiology of outcomes.

The SDNN value is lower in those who are deceased compared to the survivors. Similar to other studies [8, 11, 24, 25, 29, 30], both in this study and others, a reduced SDNN value is linked to an augmented risk of both all-cause [25] and CV mortality [8].

The CHPs with diabetes had a lower SDNN value than patients without diabetes, but this difference was not statistically significant. Diabetes mellitus is most frequently linked to autonomic dysfunction resulting from damage to the microvasculature, which leads to a distinct form of autonomic dysfunction known

as diabetic autonomic neuropathy (DAN). DAN destabilizes sympatho-vagal balance, makes changes to the HRV, and shortens the SDNN [31].

In their 2020 study [32], Yalim et al. examined 79 CHPs and reported HRV (SDNN) values of 105.5 ± 7.02 ms in 39 normotensive patients and 127.6 ± 6.2 ms in 40 patients who experienced recurrent hypotension episodes during the interdialytic period. The average SDNN value for the group of 50 normotensive CHPs in their study closely aligns with our research findings.

## 4.2. The Factors Associated with HRV Indices

The HRV (SDNN) result obtained in our study is in statistically significant inverse correlation with age, hypertension, smoking status, HD, and hs-CRP. SDNN showed a significant positive correlation with serum albumin levels and survival time.

With respect to age, SDNN is known to decrease with normal aging [33, 34]. In our study it decreased by 6.5–9 ms per decade of age (40 - 50 - 60 years interval). In addition, a statistically significant correlation of age with SDNN was found ($P < 0.0001$).

The blood pressure level is inversely correlated with HRV in CKD [35] and in the GP, even in children with hypertension [36]. The results of our study showed statistically significant inverse correlation between HRV (SDNN) and hypertension, as well. HRV has become a noninvasive method for quantitatively assessing cardiac autonomic dysregulation in hypertension. Research has shown reduced HRV in individuals with hypertension, with a correlation between HRV and blood pressure observed across a broad spectrum of blood pressure levels [37].

A statistically significant inverse correlation of smoking with SDNN interval as measure of HRV has been proven in Thio et al. [35] and our study. Smoking seems to exert a systemic dysautonomic effect by affecting both the sympathetic and parasympathetic branches of the visceral nervous system, leading to a decrease in the DNN interval [35].

Despite the established statistically significant inverse correlation of SDNN with HD, we did not prove a statistically significant difference in HD in survived and deceased CHPs. Kida et al. [13] conducted a study on 90 HD patients, did not reveal a statistically significant difference in HD among patients with or without MACCE. Their results are close to those of our study. However, the group with lower SDNN experienced significantly more MACCE compared to the group with higher SDNN, which means that the group with higher SDNN interval value during 24-hour Holter ECG showed a significantly higher survival rate [13]. It is commonly thought that chronic dialysis raises the risk of MACCE and SCD, especially in older patients, and patients suffering from diabetes, hypertension, and malnutrition, and is emphasized by the reduction of the SDNN interval [38].

Känel et al., who explored the associative links of inflammatory biomarker with HRV, showed significant inverse relationship between SDNN and hs-CRP, nearly all of the HRV measures [39], results that are

very close to the associative relationship of hs-CRP and SDNN in HRV analysis in our study. Wu et al., conducted a study exploring the relationship between markers for nutrition and HRV parameters in CHPs. They found a statistically significant positive correlation between HRV and inadequate nutritional health, as indicated by albumin levels in the serum below 38 g/L [40]. Their observations resemble those seen in malnourished CHPs in our study, as well as the positive correlation between serum albumin and HRV observed in the entire sample.

## 4.3. Survival, Cox-Regression Analysis and Prognostic Value of HRV

Patients with ESRD receiving chronic HD treatment face a notably high mortality rate, with CV issues being the primary cause. SCD accounts for most fatalities, comprising 20-30% of all deaths in the study cohort [41]. In our study, there were five cases with SCD (20.83%) which is approximately identical to the percentage of deaths in other studies [36, 39-41].

SDNN is considered the “gold standard” for assessing CV risk when measured during a 24-hour period [42]. Reduced SDNN, reflecting imbalances between sympathetic and parasympathetic control of the heart—such as increased sympathetic tone or parasympathetic (vagal) withdrawal—have been linked to an elevated risk of SCD [43].

Although CKD frequently coexists with coronary artery disease (CAD), SCD is also highly common in dialysis patients who do not have a history of CAD or reduced left ventricular ejection fraction [44]. Our study did not provide data about CAD presence and left ventricular ejection fraction percentage, which did not affect the assessment of the real correlation between the prevalence of SDNN and SCD.

Based on the Cox proportional-hazard regression analysis for independent predictors of SCD, the covariates retained in the model included only HRV (SDNN), CRP, albumin, and HD. The HRV (SDNN) interval, as a covariate with a negative regression coefficient, was associated with an increased hazard and reduced survival time. HR increases by 1.1148 (11.48%) with each 1 ms decrease in SDNN. As the SDNN value decreases, the risk of SCD increases. The mean SDNN value is significantly reduced in the deceased CHPs compared to the survivors ($P = 0.0097$). This parameter has been shown to be a strong marker for predicting SCD in the CHPs, with lower values indicating a higher risk [25]. In some studies [8, 25], the median SDNN value in deceased CHPs of SCD is so low that it reaches up to 53 ms vs. 79.2 ms in other studies caused by MACCE [13]. These indicated that the reduction of SDNN interval is an independent prognostic marker of these events. Systemic hypertension, hyperparathyroidism, increased cardiac output resulting from anemia, and neuroendocrine systems activation have all been shown to disrupt the balance between the sympathetic/parasympathetic nervous systems, contributing to a shortening of the SDNN interval and an increased risk for SCD [8, 13]. CRP, albumin, and the duration of HD did not demonstrate a statistically significant effect on predicting SCD risk. CRP and serum albumin

have a more predictive effect on CV mortality, as shown in other studies [45]. In their study, the authors concluded that CRP and serum albumin are strong independent predictors of overall and CV mortality in dialysis patients [45]. Due to the multicollinearity between age and SDNN, age was not included in the Cox regression analysis.

Diabetes is the only covariate from all demographic variables with statistically significant value in predicting the survival time and SCD in our cohort of CHPs. A significant proportion of dialysis patients have diabetes, which, along with chronic uremia, often results in autonomic neuropathy. This condition causes changes in autonomic regulation, leading to a persistent increase in sympathetic tone, which has been shown to be proarrhythmic and elevate the risk of SCD [3, 24, 31, 46].

### 4.4. Cut-off Point of SDNN Interval in Predicting SCD

The threshold value for the SDNN interval in predicting SCD was 84 ms. Scientific literature provides insufficient data to establish normal range and pathological HRV across different patient groups. HRV (SDNN) cut-off values vary significantly based on age, sex, the presence of heart disease, the classification and phase of the disease, and environmental factors. Apart from variations in pathologies, identifying normal versus pathological findings is challenging in any patient cohort (whether CHPs or the GP) using a single cut-off value [47]. Due to the lack of studies investigating SDNN interval in predicting SCD among CHPs, we will compare other population groups with different diseases in predicting lethal outcomes. La Rovere et al., established SDNN cut-off values for predicting CV death, identifying the range of 70 to 105 ms as indicative of low to well-preserved HRV [48]. The SDNN cut-off value in our study (84 ms) was similar to their value [48], and to the cut-off results in Malik et al., as well, where the range is 50 to 70 ms [49].

The potential effect of the biomarkers cut-off values for serum albumin, CRP, and HD on the SCD is negligible, that is, without statistical significance of their AUC in the ROC curve analysis, for albumin, CRP, and HD, respectively. HRV (SDNN) was determined to be a statistically significant ($P < 0.001$) and a strong independent predictor of SCD in CHPs.

## 5. Conclusion

We conclude that HRV significantly and inversely correlates with age, hypertension, smoking, HD, and with hs-CRP, but positively correlates with serum albumin and survival time. The mean value of SDNN is significantly lower in the deceased than in the survived CHPs. Reduction of SDNN interval is an independent prognostic marker of SCD. The examined covariates, CRP, serum albumin, lipids, and HD did not reveal statistically relevant impact in predicting the risk of SCD in CHPs. Diabetes, the only

covariate of demographic variables, significantly predicts survival time and SCD in CHPs. HRV is a reliable and strong independent predictor of SCD in CHPs, with HR increasing by 12.145% for each unit decrease of SDNN (ms). The threshold value of SDNN period in predicting SCD risk is 84 ms, which is suitable for the risk stratification of SCD in CHPs. Considering that HRV is a powerful and independent prognostic factor of SCD in CHPs, future research could enhance the prediction of HRV-based CV events by incorporating additional Holter ECG parameters that more precisely assess HRV, such as the number of consecutive NN intervals that differ by more than 0.050 seconds throughout the recording [50, 51].

## 6. Strengths and Limitations

One of the main advantages of this study is its rare research topic, detection of HRV impact on SCD in CHPs. The strength of this study is in the HRV measurement by 24 hour ECG Holter, because the SDNN is more accurate when measured over a 24-hour period than during shorter intervals, which refers to a duration of 5 minutes or less.

The primary limitation of this study was the relatively small sample size, especially the limited number of patients with adverse outcomes. A further prospective study involving a larger cohort of CHPs with continuous HRV monitoring and more frequent blood tests is needed to assess the predictive value of SDNN, serum albumin, and CRP for SCD. The second limitation is that we have not provided data for abnormal electrolyte (sodium, potassium, and calcium) levels during examined period. Consequently, it remains plausible that abnormal electrolytes might initiate fatal arrhythmias leading to SCD, even though routine laboratory analyses conducted on deceased SCD patients did not reveal electrolyte imbalances [8].

## Acknowledgment

None.

## Statement of Ethics

This study was conducted in accordance with the principles of the World Medical Association (WMA) Declaration of Helsinki. Ethical approval was obtained from Clinical Hospital – Bitola Ethics Committee.

## Ethical Approval

This study was approved by the Ethical Committee of our institution, with reference number 2016/2_0013, on February 9, 2016.

## Patient Informed Consent Statement

Written informed consent was obtained from all participants involved in the study, ensuring they understood the study's purpose, procedures, and their right to confidentiality.

## Conflict of Interest

The authors declare that there is no conflict of interest.

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This clinical study received no specific funding or support from any organization.

## Author Contribution

Petar Avramovski contributed by proposing the study concept, identifying the patient cohort, recommending the appropriate methods for data acquisition, and selecting adequate statistical methods for data analysis.

Maja Avramovska assisted with the ultrasound technique for Doppler measurements, contributed to manuscript writing, data collection and entry, analyzed laboratory data, and participated in discussing the results and comparing them with other studies.

Zorica Nikleski played a key role in providing English language revision, refining the text for natural language flow, correcting spelling and grammatical errors, and enhancing overall readability. She also assisted in acquiring demographic data from patient charts.

Liljana Todorovska played a significant role in processing ECG-Holter data, which includes sorting and organizing it in Excel, contributing to the writing of results, comparing and discussing findings, and assisting with statistical analysis. She had hands-on involvement across various stages of the data management and analysis workflow.

Kosta Sotiroski was instrumental in editing the manuscript, identifying appropriate statistical methods, conducting a literature review, and providing critical oversight. As a professional statistician and professor, he also supervised the manuscript and reviewed the tables, figures, and other forms of results presentation.

Vesna Siklovska was responsible for acquiring Holter data, reading and interpreting the results, and analyzing manuscripts related to heart rate intervals in comparison with our study. She provided critical review of the manuscript and engaged in discussions regarding the results.

Irena Trajcevska ensured the accuracy of references and appropriate citations in the text, wrote the discussion section, interpreted the laboratory data, and acquired demographic data.

Saso Vasilevski participated actively in writing the introduction and discussion section, where he compared the study's findings with those of similar studies, discussed matching or conflicting results, and examined the potential applications of the methods used. Additionally, he reviewed and refined the manuscript for English language and grammar accuracy.

All authors thoroughly reviewed the final manuscript multiple times and reached a consensus. They all agreed to the final version of the manuscript.

## Data Sharing Statement

The data supporting the findings of this clinical study are included within the manuscript. Due to the sensitive nature of patients' information, additional data will not be made publicly available to maintain patient confidentiality. Specific data requests will be evaluated on a case-by-case basis, with consideration of ethical and privacy requirements.

## Artificial Intelligence (AI) Disclosure Statement

AI-unassisted work.

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