

# Circadian chaos of ventricular tachyarrhythmia: a novel digital phenotype predicts mortality in high-risk SCD patients

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## ABSTRACT

**Background** While ventricular tachyarrhythmias (VTAs) exhibited circadian variation at the population level, the prognostic significance of individual VTA onset circadian patterns recorded via home monitoring in patients with high-risk SCD remains poorly defined.

**Methods** This secondary analysis of the SUMMIT registry retrospectively evaluated archived remote monitoring data. Patients were categorized into four groups based on the diurnal distribution of their VTA episodes: no VTA, daytime VTA (> 70% of episodes between 06: 00-21: 59), nocturnal VTA (> 70% between 22: 00-05: 59), and mixed VTA (no predominant pattern).

**Results** Among 756 included patients (mean follow-up 48.8 months), 443 (58.6%) experienced at least one VTA. Dominant daytime VTA onset occurred in 292 patients (65.9%), dominant nocturnal onset in 57 (12.9%), and mixed diurnal pattern in 94 (21.2%). The mixed VTA group had the highest mortality risks across four VTA groups, which demonstrated 4.4- and 2.5-fold higher risks of cardiac death (hazard ratio (HR): 4.42; 95% CI: 2.52–7.76;  $P < 0.001$ ) and all-cause mortality (HR: 2.51; 95% CI: 1.69–3.73;  $P < 0.001$ ) when compared to the no-VTA group, respectively. This association persisted even after excluding patients with electrical storms, with the mixed VTA group remaining an independent predictor of both cardiac death (adjusted HR: 2.61;  $P = 0.017$ ) and all-cause mortality (adjusted HR: 2.27;  $P = 0.002$ ).

**Conclusions** A mixed VTA circadian pattern, characterized by the absence of a dominant diurnal rhythm, is a strong, independent predictor of increased mortality in high-risk SCD patients, highlighting its value for risk stratification.

Sudden cardiac death (SCD) remains a major global health concern, with ventricular tachyarrhythmias (VTAs) being the primary cause.<sup>[1,2]</sup> While implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy defibrillators (CRT-Ds) effectively prevent SCD,<sup>[1,2]</sup> significant mortality risk persists,<sup>[3]</sup> highlighting the need for better prognostic markers.

Previously, population-based epidemiology has identified the “morning surge” phenomenon in VTAs.<sup>[4,5]</sup> However, such group-level patterns tend to mask individual differences in onset characteristics. Emerging evidence from other cardiovascular contexts suggests that the loss of normal circadian rhythmicity may be a marker of advanced disease severity and profound

autonomic dysfunction.<sup>[6,7]</sup> In patients with high risks of SCD, the circadian rhythm pattern may be disrupted, and the individuals’ VTA episodes could follow distinctly different “biological clocks.” Also, the individual circadian patterns and their prognostic significance has not been systematically evaluated in patients with high-risk SCD.

This study, therefore, aimed to leverage data from a large, multicenter, prospective registry of ICD and CRT-D patients with activated home monitoring to investigate the association between individual VTA circadian onset patterns – daytime-dominant, nocturnal-dominant, or mixed (no predominant) – and long-term survival. We hypothesized that the circadian Chaos of VTAs (mixed pattern) would independently predict

worse outcomes, reflecting severe electrical substrate vulnerability.

## METHODS

### Study Design and Population

The Safety and Efficacy of Home Monitoring Systems in Patients with Cardiac Implantable Electronic Devices (SUMMIT) study is a prospective, multicenter, observational clinical trial conducted in China (registration number: ChiCTR-ONRC-13003695). In this secondary analysis, we retrospectively evaluated archived remote monitoring data from the SUMMIT registry.

Eligible participants were the patients who received an ICD or CRT-D between May 2010 and April 2014. Inclusion required that device implantation conformed to contemporary clinical guidelines and that a compatible home monitoring system was activated immediately post-implant. Exclusion criteria encompassed: (1) missing or incomplete follow-up data; (2) age under 18 years at the time of implantation; or (3) loss to follow-up.

The study protocol adhered to the principles of the Declaration of Helsinki and received approval from the institutional review committee at each participating center (For example, Fuwai Hospital, ID: 2010-296). Written informed consent was obtained from every patient prior to enrollment.

### Device Programming

Device programming was configured as follows: a baseline pacing rate was set at 40–60 beats/min for all enrolled patients. Regardless of device type, two dedicated therapy zones were programmed. The ventricular tachycardia (VT) zone was defined for heart rates between 170 and 209 beats/min, with an initial detection requirement of 26 beats and a redetection criterion of 20 beats. The ventricular fibrillation (VF) zone was programmed to detect rhythms exceeding 210 beats/min, with a detection threshold of 12 out of 16 beats.

For VT episodes, the therapeutic sequence consisted of two to three rounds of anti-tachycardia pacing (ATP), followed by escalating-energy cardioversion if necessary. VF episodes were treated with high-energy shocks. Therapy settings remained unchanged during follow-up unless a clinical indication for adjustment arose. All detected VT/VF episodes were independently reviewed by

two blinded cardiologists based on intracardiac electrograms (IEGMs). Episodes were classified as VT, VF, or supraventricular tachycardia, and the appropriateness of delivered therapy (ATP or shock) was assessed. In case of disagreement between the initial reviewers, a third cardiologist provided a final adjudication.

### Home Monitoring Data Acquisition and Analysis

All implanted ICD or CRT-D devices were integrated with a remote home monitoring system. Continuous remote monitoring was activated immediately following device implantation. Data were transmitted daily via the CIED's embedded antenna and a CardioMessenger SMART communicator over the GSM network to a dedicated service center. For this analysis, archived home monitoring records were extracted, which included details on atrial and ventricular pacing, supraventricular episodes (such as atrial fibrillation (AF), atrial flutter, and sinus tachycardia), VT/VF episodes, ATP, and ICD shocks.

VTA events were defined as VT/VF episodes that resulted in appropriate device therapy, either ATP or shock. Nocturnal VTAs were classified as those occurring between 22:00 and 05:59, while daytime VTAs were defined as episodes happening from 06:00 to 21:59 throughout the entire follow-up period.<sup>[8]</sup> An electrical storm was defined as three or more distinct VTA episodes, each terminated by an appropriate ICD intervention, within a 24-h window. VTA burden was quantified as the total count of VT/VF episodes requiring ATP or shock therapy over the entire follow-up duration. Each electrical storm event was counted as a single VTA episode for burden calculation, with the time of onset recorded as the occurrence time of the storm.

### Follow-up and Study Endpoints

Patients were followed up regularly through a combination of remote home monitoring, routine clinic visits, and structured telephone interviews. In the event of interrupted data transmission, the research coordinator promptly contacted the patient or family members to verify clinical status, including symptoms, hospitalizations, and vital status. Deaths and corresponding dates were confirmed using death certificates provided by family members.

The primary endpoint of the study was cardiac death, as defined by ICD-10 codes I00–I09, I11, and I20–I51. The



secondary endpoint was all-cause mortality.

### Grouping Strategy

Patients were categorized based on the diurnal distribution of their ventricular tachyarrhythmia (VTA) episodes, as recorded by the home monitoring system. Individuals were classified into the nocturnal VTA group if more than 70% of their episodes occurred during the night (22: 00 to 06: 00).<sup>[9]</sup> Conversely, those with over 70% of episodes occurring during daytime hours (06: 00 to 21: 00) were assigned to the daytime VTA group.<sup>[9]</sup> Patients who did not meet either criterion – indicating no predominant timing pattern – were classified as having mixed VTA. Additionally, patients without any documented VTA episodes constituted the no-VTA group. Thus, the study cohort was divided into four distinct groups: no VTA, daytime VTA, nocturnal VTA, and mixed VTA.

### Statistical Analysis

Continuous variables are presented as mean  $\pm$  SD or median (interquartile range), depending on their distribution. Categorical variables are summarized as frequencies and percentages. Intergroup comparisons were performed using one-way ANOVA for continuous variables and chi-square tests for categorical variables.

Survival outcomes, including freedom from cardiac death and all-cause mortality, were compared among VTA groups using Kaplan-Meier curves with log-rank tests. Univariate Cox proportional hazards regression was initially performed to identify potential confounding factors. Variables with clinical relevance or a univariate  $P$ -value  $< 0.10$  were incorporated into multivariable Cox models to assess the independent association between VTA onset timing (nocturnal, daytime, mixed, or none) and long-term outcomes.

To minimize the influence of electrical storms, the Cox regression analyses were repeated in the subgroup of patients without electrical storms. To demonstrate consistency, subgroup analyses were stratified by cardiomyopathy type, device type, NYHA classification, and hypertension. Also, alternative thresholds (60%, 80%) for VTA classification were validated to strengthen the mixed VTA phenotype's robustness.

Results are reported as hazard ratios (HRs) with 95% CI. A two-sided  $P$ -value  $< 0.05$  was considered statistically significant. All analyses were performed using SPSS Statistics (version 23.0; IBM Corp., Armonk, NY, USA), R

(version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism (version 9.0; GraphPad Software, San Diego, CA, USA).

## RESULTS

### Study Population and Baseline Characteristics

A total of 756 out of 1015 initially screened patients were included in the final analysis. Exclusions were due to unavailable or incomplete data ( $n = 254$ ), age under 18 years at implantation ( $n = 3$ ), and loss to follow-up ( $n = 2$ ).

Baseline characteristics were compared across the four groups: no VTA, daytime VTA, nocturnal VTA, and mixed VTA. The overall cohort had a mean age of  $60.8 \pm 13.9$  years and was predominantly male (74.1%). Of the participants, 203 (26.9%) received CRT-D, and 553 (73.1%) received ICD. Significant differences were observed among the VTA groups in the prevalence of several baseline characteristics: male sex ( $P = 0.039$ ), prior AF ( $P = 0.025$ ), and dilated cardiomyopathy (DCM,  $P = 0.032$ ) (Table 1).

### Clinical Outcomes and Survival Analysis

Over a mean follow-up period of 48.8 months, 443 patients (58.6%) experienced at least one VTA episode. Dominant daytime VTA onset occurred in 292 patients (65.9%), dominant nocturnal onset in 57 (12.9%), and mixed diurnal pattern in 94 (21.2%). The typical cases of daytime-dominant, nocturnal-dominant, or mixed (no predominant) pattern were illustrated in Figure 1. There were 110 cardiac deaths and 202 all-cause deaths recorded during follow-up.

Cardiac mortality rates were 17.1% in the daytime VTA group, 15.8% in the nocturnal VTA group, and 29.8% in the mixed VTA group. All-cause mortality rates were 26.0%, 35.1%, and 45.7%, respectively. Kaplan-Meier survival analysis revealed that patients in the mixed VTA group had significantly higher risks of cardiac death (log-rank  $P < 0.001$ ) and all-cause mortality (log-rank  $P < 0.001$ ) compared to the other groups (Figure 2).

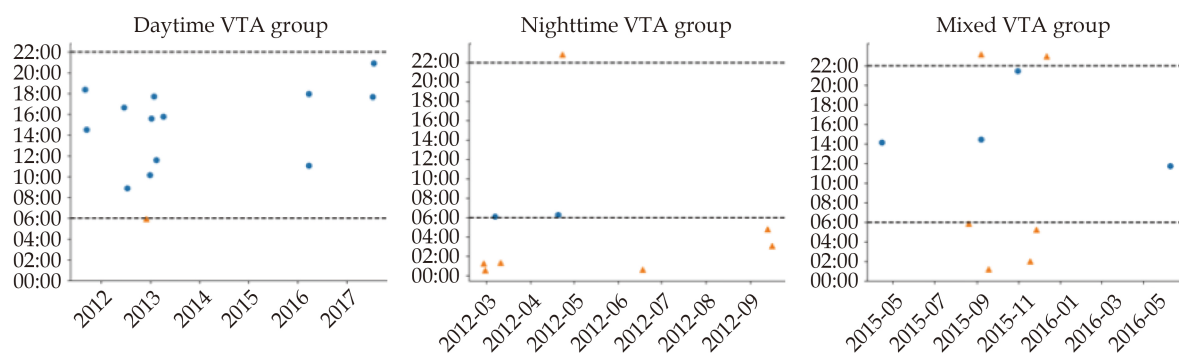
A total of 135 patients (17.9%) developed electrical storms during the follow-up period. The mixed VTA group exhibited the highest prevalence of electrical storms (46.8%), compared to 26.7% in the daytime VTA group and 22.8% in the nocturnal VTA group.



Table 1 Baseline characteristics.

| Characteristic           | Total<br>n = 756 | No VTA group<br>n = 312 | Daytime group<br>n = 292 | Nighttime group<br>n = 57 | Mixed group<br>n = 94 | P-value |
|--------------------------|------------------|-------------------------|--------------------------|---------------------------|-----------------------|---------|
| Age at implantation, yrs | 60.8 ± 13.9      | 61.2 ± 14.0             | 60.9 ± 14.5              | 58.1 ± 12.7               | 60.1 ± 12.8           | 0.503   |
| Sex (male)               | 560 (74.1%)      | 218 (69.6%)             | 220 (75.3%)              | 43 (75.4%)                | 79 (84.0%)            | 0.039   |
| BMI, kg/m <sup>2</sup>   | 23.5 ± 3.1       | 23.3 ± 2.9              | 23.6 ± 3.1               | 23.6 ± 4.2                | 23.8 ± 2.9            | 0.606   |
| CRT-D implantation       | 203 (26.9%)      | 89 (28.4%)              | 67 (22.9%)               | 18 (31.6%)                | 29 (30.9%)            | 0.253   |
| NYHA class III-IV        | 382 (50.5%)      | 153 (48.9%)             | 148 (50.7%)              | 32 (56.1%)                | 49 (52.1%)            | 0.763   |
| LVEF, %                  | 42.5 ± 14.9      | 44.0 ± 15.7             | 41.8 ± 14.1              | 41.3 ± 14.1               | 40.8 ± 14.5           | 0.144   |
| Hypertension             | 244 (32.3%)      | 102 (32.6%)             | 92 (31.5%)               | 24 (42.1%)                | 26 (27.7%)            | 0.317   |
| DM                       | 79 (10.4%)       | 27 (8.6%)               | 35 (12.0%)               | 7 (12.3%)                 | 10 (10.6%)            | 0.561   |
| DCM                      | 180 (23.8%)      | 71 (22.7%)              | 70 (24.0%)               | 22 (38.6%)                | 17 (18.1%)            | 0.032   |
| ICM                      | 258 (34.1%)      | 96 (30.7%)              | 107 (36.6%)              | 17 (29.8%)                | 38 (40.4%)            | 0.202   |
| Prior MI                 | 111 (14.7%)      | 44 (14.1%)              | 44 (15.1%)               | 7 (12.3%)                 | 16 (17.0%)            | 0.848   |
| PCI                      | 65 (8.6%)        | 30 (9.6%)               | 22 (7.5%)                | 5 (8.8%)                  | 8 (8.5%)              | 0.847   |
| Prior AF                 | 87 (11.5%)       | 23 (7.3%)               | 41 (14.0%)               | 8 (14.0%)                 | 15 (16.0%)            | 0.025   |
| Preimplant syncope       | 153 (20.2%)      | 55 (17.6%)              | 66 (22.6%)               | 13 (22.8%)                | 19 (20.2%)            | 0.453   |
| Beta-blockers            | 393 (52.0%)      | 150 (47.9%)             | 155 (53.1%)              | 36 (63.2%)                | 52 (55.3%)            | 0.140   |
| ACEI/ ARBs               | 272 (36.0%)      | 114 (36.4%)             | 100 (34.2%)              | 21 (36.8%)                | 37 (39.4%)            | 0.827   |
| Aldosterone antagonists  | 271 (35.8%)      | 112 (35.8%)             | 104 (35.6%)              | 20 (35.1%)                | 35 (37.2%)            | 0.992   |
| Statin                   | 169 (22.4%)      | 72 (23.0%)              | 64 (21.9%)               | 10 (17.5%)                | 23 (24.5%)            | 0.775   |
| Loop diuretics           | 199 (26.3%)      | 85 (27.2%)              | 79 (27.1%)               | 16 (28.1%)                | 19 (20.0%)            | 0.554   |
| Digoxin                  | 151 (20.0%)      | 63 (20.1%)              | 60 (20.5%)               | 9 (15.8%)                 | 19 (20.2%)            | 0.875   |
| Amiodarone               | 219 (29.0%)      | 87 (27.8%)              | 84 (28.8%)               | 15 (26.3%)                | 33 (35.1%)            | 0.546   |

Data are presented as mean ± SD or *n* (%). ACEIs: angiotensin-converting enzyme inhibitors; AF: atrial fibrillation; ARBs: angiotensin receptor blockers; BMI: body mass index; DCM: dilated cardiomyopathy; DM: diabetes mellitus; HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; VTA: ventricular tachyarrhythmia.

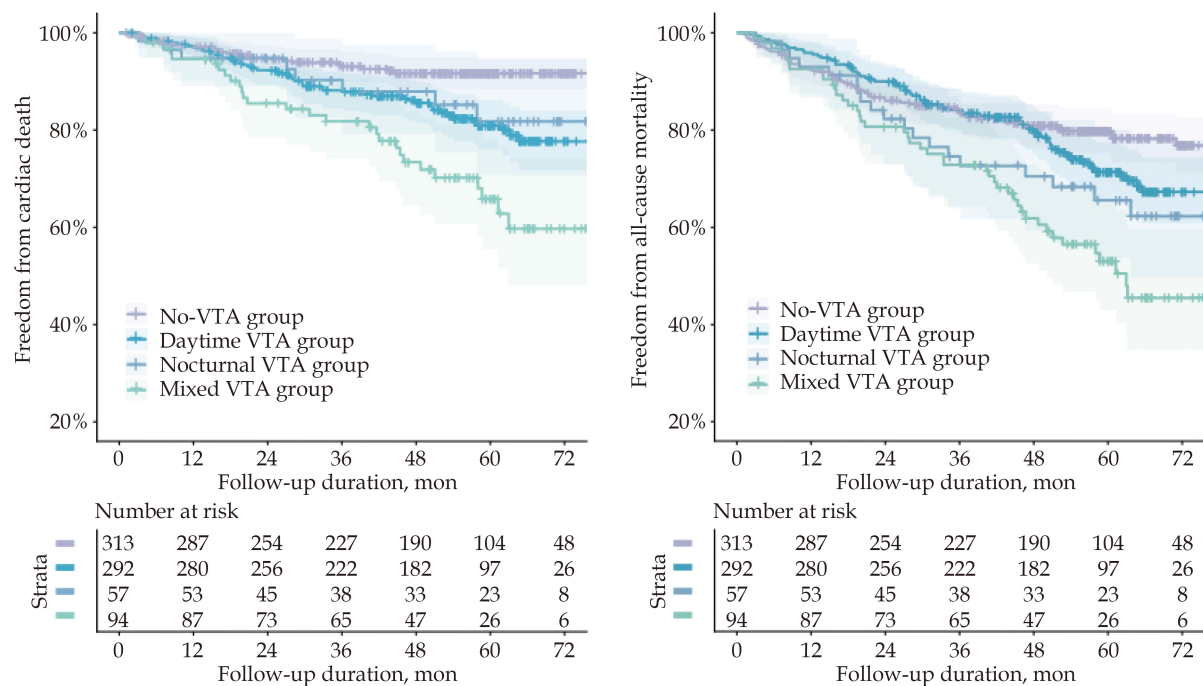


**Figure 1** The typical cases of different VTA circadian pattern. The typical cases of daytime-dominant, nocturnal-dominant, or mixed (no predominant) pattern were illustrated in Figure 1. VTA: ventricular tachyarrhythmia.

### Cox Regression Analysis of Long-Term Survival

In univariate analysis for cardiac death, both the daytime VTA group (HR = 2.28; 95% CI: 1.39–3.73; *P* = 0.001) and the mixed VTA group (HR = 4.37; 95% CI: 2.52–7.50; *P* < 0.001) showed significantly elevated risk compared

to the no-VTA group. The nocturnal VTA group did not reach statistical significance (HR = 2.15; 95% CI: 0.99–4.64; *P* = 0.052). After multivariate adjustment for age at implantation, left ventricular ejection fraction (LVEF), CRT-D implantation, hypertension, diabetes



**Figure 2 Kaplan-Meier survival analysis of cardiac death and all-cause mortality.** Kaplan-Meier survival analysis revealed that patients in the mixed VTA group had significantly higher risks of cardiac death (log-rank  $P < 0.001$ ) and all-cause mortality (log-rank  $P < 0.001$ ) compared to the other groups in Figure 2. VTA: ventricular tachyarrhythmia.

mellitus, ischemic cardiomyopathy, DCM, prior AF, and use of aldosterone antagonists, loop diuretics, and digoxin, all three VTA groups demonstrated significantly increased risk: daytime VTA (HR = 2.15; 95% CI: 1.31–3.55;  $P = 0.003$ ), nocturnal VTA (HR = 2.27; 95% CI:

1.04–4.96;  $P = 0.040$ ), and mixed VTA (HR = 4.42; 95% CI: 2.52–7.76;  $P < 0.001$ ), corresponding to 2.2-, 2.3-, and 4.4-fold increases in risk, respectively (Table 2).

For all-cause mortality, univariate analysis revealed no significant increase in the daytime VTA group (HR =

**Table 2 Cox regression analysis of long-term survival in the whole study population.**

|                     | No. of Cases | No. of death | Univariate Cox regression analysis |             | Multivariate Cox regression analysis |             |
|---------------------|--------------|--------------|------------------------------------|-------------|--------------------------------------|-------------|
|                     |              |              | HR (95% CI)                        | P-value     | HR (95% CI)                          | P-value     |
| Cardiac death       | 756          | 110 (14.6%)  |                                    |             |                                      |             |
| No-VTA group        | 313          | 23 (7.3%)    | Ref.                               |             | Ref.                                 |             |
| Daytime VTA group   | 292          | 50 (17.1%)   | 2.28 (1.39–3.73)                   | $P = 0.001$ | 2.15 (1.31–3.55)                     | $P = 0.003$ |
| Nocturnal VTA group | 57           | 9 (15.8%)    | 2.15 (0.99–4.64)                   | $P = 0.052$ | 2.27 (1.04–4.96)                     | $P = 0.040$ |
| Mixed VTA group     | 94           | 28 (29.8%)   | 4.37 (2.52–7.60)                   | $P < 0.001$ | 4.42 (2.52–7.76)                     | $P < 0.001$ |
| All-cause mortality | 756          | 202 (26.7%)  |                                    |             |                                      |             |
| No-VTA group        | 313          | 63 (20.1%)   | Ref.                               |             | Ref.                                 |             |
| Daytime VTA group   | 292          | 76 (26.0%)   | 1.27 (0.91–1.77)                   | $P = 0.162$ | 1.18 (0.84–1.66)                     | $P = 0.329$ |
| Nocturnal VTA group | 57           | 20 (35.1%)   | 1.75 (1.06–2.89)                   | $P = 0.030$ | 1.76 (1.05–2.94)                     | $P = 0.032$ |
| Mixed VTA group     | 94           | 43 (45.7%)   | 2.47 (1.67–3.64)                   | $P < 0.001$ | 2.51 (1.69–3.73)                     | $P < 0.001$ |

Data are presented as  $n$  (%) unless other indicated. Multivariate Cox regression model was adjusted for age at implantation, LVEF, CRT-D implantation, hypertension, DM, ICM, prior AF, usages of aldosterone antagonists, loop diuretics, and digoxin. AF: atrial fibrillation; CI: confidence interval; CRT-D: cardiac resynchronization therapy defibrillator; DM: diabetes mellitus; HR: hazard ratio; ICM: ischemic cardiomyopathy; LVEF: left ventricular ejection fraction; VTA: ventricular tachyarrhythmia



1.27; 95% CI: 0.91–1.77;  $P = 0.162$ ), while both the nocturnal VTA (HR = 1.75; 95% CI: 1.06–2.89;  $P = 0.030$ ) and mixed VTA groups (HR = 2.47; 95% CI: 1.67–3.64;  $P < 0.001$ ) showed significantly elevated risk. These associations persisted in multivariate analysis: daytime VTA (HR = 1.18; 95% CI: 0.84–1.66;  $P = 0.329$ ), nocturnal VTA (HR = 1.76; 95% CI: 1.05–2.94;  $P = 0.032$ ), and mixed VTA (HR = 2.51; 95% CI: 1.69–3.73;  $P < 0.001$ ) (Table 2).

### Survival Outcomes in Patients Without Electrical Storms

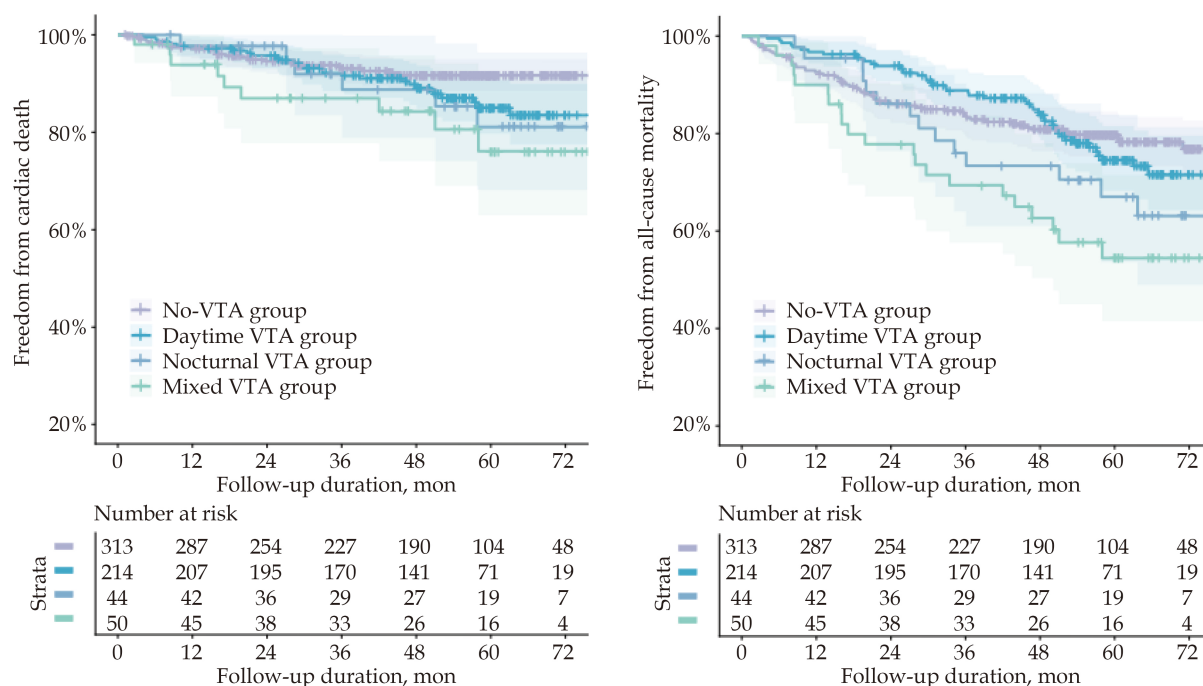
Kaplan-Meier analysis was performed to assess cardiac death and all-cause mortality in the subgroup of patients who did not experience electrical storms. Patients in the mixed VTA group demonstrated significantly lower freedom from both cardiac death (log-rank  $P = 0.041$ ) and all-cause mortality (log-rank  $P = 0.003$ ) compared to the other groups (Figure 3).

To further evaluate the independent association between VTA patterns and outcomes without the confounding influence of electrical storms, Cox regression analysis was conducted excluding those patients. In univariate analysis, neither daytime nor nocturnal VTA groups showed significantly increased risk of cardiac

death or all-cause mortality compared to the no-VTA group. However, the mixed VTA group exhibited significantly elevated risks of cardiac death (HR = 2.68; 95% CI: 1.24–5.80;  $P = 0.012$ ) and all-cause mortality (HR: 2.28; 95% CI: 1.39–3.74;  $P = 0.001$ ) (Table 3). After multivariate adjustment, the mixed VTA group remained independently associated with increased risks of cardiac death (adjusted HR = 2.61; 95% CI: 1.18–5.76;  $P = 0.017$ ) and all-cause mortality (adjusted HR: 2.27; 95% CI: 1.36–3.77;  $P = 0.002$ ), corresponding to 2.6- and 2.3-fold higher risks, respectively, compared to the no-VTA group (Table 3).

### Subgroup Analysis and Sensitivity Analysis

The subgroup analyses were stratified by cardiomyopathy type, device type, NYHA classification, and hypertension, which demonstrated the consistent results: the mixed VTA had significantly increased risks of cardiac death and all-cause mortality, compared to the no-VTA group (Figure 4). Also, alternative thresholds (60%, 80%) for VTA classification were validated, which showed the robustness of the findings: the mixed VTA phenotype was associated with the highest risks of cardiac death and all-cause mortality across the three different VTA phenotype groups (Figure 5).

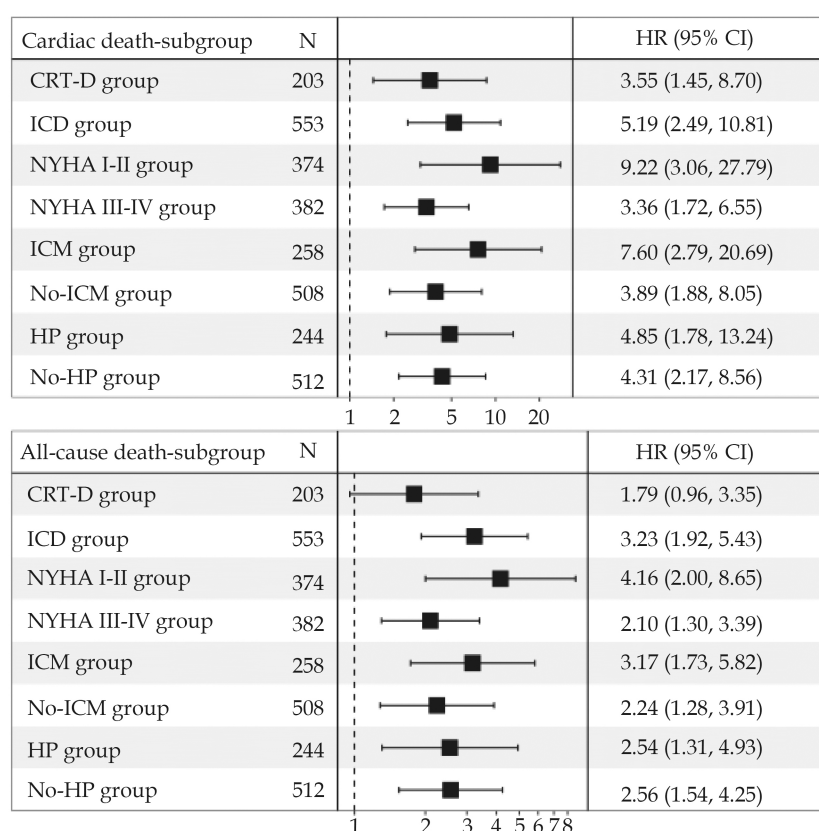


**Figure 3 Kaplan-Meier survival analysis in patients without electrical storms.** Kaplan-Meier analysis was performed to assess cardiac death and all-cause mortality in the subgroup of patients who did not experience electrical storms. Patients in the mixed VTA group demonstrated significantly lower freedom from both cardiac death (log-rank  $P = 0.041$ ) and all-cause mortality (log-rank  $P = 0.003$ ) compared to the other groups in Figure 3. VTA: ventricular tachyarrhythmia.

Table 3 Cox regression analysis of long-term survival in the patients without electrical storms.

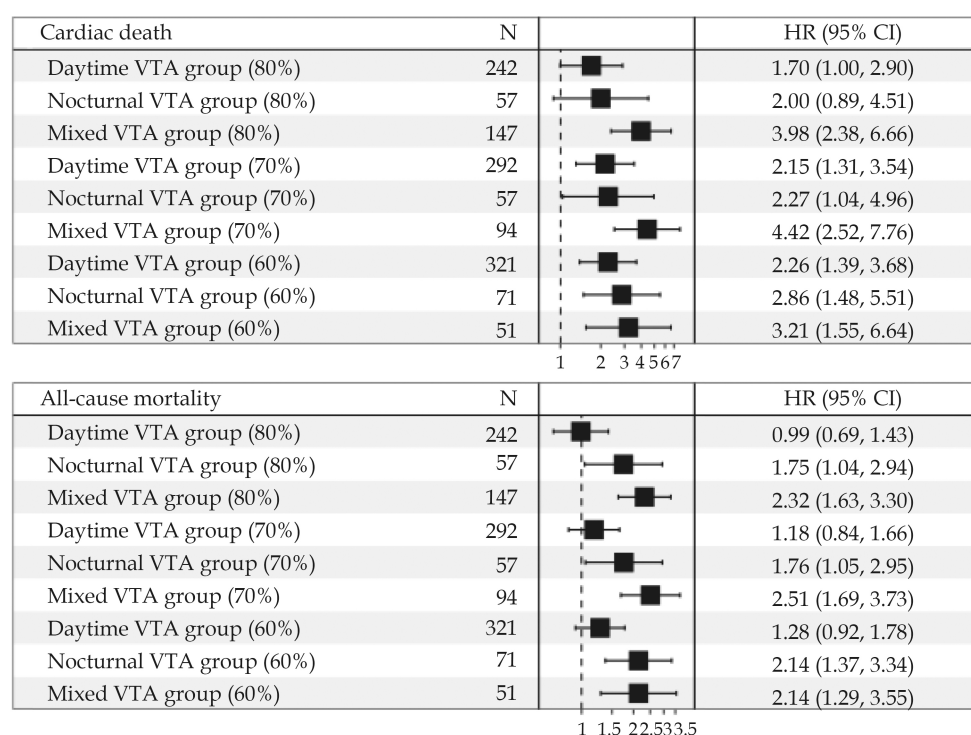
|                     | No. of cases | No. of death<br>(n, %) | Univariate Cox<br>regression analysis |                  | Multivariate Cox<br>regression analysis |                  |
|---------------------|--------------|------------------------|---------------------------------------|------------------|-----------------------------------------|------------------|
|                     |              |                        | HR (95% CI)                           | P value          | HR (95% CI)                             | P value          |
| Cardiac death       | 621          | 66 (10.6%)             |                                       |                  |                                         |                  |
| No-VTA group        | 313          | 23 (7.3%)              | Ref.                                  |                  | Ref.                                    |                  |
| Daytime VTA group   | 214          | 27 (12.6%)             | 1.63 (0.93–2.84)                      | <i>P</i> = 0.086 | 1.46 (0.83–2.57)                        | <i>P</i> = 0.187 |
| Nocturnal VTA group | 44           | 7 (15.9%)              | 2.14 (0.92–4.99)                      | <i>P</i> = 0.078 | 2.23 (0.93–5.32)                        | <i>P</i> = 0.071 |
| Mixed VTA group     | 50           | 9 (18.0%)              | 2.68 (1.24–5.80)                      | <i>P</i> = 0.012 | 2.61 (1.18–5.76)                        | <i>P</i> = 0.017 |
| All-cause mortality | 621          | 146 (23.5%)            |                                       |                  |                                         |                  |
| No-VTA group        | 313          | 63 (20.1%)             | Ref.                                  |                  | Ref.                                    |                  |
| Daytime VTA group   | 214          | 47 (22.0%)             | 1.04 (0.71–1.52)                      | <i>P</i> = 0.837 | 0.92 (0.62–1.35)                        | <i>P</i> = 0.667 |
| Nocturnal VTA group | 44           | 15 (34.1%)             | 1.66 (0.95–2.92)                      | <i>P</i> = 0.076 | 1.71 (0.96–3.05)                        | <i>P</i> = 0.070 |
| Mixed VTA group     | 50           | 21 (42.0%)             | 2.28 (1.39–3.74)                      | <i>P</i> = 0.001 | 2.27 (1.36–3.77)                        | <i>P</i> = 0.002 |

Data are presented as *n* (%) unless other indicated. Multivariate Cox regression model was adjusted for age at implantation, LVEF, CRT-D implantation, hypertension, DM, ICM, prior AF, usages of aldosterone antagonists, loop diuretics, and digoxin. AF: atrial fibrillation; CI: confidence interval; CRT-D: cardiac resynchronization therapy defibrillator; DM: diabetes mellitus; HR: hazard ratio; ICM: ischemic cardiomyopathy; LVEF: left ventricular ejection fraction; VTA: ventricular tachyarrhythmia.



**Figure 4 Forest plot for subgroup analysis.** The subgroup analyses were stratified by cardiomyopathy type, device type, NYHA classification, and hypertension, which demonstrated the consistent results: the mixed VTA had significantly increased risks of cardiac death and all-cause mortality, compared to the no-VTA group. VTA: ventricular tachyarrhythmia.





**Figure 5 Forest plot for sentivity analysis.** Alternative thresholds (60%, 80%) for VTA classification were validated, which showed the robustness: mixed VTA phenotype was associated with the highest risks of cardiac death and all-cause mortality across three different groups of VTA phenotypes. VTA: ventricular tachyarrhythmia.

## DISCUSSION

This study aimed to assess the impact of the individual VTA onset pattern on long-term survival in patients at high risk of sudden cardiac death. Our analysis yielded several key findings: First, 21.2% of patients exhibited VTA episodes without a predominant diurnal pattern, classified as the mixed VTA group. Second, patients in this mixed VTA group demonstrated the highest risks of cardiac death (adjusted HR 4.4 when compared to those without VTA episodes) and all-cause mortality (adjusted HR 2.6 when compared to those without VTA episodes) across different VTA groups. Third, although electrical storms were more frequent in the mixed VTA group, the association between mixed VTA and poorer survival persisted even after excluding patients who experienced electrical storms, highlighting the independent prognostic value of VTA circadian patterns.

Prior research has established a morning peak in the incidence of VT/VF episodes among patients with ischemic and non-ischemic heart disease.<sup>[4,5]</sup> This daytime surge may be attributed to several well-documented arrhythmogenic triggers, including increased sympathetic tone, elevated circulating catecholamine

levels, higher heart rates, augmented afterload, and enhanced platelet aggregation.<sup>[10,11]</sup> However, recent studies have failed to replicate this morning peak.<sup>[12-14]</sup> The present study investigated the individual-level circadian distribution of VTA episodes in patients with high-risk SCD. Our findings revealed that approximately two-thirds of patients exhibited a daytime-dominant VTA onset pattern, while only one-third displayed circadian chaos (no clear diurnal VTA predominance). Previous studies have shown that the circadian pattern was absent in patients with higher comorbidity burden in in-hospital cardiac arrest.<sup>[15,16]</sup> In our study, they were characterized by a higher proportion of males, greater prevalence of AF and more frequent ICM. However, no significant differences were observed in other comorbidities across the circadian pattern groups. This may be attributable to the overall advanced disease severity in our study population, as reflected by the mean LVEF of 42.5%, which might have overshadowed the contribution of additional comorbidities.

Also, the present study investigated the prognostic significance of distinct circadian patterns of VTA in high-risk SCD patients. Prior to this investigation, limited re-

search had examined this relationship at the individual level with long-term follow-up, especially in device patients. Fabrizio R. Assis *et al.* examined nocturnal predominance of premature ventricular contractions (PVCs) and its correlation with right ventricular (RV) structural phenotype in arrhythmogenic right ventricular cardiomyopathy (ARVC).<sup>[6]</sup> Their findings indicated that patients with more severe RV involvement exhibited a higher proportion of PVCs during nighttime compared to daytime. In another relevant study, Suzuki, *et al.*<sup>[7]</sup> identified midnight VT/VF during electrical storms as the sole independent predictor of heart failure-related mortality (adjusted HR = 18.9) in the multivariate analysis, suggesting its association with adverse outcomes. Both studies proposed that the loss of normal sympathetic circadian rhythm in PVCs or VT/VF may reflect advanced stages of cardiac disease.<sup>[6,7]</sup> Our findings aligned with this concept, demonstrating that individual circadian patterns of VTA episodes in high-risk SCD patients carry prognostic significance. Specifically, we established that absence of a predominant diurnal pattern—characterized as mixed VTA—was associated with significantly worse long-term survival. While further validation was warranted, these findings provided some possible mechanistic insights into arrhythmia patterns in advanced heart disease. Patients with ischemic heart disease, cardiomyopathies, or channelopathies exhibit structural and electrophysiological alterations that reduce the protective capacity of the myocardial substrate, thereby predisposing them to sustained life-threatening arrhythmias.<sup>[17,18]</sup> A simplified model for explaining the diurnal variation in the mixed VTA group proposes that the daytime increase in arrhythmogenic triggers leads to a higher incidence of sustained arrhythmias in individuals with an already vulnerable myocardial substrate.<sup>[10]</sup>

We hypothesize that the circadian pattern of VTA onset, as revealed through individualized long-term monitoring, represents an integrated manifestation of cardiac autonomic homeostasis and electrical substrate stability. Its chaos signifies a transition into the stage of end-stage electrical disease. For the first time, we have proposed and validated the “mixed VTA (no predominant)” phenotype, which reflects a loss of the heart’s normal response to circadian stressors. This group, comprising 21.2% of all VTA patients, exhibited a 4.4-fold higher risk of cardiac death compared to patients without VTA, indicating a poorer long-term prognosis. It suggests that

through straightforward remote monitoring and rhythm analysis, we can early identify ICD-implanted patients who are progressing toward end-stage heart failure and electrical death, thereby enabling prioritized resource allocation and proactive treatment intensification. Leveraging existing home monitoring data facilitates SCD risk stratification and is readily applicable in clinical practice.

### Strengths and Limitations

This study benefits from the comprehensive long-term continuous rhythm monitoring implemented in all enrolled patients, ensuring consistent and complete data collection. However, several limitations should be acknowledged. First, while nocturnal VTAs are known to be prevalent in patients with sleep-disordered breathing (SDB),<sup>[19]</sup> no systematic data on SDB were available in our cohort, preventing assessment of its potential influence on our findings. Thus, the impact of nocturnal and mixed VTAs on the long-term survival may be overestimated. Second, the programmed detection duration for tachyarrhythmias in this study (26 beats) was shorter than the contemporary guideline recommendation of at least 30 beats or 6 seconds.<sup>[20]</sup> This may have led to the inclusion of some clinically non-significant VTA episodes. Third, validation in multi-ethnic cohorts (e.g., European or US registries) is warranted to address the limited generalizability beyond the Chinese study population, due to potential ethnic differences in circadian rhythms.

In conclusion, this study demonstrates that a mixed, non-dominant circadian pattern of VTAs is a strong, independent predictor of increased mortality in high-risk SCD patients, highlighting its value for risk stratification.

### DISCLOSURE

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Sun XR and Zhang S contributed to the conception or design of the work. Sun XR contributed to the acquisition, analysis, or interpretation of data for the work. Sun XR drafted the manuscript. Zhao S and Xiaofeng Li critically revised the manuscript. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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### Declaration of Interest

None.

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