Nonsustained ventricular tachycardia does not affect the prognosis of neuromuscular diseases: A preliminary and retrospective study

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Abstract
Background: Nonsustained ventricular tachycardia (NSVT) is sometimes observed in patients with neuromuscular diseases (NMDs). The aim of this study was to assess the role of NSVT in the survival prognosis of NMD patients.

Methods: We retrospectively analyzed the patients with NMDs who had undergone Holter ECG recordings at a single center between February and August 2012. Sixty-eight patients were enrolled in this study. The 5 year follow-up was assessed according to the cumulative event-free rate.

Results: Twenty-one patients died during the follow-up, seven of whom died by cardiac death. The Kaplan–Meier survival curve that compared the patients with NSVT and those without NSVT indicated the NSVT was not related to the rate of all causes of death or cardiac death in those patients with NMDs. The survival curve was not significantly changed after the adjustment by age and ejection fraction.

Conclusion: No significant correlations between NSVT and the prognosis in patients with NMDs were found.

KEYWORDS
arrhythmia, Holter ECG recordings, neuromuscular diseases, nonsustained ventricular tachycardia, prognosis

1 | INTRODUCTION

There have been many studies that aimed to reveal the role of neuromuscular dysfunction on the regulation of the heart beat and cardiac rhythm. Davis et al1 suggested that the neuroanatomic connections between the neuromuscular system and heart might provide the links that generate cardiac arrhythmias in response to brain activation. They suggested the neuromuscular system directs the events that lead to cardiac damage by raising catecholamine levels and potentially inducing arrhythmia.

Patients with neuromuscular diseases (NMDs) exhibit various types of arrhythmia. For example, Harper and Pelargonio et al2,3 reviewed the heart problems in myotonic dystrophy. In myotonic dystrophy, various electrocardiographic abnormalities, most commonly atrioventricular block, were reported.4,5 According to Wahbi et al,6 sustained ventricular tachycardia (VT) in patients with
myotonic dystrophy type 1 might be a predictor of sudden death. Nonsustained ventricular tachycardia (NSVT) is more common than VT in the general population, and little is known about the prognostic significance of NSVT in patients with NMDs.

Therefore, we have started clinical research on the prognostic significance of NSVT in patients who were hospitalized for life under the National Hospital Care Program for NMDs in Japan. Our aim was to conclude whether NSVT in those patients with advanced NMDs is a large concern for their prognosis or not.

2 | METHODS

2.1 | Study participants

The protocol for this retrospective study has been approved by a suitably constituted Ethics Committee of the institution, and it conforms to the provisions of the Declaration of Helsinki. Ethics Committee of Suzuka National Hospital, Approval No. 17-16. There were 73 patients and 78 Holter ECG recordings from February 2012 to August 2012 in Suzuki National Hospital (Mie, Japan). Sixty-eight patients were enrolled in this study, and five patients were excluded because they did not have an NMD. Twenty patients had NSVT, which was defined as VT with a duration of shorter than 30 s and continued for more than 3 beats. Patients were evaluated by 24 hours Holter monitoring and echocardiography. A representative case of NSVT detected by Holter ECG was shown in Figure 1. The outcomes were assessed after a 5 year follow-up.

2.2 | Clinical outcomes

Cardiac death was defined as acute coronary syndrome, heart failure, sustained ventricular tachycardia, ventricular fibrillation, or sudden death. Sudden death included the following: (i) occurring within 1 hour of the onset of cardiac manifestations, in the absence of prior hemodynamic deterioration, (ii) during sleep, or (iii) within 24 hours after the patient was last seen to be clinically stable. The long-term outcome was assessed as the cumulative survival rate after Holter ECG.

![FIGURE 1](image_url) Shows a representative case of nonsustained ventricular tachycardia (NSVT) detected by Holter ECG. The duration of this NSVT was 2 s and it continued 4 beats.

2.3 | Statistical analyses

Continuous variables are shown as a mean ± SD, whereas categorical variables are reported as a number or percentage. Cumulative event-free survival (all cause of death and cardiac death) was estimated using the Kaplan–Meier method, and event-free survival among groups was compared using the log-rank test. The prediction accuracy of the models (total beats, age, and ejection fraction) was evaluated using the receiver-operating characteristic (ROC) curve.

We adjusted the cumulative event-free survival by age and ejection fraction (EF). All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for

| TABLE 1 Baseline characteristics of the study population |
|-----------------------------------------------|
|                                     | 68 patients |
|---------------------------------------------|
| Age mean (SD)                               | 41.97 (21.77) |
| Female n (%)                                | 15 (22.1) |
| Disease n (%)                               | 68 (100) |
| Duchenne muscular dystrophy n (%)           | 24 (35.3) |
| Becker muscular dystrophy n (%)             | 3 (4.4) |
| Myotonic dystrophy n (%)                    | 13 (19.1) |
| Limb-girdle muscular dystrophy n (%)        | 2 (2.9) |
| Fukuyama type congenital muscular dystrophy n (%) | 2 (2.9) |
| Unknown muscular dystrophy n (%)            | 5 (7.4) |
| Amyotrophic lateral sclerosis n (%)          | 4 (5.9) |
| Huntington's disease n (%)                  | 1 (1.5) |
| Myopathy n (%)                              | 1 (1.5) |
| Parkinson's disease n (%)                   | 10 (14.7) |
| Shy-Drager syndrome n (%)                   | 2 (2.9) |
| Werndig-Hoffmann n (%)                      | 1 (1.5) |
| Inpatient n (%)                              | 37 (54.4) |
| Noninvasive positive pressure ventilation n (%) | 11 (16.2) |
| Intubate n (%)                              | 9 (13.2) |
| Hypertension n (%)                          | 13 (19.1) |
| Diabetes mellitus n (%)                     | 5 (7.4) |
| Hyperlipidemia n (%)                        | 4 (5.9) |
| Pacemaker n (%)                             | 2 (2.9) |
| Ejection Fraction mean (SD)                 | 55.60 (17.94) |
| Total beats (SD)                            | 115286.04 (24638.26) |
| Nonsustained ventricular tachycardia n (%)  | 17 (25.0) |
| Death n (%)                                 | 21 (30.9) |
| Cardiac death n (%) [Detail]                | 7 (10.3) |
|                                          | [4 sudden deaths, 1 acute coronary syndrome, 1 VTb, and 1 heart failure] |

a: n indicated number.
b: VT indicated sustained ventricular tachycardia.
3 | RESULTS

3.1 | Baseline characteristics

The relationship between the NSVT and the prognosis was observed in 68 patients with NMDs. Baseline characteristics are presented in Table 1. The mean age of the subjects and the mean left ventricular EF were 42.0 ± 21.8 years and 55.6 ± 17.9%, respectively. Fifteen patients (22.1%) were female. Thirty-seven patients (54.4%) were inpatients. Seventeen patients had NSVT, and there were no NMD patients with sustained VT detected by Holter ECG. Table 2 indicates that the EF of the 51 patients without NSVT was significantly higher than that of the 17 patients with NSVT (58.2 ± 14.3% vs 47.7 ± 25.0%, P value .035).

3.2 | Clinical outcomes during follow-up

During a mean follow-up of 56 ± 20 months after a Holter ECG, 21 patients died, of whom 7 cases were regarded as a cardiac death. The most frequent cause of death was infection, which was found in 8 cases. The second most frequent cause of death was cardiac death, including 4 sudden deaths, 1 acute coronary syndrome, 1 VT storm, and 1 heart failure. One patient who died by VT storm had NSVT in Holter ECG. Other causes of death included 1 stroke, 1 malnutrition, 1 dehydration, and 1 aspiration problem, and 3 patients died of unknown causes.

Figure 2A shows the Kaplan–Meier survival curve that compared the patients with NSVT and those without NSVT, and the NSVT was not related to the rate of all causes of death in patients with NMDs. The survival curve for cardiac death did not show a significant difference in the two groups (Figure 2B).

Other factors as well as NSVT were also evaluated by the univariate analysis (Table 3). The cut-off value of the age, total beats,

### Table 2: Baseline characteristics of the study population which compared the patients with nonsustained ventricular tachycardia (NSVT) and those without NSVT

|                          | 51 patients without NSVT | 17 patients with NSVT | P value |
|--------------------------|--------------------------|-----------------------|---------|
| Age mean (SD)            | 40.1 (22.79)             | 47.7 (17.76)          | .22     |
| Female n (%)             | 10 (19.6)                | 5 (29.4)              | .5      |
| Disease n (%)            |                          |                       |         |
| Duchenne muscular dystrophy | 20 (39.2)               | 6 (35.3)              | .98     |
| Becker muscular dystrophy  | 2 (3.9)                  | 1 (5.9)               |         |
| Myotonic dystrophy         | 9 (17.6)                 | 4 (23.5)              |         |
| Limb-girdle muscular dystrophy | 1 (2.0)                | 1 (5.9)               |         |
| Fukuyama type congenital muscular dystrophy | 2 (3.9) | 0 (0.0) |         |
| Unknown muscular dystrophy | 2 (3.9)                 | 1 (5.9)               |         |
| Amyotrophic lateral sclerosis | 3 (5.9)                  | 1 (5.9)               |         |
| Huntington’s disease       | 1 (2.0)                  | 0 (0.0)               |         |
| Myopathy                  | 1 (2.0)                  | 0 (0.0)               |         |
| Parkinson’s disease        | 8 (15.7)                 | 2 (11.8)              |         |
| Shy-Drager syndrome       | 1 (2.0)                  | 1 (5.9)               |         |
| Werdnig-Hoffmann          | 1 (2.0)                  | 0 (0.0)               |         |
| Inpatient n (%)           | 26 (51.0)                | 11 (64.7)             | .4      |
| Noninvasive positive pressure ventilation n (%) | 8 (15.7) | 3 (17.6) | 1 |
| Intubate n (%)            | 6 (11.8)                 | 3 (17.6)              | .68     |
| Hypertension n (%)        | 9 (17.6)                 | 4 (23.5)              | .72     |
| Diabetes mellitus n (%)   | 3 (5.9)                  | 2 (11.8)              | .59     |
| Hyperlipidemia n (%)      | 4 (7.8)                  | 0 (0.0)               | .57     |
| Pacemaker n (%)           | 1 (2.0)                  | 1 (5.9)               | .44     |
| Ejection Fraction mean (SD) | 58.2 (14.3)               | 47.7 (25.0)           | .035    |
| Total beats (SD)          | 115750.33 (22336.18)     | 113893.18 (31307.67)  | .79     |
| Death n (%)               | 13 (25.5)                | 8 (47.1)              | .13     |
| Cardiac death n (%)       | 5 (9.8)                  | 2 (11.8)              | 1       |

*n indicated number.
and EF was determined by the ROC curve. The survival curve for all cause of death showed a significant difference between the patients of 36 and above and those under 35 (5 year survival rate: 0.83 vs 0.59, \( P \) value .03). Therefore, we adjusted the cumulative survival curve that compared the patients with NSVT and those without NSVT by the age. We also adjusted the cumulative survival by EF because the EF was significantly different in the two groups (Table 2). But the survival curves were not significantly changed after the adjustment by age and EF. The survival curves adjusted by the age were shown in Figure 3 (all causes of death: Figure 3A, cardiac death: Figure 3B). Those adjusted by EF were shown in Figure 4 (all causes of death: Figure 4A, cardiac death: Figure 4B).

In this context, the above statistical analyses indicated that cardiac death and all causes of death were not influenced by the co-existence of NSVT in patients with NMDs.

4 | DISCUSSION

4.1 | NSVT in patients with NMD

An atrophied respiratory muscle and deformed thorax in NMD patients can cause respiratory failure, but the ventilation assist device improves the prognosis of those NMD patients. For example, our institute has already reported that intermittent positive pressure ventilation for advanced Duchenne muscular dystrophy changed the prognosis of the disease and reduced the deaths from respiratory failure.11 Now, many NMD patients can live longer than before because the respiratory care has been developed. However, physicians should be aware of the clinical and prognostic significances of a heart problem and arrhythmia in patients with neuromuscular dysfunctions. Regarding the NSVT, its clinical significance depends on the patient’s background, that is underlying diseases, complications, age, gender, and so on.12 In general, patients with NSVT require an evaluation for structural cardiovascular disorders such as coronary, valvular, and myocardial disorders,13 but the prognostic significance of spontaneous NSVT in healthy individuals has not been established.14 For example, the previous report suggested an association between mortality and NSVT in patients with cardiac hypertrophy.15 Moreover, a negative impact of NSVT was suggested in patients with reduced EF and those with coronary artery diseases, for whom an implantable cardioverter defibrillator would be mandatory.16 But, in the patients with a permanent implanted cardiac pacemaker, NSVT was not associated with an increased mortality.17

Our aim was to decide whether NSVT had a significant influence on the prognosis of these NMD patients. This study has demonstrated that NSVT diagnosed with the Holter ECG was not significantly associated with patients’ survival.

The previous multivariate analysis indicated that only the EF was a significant predictor of major arrhythmic events.18 In fact, in our study, the EF was significantly different between the patients with NSVT and those without NSVT. Therefore, we adjusted the survival curve by the EF, and we confirmed that the co-existence of NSVT had no influence on the prognosis.

The usual work-up for patients with NSVT might rule out structural heart disease, using ECG, echocardiogram, cardiac magnetic resonance imaging (MRI), and cardiac catheterization in some cases.19 However, many of these patients could have advanced NMDs with severe motor, sensory, and respiratory dysfunction and might have difficulties in undertaking the detailed cardiac examinations with MRI and catheterization in a separate institute of cardiology.

In this study, the most prevalent cause of death was infection, such as aspiration pneumonia. Many patients with advanced NMDs could have swallowing difficulties, restrictive respiratory insufficiency, respiratory failure, and sleep apnea.20 We suggest that the prognosis of patients with NMDs is not determined by their heart
problems including arrhythmia as NSVT but by swallowing or respiratory function and their susceptibility to infection of the respiratory tract.

Therefore, we have provided new information regarding the prognostic role of NSVT in patients with NMDs. If the neurologist or the attending physician finds NSVT in a Holter ECG of a patient with NMD, he or she should expect that this kind of arrhythmia will not play a critical role in the patient’s prognosis.

### 4.2 Limitation

Regarding the limitations on this study, first of all, this was a single-center, retrospective study, and bias could be inherent in this type

| TABLE 3 | The survival rates evaluated by each factors |
|---------|------------------------------------------|
| Factor  | Group                                    | n\(^a\)=68 | All cause of death (n\(^a\)=21) | 5 y survival rate | P value | Cardiac death (n\(^a\)=7) | 5 y survival rate | P value |
| Age     | < 36 y old                               | 32         | 5                                   | 0.83              | .03      | 2                           | 0.93              | .29      |
|         | ≥ 36 y old                               | 36         | 16                                  | 0.59              | .03      | 5                           | 0.82              |         |
| Gender  | Female                                   | 15         | 7                                   | 0.66              | .16      | 1                           | 0.93              | .65      |
|         | Male                                     | 53         | 14                                  | 0.71              | .16      | 6                           | 0.86              |         |
| Disease | Duchenne muscular dystrophy              | 24         | 7                                   | 0.72              | .06      | 2                           | 0.92              | .24      |
|         | Becker muscular dystrophy                | 3          | 0                                   | 1.00              | 0        | 0                           | 1.00              |         |
|         | Myotonic dystrophy                       | 13         | 5                                   | 0.69              | 1        | 0.91                        | 1.00              |         |
|         | Limb-girdle muscular dystrophy           | 2          | 0                                   | 1.00              | 0        | 1.00                        | 1.00              |         |
|         | Fukuyama type                            | 2          | 0                                   | 1.00              | 0        | 1.00                        | 1.00              |         |
|         | Unknown muscular dystrophy               | 5          | 3                                   | N/A\(^b\)         | 1        | N/A\(^b\)                   | 1.00              |         |
|         | Amyotrophic lateral sclerosis            | 4          | 2                                   | 0.50              | 1        | 0.75                        | 1.00              |         |
|         | Huntington’s disease                     | 1          | 1                                   | N/A\(^b\)         | 1        | N/A\(^b\)                   | 1.00              |         |
|         | Myopathy                                 | 1          | 0                                   | N/A\(^b\)         | 0        | N/A\(^b\)                   | 1.00              |         |
|         | Parkinson’s disease                      | 10         | 2                                   | 0.90              | 1        | 0.90                        | 1.00              |         |
|         | Shy-Drager syndrome                      | 2          | 1                                   | 0.50              | 0        | 1.00                        | 1.00              |         |
|         | Werdnig-Hoffmann                         | 1          | 0                                   | N/A\(^b\)         | 0        | N/A\(^b\)                   | 1.00              |         |
| Patient’s status | Outpatient                | 31         | 6                                   | 0.78              | .13      | 1                           | 0.96              | .10      |
|         | Inpatient                                | 37         | 15                                  | 0.64              | 6        | 0                           | 0.80              |         |
| Non-invasive positive pressure ventilation (NPPV) | No NPPV     | 57         | 17                                  | 0.72              | .40      | 7                           | 0.86              | .31      |
|         | NPPV                                     | 11         | 4                                   | 0.60              | 0        | 1.00                        | 1.00              |         |
| Intubation | No intubation                         | 59         | 17                                  | 0.71              | .40      | 6                           | 0.88              | .91      |
|         | Intubation                               | 9          | 4                                   | 0.63              | 1        | 0.83                        | 1.00              |         |
| Hypertension (HT) | No HT                                   | 55         | 20                                  | 0.64              | .53      | 7                           | 0.84              | .15      |
|         | HT                                       | 13         | 1                                   | 0.92              | 0        | 1                           | 1.00              |         |
| Diabetes mellitus (DM) | No DM                                   | 63         | 19                                  | 0.69              | .84      | 7                           | 0.87              | .45      |
|         | DM                                       | 5          | 2                                   | 0.75              | 0        | 1.00                        | 1.00              |         |
| Hyperlipidemia (HL) | No HL                                   | 64         | 21                                  | 0.68              | .18      | 7                           | 0.87              | .45      |
|         | HL                                       | 4          | 0                                   | N/A\(^b\)         | 0        | N/A\(^b\)                   | 1.00              |         |
| Pacemaker | No pacemaker                           | 66         | 21                                  | 0.69              | .35      | 7                           | 0.87              | .60      |
|         | Pacemaker                               | 2          | 0                                   | N/A\(^b\)         | 0        | N/A\(^b\)                   | 1.00              |         |
| Ejection Fraction (EF) | < 30.7%                                | 9          | 5                                   | 0.38              | .06      | 2                           | 0.69              | .14      |
|         | ≥ 30.7%                                 | 59         | 16                                  | 0.74              | 5        | 0.90                        | 1.00              |         |
| Total beats | <123217/d                           | 44         | 11                                  | 0.77              | .12      | 3                           | 0.92              | .16      |
|         | ≥123217/d                        | 24         | 10                                  | 0.56              | 4        | 0.80                        | 1.00              |         |
| Non-sustained ventricular tachycardia (NSVT) | No NSVT          | 51         | 13                                  | 0.75              | .14      | 5                           | 0.89              | .77      |
|         | NSVT                                    | 17         | 8                                   | 0.55              | 2        | 0.84                        | 1.00              |         |

\(^a\) n indicated number.

\(^b\) N/A indicated not applicable.
Second, this study included many types of NMDs. For example, although it is known that myotonic dystrophy involves channel abnormalities and develops into arrhythmias, this pathogenetic mechanism is not always applicable to other NMDs. Third, our study had a diagnostic limitation of only single recording of Holter ECG for NSVT. There was a possibility that we might overlook NSVT in NMD patients. Finally, the number of cases of each disease was very small in this study. From the standpoint of a clinical neurologist, more cardiologists should be interested in the cardiac problems in NMDs and actively involved in daily medical practice. Hence, the authors hope that large-scale studies might be possible, and the relationship between arrhythmia and NMDs might be revealed.

5 CONCLUSION

No significant correlations between the NSVT and the prognosis in patients with NMDs were found.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.
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