

Differential diagnosis between LQT1 and LQT2 by QT/RR relationships using 24-hour Holter monitoring: a multicenter cross-sectional study

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Abstract

Background The clinical course and therapeutic strategies in the congenital long QT syndrome (LQTS) are genotype-specific. However, accurate estimation of LQTS-genotype is often difficult from the standard 12-lead ECG. **Objectives** This study aims to evaluate the utility of QT/RR slope analysis by the 24-hour Holter monitoring for differential diagnosis of LQTS-genotype between LQT1 and LQT2. **Methods** This cross-sectional study enrolled 54 genetically identified LQTS patients (29 LQT1 and 25 LQT2) recruited from 3 medical institutions. The QT-apex (QTa) interval and the QT-end (QT_e) interval at each 15-second were plotted against the R-R intervals and the linear regression (QTa/RR and QT_e/RR slopes, respectively) were calculated from the entire 24-hour and separately during the day or night-time periods of the Holter recordings. **Results** The QT_e/RR and QTa/RR slopes at the entire 24-hour were significantly steeper in LQT2 compared to those in LQT1 patients (0.262 +/- 0.063 vs 0.204 +/- 0.055, P = 0.0007; 0.233 +/- 0.052 vs 0.181 +/- 0.040, P = 0.0002, respectively). The QT_e interval was significantly longer, QT_e/RR and QTa/RR slopes at daytime were significantly steeper in LQT2 than in LQT1 patients. The receiver operating curve analysis revealed that the QTa/RR slope of 0.211 at the entire 24-hour Holter was the best cut-off value for differential diagnosis between LQT1 and LQT2 (sensitivity: 80.0%, specificity: 75.0% and area under curve: 0.804 [95%CI = 0.68-0.93]). **Conclusion** The continuous 24-hour QT/RR analysis using the Holter monitoring may be useful to predict the genotype of congenital LQTS, particularly for LQT1 and LQT2.

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cross-sectional study

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Abstract

Background

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Objectives

This study aims to evaluate the utility of QT/RR slope analysis by the 24-hour Holter monitoring for differential diagnosis of LQTS-genotype between LQT1 and LQT2.

Methods

This cross-sectional study enrolled 54 genetically identified LQTS patients (29 LQT1 and 25 LQT2) recruited from 3 medical institutions. The QT-apex (QTa) interval and the QT-end (QTe) interval at each 15-second were plotted against the R-R intervals and the linear regression (QTa/RR and QTe/RR slopes, respectively) were calculated from the entire 24-hour and separately during the day or night-time periods of the Holter recordings.

Results

The QTe/RR and QTa/RR slopes at the entire 24-hour were significantly steeper in LQT2 compared to those in LQT1 patients (0.262 +/- 0.063 vs 0.204 +/- 0.055, $P = 0.0007$; 0.233 +/- 0.052 vs 0.181 +/- 0.040, $P = 0.0002$, respectively). The QTe interval was significantly longer, QTe/RR and QTa/RR slopes at daytime were significantly steeper in LQT2 than in LQT1 patients. The receiver operating curve analysis revealed that the QTa/RR slope of 0.211 at the entire 24-hour Holter was the best cut-off value for differential diagnosis between LQT1 and LQT2 (sensitivity: 80.0%, specificity: 75.0% and area under curve: 0.804 [95%CI = 0.68-0.93]).

Conclusion

The continuous 24-hour QT/RR analysis using the Holter monitoring may be useful to predict the genotype of congenital LQTS, particularly for LQT1 and LQT2.

Key Words: ECG, long QT syndrome, Holter monitoring, QQ/RR relationships

Introduction

Congenital long QT syndrome (LQTS) is a hereditary disorder characterized by prolonged QT interval and fatal ventricular arrhythmias.^{1,2} The clinical course and the treatment consideration in the congenital LQTS are genotype-specific. The most frequent types of LQTS are LQT1 and LQT2, caused by mutations in genes of the potassium channels. Cardiac events are often associated with a sympathetic response by physical stress in LQT1 patients, and beta-blockers are more effective than those in LQT2 patients.^{3,4} Therefore, the differential diagnosis between LQT1 and LQT2 is important but can be difficult with standard 12-lead ECG.

The QT–RR relationship using Holter ECG recordings is a novel method for evaluating QT adaptation to the heart rate change, and it has been reported to be useful for detecting LQTS. Patients with LQTS showed an abnormal prolongation of the QT intervals at lower heart rate, resulting in a steeper QT/RR slope than in controls.^{5, 6} Furthermore, previous studies suggested that the heart rate dependence of QT interval was steeper in LQT2 than in LQT1, and QT intervals at slower heart rate were longer in LQT2 patients than those in LQT1 patients.^{7, 8} Therefore QT/RR relationship obtained from Holter monitoring may be useful for differential diagnosis between LQT1 and LQT2.

In the present study, we aimed to further evaluate the utility of QT/RR slope by 24-hour Holter monitoring by examining that separately at daytime and at night time for differential diagnosis between LQT1 and LQT2.

Methods

This prospective cross-sectional study included 29 LQT1 patients genetically identified, and 25 LQT2 patients (mean age 23.4 $\pm$ 14.9 years, 7 males) recruited from 3 medical institutions from April 2014 to March 2019.

Genetic studies

In the present study, all patients were already genetically diagnosed with LQT1 or LQT2 by extracting genomic DNA from the leukocytes, then using a combination of polymerase chain reaction, either denaturing high-performance liquid chromatography or single-stranded conformation polymorphism and DNA sequencing.

Standard 12-lead ECGs

We used a standard 12-lead ECG tracing at 25-mm/s paper speed and 10-mm/mV amplitude. Their standard 12-lead ECG was without any suspicious abnormalities (e.g., signs of ventricular hypertrophy, intraventricular conduction disturbances) except QT prolongation.

Holter ECG

A digital ECG recording device (Kenz Cardy 303 pico+; SUZUKEN Co., Ltd., Nagoya, Japan) with a sampling rate of 125Hz was used with an automatic measurement system (Kenz Cardy Analyzer 05®; SUZUKEN Co., Ltd., Nagoya, Japan). Consecutive sinus beats every 15 seconds were averaged, and each parameter was measured. The rate-corrected QT interval (QTc interval) was determined according to the Bazett formula. The QT_e interval was defined as the time between the QRS onset and the point at which the isoelectric line intersected a line tangent to the maximal (or minimal) downslope of the positive (or negative) T-wave. The QT_a interval was defined as the time between the QRS onset and the apex (or nadir) of the T wave (**Figure 1**). The linear regression slopes of the QT_a interval and the QT_e interval plotted against RR intervals (QT_a/RR and QT_e/RR slopes, respectively) were calculated by the least-squares method. The QT_e-QT_a interval was defined as the time between the QT apex and the QT end, and was also plotted against RR intervals (QT_e-QT_a/RR slope). These data were compared between a non-sleep period (daytime) and an actual sleep period (night time).

The study protocol was approved by the Institutional Review Board of each participating institution, and written informed consent was obtained from all patients.

Statistical analysis

Measurements are presented as mean value $\pm$ SD. Comparisons of measurements between two groups were analyzed by Mann–Whitney U test. Fisher exact test was used for discrete variables. Receiver-operator characteristics (ROC) curves were used to optimize each parameter’s cutoff value for differentiation between LQT1 and LQT2.

A p-value < .05 was considered significant. Statistical calculations were performed with SPSS version 20 software (IBM Inc., Chicago, Illinois, USA).

Results

Clinical characteristics

The clinical characteristics of both groups are shown in Table 1. No significant differences were found in age, sex, use of beta-blockers, and history of syncope.

Holter analysis

Average QTe was significantly longer, and QTe/RR and QTa/RR slopes from entire 24-hour Holter recordings were significantly steeper in the LQT2 patients than those in the LQT1 patients (472.0 ± 40.6 vs 447.1 ± 44.8 ms, $P = 0.037$; 0.262 ± 0.063 vs 0.204 ± 0.055 , $P = 0.0007$; 0.233 ± 0.052 vs 0.181 ± 0.040 , $P = 0.0002$, respectively). Representative QT trend graph in both groups are shown in **Figure 2**, and representative QTa/RR slopes from entire 24-hour, daytime and night time Holter recordings in both groups are shown in **Figure 3-5**, respectively. QTe/RR and QTa/RR slopes from daytime Holter recordings in the LQT2 patients were also significantly steeper than those in the LQT1 patients (0.197 ± 0.057 vs 0.158 ± 0.066 , $P = 0.024$; 0.190 ± 0.048 vs 0.153 ± 0.050 , $P = 0.008$, Table 1). There were no significant differences in the other parameters (**Table 1**).

ROC analysis

The receiver operating curve analysis revealed that the QTa/RR slope of 0.211 at the entire 24-hour Holter was the best cutoff value for differential diagnosis between LQT1 and LQT2 (sensitivity: 80.0%, specificity: 75.0% and area under the curve: 0.804 [95%CI = 0.68-0.93], **Figure 6**). Meanwhile, it showed an optimal cutoff point of 0.255 of the QTe/RR slope with 60.0% sensitivity and 89.3% specificity. The area under the curve of 0.774 (95% confidence interval, 0.64-0.91) was lower than that of the QTa-RR slope.

Discussion

The present study demonstrated that QTe/RR and QTa/RR slopes from entire 24-hour and daytime Holter recordings were significantly steeper in the LQT2 patients in contrary to LQT1 patients. A cutoff score of 0.211 of QTa/RR slope from entire 24-hour Holter recordings was most optimal to differentiate LQT1 from LQT2 (sensitivity, 80%; specificity, 75%). The identification of LQTS genotype is crucial because the treatment differ according to LQTS genotype. From an electrocardiographic point of view, broad-based prolonged T waves are commonly observed in the LQT1 syndrome, whereas low-amplitude T waves with a notched or bifurcated configuration are seen frequently in the LQT2 syndrome.⁹ Furthermore, the exercise-stress test and epinephrine infusion test have been proposed for differential diagnosis between LQT1 and LQT2.^{10,11} However, predicting the T wave pattern's value is relatively low, the exercise-stress test and epinephrine infusion test are both provocative tests.

QT/RR relationship analyzed based on long-term Holter recordings can evaluate the QT adaptation to a changing heart rate. It has been demonstrated that the QT/RR slope was significantly increased in patients with structural heart disease.¹²⁻¹⁴ As for LQTS patients, a previous QT/RR relationship analysis showed a linear slope equal to 0.12 ± 0.04 in healthy subjects and a significantly higher slope in LQT1 and LQT2 carriers (QT slope > 0.17). However, no significant difference was observed at the QT/RR slope between LQT1 and LQT2 (0.17 ± 0.10 vs. 0.22 ± 0.16).¹⁵ In contrast, Yamaguchi et al reported that QT/RR slope was significantly greater in LQT2 than in LQT1 patients (0.207 ± 0.032 vs. 0.163 ± 0.014 , $P < 0.05$).¹⁶

In this multicenter study with all patients genetically identified, QTe/RR and QTa/RR slopes from entire 24-hour and daytime Holter recordings were significantly steeper in the LQT2 patients compared to the LQT1 patients. Our findings support previous studies suggesting that QT/RR relationship may be useful for differential diagnosis between LQT1 and LQT2. The steeper QT/RR slope in the LQT2 than that in the LQT1 is at least due to more significant QT prolongation at an increased heart rate in the LQT1 compared to the LQT2 patients, resulting in a more gradual QT/RR slope at an increased heart rate in the LQT1 patients. Our result may support this speculation that the QT/RR slope at daytime, when a sympathetic tone is higher, was significantly steeper in the LQT2, whereas that at night time, when a sympathetic tone is

lower, was not different between the LQT1 and LQT2. The QT/RR slope is influenced by autonomic balance and has circadian variations.¹⁷ Recently, Page et al. reported that LQT1 patients showed more frequent QTc prolongation during the day than night. In contrast, LQT2 patients showed less frequent QTc prolongation during the day than at night.¹⁸

QTc-QT_a is considered to reflect transmural dispersion of repolarization (TDR) and possibly useful for differential diagnosis between LQT1 and LQT2. Our previous study from the body surface potential mapping showed that the QTc-QT_a was more decreased in LQT1 than that in LQT2 patients after beta-blockade administration.¹⁹ This may explain the reason why beta-blockers are more effective in LQT1 than LQT2. In the present study, there were no significant differences in QTc-QT_a/RR slope between the LQT1 and the LQT2, although the reason of this finding is unclear.

Study Limitations

The present study did not include control subjects, and the sample size was relatively small, limiting the study's power. More extensive prospective studies are needed to confirm our findings and evaluate the QT/RR relationships' clinical utility. However, our study has strength in that this is the first multicenter study, and all patients were genetically identified.

Conclusions

QT/RR relationships using 24-hour Holter monitoring are feasible and may be useful for differential diagnosis between LQT1 and LQT2.

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None

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Figure legends

Figure 1. QT measurement. (a) Consecutive sinus beats every 15 seconds were selected and averaged. (b) Signal averaged waveform. The QT_e interval was defined as the time between the QRS onset and the point at which the isoelectric line intersected a line tangent to the maximal (or minimal) downslope of the positive (or negative) T-wave. The QT_a interval was defined as the time between the QRS onset and the T wave's apex (or nadir). (c) This process was repeated every 15 seconds.

Figure 2. Representative the trend of QT interval along with the 24- hour study in each group. QT trend graph of the LQT2 showed that QT prolongation was more prominent in the night time.

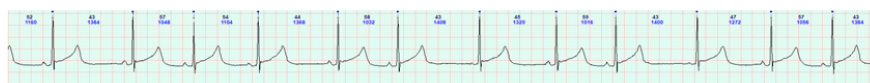
Figure 3. Representative QTa/RR, QTc/RR, QTc-QTa/RR slopes from entire 24-hour Holter recordings in the LQT1 and LQT2 patients. QTa/RR and QTc/RR slopes were steeper in the LQT2 patient than that of the LQT1 patient.

Figure 4. Representative QTa/RR, QTc/RR, and QTc-QTa/RR slopes from daytime Holter recordings in the LQT1 and LQT2 patients. QTa/RR and QTc/RR slopes were steeper in the LQT2 patient than that of the LQT1 patient.

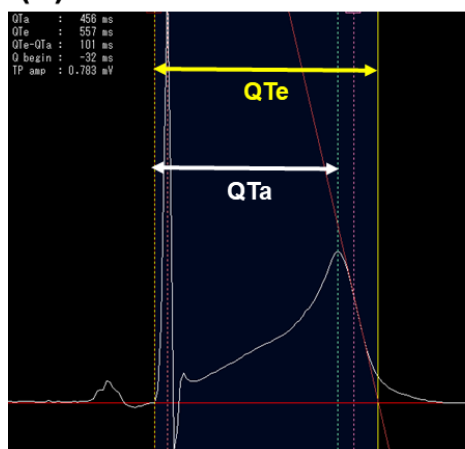
Figure 5. Representative QTa/RR, QTc/RR, QTc-QTa/RR slopes from night time Holter recordings in the LQT1 patients and LQT2 patients. Although QTa/RR slope was steeper in the LQT2 patient than that of the LQT1 patient, the degree was lower than that from entire 24-hour or daytime Holter recordings.

Figure 6. The receiver operating characteristic (ROC) curve analysis showed an optimal cutoff point of 0.211 of QTa/RR slope from entire 24-hour Holter recordings, with 80.0% sensitivity, 75.0% specificity, and an area under the curve of 0.804 (95% confidence interval, 0.68-0.93).

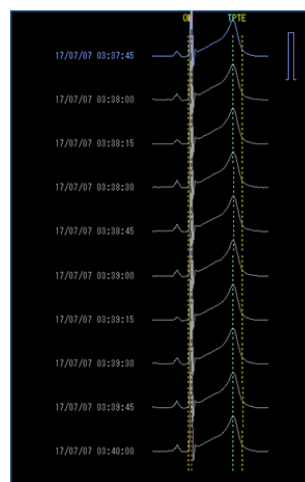
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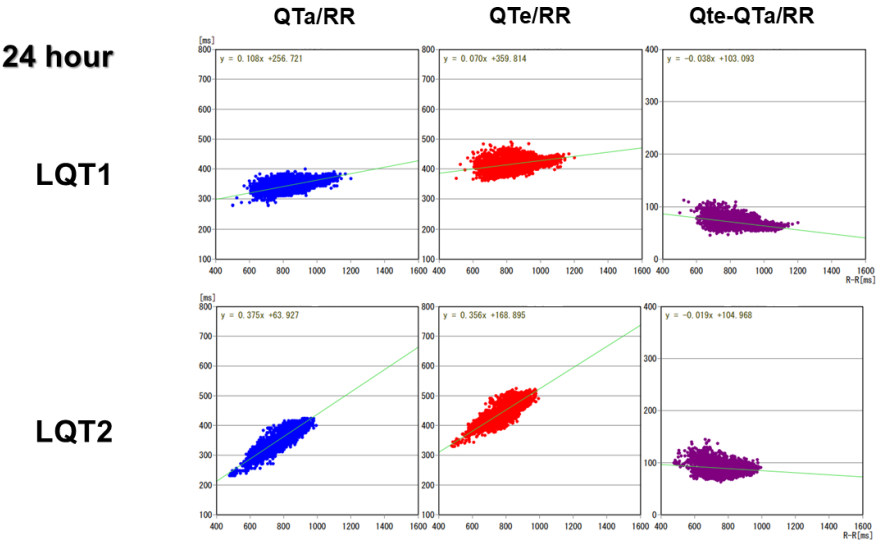
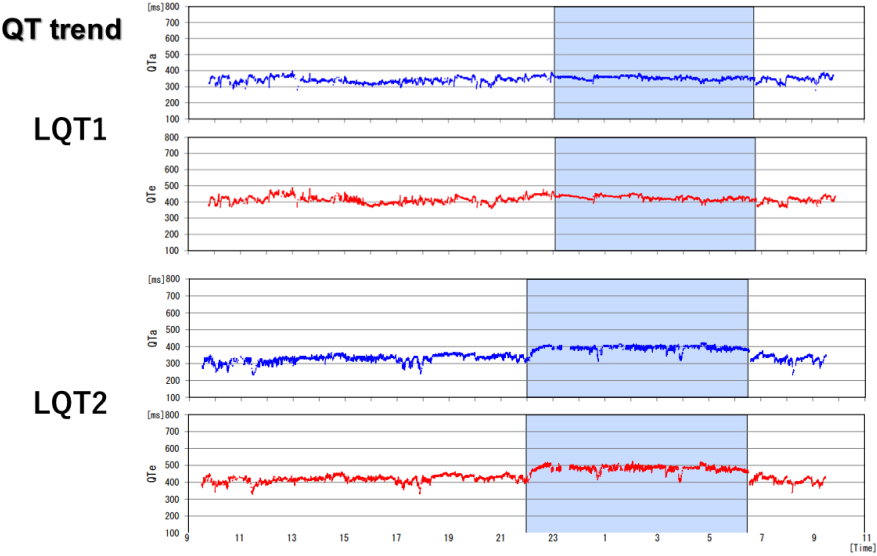


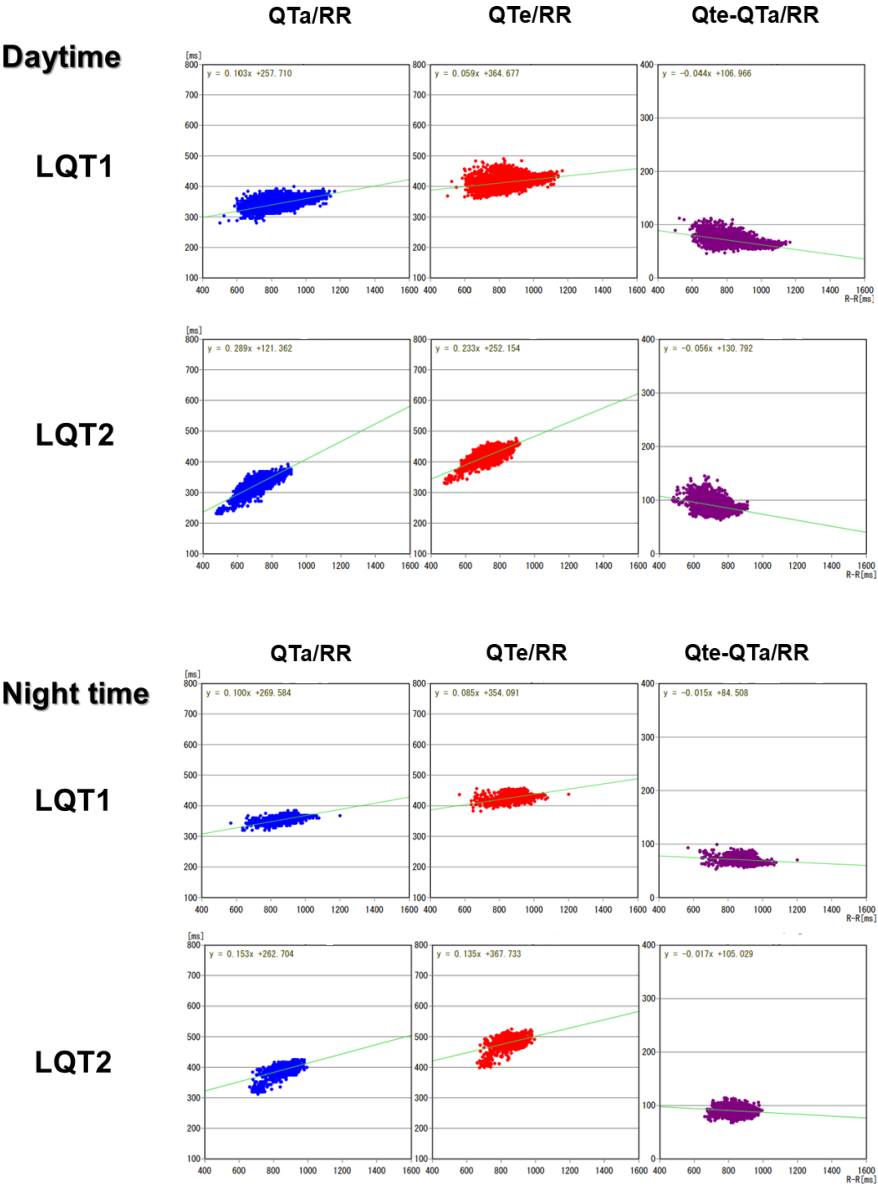
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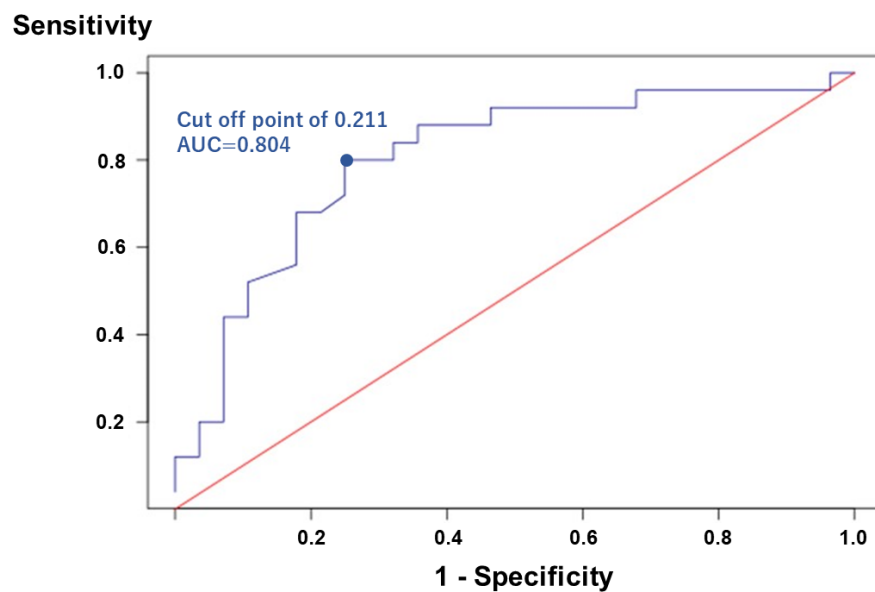


(c)









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