ESC European Society of Cardiology

Europace (2025) **27**, euaf213
https://doi.org/10.1093/europace/euaf213

CLINICAL RESEARCH

Software-based analysis of T-wave morphology: identifying the electrocardiogram signature of high-risk long QT syndrome

Alessandra Pia Porretta [1,2]*, Charles Morgat [1,3], Elodie Surget [1,4], Véronique Fressart [4,5], Adrien Bloch[4,5], Nathalie Neyroud [1,4], Fabio Badilini [6], Martino Vaglio [6], Isabelle Denjoy [1,4], and Fabrice Extramiana [1,4]

[1]CNMR Maladies Cardiaques Héréditaires Rares, APHP, Hôpital Bichat Claude-Bernard, 46 Rue Henri Huchard, Paris 75018, France; [2]Service de Cardiologie, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, Lausanne 1011, Switzerland; [3]Department of Cardiology, Arnault Tzanck Institute Saint Laurent du Var, France; [4]Research Unit on Cardiovascular and Metabolic Diseases, Sorbonne Université, INSERM, UMRS-1166, Paris, France; [5]Service de Biochimie Métabolique, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; and [6]AMPS IIc, New York, NY, USA

Received 30 May 2025; accepted after revision 3 September 2025; online publish-ahead-of-print 11 September 2025

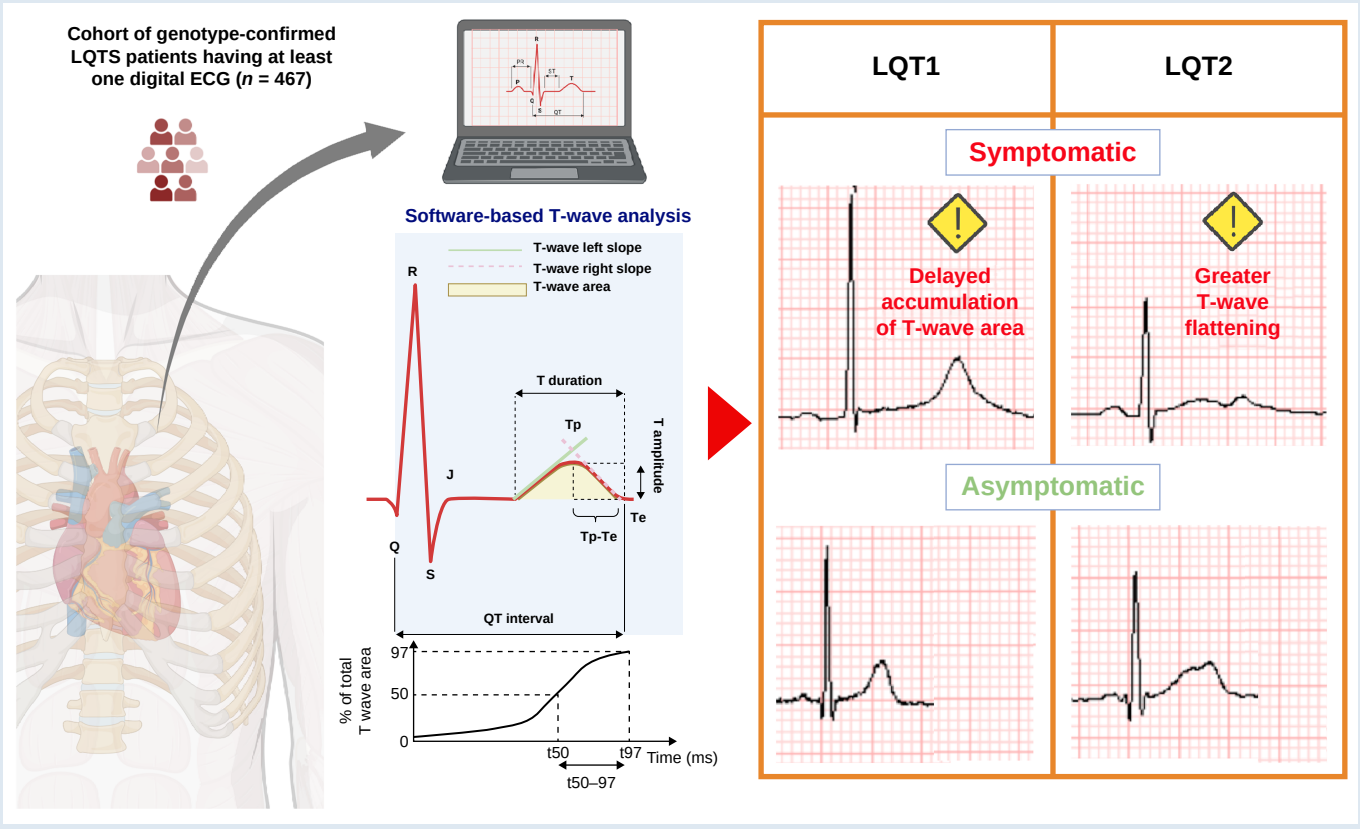
Aims Despite T-wave morphology abnormalities being well-known distinctive ECG features in patients with long QT syndrome (LQTS), the subjectivity of qualitative 'eyeballing' in T-wave characterization still hampers its integration into diagnostic/prognostic criteria. We herein evaluated whether our quantitative software-based analysis of T-wave morphology (AnTwM) applied to digital ECGs may identify predictors of cardiac events (CEs) in our cohort of LQTS patients.

Methods and results We enrolled LQT1, LQT2, and LQT3 patients having at least one digital ECG from our cohort of genotype-confirmed LQTS patients. Automated AnTwM analysis, using Glasgow and Bravo algorithms embedded in the CalECG software (AMPS-IIc, USA), provided scalar descriptors of ventricular repolarization. Cox regression analyses identified potential predictors of CEs (i.e. syncope, sudden cardiac death, resuscitated cardiac arrest, or appropriate shock delivered by implantable cardioverter defibrillators). A total of 467 (58% female) patients were followed up for 15 ± 9 years, including 253 (54.2%) LQT1, 182 (39%) LQT2, and 32 (6.8%) LQT3 patients. Corrected QT interval predicted CEs in the whole population (1 ms QTc increase: HR = 1.01, 95% CI: 1.0–1.01, $P = 0.03$) but not across genotyped subpopulations. Genotype-specific ECG markers associated with a greater risk of CEs were (i) those expressing a delayed accumulation of the mid-late T-wave area (decreased t25 and increased t50) among LQT1 patients and (ii) those expressing T-wave flattening/widening (decreased T-wave ascending/descending slopes) among LQT2 patients.

Conclusion The software-based AnTwM on digital ECGs represented a reliable tool in clinical practice and identified unique ECG T-wave 'fingerprints' that allowed prediction of CEs in a genotype-specific manner.

* Corresponding author. Tel: +33 (0)7 66 70 63 57. *E-mail address:* Alessandra-pia.porretta@chuv.ch

Graphical Abstract



Keywords Long QT syndrome • Software-based ECG analysis • T-wave morphology • Risk stratification

What's new?

- Despite T-wave morphology abnormalities being well-known distinctive ECG features in patients with long QT syndrome, the subjectivity of qualitative 'eyeballing' in T-wave characterization still hampers its integration into diagnostic/prognostic criteria.
- We evaluated the potential of a software-based T-wave analysis performed on digitally acquired ECGs to identify new electrical markers capable of discriminating symptomatic from asymptomatic patients in a cohort of genotype-confirmed LQTS patients.
- By providing a standardized evaluation of repolarization using our T-wave analytics tool, we identified unique ECG T-wave 'fingerprints', which allowed the prediction of cardiac events in a genotype-specific manner.
- We demonstrated that the quantitative analysis of repolarization morphology, using a standardized automated approach on digital ECGs, represents a feasible and reliable tool for clinical practice.
- The integration of repolarization heterogeneity features, which capture the ECG signatures of high-risk LQTS, seems to hold great promise in refining risk stratification among LQTS patients.

Introduction

Congenital long QT syndrome (LQTS) is an inherited arrhythmic syndrome characterized by prolonged ventricular repolarization potentially leading to life-threatening arrhythmias through the onset of Torsades de Pointes (TdP).[1] Despite considerable progress, one of the major gaps in knowledge is represented by the absence of clear mechanistic explanations elucidating the incomplete penetrance and the variable expressivity among LQTS patients.[2] Previous studies demonstrated that several features may contribute to refinement of risk stratification, which currently relies on the combined evaluation of clinical characteristics (*e.g.* sex, age, or history of previous arrhythmia), genetic features (*e.g.* gene type, variant location, and related functional effect)[3–7] and ECG (heart-rate corrected QT).

Importantly, as early as 1975, Schwartz *et al.*[8] already demonstrated that ECG abnormalities in LQTS were not limited to QT prolongation but encompassed T-wave abnormalities, mirroring the spatial and temporal alterations of repolarization. Subsequent studies further suggested the prognostic implications of notched T waves, which were associated with an increased risk of arrhythmic events in LQTS.[9] However, only in 1995 did Moss *et al.* first describe peculiar qualitative T-wave characteristics according to LQTS subtypes.[9–12] Type 1 LQTS (LQT1) patients often display T waves with broad base and early onset, while Type 2 LQTS (LQT2) patients present with biphasic/notched T waves, often asymmetric and of low amplitude. Finally, Type 3 LQTS (LQT3) patients frequently exhibit normal morphology T waves with typical late-onset preceded by a prolonged isoelectric ST-segment.[10,13] However, despite such well-known T-wave features, the analysis of T-wave morphology has not yet been fully and formally incorporated into diagnostic criteria, except for the presence of a notched T wave in three leads or the evidence for T-wave alternans, which both represent contributive features of the LQTS diagnostic score.[14,15] The failure to incorporate into formal

diagnostic criteria a broader assessment of T-wave morphology may be probably explained by the subjectivity of qualitative 'eyeballing' in T-wave characterization, as well as by its reliance on the cardiologist's experience, which often undermines the diagnostic contribution of T wave analysis.[16] In addition, previous attempts to quantitatively analyse repolarization were often manually performed on paper ECGs, with a significant lack of result consistency, accuracy, and reproducibility. Moreover, manual measures risk being time-consuming and thus less practical in case of systematic assessments among large amounts of patients. Thus, the quantitative and potentially automated assessment of T-wave morphology may have a huge diagnostic potential in LQTS.

In the current study, we evaluated whether our integrated and software-based T-wave analysis, performed on digitally acquired ECGs, may identify novel electrical markers to differentiate between symptomatic and asymptomatic patients in our cohort of genotype-confirmed LQTS patients. Secondly, we investigated whether this automated T-wave analysis allowed the identification of prognostic markers in a genotype-specific manner, and we further analysed their predictive performance as compared to traditional prognostic factors.

Materials and methods

Study population

The population of the present study was identified from the historical prospective registry of genotype-confirmed LQTS patients followed from September 1993 to June 2021, at the Reference Center for Inherited Arrhythmia Syndromes of the Bichat-Claude Bernard University Hospital in Paris, France. Demographic, genetic, and clinical data were systematically recorded at each visit.

Patients were enrolled for this analysis if they (i) were carriers of heterozygous pathogenic or likely pathogenic variants in *KCNQ1*, *KCNH2*, or *SCN5A* confirming the diagnosis of LQT1, LQT2, and LQT3, respectively, and (ii) had at least one digitally recorded ECG recorded at baseline and/or at follow-up visits. Conversely, patients carrying homozygous pathogenic or likely pathogenic variants in *KCNQ1* or *KCNE1* (*i.e.* affected by Type 1 or 2 Jervell and Lange-Nielsen syndrome) were excluded from the study, as were patients who did not undergo a follow-up visit within 1 year from the diagnosis or with digital ECGs of insufficient quality to allow automated analysis. For each patient enrolled, demographic and clinical data were retrospectively reviewed including personal and family history, mode of diagnosis (symptom-driven, secondary to familial screening or incidental diagnosis), age at clinical and genetic diagnosis, Schwartz score, age at symptom onset, type of symptoms (syncope or other arrhythmic events), circumstances of symptom onset, medications before and after the diagnosis, and non-pharmacological therapy (i.e. device implantation and sympathetic denervation). As about symptoms, we recorded as 'severe arrhythmic events' (SAEs) the onset of any sudden cardiac death, resuscitated cardiac arrest, or any appropriate electrical shock delivered by an implantable cardioverter defibrillator (ICD). We documented instead as 'arrhythmic events' (AEs) the onset of any SAE or syncope.

The genetic data were obtained from genetic tests and results realized in clinical practice for diagnostic purposes,[17] according to the standard protocols of the Genetics and Cytogenetics Laboratory of the APHP Pitié-Salpêtrière Hospital. The affected protein site was documented and characterized according to its location in the channel pore regions or elsewhere. We also classified the variants according to the biophysical functional effect expected for the mutant protein. Based on the literature,[7,18] we assumed haploinsufficiency for non-missense variants including truncating, frameshift, or splicing mutations, while a dominant negative effect was presumed for missense variants or in-frame deletions.

All patients or their legal representatives signed an informed consent to allow the collection of personal clinical and genetic data and their use for research purposes. In addition, the database was collected complying with the National French Data Protection [*Commission Nationale de l'Informatique et des Libertés (CNIL)*]. Due to the design of the study based on routine clinical practice, the approval of the study protocol by an institutional review board was not necessary.

Automated analysis of digitally recorded electrocardiograms

Digital ECGs were obtained from digitalization of patients' analogue cardiac electrical signals using a MAC 5500 device (General Electric©, Boston, MA, USA) with a 4.88 μV resolution and a 4 kHz sampling frequency. The automated analysis of T-wave morphology was then performed by an integrated approach which combined measurements outputted by two software programmes previously described,[19,20] namely, the Glasgow and the Bravo algorithms. In brief, both programmes analysed the reconstructed 10 s 12-lead ECG, the representative beats of each lead being identified through the embedded CalECG software (AMPS-IIc, NY, USA). This latter allowed the measurement of representative beats based on the semi-automatic or the manual determination of pivotal calliper positions (*e.g.* QRS beginning, QRS end, and T-wave end). It is important to note that prior to T-wave analysis, all determinant calliper positions related to patients' ECGs were visually checked and manually corrected by an expert operator (F.E.), when appropriate. Moreover, analysis of representative beats prevented any potential data selection bias, since software analysis was performed on the same waveforms. *Table 1* and *Figure 1* summarize the scalar time intervals and the T-wave morphology parameters computed by the two software programmes. For simplicity, repolarization features were grouped into three categories: (i) markers of T-wave area distribution during ventricular repolarization including Tx, SymArea, SymT, S1/S2, A1, and A2; (ii) markers of duration of ventricular repolarization including TpTe, QTc, mu, and QT dispersion; and (iii) markers of T-wave spread including S1, S2, Lslope, and Rslope.

Statistical analysis

Normally distributed continuous variables were expressed as mean values ± standard deviation, while non-normally distributed continuous variables were reported as median values and interquantile ranges (IQRs). Depending on distribution type (normal or non-normal), the independent-sample *t*-test, the analysis of variance (ANOVA), or the Kruskal–Wallis test was used to assess differences between continuous variables. Categorical variables were expressed as absolute number (*N*) and percentage. Differences between categorical data were evaluated using the χ^2 test or Fisher's exact test. A *P*-value <0.05 was set to identify statistical significance.

The analysis of event-free survival was performed using the Kaplan–Meier method, and event-free survival curves were compared using the log-rank test. Event collection was censored when the first cardiac event occurred during follow-up. A univariate Cox model allowed the assessment of potential risk factors for AEs/SAEs occurrence from birth. In line with the aim of our study and with previous literature, we opted for applying Cox models from birth through the end of follow-up (instead of starting follow-up from the time of ECG acquisition) to allow uniform comparison across patients with different ages, while avoiding potential lead-time and selection biases associated with the variable timing of the first available ECG. We further incorporated factors with a *P*-value <0.1 in a multivariable Cox regression model to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Notably, to assess the role of ECG markers as potential risk factors for AEs/SAEs occurrence, the first available digitalized ECG was considered for each patient. All statistical analyses were implemented using

Table 1 Repolarization parameters collected for analysis

Parameters	Description	Unit	Reference
BRAVO software			
QTc	QT corrected using Bazett's formula	ms	21
TpTe	T peak–T end interval	ms	22
Tx (25, 50, 75, 97)	Time to accumulate the x part (from 25 to 97%) of the total T-wave area divided by the absolute QT interval	%	23
Tx_X	Time to accumulate the part from x% to X% of the total T-wave area divided by the absolute QT interval	%	23
A Tot T	Total area of repolarization of the T-wave	μV*ms	
SymArea	Ratio of the areas of the T-wave before and after its peak	—	
Lslope	Coefficient of the upward slope of the T-wave	μV/ms	
Rslope	Coefficient of the downward slope of the T-wave	μV/ms	
Mu (μ)	Position in time of a function containing two hemi-Gaussian functions used to model the T wave from the main component signal of the principal component analysis (PCA)	ms	24
S1, S2	Width of the two hemi-Gaussian functions used to model the T-wave	ms	24
S1/S2	Ratio between the widths of the two hemi-Gaussian functions used to model the T-wave	—	24
A1, A2	Amplitudes of the two hemi-Gaussian functions used to model the T-wave	μV	24
GMF Error	Residual error of the function containing two hemi-Gaussian functions used to model the T wave		
Tamp	T maximum amplitude	μV	
GLASGOW software			
QT dispersion	Maximal difference between lead-related QT intervals	ms	25
QRS, ST, T frontal axis	Interval-related axes obtained from frontal leads		

R[26] [version 4.5.0 (2025-04-11), R Core Team, Vienna, Austria] with survival analyses conducted using the survival, survminer, and ggplot2 packages. Additional tests (*t*-test, ANOVA, Kruskal–Wallis, χ^2 test, and Fisher's exact test) were performed using base R functions with the stats package.

Results

Our prospective registry of genotype-confirmed LQTS patients included 1504 patients: 631 LQT1, 556 LQT2, 173 LQT3, 33 patients suffering from a Jervell and Lange-Nielsen Syndrome (JLNS), and 105 heterozygous JLNS family members.

In this cohort, 1083 12-lead digital ECGs were performed among 484 (32.2%) patients (2.2 ECGs per patient) from 217 different families, including 136 probands (proband/family ratio of 0.6). Due to not available/uncertain genetic results ($n = 12$), to the detection of JLNS homozygous variants ($n = 4$), or to uninterpretable digital ECGs ($n = 1$), 17 patients were excluded from the study.

A total of 467 (58% female) patients were finally included in the analysis encompassing 253 (54.2%) LQT1, 182 (39%) LQT2, and 32 (6.8%) LQT3 patients. *Table 2* summarizes patients' characteristics. The exhaustive list of detected variants is displayed in the Supplementary material (Supplementary material online, *Tables S1*, *S2*, and *S3*). A variant located in the channel pore regions was pointed out among 53 (11.6%) patients. According to literature criteria,[7,18] haploinsufficiency was assumed for 119 (25.5%) variant carriers while a variant with a presumed dominant negative effect was detected in the remaining 348 (74.5%) patients.

Patients presented with at least one AE at the time of diagnosis numbered 141 (30.2%), with a mean age at first AE occurrence of 18 ± 15 years and a mean interval between first AE occurrence and diagnosis of 8 ± 8 years. The global annual incidence of AEs and SAEs was 1.2 and 0.1 per 100 patients-year. As about treatment, only 23 patients (4.9%) were already treated with beta-blockers at the time of diagnosis due to extra-cardiac reasons or to anti-hypertensive purposes.

Comparing symptomatic and asymptomatic patients, we observed a greater proportion of females (65 vs. 54%, $P = 0.04$), a greater Schwartz score (5 ± 1 vs. 2.8 ± 1, $P < 0.001$), a longer QTc (477 ± 38 vs. 458 ± 33 ms, $P = 0.01$), and a greater proportion of pore mutation carriers (18, 4 vs. 8.3%, $P < 0.01$) in the symptomatic group. Conversely, a greater number of patients carrying haploinsufficient variants was detected in the asymptomatic group (28.2 vs. 19.3%, $P = 0.04$). Of note, among the 119 carriers of a haploinsufficient variant at diagnosis, 18 were heterozygous family members of JLNS patients. All 18 were asymptomatic at diagnosis, representing 19.6% (18/92) of the asymptomatic patients carrying a haploinsufficient variant. After excluding these 18 heterozygous JLNS patients from the analysis, the proportion of patients carrying haploinsufficient variants remained significantly higher in the asymptomatic group compared to the symptomatic one (24 vs. 19.3%, $P = 0.04$), indicating that the difference was not solely attributable to the presence of heterozygous JLNS carriers. No significant difference in terms of genotype distribution was observed between the symptomatic and asymptomatic groups at diagnosis.

Clinical follow-up

The mean follow-up period was 15.2 ± 9.2 years, and the study involved 445 patients. Of note, 22 patients were excluded from the follow-up analysis since they did not undergo a follow-up visit within 1 year from the diagnosis. As summarized in *Figure 2*, during follow-up, 64 patients (14.4%) developed at least one AE, including syncope in 48 patients and SAEs in 16 patients.

Among patients with SAEs, we reported seven (43.8%) resuscitated cardiac arrests, six (37.5%) sudden cardiac death, and three (18.7%) appropriate electrical shock delivered by an ICD. The AE and SAE annual

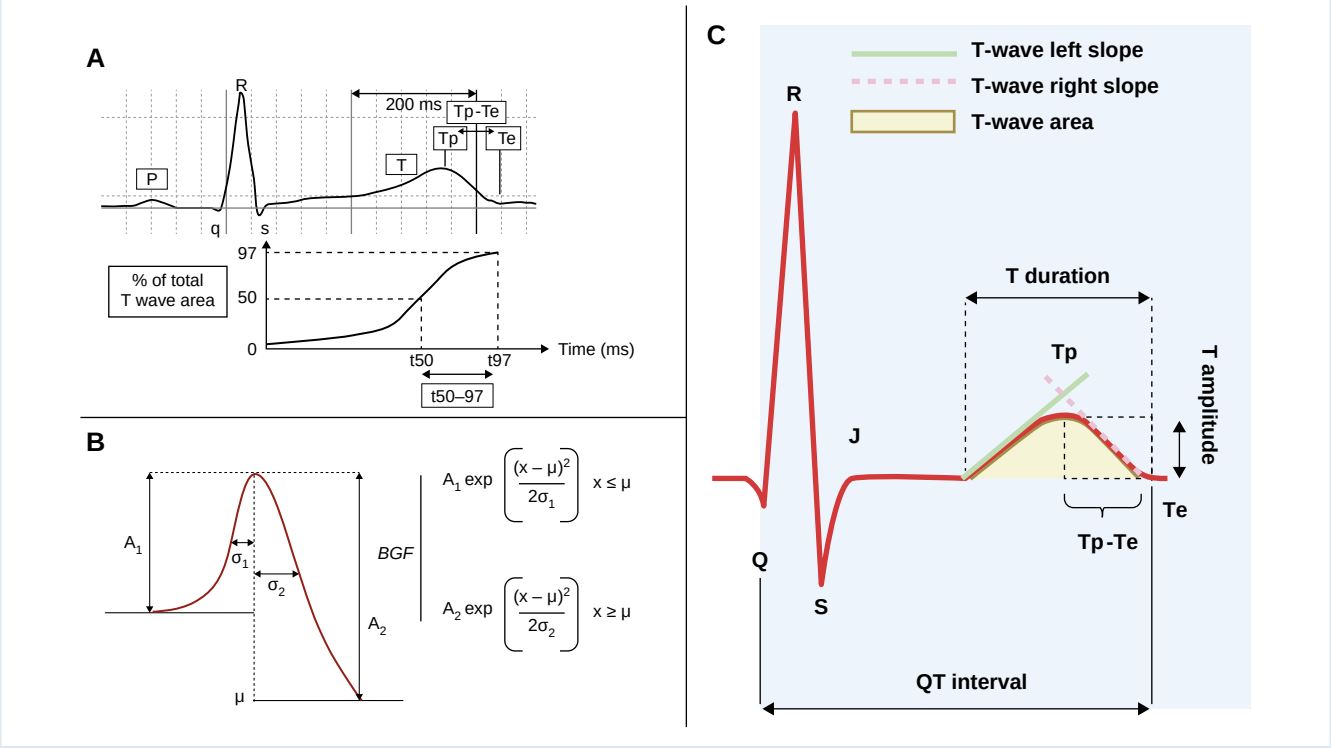


Figure 1 Illustration of the ECG features analysed by our T-wave analytics tool. Panel *A*: Adapted from Extramiana *et al.*[23] Panel *B*: Adapted from Dubois *et al.*[24] Representation of the bi-Gaussian function (BGF) as a five-parameter function made of two half-Gaussian functions with different amplitudes: μ is the location of the function in time; σ1 and σ2 are the widths of the first and second Gaussian functions, respectively; σL is the length of the horizontal segment; and A_1 and A_1 are the amplitude of each half-Gaussian function. Tp, T peak; Te, T end; TpTe, T peak–T end interval.

Table 2 Patients' clinical characteristics at diagnosis

	Whole cohort (*n* = 467)	Asymptomatic at diagnosis (*N* = 326)	Symptomatic at diagnosis (*N* = 141)	*P*
Female, *n* (%)	270 (58)	178 (54)	92 (65)	0.04
Age at diagnosis (year)	26.2 ± 19	26.3 ± 20	25.7 ± 17	0.86
Diagnosis context				
• LQTS symptoms, *n* (%)	99 (21)	7 (2)	92 (65)	<0.01
• Familial screening, *n* (%)	329 (70.4)	286 (88)	43 (30.5)	
• Incidental finding, *n* (%)	39 (8)	33 (10)	6 (4.2)	
Index case (%)	136 (28)	39 (12)	95 (67.4)	<0.01
Age at first AE (year)	17.7 ± 15		17.7 ± 15	
Interval between AE occurrence and diagnosis (year)	8.3 ± 7.8		8.3 ± 7.8	
Schwartz score	3.5 ± 1.6	2.8 ± 1	5 ± 1	<0.01
QTc (Bazett) (ms)	467 ± 36	458 ± 33	477 ± 38	0.01
Genotype				
• LQT1, *n* (%)	253 (54.2)	180 (55)	73 (51.7)	0.67
• LQT2, *n* (%)	182 (39)	122 (37.4)	60 (42.5)	
• LQT3, *n* (%)	32 (6.8)	23 (7.1)	9 (6.4)	
Pore mutation, *n* (%)	53 (11.6)	27 (8.3)	26 (18.4)	<0.01
Haploinsufficiency, *n* (%)	119 (25.5)	92 (28.2)	27 (19.3)	0.04

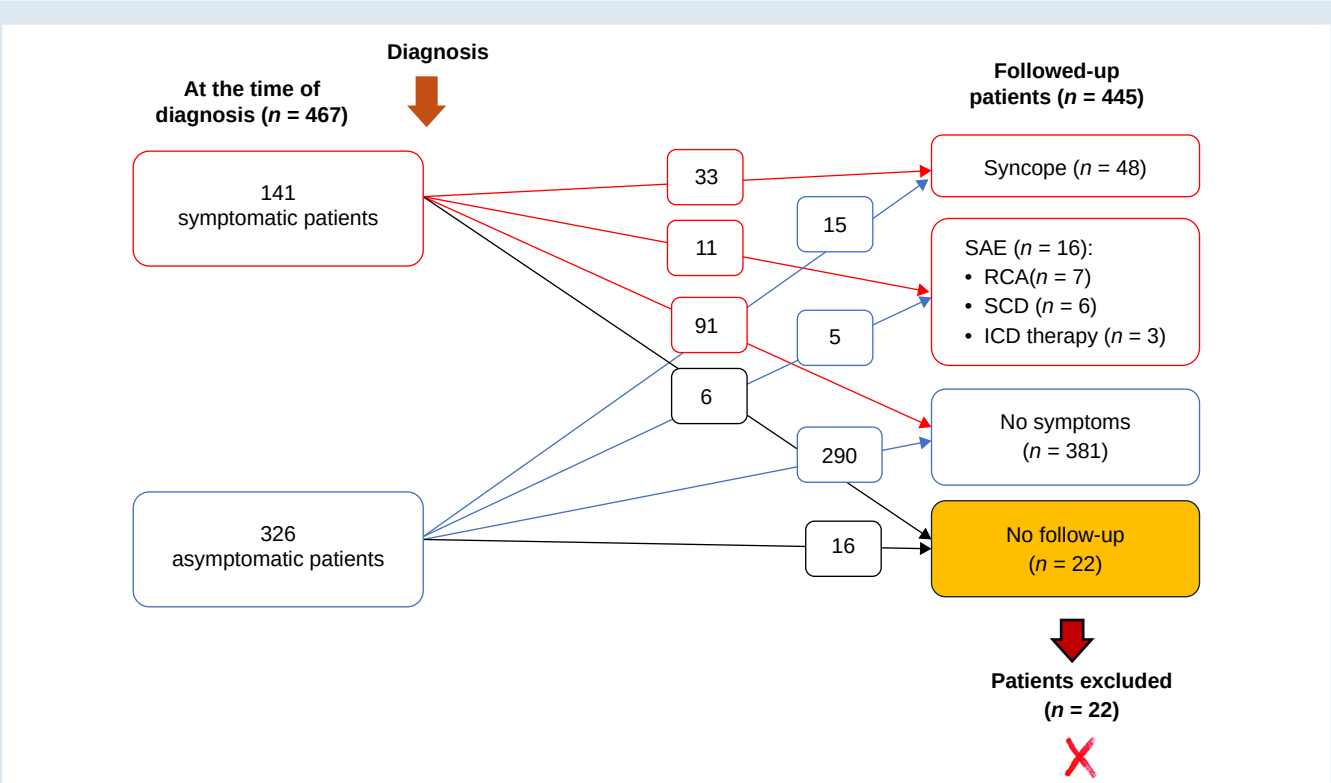


Figure 2 Flowchart of patients included in the analysis. SAE, severe adverse event; RCA, resuscitated cardiac arrest; SCD, sudden cardiac death; ICD, implantable cardiac defibrillator.

incidences were 0.9 and 0.24 per 100 patients-year, respectively, with a median delay between diagnosis and AE or SAE occurrence of 6 and 2 years, respectively. *Table 3* summarizes patients' clinical characteristics during follow-up.

Comparing symptomatic and asymptomatic patients during follow-up, the proportion of females was similar between groups. However, the sex-related event-free survival curves pointed out a greater rate of AEs among females over the age of 13 ($P < 0.01$, HR = 1.23, 95% CI: 0.99–6.02). Conversely, we did not appreciate any statistically significant association between genotype and event-free survival ($P = 0.08$, 95% CI: 0.96–1.11) (Supplementary material online, *Figures S1* and *S2*). In addition, the symptomatic group was characterized by a significantly greater number of patients diagnosed following symptoms, and a positive personal history of AEs prior to diagnosis was associated with a five-fold increase in the risk of AE recurrence during follow-up. Regarding treatment, beta-blockers were started during follow-up among 355 (79.8%) patients including, in the most part of cases, nadolol (64%) or bisoprolol (24%). Of note, 59 (92.2%) out of the 64 AEs recorded occurred despite beta-blocker treatment, accounting for an incidence of AEs despite beta-blockers of 0.86 per 100 patients-year. However, at least 15 (25.4%) patients formally acknowledged that they had not taken the treatment the day of the event. Left cardiac sympathetic denervation was performed only in two LQT2 patients for secondary prevention, due to recurrent syncope despite beta-blockers during FU, with no relapse thereafter.

T-wave analysis on digitalized electrocardiograms in the entire LQTS population

Considering the initial cohort of 467 LQTS patients, 1050 digital ECGs were performed, accounting for a mean of 2.2 ECGs per patient. After checking for determinant calliper positions (including RR, PR, QRS, and QT intervals), a manual correction was performed for 109 (10.4%) ECGs, while the erroneous QRS detection in two ECGs led to their exclusion from the analysis. The exhaustive list of patients' ECG parameters automatically computed vs. computed after visual validation is summarized in the Supplementary material (Supplementary material online, *Tables S4–S7*). The mean age at the time of their first ECG was 29 ± 18 years.

We performed univariate and multivariable Cox models to investigate AE predictors in the global population using data available since birth. The analysis was performed on the first digitalized ECG available for each patient. Notably, 123 out of 445 (27.6%) were acquired under treatment. Conversely, none of the ECGs included in the analysis was acquired under atrial/ventricular pacing, and, for both patients undergoing cardiac sympathetic denervation, the analysed ECG was recorded prior to the denervation procedure. Results of univariate analyses are reported in the Supplementary material (Supplementary material online, *Table S8*). Following multivariable analysis, the presence of a variant affecting the channel pore (HR = 1.68, 95% CI: 1.03–2.73, $P = 0.04$) was the sole genetic factor independently associated with AE occurrence. Considering ECG parameters, we demonstrated that the QTc (HR = 1.01, 95% CI: 1.0–1.01, $P = 0.03$) and the mu values, expressing repolarization duration, were both associated with an increased risk of AEs. Moreover, we observed that ECG markers translating (i) a delayed accumulation of T-wave area (greater t50, t97, and S1/s2 and lower t25) or (ii) a tendency towards the widening of the T-wave base with reduction of slope parameters (S1) were associated with an increased risk of AEs (*Table 4*). Notably, to account for the heterogeneity in the timing of ECG acquisition as a potential source of bias, we performed two additional sets of analyses. First, we included the age at first ECG acquisition as a further covariate in the model. Second, we re-applied the Cox model using the time of ECG recording, rather than the time of birth, as the

Table 3 Patients' clinical characteristics during follow-up (FU)

	Whole cohort (*n* = 445)	Asymptomatic during FU (*N* = 381)	Symptomatic during FU (*N* = 64)	*P*
Female, *n* (%)	259 (58)	215 (56.4)	44 (68.8)	0.09
Age at diagnosis (year)	26,2 ± 19	26 ± 19	24 ± 18	0.35
Diagnosis context				
• LQTS symptoms, *n* (%)	94 (21)	61 (16)	33 (51.5)	<0.01
• Familial screening, *n* (%)	311 (70)	283 (74)	28 (43.8)	
• Incidental finding, *n* (%)	39 (9)	36 (9)	3 (4.7)	
Schwartz score	3.5 ± 1.6	3.3 ± 1.5	4.7 ± 1.4	<0.01
Treatment started during FU	355 (80)	296 (78)	59 (92)	0.01
Treatment type				
Nadolol	226 (51)	176 (46)	50 (78)	<0.01
Bisoprolol	67 (20)	81 (21)	6 (9)	0.04
Other beta-blocker	13 (3)	12 (3)	1 (1.5)	0.7
Age at treatment introduction	26.2 ± 18	26 ± 18	25.8 ± 19	0.84
Treatment inobservance	57 (13)	42 (11)	15 (23)	0.05
ICD implantation	31 (7)	26 (6.8)	5 (7.8)	0.01
Left cardiac sympathetic denervation	2 (0.4)	0 (0)	2 (0.05)	
Genotype				
• LQT1, *n* (%)	236 (53)	207 (54)	29 (45)	0.32
• LQT2, *n* (%)	178 (40)	147 (39)	31 (48)	
• LQT3, *n* (%)	31 (7)	27 (7)	4 (6)	
Pore mutation	51 (11)	40 (11)	11 (17)	0.18
Haploinsufficiency	115 (26)	102 (27)	13 (20)	0.31

starting point of follow-up. In both cases, the great part of key ECG markers maintained statistical significance, consistent with the original analysis. For those ECG markers that lost significance in the revised models, the hazard ratios and 95% CI remained directionally consistent with those observed in the main analysis (see Supplementary material online, *Tables S9* and *S10*). All these findings supported the solidity of our results independently of the timing of ECG acquisition.

Genotype-specific electrocardiogram predictors of arrhythmic events

We further focused on univariate and multivariable Cox models to investigate specific AE predictors within each LQTS genotype subgroup.

- **LQT1-specific ECG predictors**

  Among LQT1 patients, arrhythmic risk was independently predicted by ECG parameters reflecting a delayed accumulation of the mid-late T-wave area. We observed indeed a higher risk of AEs associated with prolonged t50 (HR = 1.53; 95% CI: 1.04–2.26; $P = 0.03$) and t97 (HR = 1.20; 95% CI: 1.05–1.37; $P < 0.01$) values which represent the time to reach the 50% and 97% of T-wave area, respectively, translating a more delayed and protracted final stage of the repolarization process. Interestingly, longer t25 (HR = 0.56; 95% CI: 0.38–0.84; $P < 0.01$) and t20_80 (HR = 0.71; 95% CI: 0.53–0.96; $P = 0.02$), reflecting respectively a slower time to accumulate the first 25% and the central 60% of the T-wave area, were associated with a lower risk of AEs (*Table 4*).

- **LQT2-specific ECG predictors**

  We observed a completely different set of high-risk ECG predictors among LQT2 patients. Key markers included lower ascending (LSlope HR = 0.63; 95% CI: 0.38–0.84; $P < 0.01$) and descending (RSlope HR = 0.62; 95% CI: 0.45–0.85; $P < 0.01$) slopes of the T-wave, both reflecting T-wave flattening as a hallmark in high-risk LQT2 patients. Moreover, higher S1/S2 ratios (ratio between the widths of the two hemi-Gaussian functions used to model the T-wave), translating greater T-wave asymmetry and potentially altered repolarization dynamics, were associated with a higher risk of AEs (HR = 1.86; 95% CI: 1.06–3.27; $P = 0.03$) (*Table 4*). These findings highlighted that, differently from LQT1, the risk of AEs in LQT2 is not only driven by repolarization delay, but by the flattening of the T-wave and the widening of its base, translating to a greater dispersion between early and late repolarization phases (*Figure 3*).

- **LQT3-specific ECG predictors**

  Among LQT3 patients, the univariate analysis showed the association between a higher risk of AEs and ECG features translating a delayed end of repolarization such as the time to reach the 75% (HR = 1.17; 95% CI: 1.01–1.36; $P = 0.03$) and the 97% (HR = 1.19; 95% CI: 1.01–1.41; $P = 0.04$) of T-wave area. However, this association did not reach significance in multivariable analysis.

Discussion

The present study evaluated the potential of a software-based T-wave analysis performed on digitally acquired ECGs in identifying new electrical markers to discriminate between symptomatic and asymptomatic patients in a cohort of genotype-confirmed LQTS patients. In this context, beyond corroborating in our population the role of traditional clinical and genetic risk factors, we pointed out two main findings. First, the risk of AEs was associated not only with ECG features translating the well-known prolongation of ventricular repolarization (*i.e.* QTc) but also with abnormalities of T-wave morphology, which were quantitatively and objectively captured by the software-based T-wave analysis. Secondly, the T-wave analytics tool identified genotype-specific sets of ECG markers which offered complementary prognostic

Table 4 Multivariable analysis of AE predictors since birth

	Whole population		LQT1 population		LQT2 population	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Clinical criteria						
Female sex	1.23 (0.94–1.54)	0.081	1.44 (0.96–1.88)	0.072	1.09 (0.63– 1.86)	0.092
Genetic criteria						
Haploinsufficiency	0.78 (0.38– 1.16)	0.096	0.83 (0.62– 1.33)	0.076	1.11 (0.47– 1.33)	0.673
Pore mutation	1.68 (1.03– 2.73)	0.042	1.78 (0.98– 2.37)	0.069	1.44 (0.37– 1.99)	0.211
ECG criteria						
QTc (ms)	1.01 (1–1.01)	0.033	1.01 (0.99–1.00)	0.066	1.01 (0.98–1.00)	0.071
RR (ms)	1.22 (0.80–1.36)	0.891	1.11 (0.54–1.87)	0.817	0.96 (0.33–2.21)	0.551
t50	1.17 (1.01–1.36)	0.044	1.53 (1.04–2.26)	0.035	1.13 (0.76–1.66)	0.191
t25	0.74 (0.56–0.97)	0.034	0.56 (0.38–0.84)	<0.01	1.10 (0.51–2.00)	0.223
t75	1.24 (0.79–1.12)	0.092	1.78 (0.95–1.09)	0.067	0.88 (0.34–2.44)	>0.9
t97	1.20 (1.05–1.37)	<0.01	1.20 (1.05–1.37)	<0.01	1.09 (0.31–1.71)	0.661
t25_50	0.91 (0.15–1.21)	0.093	0.87 (0.11–1.23)	0.770	1.35 (0.77–1.91)	0.361
t50_75	1.07 (0.66–1.44)	0.401	1.89 (0.88–2.66)	0.067	1.22 (0.41 –2.88)	0.674
t20_80	1.04 (0.61–1.73)	0.09	0.71 (0.53–0.96)	0.024	1.27 (0.27 –1.88)	0.291
LSlope	0.96 (0.31–1.64)	0.362	1.14 (0.56–1.41)	>0.9	0.63 (0.17–0.75)	<0.01
RSlope	1.09 (0.66–1.96)	0.551	1.26 (0.61–1.87)	0.682	0.62 (0.45–0.85)	<0.01
Mu (ms)	1.01 (1.01–1.02)	<0.01	1.13 (0.44–2.01)	0.289	1.02 (1.01–1.03)	<0.01
S1 (ms)	0.98 (0.97–0.99)	<0.01	1.33 (0.14–1.79)	>0.9	0.98 (0.95–1)	0.025
S1/s2	1.43 (1.06–1.91)	0.022	1.06 (0.57–1.21)	0.091	1.86 (1.06–3.27)	0.031
TpTe (ms)	1.23 (0.88–1.44)	0.083	1.44 (0.97–1.66)	0.061	1.44 (0.51–1.32)	>0.9

QTc, QT corrected using Bazett's formula; RR, RR interval; Tx (25, 50, 75, 97), time to accumulate the x part (from 25% to 97%) of the total T-wave area divided by the absolute QT interval; Lslope, coefficient of the upward slope of the T-wave; Rslope, coefficient of the downward slope of the T-wave; Mu, position in time of a function containing two hemi-Gaussian functions used to model the T wave from the main component signal of the principal component analysis (PCA); S1, width of the first hemi-Gaussian function used to model the T-wave; S1/S2, ratio between the widths of the two hemi-Gaussian functions used to model the T-wave; TpTe, T peak–T end interval.

insights. These results support the concept that spatial heterogeneity of ventricular repolarization is associated with an increased risk of life-threatening arrhythmias and contribute to T-wave morphologic alterations, which may be reliably quantified through automated scalar measures. The integration of features that mirror the heterogeneity of ventricular repolarization holds then a major potential to refine risk stratification among LQTS patients.

Contribution of our automated T-wave analysis to LQTS prognostic prediction

Our study provides two major proofs of concept.

First, the quantitative analysis of repolarization morphology using a standardized automated approach on digital ECG represents a feasible and reliable tool in clinical practice. By providing a standardized evaluation of repolarization, our T-wave analytics tool guarantees measurement accuracy and reproducibility while avoiding the subjective qualitative 'eyeballing' in T-wave characterization. Moreover, we tried to further enhance software reliability by visually checking for determinant calliper positions. For this reason, a manual correction was performed in 10.4% of ECGs, while major errors were pointed out only in 0.6% of cases.

Secondly, beyond confirming the role of traditional prognostic factors, we identified distinctive sets of ECG markers able to differentiate between symptomatic and asymptomatic LQTS patients in a genotype-specific manner.

- **Traditional prognostic markers**

  Focusing on established prognostic markers, we demonstrated that ECG features of prolonged repolarization (*i.e.* the QTc and mu values) and pathogenic variants affecting the channel pore were associated with a higher risk of AEs. In line with previous studies,[7,18,27] our results confirm that QTc prolongation and variant location significantly affect clinical expression. Conversely, according to our findings, genotype did not significantly impact free-event survival, diverging from previous studies,[3,5] which showed a different risk of life-threatening events according to genotype. Mazzanti *et al.*[5] reported indeed a greater risk of AE for LQT2 and LQT3 patients compared to LQT1 patients, independently from QTc duration. Based on these results, the same authors proposed a 5-year LQTS-risk prediction model (the 1-2-3-LQTS-Risk calculator) based only on the QTc interval and genotype, with major implications for clinical management.[4,5] In the latest 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death,[28,29] the 1-2-3-LQTS-Risk calculator has been integrated into clinical practice, being the basis for a Class IIb recommendation for ICD implantation in asymptomatic LQTS patients with a high-risk profile (i.e. 5-year risk ≥5%). We do however mention the modest predictive performance of the 1-2-3-LQTS-Risk calculator as attested by the study C-index of 0.79 (95% CI: 0.70–0.88) in the discovery cohort and 0.69 (95% CI: 0.61–0.77) in the validation one.[4] In contrast, our results align with the more recent study by Dusi *et al.*[30], who similarly reported that genotype was not associated with clinical outcomes. Such results further corroborated earlier evidence supporting the construction of the M-FACT scoring system, elaborated to predict the probability of ICD shocks in LQTS patients, based on

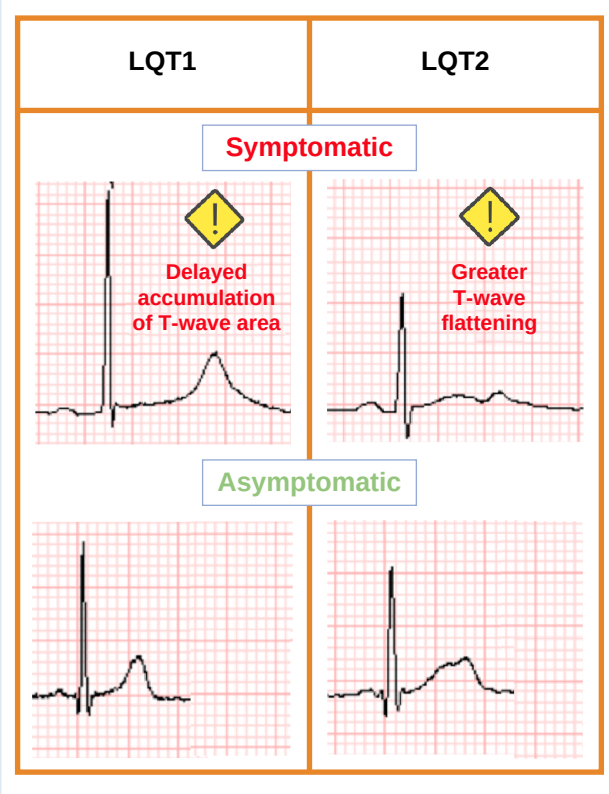


Figure 3 Genotype-specific ECG T-wave 'fingerprints' of high-risk LQTS. LQT1, Type 1 long QT syndrome; LQT2, Type 2 long QT syndrome.

pre-implantation clinical features.[31] As early as 2010, Schwartz *et al.*[31] had already reported that genotype (except in the case of double mutations) was not associated with the probability of ICD therapy during follow-up. In their multivariable analysis, only a prior aborted cardiac arrest, cardiac events despite therapy, a markedly prolonged QTc interval, and a younger (<20 years) age at implantation were found to be independent predictors of future appropriate shocks. In conclusion, our results are in line with the evolving understanding suggesting that, despite its fundamental mechanistic and diagnostic value, the 'static' role of common genotypes (LQT1, LQT2, and LQT3) in risk stratification might be more limited than previously assumed. As recently highlighted by Wilde and van der Welf,[32] accurate risk stratification should probably move beyond simplistic and static models, while incorporating evolving clinical and therapeutic factors which capture the dynamic evolution of risk.

- **ECG prognostic markers**

  We observed that ECG markers mirroring abnormal features of repolarization were independently associated with AE occurrence across the whole LQTS population. These encompassed both timing-related features, translating a delayed accumulation of the mid-late T-wave area (i.e. greater t50, t97, S1/s2, and lower t25) and morphological features, such as a widening/flattening of the T wave (i.e. lower S1, LSlope Val, and RSlope Val). Despite study comparisons are currently limited by the different types of ECG features used to quantify T-wave abnormalities, our study corroborates the work of Sugrue *et al.*[33] These authors demonstrated that the upward slope of the T wave was one of the top three features (with the T-wave centre of gravity and the T peak–T end interval) identified by their T-wave analytics tool to discriminate between LQTS patients and controls. Lower T-wave upward slopes characterized indeed both patients with manifest QTc prolongation and LQTS patients with completely normal QTc, as compared to healthy controls.[31] Moreover, in a second study, Sugrue *et al.*[34] also pointed out that lower left slopes of the T wave in lead V6 were independent predictors of future breakthrough cardiac events in a cohort of LQT1 and LQT2 patients. Specifically, the integrated assessment of the T-wave left slope in lead V6 and of the T-wave centre of gravity *x*-axis in lead I resulted in a greater discriminative power, as compared to QTc alone.

  Moreover, focusing on the multivariable Cox model by genotype subgroups, we demonstrated distinctive genotype-specific repolarization markers associated with increased arrhythmic risk. Among LQT1 patients, arrhythmic risk was independently predicted by a set of ECG markers reflecting a slowed and delayed mid-late phase of repolarization (i.e. prolonged t50 and t97 values; HR = 1.53 and HR = 1.20, respectively). Conversely, among LQT2 patients, lower ascending (LSlope HR = 0.63) and descending (RSlope HR = 0.62) slopes of the T-wave, both reflecting T-wave flattening, as well as higher S1/S2 ratios (HR = 1.86) translating greater T-wave asymmetry and altered repolarization dynamics, were associated with a higher risk of AEs. These results thus seem to suggest two completely different genotype-specific T-wave fingerprints associated to AE occurrence. The loss of T-wave symmetry and the T-peak right shift from the QRS identified high risk LQT1 patients. Conversely, the risk of AEs in LQT2 is not only driven by repolarization delay but also by the flattening of the T-wave and the widening of its base, translating a greater dispersion between early and late phases of repolarization. These results are substantially in line with the study by Platonov *et al.*[35] demonstrating in a cohort of LQT2 patients, that the presence of qualitatively appreciated T wave abnormalities (including broadness and flatness) was associated with a higher risk of cardiac events, regardless of QTc values and after adjustment for sex and beta-blocker therapy. Similarly, Sugrue *et al.*[34] showed that a decreasing left slope of the T wave in lead V6 enhanced genotype-specific risk stratification by identifying LQT2 patients, who remained at increased risk of breakthrough cardiac events.

  Taken together, our findings support the integration of ECG quantitative morphological analysis of repolarization to provide relevant genotype-specific prognostic insights into LQTS. Our results perfectly align with the current perspective in the field of inherited arrhythmic diseases, which—despite persisting challenges in fully integrating genetic testing into prognostic/therapeutic assessment[36]—has progressively evolved from early gene discovery to more sophisticated gene-tailored clinical management.[37]

Limitations

Despite the novel clinical findings and the substantial follow-up duration of our study, several limitations should be acknowledged. First, digital ECGs were acquired at different time points of clinical follow-up. Such heterogeneity may have affected our results in the case of time-dependent variation of our pre-specified ECG features. However, the identification of QTc as a risk factor for AE occurrence corroborates previous results of the literature[38] and indirectly supports the interest of our analysis on ECG features, independently from ECG acquisition time. Moreover, several prior studies have applied survival analysis from birth when evaluating ECG prognostic markers in LQTS patients or have chosen arbitrary time points as the start of follow-up, independently of the timing of ECG acquisition. Such an approach is commonly used in LQTS literature[35,39] since the arrhythmic risk, despite being modulated by different factors over the life span, exists from the earliest stages of life. In addition, using time from birth allowed uniform comparison across patients with different ages at first ECG and avoided potential lead-time and selection biases associated with the variable timing of the first available ECG.

Secondly, the retrospective approach might have hampered the rigorous record of cardiac events during follow-up. Similarly, we were only able to retrieve the type of prescribed treatment. Conversely, the systematic recording of beta-blocker dosage was not available for each patient, preventing any dedicated consideration about the relation between beta-blocker dosage and risk of cardiac events. Moreover, we could not exclude a potential attrition bias associated

with the non-negligible proportion (11.5%) of patients who were lost to follow-up.

Thirdly, the analysis of risk factors for AEs was entirely based on clinical data from patients' birth onwards. Such an approach prevented us from investigating the role of treatment in modifying the arrhythmic risk and the pre-specified prognostic factors. In addition, we used Cox regression models to explore potential risk factors for AEs/SAEs occurrence from birth. Such methodology assumes a linear relationship between covariates and the hazard of the outcome, which might not fully reflect the potential non-linear behaviour of biological phenomena. However, our primary objective was to identify ECG predictors of cardiac events in LQTS using a standardized and reproducible modelling framework to facilitate clinical application and direct comparability with prior studies. Indeed, several previously published studies in the field used linear models in the same context.[34,35] In addition, applying non-linear transformations (i.e. restricted cubic splines) in the context of high-dimensional multivariable models (due to the high number of ECG covariates) would have significantly increased model complexity and the risk of overfitting, especially considering the limited number of available events. For all these reasons, we specifically choose to apply linear modelling in order to balance clinical applicability, comparability among studies, and robustness of the results.

Finally, the validation of our T-wave analytics tool on an independent cohort is necessary before the results can be generalized and the tool can be routinely applied in clinical practice. Moreover, our T-wave software programme could be further boosted by the integration of artificial intelligence (AI) algorithms, which may enhance the identification of subtler patterns as well as the performance of predictive models.

Conclusions

The quantitative assessment of repolarization morphology using a software-based T-wave analysis on digital ECG represents not only a feasible and reliable tool in clinical practice but also provides valuable ECG markers to discriminate between symptomatic and asymptomatic LQTS patients. In particular, we identified unique ECG T-wave 'fingerprints', which allowed us to predict cardiac events in a genotype-specific manner. The integration of such repolarization heterogeneity features which capture the ECG signatures of high-risk LQTS holds then great promise in refining risk stratification among LQTS patients.

Supplementary material

Supplementary material is available at *Europace* online.

Acknowledgements

The authors thank the Emma Muschamp Foundation and the Gottfried & Julia Bangerter-Rhyner Foundation for their support to the first author (APP). The authors are grateful to Jean-François Pruny, Houria Nait Kadi, and Cécile Guérin for their precious help in the implementation and in the rigorous collection of data for the prospective registry of genotype-confirmed LQTS patients of the Reference Center for Inherited Arrhythmia Syndromes of the Bichat-Claude Bernard University Hospital in Paris, France.

Funding

The authors have nothing to declare.

Conflict of interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Schwartz PJ, Ackerman MJ, Antzelevitch C, Bezzina CR, Borggrefe M, Cuneo BF *et al.* Inherited cardiac arrhythmias. *Nat Rev Dis Primers* 2020;**6**:58.
2. Schwartz PJ, Sala L. The impact of genetics on the long QT syndrome: myth or reality? *Curr Opin Cardiol* 2023;**38**:149–56.
3. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M *et al.* Risk stratification in the long-QT syndrome. *N Engl J Med* 2003;**348**:1866–74.
4. Mazzanti A, Trancuccio A, Kukavica D, Pagan E, Wang M, Mohsin M *et al.* Independent validation and clinical implications of the risk prediction model for long QT syndrome (1-2-3-LQTS-Risk). *Europace* 2022;**24**:614–9.
5. Mazzanti A, Maragna R, Vacanti G, Monteforte N, Bloise R, Marino M *et al.* Interplay between genetic substrate, QTc duration, and arrhythmia risk in patients with long QT syndrome. *J Am Coll Cardiol* 2018;**71**:1663–71.
6. Barsheshet A, Dotsenko O, Goldenberg I. Genotype-specific risk stratification and management of patients with long QT syndrome. *Ann Noninvasive Electrocardiol* 2013;**18**:499–509.
7. Morgat C, Fressart V, Porretta AP, Neyroud N, Messali A, Temmar Y *et al.* Genetic characterization of KCNQ1 variants improves risk stratification in type 1 long QT syndrome patients. *Europace* 2024;**26**:euae136.
8. Schwartz PJ, Periti M, Malliani A. The long Q-T syndrome. *Am Heart J* 1975;**89**:378–90.
9. Malfatto G, Beria G, Sala S, Bonazzi O, Schwartz PJ. Quantitative analysis of T wave abnormalities and their prognostic implications in the idiopathic long QT syndrome. *J Am Coll Cardiol* 1994;**23**:296–301.
10. Moss AJ, Zareba W, Benhorin J, Locati EH, Hall WJ, Robinson JL *et al.* ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. *Circulation* 1995;**92**:2929–34.
11. Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. *Circulation* 1996;**93**:372–9.
12. Vaglio M, Couderc JP, McNitt S, Xia X, Moss AJ, Zareba W. A quantitative assessment of T-wave morphology in LQT1, LQT2, and healthy individuals based on Holter recording technology. *Heart Rhythm* 2008;**5**:11–8.
13. Porta-Sánchez A, Spillane DR, Harris L, Xue J, Dorsey P, Care M *et al.* T-wave morphology analysis in congenital long QT syndrome discriminates patients from healthy individuals. *JACC Clin Electrophysiol* 2017;**3**:374–81.
14. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. *Circulation* 1993;**88**:782–4.
15. Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. *Circulation* 2011;**124**:2181–4.
16. Hermans BJM, Bennis FC, Vink AS, Koopsen T, Lyon A, Wilde AAM *et al.* Improving long QT syndrome diagnosis by a polynomial-based T-wave morphology characterization. *Heart Rhythm* 2020;**17**:752–8.
17. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J *et al.* Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;**17**:405–24.
18. Moss AJ, Shimizu W, Wilde AAM, Towbin JA, Zareba W, Robinson JL *et al.* Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. *Circulation* 2007;**115**:2481–9.
19. Extramiana F, Laporte PL, Vaglio M, Denjoy I, Maison-Blanche P, Badilini F *et al.* Computerized automated algorithm-based analyses of digitized paper ECGs in Brugada syndrome. *J Electrocardiol* 2021;**69S**:61–6.
20. Kligfield P, Badilini F, Denjoy I, Babaeizadeh S, Clark E, De Bie J *et al.* Comparison of automated interval measurements by widely used algorithms in digital electrocardiographs. *Am Heart J* 2018;**200**:1–10.
21. Vink AS, Neumann B, Lieve KVV, Sinner MF, Hofman N, El Kadi S *et al.* Determination and interpretation of the QT interval. *Circulation* 2018;**138**:2345–58.
22. Xia Y, Liang Y, Kongstad O, Holm M, Olsson B, Yuan S. Tpeak-Tend interval as an index of global dispersion of ventricular repolarization: evaluations using monophasic action potential mapping of the epi- and endocardium in swine. *J Interv Card Electrophysiol* 2005;**14**:79–87.
23. Extramiana F, Denjoy I, Badilini F, Chabani I, Neyroud N, Berthet M *et al.* Heart rate influences on repolarization duration and morphology in symptomatic versus asymptomatic KCNQ1 mutation carriers. *Am J Cardiol* 2005;**95**:406–9.
24. Dubois R, Roussel P, Vaglio M, Extramiana F, Badilini F, Maison-Blanche P, *et al.* Efficient modeling of ECG waves for morphology tracking. *36th Annual Computers in Cardiology Conference (CinC)*, Park City, UT, USA 2009:313–6.
25. Elming H, Holm E, Jun L, Torp-Pedersen C, Køber L, Kircshoff M *et al.* The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. *Eur Heart J* 1998;**19**:1391–400.
26. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2024.
27. Ruwald MH, Xu Parks X, Moss AJ, Zareba W, Baman J, McNitt S *et al.* Stop-codon and C-terminal nonsense mutations are associated with a lower risk of cardiac events in patients with long QT syndrome type 1. *Heart Rhythm* 2016;**13**:122–31.

28. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA *et al.* 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;**43**:3997–4126.
29. Könemann H, Dagres N, Merino JL, Sticherling C, Zeppenfeld K, Tfelt-Hansen J *et al.* Spotlight on the 2022 ESC guideline management of ventricular arrhythmias and prevention of sudden cardiac death: 10 novel key aspects. *Europace* 2023;**25**:euad091.
30. Dusi V, Dagradi F, Spazzolini C, Crotti L, Cerea P, Giovenzana FLF *et al.* Long QT syndrome: importance of reassessing arrhythmic risk after treatment initiation. *Eur Heart J* 2024;**45**:2647–56.
31. Schwartz PJ, Spazzolini C, Priori SG, Crotti L, Vicentini A, Landolina M *et al.* Who are the long-QT syndrome patients who receive an implantable cardioverter-defibrillator and what happens to them? Data from the European Long-QT Syndrome Implantable Cardioverter-Defibrillator (LQTS ICD) Registry. *Circulation* 2010;**122**:1272–82.
32. Wilde AAM, van der Werf C. Risk scores in congenital long QT syndrome: friend or foe? *Eur Heart J* 2024;**45**:2657–9.
33. Sugrue A, Noseworthy P, Kremen V, Bos JM, Qiang B, Rohatgi RK *et al.* Identification of concealed and manifest long QT syndrome using a novel T wave analysis program. *Circ Arrhythm Electrophysiol* 2016;**9**:e003830.
34. Sugrue A, Rohatgi RK, Noseworthy PA, Kremen V, Bos JM, Qiang B *et al.* Architectural T-wave analysis and identification of on-therapy breakthrough arrhythmic risk in type 1 and type 2 long-QT syndrome. *Circ Arrhythm Electrophysiol* 2017;**10**:e005648.
35. Platonov PG, McNitt S, Polonsky B, Rosero SZ, Kutyifa V, Huang A *et al.* Risk stratification of type 2 long-QT syndrome mutation carriers with normal QTc interval: the value of sex, T-wave morphology, and mutation type. *Circ Arrhythm Electrophysiol* 2018;**11**:e005918.
36. Zeljkovic I, Gauthey A, Manninger M, Malaczynska-Rajpold K, Tfelt-Hansen J, Crotti L *et al.* Genetic testing for inherited arrhythmia syndromes and cardiomyopathies: results of the European Heart Rhythm Association survey. *Europace* 2024;**26**:euae216.
37. Crotti L, Brugada P, Calkins H, Chevalier P, Conte G, Finocchiaro G *et al.* From gene-discovery to gene-tailored clinical management: 25 years of research in channelopathies and cardiomyopathies. *Europace* 2023;**25**:euad180.
38. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J *et al.* The long QT syndrome. Prospective longitudinal study of 328 families. *Circulation* 1991;**84**:1136–44.
39. Goldenberg I, Horr S, Moss AJ, Lopes CM, Barsheshet A, McNitt S *et al.* Risk for life-threatening cardiac events in patients with genotype-confirmed long-QT syndrome and normal-range corrected QT intervals. *J Am Coll Cardiol* 2011;**57**:51–9.