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ORIGINAL PAPER

Predictive value of Shanghai score system in patients with drug-induced type 1 Brugada electrocardiographic pattern

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Abstract

Background The Shanghai score system was developed to enhance the risk stratification in Brugada Syndrome (BrS); however, its prognostic value in drug-induced type 1 BrS remains unclear.

Methods This study involved 698 patients with drug-induced type 1 BrS, confirmed via pharmacologic challenge (flecainide or ajmaline), from 21 centers in Italy and Switzerland. Patients were classified according to the Shanghai score system: probable/definite BrS (score ≥ 3.5) and possible BrS (score < 3.5). The primary outcome was appropriate ICD therapy or sudden cardiac death (SCD)/sustained ventricular arrhythmias; the secondary outcome includes the identification of clinical predictors of primary outcome events. Kaplan–Meier and Cox regression analyses were used.

Results Our study population included 239 patients (34.2%) with probable/definite BrS and 459 (65.8%) patients with possible BrS. During a median follow-up of 57.4 months, 20 patients (2.9%) experienced the primary outcome. Kaplan–Meier analysis revealed a significantly lower event rate in possible BrS (0.11% over 10 years) compared to probable/definite BrS (0.42%). *SCN5A* pathogenic variants were a significant predictor of primary endpoint in the possible BrS group (OR: 12.5).

Conclusions Shanghai score system for BrS diagnosis may be useful as a tool for risk stratification of life-threatening arrhythmias among patients with drug-induced type I BrS ECG. Identifying the *SCN5A* mutations is of pivotal importance for refining the risk stratification.

Vincenzo Russo and Alfredo Caturano equally contributed to the manuscript.

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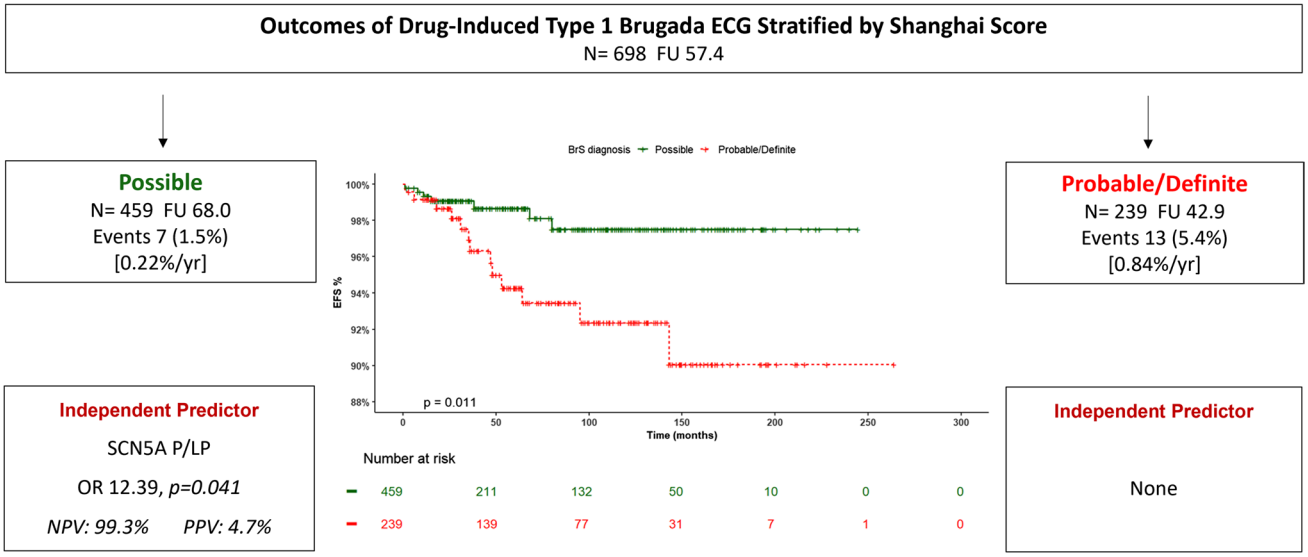
Graphical Abstract



Keywords Brugada syndrome · Brugada pattern · Drug-induced type 1 · Syncope · Programmed ventricular stimulation · Genetic testing · Shanghai score

Abbreviations

AF	Atrial fibrillation
ATP	Anti-tachycardia pacing
BrS	Brugada syndrome
ICD	Implantable cardioverter-defibrillator
PVS	Programmed ventricular stimulation
VF	Ventricular fibrillation
VT	Ventricular tachycardia
SCD	Sudden cardiac death
ECG	Electrocardiographic
SCB	Sodium channel blocker

Introduction

Brugada syndrome (BrS) is a hereditary cardiac channelopathy that predisposes one to sudden cardiac death (SCD), often in the absence of apparent structural heart abnormalities as detected by conventional investigations [1–3]. A type 1 BrS electrocardiographic (ECG) pattern, spontaneous or induced by fever or sodium channel–blocking drugs, is considered diagnostic for BrS in patients with no other evidence of heart disease [4]. In patients with type 1 drug-induced BrS ECG, the incidence of life-threatening arrhythmias remains relatively low, complicating the process of effective risk stratification [5]. This challenge is further amplified by the complications associated with implantable cardioverter-defibrillator (ICD) implantation for primary prevention, which include device-related issues such as infection, lead fractures, and inappropriate shocks [6]. The Shanghai score system has been developed to standardize the diagnosis of BrS [7]; however, its prognostic value remains uncertain [8], especially in patients with type 1 drug-induced BrS pattern, for whom no data are currently available. This study aims to describe the prognostic significance of the Shanghai score system in a large cohort of patients with type 1 drug-induced BrS ECG pattern.

Materials and methods

Study population

This retrospective study included all consecutive patients diagnosed with drug-induced BrS, defined by a positive ajmaline or flecainide challenge test. Baseline and post-challenge ECGs were independently reviewed at the time of the diagnosis by at least two expert cardiologists at the participating referral centers; in case of disagreement, a third specialized cardiologist blinded to the diagnosis or clinical assessment reviewed the ECGs. Patients with spontaneous or fever-induced type 1 ECG were excluded. A total

of 756 consecutive patients with type 1 drug-induced BrS ECG pattern from 21 tertiary referral hospitals across Italy and Switzerland were included. These patients were diagnosed between July 1997 and May 2021, and follow-up data were censored in December 2022. Patients were excluded for the following reasons: ejection fraction < 35% ($n = 6$), diagnosis following malignant arrhythmias ($n = 4$), failure to attend the scheduled follow-up immediately post-diagnosis ($n = 32$), incomplete data ($n = 14$), and withdrawn consent ($n = 2$). A final cohort of 698 patients with drug-induced type 1 Brugada ECG was analyzed. The diagnosis of drug-induced type 1 Brugada ECG was confirmed when a type 1 ECG pattern (coved ST-segment elevation ≥ 2 mm) was elicited during a pharmacologic challenge using flecainide (2 mg/kg over 10 min) or ajmaline (1 mg/kg over 5 min). A positive test required documentation of the type 1 pattern in at least one right precordial lead (V1 or V2) placed in the second, third, or fourth intercostal spaces. Family history of SCD was defined as a history of sudden or unexplained death in a family member aged < 40 years. A family history of BrS was defined as a diagnosis of BrS in a first- or second-degree relative. Unexplained nonvasovagal syncope was defined as at least one syncope episode with suspected arrhythmic origin or syncope not distinctly attributed to vasovagal origin at the end of comprehensive clinical evaluation. The comprehensive clinical evaluation included a careful history taking concerning present and previous attacks, physical examination, supine and standing blood pressure measurements, and electrocardiogram (ECG); moreover, based on the results of initial evaluation, ECG monitoring, echocardiogram, carotid sinus massage (CSM), head up tilt test, and implantable loop recorder (ILR) implantation were performed when indicated. The electrocardiographic monitoring of BrS patients was performed by 12-lead Holter recording in 158 patients (22.6%), implantable loop recorder in 52 patients (7.5%), and ICD in 288 patients (41.3%); the remaining patients (28.6%) were monitored with at least one 12-lead ECG yearly.

Programmed ventricular stimulation (PVS) was conducted in accordance with the clinical practices of the enrolling center. The procedure utilized double and triple extrastimuli at two sites (right ventricular apex and right ventricular outflow tract) at two drive cycle lengths (600 and 400 ms). The coupling interval of the extrastimuli was reduced by 10-ms steps until chamber refractoriness or a minimum coupling interval of 200 ms was reached. The protocol was halted if ventricular fibrillation (VF) or sustained/syncopal polymorphic ventricular tachycardia lasting ≥ 30 s occurred. Until 2007, ICDs were programmed with a VT window (cut-off rate 180–220 bpm) and/or a single VF zone (cut-off rate ≥ 220 bpm). From 2007, a single VF detection zone (cut-off rate 222–250 bpm) and a maximum of 6 shocks were programmed. Subcutaneous ICD devices were programmed with a conditional zone, between 200 and 250 bpm, and a shock zone > 250 bpm.

Calculation of the Shanghai score

The Shanghai score was calculated for each patient to assess the likelihood of BrS based on clinical, electrocardiographic, and familial data. It includes five categories, each contributing points toward a total score [9] (Table 1).

Table 1 Shanghai risk score system

ECG (12-lead/ambulatory)	
Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge	+2
Fever-induced type 1 Brugada ECG pattern at nominal or high leads	+3
Spontaneous type 1 Brugada ECG pattern at nominal or high leads	+3.5
Clinical history	
No clinical history	0
Atrial flutter/fibrillation in patients < 30 yrs without alternative etiology	+0.5
Syncope of unclear mechanism/unclear etiology	+1
Suspected arrhythmic syncope	+2
Nocturnal agonal respirations	+2
Unexplained cardiac arrest or documented VF/polymorphic VT	+3
Family history	
No family history	0
Unexplained SCD < 45 yrs in 1st or 2nd degree relative with negative autopsy	+0.5
Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a 1st or 2nd degree relative	+1
1st or 2nd degree relative with definite Brugada syndrome	+2
Genetic test result	
No pathogenic mutation in BrS susceptibility gene	0
Probable pathogenic mutation in BrS susceptibility gene	+0.5

In the ECG category, a spontaneous type 1 Brugada pattern observed in either nominal or high leads is assigned to have the highest score of 3.5 points. A similar type 1 pattern induced by fever scores 3 points, while a type 1 pattern induced by a sodium-channel blocker scores 2 points. The clinical history domain focuses on arrhythmia-related events, with unexplained cardiac arrest or documented VF or polymorphic VT scoring 3 points. Symptoms such as nocturnal agonal respiration or suspected arrhythmic syncope each contribute 2 points, whereas syncope of unclear etiology is assigned 1 point. Atrial fibrillation or flutter occurring in patients younger than 30 years without an alternative cause is scored at 0.5 points. Family history also contributes to the diagnosis. A confirmed definite diagnosis of Brugada syndrome (Shanghai score ≥ 3.5), collected at study inclusion, in a first- or second-degree relative scores 2 points, while suspicious sudden cardiac death (SCD), such as cases involving fever or Brugada-aggravating drugs, scores 1 point. An unexplained SCD in a family member under 45 years of age with a negative autopsy adds 0.5 points. Finally, genetic testing can provide additional support for the diagnosis. The presence of a pathogenic or likely pathogenic genetic variant in the *SCN5A* gene contributes 0.5 points to the overall score. A score ≥ 3.5 was indicative of probable/definite BrS; 2–3 points indicated possible BrS, and < 2 points was considered non-diagnostic.

Study endpoints

The primary outcome was a composite of appropriate ICD therapies and SCD or sustained ventricular arrhythmias. Appropriate ICD therapies included both ICD shocks and anti-tachycardia pacing (ATP) for ventricular tachycardia (VT) or ventricular fibrillation (VF). The diagnosis of appropriate ICD therapy was based on stored ICD electrograms reviewed by at least two expert cardiologists; a third specialized cardiologist reviewed device interrogation in case of disagreement. The secondary outcome was to assess clinical predictors of primary outcomes across the two subgroups of possible and probable/definite BrS patients.

Statistical analysis

Categorical variables are presented as counts and percentages, while continuous variables are expressed as either median (interquartile range (IQR)) or mean ± standard deviation (SD), depending on their distribution as assessed by the Kolmogorov–Smirnov and Shapiro–Wilk tests. The χ^2 test was used for categorical variable comparisons, with Yates correction applied where appropriate. Continuous variables were compared using either the parametric Student's *t*-test or the nonparametric Mann–Whitney *U* test and Wilcoxon test, depending on their distribution. Univariate Cox regression models were employed to identify potential predictors of the primary outcome in the overall cohort, with variables yielding a p-value < 0.10 in univariate analysis considered for multivariate analysis using a stepwise method. Subgroup analyses were conducted for patients with probable/definite versus possible BrS diagnoses based on the Shanghai score. Kaplan–Meier analyses were performed to assess the risk of primary outcome events, with subgroup analyses for patients with a possible diagnosis stratified by genetic testing results. We also computed the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of *SCN5A* P/LP variant in predicting the occurrence of primary outcome events in patients with a possible BrS diagnosis. Comparisons were made using the log-rank test. A p-value < 0.05 was considered statistically significant. All analyses were conducted using RStudio software (RStudio, Boston, MA).

Results

A total of 698 patients with drug-induced type I BrS ECG (mean age 48.9 ± 14.8 years, 70% men) were included in the study and grouped according to the Shanghai score in probable/definite BrS (*n*: 239; 34.2%) and possible BrS (459; 65.8%). The baseline characteristics of the study population are shown in Table 2.

During a median follow-up of 57.4 [24.0–117.0] months, 20 patients (2.9%) experienced a primary outcome event; in particular, 19 (5.4%) received appropriate ICD therapy for ventricular fibrillation, and 1 (1.5%) patient suddenly died. The Kaplan–Meier analysis showed significant reduction in the cumulative incidence of the primary outcome events among patients with possible BrS (log-rank $p = 0.011$, Fig. 1). The median annual event rate for patients with probable/definite BrS was 0.84% [0.43–0.86%] over 5 years and 0.42% [0.00–0.74%] over 10 years. In contrast, patients with possible BrS had a significantly lower event rate of 0.22% [0.00–0.22%] over 5 years and 0.11% [0.00–0.22%] over 10 years. Baseline characteristics of patients who developed clinical events during follow-up are presented in Supplementary Table 1.

Table 2 Baseline characteristics of the overall study population divided according to the diagnosis stratification by Shanghai score

	Overall population ($n=698$)	Probable/definite BrS ($n=239$)	Possible BrS ($n=459$)	p
Male gender, *n* (%)	490 (70.2)	161 (67.4)	329 (71.7)	0.237
Age (years), mean ± SD	48.9 ± 14.8	50.2 ± 16.3	48.3 ± 14.0	0.122
BrS family member, *n* (%)	187 (26.8)	73 (15.9)	114* (24.8)	0.106
Family history of SCD, *n* (%)	227 (32.5)	82 (36.9)	134 (29.2)	0.037
History of AF, *n* (%)	51 (7.3)	16 (6.7)	35 (7.6)	0.654
Sinus rhythm, *n* (%)	682 (97.7)	227 (95.0)	455 (99.1)	0.0005
Fever-induced pattern, *n* (%)	6 (0.9)	3 (1.3)	3 (0.7)	0.414
Left ventricular ejection fraction, median [IQR]	60 [60.0–61.0]	60 [60.0–60.0]	60 [60.0–62.0]	0.109
Unexplained non-vasovagal syncope, *n* (%)	204 (29.2)	204 (85.4)	0 (0)	< 0.0001
Vasovagal syncope, *n* (%)	55 (8.2)	7 (2.9)	48 (10.5)	0.001
Asymptomatic status, *n* (%)	494 (70.8)	35 (14.6)	459 (100.0)	< 0.0001
PVS positivity, *n* (%)	143/427 (33.5)	73/164 (44.5)	70/263 (26.6)	0.0001
SCN5A mutation, *n* (%)	65/299 (21.7)	22/106 (20.8)	43/193 (22.3)	0.760
ICD-recipients, *n* (%)	288 (41.3)	160 (66.9)	128 (27.9)	< 0.0001
ILR-recipients, *n* (%)	52 (7.5)	35 (14.6)	17 (3.7)	< 0.0001
Shanghai risk score (*n*), median [IQR]	2.5 [2.0–4.0]	4.0 [4.0–4.5]	2.0 [2.0–2.5]	< 0.0001
Follow-up (months), median [IQR]	57.4 [24.0–117.0]	42.9 [23.0–110.0]	68.0 [30.0–129.3]	0.002
Time to event (months), median [IQR]	33.5 [9.5–58.5]	13.0 [4.5–53.0]	41.5 [22.0–58.5]	0.246
ICD therapies/SCD, *n* (%)	20 (2.9)	13 (5.4)	7 (1.5)	0.0033

SD standard deviation, *SCD* sudden cardiac death, *AF* atrial fibrillation, *IQR* interquartile range, *ICD* implantable cardioverter-defibrillator, *ILR* implantable loop recorder

*Not definite diagnosis

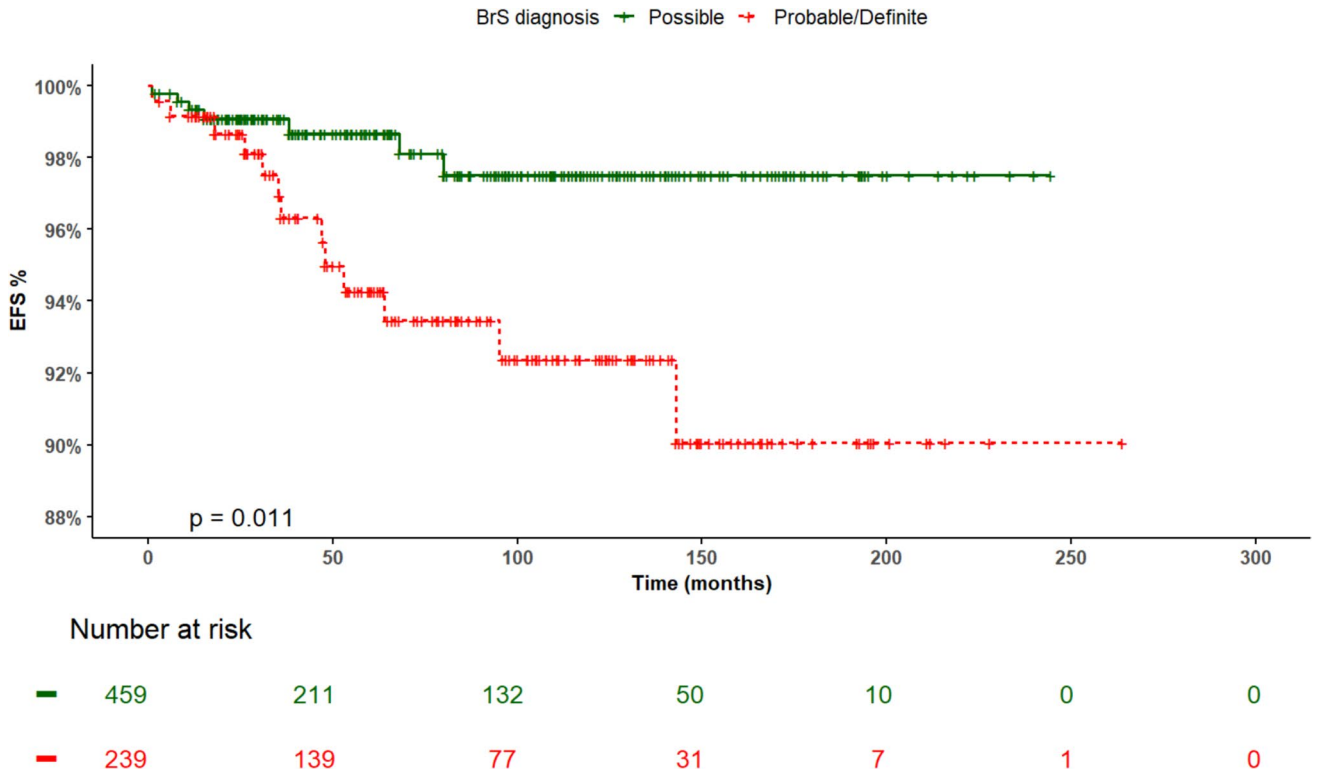


Fig. 1 Kaplan–Meier estimating event-free survival according to possible or probable/definite BrS at Shanghai score. EFS, event-free survival; BrS, Brugada syndrome

Table 3 Cox regression model for primary outcome events among patients with possible BrS

Parameter	Univariable analysis			
	OR	95% CI		*p*
Age	1.03	0.92	1.03	0.973
Sex				
M (ref)	1			
F	0.42	0.05	3.49	0.421
Family history of SCD	0.91	0.18	4.67	0.907
Family history of BrS	0.00	0.00	inf	0.963
PVS positivity	0.00	0.00	inf	0.941
Fever-induced pattern	0.00	0.00	inf	0.964
SCN5A mutation	12.39	1.11	138.8	0.041
History of AF	4.45	0.86	22.97	0.075

SCD sudden cardiac death, *BrS* Brugada syndrome, *PVS* programmed ventricular stimulation, *AF* atrial fibrillation

Subgroup analysis

Among possible BrS group (*n*: 459, 65.8%), 7 (1.5%) patients experienced the primary outcome events. At the univariate Cox regression analysis, only the presence of *SCN5A* P/LP variant was a clinical predictor for primary outcome events (OR: 12.39; 95% CI: 1.11–138.8, $p = 0.041$) (Table 3). The Kaplan–Meier analysis showed a significantly different risk of primary outcome events between possible BrS patients stratified according to *SCN5A* variant (log-rank, $p = 0.009$) (Fig. 2). The presence of *SCN5A* P/LP served as a predictor for primary outcome events with a sensitivity of 66.7%, a specificity of 78.4%, a PPV of 4.7%, and an NPV of 99.3%.

Among probable/definite BrS group (*n*: 239; 34.2%), 13 (5.4%) patients experienced the primary outcome event. At the univariate Cox regression analysis, no clinical variable, including *SCN5A* variant, family history of SCD, unexplained syncope, or positive PVS, was a predictor for primary outcome events (Table 4).

Discussion

The main findings of our study are the following: among patients with drug-induced type 1 BrS ECG pattern, the Shanghai score stratified those at increased risk of life-threatening arrhythmias; *SCN5A* P/LP variants were associated with a higher risk of major arrhythmic events among those with possible BrS; in contrast, no clinical predictors were identified among those with probable/definite BrS.

The Shanghai score system is considered an appropriate diagnostic criterion for the diagnosis of BrS [10], and it has

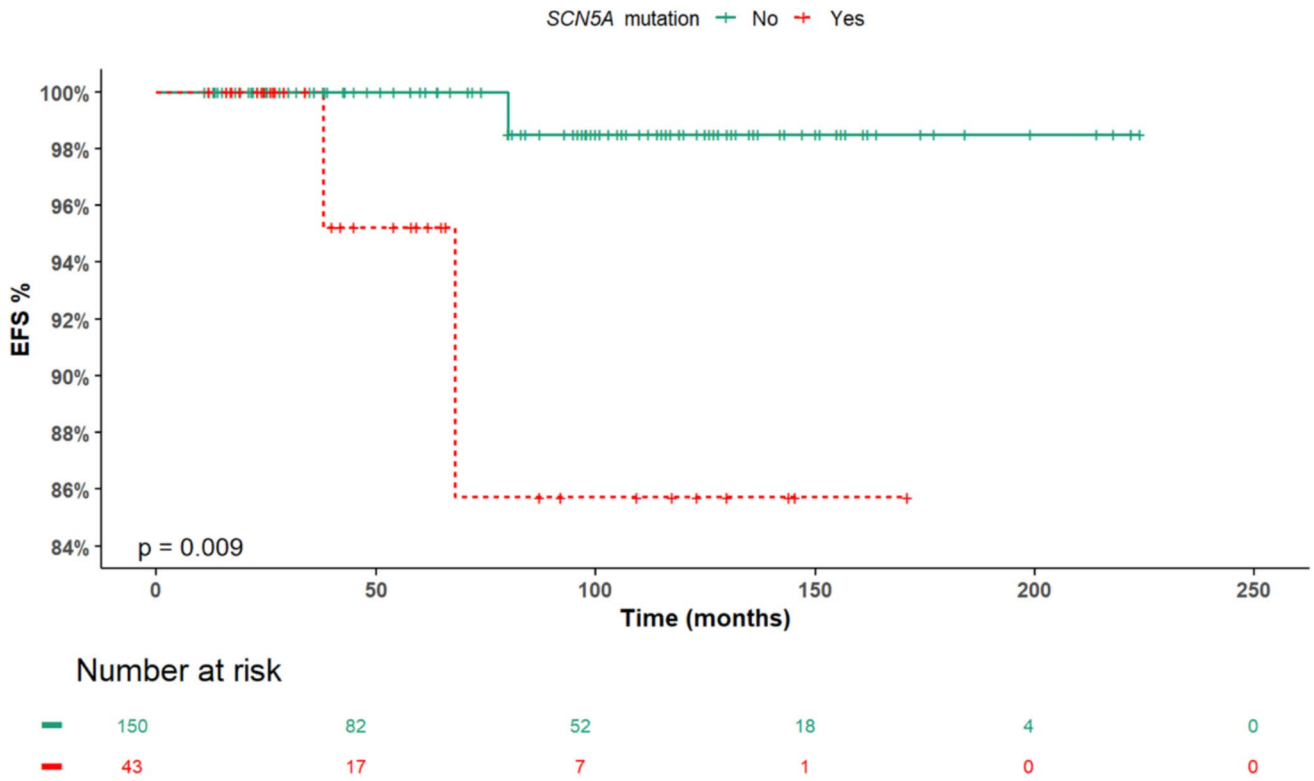


Fig. 2 Kaplan–Meier estimating event-free survival according to *SCN5A* mutation among possible BrS patients. EFS, event-free survival

Table 4 Cox regression model for primary outcome events among patients with probable/definite BrS

Parameter	Univariable analysis			
	OR	95% CI		*p*
Age	0.99	0.96	1.03	0.923
Sex				
M (ref)	1			
F	1.74	0.57	5.35	0.334
Family history of SCD	0.80	0.24	2.60	0.705
Family history of BrS	0.67	0.15	3.04	0.599
History of unexplained syncope not vasovagal	0.57	0.12	2.60	0.568
PVS positivity	1.58	0.45	5.62	0.478
Fever-induced pattern	0.00	0.00	inf	0.966
SCN5A mutation	2.86	0.63	12.9	0.173
History of AF	0.95	0.12	7.36	0.966

demonstrated to be effective as a risk stratification tool among BrS patients [7, 11]. In a retrospective single-center study by Kawada et al. [7], which included 393 BrS patients (79.1% with spontaneous BrS ECG pattern), the Shanghai score effectively stratified patients at increased risk for Life-threatening arrhythmic events over a mean follow-up of 4.5 years. In a recent prospective multicenter study by Probst et al. [11], involving 1613 BrS patients (31% with spontaneous BrS ECG pattern), the Shanghai score successfully identified those at very high and low arrhythmic risk; however, its utility in distinguishing intermediate-risk patients was limited.

This score system assigns significant weight to the spontaneous type 1 BrS ECG pattern, a factor that alone contributes 3.5 points to the overall risk score as originally proposed and validated by Kawada et al. [7]. While this parameter plays a critical role in patient stratification, the score's emphasis on spontaneous ECG presentation raises concerns about its diagnostic accuracy for patients with drug-induced BrS ECG. Our results suggest that the Shanghai score system may be used as an arrhythmic risk stratification tool among patients with drug-induced type 1 BrS ECG, since patients with probable/definite diagnosis showed an approximately fourfold increased risk of life-threatening arrhythmias compared to those with possible BrS. The overall low incidence of life-threatening arrhythmic events among our study population was in line with early large registry data [12, 13].

Two recent meta-analyses [14, 15] have reinforced the association between *SCN5A* mutations and arrhythmic risk in Brugada syndrome (BrS). In a meta-analysis including 1780 BrS patients across 17 studies, Chen et al. [14] found that *SCN5A* mutations are Linked to a higher risk of major arrhythmic events in both Asian and Caucasian populations. Similarly, Doundoulakis et al. in a larger meta-analysis including 3568 BrS patients from 17 studies, reported that, among the 3030 patients who underwent genetic testing, those with *SCN5A* variants had a significantly increased risk of major arrhythmic events (pooled odds ratio 2.14) [15]. Among our study population, SCN5A mutations were predictive of life-threatening arrhythmias only among patients with possible BrS, suggesting its capability to differentiate true BrS patients at risk from possible BrS phenocopies. The absence of reliable arrhythmic risk predictors in patients with probable or definite BrS poses a major clinical challenge, as it may lead to an increased number of unnecessary ICD implantations in this subgroup.

The association between *SCN5A* mutation and poorer prognosis may reflect the more pronounced electrophysiological abnormalities often observed in these patients, including an expanded epicardial arrhythmogenic substrate and prolonged abnormal electrograms [16–19]. However, it is important to note that genetic testing has a low PPV and a high NPV, suggesting that it is more suitable for identifying patients at low risk.

We found a low arrhythmic risk among patients with induced type 1 BrS ECG and a possible BrS classification according to the Shanghai score system. However, this does not equate to zero risk, as this subgroup experienced a median annual event rate of 0.22% over 5 years and 0.11% over 10 years. Recently, Gaita et al. [20] reported a 0.03% annual event rate in asymptomatic, drug-induced patients. However, the characteristics of this subgroup were not detailed, making a direct comparison between subgroups challenging. In our analysis, focusing exclusively on asymptomatic patients without positive provocative tests or genetic testing—while including cases where testing was not performed—we observed a mean annual event rate of 0.05% per person.

The sodium channel blocker (SCB) challenge test remains a central tool in the clinical diagnosis of BrS; moreover, due to its high sensitivity, it allows clinicians to effectively rule out the BrS diagnosis [9]. Despite this, the SCB test has limited specificity, with a risk of false positives, especially in patients with a low pretest probability for BrS [21]. Recently, caution has been advised in the use of SCB testing, particularly for asymptomatic individuals or those without clear risk indicators. Finally, in patients with drug-induced type 1 BrS, the absolute risk of life-threatening arrhythmic events is low; given this, along with the younger age of many patients and the non-negligible risk of ICD-related complications, ICD implantation for primary prevention should be guided by a careful and individualized risk–benefit assessment.

Strengths and limitations

Our study has several strengths, including a large sample size, the use of the standardized Shanghai score for BrS classification, and the inclusion of genetic testing data. The long

follow-up period further enabled us to capture clinically meaningful outcomes over time. However, several Limitations should be noted. First, due to the nature of registry-based enrolment, selection bias cannot be excluded. Participation may have been influenced by referral patterns, access to specialized care, or clinical suspicion, possibly resulting in overrepresentation of higher-risk or more clinically recognized cases. This may Limit the generalizability of our findings to the broader BrS population, especially those not referred for provocative testing or genetic evaluation. Second, the overall event rate was relatively low, in particular among patients with possible BrS; however, this finding aligns with previous studies on drug-induced BrS, which generally report lower event rates than those seen in patients with spontaneous type 1 ECGs [12]. While this reflects the true risk profile of this population, the low event rate may have Limited the statistical power to detect significant differences between groups, potentially impacting the generalizability of our findings to other populations and clinical settings. Third, as a retrospective study, our analysis shares the common Limitations of this design, such as the inability to continuously monitor patients for intermittent spontaneous type 1 Brugada ECG patterns. Some patients initially classified as having drug-induced BrS may have transitioned to spontaneous BrS during follow-up, potentially affecting classification accuracy. Fourth, both genetic testing and PVS were not performed in all patients, limiting our ability to thoroughly assess their roles in risk stratification. Additionally, our reliance on historical data for symptoms, such as syncope, could also overestimate risk, as syncope is a common symptom in the general population and may not always indicate an arrhythmic cause. Furthermore, the lack of data on specific *SCN5A* mutation loci, along with baseline ECG abnormalities and their evolution over time, especially during provocative testing, limited our ability to assess both *SCN5A* mutation loci and dynamic ECG changes as potential predictors of patient outcomes. Moreover, the higher number of patients with ICDs in the probable/definite group may have influenced the endpoint. However, the percentage of ICD therapies, adjusted for the number of implantations, is similar between the two groups (7.5% vs. 5.5%, $p=0.474$). Finally, while our study included data from multiple centers and patients across diverse geographic regions, the cohort was ultimately selective, which could limit the applicability of our findings to broader ethnic groups and healthcare settings. Future studies involving more diverse populations and prospective designs are warranted to validate our results across varied cohorts and enhance risk stratification in drug-induced BrS.

Conclusions

The Shanghai score system for BrS diagnosis may be useful as a tool for risk stratification of life-threatening arrhythmias among patients with drug-induced type I BrS ECG. The association between *SCN5A* P/LP variants and adverse outcomes among patients with a possible BrS diagnosis highlights the importance of genetic testing even in this subgroup.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00392-025-02738-w.

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Data Availability The dataset analyzed in the current study is available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

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