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A novel prediction model for risk stratification in patients with a type 1 Brugada ECG pattern☆

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ABSTRACT

Background: Risk stratification in Brugada syndrome remains a controversial and unresolved clinical problem, especially in asymptomatic patients with a type 1 ECG pattern. The purpose of this study is to derive and validate a prediction model based on clinical and ECG parameters to effectively identify patients with a type 1 ECG pattern who are at high risk of major arrhythmic events (MAE) during follow-up.

Methods: This study analysed data from 103 consecutive patients with Brugada Type 1 ECG pattern and no history of previous cardiac arrest. The prediction model was derived using logistic regression with MAE as the primary outcome, and patient demographic and electrocardiographic parameters as potential predictor variables. The model was externally validated in an independent cohort of 42 patients.

Results: The final model (Brugada Risk Stratification [BRS] score) consisted of 4 independent predictors (1 point each) of MAE during follow-up (median 85.3 months): spontaneous type 1 pattern, QRS fragments in inferior leads≥3,S wave upslope duration ratio ≥ 0.8, and T peak – T end ≥ 100 ms. The BRS score (AUC = 0.95,95% CI 0.0.92–0.98) stratifies patients with a type 1 ECG pattern into low (BRS score ≤ 2) and high (BRS score ≥ 3) risk classes, with a class specific risk of MAE of 0–1.1% and 92.3–100% across the derivation and validation cohorts, respectively.

Conclusions: The BRS score is a simple bed-side tool with high predictive accuracy, for risk stratification of patients with a Brugada Type 1 ECG pattern. Prospective validation of the prediction model is necessary before this score can be implemented in clinical practice.

Introduction

Risk stratification in Brugada syndrome (BS) remains a controversial and unresolved clinical problem, especially in asymptomatic patients with a type 1 ECG pattern [1,2]. In these patients the absolute risk of developing spontaneous ventricular fibrillation (VF) leading to sudden death is approximately 0.5% annually and the risk of long-term complications from implantable cardioverter-defibrillator (ICD) is significantly higher [3,4].Although several non-invasive and invasive parameters have been identified as independent predictors of increased arrhythmic risk, they lack consistency and reproducibility [3,5–11]. Recently, Kawazoe and colleagues have a constructed an elegant logistic prediction model for risk stratification utilizing a combination of clinical and ECG markers [12]. However, the primary obstacles to the development of such a composite risk stratification method are low event rates, lack of large multicentre prospective studies, and phenotypic variability between various patient populations [13].

Although many indices have been reported as prognostic predictors, they are not always useful for identifying high-risk patients who do not have documented VF. Identification of higher risk asymptomatic patients is of importance as cardiac arrest is likely to be their presenting symptom. Therefore, there is a pressing need to develop a novel, sufficiently sensitive and specific, andeasily applicable method for risk stratification. The purpose of this study is to derive and validate a prediction model based on simple clinical and ECG parameters, to effectively identify patients with a type 1 ECG pattern who are at high risk of arrhythmic events during follow-up.

Methods

Patient identification and eligibility

A total of 103 consecutive patients diagnosed with Brugada Type 1 ECG pattern between January 2007 and December 2016 were

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retrospectively enrolled in this study. No patients had a history of cardiac arrest or documented VF. Patients older than 18 years of age were eligible for this study if they met the following inclusion criteria: [1] spontaneous or pharmacologically induced Type 1 ECG pattern with coved ST-segment elevation (>2 mm) in one or more leads from V1 to V3; [2] absence of underlying structural cardiac abnormalities demonstrated by chest radiography, echocardiography, laboratory tests, and other examinations, if appropriate. In addition, patients with type 1 Brugada pattern related to conditions causing the 'Brugada phenocopy' were excluded [14,15]. The study was approved by the institutional review board and ethics committee of our hospital.

Baseline predictor variables

The baseline variables used to derive our prediction rule were obtained by combining clinical and electrocardiographic parameters in all eligible patients. Patients were classified into two groups according to the circumstances of their initial clinical presentation at which time a Brugada Type 1 Pattern in ECG was documented: during evaluation of syncope or routine examination. Syncope was defined as abrupt loss of consciousness, probably of arrhythmic origin. The family history of Brugada syndrome and sudden cardiac death was collected.

The electrocardiograms were recorded with a standard digital recorder at a paper speed of 25 mm/s and an amplification of 1 cm/mV with a 0–150 Hz filter. The measurement of each parameter was obtained averaging two consecutive beats. The ECG's were digitized with a high-resolution scanner and measured with the aid of digital calipers (CardioCalipers Version 2.0, Chicago), that were calibrated prior to each ECG analysis. Two blinded investigators independently assessed the following ECG parameters and discrepancies were resolved by consensus. The RR interval, PR interval, PQ interval, QRS width, QT interval, corrected QT interval (Bazett's method) were measured in lead II and V6. ST segment elevation (mV) at J point and S wave amplitude (mV) were measured in the right precordial lead (V1-V3) with the maximum J point elevation. QRS fragmentation was defined as a QRS complex with >2 positive spikes within the QRS complex in 2 contiguous leads, according to previous studies [16,17]. The presence of QRS fragmentation was evaluated in right precordial leads (V1-V3) and inferior leads (L I, L III,aVF) (Fig. 1). The amplitude (mV) and duration (ms) of the S wave in lead I was also measured [10]. Early repolarization pattern was defined as a notched ≥1 mm J wave of ≥1 mm J point elevation in inferior (II,III, aVF) or lateral (I,aVL) leads [7]. The Tpeak- Tend intervals in the precordial leads were obtained from the difference of the QT interval and QT peak interval, as described in previous studies [8,18]. As previously described by us, the S wave upslope duration ratio (Fig. 2), measured in the right precordial lead with the maximum ST elevation, was defined as the ratio between duration from S wave nadir to the J point to that between the earliest deflection of the QRS complex to the J point (R-J point interval) [19].

Protocol for programmed electrical stimulation was similar to that reported by the PRELUDE investigators [5]. In brief, the stimulation protocol consisted of 2 drive cyclces (600 and 400 ms) and up to 3 extrastimuli with a minimum coupling interval of premature beats set to 200 ms. The protocol was performed from the apex of the right ventricle and the right ventricular outflow tract, unless the electrophysiological study (EPS) was positive at the first location. A positive EPS was defined as PES induced ventricular fibrillation, sustained polymorphic ventricular tachycardia (>30 s) or polymorphic ventricular tachycardia requiring direct current shock.

Outcomes

As per the standard of care in our clinic, the first follow-up visit for all patients was at 3 months, and subsequently every 6 months or earlier in the event of symptoms. Major arrhythmic events (MAE) at follow-up were defined as the occurrence of sudden cardiac death (SCD) or "appropriate shocks" (defined as shocks delivered for sustained polymorphic ventricular tachycardia (VT) or VF) in patients with ICD. VF was defined as consecutive beats recorded from the device at a cycle length of 240 milliseconds or less. In order to increase the likelihood that MAE consisted of life-threatening arrhythmias, ventricular arrhythmias terminated by anti-tachycardia pacing were decided not to be included in the primary outcome. These outcomes were assessed using a combination of outpatient hospital records and patient phone interviews.

Derivation of the prediction model

The prediction rule was derived using a stepwise logistic regression, with major arrhythmic events as the outcome, and the clinical and ECG parameters previously described as predictors. Variables with a p-value < 0.05 in the univariate analysis were selected for testing in a (backward elimination) logistic regression model. In order to define the discriminant power of continuous variables, receiver- operating characteristic (ROC) curves were utilized to identify the optimal cutoff point (curve point with a specificity > 80%). Variables associated with a p-value $<$ 0.05 were retained in the final model. On the basis of B-coefficients of the model, a point score was generated that divides patients into low and high risk of major arrhythmic events during follow-up.

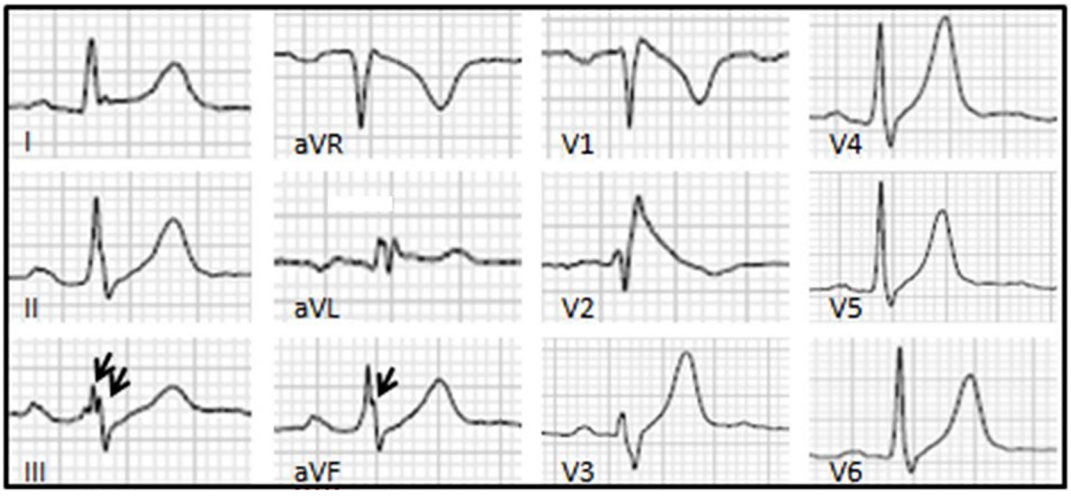

Fig. 1. Fragmented QRS - Example of f-QRS in the inferior leads (II, III, aVF) in a patient with type 1 Brugada ECG pattern. Leads III (2 fragments) and aVF (1 fragment) had a total of 3 fragments (arrows). Leads V1 and V2 showed coved ST- segment elevation.

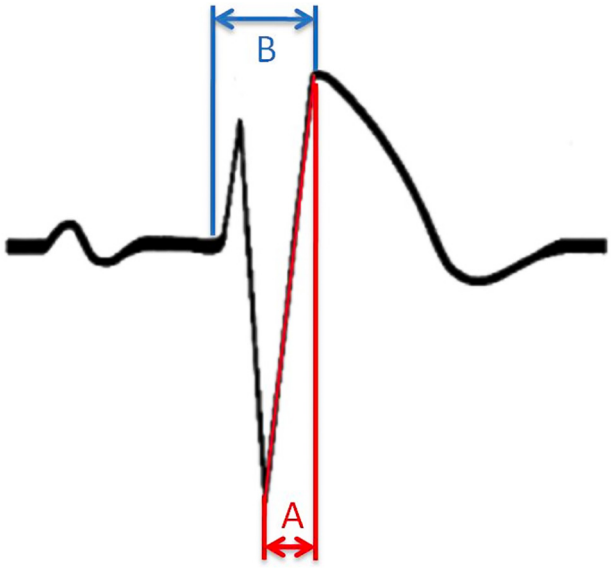

Fig. 2. S wave upslope duration ratio (A/B) - A is the duration (ms) from the S wave nadir to the J point and B is the duration (ms) between the earliest deflection of the QRS complex to the J point (R-J interval) [19].

External validation of the prediction model

The prediction rule was validated in an independent patient population using data from 42 patients with Type 1 Brugada ECG pattern at a tertiary care hospital in Mangalore, India. Follow-up information was obtained by phone interview of patients, primary care physicians, apart from the medical records review.

Statistical analysis

The Shapiro-Wilk test was performed to find whether a parameter is distributed normally. Continuous data are presented as median and interquartile range. Categorical data was expressed as proportions. Inter-observer agreement between the ECG parameters of both blinded observers was assessed with intraclass correlation coefficients. The kappa statistic was assessed for agreement in classification between the two observers using Fleiss' agreement scale. The Fisher exact test was used to compare categorical variables. The Mann-Whitney and Kruskal-Wallis tests were used for continuous parameters. Survival curves were constructed by means of the Kaplan- Meier method and compared by the log-rank test. Mortality rates were compared between both risk classes across the derivation and validation cohorts with the use of chi-square statistics. A receiver operating characteristic (ROC) curve was used to estimate the discriminatory power of our rule to predict major arrhythmic events during follow-up across both cohorts. Discrimination was quantified by calculating the sensitivity, specificity, positive and negative predictive value. In addition, the discriminative value of our score was compared with the previous model utilizing the net reclassification improvement (NRI) index, as suggested by Pencina et al. [20]. For all analysis, a two-tailed P value < 0.05 was used to define statistical significance.

Results

Baseline patient characteristics and outcomes

Of the 103 patients with Type 1Brugada ECG pattern studied, 89 (86.4%) were male and the median age was 48 (range, 19–63). With regards to the baseline ECG pattern, 65% had a spontaneous type 1 pattern, while in the remainder, a type 1 ECG pattern was induced by flecanide administration. ICD implantation was performed in 31 patients. Among the 22 asymptomatic patients who underwent primary prophylaxis ICD implantation, indications included inducible ventricular arrhythmia at electrophysiological study ($n = 20$), family history of Brugada syndrome and SCD ($n = 1$), and spontaneous non-sustained ventricular arrhythmias (n = 1).

The baseline clinical and ECG characteristics of the derivation and validation cohort were similar ($p > 0.05$, Table 1). The intraclass coefficients assessing interobserver agreement were between 0.92 and 0.96 for all the ECG parameters and the kappa statistic for classification agreement was 0.822 ($p < 0.001$).

During follow-up (median 85.3 months, range 8.3–109.6 months) of 103 patients, 13 patients (12.6%) had major arrhythmic events (8 recorded VT/VF by ICD and 5 SCD) in the derivation cohort.

Derivation of prediction model (BRS score)

Logistic regression identified the following factors to be independently associated with major arrhythmic events during follow-up: Spontaneous type 1 Brugada pattern, S wave upslope duration ratio > 0.8, QRS fragments in inferior leads > 3, and T peak – T end > 100 ms (Table 2). Utilizing the regression coefficients an equally weighted score (1 point each) was derived and shown in Table 3. High risk (BRS ≥ 3) and low risk patients (BRS ≤ 2) were delineated based on receiver operating curve analysis (area under the curve = 0.95, $p < 0.001$).

Validation and applications of the prediction model

The prediction model classified similar proportions of patients in both risk classes in the derivation (low risk 87.4%, high risk 12.6%) and validation (low risk 85.8%, high risk 14.2%) samples. The class- specific risk of MAE was 1.1%, 0% in low risk and 92.3%, 100% in high-risk

Table 1
Demographic, clinical, and electrophysiological characteristics of patients in the derivation and validation cohort.

	Derivation Cohort ($N = 103$)	Validation Cohort ($N = 42$)
Demographics		
Age	48 (35–60)	47 (37–58)
Male sex	89 (86.4%)	37 (88.1%)
Clinical presentation		
Asymptomatic	91 (88.3%)	35 (83.3%)
Syncope	12 (11.7%)	7 (16.7%)
Family history of SCD	33 (32.0%)	14 (33.3%)
ECG parameters		
Spontaneous type 1 pattern	67 (65.0%)	28 (66.7%)
Flecainide induced type 1 pattern	36 (35.0%)	14 (33.3%)
ST elevation in V1-V3 (mV)	0.27 (0.18–0.34)	0.24 (0.14–0.33)
S wave amplitude in V1–V3 (mV)	0.63 (0.38–0.79)	0.61 (0.35–0.81)
S wave amplitude in lead I (mV)	0.10 (0.06–0.14)	0.09 (0.06–0.12)
S-wave duration in lead I (ms)	45 (32–53)	44 (35–50)
S wave upslope duration ratio (ms)	0.64 (0.53–0.80)	0.66 (0.50–0.84)
HR (beats/min)	66 (60–77)	67 (61–80)
PR interval (ms)	174 (152–188)	176 (150–195)
PQ interval (ms)	192 (176–215)	196 (170–218)
QRS width (ms)	104 (92–111)	103 (90–112)
QT (ms)	424 (380–472)	420 (385–458)
QTc (ms)	445 (392–503)	449 (399–505)
Early repolarisation (Inferolateral leads)	34 (33.0%)	13 (31.0%)
QRS fragmentation in V1–V3	24 (23.3%)	10 (23.8%)
QRS fragmentation in II, III,aVF	35 (34.0%)	15 (35.7%)
Number of fragments in V1–V3	2 (1–3)	2 (1–3)
Number of fragments in II,III, aVF	3 (1–4)	4 (3–5)
T peak – T end interval (ms)	84 (72–109)	87 (70–116)
ICD placement	31 (30.1%)	14 (33.3%)
Major arrhythmic events (MAE)	13 (12.6%)	6 (14.2%)
Sudden cardiac death	5/13 (38.5%)	3/6 (50.0%)
Appropriate device therapy	8/13 (61.5%)	3/6 (50%)
Duration of follow up (months)	85.3 (55.7–97.1)	83.6 (51.1–97.9)

Table 2
Baseline variables associated with major arrhythmic events (MAE) during long term follow up.

	No major arrhythmic events ($N = 90$)	Major arrhythmic events ($N = 13$)	P value, logistic regression analysis	
			Univariate	Multivariate
Demographics				
Age	48 (34–56)	47 (38–56)	0.613	
Male sex	78 (86.7%)	11 (84.6%)	0.822	
Clinical presentation				
Asymptomatic	82 (91.1%)	9 (69.2%)	0.022	
Syncope	8 (8.9%)	4 (30.8%)	0.022	
Family history of SCD	29 (32.2%)	4 (30.8%)	0.816	
ECG parameters				
Spontaneous Type 1 Pattern	55 (61.1%)	12 (92.3%)	0.028	
Flecanide Induced Type 1 Pattern	35 (38.9%)	1 (7.7%)	0.028	
ST elevation in V1–V3 (mV)	0.27 (0.17–0.39)	0.28 (0.18–0.43)	0.437	
S wave amplitude in V1–V3 (mV)	0.66 (0.53–0.72)	0.42 (0.28–0.59)	0.026	0.328
S wave amplitude in lead I (mV)	0.10 (0.06–0.12)	0.11 (0.08–0.16)	0.234	
S wave duration in lead I (ms)	45 (37–56)	48 (40–51)	0.351	
S wave upslope duration ratio	0.61 (0.54–0.75)	0.84 (0.61–0.89)	0.003	0.014
HR (beats/min)	67 (60–74)	65 (60–72)	0.546	
PR interval (ms))	178 (155–190)	170 (152–185)	0.634	
PQ interval (ms)	191 (178–213)	195 (179–216)	0.427	
QRS width (ms)	106 (92–112)	103 (100–116)	0.623	
QT (ms)	421 (385–471)	429 (402–474)	0.128	
QTc(ms)	445 (392–510)	447 (401–512)	0.278	
Early repolarisation (Inferolateral leads)	30 (33.3%)	4 (30.8%)	0.746	
QRS fragmentation in V1–V3	21 (23.3%)	3 (23.1%)	0.613	
QRS fragmentation in II, III,aVF	25 (27.8%)	10 (76.9%)	<0.001	0.022
Number of fragments in V1–V3	2 (1–3)	2 (2–4)	0.322	
Number of fragments in II,III, aVF	2 (1–3)	4 (4–5)	0.029	0.041
T peak – T end interval	80 (71–92)	110 (91–128)	<0.001	0.029
Electrophysiological study (EPS)	45 (50.0%)	8 (61.5%)	0.440	
Positive EPS	19/45 (42.2%)	3/8 (37.5%)	0.801	
ICD placement	23 (25.6%)	8 (61.5%)	0.009	
Duration of follow up	85.5 (50.2–95.2)	84.3 (54.4–96.7)	0.310	

patients across both cohorts, respectively. The prediction model's discriminatory power for MAE was nearly identical in the derivation and validation cohorts, with a C – statistic of 0.95 and 0.99, respectively.

Table 3
Brugada risk stratification (BRS) score: Independent predictors of major arrhythmic events (MAE).

	B coefficients	95% confidence interval	Points
Spontaneous type 1 pattern	4.10	2.05–6.16	+ 1
S wave upslope ratio > 0.8	3.84	1.94–5.75	+ 1
QRS fragments in inferior leads ≥ 3	2.99	1.24–4.75	+ 1
T peak – T end interval > 100 ms	3.65	1.98–5.32	+ 1

Considering survival free of major arrhythmic events (Fig. 3), the BRS score showed a significant correlation to mode of clinical presentation (Fig. 3A) (asymptomatic, BRS score1.05 ± 0.99, syncope, BRS score 1.83 ± 1.31,$p = 0.017$) and provocation of Type 1 ECG pattern (Fig. 3B) (spontaneous, BRS score 1.36 ± 1.27, flecanide induced, BRS score0.84 ± 0.73, $p = 0.032$). Event free survival analysis of patients and their corresponding BRS score showed a similar trend (log rank $p < 0.001$) in the derivation (Fig. 3C) and validation cohorts (not shown).

Among the 31 patients with implanted ICD in the derivation cohort, 8 patients (25.8%) had "appropriate shocks" during follow up. (Table 4) In comparison to the asymptomatic cohort, patients with syncope had a similar mean delay to first shock (31.5 ± 12.2 vs. 32.7 ± 16.3 months, $p = 0.438$). The BRS score was higher in patients with appropriate shocks. Inappropriate shocks due to supraventricular arrhythmias occurred in

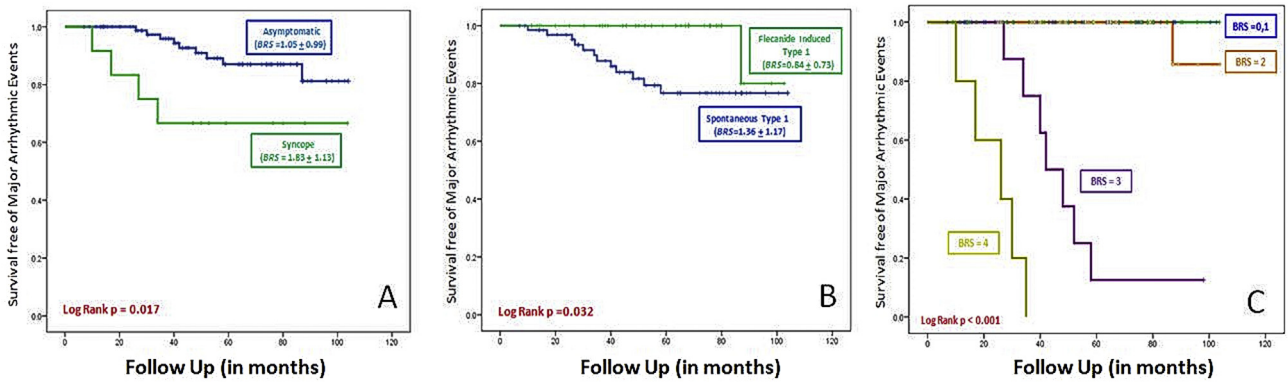

Fig. 3. Kaplan-Meier analysis of major arrhythmic events during follow-up in the derivation cohort depending on symptom at clinical presentation (Fig. 3A), provocation of type 1 ECG pattern (Fig. 3B), and corresponding BRS score (Fig. 3C).

Table 4
Clinical characteristics and BRS score in patients with implanted ICD according to presence of "appropriate shocks" during follow-up.

	Patients with "appropriate shocks" during follow up (N = 8)	Patients without "appropriate shocks" during follow up (*N* = 23)	P-value
Age[a]	47 (35–58)	47 (32–56)	0.345
Male sex	N = 9 (81.8%)	*N* = 16 (80.0%)	0.876
ICD indication			
Syncope	N = 2 (25.0%)	*N* = 7 (30.4%)	0.675
Asymptomatic	*N* = 6 (75.0%)	N = 16 (69.6%)	0.675
Mean delay to 1st shock, months (±SD[b])	32.4± 14.2	–	–
Mean shocks (±SD)	3.9 ± 1.8	–	–
BRS SCORE	3.1± 0.9	1.4± 0.7	<0.001
Follow-up (months)*	86.4 (52.1–94.8)	83.8 (53.7–93.4)	0.417

[a]Data represented as median, interquartile range; [b]SD: Standard deviation.

one patient. There were no other device related complications in these patients.

In comparison to the previously derived model by Kawasoe and colleagues the BRS score had a higher accuracy and discriminative ability. (Table 5) In addition, the BRS score significantly improved the reclassification across both the derivation (NRI = 39.1%, $p < 0.001$) and validation (NRI = 29.5%, $p < 0.001$) cohorts.

Discussion

In this study to develop a novel prediction model to risk stratify patients with a Type 1 Brugada pattern, four independent risk factors were identified that classify patients into low and high risk of major arrhythmic events during long-termfollow-up. Incorporating these risk factors, a novel, user-friendly risk stratification model, Brugada Risk Stratification Score, was derived which demonstrated good predictive accuracy. When validated in a prospectively identified external validation sample, the performance of our BRS score was highly reliable.

Novel ECG parameters

In the development of a composite risk stratification score, this study sought to combine a quantitative assessment of clinical and electrophysiological parameters representing different aspects of arrhythmogenesis (both depolarisation and repolarisation abnormalities). Although previous studies have observed that widening of the S wave and increased R-J interval in the precordial leads are more frequent in symptomatic patients, the S wave upslope duration ratio (OR 59.6, 95% CI 10.3–167.3) is a novel marker of increased arrhythmic events during follow-up [21,22]. The presence of fragmented QRS complexes in right precordial leads has been associated with a higher risk of spontaneous VF in a majority of studies [5,6,23]. In concurrence with our results, Morita and colleagues also found that fQRS in the inferior leads to be a significant predictor of ventricular fibrillation [17]. Although delayed potentials are usually localized to the anterior RV and RVOT epicardium, they have also been shown to appear at the inferior wall of the ventricle [24].These findings may favour the importance of conduction delay in multiple regions in the genesis of ventricular arrhythmias in Brugada syndrome.

Utility of the BRS score

Our prediction rule accurately identifies asymptomatic patients who are at high risk of major arrhythmic events during long-termfollow up. Due to the lower absolute risk of developing spontaneous VF and increased long-term complications from ICD implantation, the management of asymptomatic patients with Type 1 ECG pattern remains controversial. Currently, there are no reliable methods for identification of "high risk" asymptomatic patients. Of the 91 asymptomatic patients (BRS low risk ($n = 82$), BRS high risk ($n = 9$)), all nine BRS high-risk patients subsequently had major arrhythmic events. Three patients had SCD and six patients had appropriate device therapy during follow-up. Thus, the BRS score provides clinicians with an explicit tool for identifying high-risk asymptomatic patients who may be potential candidates for ICD implantation. However, it is important to note that our rule is intended to supplement, not replace, clinical judgement.

In post-ICD implantation patients, the BRS score was able to identify a high risk group with multiple appropriate shocks during follow up. However, in concurrence with previous studies, there was no significant difference with regards to incidence of appropriate device therapy and time delay to the first shock in patients with syncope as compared to asymptomatic patients [25,26]. Due to small sample size the present study does not have the power to ascertain the ability of the BRS score in identification of patients at higher risk of recurrent VT/VF after ICD implantation. Future studies on non-invasive predictors of recurrent ventricular arrhythmias and device therapy after ICD implantation are crucial in identification of high risk BS patients that may require adjuvant medical treatment.

Arrhythmic events in asymptomatic patients

Considerable variation in the documented arrhythmic event rate in asymptomatic patients is likely due to the heterogeneous nature of the populations studied and varying durations of long term follow up

Table 5
Prognostic value of two different risk stratification models to identify high – risk patients with a Type 1 Brugada ECG Pattern.

	Derivation cohort		Validation cohort	
	BRS score (95% CI[a])	KAWAZOE et al. (95% CI)	BRS score (95% CI)	KAWAZOE et al. (95% CI)
Sensitivity	92.3 (64.0–99.8)	77.0 (56.9–97.0)[b]	100 (39.8–99.9)	75.0 (19.4–99.4)[b]
Specificity	98.9 (94.0–99.9)	73.9 (61.9–85.9)[b]	100 (86.8–99.9)	81.8 (59.7–94.8)[b]
Positive predictive value	92.3 (62.9.1–98.8)	40.7 (27.8–53.6)[b]	100 (39.8–99.9)	42.9 (9.9–81.6)[b]
Negative predictive value	98.9 (93.1–99.8)	90.1 (81.6–99.8)[c]	100 (86.8–99.9)	94.7 (74.0–99.9)[b]
C - Statistic	0.95 (0.92–0.98)	0.86 (0.78–0.93)[b]	0.99 (0.99–0.99)	0.83 (0.74–0.91)[b]

[a]CI = confidence interval; [b]$p < 0.001$, comparisons between BRS versus Kawazoe et al. [c]$p < 0.05$, comparisons between BRS versus Kawazoe et al.

[3,27–30]. The higher arrhythmic event rate in asymptomatic patients in this study (9.9%) suggests this was an a priori high risk population. Although no study has compared the risks directly, phenotypic variability between Asian and European patients may account for this difference [31].

Comparison with other risk stratification models

In comparison to logistic prediction model suggested by Kawazoe et al., the BRS score has a higher sensitivity ($p < 0.001$), specificity ($p < 0.001$), and C-statistic ($p < 0.001$) across both the derivation and external validation cohorts. In addition, it better reclassified (NRI, $p < 0.001$) patients who developed MAE during follow up. Although both models utilized a combination of depolarization and repolarisation parameters, the lack of external validation, inter-observer measurement and the use of non – independent parameters (V1 rJ interval and V6 QRS duration) with rather similar values are limitations of the former model [32].

Compared to other risk stratification models, our prediction model has several distinctive strengths [33,34]. It consists of clearly defined, easily available ECG parameters, without relying on invasive inducible electrophysiological studies. The accuracy and reproducibility of the risk stratification score are supported by its external validation in an independent cohort. In addition, the data reported in this study represent a broad disease spectrum with the longest follow-up so far of patients with a type 1 ECG pattern.

Study limitations

Our study also has potential limitations. First, although the follow-up of this study is one of the longest reported thus far, due to the protracted natural history of Brugada syndrome it may still be too short to draw final conclusions regarding long-term prognosis. Second, as acknowledged by other authors, sustained VT/VF interrupted by an appropriate shock is only a surrogate of sudden death [28]. Third, our approach to risk stratification of asymptomatic patients with a type 1 pattern has varied over the course of time that the data was collected. In particular, the use of an electrophysiological study for risk stratification in this cohort has varied. However in patients presenting with syncope and aborted cardiac arrest (not included in this study), management strategies were consistent with established guidelines [1]. Finally, due to our relatively small study cohorts and retrospective nature of this study, further evaluation is needed to improve our understanding of predictors of major arrhythmic events in patients with a type 1 ECG pattern.

Conclusions

In conclusion, the BRS score is a simple bed-side tool with high predictive accuracy, for risk stratification of patients with a Brugada Type 1 ECG pattern. The BRS score provides a unique window of opportunity for early intervention in such patients who currently lie in a true grey zone with respect to prognostication. Prospective validation of our prediction model is necessary before this score can be implemented in clinical practice.

Conflict of interest

The authors declare that they have no conflict of interest.

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