Predictive risk models for forecasting arrhythmic outcomes in Brugada syndrome: a focused review

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Abstract

Brugada syndrome (BrS) is a rare disorder characterized by coved or saddle-shaped ST-segment elevation in the right precordial leads on the electrocardiogram. Risk stratification in BrS remains challenging. A number of clinical, electrocardiographic, programmed ventricular stimulation and genetic risk factors have been identified as important predictors of future major arrhythmic events. There is a positive association between the number of risk factors and arrhythmic events. Hence, a multi-parametric approach would provide comprehensive risk assessment and more accurate risk stratification, assisting in therapeutic decisions making, including implantable cardioverter-defibrillator placement or identification of low-risk individuals. However, the extent to which each variable influences the risk and non-linear interactions between the different risk variables make risk stratification challenging. This paper aims to provide a focused review of the multi-parametric risk models for BrS risk stratification published in the literature.

Keywords: Brugada syndrome; risk stratification; risk stratification; depolarization; repolarization

Introduction

Brugada syndrome (BrS) is a rare disorder characterized by coved or saddle-shaped ST-segment elevation in the right precordial leads on the electrocardiogram (ECG) (1). It is associated with increased risks of ventricular arrhythmias (VAs) such as ventricular tachycardia/ventricular fibrillation (VT/VF), which can lead to sudden cardiac death (SCD) (2). The global prevalence of BrS is estimated to be 0.5 per 1000, with a higher prevalence in Southeast Asia (3).

The diagnosis of BrS is based on the presence of a type 1 Brugada pattern on the ECG. In the absence of a spontaneous type 1 Brugada pattern, pharmacological challenge tests using sodium channel inhibitors such as ajmaline, procainamide or flecainide can be used to reveal the Brugada phenotype (4). Although BrS has traditionally been perceived as an electrophysiological disorder, it was only until recently that structural abnormalities such as myocardial atrophy, fibrosis and lipid infiltration were found in BrS (5). As the clinical presentation of BrS is similar to other cardiac-related diseases, BrS patients may be misdiagnosed or initially, asymptomatic BrS patients may be undiagnosed. Thereby, they are unable to receive prompt treatment (6). While symptomatic BrS patients are directed to receive an implantable cardioverter-defibrillator (ICD), this decision remains controversial for asymptomatic patients, especially those with only drug-induced type 1 BrS ECG pattern (7). It is estimated that over 20% of worldwide sudden deaths where patients had structurally normal hearts are caused by concealed BrS (4) .

In spite of expanding research, the underdiagnosis of symptoms associated with BrS highlights the absence of an extensive screening model and effective screening tools (8). Hence, a multi-parametric approach involving multiple clinical and electrophysiological variables is necessary to provide accurate risk stratification (9). However, the extent to which each variable influences the risk and non-linear interactions between the different risk variables make risk stratification challenging. The aim of this paper is to provide an overview of the multi-parametric risk models for BrS risk stratification that have been published in the literature.

Risk factors of future arrhythmic events

Risk factors described in the literature can be categorized into demographic variables, family history, clinical symptoms, ECG markers and other test results (**Table 1**). A family history of BrS has been identified as a significant risk factor (10). Regarding clinical symptoms, syncope has been associated with arrhythmic events (11). Specifically, the risk of arrhythmic events depends on the type of syncope, with those of cardiac/arrhythmic origin showing higher risks than reflex syncope, highlighting the importance of detailed history taking (12). Other significant clinical risk factors include spontaneous type 1 Brugada pattern, sinus node dysfunction and male sex were also identified as important predictors (13, 14).

ECG markers can be broadly divided into those reflecting depolarization, repolarization or both (15). The repolarization theory argues that the inhomogeneous repolarization of myocardial cells is closely related to BrS. By contrast, the depolarization theory suggests that the presence of conduction abnormalities in BrS is a result of structural and electrical irregularities in the epicardium (16). Some research studies utilise treadmill tests to exacerbate changes in risk markers, which may be useful for further risk stratification (17). Moreover, type 1 BrS ECG pattern revealed during exercise test might be associated with an elevated risk of arrhythmic events during physical exercise (17). Invasive tests such as electrophysiological studies (EPS) can be useful, although patient selection and procedural protocols need to be standardised across institutions (18). A meta-analysis by Fauchier *et al.* utilised a sample of over 1000 asymptomatic BrS patients with inducible VT/VF in an EPS, correlated with higher occurrence of cardiac events (19). Similarly, in Letsas *et al*., EPS inducibility was identified as a significant predictor for asymptomatic BrS patients. However, the predictive value of a positive EPS test remains controversial (14, 19). Shinohara *et al*. found that the use of non-aggressive EPS protocol was not associated with

predicting cardiac events in asymptomatic patients, therefore limiting the applicability scope of the inducible arrhythmias on EPS testing for BrS patients (20).

Another important predictor for arrhythmic risk is the presence of a first-degree atrioventricular (AV) block on the ECG. A study by Migliore *et al.* found that patients with first-degree AV block showed wider QRS complexes and were more likely to have left anterior hemiblock (21). Compared to spontaneous type 1 Brugada pattern, first-degree AV block was a stronger predictor of arrhythmic outcomes. The relationship between first-degree AV block, prolonged PR interval with increased arrhythmic events is also well-supported in other reviews and meta-analyses (22, 23).

In addition to the EPS, invasive risk markers of BrS can also be identified using epicardial mapping. Pannone *et al.* demonstrate promising evidence of the use of high-density epicardial electroanatomic mapping (EAM) (16). In this study, the high-frequency potential was identified as a potential risk marker, suggesting that BrS is associated with the presence of abnormal depolarization. In addition, BrS patients with a prior history of aborted SCD had longer fractionated EGMs. After ajmaline administration, BrS patients with prior aborted SCD experienced longer high frequency potential activation time, low-frequency potential (LFP) activation time and LFP duration. This was further extended by Pannone *et al.,* which identified an independent association between VT/ VF inducibility versus substrate size. It was found that the optimal threshold substrate cut-off value to identify inducible arrhythmias is 4 cm^2 (24). Moreover, endocardial mapping can be used to reveal epicardial abnormalities and can provide utility for further risk stratification (25-27).

A combination of the aforementioned electrocardiographic markers, laboratory tests and clinical symptoms can be used to construct various risk stratification models (28), the characteristics for which are summarised in **Table 2.**

Shanghai score for diagnosis of BrS

The Shanghai BrS score was proposed at the J-Wave Syndromes Consensus Conference held in Shanghai in 2015. It includes three parameters: spontaneous/fever-induced type 1 ECG, clinical histories such as nocturnal agonal respirations and pathogenic mutations in the SCN5A gene (29). A score of ≥3.5, 2-3 and <2 indicates probable/definite, possible or non-diagnostic results, respectively (30). Kawada *et al*. selected patients that displayed fever, fever-induced-type 1 ECGs, drug-induced or appeared spontaneously (n = 393) (30). The researchers found that the incident VT/VF rates were significantly different amongst the ≥5.5, 3.5 to 5.5, 2 to 3, and <2 points. By contrast, Probst *et al*. found that patients with Shanghai score ≥7 had significantly lower event-free survival rates compared to those with lower scores (n = 1613), but this score was unable to further risk stratify the remainder of the study cohort (31). In concurrence, despite the time-dependent nature of clinical symptoms and ECG patterns, some researchers found no changes in the Shanghai score in the cohort (32). This was further validated by Mellor *et al*. as the study found that no arrhythmic events occurred for 27 subjects that did not fulfill the diagnostic criteria (33). In comparison, Papatheodorou *et al.,* studying 85 families and 149 relatives, revealed that the Shanghai score is not as accurate as previously perceived. It excludes a large proportion of sudden arrhythmic death subjects who are also likely BrS patients (34). With the model, 20% of families and 30% of relatives were labeled as non-diagnostic after the follow-up. Using an external validation cohort, Lee *et al*. found that the Shanghai score had an overall area under the receiver-operator-characteristic curve (AUC) of 0.70, indicating a good performance (35). With a cut-off point of 3.75, sensitivity, specificity, and AUC were 77%, 56% and 0.67, respectively. In the same study, it was found that the performance was lower with an AUC of 0.49 when the score was applied to the intermediate-risk cohort. It must be noted that the Shanghai score demonstrates potential as a diagnostic tool and not a prognostic tool (36).

Delise model (2011)

The Delise model includes four variables: spontaneous type 1 BrS ECG, positive EPS, syncope and family history of SCD (37). The model was created using a cohort of 320 patients with type 1 BrS ECG by combining data from five Italian centres (37). In another study consisting of 243 BrS patients, Delise *et al.* reported that drug-induced type 1 BrS ECG pattern does not necessarily predict low arrhythmic risk in BrS patients (38). One of the explored variables, EPS, was found to have a positive predictive value of 14% and a negative predictive value of 100%. However, variables evaluated as an independent risk factor had limited utility for predicting major arrhythmic events (C-statistic: 0.58-0.71) (37). Interestingly, while spontaneous type 1 BrS ECG pattern was found to be a significant predictor of arrhythmic events, patients with drug-induced ECG patterns were associated with low-risk of arrhythmic events (<2%) (37). Furthermore, the positive predictive values (PPV) were found to be low, with a value of 8.6% for spontaneous type 1 BrS ECG pattern, 7.4% for family history of SCD and 10.4% for syncope history. This suggests poor performance for the three clinical risk factors. Letsas *et al.* showed that in a Greek cohort of BrS patients, the Delise model had a sensitivity and specificity of 71.4% and 86.5%, respectively, but a low PPV of 41.7% (28). However, the Delise model achieved better performance compared to the PPV of the Okamura and Sieira models, which were found to be 24.1% and 21.9%, respectively (28). Using an external validation cohort, Lee *et al*. found that the score had an overall AUC of 0.66, indicating a moderate performance. Using a cut-off point of 1.5, the sensitivity, specificity and AUC were 64%, 68% and 0.66, respectively (35). In the same study, it was found that the performance was lower with an AUC of 0.53 when the score was applied to the intermediate-risk cohort.

Okamura model (2015)

The Okamura model uses spontaneous type 1 ECG pattern, syncope presumed due to ventricular arrhythmia and positive electrophysiological study for risk prediction (39). The system was developed based on a cohort of suspected BrS patients without a history of cardiac arrest or VF (n = 218) from the

National Cerebral and Cardiovascular Center and Okayama University Hospital in Japan. Unlike a type 1 BrS ECG pattern and syncope, a positive EPS test was not an independent risk predictor, although there was a correlation between positive test status and higher arrhythmic events. This is supported by Asada *et al.,* where the use of an aggressive EPS protocol can predict VT in 125 asymptomatic BrS patients (18), whilst a pooled analysis by Sroubek *et al.* identifies non-aggressive protocol for VA induction correlates with greater arrhythmic risk (n = 1312) (40). Letsas *et al.* (n = 111) also determined the sensitivity and specificity of the Okamura model to be 100% and 57.7%, respectively (28).

Sieira model (2017)

The score developed by Sieira *et al*. consists of six variables: spontaneous type 1 pattern (1 point), positive EPS (2 points), early familial SCD (1 point), syncope (2 points), aborted SCD (4 points) and SND (3 points), with a score >2 would classify a patient as high-risk (28). It was developed from a cohort of 400 BrS patients from Universitair Ziekenhuis Brussel. The inclusion criteria were patients with drug-induced or spontaneous Brugada type 1 ECG with follow-up of at least one-year duration. This score has been validated externally by two studies. Firstly, Probst *et al*. (n = 1613), using sudden death and non-sudden death as the endpoint, identified that scores ≥5 had significantly higher event rates than those with scores of 0 or 1 (31). However, they were not significantly different from those with scores 2-4. It must be noted that the predictive performance for asymptomatic patients using the Sieira score is significantly less than for symptomatic patients (0.59 vs 0.71), indicating the difficulty in risk stratifying the subgroup of patients at intermediate risks (31). This is further examined by Letsas *et al*., who identified the sensitivity and specificity values to be 100% and 51.9%, respectively (28).

In an external validation cohort, Chow *et al*. found the sensitivity and specificity of the score was 23% and 58%, respectively (n=150) (41). The apparently suboptimal performance may have been a result of higher mean age, the incidence of SCD and a greater proportion of symptomatic subjects (41). By

contrast, in a recent external validation by Lee *et al*., the score had an overall AUC of 0.80, indicating good performance. With a cut-off point of 2.5, sensitivity, specificity, and AUC was 82%, 67% and 0.74, respectively (35). In the same study, it was found that the performance was lower with an AUC of 0.57 when the score was applied to the intermediate-risk cohort.

Letsas model (2019)

The Letsas Model uses six variables for risk stratification: history of syncope, spontaneous type 1 BrS ECG pattern, positive EPS, family history of SCD, fragmented QRS and QRS duration in lead V2. This model was built from a cohort of 111 BrS patients from nine hospitals in Greece (28). Specifically, the highest event rates occurred for patients with syncope, spontaneous type 1 BrS ECG pattern and inducible VAs on EPS. In another meta-analysis of 1104 asymptomatic BrS patients, Letsas *et al*. revealed strong supporting evidence of the use of inducible ventricular arrhythmias for predicting future arrhythmic events (42). Using an external validation cohort, Lee *et al*. found that the score had an overall AUC of 0.66, indicating a moderate performance. With a cut-off point of 1.5, sensitivity, specificity, and AUC was 73%, 54% and 0.63, respectively (35). In the same study, it was found that the performance was lower with an AUC of 0.48 when the score was applied to the intermediate-risk cohort.

Subramanian model (2019)

The Brugada Risk Stratification (BRS) score proposed by Subramanian *et al*. has four predictors: spontaneous type 1 BrS ECG pattern, S-wave upslope duration ratio ≥0.8, fragmented QRS (≥3 spikes) in inferior leads and $T_{peak} - T_{end}$ interval ≥ 100 ms (43). A cohort of 103 patients with Brugada type 1 ECG was used for the model development study. The inclusion criteria were patients that had no structural cardiac abnormalities and displayed a type 1 BrS ECG pattern with coved ST-segment elevation. Each predictor is assigned 1 point, and patients with a BRS score of ≤2 and ≥3 will be stratified into low and

high risk, respectively (43). In their 2017 study examining 75 asymptomatic BrS patients and 88 healthy control subjects, they found three key associations between ECG pattern and exercise phase: (1), the S wave upslope duration ratio in the precordial leads is present during peak exercise; (2) In late recovery, the pattern of augmentation of J point elevation in lead aVR >2mm was evident and (3) delayed heart rate recovery were independent predictors of major arrhythmic events in asymptomatic BrS patients (17). A benefit of this model is the ability to predict high risk, asymptomatic patients. All 9 out of 91 asymptomatic patients who were stratified as high risk had major arrhythmic events during follow up (43). The model was externally validated based on four ECG parameters on an independent patient cohort of 42 subjects from India. From a combination of interviews of primary care physicians, patient phone interviews and past medical records, the authors found comparable baseline clinical and ECG characteristics in the derivation and validation cohorts (43).

Shinohara model (2020)

The Shinohara model includes a combination of four factors: Spontaneous type 1 ECG, presence of J wave in inferior and lateral leads, QRS duration in lead V2 >90 ms and family history of sudden cardiac death. This system was developed from studying a cohort of 193 asymptomatic BrS patients from Japan (20). Patients with normal findings during clinical examination and who do not take antiarrhythmic drugs were included in the study. It was only until recently that more emerging research focused on the risk stratification of asymptomatic BrS patients. Patients with three or all risk factors present were significantly more susceptible to risks of cardiac events compared to those with one risk factor. The incidence of cardiac events was low amongst asymptomatic patients, which is similar to the incidence of annual arrhythmic events identified in the FINGER and PRELUDE registry (13, 14). There were only slight differences in the cardiac event occurs between the presence of positive EPS (0.4%) and negative EPS (0.5%) findings. EPS demonstrated high specificity (73%) but low sensitivity (14%) (20). The

negative predictive value was 96%, while the positive predictive value was 2.0% which would suggest low accuracy (20). However, the inducibility of VA was insignificant for the prediction of cardiac events for asymptomatic patients.

Honarbakhsh model (2021)

Honarbakhsh *et al*. evaluated a cohort of 1110 BrS patients from eight countries. They identified the four most important risk factors of five-year VA/SCD: probable arrhythmia-related syncope, spontaneous type 1 BrS ECG pattern, early repolarization pattern and type 1 Brugada pattern in the peripheral leads (44). Through this study, the presence of all four factors correlated with a lower mean restricted survival compared to the remaining subgroup of patients with fewer risk factors. The score adopts a point system with a maximum score of 47, revealing a specificity and sensitivity of 80.2% with 71.2%, respectively. Internal validation was performed using the C-statistic, while external validation using cross-validation was performed based on data from different countries. The results demonstrated that all four factors showed consistent results across all samples. This was possible due to the multicentre nature of the cohort, thus enhancing the generalisability of the results. To corroborate, the importance of recalibration is also emphasised due to variable needs in each country to refine the precision of the stratification data (44). Using an external validation cohort, Lee *et al*. found that the score had an overall AUC of 0.59, indicating a moderate performance. With a cut-off point of 18.5, sensitivity, specificity and AUC were 48%, 74% and 0.61, respectively (35). In the same study, it was found that the performance was lower with an AUC of 0.48 when the score was applied to the intermediate-risk cohort.

Lee models (2021)

While previous studies predominantly focused on adult cohorts, additional research compared the important characteristics between paediatric or young adult (≤25 years old) and older adult (>25 years old)

presenters. In a multicenter cohort study of 505 patients from all hospitals in Hong Kong, China, the authors found that younger BrS patients were at a higher risk of spontaneous VT/VF (45). Initial presentation with VT/VF and the presence of SCN5A mutations were significant predictors of VT/VF for the paediatric/young patient subgroup; spontaneous, type 1 Brugada ECG pattern was not. Some factors, such as prolonged PR intervals, are influenced by age and further contribute to the intergroup differences (45). This may be attributed to changes in autonomic and hormonal triggers in later life, resulting in changes in the predictive value of genetic or physiological variables (46). In another study by Lee *et al*. (n = 516), the initial presentation of VT/VF and the standard deviation of P-wave duration across successive visits were identified as useful risk predictors. Machine learning algorithms such as random survival forests and non-negative matrix factorisation provide additional value for the importance ranking of the risk variables and improve the accuracy of risk prediction (47). Conte *et al*. found that child patients (n = 40) experience more frequent episodes of sinus node dysfunction compared to older participants (48). A decision-analytic model based on simulating 2,000,000 asymptomatic patients developed by Khurshid *et al.* highlighted ICD-based approaches as optimal management for asymptomatic patients (49). The aforementioned studies lend strong support that the management and susceptibility to BrS for young and older demographics are different. Thus, this supports that the current score systems may not be fully generalisable to younger patients. Hence, the age factor at initial presentation must be carefully evaluated during the development of risk stratification models.

Comparisons of the different models

Additional studies have validated the effectiveness of several models described above. Similar to previous studies, six markers related to syncope, ECG, EPS, SCD and QRS duration were found to be significant predictors, especially in patients with four or more factors present (28). Furthermore, the Delise, Okamura and Sieira model was also validated, revealing excellent negative predictive value, high

sensitivity, and specificity. The majority of models demonstrated syncope and family history of SCD as robust predictors and were associated with a nine-fold increase in risk for arrhythmic events (28). By contrast, a study by Lee *et al.* found that syncope was not a significant predictor in multivariable Cox regression, which may have been due to the inclusion of non-cardiogenic syncope or underreporting of symptoms (50). Rodríguez-Mañero *et al*. further validated the Sieira, Delise and Shanghai scores and found all risk factors to be associated with arrhythmic events in a cohort of 831 patients with previously diagnosed BrS and performed EPS. However, the discriminatory abilities were modest, especially for asymptomatic patients (51). Interestingly, a stepwise increase in the risk of death was identified during this study. Here, the spontaneous type 1 BrS ECG pattern was identified as the most significant predictor. Moreover, while the Delise score demonstrates that family history of SCD does not independently correlate with arrhythmic risk, the Sieira score shows that early SCD in first-degree relatives before 35 years old does influence risk stratification (35).

Limitations of BrS risk stratification models

A major limitation of all composite risk score systems is the lack of predictive value for patients classified with intermediate scores, which may limit the clinical utility of risk models for decision making. It is crucial that patients with intermediate scores are followed up with further investigations. For example, patients who were assessed with the Sierra score could also be assessed based on other factors such as BrS familial history, which is a factor included in the Shanghai score approach (52). This notwithstanding, asymptomatic patients represent the largest but most difficult subgroup of patients to risk stratify amongst all models, which is closely followed by the intermediate risk subgroup of patients. From the existing literature, data on asymptomatic patients are often incorporated with patients with syncope or other clinical characteristics. In addition, many studies only recorded a low number of cardiac event occurrences during follow-up, which restricts the ability to identify potential risk factors and introduces larger variability.

Subsequently, the number of events and duration of follow-up amongst low to intermediate risk patients, is simply too low for anything other than well-established variables to emerge as a reliable risk indicator. By improving the sensitivity and diversity of parameters in the models, better risk stratification of patients at intermediate risks can be achieved. Alternatively, risk stratification models specific for asymptomatic and intermediate risk BrS patients can be developed (53).

The lack of inclusion of social factors such as financial resources and medical literacy, which has a significant influence on disease prognosis, may have reduced the predictive validity of the BrS risk stratification models. However, these data fields are not routinely collected as part of cardiac clinic consultations and are likely not widely available. Moreover, the heterogeneity of data collection and clinical testing may also impact the credibility of findings. For example, patients who did not conduct the SCN5A gene analysis, an essential variable measured in the Shanghai system, would be omitted from the cohort. Resultantly, this may produce selection bias during data collection. There is also controversy surrounding the use of programmed ventricular stimulation as a risk predictor. Some studies often omit these findings during multivariate analysis due to the small proportion of patients who have performed the procedure in the cohort. If clinical practices were to adopt a model that includes programmed ventricular stimulation as a predictor, they may have to alter their existing stimulation protocol to match the one used during model development (54). Thus, this lends insight into the importance of a uniform data collection methodology to ensure all participants can be included. It remains challenging to compare the validity of different BrS risk stratification models in different studies due to the variation in the data collection process and circumstances. As ECG features may range amongst different ethnicities, the majority of findings demonstrate a lack of cross-cultural generalisability (55). There may also be underlying discriminatory bias towards specific subgroups of the population such as patients of lower socioeconomic status, who may perform fewer diagnostic tests or are less likely to seek treatment.

Resultantly, this may to a skewed data representation that misinterprets certain subgroups as being of lower risk of BrS.

Future model development

Expanding on the findings of published models, existing models can dive deeper into the use of genetics in BrS risk stratification. BrS was previously categorised as an autosomal dominant Mendelian disorder (56). However, the notion surrounding the predictive utility of genetic testing on BrS has remained controversial as not all BrS are hereditary based (56). The current data on genetics is relatively scarce, where models often include whether a mutation is a pathogenic variant of SCN5A (57, 58). However, no further attempts are made to distinguish it. It is prudent to recognize the need to explore the features of individual variants and view BrS as an oligogenic disorder, rather than oversimplifying all variants as a singular entity (56). Resultantly, this could lead to the innovation of a polygenic risk score (59). Further research would be required to verify the intricate interactions and influences of gene variants. In the future, the development of AI solutions can potentially generate more risk predictions for the asymptomatic and intermediate risk patients, potentially by incorporating nonlinear interactions between different variables (60).

Conclusion

In conclusion, an increasing variety of models have been developed for risk stratification of BrS patients. Only a few clinical predictors have been studied thoroughly, while the predictive values of the remaining variables have not been fully elucidated. The use of an individualised risk model is crucial for clinical practice, allowing early but appropriate intervention with ICD implantation. Determination of optimal thresholds and specific cut points in the risk models will better refine risk stratification, reducing

the number of unnecessary invasive therapy in truly low-risk patients, hence maximising the quality of care. Prospective analysis is necessary before applying specific models for clinical decision-making. As numerous other variables remain to be discovered, current models should be approached as a supplementary tool but not a substitution for clinical judgement.

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Tables

Table 1. List of risk factors of future arrhythmic events.

Category	Variables	References
Demographic variables	Male sex	(13)
Family history	Sudden cardiac death	(61)
	Brugada syndrome	(46)
	Genetic mutation of SCN5A	(62, 63)
Clinical characteristics	Syncope	(11)
	VT/VF/SCD	(2)
	Fever	(64)
	Atrial flutter or fibrillation	(65)
	Sinus Node Dysfunction	(66)
	First-degree atrioventricular block	(23)
Genetics	Genetic test positive	(63)
Electrocardiography	Spontaneous type 1 Brugada ECG pattern	(38, 67)
	QRS duration >120 ms	(61)
	QRS dispersion	(68)
	Prominent R wave in lead aVR	(69)
	S wave in L1 (≥40 ms)	(15)
	Tzou criteria (V1R >0.15 mV, V6S >0.15 mV, and V6 S:R>0.2)	(70)

	Amplitude (≥40 ms, amplitude ≥0.1 mV, area ≥1 mm^2)	(15)
	Fragmented QRS	(71)
	Early repolarization pattern in inferolateral leads	(72)
	ST-segment depression	(15)
	QTc and QTc dispersion	(23)
	Tpeak-Tend and Tpeak-Tend dispersion	(73)
	T-wave alternans	(15)
Treadmill test	Increase in S wave upslope duration ratio >30% at peak exercise	(74)
	Augmentation of J point elevation in lead aVR >2 mm in late recovery	(74)
	Delayed HR recovery	(74)
Electrophysiological studies	Positive test	(14, 40, 75, 76)
	Increased restitution gradients at the endocardium and epicardium	(77-80)
	Increase in activation time with decreasing coupling interval	(81)
Electroanatomical mapping	Low voltage areas on unipolar and bipolar signals	(82, 83)

Table 2. Summary of the different models.

Model*	Variables	Maximum no. of points	Definition of Intermediate-Risk subgroup	AUC (own cohort)	AUC (external validation)	AUC for (intermediate-risk groups)
Shanghai Score	ECG (12-lead/ambulatory), clinical history, family history and SCN5A mutation	9	4 - 6.5	0.698	0.730	0.490
Delise model (2011)	Spontaneous type 1 ECG, positive EPS, syncope and family history of SCD	/	/	0.661	0.870	0.531
Okamura model (2015)	Spontaneous Type-1 ECG pattern, syncope and PES+	/	1 risk factor	0.667	0.87	0.543
Sieira model (2017)	Spontaneous type 1 pattern, positive EPS, early familial SCD in first-degree relatives, syncope, aborted SCD, SND	13	2 - 4	0.805	0.87	0.567
Letsas model (2019)	History of syncope, spontaneous type 1 BrS ECG pattern, positive EPS, family history of SCD, fragmented QRS and QRS duration in lead V2	/	/	0.656	/	0.483

Shinohara model (2020)	Spontaneous type 1 ECG, presence of J wave in inferior and lateral leads, QRS duration in lead V2 >90 ms and family history of sudden cardiac death	/	/	/	/	/
Honarbakhsh model (2021)	Spontaneous type 1 ECG pattern, S wave upslope duration ratio ≥0.8, QRS fragment in inferior leads ≥3 and T peak – T end ≥ 100 ms	47	2 - 3	0.592	0.95	0.452
Lee model (2021)	Initial presentation with VT/VF, SCN5A mutation, standard deviation of P-wave duration across successive visits	/	/	0.855	/	0.704

**Different models have slightly different definitions of syncope and outcomes.*

Table 3. Summary of the different models.

Variables	Shanghai	Deise	Okamura	Sieira	Letsas	Subramanian	Shinohara	Honarbakhsh	Lee	Chen	Lee
Year	2016	2011	2015	2017	2019	2019	2020	2021	2021	2021	2021
Number of patients for model development	-	320	218	400	111	103	193	1100	516	134	548
First/second degree relative with definite BrS	✓										
First/second-degree relative Suspicious FH SCD	✓	✓		✓	✓		✓			✓	✓
First/second-degree relative unexplained SCD <45 years with negative autopsy	✓										
Age										✓	
Ethnicity										✓	
Unexplained cardiac arrest / documented VA	✓			✓	✓				✓		✓
Nocturnal agonal respiration	✓										
Suspected arrhythmic syncope	✓	✓	✓	✓	✓			✓	✓		✓

Syncope of unclear origin	✓									
AF < 30 years old without alternative aetiology	✓									
Pathogenic mutation in BrS susceptibility gene	✓									
Spontaneous type 1 Brugada pattern at nominal or high leads	✓	✓	✓	✓	✓	✓	✓	✓		✓
Spontaneous type 1 Brugada pattern peripheral leads								✓		
Fever induced type 1 Brugada pattern at nominal or high leads	✓									
Drug-induced type 1 Brugada pattern	✓									
Evolving Brugada pattern										✓
Other cardiac arrhythmias									✓	✓
Sinus node dysfunction				✓						✓
Positive PVS test			✓	✓			✓			
P-wave variables									✓	

QRS duration	✓		✓		✓			
QRS axis					✓			
Fragmented QRS	✓	✓						
Late potential			✓					
aVR sign							✓	
ER pattern / J-wave			✓	✓			✓	
S-wave in lead I			✓				✓	
S-wave upslope ratio		✓						
QTc interval					✓		✓	
T_{peak}-T_{end}		✓				✓		