# Comparing the Performance of Published Risk Scores in Brugada Syndrome: A Multi-center Cohort Study

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**Abstract: The management of Brugada Syndrome (BrS) patients at intermediate risk of arrhythmic events remains controversial. The present study evaluated the predictive performance of different risk scores in an Asian BrS population and its intermediate risk subgroup. This retrospective cohort study included consecutive patients diagnosed with BrS from January 1, 1997 to June 20, 2020 from Hong Kong. The primary outcome is sustained ventricular tachyarrhythmias. Two novel risk risk scores and 7 machine learning-based models (random survival**

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**forest, Ada boost classifier, Gaussian naÿve Bayes, light gradient boosting machine, random forest classifier, gradient boosting classifier and decision tree classifier) were developed. The area under the receiver operator characteristic curve (AUC) [95% confidence intervals] was compared between the different models. This study included 548 consecutive BrS patients (7% female, age at diagnosis: 50 ± 16 years, follow-up: 84 ± 55 months). For the whole cohort, the score developed by Sieira et al showed the best performance (AUC: 0.806 [0.747-0.865]). A novel risk score was developed using the Sieira score and additional variables significant on univariable Cox regression (AUC: 0.855 [0.808-0.901]). A simpler score based on non-invasive results only showed a statistically comparable AUC (0.784 [0.724-0.845]), improved using random survival forests (AUC: 0.942 [0.913-0.964]). For the intermediate risk subgroup (N = 274), a gradient boosting classifier model showed the best performance (AUC: 0.814 [0.791-0.832]). A simple risk score based on clinical and electrocardiographic variables showed a good performance for predicting VT/VF, improved using machine learning. (Curr Probl Cardiol 2022;47:101381.)**

## Introduction

Cardiac ion channelopathies are rare yet important causes of sustained ventricular tachycardia/fibrillation (VT/VF), which can lead to sudden cardiac death (SCD).[1-3] Of these, Brugada Syndrome (BrS) is characterized by an electrocardiographic (ECG) ST-elevation followed by either a coved-shaped (type 1) or saddle-shaped (type 2) slope, in the absence of overt structural abnormalities.[4,5] Therefore, the stratification of VT/VF/SCD risk in BrS patients is critical to the management of BrS.[4,5] Although BrS has a higher prevalence in Asia, a large proportion of existing research was based on registries that include mostly Caucasian subjects.[6-10] As a result, the VT/VF/SCD risk stratification tools derived were also largely based on the Western population.[11-13]

Intermediate risk refers to the presence of risk factors suggestive of high and low risks, such as an asymptomatic patient presenting with spontaneous type 1 Brugada pattern (BrP).[14] Whilst it is clear that high

risk patients should be referred for implantable cardioverter-defibrillator implantation, and low risk patients should be monitored regularly, it is the management of these intermediate risk patients that remains controversial.[15] Recently, Probst et al evaluated the predictive value of the Shanghai and Sieira score against intermediate risk BrS patients in the largest cohort of BrS patients to date and concluded that risk scores could not stratify the arrhythmic risk in this subpopulation.[14] However, other existing risk scores were not evaluated, with the Shanghai score not designed to be a prognostic tool. In addition, the Asian population was not assessed despite the greater prevalence of BrS in Asia. Therefore, the present study aims to evaluate the predictive performance of different risk scores in the overall Asian BrS population and its intermediate risk subpopulation, thus examining the applicability of simple risk scores in a clinical setting.

# Methods

## *Patient Cohort and Data Collection*

Ethics approval for the present study was obtained from The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee. The present cohort consists of consecutive patients diagnosed with BrS from January 1, 1997 to June 20, 2020 at centers managed in the Hong Kong public sector. Patients were identified using Clinical Data Analysis and Reporting System, a territory-wide database that centralizes patient information from 43 local hospitals and their associated ambulatory and outpatient facilities to establish comprehensive medical data, including clinical characteristics, disease diagnosis, laboratory results, and medication prescription details. The system has been previously used by local teams in Hong Kong to conduct registry-based and population-based studies,[16-18] including rare arrhythmic syndromes.[19-22] Diagnosis of BrS was confirmed by G.T. and N.S.M. after reviewing the relevant case notes and ECGs of the patients based on the Expert Consensus Statement proposed in 2017.[23]

The following clinical data were extracted: (1) sex; (2) presentation at diagnosis: age, type of BrP, symptom (asymptomatic, syncope, or VT/VF), fever-induced BrP; (3) performance and results of drug challenge test, electrophysiological study (EPS) and genetic test; (4) family history of SCD and BrS; (5) follow-up: duration, the occurrence of VT/VF and time from diagnosis if present, mortality and cause if relevant, presence of type 1 BrP; (6) baseline concomitant presence of other arrhythmias

(sick sinus syndrome, bradycardia, atrioventricular block, supraventricular tachycardia, supraventricular ectopic beats, atrial fibrillation, atrial tachycardia, or atrial flutter). An asymptomatic presentation is defined as the absence of syncope and VT/VF. The presence of a family history of BrS and SCD was evaluated for the entire cohort, and there is no age restriction to the family history of SCD and BrS. The evolution of BrP refers to the presentation of other types of BrP other than the type presented at diagnosis. Amongst patients with a negative drug challenge test, the diagnosis was made based on the subsequent presentation of type 1 BrP or inducible EPS.

Automatically measured baseline ECG indices were extracted: (1) heart rate; (2) PR interval; (3) QRS interval; (4) QT and corrected QT (QTc) interval; (5) P, QRS, and T wave axis. These ECG parameters were averaged across the 12 leads. In addition, G.T. and G.B. identified the following ECG features: (1) early repolarization in peripheral leads; (2) aVR sign (ST elevation in lead aVR); (3) significant S wave in lead 1 (S wave $>$ 0.1 mV or $>$40 ms); (4) fragmented QRS. The aforementioned ECG indices were extracted given their potential in reflecting BrS-related ECG changes, thus have a potential risk stratification value.[24,25]

## Outcomes and Statistical Analysis

The primary outcome is sustained VT/VF occurring during follow-up. This was obtained from case notes by the physicians during inpatient or outpatient encounters, and/or implantable cardioverter-defibrillator documentation where available. Continuous variables were reported as mean (standard deviation), whilst discrete variables were reported as total count (percentage). To identify predictors of the primary outcome, univariable Cox regression was performed. Significant univariable predictors were used as inputs for multivariable Cox regression. Findings from the drug challenge test and EPS were not included in the multivariable model since they were not universally performed. For continuous variables, cut-off values were identified using the Youden method with no adjustment (*cutpt* function, Stata). The hazard ratio (HR) and 95% confidence interval (CI) were reported. The weighting of each parameter was adopted from the HR calculated from the results of Cox regression.

## Development of Risk Scores and Machine Learning Models

The performance of the different risk models was assessed using receiver operating characteristic curve (ROC) analysis. The area under

the receiver-operator-characteristic curve (AUC) and its 95% CI were determined. To develop our own score, the best performing score with the highest AUC was selected using the original weighting of the variables. Additional risk factors that were significant on univariable Cox regression were selected, allowing a modified risk score to be devised. To create a simpler risk score that does not require invasive testing, EPS and sinus node dysfunction (SND) were excluded (novel risk score).

Machine learning algorithms have demonstrated utility in terms of improving risk stratification. Therefore, a number of machine learning models were developed in this study: random survival forest,[26] ada boost classifier,[27] Gaussian Naïve Bayes,[28] light gradient boosting machine,[29] random forest classifer,[30] gradient boosting classifier[31] and decision tree classifier.[32] The foundamental problem of risk stratification is binary classification with next VT/VF as outcome. We followed the implimentations of these machine learning models in Scikit-Learn (Version 1.0.2).

### *Comparison of the Performance of the Different Scores and Models*

To compare the performance of the novel risk scores and machine learning models against the published scores[12,24,25,33-35] (Supplementary Table 1), The following cohorts were used to test the performance: (1) whole cohort; (2) intermediate risk cohort (defined as patients in quartiles 2 and 3 based on score ranking of the novel risk score); (3) patients without prior VT/VF at initial presentation; and (4) patients with positive EPS. All analyses were performed using Stata (Version 16) or R Studio (Version: 1.3.1073).

## Results

### *Baseline Characteristics and Predictors*

The present cohort consists of 548 patients (7.3% females, age at diagnosis: 49.9 ± 16.3 years old, follow-up duration: 84 ± 55 months) (Table 1). In total, 66 patients experienced at least one episode of sustained VT/VF during follow-up. The incidence rate, calculated by the number of patients with the primary outcome divided by the person-years on follow-up for the whole cohort was 1.91% (Supplementary Table 2). Of the different subgroups, the highest incidence rate was observed for those with initial VT/VF (1.91%), followed by symptomatic individuals (4.39%) and those with a type 1 BrP on initial presentation (2.01%).

**Table 1.** Baseline and clinical characteristics of the study cohort of patients with Brugada syndrome

| Characteristics | All (N = 548) mean (SD); N or frequency(%) | VT/VF in follow-up (N = 66) mean(SD); N or frequency(%) | No VT/VF in follow-up (N = 482) mean(SD); N or frequency(%) | *P*-value |
|---|---|---|---|---|
| ***Clinical*** | | | | |
| Male gender | 508(92.70%) | 64(96.96%) | 444(92.11%) | 0.155 |
| Baseline age, y | 49.9(16.3) | 48.1(17.8) | 50.1(16.1) | 0.348 |
| Initial type 1 BrP | 340(62.04%) | 39(59.09%) | 301(62.44%) | 0.598 |
| Evoluation of BrP | 187(34.12%) | 18(27.27%) | 169(35.06%) | 0.211 |
| Fever-induced BrP | 86(15.69%) | 5(7.57%) | 81(16.80%) | 0.053 |
| Family history of BrS | 17(3.10%) | 3(4.54%) | 14(2.90%) | 0.471 |
| Family history of SCD | 45(8.21%) | 5(7.57%) | 40(8.29%) | 0.841 |
| Syncope | 231(43.25%) | 46 (69.70%) | 185 (38.38%) | <**0.0001***** |
| Initial VT/VF | 43(7.85%) | 25 (37.88%) | 18 (3.73%) | <**0.0001***** |
| Other arrhythmia | 83(15.14%) | 20(30.30%) | 63(13.07%) | <**0.0001***** |
| Drug challenge test | 234 (42.70%) | 32 (48.48%) | 202 (41.91%) | 0.263 |
| Positive drug challenge test | 205 (87.61%) | 25 (78.13%) | 180 (37.34%) | **0.033*** |
| EPS | 112 (20.44%) | 25 (37.88%) | 87 (18.05%) | <**0.0001***** |
| Positive EPS | 76 (67.86%) | 21 (31.82%) | 55 (63.22%) | 0.094 |
| Genetic test | 52 (9.49%) | 14 (21.21%) | 38 (7.88%) | **0.001**** |
| Positive genetic test | 17 (32.69%) | 4 (28.57%) | 13 (34.21%) | 0.701 |
| *Baseline electrocardiogram* | | | | |
| Early repolarization in peripheral leads | 39.0(7.11%) | 13.0(19.69%) | 26.0(5.39%) | <**0.0001***** |
| aVR sign | 55.0(10.03%) | 15.0(22.72%) | 40.0(8.29%) | <**0.0001***** |
| Significant S wave in lead 1 | 101.0(18.43%) | 29.0(43.93%) | 72.0(14.93%) | <**0.0001***** |
| Fragmented QRS | 62.0(11.31%) | 14.0(21.21%) | 48.0(9.95%) | **0.004**** |
| Heart rate | 81.1(19.8) | 82.4(20.1) | 81.0(19.8) | 0.615 |
| PR interval | 169.0(28.7) | 167.8(27.3) | 169.2(29.0) | 0.733 |
| QRS interval | 105.8(22.2) | 107.1(15.9) | 105.7(23.0) | 0.545 |
| QTc interval | 416.5(32.7) | 428.7(36.8) | 414.9(31.8) | **0.003**** |
| QT interval | 368.2(41.7) | 377.6(40.6) | 367.0(41.7) | 0.074 |
| P wave axis | 61.7(22.6) | 59.4(24.9) | 62.0(22.3) | 0.424 |
| QRS axis | 59.4(40.1) | 62.5(47.5) | 59.0(39.1) | 0.545 |
| T wave axis | 54.7(26.2) | 51.3(31.7) | 55.2(25.4) | 0.298 |

BrP, Brugada electrocardiographic pattern; BrS, Brugada syndrome; SCD, sudden cardiac death; SD, Standard deviation; VF, ventricular fibrillation; VT, ventricular tachycardia.
*, ** and *** denote P<0.05, P<0.01 and P<0.001, respectively.

Univariable Cox regression identified the following predictors of the primary outcome: (1) evolution of BrP (HR: 0.52, 95% CI: [0.29-0.94], $P = 0.023$); (2) presentation of syncope (HR: 3.81, 95% CI: [2.14-6.78], $P < 0.0001$); (3) other arrhythmia (HR: 2.89, 95% CI: [1.68-4.96], $P < 0.001$); (4) early repolarization in peripheral leads (HR: 3.27, 95% CI: [1.62-6.62], $P = 0.004$); (5) aVR sign (HR: 2.75, 95% CI: [1.42-5.33], $P = 0.006$); (6) significant S wave in lead 1 (HR: 3.46, 95% CI:

**Table 2.** Significant univariable and multivariable predictors of VT/VF during follow-up from Cox regression

| Characteristics | Univariable HR [95% CI]; *P*-value | Multivariable HR [95% CI]; *P*-value |
|---|---|---|
| Male gender | 5.30 [0.73-38.37]; 0.099 | - |
| Age | 1.00 [0.98-1.02]; 0.8616 | - |
| Initial type 1 BrP | 1.10 [0.65-1.87]; 0.7306 | - |
| Evolution of BrP | 0.52 [0.29-0.94]; **0.0234*** | 0.64 [0.31-1.30]; 0.215 |
| Fever-induced BrP | 0.48 [0.17-1.34]; 0.1204 | - |
| Family history of BrS | 0.87 [0.21-3.56]; 0.8385 | - |
| Family history of SCD | 1.09 [0.44-2.74]; 0.8489 | - |
| Syncope | 3.81 [2.14-6.78]; <**0.0001**‡ | 2.67 [1.32-5.41]; **0.006**† |
| Initial VT/VF | 8.12 [4.70-14.02]; <**0.0001**‡ | 3.98 [2.02-7.86]; <**0.0001**‡ |
| Other arrhythmias | 2.89 [1.68-4.96]; **0.0001**‡ | 2.45 [1.20-5.00]; **0.014*** |
| Early repolarization in peripheral leads | 3.27 [1.62-6.62]; **0.0035**† | 1.61 [0.59-4.40]; 0.353 |
| aVR Sign | 2.75 [1.42-5.33]; **0.0060**† | 1.13 [0.48-2.66]; 0.277 |
| Significant S wave in lead 1 | 3.46 [1.96-6.10]; <**0.0001**‡ | 2.36 [1.12-4.97]; **0.024*** |
| Fragmented QRS | 1.75 [0.86-3.57]; 0.1451 | - |
| Heart rate | 1.00 [0.99-1.02]; 0.5197 | - |
| PR interval | 1.00 [0.99-1.01]; 0.8204 | - |
| QRS interval | 1.00 [0.99-1.01]; 0.8176 | - |
| QTc Interval | 1.01 [1.00-1.02]; **0.0051**† | 1.0004 [0.996-1.012]; 0.303 |
| QT interval | 1.01 [1.00-1.01]; **0.0050**† | - |
| P wave axis | 1.00 [0.99-1.01]; 0.9948 | - |
| QRS axis | 1.00 [0.99-1.01]; 0.9247 | - |
| T wave axis | 1.00 [0.99-1.01]; 0.8240 | - |

BrP, Brugada electrocardiographic pattern; BrS, Brugada syndrome; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.
For the multivariable model, variables with P<0.05 on univariable analysis were included.
*for $P \leq 0.05$.
†for $P \leq 0.01$.
‡for $P \leq 0.001$.

[1.96-6.10], $P < 0.0001$); (7) QTc interval (HR: 1.01, 95% CI: [1.00-1.02], $P = 0.005$); (8) initial VT/VF (HR: 8.12, 95% CI: [4.70-14.02], $P < 0.0001$). Syncope, initial VT/VF, other arrhythmias and significant S-wave in lead I remained significant on multivariable analysis (Table 2).

## *Development of Novel Risk Scores Without Machine Learning*

ROC analysis was used to assess the performance of the different scores (Fig 2). The score developed by Sieira et al showed the best performance with an AUC of 0.806 (95% CI: 0.747-0.865), followed by the Shanghai score (0.704 [0.630-0.777]), and the scores by Okamura et al

**Table 3.** Novel risk score derived from the best performing score (Sieira score) and additional significant univariable predictors

| Sieira score with significant variables | | Novel risk score | |
|---|---|---|---|
| Characteristics | Points | Characteristics | Points |
| Spontaneous type 1 Brugada pattern | 1 | Spontaneous type 1 Brugada pattern | 1 |
| Family history of SCD | 1 | Family history of SCD | 1 |
| Positive EPS | 2 | Syncope | 2 |
| Syncope | 2 | Initial VT/VF | 4 |
| Sinus node dysfunction | 3 | Other arrhythmias (AT, AF, SVT) | 1 |
| Initial VT/VF | 4 | ER pattern on peripheral leads | 1 |
| Other arrhythmias (AT, AF, SVT) | 1 | aVR sign | 1 |
| ER pattern on peripheral leads | 1 | S-wave in lead I | 1 |
| aVR sign | 1 | QTc $\geq$ 436 ms | 1 |
| S-wave in lead I | 1 | | |
| QTc $\geq$ 436 ms | 1 | | |

AF, atrial fibrillation; AT, atrial tachycardia; EPS, electrophysiological study; ER, early repolarization; SCD, sudden cardiac death;SVT, supraventricular tachycardia.

(0.667 [0.600-0.733]), Delise et al (0.661 [0.596-0.727]), Letsas et al (0.657 [0.592-0.723]) and Honarbakhsh et al (0.597 [0.517-0.676]).

A novel risk score was developed based on the following steps. Firstly, the best performing score with the highest AUC was selected from the existing scores (the Sieira score), using the original weighting for the different variables. Additional risk factors that were significant on univariable Cox regression were selected (arrhythmias other than ventricular tachyarrhythmias, early repolarization pattern in the peripheral leads, aVR sign, S-wave in lead I, QTc $\geq$ 436 ms) (Table 3). This *modified Sieira score* has the highest AUC of 0.855 (95% CI: 0.808-0.902) (Table 4**,** *second column*).

However, because this requires invasive EPS for identifying inducible ventricular arrhythmias and SND, a simpler score was created by omitting EPS and SND (*novel risk score*). This score has a statistically comparable performance with an AUC of 0.784 (95% CI: 0.724-0.845). The Kaplan-Meier curves for incident VT/VF events stratified by quartiles of the novel risk score showed a progressive increase in VT/VF risk with higher scores (Fig 1). The 5-year and 10-year predicted risks are shown in Supplementary Table 3, whereas the incidence rate of patients in the various point categories for different risk scores is shown in Supplementary Table 4.

An intermediate risk subgroup was created by ranking the patients based on our score into quartiles, and identifying those who were in the second and third quartiles. All of the scores applied to this subgroup showed significantly lower AUCs (Table 4, *third column*; Fig 3). The

**Table 4.** Comparison of the performance of different scores or machine learning models

| Risk scores | AUC [95% CI] for whole cohort (n = 548) | AUC [95% CI] for intermediate risk group (n = 274) | AUC (95% CI) for subgroup without initial VT/VF (n = 505) | AUC (95% CI) for subgroup with EPS results only (n = 112) |
|---|---|---|---|---|
| Random survival forests | 0.942[0.913, 0.964] | 0.734[0.713, 0.762] | 0.816[0.783, 0.852] | 0.654[0.635, 0.672] |
| Ada boost classifier | 0.872[0.831, 0.923] | 0.743[0.703, 0.772] | 0.752 [0.733,0.793] | 0.662[0.643, 0.692] |
| Gaussian naïve Bayes | 0.832[0.803, 0.861] | 0.632[0.621, 0.673] | 0.662[0.642, 0.682] | 0.654[0.634. 0.681] |
| Light gradient boosting machine | 0.812[0.781, 0.831] | 0.753[0.732,0.793] | 0.743[0.731, 0.782] | 0.713[0.692, 0.726] |
| Random forest classifier | 0.783[0.764, 0.821] | 0.783[0.741, 0.824] | 0.753[0.732, 0.792] | 0.723[0.712, 0.741] |
| Gradient boosting classifier | 0.762[0.751, 0.802] | 0.814[0.791, 0.832] | 0.712[0.703, 0.754] | 0.653[0.625, 0.683] |
| Decision tree classifier | 0.683[0.651, 0.713] | 0.682[0.664, 0.722] | 0.612[0.591, 0.643] | 0.672[0.653, 0.685] |
| Novel risk score | 0.784 [0.724-0.845] | 0.653 [0.551-0.755] | 0.744 [0.661-0.828] | 0.564 [0.442-0.687] |
| Modified sieira score | 0.855 [0.808-0.902] | 0.760 [0.655-0.865] | 0.809 [0.744-0.875] | 0.673 [0.556-0.790] |
| Sieira score | 0.806 [0.747-0.865] | 0.743 [0.620-0.866] | 0.730 [0.650-0.811] | 0.664 [0.544-0.783] |
| Shanghai score | 0.704 [0.630-0.777] | 0.603 [0.478-0.729] | 0.688 [0.598-0.778] | 0.593 [0.473-0.712] |
| Honarbakhsh score | 0.597 [0.517-0.676] | 0.429 [0.279-0.579] | 0.652 [0.552-0.751] | 0.507 [0.374-0.639] |
| Okamura score | 0.667 [0.600-0.733] | 0.607 [0.462-0.751] | 0.711 [0.626-0.796] | 0.555 [0.443-0.667] |
| Letsas score | 0.657 [0.592-0.723] | 0.545 [0.398-0.692] | 0.674 [0.589-0.759] | 0.526 [0.411-0.642] |
| Delise score | 0.661 [0.596-0.727] | 0.598 [0.463-0.733] | 0.702 [0.619-0.784] | 0.516 [0.406-0.626] |

The area under the curve (AUC) of the best performing model was underlined for each cohort. Machine learning models are evaluated with 5-fold cross validation approach using minority sampling technique to deal with imbalance.

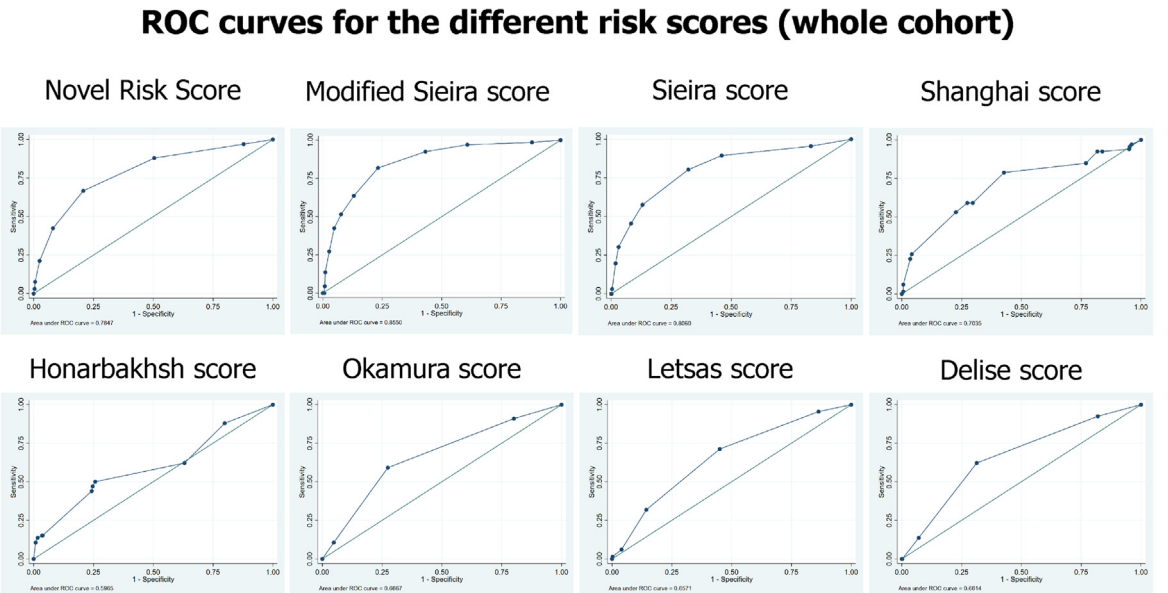


**FIG 1.** Kaplan-Meier curves of new risk score to predict VT/VF during follow-up in the whole cohort stratified by quartiles of the novel risk score. (Color version of figure is available online.)

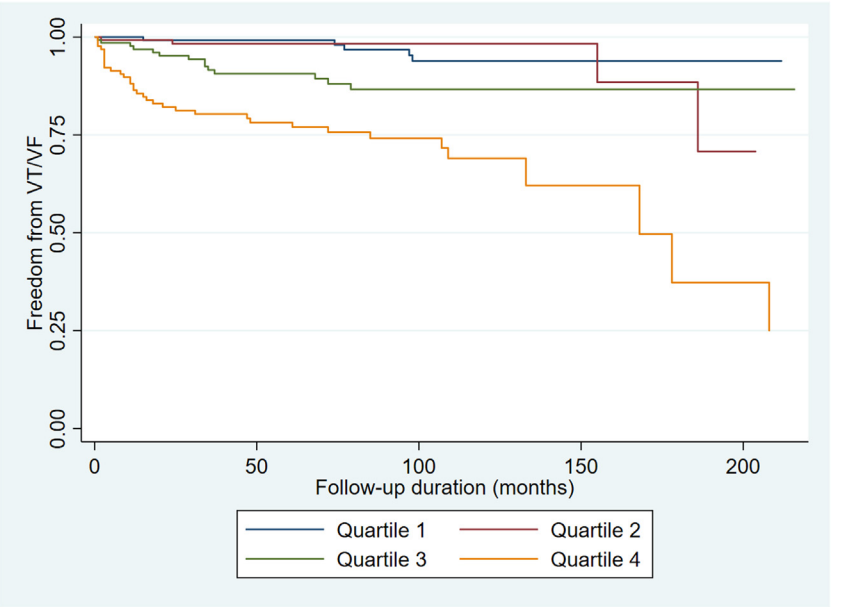


**FIG 2.** ROC curves of different scores for predicting incident VT/VF for the whole cohort (N = 548).

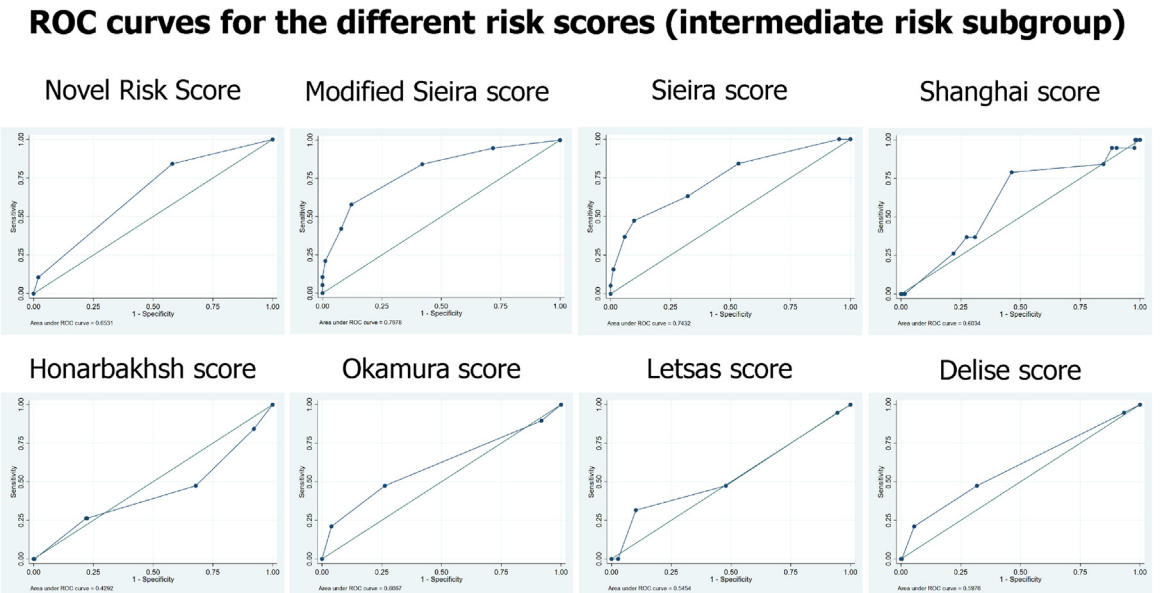


**FIG 3.** ROC curves of different scores for predicting incident VT/VF for the intermediate risk subgroup (N = 274). (Color version of figure is available online.)

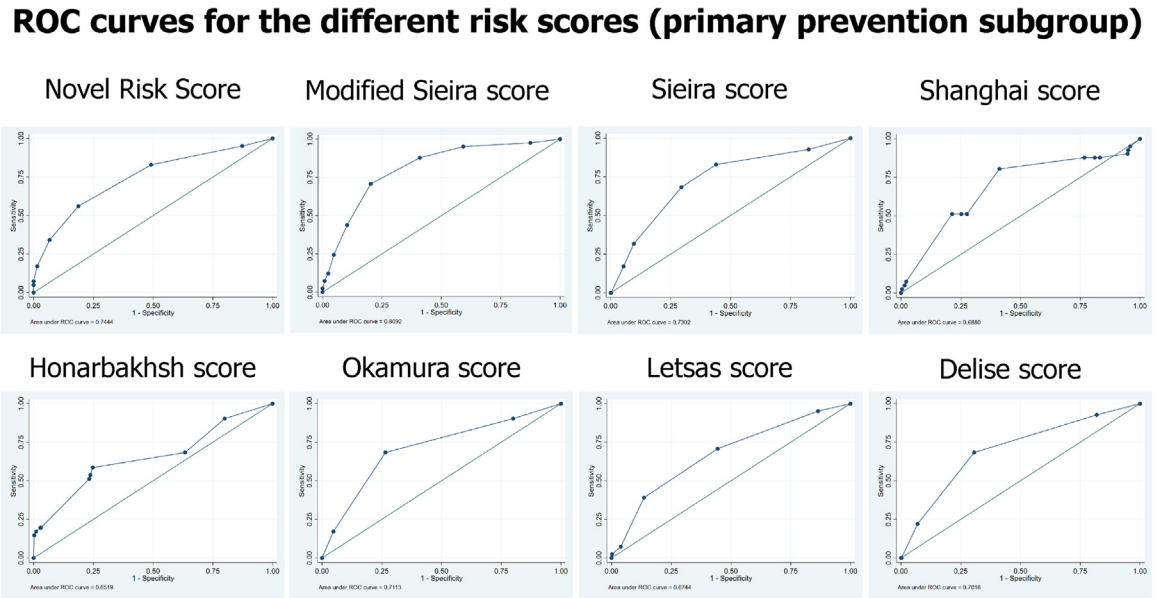


**FIG 4.** ROC curves of different scores for predicting incident VT/VF for patients without initial VT/VF (N = 505). (Color version of figure is available online.)

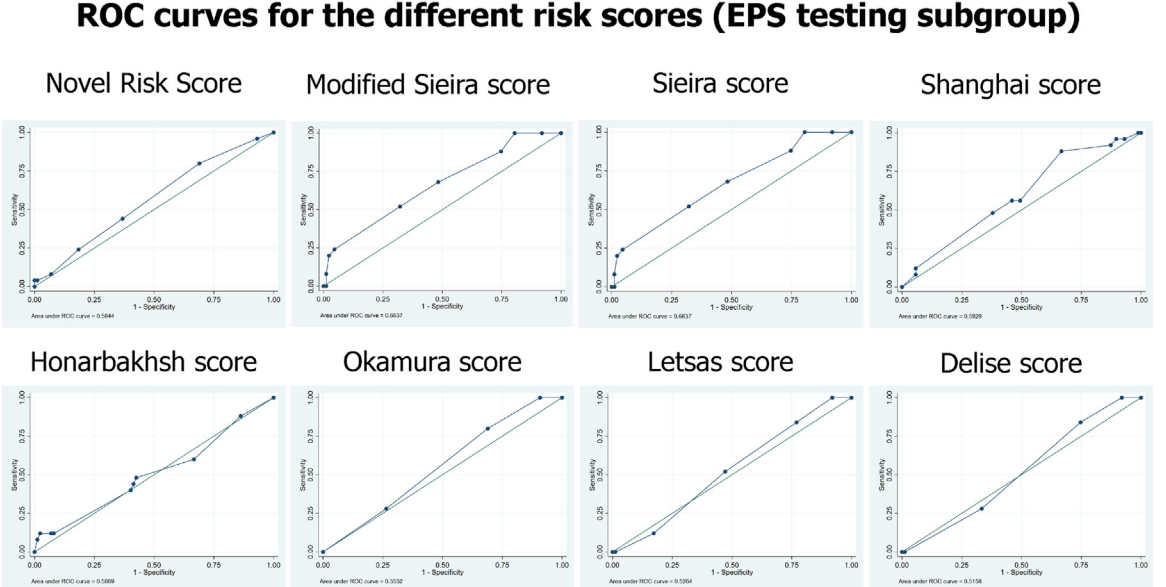


**FIG 5.** ROC curves of different scores for predicting incident VT/VF for patients who underwent EPS (N = 112). (Color version of figure is available online.)

newly developed score showed the best performance with an AUC of 0.704, followed by the scores by Sieira et al, Okamura et al, Delise et al, Shanghai score, Letsas et al and Honarbakhsh et al (Table 3, *third column*). The performance of the models for the primary prevention cohort (patients without initial VT/VF) and patients undergoing EPS testing was also assessed (Table 4, *fourth and fifth columns)*. The ROC curves are shown in Figures 4 and 5, respectively.

## *Development of Machine Learning Models*

A number of machine learning models were developed in this study. Firstly, Pearson correlation test was performed to ensure that no pairs of variables were highly correlated (Supplementary Figure 1). Their ability to predict sustained VT/VF on follow-up was determined using a 5-fold cross validation approach. The regression-based risk scores were used as a benchmark for comparative analyses. ROC curves of the different models when applied to the whole cohort are shown in Supplementary Figure 2. The micro-average ROC is the sum of true positive rate divided by the sum of false positive rate. Micro-average ROC works by calculating all of the true positive results for each class and using that as the numerator, and then calculating all of the true positive and false positive results for each class, and using that as the denominator. In this case, rather than each class having equal weight, each observation gets equal weight. A macro-average works by computing the metric independently for each class and then taking the average (hence treating all classes equally), whereas a micro-average will aggregate the contributions of all classes to compute the average metric. Micro-average is preferable if there is class imbalance (ie, many more instances of one class than of other class). Random survival forest outperformed the score-based models, with ada boost classifier and Gaussian Naïve Bayes showing a comparable performance. By contrast, light gradient boosting machine, random forest classifier, gradient boosting classifier and decision tree classifier showed worse performance than score-based models. The corresponding ROC curves for the intermediate risk subgroup, primary prevention subgroup and patients undergoing EPS testing Supplementary Figures 3, 4 and 5, respectively. The details for the top performing model, RSF model, including optimal tree number selection, variable importance ranking, out-of-bag survival curve, cumulative hazard curve, and time-dependent AUC curve for the whole cohort, intermediate risk subgroup, primary prevention subgroup and patients undergoing EPS testing are shown in Supplementary Figures 6, 7 and 8 and 9, respectively.

## Discussion

To the best of our knowledge, this is the first Asian territory-wide BrS cohort study that directly compared all of the published risk scores for arrhythmic risk stratification. The major findings of the present study include: (1) simple multiparametric scores based on the combination of clinical and baseline ECG parameters can be used for risk stratification in BrS; (2) interactions between predictors can influence the predictive performance of the score; (3) spontaneous type 1 BrP, family history of SCD, syncope and inducible EPS can be useful for the risk stratification of intermediate risk patients.

Over the past decade, there have been increasing efforts in developing simple-to-use predictive scores for risk stratification in BrS. However, many either include findings from investigations that are only indicated for certain patient groups such as EPS, or include clinical or crude ECG parameters.[12,24,25,33-35] As a result, the scores are either difficult to be universally applied amongst all BrS patients, or have insufficient predictive power. Also, it should be noted that the Shanghai score was initially developed for a diagnostic, instead of a prognostic purpose.[33] The evidence supporting its use in risk stratification was based on demonstrations of differences in the arrhythmic events between patients with $\leq$3, 3.5, 4-5, and $\geq$5.5 points.[36] By contrast, Probst et al found that whilst the Shanghai score had an AUC of 0.73 and was able to distinguish between extreme risk groups, it was unable to further stratify patients at intermediate risks.[14]

The improved predictive performance of the novel risk score demonstrates that the inclusion of comprehensive clinical and baseline ECG indices is needed for accurate risk stratification. For the prediction of intermediate risk patients, spontaneous type 1 BrP, family history of SCD, syncope and inducible arrhythmias detected during EPS are parameters common to the 3 predictive scores with the highest AUC. Since the manifestation of spontaneous type 1 BrP is a cornerstone of the diagnosis of BrS, the clinical presentation of the patient can range from asymptomatic to VT/VF.[37] Moreover, patients who exhibit spontaneous type 1 BrP are considered to be at a higher risk with greater degrees of ECG abnormalities.[38] Therefore, a comprehensive clinical assessment with ECG analysis is required for accurate risk stratification.[34,39,40] Similarly, the plethora of possible etiologies underlying syncope in BrS, ranging from benign causes to malignant arrhythmias, renders the need for multiparametric assessment in patients presenting with syncope.[41] By contrast, a family history of SCD as a marker for intermediate risk is likely due to the polygenic inheritance, variable expression and incomplete penetrance

in BrS.[42] Whilst the presence of pathogenic SCN5A mutation increases the risk of BrS manifestation, clinical and environmental factors are required to drive the degree of electrophysiological dysfunction across the disease threshold, which may explain the insignificant predictive value of a SCD family history in the present study.[43,44] Although genetic data were not examined in the present study, the predictive value of genetic and genomic findings should be explored in the future.[45]

The prognostic value of EPS remains controversial. The current evidence on the predictive power is mixed, varying between different patient subgroups.[24,46,47] A recent meta-analysis suggests that its risk stratification value is operator- and protocol-dependent, which may explain the preserved predictive performance of risk scores that included EPS inducibility as a predictor initially, such as the score by Okamura et al.[48] Although data on EPS inducibility is limited in the present study, the good predictive performance of the score suggests that clinical parameters, such as the spontaneous type 1 BrP and syncope, may be more reliable predictors. Therefore, EPS should be applied on an individual basis with particular considerations towards patient factors, using standardized protocols with predefined locations for the placement of stimulation electrodes and the pacing protocols. It may be useful for particular subgroups of patients, for example, prior studies have reported that in the case of syncope of unknown etiology, the presence of inducible EPS may reflect a higher SCD risk.[49,50]

## *Limitations*

Several limitations of the present study should be noted. Firstly, due to the limitations in the availability of certain variables needed for particular risk scores, these scores could not be fully applied to the present cohort. For example, nocturnal agonal respiration and family history of second-degree relatives were not recorded in case notes, and thus only a limited version of the Shanghai score was calculated. Contrary to the score by Sieira et al, where the family history of SCD is limited to less than 35 years old, there is no age restriction in the family history of SCD in the present cohort. $T_{peak}$-$T_{end}$ is another example of a parameter that is commonly used in some risk scores but has not been manually measured in this cohort. This will be explored in the near future. Secondly, the etiology of syncope was not documented, thus syncope of non-arrhythmic origin may be included. Thirdly, given the low rates of EPS and genetic test performance, the predictive value of findings from these 2 tests was not assessed. As a result, the predictive value of risk scores that accounts for EPS inducibility,

including the scores by Sieira et al, Delise et al, and Okamura et al were not fully assessed. In addition, it should be noted that only 7% of the present cohort is female. Although BrS is a male-predominant disease, the significant gender imbalance reduces the applicability of the present findings to female BrS patients. In addition, since the extraction of the study outcome is based on the International Classification of Disease, Nineth Edition (ICD-9) coding, we are unfortunately unable to differentiate between sustained VT/VF, aborted SCD and SCD episodes, which can reduce the clinical accuracy of the present findings. Finally, our score does not incorporate latent interactions between the risk variables, which have previously been shown to be important for risk stratification.[51,52] Future studies with the integration of machine learning techniques into the predictive scores may improve the accuracy of risk stratification through the recognition of latent interactions between predictors.

## Conclusion

In conclusion, simple risk scores consisting of clinical and baseline ECG indices are useful in the risk stratification of the overall BrS population. However, the inclusion of investigation results and more complex models are needed to improve the predictive performance of risk scores against the intermediate risk BrS population. The incorporation of machine learning and genomics may be a direction for future research to improve the stratification of SCD risk amongst BrS patients.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2022.101381.

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