Predicting arrhythmic event score in Brugada syndrome: Worldwide pooled analysis with internal and external validation

Pattara Rattanawong, MD,[*†] Natthinee Mattanapojanat, MD,[‡] Carolyn Mead-Harvey, MS,[§] Charles Van Der Walt,[§] Jakrin Kewcharoen, MD,[¶] Chanavuth Kanitsoraphan, MD,[||] Wasawat Vutthikraivit, MD,[**] Narut Prasitlumkum, MD,[††] Prapaipan Putthapiban, MD,[¶] Kumpol Chintanavilas, MD,[‡‡] Dujdao Sahasthas, MD,[‡] Tachapong Ngarmukos, MD,[†] Ammarin Thakkinstian, PhD,[§§] Dan Sorajja, MD, FHRS,[*] Pattarapong Makarawate, MD, FHRS,[‡] Win-Kuang Shen, MD, FHRS[*]

From the [*]Department of Cardiovascular Medicine, Mayo Clinic, Phoenix, Arizona, [†]Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [‡]Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand, [§]Department of Quantitative Health Sciences, Mayo Clinic, Scottsdale, Arizona, [¶]Loma Linda University, Loma Linda, California, [||]John H. Stroger, Jr. Hospital of Cook County, Chicago, Illinois, [**]Division of Cardiovascular Diseases, Department of Internal Medicine, University of Iowa, Iowa City, Iowa, [††]University of California Riverside, Riverside, California, [‡‡]Chulabhorn International College of Medicine, Thammasat University, Pathum Thani, Thailand, and [§§]Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

BACKGROUND Brugada syndrome is an inherited arrhythmic disease associated with major arrhythmic events (MAE). Risk predictive scores were previously developed with various performances.

OBJECTIVE The purpose of this study was to create a novel score—Predicting Arrhythmic evenT (PAT)—with internal and external validation.

METHODS A systematic review was performed to identify risk factors for MAE. The odds ratios (ORs) of each factor were pooled across studies. The PAT scoring scheme was developed based on pooled ORs. The PAT score was internally validated with published 105 Asian patients (follow-up 8.0 ± 4.1 [SD] years) and externally validated with unpublished 164 multiracial patients (82.3% White, 14.6% Asian, 3.2% Black; mean follow-up 8.0 ± 6.9 years) with Brugada syndrome. Performances were assessed and compared with previous scores using receiver operating characteristic curve (ROC) analysis.

RESULTS Sixty-seven studies published between 2002 and 2022 from 26 countries (7358 patients) were included. Pooled ORs were estimated, indicating that 15 of 23 risk factors were significant. The PAT score was then developed accordingly. The PAT score had significantly better discrimination (ROC 0.9671) than the BRUGADA-RISK score (ROC 0.7210; $P = .006$), Shanghai Score System (ROC 0.7079; $P = .003$), and Sieira et al score (ROC 0.8174; $P = .026$) in an external validation cohort. PAT score ≥ 10 predicted the first MAE with 95.5% sensitivity and 89.1% specificity (ROC 0.9460) and the recurrent MAE (ROC 0.7061) with 15.4% sensitivity and 93.3% specificity.

CONCLUSION The PAT score was shown to be useful in predicting MAE for primary prevention in patients with Brugada syndrome.

KEYWORDS Brugada syndrome; Arrhythmic events; Predictive score; Meta-analysis; Sudden cardiac death; Validation

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Introduction

Brugada syndrome (BrS), first described as a clinical syndrome in 1992, is an inherited arrhythmic disease associated with an increased risk of ventricular tachycardia (VT), ventricular fibrillation (VF), and sudden cardiac death (SCD). Patients typically present in the third or fourth decade of life. The condition is marked by an atypical right bundle branch block coved-type ST elevation in the right precordial leads.[1–3]

Address reprint requests and correspondence: Dr Win-Kuang Shen, Department of Cardiovascular Medicine, Mayo Clinic, Phoenix, AZ 85054. E-mail address: wshen@mayo.edu; or Dr Pattarapong Makarawate, Faculty of Medicine, Khon Kaen University, Khon Kaen, 40002, Thailand. E-mail address: pattarapong@kku.ac.th.

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Recent studies have suggested that the prevalence of asymptomatic patients with Brugada electrocardiogram (ECG) pattern varies among different populations and ranges between 0% and 0.4%, making it challenging to determine the exact disease burden.[1–3] Even though most patients (approximately 63%) are asymptomatic at the time of diagnosis, major arrhythmic events (MAE) can develop at a rate of 12% over 10 years.[4–6] The disease is most prevalent in Southeast Asia, where the prevalence has been reported as 3.7 per 1000 persons and up to 17.7 per 1000 persons in Thailand.[2,7]

Identifying prognostic factors of MAE in BrS patients is crucial in preventing undesirable outcomes such as MAE or SCD. Currently only a few well-established risk factors can predict MAE in BrS.[8] Identifying BrS patients who need an implantable cardioverter-defibrillator (ICD) for primary prevention is critical because SCD is the most concerning manifestation. Several risk predicting scores have been proposed, including the BRUGADA-RISK score,[9] Shanghai Score System,[10] and score of Sieira et al.[11] However, ventricular arrhythmia risk stratification remains challenging and controversial. Previous models have not been validated in multiple external cohorts among different races[9–11] and are not broadly implemented in clinical care. There is a need for an optimal scoring system that will work for both Asian and multiethnic populations.

In this study, we aimed to perform a systematic review and meta-analysis of risk factors associated with and may be predictive factors of an MAE in BrS. The magnitude of associations (measured by odds ratio [OR]) was pooled across studies. Then, our risk Predicting Arrhythmic evenT (PAT) scores were constructed based on significant risk factors suggested by meta-analysis results. The PAT scores were used as a clinical tool for predicting an MAE in patients who were candidates for ICD implantation in BrS.

Method

Systematic review of risk factors

This systematic review was conducted in compliance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline (Supplemental Table 1),[12] and its protocol was registered in the International Prospective Register of Systemic Reviews (PROSPERO) (CRD42020157877).

The professional librarian searched for published studies indexed in PubMed, EMBASE, Scopus, Web of Science, and Cochrane databases from inception to June 2020 (Supplemental Appendix: Search Terms). A manual search for additional pertinent studies and review articles using references from retrieved articles was also completed (PR). Observational studies were eligible for review if they included adult patients with BrS, assessed associations between risk factors and MAEs, and a reported magnitude of associations such as ORs, risk ratio, and 95% confidence intervals (CIs). Only risk factors published in at least 2 nonduplicated populations were included. The authors were contacted for extraction clarification. A standardized data extraction form was used to obtain the information from each study. The Newcastle-Ottawa quality assessment scale was used to assess each study's quality (Supplemental Table 2).[13]

The point estimates of OR and variance from each study were extracted (adjusted ORs were prioritized over the unadjusted ORs) and pooled using a random effects model.[14] Publication bias was assessed via funnel plot and Egger test.[15]

Score derivation and validation

The study was approved by the institutional review boards of Mayo Clinic (Rochester, Minnesota; Scottsdale, Arizona; and Jacksonville, Florida), Ramathibodi Hospital (Mahidol University, Bangkok, Thailand), and Khon Kaen University (Khon Kaen, Thailand). We retrospectively conducted 2 cohorts of the BrS registry from Mayo Clinic from 1998 to 2020, the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, and the Khon Kaen University database from 2002 to 2020. Characteristic and clinical data, including age, sex, ethnicity, comorbidities, syncope, ECG parameters, family history, pathogenic/likely pathogenic *SCN5A* variants, electrophysiological study, history of SCD, ICD implantation, and follow-up duration, were retrieved using a standardized collection platform (Research Electronic Data Capture system [REDCap]).

MAE was defined as sudden cardiac arrest (SCA), SCD, sustained VT, VF, or appropriate ICD therapy. Primary prevention was defined as ICD placement to prevent SCD in a patient without sustained VT, VF, or SCA but at an increased risk for these events. Secondary prevention was defined as ICD placement in a patient with previous SCA, VF, sustained VT, or syncope with positive extra stimuli.[16,17]

Only significant pooled ln(ORs) of risk factors were collected and used to generate a linear combination of PAT scores to predict MAE. The distribution of these substantial risk factors in the cohort data was explored and described by MAE groups using mean ± SD or median [interquartile range], where appropriate for continuous data and frequency for categorical data.

The PAT score was then calculated for individual patients based on their medical records and measurements from the first documented ECG showing Brugada pattern. The association between PAT scores and MAEs was assessed using logistic regression. Performance in calibration and discrimination was evaluated using *C*-statistic with Wald 95% confidence limits.[18] Model revision and/or update was performed where appropriate according to the suggestion of PAT scores' performance.

Performances were assessed and compared with previous scores using receiver operating characteristic curve (ROC) analysis.[19] The cutpoint was identified as the point that maximized the Youden index. PAT score was compared with BRUGADA-RISK (≥21),[9] Shanghai Score System (≥7),[10,20] and Sieira et al (≥5) scores.[11,20] Data analysis was performed using SAS Version 9.4 (SAS Institute,

Cary, NC) and STATA SE Version 14.2 (StataCorp LP, College Station, TX). $P < .05$ was considered significant.

Results

Search results

A total of 1608 potentially relevant articles were identified from the 5 databases (Supplemental Appendix, Diagram 1). After duplicated articles were excluded, 752 of the remaining 912 articles were excluded through title/abstract reviews, leaving 160 articles for full-length reviews. Finally, 67 studies met the criteria and were included in this meta-analysis. The reasons for exclusion for all review steps are detailed in Supplemental Appendix, Diagram 1.

Description of included studies

Sixty-seven studies (58 cohorts, 9 case controls) published between 2000 to 2022 from 26 countries (232 centers) involving 7358 nonduplicated patients with BrS were included. Mean age was 43.4 ± 14.3 years; most patients were predominately men (76.9%) and asymptomatic (63.0%). Mean follow-up was 50.9 ± 38 months. In each predicting factor pooled analysis, included studies were selected to yield a maximum total number of sample sizes without population duplications across the studies. Characteristics of included studies are given in Supplemental Table 3.

Pooled analysis results: Predicting factors of MAE

Fifteen of 23 predicting factors were identified as significantly associated with MAE in BrS (Figure 1). Individual forest plots, funnel plots, and Egger tests for each factor are shown in Supplemental Figures 1–23. The pooled ORs (95% CI) of a history of MAE (SCD, SCA, sustained VT, or VF) and MAE during drug challenge testing were 8.73 (95% CI 5.15–14.82; $P < .001$) and 3.73 (95% CI 1.77–7.86; $P = .001$), respectively (Supplemental Figures 1 and 2).

Seven ECG factors were significantly associated with MAE: T-peak to T-end duration ≥100 ms (pooled OR 4.99; 95% CI 1.99–12.54; $P = .001$); prolonged PR duration ≥200 ms (pooled OR 3.77; 95% CI 2.17–6.57; $P < .001$); fragmented QRS (pooled OR 2.73; 95% CI 1.81–4.11; $P < .001$); type 1 ECG in peripheral leads (pooled OR 2.71; 95% CI 1.78–4.12; $P = .003$); early repolarization in inferolateral leads (pooled OR 2.65; 95% CI 1.67–4.21; $P < .001$); aVR sign (pooled OR 2.71; 95% CI 1.46–5.04; $P = .003$); and spontaneous type 1 ECG (pooled OR 1.71; 95% CI 1.19–2.44; $P < .001$) (Supplemental Figures 3–9).

Four risk factors of history are also significantly associated with MAEs: arrhythmic syncope (pooled OR 5.52; 95% CI 4.04–7.55; $P < .001$); unexplained syncope (pooled OR 5.74; 95% CI 2.00–16.42; $P < .001$); SCD in the family at age <40 years (pooled OR 2.03; 95% CI 1.11–3.73; $P = .022$); and atrial fibrillation (pooled OR 1.74; 95% CI 1.23–2.45]; $P = .002$). Finally, 2 risk factors of the laboratory are also significantly associated with MAE: positive electrophysiological study (pooled OR 1.74; 95% CI 1.21–2.51; $P = .003$); and positive pathogenic/likely pathogenic *SCN5A* variants (pooled OR 1.39; 95% CI 1.07–1.81; $P = .013$) (Supplemental Figures 10–16)

Vasovagal syncope (pooled OR 2.90; 95% CI 0.09–98.45; $P = .554$), sinus nodal dysfunction (pooled OR 2.50; 95% CI 0.77–8.14; $P = .127$), S wave in lead I (pooled OR 2.0; 95% CI 0.91–4.41; $P = .086$), ST-segment augmentation with exercise (pooled OR 1.37; 95% CI 0.54–3.52; $P = .509$), QRS >120 ms (pooled OR 1.27; 95% CI 0.90–1.80; $P = .178$), male (pooled OR 1.19; 95% CI 0.94–1.51;

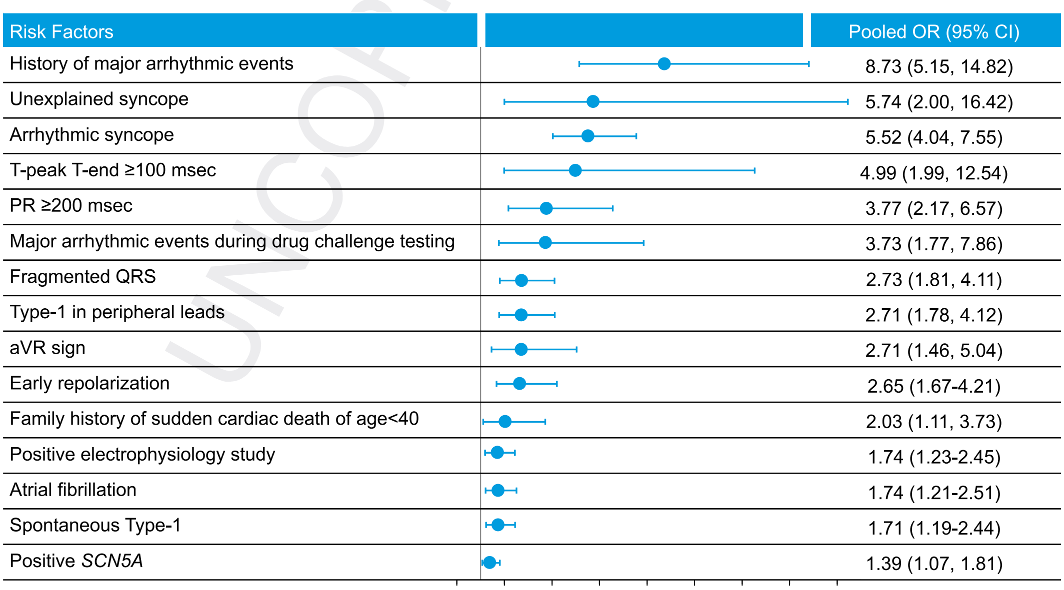

Figure 1 Fifteen predicting factors were identified as significantly associated with major arrhythmic events in Brugada syndrome and their pooled odds ratio (OR) with 95% confidence interval (CI).

P = .149), late potential (pooled OR 1.17; 95% CI 0.62–2.21; P = .632), and ventricular effective refractory period <200 ms (pooled OR 0.86; 95% CI 0.42–1.77; P = .688) did not significantly predict MAE in the pooled analysis.

Development of the PAT score

Derivation

Fifteen significant pooled ORs of predicting factor were pooled in the natural-log scale [ln(OR)], multiplied by 3, and rounded to the absolute number; thereafter, the absolute number was used to generate a linear combination of PAT scores for prediction of the MAE by a summation of each factor weighted (Table 1). Of note, we aimed to derive a score that predicts the first MAE. Therefore, the history of MAE was not included in the score derivation.

Characteristics of the internal and external validation cohort

A previously published cohort of patients with BrS from Khon Kaen University included in the score derivation from the worldwide pooled analysis was used as an internal validation cohort (follow-up 8.0 ± 4.1 years). Unpublished cohorts of patients with BrS from Ramathibodi Hospital (follow-up 7.9 ± 7.1 years) and Mayo Clinic (follow-up 9.4 ± 4.5 years) were used as external validation cohorts (82.3% White, 14.6% Asian, 3.2% Black; mean age 46.5

Table 1 Pooled ORs and 95% CI of 15 significant and 8 nonsignificant predicting factors, natural-log scale, and linear combination of PAT scores

Predicting factors	Studies (N)	Total population (n)	Positive (%)	Pooled OR	95% CI	P value	I^2	ln(OR)	PAT score
Major arrhythmic events									
History of SCD/SCA/VT/VF	17	3619	10.8	8.73	5.15–14.82	<.001	52.6	2.17	7*
MAE during drug challenge testing	3	776	4.6	3.73	1.77–7.86	.001	0	1.32	4
Baseline ECG									
T-peak to T-end ≥ 100 ms	6	1045	41.3	4.99	1.99–12.54	.001	57.2	1.53	5
Prolonged PR ≥ 200 ms	3	695	28.3	3.77	2.17–6.57	<.001	0.0	1.33	4
Fragmented QRS	16	3304	17.6	2.73	1.81–4.11	<.001	31.0	1.00	3
Type 1 in peripheral leads	3	1462	7.4	2.71	1.78–4.12	<.001	0.0	1.00	3
aVR sign	6	1548	16.4	2.71	1.46–5.04	.003	36.4	1.00	3
Early repolarization in inferolateral leads	10	3593	11.0	2.65	1.67–4.21	<.001	31.8	0.97	3
Spontaneous type 1	19	5112	43.8	1.71	1.19–2.44	<.001	64.3	0.54	2†
History									
Arrhythmic syncope	7	3183	24.9	5.52	4.04–7.55	<.001	0.0	1.71	5
Unexplained syncope	6	381	33.0	5.74	2.00–16.42	.001	24.0	1.75	5
Family history of SCD at age <40 y	3	805	16.6	2.03	1.11–3.73	.022	0.0	0.71	2†
Atrial fibrillation	9	3767	9.0	1.74	1.23–2.45	.002	18.9	0.55	2†
Laboratory tests									
Positive electrophysiological study	12	3018	33.4	1.74	1.21–2.51	.003	29.1	0.55	2†
Positive *SCN5A*	12	2280	19.6	1.39	1.07–1.81	.013	42.1	0.33	1†
Nonsignificant factors									
Vasovagal syncope	2	352	23.6	2.90	0.09–98.45	.554	70.9	N/A	N/A
Sinus nodal dysfunction	3	1621	0.9	2.50	0.77–8.14	.127	46.5	N/A	N/A
S wave in lead I	6	2107	34.7	2.00	0.91–4.41	.086	68.6	N/A	N/A
ST-segment augmentation with exercise	3	475	34.8	1.37	0.54–3.52	.509	64.8	N/A	N/A
QRS ≥ 120 ms	4	2161	11.9	1.27	0.90–1.80	.178	0.0	N/A	N/A
Male	22	5079	77.5	1.19	0.94–1.51	.149	10.5	N/A	N/A
Late potential	5	743	58.9	1.17	0.62–2.21	.632	21.3	N/A	N/A
VERP <200 ms	3	462	20.1	0.86	0.42–1.77	.688	0.0	N/A	N/A

ECG = electrocardiogram; N/A = not applicable; OR = odds ratio; PAT = Predicting Arrhythmic evenT; SCA = sudden cardiac arrest; SCD = sudden cardiac death; VERP = ventricular effective refractory period; VF = ventricular fibrillation; VT = ventricular tachycardia.

*Minor factors excluded after receiver operating characteristic curve analysis.

†We aimed to derive a score that predicts the first major arrhythmic event (MAE); therefore, the history of MAE was not included in score derivation.

± 14.3 years; mean follow-up 8.0 ± 6.9 years). The characteristics of the cohorts between centers are given in Supplemental Table 4. Mean age was higher in the Khon Kaen University cohort. Spontaneous type 1 Brugada pattern in the Khon Kaen University cohort was more common than in the Mayo Clinic cohort but less common than in the Ramathibodi Hospital cohort. Family history of SCD, sinus nodal dysfunction, and atrial fibrillation were not significantly different. None of the patients with BrS from Khon Kaen University had a positive electrophysiological study or *SCN5A* testing. Patients from Ramathibodi Hospital and Khon Kaen University were more symptomatic (cardiac or unclear etiology syncope), were 100% Asian, and more frequently underwent ICD implantation (Supplemental Table 4).

High-impact and low-impact scores in the internal validation cohort

Scores ranging from 1 to 2 were considered low-impact scores (SCD in the family at age <40 years, positive electrophysiological study, spontaneous type 1 ECG, atrial fibrillation, positive pathogenic/likely pathogenic *SCN5A* variants), and scores from 3–5 were considered high-impact scores (type 1 ECG in peripheral leads, T-peak to T-end duration ≥100 ms, aVR sign, arhythmic syncope, unexplained syncope, prolonged PR duration ≥200 ms, MAE during drug challenge testing, fragmented QRS, and early repolarization in inferolateral leads) (Table 1).

The area under the curve (AUC) for the overall score (14 factors) was 0.7157 (95% CI 0.6208–0.8106) and for only high-impact scores (9 factors) was 0.7265 (95% CI 0.6374–0.8156). The difference in AUC was not statistically significant ($P = .60$) (Figure 2A). Because the scores have similar performance and practical clinical score systems, we conducted the remainder of the analysis only with the high-impact PAT score.

Model performance and score cutpoint in the internal validation cohort

A cutpoint was chosen to maximize the Youden index, calculated as sensitivity + specificity – 1. The cutpoint ≥10 was found to maximize the Youden index in the subgroup of patients with BrS with the first MAE (primary prevention) of the internal validation cohort. Bifurcating risk as score ≥10 (high risk) vs <10 (low risk) well predicted MAE in the internal validation cohort, with sensitivity 26.7% (95% CI 15.5%–37.9%) and specificity 93.3% (95% CI 86.1%–100.0%). In the internal validation cohort from Khon Kaen University (n = 105), median PAT scores in MAE and non-MAE groups were 6.0 [5–0-10.0] and 5.0 [3.0–5.0], respectively (Supplemental Table 5).

Model performance in the external validation cohort

For the external validation cohort from the Mayo Clinic cohort (n = 150), median PAT scores in the MAE and non-MAE groups were 15.0 [IQR 12.0–17.0] and 3.0 [0.0–6.0], respectively. In the Ramathibodi Hospital cohort (n = 14), median PAT scores in the MAE and non-MAE groups were 11.0 [11.0–11.0] and 5 [5.0–7.0], respectively (Supplemental Table 5). The estimated *C*-statistic in the external validation cohort was 0.9671 (95% CI 0.9409–0.9934), indicating the model discriminated BrS with MAE from BrS without MAE during follow-up. PAT score ≥10 predicts MAE in an external validation cohort with sensitivity 92.9% (95% CI 66.1%–99.8%) and specificity 88.7% (95% CI 82.5%–93.3%).

Subgroup analysis of first MAE and recurrent MAE

In the subgroup analysis of PAT score predicting the first MAE (n = 187) in patients with BrS, median PAT scores in the MAE and non-MAE groups were 12.5 [10.0–17.0] and 4 [3–6], respectively. The estimated *C*-statistic in the subgroup without previous MAE was 0.9460 (95% CI 0.9054–0.9866) (Figure 2C). PAT score ≥10 predicts the first MAE in the overall cohort with sensitivity 95.5% (95% CI 77.2%–99.9%) and specificity 89.1% (95% CI 83.3%–93.4%) (Table 2).

In the subgroup analysis of PAT score predicting recurrent MAE in patients with BrS who previously had documented MAE (n = 82), median PAT scores in the MAE and non-MAE groups were 5.0 [0.0–6.0] and 5.0 [5.0–8.0], respectively. The estimated *C*-statistic in the recurrent MAE subgroup was 0.7061 (95% CI 0.5859–0.8263) (Figure 2D). PAT score ≥10 predicted recurrent MAE in the overall cohort with sensitivity 15.4% (95% CI 6.9%–28.1%) and specificity 93.3% (95% CI 77.9%–99.2%) (Table 2).

Comparison of PAT score and previous scores

In the external validation cohort (n = 164), PAT score showed significantly higher discrimination relative to other previous scores, including BRUGADA-RISK, Shanghai Score System, and Sieira et al scores, with the *C*-statistic for our score (95% CI: χ^2) and these 3 corresponding scores (95% CI: χ^2 : *P* value) of 0.9671 (0.9409–0.9934), 0.7210 (0.5446–08974: $P = .006$), 0.7079 (0.5328–0.8829: $P = .003$), and 0.8174 (0.6876–0.9472: $P = .026$). respectively (Figure 3A).

In the external validation cohort without a history of MAE (n = 153), PAT score showed higher discrimination relative to other previous scores, including BRUGADA-RISK, Shanghai Score System, and Sieira et al scores, with the *C*-statistic for our score (95% CI: χ^2) and these 3 corresponding scores (95% CI: χ^2 : *P* value) of 0.9776 (0.9564–0.9987), 0.7913 (0.6084–0.9742: $P = .052$), 0.7958 (0.6177–0.9739: $P = .050$), and 0.8198 (0.6577–0.9818: $P = .056$), respectively (Figure 3B).

PAT score ≥10 well predicted the first MAE in patients with BrS who never had a documented MAE (n = 187) with sensitivity 95.5% and specificity 89.1%, whereas BRUGADA-RISK (≥21), Shanghai Score System (≥7),

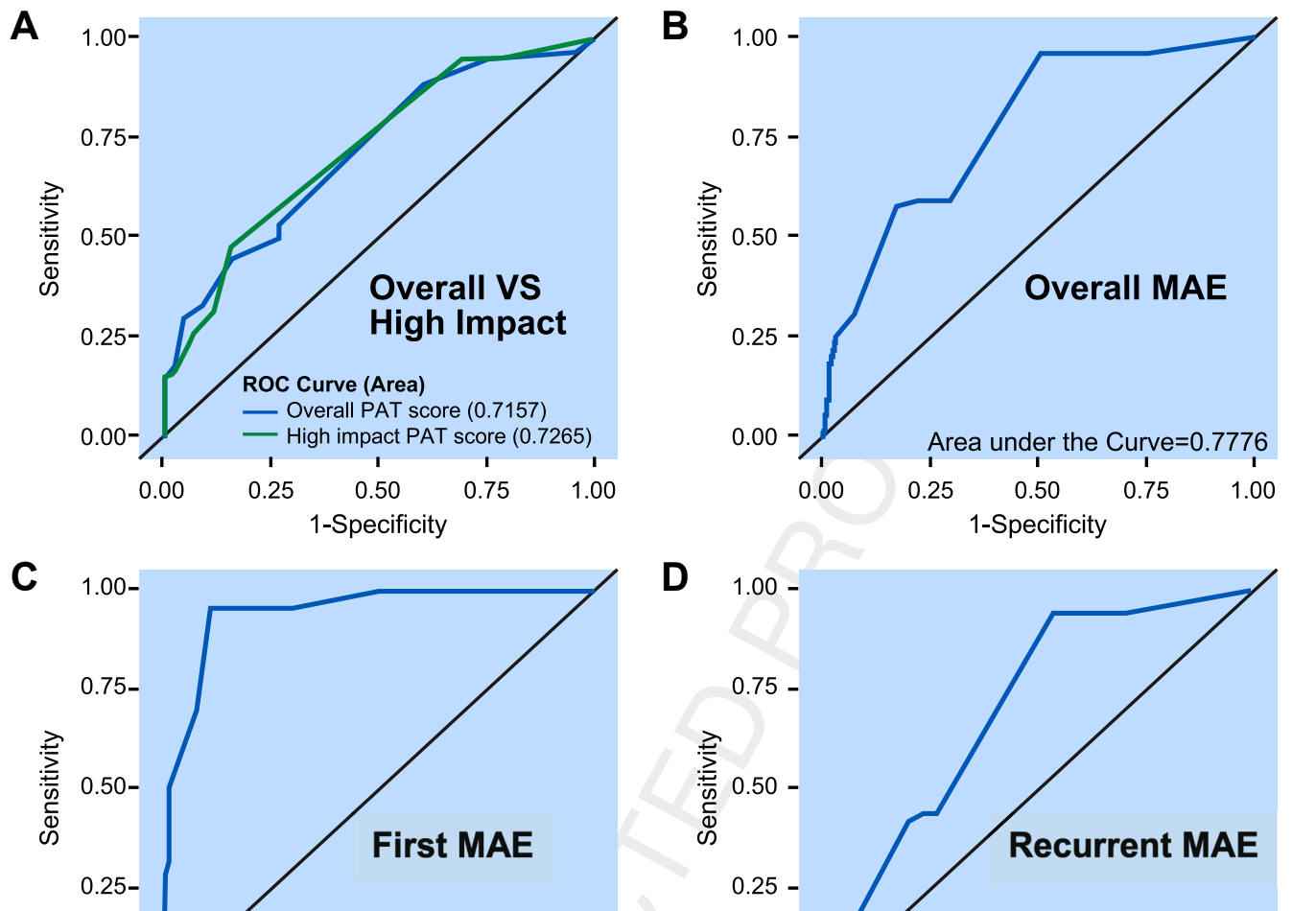

Figure 2 **A:** Area under the curve (AUC) for the overall Predicting Arrhythmic evenT (PAT) score was 0.7157 (95% confidence interval [CI] 0.6208–0.8106), and the only high-impact PAT score was 0.7265 (95% CI 0.6374–0.8156). The difference in AUC was not statistically significant ($P = .60$). **B:** Receiver operating characteristic curve (ROC) of PAT score for overall Brugada syndrome. **C:** ROC of PAT score performance among patients without a history of major arrhythmic events (MAE) (primary prevention). **D:** ROC of PAT score performance among patient with a history of MAE. Q12

Shanghai Score System (≥5.5), and Sieira et al (≥ 5) scores were 81.8% and 72.1%, 9.1% and 100.0%, 81.1% and 67.2%, and 22.7% and 98.8%, respectively (Table 2). The incidences of the first MAE for PAT scores 0–4, 5–9, 10–14, and ≥ 15 were 0.00, 0.18, 5.42, and 6.59 per 100 person-years, respectively (Supplemental Table 6).

In the subgroup analysis of PAT score predicting recurrent MAE in patients with BrS who had documented MAE (n = 82), PAT score ≥10 predicted MAE with sensitivity 15.4% and specificity 93.3%, whereas BRUGADA-RISK (≥21), Shanghai Score System (≥7), Shanghai Score System (≥5.5), and Sieira et al (≥5) scores were 7.7% and 86.7%, 5.8% and 80.0%, 86.4% and 74.6%, and 80.8% and 23.3%, respectively (Table 2). The incidences of at least 1 recurrent MAE for PAT scores 0–4, 5–9, 10–14, and ≥15 were 2.20, 8.56, 11.98, and 5.97 per 100 person-years, respectively (Supplemental Table 6).

In the combined patients with BrS from 3 centers (n = 264), PAT score ≥10 predicted MAE with sensitivity 39.2% and specificity 89.7%, whereas BRUGADA-RISK (≥21), Shanghai Score System (≥7), Shanghai Score System (≥5.5), and Sieira et al (≥5) scores were 29.7% and 74.4%, 6.8% and 96.9%, 78.9% and 26.7%, and 63.5% and 87.2%, respectively (Table 2). The incidences of combined first and at least 1 recurrent MAE for PAT scores 0–4, 5–9, 10–14, and ≥ 15 were 0.44, 4.09, 6.55, and 6.46 per 100 person-years, respectively (Supplemental Table 6).

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Table 2 Sensitivity and specificity (with Clopper-Pearson exact confidence limits) between risk score systems using The overall (first and recurrent MAE), first MAE, and recurrent MAE Brugada syndrome cohort

	First MAE (N = 187)		Recurrent MAE (N = 82)		Overall (N = 246)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
PAT score (≥10)	0.9545 (0.7716–0.9988)	0.8909 (0.8331–0.9341)	0.1538 (0.0688–0.2808)	0.9333 (0.7793–0.9918)	0.3919 (0.2804–0.5123)	0.8974 (0.8460–0.9362)
BRUGADA-RISK score (≥21)	0.8182 (0.5972–0.9481)	0.7212 (0.6462–0.7881)	0.0769 (0.0214–0.1854)	0.8667 (0.6928–0.9624)	0.2973 (0.1966–0.4148)	0.7436 (0.6763–0.8033)
Shanghai Score System (≥7.0)	0.0909 (0.0112–0.2916)	1.0000 (0.9779–1.0000)	0.0577 (0.0121–0.1595	0.8 (0.6143–0.9229)	0.0676 (0.0223–0.1507)	0.9692 (0.9342–0.9886)
Shanghai Score System (≥ 5.5)	0.8108 (0.7030–0.8925)	0.6718 (0.6011–0.7372)	0.8636 (0.6509–0.9709)	0.7455 (0.6719–0.81)	0.7885 (0.653–0.8894)	0.2667 (0.1228–0.4589)
Sieira et al. score (≥ 5)	0.2273 (0.0782–0.4537)	0.9879 (0.9569–0.9985)	0.8077 (0.6747–0.9037)	0.2333 (0.0993–0.4228)	0.6351 (0.5151–0.7440)	0.8718 (0.8166–0.9153)

CI = confidence interval; MAE = major arrhythmic event; PAT = Predicting Arrhythmic eventT.

Comparison of PAT scores between Asian and White patients

PAT scores ≥10 well predicted the first MAE in patients with BrS who never had a documented MAE with sensitivity 100.0% and specificity 89.3% in White patients (ROC 0.9835; 95% CI 0.9637–1.000), and sensitivity 91.7% and specificity 88.4% in Asian patients (ROC 0.9070; 95% CI 0.8126–1.000) (Supplemental Table 7).

In the overall first and recurrent MAE, PAT score ≥10 predicted MAE with sensitivity 92.3% and specificity 89.7% in White patients (ROC 0.9776; 95% CI 0.954–1.000), and sensitivity 27.9% and specificity 91.1% in Asian patients (ROC 0.7131; 95% CI 0.6295–0.7967) (Supplemental Table 7).

PAT score ≥10 well predicted the recurrent MAE in patients with BrS who had a documented MAE with sensitivity 66.7% and specificity 100.0% in White patients (ROC 1.0000; 95% CI 1.0000–1.0000), and sensitivity 12.2% and specificity 95.8% in Asian patients (ROC 0.7436; 95% CI 0.6221–0.8651) (Supplemental Table 7).

Discussion

In this study, we developed the PAT score to determine who benefits from ICD therapy to prevent fatal arrhythmia events by compiling all available studies assessing MAE. To the best of our knowledge, this is the most extensive pool of data identifying 15 significant risk factors, categorized into 4 main groups: arrhythmic events, baseline ECG, clinical history, and laboratory test. The PAT score showed 95.5% sensitivity and 89.1% specificity in predicting the first MAE for primary prevention in the overall cohort of patients with BrS. Importantly, our ROC suggested discrimination of the PAT score outperforms that of BRUGADA-RISK, Shanghai Score System, and Sieira et al scores.[10,11]

Internal and external validation cohorts

Our study used true internal and external validation cohorts. Previously published Khon Kean University cohorts of patients with BrS included in the score derivation from the worldwide pooled analysis were used as an internal validation cohort. An unpublished cohort of patients with BrS from Ramathibodi Hospital and Mayo Clinic was used as external validation cohorts. Compared to the BRUGADA-RISK score, which was validated with out-of-sample cross-validation[9] without true external validation. Moreover, the PAT score was derived from 67 studies from 232 centers in 26 countries, with a total of 7358 nonduplicated patients with BrS, which is 5-fold larger than the BRUGADA-RISK score system. Moreover, BRUGADA-RISK was only internally validated in 172 patients without previous MAE compared to the PAT score, which was internally and externally validated in 187 patients without previous MAE.

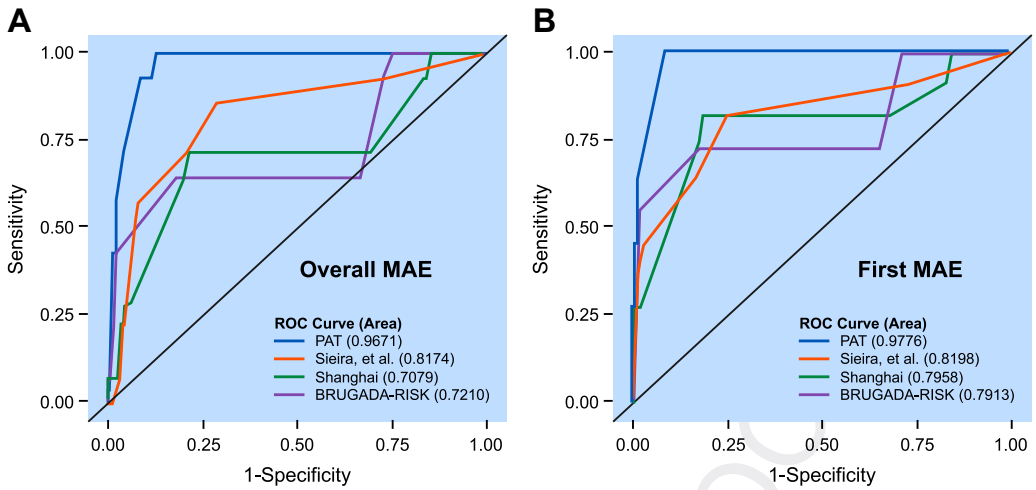

Figure 3 ROC curve representing a comparison of PAT score, BRUGADA-RISK score, Sieira et al score, and Shanghai Score System in the external validation cohorts. **A:** Overall MAE. **B:** First MAE. Abbreviations as in Figure 2.

Pathogenic SCN5A variant, family history of SCD, and atrial fibrillation

Rattanawong et al[21] previously demonstrated a correlation between pathogenic *SCN5A* variants and MAE, finding a 2-fold increase in risk. In the same study, the correlation seemed most pronounced in the Asian population.[21–23] With regard to pathophysiology, several studies supported that pathogenic *SCN5A* variants cause cardiac tissue fibrosis and conduction alteration, regressing into an arrhythmic substrate.[24,25] Many studies consistently investigated atrial fibrillation, which showed inconsistent MAE associations.[26–28] A study by Kewcharoen et al[29] demonstrated increased MAE risk in BrS up to 2.4-fold, similar to our pooled OR. The relationship between family history of SCD and its prognostication in BrS seems equivocal. Previous studies suggested that family history was not a strong risk factor.[30–32] However, those studies did not explicitly focus on younger probands of the family. A meta-analysis by Rattanawong et al[33] found that a family history of SCD, especially in members younger than 40 years, was associated with an increased risk of MAE up to 2-fold.

However, pathogenic/likely pathogenic *SCN5A* variants, atrial fibrillation, and family history of SCD provided a pooled OR of 1.39, 1.74, and 2.03, respectively, in our study, considered low-impact factors. ROC analysis between the overall PAT score and only high-impact PAT score showed discrimination was not significantly different; therefore, these factors were not included.

ECG markers and their prognostication

Several ECG markers have been proposed as possible MAE risk factors in patients with BrS. A previous study suggested an interesting risk score tool using 4 ECG markers—spontaneous type 1, T-peak to T-end duration ≥100 ms, aVR sign, and fragmented QRS—showing very high performance predicting MAE, ranging from 90%–100%.[34] Nevertheless, this study only used specific patterns in the ECG, which were uncommon. As a result, sensitivity was widely variable from 39.8%–99.9%. In our study, in addition to the ECG markers mentioned, we added prolonged PR ≥ 200 ms together with clinical history and laboratory testing, enhancing the sensitivity and specificity to predict high-risk patients.

Comparison to other known risk scores

BRUGADA-RISK was not validated in a true external cohort. The Shanghai Score System was validated in Asian[10] and White[20] patient external cohorts. The Sieira et al score system was only validated in a White patient external cohort.[20] The PAT score is the first score system that was validated in a multiracial (Asian, White, Black, and Others) external unpublished cohort. Moreover, our score system was derived from the largest number of nonduplicated patients with BrS (N = 7358).

Medians of PAT scores were consistently significantly higher in patients without MAE during follow-up in all 3 centers. With our external validation cohort, the PAT score provided better performance in MAE risk prognostication than the Shanghai Score System,[10] Sieira et al score,[11] and BRUGADA-RISK score,[9] with substantially higher ROC AUC. In the combined internal and external validation cohort, AUC was 0.7776 overall (Figure 2B), 0.9460 in predicting the first MAE (Figure 2C), and 0.7061 in predicting recurrent MAE (Figure 2D). The good discriminatory performance (sensitivity 95.5%, specificity 89.1%) at ≥10 as a cutoff for predicting the first MAE (primary prevention) is likely due to our extensive use of ECG markers. This is unique compared to other risk stratification tools. In addition to standard ECG profiles, aVR sign, PR prolongation, fragmented QRS, and T-peak to T-end duration were included in the PAT score, enhancing higher test performance in our study. The PAT score yielded higher sensitivity (95.5% vs 81.1%) and specificity (89.1% vs 67.2%) compared to the Shanghai Score System at cutpoint ≥5.5. Although the PAT score

yielded slightly lower specificity (89.1%) for primary prevention compared to the Shanghai Score System at cutpoint ≥7.0 (100.0%) and Sieira et al score (98.8%), sensitivity was much better (95.5% vs 9.1% and 22.7%, respectively) (Table 2). In the previous study cohort, the BRUGADA-RISK score predicted MAE with sensitivity 71.% and specificity 80.2%.[9] In our overall internal and external validation cohort, the PAT score yielded higher sensitivity (39.2% vs 29.7%) and specificity (89.7% vs 74.4%). More specific markers were used in those scores, such as definite family history of BrS and agonal respiratory breathing. Incorporating these factors may result in the highest predictability because these elements are part of the ICD implantation criteria.[17,35] There were insufficient reported data to pool the OR of definite family history of BrS and agonal respiratory breathing; therefore, it was not included in our score derivation. Nevertheless, in asymptomatic patients, these tools may not be sensitive enough to screen for eligible candidates with substantial high risks of MAE.

Implementation of the PAT score

We performed a pooled analysis of previously published studies in the broader context. The recent 2022 European Society of Cardiology guideline only recommended ICD implantation based on individual 3 risk factors: previous MAE (class I), arrhythmic syncope (class IIa), and positive electrophysiological study (class IIb).[35]

Our pooled analysis provided new information to the current practice guideline. Unexplained syncope has a similar high-yield risk (pooled OR 5.74) compared to arrhythmic syncope (pooled OR 5.52), whereas positive electrophysiological study is a low-yield risk factor (pooled OR 1.74). T-peak to T-end duration ≥100 ms shares a similar high-yield risk of MAE (pooled OR 4.99) compared to arrhythmic syncope. PAT score also well predicted the first MAE in patients with BrS both in White (ROC 0.9835) and Asian (ROC 0.9070) patients. Our comprehensive, evidence-based score system includes all reported risk factors that represent real-world data from the largest pooled analysis. We lay out each risk factor based on their pooled OR, validated with a multiracial and true external cohort; therefore, it should be considered for implementation in the clinical practice.

Study limitations

First, conventional and unconventional risk factors included in our analysis to determine the risk (eg, atrial fibrillation, family history, and electrophysiological study, and their association with MAE) are still unclear. Therefore, using this risk score should be carefully interpreted. Nevertheless, our investigation performed a validity test on this risk score, suggesting excellent risk prediction. Second, despite its comprehensiveness entailing all clinical and laboratory aspects, its use may be limited, especially in the setting of no dedicated electrophysiological study for BrS. Third, the patient characteristics in internal and external validation differed between cohorts as well as the included studies for the score derivation, and the overall risk model performance may not be generalizable. Fourth, despite providing a higher evidence level for decision-making, meta-analyses are limited by the heterogeneity of the included studies. Fifth, pooled OR of some risk factors, with only a few studies available, may have biases. Furthermore, complexities of ECG markers in this study (eg, fragmented QRS, T-peak to T-end duration) ,may limit its use in general practices. Nevertheless, at least equal or better scores of performances are anticipated.

Conclusion

We report the most extensive worldwide pooled analysis of BrS studies identifying 15 significant risk factors predicting MAE in BrS, and we developed the PAT score accordingly. The PAT score outperforms the previous scoring system in BrS, and it should be useful in predicting the first MAE for the primary prevention of patients with BrS. More validation studies are needed to evaluate its performance among predictive scores.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at 10.1016/j.hrthm.2023.06.013.

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