

Review

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Artificial intelligence streamlines diagnosis and assessment of prognosis in Brugada syndrome: a systematic review and meta-analysis

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Abstract

Aim: The objective of this systematic review and meta-analysis was to determine the diagnostic and prognostic utility of artificial intelligence/machine learning (AI/ML) algorithms in Brugada Syndrome (BrS).

Methods: A systematic review and meta-analysis of the literature was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. MEDLINE, EMBASE, SCOPUS, and WEB OF SCIENCE databases were searched for relevant articles. Abstract and title screening, full-text review, and data extraction were conducted independently by two of the authors. Conflicts were resolved via discussion among authors. A risk-of-bias assessment was performed using the QUADAS-2 tool for diagnostic studies and the PROBAST tool for prognostic studies. Forest plots and the summary area under the receiver operating characteristic (SAUROC) curve were done in R.

Results: A total of 12 papers were included in our study. Among the best-performing diagnostic algorithms from each study, the sensitivity and specificity ranged from 0.80 to 0.89 and 0.74 to 0.97, respectively. In overall studies, sensitivity was 0.845 ± 0.014 and specificity was 0.892 ± 0.062 using a random effects model. A pooled analysis of the summary area under the receiver operating characteristic curve (SAUROC) was 0.77 for diagnostic studies. Prognostic studies showed good performance as well, with the AUC of the best-performing prognostic algorithms ranging from 0.71 to 0.90.



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Conclusions: Overall, AI/ML algorithms had high diagnostic and prognostic accuracy. These results highlight the potential of AI/ML algorithms for the diagnosis and prognosis of BrS and permit a choice of the best-performing ML algorithms.

Keywords: Brugada syndrome, artificial intelligence, machine learning, diagnostic criteria, prognosis

INTRODUCTION

Brugada syndrome (BrS) is a rare inherited cardiac channelopathy that can lead to sudden cardiac death (SCD) and/or ventricular tachycardia/fibrillation (VT/VF) in persons with structurally normal hearts^[1]. Genetically, it is attributed to loss of function mutations in the *SCN5A* gene, present in 20% of diagnosed patients. BrS can result in myocardial fibrosis and expression of gap junction proteins, which may be mediated by inflammation^[2-4].

BrS is a challenging entity from the perspective of its diagnosis and prediction of the development of serious, potentially fatal arrhythmias. BrS is diagnosed on the basis of a 12-lead ECG in addition to clinical findings. The typical findings of the Brugada pattern on ECG are a pseudo-right bundle branch block and persistent ST-segment elevation in V1 and/or V2^[5]. Other ECG findings characteristic of BrS include “J” waves, QT interval prolongation, and increased S wave voltage and duration. Since 40% of patients with BrS present with a normal or non-diagnostic ECG, a drug challenge using a sodium-channel-blocker (e.g., flecainide, procainamide, or ajmaline) may be used to unmask the type 1 pattern and aid in diagnosis^[6]. However, sodium channel blockers (SCBs) have a risk of producing life-threatening arrhythmias^[7,8]. Additionally, ajmaline, the most effective drug for unmasking the type-1 Brugada pattern, is unavailable in many countries^[9]. Given the shortcomings associated with SCBs, implementation of ML algorithms in a clinical setting could streamline diagnosis to help identify ECGs with Brugada patterns. The ML deep-learning models proposed by some investigators, such as Liao *et al.*^[10] and Liu *et al.*^[11], appear to outperform cardiologists in sensitivity (but not specificity). These results highlight the potential of AI to serve as a screening tool to aid in streamlining the diagnosis of BrS.

Another challenging problem in the management of BrS is the identification of patients at high risk of sudden death who might benefit from the implantation of a cardioverter-defibrillator (ICD). Most individuals with BrS are asymptomatic and have a low risk of sudden death. However, sudden death in BrS occurs in individuals who had been previously asymptomatic. The development of algorithms that would improve the assessment of prognosis is an urgent need. In addition, these models may aid clinicians in the risk stratification of BrS. This review aims to systematically evaluate current AI models for the diagnosis and risk stratification of BrS.

METHODS

Study selection

This review was directed in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses^[12]. Electronic searches were conducted in MEDLINE, EMBASE, SCOPUS, and WEB OF SCIENCE from database inception to November 6, 2023, with keywords “artificial intelligence” OR “deep learning” OR “machine learning” AND ECG or electrocardiogram AND “Brugada” or Brugada syndrome (see [Supplementary S1](#) for full search strategy). A filter to retrieve studies related to artificial intelligence developed by the University of Alberta was used^[13].

The inclusion criteria were all primary research papers published in English that examined the utility of AI, machine learning, and ECG data in diagnosing or predicting adverse cardiac events in patients with Brugada syndrome. The exclusion criteria were: pediatric patients and non-human studies. Abstracts, editorials, case reports, and reviews were also excluded.

All references were uploaded to Covidence and were electronically merged to remove duplicates^[14]. Two authors (CL and SS) individually reviewed studies to determine their inclusion or exclusion. The data extracted from each study were: study design, country in which the study was conducted, AI training cohort size, Brugada sample size, and control sample size. In addition, the following algorithm characteristics were extracted from each study: sensitivity, specificity, positive predictive value, negative predictive value, accuracy, area under the curve (AUC), and F1 score. Two reviewers (CL, JS) examined each paper independently to determine whether they fit the inclusion or exclusion criteria. Data extraction was conducted by two reviewers (CL, JS) and a consensus was reached for any conflicts.

Data analysis

Risk of bias assessment was conducted by CL. The QUADAS-2 tool was used to assess the risk of bias in diagnostic algorithm accuracy studies, whereas the PROBAST tool was used to assess the risk of bias in prognostic algorithm accuracy studies^[15,16]. Diagnostic studies were assessed based on the domains of patient selection, index test(s), reference standard, and flow and timing. Prognostic studies were assessed based on the domains of participants, predictors, outcomes, and analysis.

Statistical analysis

Forest plots were used to quantify results and depict the standard difference of means, 95% confidence interval, and *P*-value. Data analysis was conducted in R using the Meta-Analysis of Diagnostic Accuracy (mada) package^[17]. Forest plots and the summary area under the receiver operating characteristic (SAUROC) curve were done in R. The meta-analysis was carried out using Comprehensive Meta-Analysis (Biostat Inc., NJ, USA) by fitting the random effects model with inverse-variance weighting.

RESULTS

One hundred forty-one studies were identified from our search and uploaded to Covidence for screening [Figure 1]. Sixty-one references were marked as duplicates and removed. Seventy-four studies were screened for relevance by title and abstract independently by two authors (CL and SS), and of these, 53 were excluded. 21 studies were eligible for full-text review and screened independently by CL and SS. Nine studies were excluded at this stage for reasons specified in Figure 1. In total, 12 studies were included in our review.

Study characteristics

Studies were conducted in 7 different countries/regions including Italy ($n = 3$), Switzerland ($n = 1$), Japan ($n = 1$), Taiwan ($n = 1$), Canada ($n = 1$), China ($n = 3$), France ($n = 2$). The year of publication of included studies ranged from 2016-2023. Five studies used AI as a diagnostic tool for BrS [Table 1]. Seven studies used AI as a tool to prognose adverse cardiac outcomes related to BrS [Table 2]. Most studies reported training sample size as the number of patients; however, only three studies reported the number of ECG readings (and not patients) used in the training of the algorithm. The total training sample size of all included studies was $n = 1,868$ for diagnostic studies and $n = 1,859$ for prognostic studies. Gender was only reported for two diagnostic studies and four prognostic studies and the range was from 69.6% male to 95% male. Mean age was only reported for one diagnostic study and five prognostic studies, ranging from 36 to 50 years old. Lee *et al.* and Lee *et al.* trained their models using the same dataset, based in Hong Kong^[18,19].

Table 1. Diagnostic study characteristics

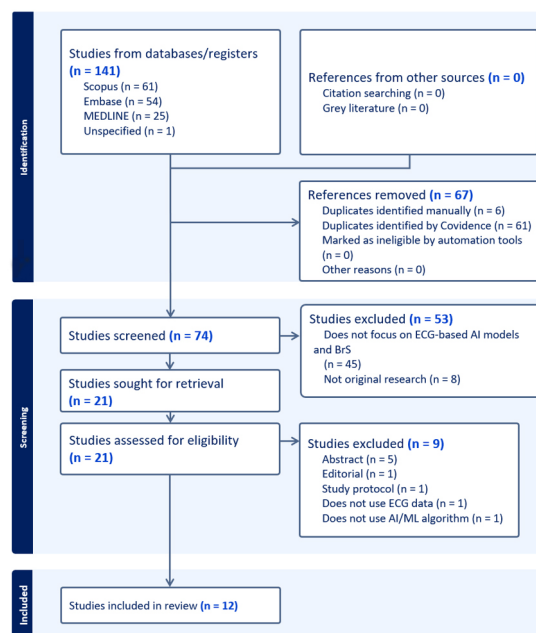
Study ID	Country	Diagnosis	Training sample size	BrS		Control (BrS negative)		
				% male	Mean age (\pm SD)	Training sample size	% male	Mean age (\pm SD)
Micheli <i>et al.</i> ^[24] (2023)	Italy	Physician Diagnosed	123 ECGs	NR	NR	183 ECGs	NR	NR
Melo <i>et al.</i> ^[9] (2023)	Italy	Physician Diagnosed	596 ECGs	NR	NR	558 ECGs	NR	NR
Zanchi <i>et al.</i> ^[25] (2023)	Switzerland	79 were physician diagnosed, 44 underwent ajmaline challenge	79	69.6%	47 \pm 14	44	63.60%	36 \pm 14
Liu <i>et al.</i> ^[11] (2022)	Taiwan	Physician verified (cardiologist)	138 ECGs	NR	NR	138 ECGs	NR	NR
Liao <i>et al.</i> ^[10] (2022)	Canada	Procainamide or Brugada type 1 ECG pattern in the standard precordial	105	77%	NR	76	53%	NR

ECGs: number of ECG scans; NR: not reported.

Table 2. AUC of diagnostic study algorithm

Study	Algorithm	AUC	95%CI
Micheli <i>et al.</i> ^[24] (2023)	NR	NR	NR
Melo <i>et al.</i> ^[9] (2023)	DNN	0.934	0.907-0.961
Zanchi <i>et al.</i> ^[25] (2023)	NR	NR	NR
Liu <i>et al.</i> ^[11] (2022)	DNN	0.96	0.93-0.98
Liao <i>et al.</i> ^[10] (2022)	Convolutional DNN (12-lead ECG)	0.976	0.973-0.979
	Convolutional DNN (12-lead Holter)	0.975	0.966-0.983

Algorithms with the best performance are bolded. NMF: Non-negative matrix factorization; AUC: area under the curve; DNN: Deep neural network; NR: Not reported.

**Figure 1.** PRISMA flow diagram

More information regarding the study validation method, data selection, and the preparation process can be found in [Supplementary Table 2](#).

Risk of bias assessment

Diagnostic studies were assessed based on the domains of patient selection, index test(s), reference standard, and flow and timing. Two diagnostic studies were determined to be at high or unclear risk of bias. Prognostic studies were assessed on the domains of participants, predictors, outcomes, and analysis. Four prognostic studies were determined to be at high or unclear risk of bias. Detailed results are provided in [Supplementary Tables 3 and 4](#).

Model testing and validation

ML algorithms were evaluated based on the area under the curve (AUC) of the receiver operating characteristic curve (ROC). Accuracy, positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, and F1 were also used as evaluation metrics. Accuracy is defined as the number of overall cases correctly identified, but it may be misleadingly high if the model is trained on an imbalanced dataset. PPV (i.e., precision) is the ratio of predicted positives to true positives. NPV is the ratio of predicted negatives to true negatives. Sensitivity is the model's ability to identify true positive cases, whereas specificity is the probability that a predicted negative is truly negative. F1 score is the harmonic mean of precision and recall, balancing the two metrics.

Notably, these metrics are dependent on a defined threshold value, which determines the classification boundary between positive and negative cases. A higher threshold may increase sensitivity at the cost of specificity. Conversely, a lower threshold may decrease sensitivity at the cost of specificity. Threshold selection techniques varied between selecting an optimal value based on the ROC curve, using optimal precision vs recall, Youden's J statistic, and using predefined sensitivity values [[Supplementary Table 4](#)].

The AUC of the best-performing diagnostic study algorithms ranged from 0.934-0.976. The AUC of the best-performing prognostic study algorithms ranged from 0.7092 to 0.942. However, the included studies did not consistently report all of the metrics, with several studies not reporting both AUC and a 95%CI.

Different studies used a variety of machine learning algorithms. Lee *et al.* trained a random forest model to predict spontaneous VT/VF on latent risk factors extracted by non-negative matrix factorization (NMF)^[18]. The total sample size was 516 and included 314 asymptomatic patients. Liao *et al.* trained several convolutional neural networks (CNN) to identify and diagnose the type 1 Brugada ECG pattern^[10]. The highest-performing algorithm was the convolutional deep neural network (DNN) trained on 12-lead ECG data, which had an AUC of 0.976 (96%CI: 0.973-0.979). Liu *et al.* used a learning transfer strategy on a model originally used to classify right bundle branch block (RBBB) and adapted it to classify the type 1 Brugada pattern^[11]. Melo *et al.* trained a DNN on 12-lead ECG data in a cohort of 1,154 patients (596 BrS positive, 558 controls)^[9]. Only a small fraction of patients showed a type 1 Brugada pattern and these patients were identified with 100% accuracy. Randazzo *et al.* trained two models, a multi-layer perceptron neural network (MLP) and a boosted decision tree (BDT), on ECG features extracted manually by cardiologists to predict retrospective arrhythmic events^[20]. Tse *et al.* trained a regression model with latent variables extracted by NMF to predict spontaneous VT/VF incidence^[21]. These included clinical variables such as syncope and AF as well as ECG variables such as type 1 Brugada pattern, QRS duration, QTc interval and others. When validated on an external cohort from multiple different countries, they found that the model's performance was optimal when trained on five latent variables. Romero *et al.* trained an ensemble classifier to distinguish BrS patients according to symptomatology using features extracted from the QRS complex, HRV markers, or both^[22]. Romero *et al.* utilized a multivariate ensemble classifier trained

on ECG data for risk stratification in 110 BrS patients, of which 25 showed symptoms^[23]. Lee *et al.* compared the performance of 7 different machine learning models with respect to the prognosis of VT/VF^[19].

Diagnostic algorithm performance

Five studies used ML algorithms for the diagnosis of BrS [Tables 3 and 4]. Micheli *et al.* used a CNN trained on ECG data for the diagnosis of BrS on a dataset of 306 ECGs from the BrAID (Brugada syndrome and Artificial Intelligence applications to Diagnosis) project^[24]. The model showed excellent performance with a sensitivity of 0.8773 and a specificity of 0.9234. Melo *et al.* trained a DNN on a cohort of 596 BrS-positive and 558 control patients^[9]. On an external validation cohort of 370 ECGs, the model demonstrated good performance in diagnosing BrS without the use of a SCB (0.934 AUC, 95%CI: 0.973-0.979). Zanchi *et al.* compared various ML models trained on P-wave features for the diagnosis of BrS in a cohort of 123 patients^[25]. The worst-performing model was the K-nearest neighbors' model, with a reasonable sensitivity (0.843) but poor specificity (0.513). The best-performing model was the AdaBoost model, with a sensitivity of 0.865 and specificity of 0.738. Liu *et al.* compared the performance of a deep-learning model with that of two cardiologists in the diagnosis of BrS based on ECG^[11]. The model showed higher sensitivity (0.884 *vs.* 0.627) than the cardiologists but poorer specificity (0.891 *vs.* 0.985). The model had a higher AUC than the cardiologists (0.96 *vs.* 0.81). Similarly, the deep-learning model in Liao *et al.* outperformed two cardiologists in the classification of BrS type 1^[10]. The model achieved a sensitivity of 0.96 and specificity of 0.90, which was higher than the first cardiologist (sensitivity = 0.889, specificity = 0.880) and was similar to a second cardiologist (sensitivity = 0.925, specificity = 0.920).

Overall, ML algorithms for the diagnosis of BrS via ECG data showed good performance with regard to sensitivity and specificity. We performed a pooled analysis of the best-performing algorithm from each study. The sensitivity and specificity of the best-performing diagnostic algorithms ranged from 0.80 to 0.89 and 0.74 to 0.97, respectively. A meta-analysis showed that overall studies sensitivity was 0.848 ± 0.015 (SEM, $z = 57.3$ m, $P < 0.0001$) [Figure 2] and specificity was 0.892 ± 0.061 (SEM, $z = 14.5$, $P < 0.0001$) using a random effects model [Figure 3]. An analysis for publication bias using the classic Failsafe-N test would require over 7,000 negative studies to invalidate the result for sensitivity and over 2,000 negative studies to invalidate the result for specificity.

Since the majority of studies did not explicitly report 2×2 contingency tables, these were imputed algebraically from their data, where necessary, using sensitivity, specificity, sample size, and number of condition-positive patients. The heterogeneity of studies was assessed using Chi-squared tests for equality of sensitivities and specificities (Test for equality of sensitivities: X-squared = 7.4429, df = 4, P -value = 0.114; Test for equality of specificities: X-squared = 79.9133, df = 4, P -value $\leq 2 \times 10^{-16}$). This suggests that there are significant differences in specificity but not sensitivity among diagnostic studies. Next, a bivariate approach was used to calculate the pooled SROC. Using the mada package in R, we fit a bivariate diagnostic random-effects meta-analysis^[17]. Among five diagnostic studies, the overall pooled summary area under the receiver operator characteristic curve (SAUROC) for diagnosis of BrS was 0.877 [Figure 4]. The SAUROC represents the pooled AUC of all the included studies. It was calculated by combining the true positive rates and false positive rates from the included studies and plotting them against each other. A higher SAUROC represents greater diagnostic/prognostic accuracy across several ML models and datasets.

Prognostic algorithm performance

The AUC of the best-performing prognostic algorithms ranged from 0.71-0.90 for five of seven studies that reported it [Tables 5 and 6]. Unlike the diagnostic studies, the sensitivity and specificity were only reported for four of the seven studies, so a pooled analysis was not possible. Tse *et al.* utilized a logistic regression model trained on latent variables extracted via a non-negative matrix factorization method to predict

Table 3. Test accuracy of diagnostic algorithms study

	Algorithm	F1	Sensitivity (aka recall)	Specificity	NPV	PPV (aka precision)	Accuracy
Micheli <i>et al.</i> ^[24] (2023)	Convolutional neural network (6 blocks V2)	NR	0.8773	0.9234	NR	NR	0.9053
	CNN (6 blocks V1)	NR	0.8536	0.8581	NR	NR	0.8562
	CNN (6 blocks V1, V2)	NR	0.8987	0.8943	NR	NR	0.902
Melo <i>et al.</i> ^[9] (2023)	Deep Neural Network	NR	0.796	0.936	0.813	0.609	0.884
Zanchi <i>et al.</i> ^[25] (2023)	K nearest neighbors	MF1 = 0.681, WF1 = 0.711	0.843	0.513	NR	NR	0.725
	Decision tree (with Adasyn)	MF1 = 0.661, WF1 = 0.668	0.562	0.855	NR	NR	0.663
	Random forest (with SMOTE)	MF1 = 0.765, WF1 = 0.784	0.824	0.721	NR	NR	0.783
	Stacking (with SMOTE)	MF1 = 0.780, WF1 = 0.799	0.902	0.498	NR	NR	0.798
	Support vector machining (with SMOTE)	MF1 = 0.704, WF1 = 0.722	0.717	0.734	NR	NR	0.716
	Majority voting	MF1 = 0.692, WF1 = 0.721	0.799	0.581	NR	NR	0.723
	Bagging	MF1 = 0.780, WF1 = 0.799	0.836	0.736	NR	NR	0.798
	AdaBoost (with Weighted class)	MF1 = 0.795, WF1 = 0.814	0.865	0.738	NR	NR	0.814
	GBoost (with SMOTE)	MF1 = 0.771, WF1 = 0.789	0.811	0.754	NR	NR	0.788
	Deep learning model	0.887 (0.899-0.940)	0.884 (0.819-0.942)	0.891	NR	NR	NR
Liu <i>et al.</i> ^[11] (2022)	Convolutional deep neural network (12-lead ECG)	0.672	0.5	1	0.905	1	NR
	Convolutional deep neural network (12-lead ECG)	0.833	0.8	0.972 (0.95-0.994)	0.96 (0.959-0.960)	0.862 (0.762-0.954)	NR
	Convolutional deep neural network (12-lead ECG)	0.77	0.9	0.905	0.973	0.672	NR
	Convolutional deep neural network (12-lead Holter)	0.629	0.5	0.993	0.973	0.817	NR
	Convolutional deep neural network (12-lead Holter)	0.694	0.8	0.968	0.989	0.603	NR
	Convolutional deep neural network (12-lead Holter)	0.632	0.9	0.942	0.995	0.482	NR
	Convolutional deep neural network (12-lead Holter)						

Algorithms with the best performance are bolded; NMF: Non-negative matrix factorization; CNN: Convolutional neural network; DNN: Deep neural network; NR: Not reported; MF1: Mean F1-score; WF1: Weighted F1-score.

VT/VF in BrS patients^[21]. Their model performed optimally when trained on five latent variables, giving an AUC of 0.7092 when validated on an external cohort of 227 patients. Syncope, atrial fibrillation, QRS duration, and QTc interval were significant predictors of spontaneous VT/VF. Romero *et al.* used a multivariate ensemble classifier to predict syncope, VF, or SCD. Their model performed the best when trained on the features of heart rate recovery (HRV) and morphological indices of QRS, with an AUC of 0.9^[23]. Randazzo *et al.* compared several models, including a multi-layer perceptron (MLP), boosted decision tree (BDT), decision tree, Support Vector Machine, and Naïve Bayes (NB) classifiers for the prediction of SCD or VF^[20]. All models were trained on the same dataset of 209 ECGs. However, the number of patients included and their characteristics were not reported. On validation, all models showed a high NPV, but the

Table 4. Prognostic study characteristics

Study ID	Country	Outcome predicted	Outcome		Mean age (\pm SD)	Control		
			Training sample size	% male		Sample size	% male	Mean age (\pm SD)
Tse <i>et al.</i> ^[21] (2020)	Hong Kong	VT/VF	32	95%	49 (35-68) Median, LQ, UQ	117	81%	50 (39-59) Median, LQ, UQ
Romero <i>et al.</i> ^[22] (2016)	France	Syncope, VF, or SCD	14	NR	NR	48	NA	NA
Randazzo <i>et al.</i> ^[20] (2023)	Italy	SCD or VF	41 ECGs	NR	NR	168 ECGs	NR	NR
Lee <i>et al.</i> ^[18] (2021)	Hong Kong	VT/VF	516	92%	50 \pm 16	NA	NA	NA
Romero <i>et al.</i> ^[23] (2022)	France	Syncope, VF, or SCD	25	Total training: 74.5% male, 25.5% female (not reported for individual groups)	Total training: 44.6 \pm 13.7	85	NA	NA
Lee <i>et al.</i> ^[19] (2022)	Hong Kong	VT/VF	548	92.70%	49.9 \pm 16.3	NA	NA	NA
Nakamura <i>et al.</i> ^[26] (2023)	Japan	Fatal arrhythmia	157	90.40%	44.8 \pm 14.8	NA	NA	NA

Not reported for individual groups*; Median (lower quartile-upper quartile)**; VT: Ventricular tachycardia; VF: ventricular fibrillation; SCD: Sudden cardiac death; NR: Not reported.

BDT performed the best on the basis of F1 score (0.67). Lee *et al.* used a random-survival forest (RSF) model trained on latent features extracted via NMF for the prediction of VT/VF^[19]. The model performed well with respect to F1 score (0.8769), sensitivity (0.8881), and PPV (0.8712). Romero *et al.* trained a multivariate classifier on a cohort of 110 BrS patients for the identification of novel symptom-related markers from autonomic and dynamic ECG responses during exercise testing^[23]. The best-performing model was the multivariate classifier trained on three features: (1) T-wave intervals ratio in lead V5 at baseline; (2) Ratio T-peak-T-end/QT in lead V5 at baseline; (3) T-peak-T-end interval in lead V5 at baseline. This model had an AUC of 0.796 (95%CI: 0.719-0.873) on cross-validation. Lee *et al.* compared the performance of several ML models with published risk scores in a multi-centered cohort study based in Hong Kong^[18]. They found that the random survival forest outperformed all other models as well as published risk scores in the prediction of VT/VF, with an AUC of 0.942 (95%CI: 0.913-0.964). Additionally, they found that P wave duration and the presence of other arrhythmias, such as atrial fibrillation (AF), mean QRS duration, and QTc intervals were predictors of spontaneous VT/VF. They suggested an additional role for atrial arrhythmias and abnormalities in ventricular repolarization in predicting adverse outcomes in BrS.

Nakamura *et al.* trained a CNN for the prediction of fatal arrhythmia. The model performed the best when trained on a per-patient basis, showing an AUC of 0.81 (95%CI: 0.72-0.90)^[26].

Table 5. AUC of prognostic study algorithm

Study	Algorithm	AUC	95%CI
Tse <i>et al.</i> ^[21] (2020)	Benchmark using logistic regression (# latent variables = 0)	0.6383	NR
	NMF (# latent variables = 2)	0.6759	NR
	NMF (# latent variables = 3)	0.6809	NR
	NMF (# latent variables = 4)	0.6993	NR
	NMF (# latent variables = 5)	0.7092	NR
Romero <i>et al.</i> ^[22] (2016)	NMF (# latent variables = 6)	0.6856	NR
	Ensemble classifier (HRV-based model)	0.87	NR
	Ensemble classifier (QRS-based model)	0.73	NR
	Ensemble classifier (HRV + QRS combination based model)	0.9	NR
Randazzo <i>et al.</i> ^[20] (2023)	NR	NR	NR
Lee <i>et al.</i> ^[18] (2021)	Model 1 (multivariate classifier with 9 features)	0.819	0.756-0.882
	Model 2 (multivariate classifier with 7 features)	0.817	0.741-0.893
Romero <i>et al.</i> ^[23] (2022)	Model 3 (multivariate classifier with 3 features)	0.796	0.719-0.873
Lee <i>et al.</i> ^[19] (2022)	Random survival forest	0.942	0.913-0.964
	Ada boost classifier	0.872	0.831-0.923
	Gaussian naive Bayes	0.832	0.803-0.861
	Light gradient boosting machine	0.812	0.781-0.831
	Random forest classifier	0.783	0.764-0.821
	Gradient boosting classifier	0.762	0.751-0.802
	Decision tree classifier	0.683	0.651-0.713
	CNN (Average of 5-fold cross validation on an ECG basis)	0.8	0.73-0.87
Nakamura <i>et al.</i> ^[26] (2023)	CNN (Average of 5-fold cross validation on an patient basis)	0.81	0.72-0.90

Algorithms with the best performance are bolded; NMF: Non-negative matrix factorization; CNN: Convolutional neural network; DNN: Deep neural network; NR: Not reported.

DISCUSSION

In this systematic review and meta-analysis, we evaluated the performance of ML algorithms in diagnosing BrS and predicting adverse cardiac events. Overall, the pooled estimation showed that ML algorithms performed well in diagnosing BrS and predicting adverse cardiac events, but there are meaningful differences between different algorithms.

Considering the high accuracy of ML algorithms in diagnosing BrS and the shortcomings associated with SCBs, implementing ML algorithms in a clinical setting could streamline diagnosis and help identify ECGs with Brugada patterns. The diagnostic algorithm with the highest performance as measured by AUC and combination of sensitivity and specificity was the convolutional DNN based on 12-lead ECG proposed by Liao *et al.*^[10]. This algorithm had an AUC of 0.976 (95%CI: 0.973-0.979) and sensitivity and specificity of 0.8 and 0.972, respectively. In a follow-up random sample of patients from the 50 ECGs testing cohort, the ML model performed just as well as cardiologists, scoring a sensitivity and specificity of 96% and 90% compared with cardiologist 1 (sensitivity = 88.9%, specificity = 88.0%) and cardiologist 2 (sensitivity = 92.5%, specificity = 92.0%). The second best-performing diagnostic algorithm was the DNN in the study by Melo *et al.*^[9], with an AUC of 0.934 (95%CI: 0.907-0.961), sensitivity of 0.796, and specificity of 0.936. Unfortunately, two studies did not report AUC values, making it difficult to compare these algorithms. Most of the included diagnostic studies use ECG data containing the typical type-1 Brugada waveform, easily identifiable by sustained ST-elevation and T wave inversion in leads 1 and/or 2^[5]. The exception was Melo *et al.*^[9], whose algorithm was able to successfully recognize BrS ECGs without a type-1 pattern or the

Table 6. Test accuracy of prognostic algorithms

Study	Algorithm	F1	Sensitivity (aka recall)	Specificity	NPV	PPV (aka precision)	Accuracy
Tse et al.^[21] (2020)	Benchmark using logistic regression (# latent variables = 0)	0.6056	0.6131	NR	NR	0.5983	NR
	NMF (# latent variables = 2)	0.6559	0.6552	NR	NR	0.6567	NR
	NMF (# latent variables = 3)	0.6769	0.6567	NR	NR	0.6984	NR
	NMF (# latent variables = 4)	0.6973	0.6899	NR	NR	0.7048	NR
	NMF (# latent variables = 5)	0.7048	0.696	NR	NR	0.7139	NR
	NMF (# latent variables = 6)	0.6925	0.6738	NR	NR	0.7123	NR
Romero et al.^[22] (2016)	Ensemble classifier (HRV-based model)	NR	1	0.67	NR	NR	NR
	Ensemble classifier (QRS-based model)	NR	0.75	0.67	NR	NR	NR
	Ensemble classifier (HRV + QRS combination based model)	NR	1	0.83	NR	NR	NR
Randazzo et al.^[20] (2023)	Boosted decision tree (BDT)	0.67	NR	NR	0.8947	1	0.9048
	Multi-layer perceptron neural network (MLP)	0.27	NR	NR	0.8333	0.5	0.8095
	MLP opt. threshold	0.43	NR	NR	0.8979	0.3143	0.6547
	Decision tree	0.35	NR	NR	0.839	0.9	0.842
	Naive bayes	0.45	NR	NR	0.857	0.577	0.823
	Support vector machine	0.18	NR	NR	0.819	1	0.823
Lee et al.^[18] (2021)	Cox model	0.742	0.728	NR	NR	0.7565	NR
	RSF model	0.8433	0.8531	NR	NR	0.8338	NR
	RSF-NMF model	0.8769	0.8881	NR	NR	0.8712	NR
Romero et al.^[23] (2022)	Model 1 (multivariate classifier with 9 features)	NR	0.791 ± 0.087	0.796 ± 0.0103	NR	NR	NR
	Model 2 (multivariate classifier with 7 features)	NR	0.850 ± 0.111	0.777 ± 0.076	NR	NR	NR
	Model 3 (multivariate classifier with 3 features)	NR	0.853 ± 0.106	0.724 ± 0.096	NR	NR	NR
Lee et al.^[19] (2022)	NR						
Nakamura et al.^[26] (2023)	CNN (Average of 5-fold cross validation on an ECG basis)	0.75 ± 0.09	0.73 ± 0.09	NR	0.87 ± 0.06	0.49 ± 0.22	0.73 ± 0.09
	CNN (Average of 5-fold cross validation on an patient basis)	0.81 ± 0.11	0.77 ± 0.14	NR	0.94 ± 0.11	0.44 ± 0.29	0.77 ± 0.14

Algorithms with the best performance are bolded; NMF: Non-negative matrix factorization; CNN: Convolved neural network; DNN: Deep neural network; NPV: negative predictive value; NR: Not reported.

use of SCBs to unmask the type-1 pattern.

One of the most challenging aspects for clinicians in the management of BrS patients is risk stratification, as many cases are asymptomatic and present with a Brugada pattern on ECG. Patients with a previous history of syncope or aborted cardiac arrest have a high risk for sustained VT/VF. The risk of VT is 1.9%-8.8% and 7.7%-13.8% for VF^[27,28]. However, risk stratification in patients with no previous history of cardiac events is less clear. Thus, AI may be a valuable tool to aid clinicians in assessing prognosis and deciding which patients need an ICD. Regarding prognostic algorithms, the Ensemble classifier trained on QRS and HRV

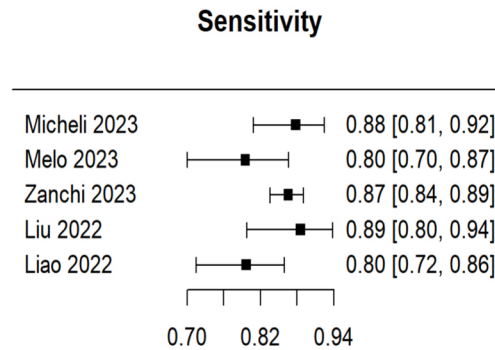


Figure 2. Forest plot of sensitivity of diagnostic studies. Error bars represent 95% confidence intervals.

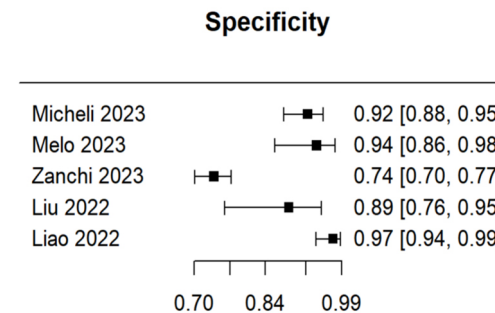


Figure 3. Forest plot of specificity of diagnostic studies. Error bars represent 95% confidence intervals.

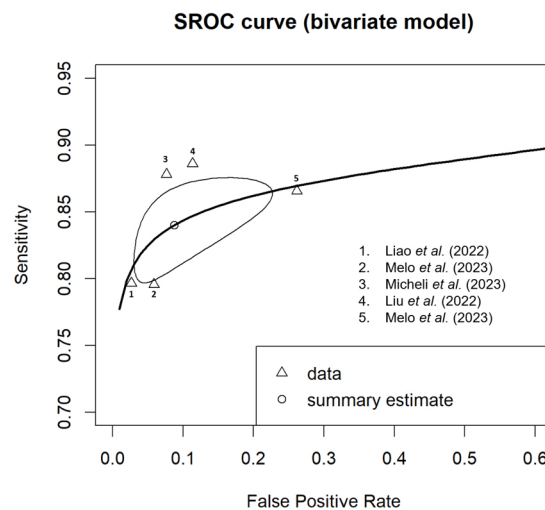


Figure 4. Summary area under the receiver operating characteristic curve (SAUROC) of ML algorithms for diagnosing BrS.

data was the top performer with an AUC of 0.90, sensitivity of 1, and specificity of 0.83 in determining the risk of VF, SCD, or syncope^[22]. This suggests that a combination of QRS morphology and HRV markers is suitable for the classification of BrS patients based on symptomatology. The second best-performing prognostic algorithm was the Gaussian naïve Bayes model used by Lee *et al.*^[19], with an AUC of 0.832 (95%CI: 0.803-0.861) in its prediction of VT/VF. Sensitivity and specificity values were not reported in that study.

Integration of clinical factors and ECG patterns in AI models

Clinical factors can play a valuable role in enhancing the prognostic accuracy of ML algorithms. An interesting approach was that of Tse *et al.* who used an NMF method to extract latent features, which are relationships between clinical variables that were only discoverable after applying a dimensionality reduction technique^[21]. These latent features were then incorporated into the training of their ML model. Clinical factors associated with spontaneous VT/VF included syncope, AF, QRS duration, and QTc interval prolongation. Additionally, Lee *et al.* found that symptoms on initial presentation were statistically significant predictors of VT/VF during follow-up^[18]. Patients presenting with syncope or VT/VF were at increased risk for spontaneous VT/VF during follow-up at every time point. Lastly, Lee *et al.* performed a Cox regression using a multivariate model and found that syncope, initial VT/VF, other arrhythmias, and significant S wave in lead I were statistically significant predictors of VT/VF during follow-up^[19].

BrS and multi-modal training in medical AI models

Recently, there has been much progress in the integration of different data modalities in the training of diagnostic algorithms. For instance, Contrastive Language-Image Pre-Training (CLIP) models connect medical imaging (X-ray, MRI, CT, *etc.*) to medical descriptions and notes^[29]. This integration allows CLIP models to assist in automated diagnosis and medical research - both pertinent to the diagnosis of BrS. There are two types of CLIP models: (1) Medical Vision-Language Pre- Training (MED-VLP) with Frozen Language Models and Latent Space Geometry Optimization (M-FLAG) and (2) Unifying Cross-Lingual Medical Vision-Language Pre-Training by Diminishing Bias (MED-UniC). M-FLAG frozen language models are pre-trained on large data sets and then are fine-tuned to accomplish specific tasks^[30]. This approach makes it easier to train the model on specific functions. M-FLAG utilizes Latent Space Geometry Optimization, a technique that optimizes the space in which data are projected. Effective space manipulation leads to improved model performance by ensuring representations of both text and image modalities are compatible and can be efficiently combined to make diagnostic predictions. In contrast, MED-UniC models involve medical data streams from multiple sources of data, such as imaging (e.g., radiography) and text data (e.g., consult notes)^[31]. Medical vision and language pre-training (MED-VLP) hopes to integrate and jointly process these data to generalize representations from large-scale medical image-text data. Subsequently, it enables a vision-and-language model to address a wide range of medical vision-and-language tasks, which can be crucial for mitigating the data scarcity problem in the medical field and aid in integrating the knowledge from pictures and text. The current literature on AI algorithms for the diagnosis and prognosis of BrS mainly incorporates only ECG data (and sometimes clinical data). The high accuracy of multi-modal AI models highlights the potential of integrating CLIP models in the diagnosis/prognosis of BrS. Future work is needed to explore this further.

AI in the diagnosis of other cardiac diseases

The utility of AI and ML in diagnosing other cardiac conditions strengthens the case for using AI models in the diagnosis and prognosis of BrS. AI and ML have helped characterize different types of heart failure with preserved ejection fraction^[32], AI-enabled ECG-based screening tool for the diagnosis of left ventricular systolic dysfunction^[33], and prediction of atrial fibrillation^[34]. ECG-based ML algorithms are being used for the diagnosis of other inherited arrhythmias, such as long QT syndrome (LQTS)^[35]. They found that among eight studies, the pooled SAUROC was 0.95 (95%CI: 0.31-1.00), sensitivity was 0.87 (95%CI: 0.83-0.90), and specificity was 0.91 (95%CI: 0.88-0.93), indicating good diagnostic performance. These metrics were slightly higher than the SAUROC calculated in our review, suggesting that ML algorithms may perform better for diagnosing LQTS compared to BrS. Another interpretation of this comparison is that algorithms for the diagnosis of BrS may not yet be well optimized, and further work must be done with larger datasets to attain higher diagnostic accuracy.

Strengths and limitations

Our study had several strengths. A thorough search of the literature and in-depth analysis was conducted. Included studies explored a variety of different machine learning algorithms. A pooled analysis was conducted to evaluate the SROC of diagnostic studies, which indicated that ML algorithms perform well in the diagnosis of BrS.

The primary limitations of our study are outlined. (1) Prognostic studies did not consistently report both sensitivity and specificity, so a pooled analysis of prognostic studies was not possible; (2) Several studies displayed an unclear or high risk of bias. There were a few reasons for this conclusion; primarily, these studies did not report patient inclusion/exclusion criteria, demographic characteristics of the patients, or the method used to diagnose BrS. Additionally, although most models underwent internal cross-validation, few were externally validated with other datasets. Therefore, there is the possibility of overfitting of the models; (3) Since BrS is a relatively rare disease, the total sample size of all included studies was not high ($n = 1,868$ for diagnostic studies and $n = 1,859$ for prognostic studies), which may limit the generalizability of our findings; (4) Clinically, BrS is often diagnosed after a drug challenge with a SCB which can sometimes unmask the type-1 BrS ECG pattern, aiding in diagnosis^[36]. Our meta-analysis was unable to stratify patients based on whether or not they received a drug challenge as there were insufficient data reported on whether this procedure was used; (5) Some studies explored the utility of ML algorithms for diagnosis/prognosis of BrS mainly based on ECG data alone. Other non-ML risk score models that incorporate clinical risk factors and ECG features exist, but these were not employed. For instance, the Shanghai scoring system incorporates ECG features, clinical history, and family history^[37]. The Sieira score is based on ECG pattern, in addition to family history of SCD and clinical presentation (e.g., syncope or aborted SCD)^[38]. Future ML models should be trained on ECG data and clinical risk factors to achieve optimal performance; (6) Another limitation is the lack of reporting on survival data according to age and time of diagnosis. Thus, we were not able to construct survival curves merging data from all studies; (7) A major concern with the use of ML algorithms as a diagnostic/prognostic tool is the potential bias in data collection for training of the model. Overrepresentations of specific demographic groups, such as by ethnic/racial groups, age groups, or gender, may also lead to overfitting of the model and loss of generalizability to other populations. For instance, the vast majority of our sample consisted of patients who were males of European descent. Therefore, caution may be necessary when interpreting the accuracy or applicability of models trained on datasets that lack diversity. Additionally, all included studies trained models on retrospective cohorts, which could serve as another source of bias. Performance metrics of models should be interpreted cautiously until the models can be validated on more robust, prospectively collected validation datasets. In the development of future models, care should be taken to address bias in data collection for model training in terms of population and data quality; (8) Lastly, since models are usually trained on high-quality databases and ECGs of well-phenotyped patients, their applicability in a "real-world clinical setting" remains to be defined^[39]. Future studies are needed to evaluate how AI algorithms can be best integrated within real-world clinical settings and whether they provide utility in improving outcomes for patients.

CONCLUSION

This systematic review and meta-analysis demonstrated the utility of AI/ML algorithms for the diagnosis and prognosis of BrS. Pooled analysis of AUC demonstrated good diagnostic performance of BrS according to ECG algorithms. These findings have clinical relevance because they suggest that the use of AI/ML in a care setting may help clinicians streamline diagnosis and risk stratification in BrS patients. Future research is needed to directly compare the performance of each AI/ML algorithm using the same robust dataset and ascertain their clinical utility.

DECLARATIONS

Authors' contributions

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Conceptualization, supervision, and manuscript writing: Rabkin SW

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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