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*Review Article*

# Artificial intelligence for Brugada syndrome diagnosis and gene variants interpretation

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**Abstract:** Brugada Syndrome (BrS) is a hereditary cardiac condition associated with an elevated risk of lethal arrhythmias, making precise and prompt diagnosis vital to prevent life-threatening outcomes. The diagnosis of BrS is challenging due to the requirement of invasive drug challenge tests, limited human visual capacity to detect subtle electrocardiogram (ECG) patterns, and the transient nature of the disease. Artificial intelligence (AI) can detect almost all patterns of BrS in ECG, some of which are even beyond the capability of expert eyes. AI is subcategorized into several models, with deep learning being considered the most beneficial, boasting its highest accuracy among the other models. With the capability to discriminate subtle data and analyze extensive datasets, AI has achieved higher accuracy, sensitivity, and specificity compared to trained cardiologists. Meanwhile, AI proficiency in managing complex data enables us to discover unclassified genetic variants. AI can also analyze data extracted from induced pluripotent stem cell-derived cardiomyocytes to distinguish BrS from other inherited cardiac arrhythmias. The aim of this study is to present a synopsis of the evolution of various algorithms of artificial intelligence utilized in the diagnosis of BrS and compare their diagnostic abilities to trained cardiologists. In addition, the application of AI for classification of BrS gene variants is also briefly discussed.

**Keywords:** Brugada syndrome, artificial intelligence, machine learning, inherited cardiac arrhythmia

## Introduction

Brugada syndrome (BrS) is a rare hereditary sodium channelopathy of the heart associated with lethal arrhythmias and sudden cardiac death (SCD) [1]. It predominantly affects individuals under the age of 35 and is 8 to 10 times more prevalent among men [2]. Its prevalence is 3-5 cases in 10,000 among Caucasians, and it is 3-5 times higher among East Asians [3]. Even though BrS is considered a rare disease, it accounts for 20% of SCDs in those with no apparent cardiac structural abnormalities [2, 4].

BrS has an autosomal dominant inheritance pattern with incomplete penetrance and variable expressivity. So far, 23 genes have been associated with BrS. The most frequently related gene is SCN5A, responsible for coding the alpha subunit of the sodium channel; however, it only accounts for 18%-30% of BrS cases [5-7].

The diagnosis of BrS mainly relies on identifying the disease patterns on the right precordial ECG leads (V1-V3). This syndrome has three patterns (**Figure 1**): Type 1 is identified by an elevation of the ST-segment by a minimum of 2 mm, followed by a coved-shaped slope with a subsequent negative T wave [8, 9]. Type 2 is identified by an initial saddleback ST-segment elevation of at least 2 mm, followed by a positive T wave. Type 3 is identified by an elevation of the ST-segment, but it does not exceed a maximum of 1 mm [10]. Identifying these ECG patterns is challenging due to their transient presence. Even the administration of sodium channel blockers like flecainide and ajmaline, which can provoke BrS patterns, would only unmask 33% of asymptomatic Brugada cases, leaving a majority of the patients concealed [11]. The accurate diagnosis of this disease primarily hinges on the physician's skills; however, even a highly professional practitioner might misdiagnose BrS patients with more prevalent differential diagnoses such as ST-elevation

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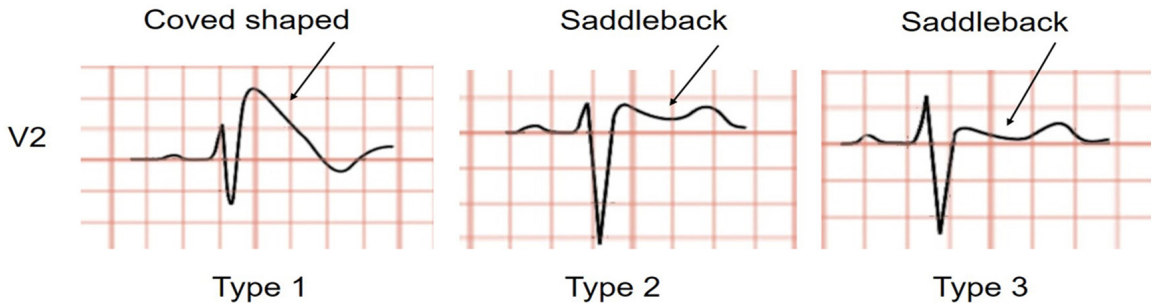


**Figure 1.** Three different types of Brugada patterns with arrows indicating the ST segment elevation.

myocardial infarction (STEMI) or early repolarization and pericarditis [12]. Although the majority (approximately 60%) of patients with this condition remain asymptomatic, the first symptom is often a life-threatening cardiovascular event such as ventricular tachycardia (VT), ventricular fibrillation (VF), or even a mortal condition such as SCD [13].

The issues mentioned above highlight the requirement for a more precise and reliable screening tool and diagnostic strategy for early diagnosis, which is crucial for mitigating lethal cardiovascular events and ensuring timely therapeutic interventions.

In recent years, Artificial Intelligence (AI) technology has witnessed tremendous advances, enhancing our ability to process vast datasets such as ECG data by leveraging its learning, analyzing, and problem-solving capabilities. These advancements reduce the health staff workload, minimize potential human errors, and eliminate time wastage in repetitive tasks.

In the medical domain, the use of AI and machine learning is growing increasingly. The applications of machine learning in medicine include, but are not limited to, analyzing medical images and detecting infectious disease outbreaks to enhance decision-making in surgery. To the best of the authors' knowledge, there is no previous study on the application of AI to Brugada syndrome diagnosis before 2020, but it has attracted considerable attention afterward (**Table 1**).

This study discusses how AI and machine learning facilitate the rapid and accurate detection of BrS, a rare but fatal cardiac condition [14, 15]. We evaluated the capability of different machine learning models in recognizing the pattern of BrS on ECG and compared their diagnostic performance with that of trained cardiologists. We also discussed the clinical applicability of machine learning models in daily clinical practice and provided a futuristic perspective on the topic and potential challenges in diagnosing the disease.

## An overview of artificial intelligence models utilized in Brugada syndrome

AI is a rapidly growing field that utilizes computers to create algorithms that mimic human thinking. AI can perform tasks such as learning, problem-solving, and understanding natural language, previously exclusive to humans. This transformative capability has led to its recognition as the fourth industrial revolution [16]. The use of AI in the medical field has the potential to revolutionize healthcare practices, making the diagnosis of diseases and medical interventions more efficient and accurate [17]. There are numerous models and algorithms in artificial intelligence with a vast variety of medical applications. Some recruit non-image-based analysis, while others use diagnostic algorithms to interpret digitalized image patterns such as ECG records. Here, we introduce and categorize the models utilized in Brugada syndrome diagnosis as follows (**Figure 2**; **Table 1**).

Machine learning (ML) is the dominant subset of AI, associated with algorithms and models that can adapt and learn autonomously from data without manual programming [18].

ML algorithms can be categorized into four main domains based on the learning method (**Figure 2**): Supervised learning, Unsupervised learning, Semi-supervised learning, and reinforcement [19]. Supervised ML is one of the

**Table 1.** A timeline overview of studies employing machine learning models for the detection of Brugada syndrome

| Year | Author | Sample size | Machine learning model | Outcome |
|---|---|---|---|---|
| 2020 | Bonet-Luz [34] | 78 ECG leads from 42 mice, consisting of 42 wild-type and 36 SCN5A mutant mice | KNN and SVM | Accuracy 96% |
| 2021 | Morales [35] | Part A: a retrospective study consisting of 300 ECG collected from 75 spontaneous BrS, 150 suspected BrS, and 75 controls | Not determined | - |
| 2021 | Dimitri [36] | 156 ECGs were collected from 88 diagnosed BrS patients and 68 healthy individuals | ESNs | Accuracy 76.9% |
| 2022 | Vozzi [37] | A total of 306 ECGs were collected in 4 groups: spontaneous type 1 Brugada pattern, drug-induced Brugada pattern, healthy negative Brugada ECG, and healthy controls | ESNs | Accuracy 80.2%<br>Specificity 91%<br>Sensitivity 74% |
| 2022 | Liu [39] | Total 4512 ECGs (2257 RBBB ECGs and 2257 non-RBBB ECGs)<br>And 552 ECGs (276 ECGs from diagnosed BrS patients and 276 ECGs from non-Brugada individuals) | LSTM, CNN, and MLT | AUC 96%<br>Specificity 89.1%<br>Sensitivity 88.4%<br>kappa coefficient 63% for cardiologists and 78% for AI |
| 2022 | Liao [40] | Training set consisting of 1190 12-lead ECGs and 380, 12-lead Holters.<br>A validation set consisting of 474, 12-lead ECGs and 716, 12-lead Holters | CNN | Accuracy 90.5% from ECG and 94.1% from Holters<br>AUC 97.6% from ECG and 97.5% from Holters<br>Specificity 90.0% for cardiologists and 97% for AI<br>Sensitivity 90.70% for cardiologists and 96% for AI<br>F1 score 77.0%<br>NPV 97.8%<br>PPV 67.2% |
| 2023 | Micheli [42] | 306 ECGs collected from 123 diagnosed BrS patients and 183 negative individuals | CNN | Accuracy 90.53%<br>Specificity 92.34%<br>Sensitivity 87.73% |
| 2023 | Pannone [43] | 1188 patients | DCNN | AUC 94.5% and 80.5% before ajmaline |
| 2023 | Melo [44] | 480 subjects | DNN | AUC 93.4%<br>Accuracy 88.4%<br>Sensitivity 79.6%<br>Specificity 93.6% |
| 2023 | Melo [45] | 1455 ECGs for the training set and 387 ECGs from new individuals for the validation set | DNN | Accuracy 72.4% for cardiologists and 88.4% for AI<br>AUC 72.2% for cardiologists and 93.4% for AI<br>Specificity 73.0% for cardiologists and 93.6% for AI<br>Sensitivity 71.5% for cardiologists and 85.4% for AI<br>NPV 81.3 for cardiologists and 88.6% for AI<br>PPV 60.9% for cardiologists and 87.9% for AI |
| 2023 | Zanchi [47] | A total of 33,420 P-waves were obtained from 5 minutes of ECG recordings from 123 individuals (79 BrS+ and 44 BrS-) | KNN, SVM, DT, RF, AdaBoost, GBoost, Majority Voting, Stacking, and Bagging | Accuracy 81.4%<br>Sensitivity 86%<br>Specificity 73% |
| 2024 | Vozzi [38] | Group A: 87 spontaneous type1 BrS<br>Group B: 36 drug induced type1 BrS<br>Group C: 14 BrS negative drug challenge test<br>Group D: 169 controls | ESN | Accuracy 88.0% For cardiologists and 91.5% for AI<br>Sensitivity 86.09% For cardiologists and 87.0% for AI<br>Specificity of 89.1% For cardiologists and 94.5% for AI<br>PPV 84.2% For cardiologists and 91.4% for AI<br>NPP 91.1% For cardiologists and 91.5% for AI |

AI, artificial intelligence; AUC, area under the curve; BrS, brugada syndrome; CNN, convolutional neural network; DCNN, deep convolutional neural network; DNN, deep neural network; DT, decision tree; ECG, electrocardiogram; ESNs, echo state networks; KNN, K-nearest neighbor; LSTM, long short-term memory; MLT, multi-task learning; NPV, negative predictive value; PPV, positive predictive value; RBBB, right bundle branch block; RF, random forest; SVM, support vector machine.

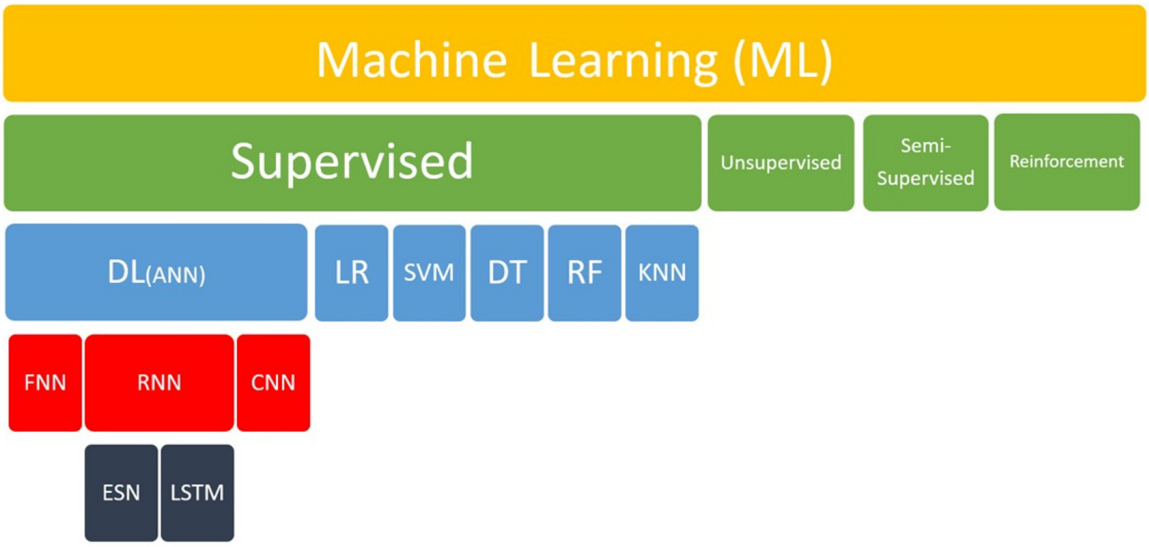


**Figure 2.** Classification of machine learning models utilized in Brugada syndrome Diagnosis. CNN, convolutional neural networks; DL, deep learning; DT, decision tree; ESN, echo state network; FNN, feedforward neural network; KNN, K-nearest neighbor; LSTM, long short-term memory; LR, logistic regression; RF, random forest; RNN, recurrent neural networks; SVM, support vector machine.

most common methods for classification and risk prediction of cardiovascular diseases. It is a method where the algorithm learns from labeled training samples to classify and make predictions about the test dataset. Deep learning (DL), logistic regression, support vector machine, decision tree, random forest, and K-nearest neighbor are some of the supervised machine learning models [17]. In contrast, Unsupervised machine learning explores unlabeled data to find patterns and generative features without human supervision [20].

DL is a special field of artificial intelligence that demonstrates superior performance compared to other machine learning methods in learning from large and unstructured datasets [18, 21, 22]. DL basis originated from artificial neural networks [23], a subsidiary of supervised ML. Artificial neural network algorithms imitate the natural neural network architecture and function of the human nervous system [24]. They process the input data through interconnected nodes, organized into three layers-input, hidden, and output [25]. Feedforward neural networks, recurrent neural networks, and convolutional neural networks (CNN) are some of the most common algorithms of artificial neural networks. Feedforward neural networks are typically applied for simple tasks, while recurrent neural networks and CNN are recruited to analyze more complicated data. CNN is specific for image recognition by utilizing the two-dimensional structure of input data and is capable of extracting distinctive features without human intervention. On the other hand, recurrent neural networks such as Echo State Networks (ESN) and Long Short-Term Memory (LSTM) primarily analyze sequential data, such as time series and sentence comprehension [26-29].

Ensemble learning is a machine learning technique that solves machine learning problems by combining the strengths of multiple inducers [30]. It utilizes methods like bagging and boosting to enhance predictive accuracy. Bagging improves stability through diverse model training while boosting sequentially corrects errors, refining overall performance iteratively. Random forest is an example of a bagging method, while Adaptive boosting (AdaBoost), boosted decision trees, and gradient boosting machine (GBoost) are examples of boosting methods (**Figure 3**) [31].

## Artificial intelligence in diagnosis of Brugada syndrome

A significant proportion of BrS patients remain asymptomatic until a major cardiovascular event occurs as their first clinical manifesta-

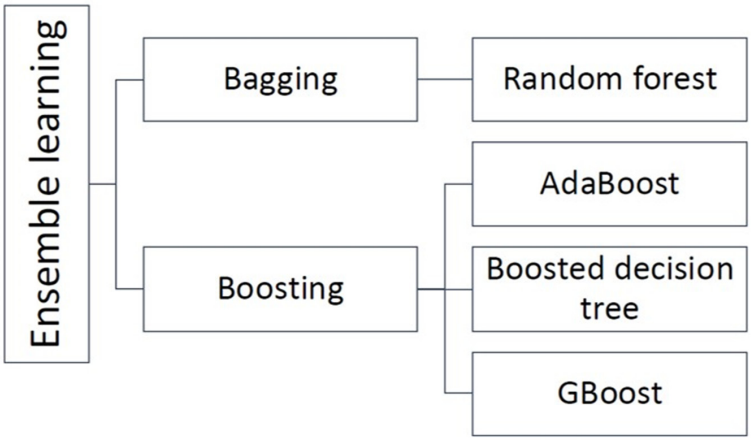


**Figure 3.** Classification of ensemble learning techniques.

tion. Consequently, timely detection is imperative to prevent sudden death that mainly involves young adults. The diagnosis of BrS relies on ECG, an affordable, noninvasive, and readily available method. However, the rarity of BrS has made its diagnosis a challenging and elusive task that increases the risk of misdiagnosis, as some physicians may not discern the Brugada pattern on ECGs. Consequently, the syndrome may be overshadowed by more common conditions that exhibit similar ECG patterns [32].

Recently, AI has aided humans in various domains and has made significant improvements in the field of cardiovascular medicine [33]. In order to apply machine learning for BrS detection, a new method was used for ECG analysis in 2020, combining waveform data from ECG signals with machine learning algorithms to detect mutations in the SCN5A gene of mice. Features were extracted using ECG intervals and amplitudes, along with a novel mathematical method that involved plotting the ECG data to create 2-dimensional pictures. They achieved a high accuracy rate of 96% by using their novel mathematical method as input data for K-nearest neighbor and Support Vector Machine to detect SCN5A mutation [34].

In 2021, Morales proposed the BrAID study protocol (Brugada syndrome and Artificial Intelligence applications to Diagnosis), designed in 3 parts. Part A was a retrospective cohort that aimed to train ML in diagnosing BrS type 1 pattern on ECG. This cohort utilized 300 ECGs collected from spontaneous BrS patients, suspected BrS patients, and healthy controls. This part aimed to create a novel diagnostic strategy for BrS recognition and assist physicians in the diagnosis of Type 1 BrS at an earlier point and reduce the SCD rate. Part B aimed to create a well-developed risk stratification system by utilizing ML methods, and part C was performed for a validation study [35].

Based on the BrAID platform, a study employed 156 ECGs (88 patients and 68 healthy individuals) with the application of ESNs for BrS detection. The researchers set the first baseline for detecting BrS using ECG signals. The best results were achieved in the validation phase using V2 lead of ECG as input, achieving a promising test accuracy of 76.9% [36]. Next year, they improved the performance of their ESNs in a study with a larger dataset of 306 ECGs, extracting input data from 4 beats, and achieved an accuracy of 80.2% by exclusively utilizing data extracted from the V2 lead [37]. In 2024, they further expanded their work and made significant enhancements to their ESN performance. They divided the study population into four groups: spontaneous type 1 BrS, drug-induced BrS, BrS negative individuals, and a control group (**Table 1**). Using a single beat extracted from the V2 lead as input, they trained and evaluated the ESN model. The model demonstrated a higher accuracy in discriminating type 1 BrS patterns compared to four trained electrophysiology cardiologists (91.5% vs. 88.0%). Additionally, the machine learning model surpassed expert clinicians in sensitivity and specificity (**Table 1**). Their machine learning approach shows promise as a diagnostic tool for clinical practice, potentially enhancing its performance when exposed to larger datasets [38].

Owing to the rarity of BrS, the challenge in previous studies was the limited and insufficient dataset size. To address this issue, Liu used LSTM, CNN, and multi-task learning technique to employ a two-stage deep learning analysis. In the first stage, they trained the source network on a larger dataset of a more prevalent

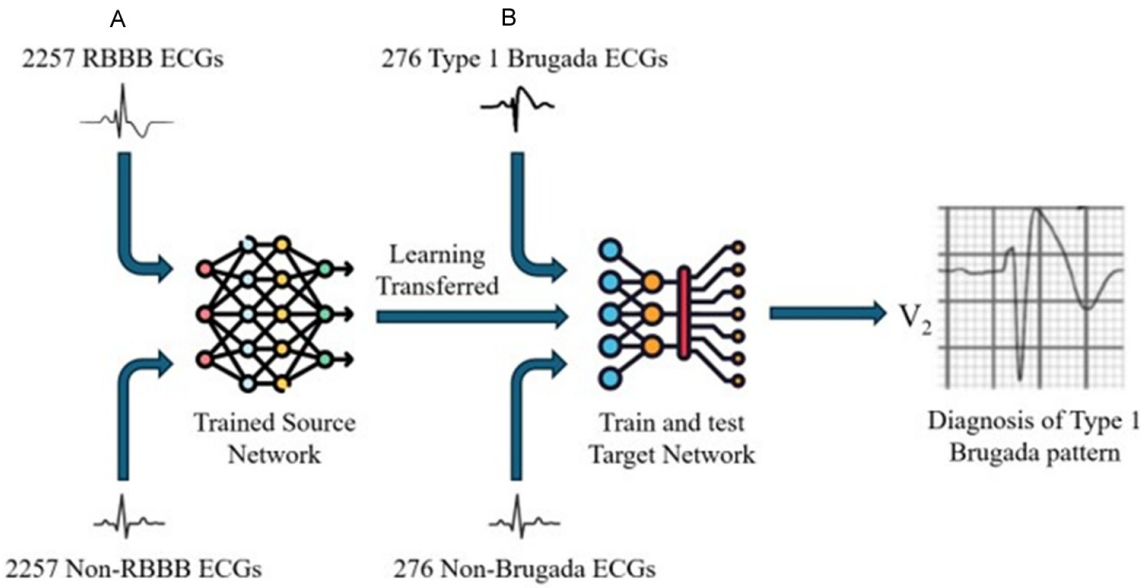


**Figure 4.** A: RBBB ECGs were utilized to train the source network; B: The target network used the learning in the first step along with a dataset of type 1 Brugada ECGs for diagnosis of type 1 Brugada syndrome.

condition. They selected right bundle branch block (RBBB) ECGs due to the similar morphological ECG pattern of RBBB to type 1 BrS. The dataset consisted of 2257 RBBB ECGs and an equal number of non-RBBB ECGs. Subsequently, they transferred the knowledge gained from the source network to a target network. The target network was then trained and tested using a smaller dataset of 552 ECGs for BrS detection, with half of them (276 ECGs) displayed type 1 Brugada pattern, which resulted in a significant enhancement in diagnostic performance (**Figure 4**). The model presented in this study demonstrated excellent performance, with an area under the curve (AUC) of 96%, a sensitivity of 88.4%, and a specificity of 89.1%. Furthermore, the consistency of DL and cardiologists with a standard diagnosis was evaluated and quantified by kappa coefficient. DL outperformed board-certified cardiologists (kappa coefficient: 78% vs. 63%) [39]. Subsequently, Liao made a significant advancement towards providing a reliable and scalable screening method by applying deep learning algorithms to wearable ECG monitoring technology. Their novel approach successfully detected spontaneous type 1 syndrome in 48% of patients who were previously categorized as procainamide-induced and in 33% of those with suspected disease-preventing potential cases from going undiagnosed. Subsequently, they applied a CNN method exhibiting strong performance with an AUC of 97% for distinguishing Brugada type 1 on both 12-lead ECGs and 12-lead Holter recordings. Compared with cardiologists, it presented the same level of accuracy but a higher level of specificity (97% vs. 90%). They also took an innovative step to enhance risk prediction of malignant arrhythmias in BrS patients. The DL model allows for spontaneous BrS type 1 signature detection, recognized as the gold standard prognostic factor in these individuals [40].

Another research aimed to enhance the interpretability of CNN models in diagnosing BrS from ECG time series data. In the first step, the researchers evaluated the CNN model for the detection of BrS using a dataset of 306 ECGs obtained from the BrAID project. Next, they applied Gradient-weighted Class Activation Mapping (a method used for creating visual explanations for CNN decisions) to understand how CNN identifies BrS patients [41]. The proposed approach introduces a tool for visualizing and understanding specific areas within the ECG time series that contribute to the diagnosis of BrS. The model achieved superior performance compared to the previous works of the researchers with an accuracy of 90.5%, specificity of 92.3%, and sensitivity of 87.7% [36, 37, 42].

In a recent study, researchers developed a deep convolutional neural network to predict the appearance of the BrS type 1 signature before the administration of ajmaline. The model was trained on ECG tracings from baseline and during ajmaline infusion from a total of 1188 patients. Results showed that the machine learning model successfully identified BrS type I patterns during ajmaline administration with an AUC of 94.5%. The model predicted the appearance of BrS type 1 pattern on ECG before the administration of a sodium channel blocker with an AUC of 80.5%, reducing the need for invasive drug challenge procedures, as 55-70% of all BrS patients are drug-provoked [43].

Another research group developed a DNN to detect the BrS pattern on ECG without the administration of a sodium channel blocker. The machine learning model was trained and validated using two separate cohorts. The internal validation cohort comprised 370 subjects, while the external validation cohort consisted of 110 subjects. In the validation cohorts, their multivariate machine learning algorithm demonstrated a sensitivity of 79.6%, specificity of 93.6%, accuracy of 88.4%, and an AUC of 93.4% for classifying ECGs indicative of BrS. Additionally, the DNN model accurately detected the BrS pattern in all spontaneous BrS patients, achieving a perfect 100% accuracy rate [44]. Afterward, they extended their work and created a DNN model capable of detecting the subtle BrS pattern on ECG, unrecognizable by the human eye. Unlike traditional approaches that rely on the administration of sodium channel blockers, the researchers enabled a machine-learning algorithm to analyze clinical ECGs without the need for provocative drug challenges. The DNN model was trained on noise-free single heartbeats from a dataset of 1455 ECGs and demonstrated significant performance in validation datasets. In comparison to a highly experienced cardiologist, the DNN exhibited superior accuracy, achieving 88.4% compared to 72.4% and a higher AUC of 93.4% compared to 72.2%. Notably, a trained clinical resident achieved only an AUC of 58.2% in the classification of ECG data for BrS. This non-invasive method has the potential to screen for BrS without the associated risks of proarrhythmic side effects from drug challenge tests with even higher sensitivity and specificity compared to the trained cardiologists, presenting a significant advancement in diagnosing the electrophysiological signature of BrS [45].

Recent research has found that individuals with BrS exhibit changes in their atrial characteristics, including abnormal P-wave parameters [46]. Additionally, there is evidence of a mismatch between atrial and ventricular ECG phenotypes, with abnormalities in P-waves being present even without obvious Brugada type 1 ECG patterns. In a recent 2023 study, researchers successfully employed a machine-learning model to diagnose BrS patients solely based on the characteristics of P-waves. They recorded continuous 5-minute 12-lead ECGs containing 33,420 P-waves from a total of 123 individuals, with about two-thirds being BrS positive. The ECG signals were processed and segmented into 15-second epochs within which P-waves were identified and averaged. From 80% of these averaged P-waves (2,228), 67 features were extracted and recruited to train nine supervised machine learning models. The remaining 20% of averaged P-waves were reserved for the testing phase. The study also revealed that the P-wave duration in BrS patients is relatively longer compared to healthy controls (136 ms vs. 124 ms). BrS patients also exhibited higher terminal force in lead V1 (2.5 au vs. 1.7 au). The AdaBoost model demonstrated the highest performance among the nine machine learning models, achieving an accuracy of 81.4%, a sensitivity of 86%, and a specificity of 73%. These findings open new horizons in novel diagnostic approaches for identifying BrS, extending them beyond solely examining ventricular abnormalities and considers atrial features as well [47].

### Artificial intelligence in classification of Brugada syndrome gene variants

As mentioned, BrS is an autosomal dominant genetic disorder with variable expressivity and incomplete penetrance [6]. Currently, 23 genes are implicated in BrS, with the SCN5A gene being the most prevalent, accounting for 20-30 percent of cases [7]. SCN5A gene variants include benign, likely benign, conflicting interpretation, pathogenic, likely pathogenic, and variants of uncertain significance (VUS). Notably, VUS comprises the majority of these variants [48].

There has been a substantial increase in identifying genetic variants in cardiac disease, including BrS, presenting both significant gains and challenges in understanding the clinical relevance of VUS [48]. Identifying pathogenic rare variants and VUS continues to be a key focus in gene interpretation. Identifying pathogenic variations and addressing VUS continues to be a key focus in clinical genome interpretation. In cardiovascular medicine, AI techniques are employed to uncover new genotypes and phenotypes. For instance, one study delved into the functional effects of missense variants in voltage-gated sodium and calcium channels. Utilizing machine learning, researchers successfully predicted likely pathogenic variants, achieving an AUC of 85% [49].

In another investigation, a disease-specific variant classifier was introduced known as CardioBoost. This tool determines the likelihood of pathogenicity of rare missense variants in inherited cardiomyopathies and arrhythmias. It demonstrated remarkable accuracy (precision-recall [AUC] of 96% for inherited cardiac arrhythmias) in variant discrimination, with up to 24% improvement from existing methods. It also achieved an accuracy of 91.9% in variant classification [50]. Furthermore, an adaptive rule-based classifier was designed using Decision tree and K-nearest neighbor algorithms for the classification of biological data. The classifier performance was tested on 148 Exome data sets from BrS. It accurately classified 91% of BrS gene variants [51]. These studies collectively illustrate the growing importance of AI-driven approaches in unraveling the complexities of genetic variations within cardiovascular medicine, ultimately advancing our understanding and clinical management of these diseases.

### Machine learning for Brugada syndrome classification using iPSC-CMs

Detecting and characterizing abnormalities in calcium cycling is crucial for understanding arrhythmias linked to cardiac disorders. This is significant for identifying patient phenotypes and enhancing recognition and diagnosis of cardiac diseases. Induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) play a vital role in recent studies of genetic cardiac diseases as an effective experimental platform for modeling cardiac function and various cardiac abnormalities [52, 53]. While several studies have employed iPSC-CMs to classify various inherited cardiac arrhythmias, there is a notable absence of research utilizing ML to analyze data extracted from iPSC-CMs to distinguish pathogenic mutations and offer a risk stratification system based on genotype and phenotype, tailored for BrS. In a recent study, researchers explored the complexity of data involving calcium transient signals obtained from iPSC-CMs. They utilized random forests, feedforward artificial neural networks, and K-nearest neighbor searching to classify seven inherited cardiac disease classes along with healthy controls. These diseases included hypertrophic cardiomyopathy, dilated cardiomyopathy, long QT syndrome type 1 and 2, BrS, and catecholaminergic polymorphic ventricular tachycardia. By analyzing calcium transient signals, the researchers successfully classified the genotype of all of the tissue donors of iPSC-CMs using machine learning techniques. Random forests yielded the highest classification accuracies, reaching 68% for all eight classes and an average sensitivity of 69.3% for BrS classification [54]. Similarly, iPSC-CMs and machine learning techniques were leveraged in a related investigation to classify different inherited cardiac diseases and healthy controls based on calcium transient signals. The study employed 55 different machine learning algorithms with the highest classification accuracy approaching 69% via Random forests. These two studies underscore the valuable insights provided by iPSC-CMs into disease mechanisms and highlight the promising potential of machine learning approaches in disease classification [55].

### Discussion

In recent years, the use of AI in healthcare has grown rapidly. The majority of studies in the literature focus on analyzing ECG for the detection of BrS. Supervised ML, particularly DL, is the most commonly utilized model for detection of BrS. Studies employing CNNs and DNNs achieved higher accuracy and efficiency in detecting BrS. Diagnosing BrS presents challenges including the intermittent presence of BrS patterns on ECGs. Researchers have attempted to overcome these issues by using innovative approaches like the utilization of

24-hour Holter monitoring, which has resulted in about a 30% increase in diagnostic accuracy [56]. We should highlight the potential challenge of small dataset sizes due to the rarity of BrS cases. To address this issue, a more prevalent pathology similar to BrS was recruited to train the machine learning model. This strategy has notably improved the diagnostic performance of BrS [39]. There is a shortage of studies that gather data from multicenter databases. As a result, the validation of findings and the applicability of AI in real-world scenarios remain uncertain. It is essential for these approaches to be validated in larger-scale clinical studies to ensure their reliability and generalizability [15].

There is a great potential for improving BrS management and increasing life expectancy of these patients given AI significant achievements in timely diagnosis of BrS. There are challenges in analyzing genomic data due to its high dimensionality and inconsistency. Despite the increasing number of studies employing machine learning to interpret complex genetic information, there remains a lack of research focused on using machine learning models to identify pathogenic variants and VUS in BrS [51]. However, from the clinical point of view, studies have consistently shown that ML algorithms, trained on vast datasets of ECGs, exhibit superiority in all performance metrics including accuracy, AUC, sensitivity, specificity, negative predictive value, and positive predictive value compared to even highly experienced cardiologists [38, 40, 45, 57]. Machine learning capability to analyze substantial volume of ECGs, discriminate crucial data beyond human visual capacity in ECG readings. Its integration with wearable ECG technology has the potential to become a reliable and cost-effective clinical support tool for automated diagnosis and monitoring of BrS patients. Due to high specificity that exceeds 90%, AI technology minimizes the likelihood of false-positive diagnoses that can be emotionally taxing for patients and their families [39, 56]. Moreover, it seems that the ML models will be sensitive enough to decrease the rate of misdiagnosed BrS patients in the future. Recent research suggests that machine learning models can effectively identify BrS based solely on abnormal P-waves. It showcases a promising step forward by illustrating the possibility of examining atrial features alongside the ventricular characteristics [47]. In the future, by applying ML we might be able to develop guidelines for BrS detection and detect patients before the use of invasive drug tests and even eliminate them [43].

Generally, the AI models initially could not exceed the human eye; however, with the development of improved algorithms, their diagnostic abilities could compete the cardiologists.

It seems DL brings about the most desirable results among the various AI algorithms. The best accuracy obtained so far by DL is 91.5% versus 88% for trained experts in Brugada syndrome diagnosis. The specificity of AI models for diagnosing Brugada syndrome often excels their sensitivity by 5.12% on an average basis; however, even its apparently lower sensitivity outperforms an expert eye. Consequently, it seems that AI can potentially be used in clinical settings as a reliable assistant for clinicians.

It is plausible that in the future, by continuous improvement in AI models, the diagnostic pattern of Brugada syndrome and other aberrant cardiovascular ECGs can be added to monitoring devices or Holter, so any abnormalities in the records can be recognized and reported automatically and practically instantaneously.

The importance of this potentiality is especially highlighted for rare cardiac arrhythmias, which are lethal and more likely to be overlooked or misdiagnosed. Although the integration of AI algorithms into monitoring and recording devices may be expensive, the decreased burden of disease and the number of deaths that are prevented might justify the costs.

## Limitation

The difficulty in comparing the study results due to the utilization of diverse metrics and heterogeneity of ML methods, was a limitation in our review.

## Conclusion

Machine learning can detect BrS without the use of invasive provocative tests with even higher accuracy, sensitivity, and specificity compared to trained cardiologists.

By overcoming data complexity, AI can identify unclassified genetic variants and perform a

precise analysis of complex data from iPSC-CMs, which enhances disease understanding, patient phenotyping, and personalized treatment strategies for BrS.

## Disclosure of conflict of interest

None.

## Abbreviations

AI, artificial intelligence; AUC, area under the curve; BrS, Brugada syndrome; CNN, convolutional neural network; DL, deep learning; DNN, deep neural network; ECG, electrocardiogram; ESNs, echo state networks; iPSC-CMs, induced pluripotent stem cell-derived cardiomyocytes; LSTM, long short-term memory; ML, machine learning; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia; VUS, variants of uncertain significance.

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## References

[1] Antzelevitch C and Patocskai B. Brugada syndrome: clinical, genetic, molecular, cellular, and ionic aspects. Curr Probl Cardiol 2016; 41: 7-57.

[2] Brugada P and Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome: a multicenter report. J Am Coll Cardiol 1992; 20: 1391-1396.

[3] Vutthikraivit W, Rattanawong P, Putthapiban P, Sukhumthammarat W, Vathesatogkit P, Ngarmukos T and Thakkinstian A. Worldwide prevalence of Brugada syndrome: a systematic review and meta-analysis. Acta Cardiol Sin 2018; 34: 267-277.

[4] Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C and Van Veldhuisen DJ; Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Europace 2015; 17: 1601-1687.

[5] Cerrone M, Costa S and Delmar M. The genetics of Brugada syndrome. Annu Rev Genomics Hum Genet 2022; 23: 255-274.

[6] Sebastian SA, Panthangi V, Sethi Y, Padda I, Khan U, Affas ZR, Mareddy C, Dolack L and Johal G. Precision medicine and cardiac channelopathies: human iPSCs take the lead. Curr Probl Cardiol 2023; 48: 101990.

[7] Zhao Y, Jiang D and Xia Y. Epigenetic and transcriptional networks underlying ventricular and atrial arrhythmias. Front Cardiovasc Med 2022; 9: 978891.

[8] Lee S, Zhou J, Chung CT, Lee ROY, Bazoukis G, Letsas KP, Wong WT, Wong ICK, Mok NS, Liu T, Zhang Q and Tse G. Comparing the performance of published risk scores in Brugada syndrome: a multi-center cohort study. Curr Probl Cardiol 2022; 47: 101381.

[9] Aziz HM, Zarzecki MP, Garcia-Zamora S, Kim MS, Bijak P, Tse G, Won HH and Matusik PT. Pathogenesis and management of Brugada syndrome: recent advances and protocol for umbrella reviews of meta-analyses in major arrhythmic events risk stratification. J Clin Med 2022; 11: 1912.

[10] Benito B, Brugada J, Brugada R and Brugada P. Brugada syndrome. Rev Esp Cardiol 2009; 62: 1297-1315.

[11] Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K and Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. Circulation 2002; 105: 73-78.

[12] Hanna EB and Glancy DL. ST-segment elevation: differential diagnosis, caveats. Cleve Clin J Med 2015; 82: 373-384.

[13] Chutani S, Imran N, Grubb B and Kanjwal Y. Propafenone-induced Brugada-like ECG changes mistaken as acute myocardial infarction. Emerg Med J 2008; 25: 117-118.

[14] Satapathy P, Pradhan KB, Rustagi S, Suresh V, Al-Qaim ZH, Padhi BK and Sah R. Application of machine learning in surgery research: current uses and future directions - editorial. Int J Surg 2023; 109: 1550-1551.

[15] Haug CJ and Drazen JM. Artificial intelligence and machine learning in clinical medicine, 2023. N Engl J Med 2023; 388: 1201-1208.

[16] Schwab K. The fourth industrial revolution: what it means, how to respond 1. In: editors.

Handbook of Research on Strategic Leadership in the Fourth Industrial Revolution. Edward Elgar Publishing; 2024. pp. 29-34.
[17] Ahsan MM, Luna SA and Siddique Z. Machine-learning-based disease diagnosis: a comprehensive review. Healthcare (Basel) 2022; 10: 541.
[18] Sarker IH. Machine learning: algorithms, real-world applications and research directions. SN Comput Sci 2021; 2: 160.
[19] Gao K, Mei G, Piccialli F, Cuomo S, Tu J and Huo Z. Julia language in machine learning: algorithms, applications, and open issues. Computer Science Review 2020; 37: 100254.
[20] Lopes N and Ribeiro B. Machine learning for adaptive many-core machines-a practical approach. Springer; 2015.
[21] Shiri FM, Perumal T, Mustapha N and Mohamed R. A comprehensive overview and comparative analysis on deep learning models: CNN, RNN, LSTM, GRU. arXiv preprint arXiv:2305.17473 2023.
[22] Liu W, Wang Z, Liu X, Zeng N, Liu Y and Alsaadi FE. A survey of deep neural network architectures and their applications. Neurocomputing 2017; 234: 11-26.
[23] Karhunen J, Raiko T and Cho K. Unsupervised deep learning: a short review. Advances in Independent Component Analysis and Learning Machines 2015; 125-142.
[24] Nichols JA, Herbert Chan HW and Baker MAB. Machine learning: applications of artificial intelligence to imaging and diagnosis. Biophys Rev 2019; 11: 111-118.
[25] Uddin S, Khan A, Hossain ME and Moni MA. Comparing different supervised machine learning algorithms for disease prediction. BMC Med Inform Decis Mak 2019; 19: 281.
[26] Krizhevsky A, Sutskever I and Hinton GE. ImageNet classification with deep convolutional neural networks. Communications of the ACM 2017; 60: 84-90.
[27] Wu H, Zhou Y, Luo Q and Basset MA. Training feedforward neural networks using symbiotic organisms search algorithm. Comput Intell Neurosci 2016; 2016: 9063065.
[28] Qiu X, Gao J, Yang J, Hu J, Hu W, Kong L and Lu JJ. A comparison study of machine learning (random survival forest) and classic statistic (cox proportional hazards) for predicting progression in high-grade glioma after proton and carbon ion radiotherapy. Front Oncol 2020; 10: 551420.
[29] Sarker IH. Deep cybersecurity: a comprehensive overview from neural network and deep learning perspective. SN Comput Sci 2021; 2: 154.
[30] Sagi O and Rokach L. Ensemble learning: a survey. Wiley Interdiscip Rev Data Min Knowl Discov 2018; 8: e1249.
[31] Mohammed A and Kora R. A comprehensive review on ensemble deep learning: opportunities and challenges. J King Saud Univ Comput Inf Sci 2023; 35: 757-774.
[32] Bleijendaal H and Wilde AAM. From a polish 3-year-old boy who visited maastricht to automatic detection using deep learning: brugada syndrome is being revolutionised. Can J Cardiol 2022; 38: 149-151.
[33] Siontis KC, Noseworthy PA, Attia ZI and Friedman PA. Artificial intelligence-enhanced electrocardiography in cardiovascular disease management. Nat Rev Cardiol 2021; 18: 465-478.
[34] Bonet-Luz E, Lyle JV, Huang CL, Zhang Y, Nandi M, Jeevaratnam K and Aston PJ. Symmetric projection attractor reconstruction analysis of murine electrocardiograms: retrospective prediction of Scn5a+/-genetic mutation attributable to Brugada syndrome. Heart Rhythm O2 2020; 1: 368-375.
[35] Morales MA, Piacenti M, Nesti M, Solarino G, Pieragnoli P, Zucchelli G, Del Ry S, Cabiati M and Vozzi F. The BrAID study protocol: integration of machine learning and transcriptomics for brugada syndrome recognition. BMC Cardiovasc Disord 2021; 21: 494.
[36] Giovanna Maria D, Claudio G, Alessio M, Morales MA, Emanuele U and Federico V. A preliminary evaluation of Echo State Networks for Brugada syndrome classification. 2021 IEEE Symposium Series on Computational Intelligence (SSCI) 2021; 01-08.
[37] Vozzi F, Dimitri G, Piacenti M, Zucchelli G, Solarino G, Nesti M, Pieragnoli P, Gallicchio C, Persiani E and Morales M. Artificial intelligence algorithms for the recognition of Brugada type 1 pattern on standard 12-leads ECG. Europace 2022; 24: euac053. 558.
[38] Vozzi F, Pedrelli L, Dimitri GM, Micheli A, Persiani E, Piacenti M, Rossi A, Solarino G, Pieragnoli P, Checchi L, Zucchelli G, Mazzocchetti L, De Lucia R, Nesti M, Notarstefano P and Morales MA. Echo state networks for the recognition of type 1 Brugada syndrome from conventional 12-LEAD ECG. Heliyon 2024; 10: e25404.
[39] Liu CM, Liu CL, Hu KW, Tseng VS, Chang SL, Lin YJ, Lo LW, Chung FP, Chao TF, Tuan TC, Liao JN, Lin CY, Chang TY, Shen-Jang Fann C, Higa S, Yagi N, Hu YF and Chen SA. A deep learning-enabled electrocardiogram model for the identification of a rare inherited arrhythmia: Brugada syndrome. Can J Cardiol 2022; 38: 152-159.
[40] Liao S, Bokhari M, Chakraborty P, Suszko A, Jones G, Spears D, Gollob M, Zhang Z, Wang B and Chauhan VS. Use of wearable technology and deep learning to improve the diagnosis of

Brugada syndrome. JACC Clin Electrophysiol 2022; 8: 1010-1020.
[41] Selvaraju RR, Cogswell M, Das A, Vedantam R, Parikh D and Batra D. Grad-CAM: visual explanations from deep networks via gradient-based localization. 2017 IEEE International Conference on Computer Vision (ICCV) 2017; Oct 22-29.
[42] Micheli A, Natali M, Pedrelli L, Simone L, Morales MA and Piacenti M. Analysis and interpretation of ECG time series through convolutional neural networks in Brugada syndrome diagnosis. Artificial Neural Networks and Machine Learning - ICANN 2023: 32nd International Conference on Artificial Neural Networks, Heraklion, Crete, Greece, September 26-29, 2023, Proceedings, Part IV. Berlin, Heidelberg: Springer-Verlag 2023; 26-36.
[43] Pannone L, Calburean PA, Monaco C, Della Rocca DG, Sorgente A, Almorad A, Bala G, Ramak R, Overeinder I and Ströker E. Recognizing and predicting drug-induced type I Brugada pattern using ECG-based deep learning. Circulation 2023; 148: A12631-A12631.
[44] Melo L, Ciconte G, Christy A, Vicedomini G, Anastasia L, Grant E and Pappone C. Abstract P3144: a deep neural network algorithm for accurate detection of Brugada syndrome features in electrocardiograms. Circulation Research 2023; 133: AP3144-AP3144.
[45] Melo L, Ciconte G, Christy A, Vicedomini G, Anastasia L, Pappone C and Grant E. Deep learning unmasks the ECG signature of Brugada syndrome. PNAS Nexus 2023; 2: pgad327.
[46] Conte G, Caputo ML, Volders PG, Luca A, Mairardi L, Schotten U, Corino VD, Regoli F, Zeemering S, Zink M, Yazdani S, Kappenberger L, Moccetti T, Vesin JM and Auricchio A. Concealed abnormal atrial phenotype in patients with Brugada syndrome and no history of atrial fibrillation. Int J Cardiol 2018; 253: 66-70.
[47] Zanchi B, Faraci FD, Gharaviri A, Bergonti M, Monga T, Auricchio A and Conte G. Identification of Brugada syndrome based on P-wave features: an artificial intelligence-based approach. Europace 2023; 25: euad334.
[48] Anderson CL, Munawar S, Reilly L, Kamp TJ, January CT, Delisle BP and Eckhardt LL. How functional genomics can keep pace with VUS identification. Front Cardiovasc Med 2022; 9: 900431.
[49] Heyne HO, Baez-Nieto D, Iqbal S, Palmer DS, Brunklaus A, May P; Epi25 Collaborative, Johannesen KM, Lauxmann S, Lemke JR, Møller RS, Pérez-Palma E, Scholl UI, Syrbe S, Lerche H, Lal D, Campbell AJ, Wang HR, Pan J and Daly MJ. Predicting functional effects of missense variants in voltage-gated sodium and calcium channels. Sci Transl Med 2020; 12: eaay6848.
[50] Zhang X, Walsh R, Whiffin N, Buchan R, Midwinter W, Wilk A, Govind R, Li N, Ahmad M, Mazzarotto F, Roberts A, Theotokis PI, Mazaika E, Allouba M, de Marvao A, Pua CJ, Day SM, Ashley E, Colan SD, Michels M, Pereira AC, Jacoby D, Ho CY, Olivotto I, Gunnarsson GT, Jefferies JL, Semsarian C, Ingles J, O'Regan DP, Aguib Y, Yacoub MH, Cook SA, Barton PJR, Bottolo L and Ware JS. Disease-specific variant pathogenicity prediction significantly improves variant interpretation in inherited cardiac conditions. Genet Med 2021; 23: 69-79.
[51] Farid DM, Al-Mamun MA, Manderick B and Nowe A. An adaptive rule-based classifier for mining big biological data. Expert Syst Appl 2016; 64: 305-316.
[52] Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K and Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007; 131: 861-872.
[53] Shah D, Prajapati C, Penttinen K, Cherian RM, Koivumäki JT, Alexanova A, Hyttinen J and Aalto-Setälä K. hiPSC-derived cardiomyocyte model of LQT2 syndrome derived from asymptomatic and symptomatic mutation carriers reproduces clinical differences in aggregates but not in single cells. Cells 2020; 9: 1153.
[54] Juhola M, Joutsijoki H, Penttinen K, Shah D and Aalto-Setälä K. A method to measure data complexity of a complicated medical data set. Int J Imaging Syst Technol 2022; 32: 1822-1831.
[55] Juhola M, Joutsijoki H, Penttinen K, Shah D, Pölönen RP and Aalto-Setälä K. Data analytics for cardiac diseases. Comput Biol Med 2022; 142: 105218.
[56] Karam CS and Akar FG. Modern day wearables to evade the widow-ghost in Brugada syndrome: from mythology to deep-learning methodology. JACC Clin Electrophysiol 2022; 8: 1021-1023.
[57] Dehkordi NR, Dehkordi NR, Toudeshki KK and Farjoo MH. Artificial intelligence in diagnosis of long QT syndrome: a review of current state, challenges, and future perspectives. Mayo Clin Proc Digit Health 2024; 2: 21-31.