

Research article

Echo state networks for the recognition of type 1 Brugada syndrome from conventional 12-LEAD ECG

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ABSTRACT

Artificial Intelligence (AI) applications and Machine Learning (ML) methods have gained much attention in recent years for their ability to automatically detect patterns in data without being explicitly taught rules. Specific features characterise the ECGs of patients with Brugada Syndrome (BrS); however, there is still ambiguity regarding the correct diagnosis of BrS and its differentiation from other pathologies.

This work presents an application of Echo State Networks (ESN) in the Recurrent Neural Networks (RNN) class for diagnosing BrS from the ECG time series.

12-lead ECGs were obtained from patients with a definite clinical diagnosis of spontaneous BrS Type 1 pattern (Group A), patients who underwent provocative pharmacological testing to induce BrS type 1 pattern, which resulted in positive (Group B) or negative (Group C), and control subjects (Group D). One extracted beat in the V2 lead was used as input, and the dataset was used to train and evaluate the ESN model using a double cross-validation approach. ESN performance was compared with that of 4 cardiologists trained in electrophysiology.

The model performance was assessed in the dataset, with a correct global diagnosis observed in 91.5 % of cases compared to clinicians (88.0 %). High specificity (94.5 %), sensitivity (87.0 %) and AUC (94.7 %) for BrS recognition by ESN were observed in Groups A + B vs. C + D.

Our results show that this ML model can discriminate Type 1 BrS ECGs with high accuracy comparable to expert clinicians. Future availability of larger datasets may improve the model performance and increase the potential of the ESN as a clinical support system tool for daily clinical practice.

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1. Introduction

Brugada Syndrome (BrS) is a hereditary arrhythmogenic disease with a peculiar electrocardiographic (ECG) pattern characterised by ST-segment elevation in V1–V3 leads and risk of sudden cardiac death [1]. The prevalence of BrS is believed to range from 1 in 5.000 to 1 in 2.000. It is responsible for 4 %–12 % of sudden deaths and up to 20 % of sudden deaths in patients with structurally normal hearts, and it is 8–10 times more prevalent in men than women. The currently accepted percentages of sudden cardiac death (SCD) due to BrS need to be updated as more data becomes available to establish the incidence of this syndrome in unexpected deaths in different populations [2].

At a clinical level, Type 1 BrS presents specific ECG pattern features, such as a coved ST-segment elevation of at least 2 mm (0.2 mV) followed by the negative T-wave in the three right precordial leads (V1–V3) [3]. Although these criteria have a broad consensus and should help clinicians in disease recognition, difficulties in ECG interpretations still exist due to the extreme variability of the ECG pattern that may change with time and during situations such as sleep, fever, and vagal stimulation [4,5]. One of the main difficulties is the absence of a clear cut-off value on which to base the diagnosis, in contrast to what is found for the long QT syndrome. The recognition of specific ECG patterns (coved aspect, typical of Type 1 and saddleback pattern) is challenging and may be hampered by the subjective evaluation of less skilled clinicians.

Although specific patterns are clearly described in scientific literature, different ECGs, even in the same subject, may present several modulations, often making the diagnosis questionable. Therefore, applying new Artificial Intelligence (AI) methodologies to identify BrS patterns in the ECG signal could significantly help clinicians to diagnose the disease.

Through an automatic analysis of the ECG time series, it is possible to overcome the variability of interpretation among clinicians and the possibility that the clearcut Brugada pattern on ECG analysis may be intermittent; in this condition, clinicians may therefore decide to induce the typical Brugada pattern through intravenous infusion of class I antiarrhythmic drugs (ajmaline or flecainide), antiarrhythmic drugs commonly used in clinical practice, to unveil hidden forms.

Based on these premises, the use of Machine Learning (ML) models and, more specifically, Deep Neural Networks (DNN) models could offer a valid clinical support system tool.

Several papers have focused on applying ML methodologies to detect cardiac arrhythmias [6–8]. In this field, a few benchmark datasets have been released, for example, the MIT-BIH Arrhythmia database [9], which has been widely used in several works related to ECG and cardiac disease applications of machine learning, although not considering the BrS [9–13].

In this work, we present an extension of the work presented in Ref. [14], which provided a preliminary analysis of the first part of the BrAID (Brugada syndrome and Artificial Intelligence applications to Diagnosis project) collected dataset, which consisted of a cohort of 156 patients. We increased the cohort (306 patients) and extended the experimental setting (providing a more extensive evaluation). In this experimental setting, we examined various input configurations of leads V1, V2, and V3, the reference leads used for diagnosing Type 1 BrS. Additionally, we explored different data normalisation techniques, including maximum absolute normalisation and temporal normalisation, where the time series length was fixed at 500 timesteps (1 s). This approach allowed us to investigate patterns independently of heart rate. Another noteworthy contribution of this study is comparing the ML approach results with the independent ECG-blinded classification performed by four cardiologists. Our proposed approach is based on the Echo State Network (ESN), which is well-suited for applications involving datasets composed of different time-series data (e.g., scanned paper and digital format ECGs) characterised by noise [15]. Specifically, compared to typical ML models, ESN allows us to develop an extremely efficient approach to estimate ECGs accurately by directly processing the whole time series without needing specific feature extraction and further feature pre-processing. Finally, we evaluated the ML model through robust double cross-validation (5 outer and 4 inner folds).

2. Methods

2.1. Study design and population

The BrAID study is a multicentric (5 clinical centres), not randomised, and retrospective study with a total of 306 patients enrolled (male 63 %, female 37 %). Subjects aged 14–75 years (inclusive, median age 48 ± 15) with spontaneous Type 1 BrS or a suspected BrS pattern were eligible to participate in the study. They were selected by clinicians of the 5 clinical centres who have access to their complete clinical history. The suspected BrS group was subjected to the pharmacological provocative test (ajmaline or flecainide, intravenous administration at a dosage of 1.0 and 2.0 mg/kg body weight, respectively) to uncover the BrS ECG pattern: if the Type 1 BrS pattern was visualised on the ECG, the patient was classified as positive. Patients with premature ventricular contractions, normal ventricular function, and a negative provocative test were selected for the control group. Subjects were excluded from the studies if they had any significant clinical medical history, including cardiac pathology. These concomitant diseases could invalidate the protocol, pregnancy, unstable angina, acute myocardial infarction, kidney disease, or liver disease. This study complied with the Declaration of Helsinki and was approved by the local Ethical Committee “Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana Sezione: AREA VASTA NORD OVEST”.

2.2. Definition of type 1 BrS syndrome and standard reference

We defined the Type 1 BrS syndrome according to the 2013 Heart Rhythm Society, European Heart Rhythm Association, and Asia Pacific Heart Rhythm Society expert consensus statement [16], the 2015 European Society of Cardiology guidelines [17], and the 2017

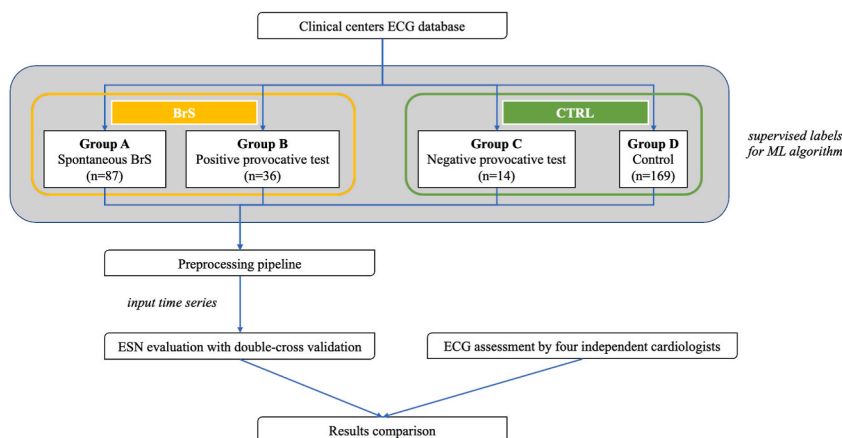


Fig. 1. Workflow of the implemented machine learning approach and comparison with clinical evaluation.

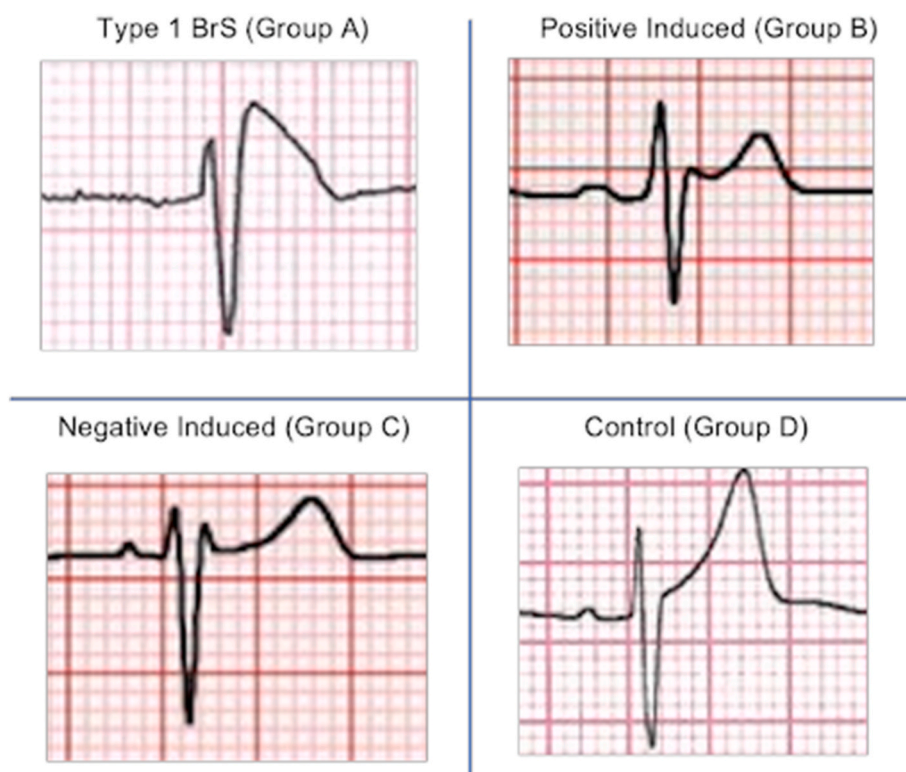


Fig. 2. Examples of 1 beat extracted from V2 leads for each of the 4 groups of individuals (Group A, B, C, and D).

American Heart Association guidelines [18]: a prominent coved ST-segment elevation with a J wave amplitude or ST-segment elevation >2 mm at its peak, followed by a negative T-wave, with little or no isoelectric separation in the right precordial leads (V1 to V3). For the provocative test, cardiologists from the BrAID clinical centres provided the ECG classification after the test.

To compare the performance of the ESN algorithm, the anonymised 12-leads ECGs were provided to four independent cardiologists trained in electrophysiology and not involved in the BrAID study, which independently evaluated and performed blinded classification into: spontaneous, suspected, and control. Cardiologist scores were presented as mean accuracy and compared to ESN. The interobserver agreement (Cohen's kappa statistic) was calculated for the classification of ECGs performed by the clinicians.

2.3. Data collection

306 conventional 12-lead ECG were collected from the clinical centres' database, as described in the flowchart (Fig. 1). For what

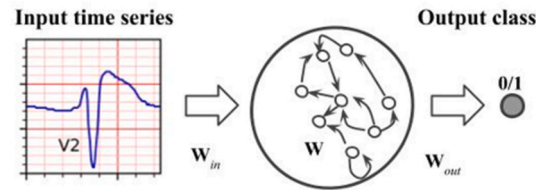


Fig. 3. An instance of ESN architecture fed by the ECG input signal.

concerns the V leads, these were placed in the standard positions: V1 in the 4th intercostal space, right of the sternum; V2 in the 4th intercostal space, left of the sternum; V3 between V2 and V4, V4 at 5th intercostal space in the nipple line.

Data was collected in scanned paper and electronic formats. After a clinical analysis of the patient at the time of recovery, the ECGs were divided into different sub-classifications by the cardiologists of the 5 clinical centres: 87 were spontaneous Type 1 BrS (Group A), 36 ECGs from patients with a Type 1 pattern after the provocative test (Group B), 14 without a Type 1 pattern after the provocative test (Group C), and 169 as Control group (Group D). This sub-classification process was required to define the labels for the ML algorithm task (Fig. 1).

The ECGs, collected in scanned paper and electronic formats, were pre-processed through a pipeline defined in Ref. [19]. The creation of the dataset for machine learning purposes was performed by the mentioned pre-processing pipeline, in which the data was treated by filtering, resampling, and interpolation to consider the heterogeneity of the ECG origin (several clinical centres), the type of ECG collected (electronic or scanned paper ECG), and the presence of noise and artefacts in the signal (see Ref. [19] for details). Several image processing filters were applied to reduce the source of noise from manual procedures. In particular, paper format ECGs were scanned by the clinical centre, and, to limit the loss of information during the extraction process, a second-order spline interpolation was used in combination with a 50 Hz Butterworth filter of order 2. Finally, each recording was resampled to a frequency of 500Hz with a single beat selected as suggested by clinicians to maintain a time window within a 1-s duration. Fig. 2 shows one beat extracted in V2 from individuals from the 4 groups considered in our study. As can be observed, the behaviour of the ECG differs significantly among the 4 groups, showing instances of the different waveforms obtained in the 4 cases. The pre-processing pipeline's time series extracted from the ECGs was used to train the ESN model [19,20].

Finally, the collected ECGs were reassessed by four blinded cardiologists to compare the results of their diagnosis with those of the ESN model.

2.4. ESN model development and validation

ESNs are a class of Recurrent Neural Networks (RNNs) implemented within the Reservoir Computing (RC) paradigm [19,20]. Fig. 3 shows an example of an ESN architecture that can classify the BrS class starting from the time series of the input ECG signal by using the V2 lead.

The input is fed with a sequence of temporal samples (the time series of the ECG). The values of the matrices W_{in} , W , and W_{out} in Fig. 3 represent the weights of the input, recurrent, and output layers, respectively. In ESN architectures, the non-linear recurrent layer is called the reservoir, aiming to encode and memorise the dynamic of the input signals. The reservoir weights are randomly initialised and left untrained. The weights initialisation is performed considering the Echo State Property (ESP) [21]. This property is needed to control the stability of the dynamical system represented by the reservoir. The output of the network is computed by a linear layer called readout. In this application, the model estimated a negative class if the output ≤ 0 and a positive class if the output is > 0 . The readout (represented by the output weight matrix W_{out}) was trained through regularised linear regression approaches. Since only the output layer (readout) is trained, ESNs are significantly more efficient than typical RNN approaches based on backpropagation through time (including LSTM models). In the experiments, the first step was to consider 3 input leads, V1, V2, and V3, the reference leads used to diagnose Type 1 BrS. In addition, the time series were normalised in the temporal dimension to have a fixed length of 500 timesteps (1 s), allowing us to investigate patterns independently of heart rate. Data analysis (data not shown) showed how V2 and temporal normalisation provided the best results for syndrome recognition. This work presented only the results achieved with this one as time series input for our model. Overall, the dataset used in this paper comprised a 306-time series of 1 dimension (lead V2) with a length of 500 timesteps (1 s of the ECG signal). In particular, 87 series belong to Group A, 36 to Group B, 14 to Group C, and 169 to Group D. For the BrS classification task, Group A + B was considered positive and Group C + D as negative classes.

The results were obtained by an ensemble of 5 random initialised instances of the ESN model using the lead V2 in input. The final ECG classification was obtained by taking the most frequent class estimated by the 5 instances of the ensemble. Finally, test results were obtained by the best model selected on the validation set through a robust double cross-validation approach with 5 external and 4 internal folds. The dataset was first randomly shuffled with uniform distribution and then split into 5 external folds (20 % of data in each test fold) for the double cross-validation. In this way, each test fold had a similar number of samples and a similar distribution of classes and ECG formats. As highlighted in Ref. [22], double cross-validation allowed us to perform a model selection in a robust way, especially in health informatics applications characterised by small datasets, as in this case. Table 1 shows the range of hyper-parameters used in the grid search for the double cross-validation for the model selection. Recurrent units are the number of units in the reservoir, the Spectral radius is the maximum absolute eigenvalue of the recurrent weight matrix, and it is initialised to control the

Table 1
Range of hyperparameters used in the grid search for the double cross-validation.

	Hyperparameters
Recurrent units	500, 1000, 1500, 2000
Spectral radius	0.999
Leaky integrator	0.1, 0.5, 1.0
Bias scaling	0.1, 0.5, 1.0
Input scaling	0.5, 1.0, 1.5
Regularisation	0.0001, 0.001, 0.01, 0.1, 1.0

Table 2

ECG distribution among the BrAID study groups. Type 1 BrS (Group A), positive to Type 1 pattern after the provocative test (Group B), negative to Type 1 pattern after the provocative test (Group C), Control (Group D).

	Group A	Group B	Group C	Group D
ECG (nr.)	87	36	14	169
	123		183	
ECG (%)	28.4	11.8	4.6	55.2
	40.2		59.8	

Table 3

The diagnostic performance achieved in the test set by the 4 Clinicians (average and each value) and the ESN model (in test folds) by using the V2 lead of the ECGs as input time series in the classification of Type 1 BrS (Confidence Interval (CI) in the brackets).

	Sensitivity (95 % CI)	Specificity (95 % CI)	Accuracy (95 % CI)	Positive Predictive Value (95 % CI)	Negative Predictive Value (95 % CI)	Likelihood Ratio
ESN	87.0 (79.9–91.8)	94.5 (90.2–97.0)	91.5 (91.5–91.5)	91.4 (85.0–95.3)	91.5 (86.7–94.7)	15.92
Clinicians	86.9 (79.9–91.8)	89.1 (83.7–92.8)	88.0 (87.9–88.0)	84.2 (76.7–89.5)	91.1 (86.0–94.4)	7.96
Clinician 1	86.9 (79.9–91.8)	86.3 (80.6–90.5)	86.6 (86.0–87.2)	81.0 (73.5–86.8)	90.8 (85.6–94.2)	6.37
Clinician 2	86.2 (78.9–91.2)	91.3 (86.3–94.5)	89.2 (88.6–89.8)	86.9 (79.7–91.8)	90.8 (85.7–94.1)	9.86
Clinician 3	85.4 (78.0–90.5)	88.5 (83.1–92.4)	87.3 (86.7–87.9)	83.3 (75.9–88.8)	90.0 (84.7–93.6)	7.44
Clinician 4	87.8 (80.8–92.5)	89.6 (84.3–93.2)	88.9 (88.3–89.5)	85.0 (77.8–90.2)	91.6 (86.6–94.9)	8.46

stability of the dynamical system [21], Leaky Integrator regulates the velocity of the dynamics in the case of leaky integrator ESNs [23], Bias scaling is the scalar value of the unit's input bias, Input scaling is the scalar multiplied by the input of the network, and Regularisation is the parameter of Tikhonov regularisation typically used in ESN readout [21]. [22].

The experimental assessment was implemented in Python 3.7.12. In particular, the ML model is implemented in TensorFlow 2.11.0, NumPy 1.21.6 and SciPy 1.7.3.

2.5. Statistical analysis

Categorical variables were presented as absolute numbers and percentages and were compared using the 2-way ANOVA test. The Area under the receiver operating characteristic Curve (AUC) was used as a metric [24]. The receiver operating characteristic (ROC) curve and the AUC for ESN models were computed with the Scikit-learn library. A two-tailed P-value <0.05 was considered significant for all tests [25]. The interobserver agreement (Cohen's kappa statistic) [26] was calculated with GraphPad Prism 9 (GraphPad Software, Boston, Massachusetts, USA, www.graphpad.com).

Sensitivity, specificity, and positive and negative predictive values were calculated using the clinicians' diagnosis as the gold standard. All the test results (accuracy, sensitivity, specificity, and positive and negative predictive values) achieved by the ML model were obtained through a double cross-validation approach using 5 external and 4 internal folds. In particular, the model hyperparameters were selected through the inner cycle of the double cross-validation, while the external cycle was used for the model assessment (test). This approach gave us a reliable estimation of the model extended to the whole data set.

3. Results

3.1. Dataset characteristics

The BrAID dataset (Table 2) included 40.2 % of ECGs with spontaneous and provoked Type 1 BrS patterns (Group A + B) the

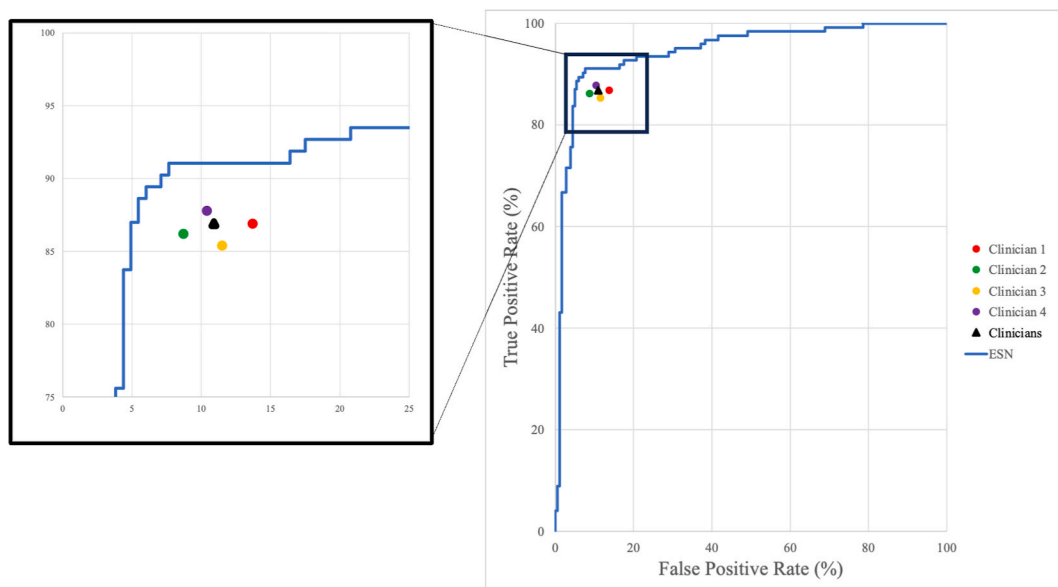


Fig. 4. The ESN ROC curve and the accuracy of Clinicians (each (●, ●, ●, ●) and average (▲) value) for diagnosing Type 1 BrS ECG. The ROC curve shows the True Positive Rate achieved by the ESN approach depending on the False Positive Rate.

Table 4

Accuracy of Clinicians (each and average value) compared to the accuracy obtained in test folds by ESN per single group.

	Clinician 1		Clinician 2		Clinician 3		Clinician 4		Clinicians (average)		ESN	
	Nr	%	Nr	%	Nr	%	Nr	%	Nr	%	Nr	%
Group A	76	87.4	73	83.9	75	86.2	74	85.1	75	85.6	76	87.4
Group B	31	86.1	33	91.7	30	83.3	34	94.4	32	88.9	31	86.1
Group C	10	71.4	12	85.7	11	78.6	11	78.6	11	78.6	10	71.4
Group D	148	87.6	155	91.7	151	89.3	153	90.5	152	89.8	163	96.4

remaining ECGs are those of controls (Group C + D). The dataset showed a well-balanced number of male and female patients in Group D.

3.2. ESN results

In this section, the results from the proposed approach were presented and compared with the labels predicted by only the ECG-based classification of 4 clinical electrophysiologists. Table 3 shows the performances (in test folds) achieved by the ESN model in the classification of Type 1 BrS of the whole dataset (Group A + B + C + D), starting from the V2 lead of the ECGs as input time series in comparison with the clinicians. Supplementary Material Table 1 presented the results of the BrAID ECG classification of each of the four clinicians and the ML model.

The ESN model correctly classified 280 out of 306 ECGs (91.5 %), with a performance of 3.6 points superior to clinicians (269/306, 88.0 %). ESN's sensitivity (87.0 % vs. 86.9 %) and specificity (94.5 % vs. 89.1 %) were comparable to or greater than those of clinicians (Table 2). The Positive and Negative Predictive values and the Likelihood ratio presented were higher for ML with respect to clinicians (15.92 vs. 7.96).

The same trend was observed for the AUC of ESN, which showed a greater value (94.77, 95 % CI: 93.8–96.3) with respect to the accuracy of each clinician and their average value (Fig. 4).

The interobserver coefficient (Cohen's kappa value) among the four cardiologists was evaluated, presenting an average value of 0.21, with slight agreement.

The subdivision of the BrAID population into the different groups allowed us to compare the performance of the ESN in the single sub-cohorts, as reported in Table 3. From the results, it was possible to observe comparable recognition of Spontaneous BrS (Group A, 87.4 % vs. 85.6 %) between clinicians (as average value) and ESN, and a strong recognition of the ESN model in Group D (96.4 % vs. 89.8 %). In the patients with suspected BrS, it was possible to observe how close the ESN model was to clinicians in the recognition of the syndrome (Group B) and the negative tests (Group C) (Table 4).

3.3. Study limitations

The present study has specific limitations. First, since the rare nature of the syndrome, it will be necessary to validate this model in a larger cohort of patients. This is important for the general BrS recognition and specific cases, such as those subjected to the provocative test, which requires a wider number of processed ECGs than those presented in this work. We have planned and is currently undertaking a patient recruitment campaign to validate this ESN approach further. Second, further studies are needed to investigate the integration of the different leads typically used in BrS diagnosis, especially V1, V2, and V3, possibly with specific characteristics of the ECG waves. Third, in our study, the prevalence of Type 1 BrS was lower (40.2 %) compared to controls (59.8 %), which may cause class imbalance, affecting sensitivity and generating a lower positive predictive value. To verify this aspect, the performance of our ESN model was compared with cardiologists with good results, as shown in Table 2 and Fig. 2.

4. Discussion

Artificial Intelligence and Machine Learning nowadays present the capability to extract latent information from 12-lead ECG, classify the presence of a specific disease and even predict a future disease [27]. For example, specific models and algorithms were developed to classify coronary artery diseases by using ECG [28], to estimate the prognosis and potentially guide therapy in adult congenital heart disease [29] and to diagnose arrhythmic syndromes as long QT syndrome [30].

At the same time, few studies have aimed to develop an ML system to recognise Type 1 BrS on ECG [31–33] due to the challenging and peculiar aspects of the syndrome: the variability of the pattern over time and under specific conditions (fever, sleep, vagal stimulation), the low prevalence in the population and the scarce availability of data. As a result, when BrS is suspected based on anamnestic data and/or controversial ECG, patients undergo a series of tests, including genetic profile analysis and pharmacological provocation, to uncover the diagnostic pattern.

In this work, we applied ML, namely an ESN-based algorithm, to recognise Type 1 BrS on conventional 12-lead ECG, intending to support clinicians in the diagnosis. The important finding was that ESN could discriminate BrS ECG with a diagnostic performance at least comparable to that of expert cardiologists.

The results of our study showed that the ESN system has a globally comparable recognition rate with respect to cardiologists: in particular, the ESN model has a high specificity (94.5 % vs. 89.1 %), which reduces the number of false positive cases, and sensitivity (87.0 % vs. 86.9 %) close to that of clinicians in the diagnosis of BrS.

Among the few available papers where a BrS dataset is analysed, Lee et al. analysed ECG markers and arrhythmic outcomes in BrS patients [13]. However, this work did not apply an ESN algorithm but was limited to analysing ECG markers and arrhythmic outcomes in BrS patients. In addition, a comparison was made between asymptomatic and high-risk but symptomatic patients, considering a previous clinical history of syncope or other ventricular cardiac diseases. The first paper, in which a deep learning approach based on an application of recurrent neural networks (in particular ESN) for the prediction of BrS from ECG signal, was presented in our preliminary work [14]. In the work, the authors showed preliminary results using a novel dataset collected within the BrAID project, built to provide an innovative system for early detection and classification of Type 1 BrS. The dataset consisted of 156 ECGs collected in scanned paper and electronic formats. In the paper, the authors described the thorough pre-processing applied to extract the signal from the scanned ECGs and the pre-processing dedicated to addressing the heterogeneity of the data available in the project. Several types of experiments were carried out to evaluate the best-performing ESN reservoir architecture, with the highest accuracy of 76.9 % achieved on the validation set, using the end-only V2 lead as input to the ESN. A second paper in the field where deep learning was applied to BrS is proposed by Liu [31], where the authors analysed 276 ECGs diagnosed as Type 1 Brugada. The approach used was based on the transfer learning technique. Specifically, the authors first trained a network to identify the right bundle branch block patterns, and the trained network was later used to diagnose BrS. The model was based on Convolutional Neural Networks (CNN) and Bidirectional Long Short-Term Memory (BiLSTM) and took the raw 12 leads ECG as input. Performances were then compared to the ones obtained by clinicians, and the model was also validated in an independent cohort from hospitals based in Taiwan and Japan. The authors obtained an AUC of 96.0 %, with a sensitivity of 88.4 % and a specificity of 89.1 %, confirming the results in the independent cohort analysed. Liao et al. applied Deep learning with another approach, based on a 1D CNN architecture inspired by the ResNet18 model, to detect BrS [32]. They showed the application of a CNN-based model able to predict the presence of BrS by using 12-h lead Holter and 12-lead ECG monitoring. The training cohort consisted of 51 BrS patients for the ECG and 10 BrS patients for the 12-lead Holter cohort, and 39 suspected BrS patients (induced with procainamide) for the 12-lead ECG monitoring. The authors reported an AUC of approximately 97.0 % for both experiments (with the Holter and the 12-lead ECG). To the best of our knowledge, no other deep-learning approaches for detecting BrS are in the literature.

Compared with the literature approaches, this work has presented an extensive model evaluation in the classification of Type 1 BrS using the ESN architecture, which can efficiently and accurately estimate ECGs by analysing the whole time series of the V2 lead without the need for specific feature pre-processing. In particular, the ESN model is suitable for this type of application, which is characterised by heterogeneous and noisy time series [15]. Moreover, as detailed in the Methods section, the ESN model was significantly more efficient than the typical neural networks based on backpropagation training algorithms [31,32]. From the point of view of model evaluation, the use of a double cross-validation approach allowed us to assess the model on the whole dataset (by means of test folds) with reference to the traditional hold-out approach, where the test set was represented by a subset of the dataset (using the test set) as performed in Refs. [31,32]. The results presented in Ref. [32] were not comparable to our approach since Liao et al. considered only a hold-out (not cross-validated) test set of 50 elements. Finally, although, again, the comparison could have a limited scope due to the use of different datasets and different cross-validation (less robust in the case of [31]), the sensitivity obtained by our

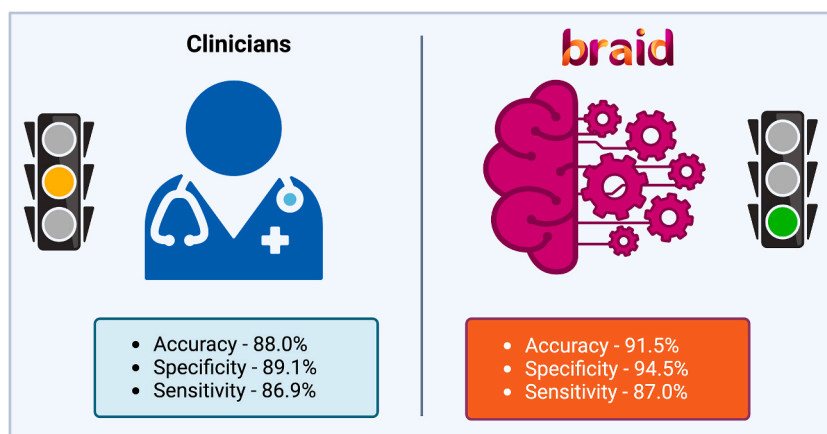


Fig. 5. Main results of the BrAID study and comparison with clinicians. Created with [BioRender.com](https://www.biorender.com).

model (87.0 %) was slightly worse (88.4 %). In comparison, the specificity obtained by our approach (94.5 %) was significantly better than [31] (89.1 %).

Regarding interobserver agreement among clinicians on the ECG evaluation, Cohen's kappa value obtained in this work was quite in line with what is reported in the literature [34,35]. These results explain the difficulties in the analysis of ECG for Brugada syndrome and the potential support ML solutions could provide in diagnosing the syndrome. Summarising, in this work, using the ESN models in the BrS recognition represents a novelty. However, there are few works regarding the analysis of BrS with ML, and it is still difficult to thoroughly compare the results with the literature. Compared to other works, we have obtained comparable results with respect to clinicians using a more robust approach (double cross-validation) to evaluate the ML model and address potential statistical biases. Furthermore, using the ESN model allows us to efficiently analyse time series data without manual pre-processing to extract ECG characteristics, which could be a source of domain expert bias. Taking these considerations into account, the proposed approach in this study represents a promising research direction, particularly when larger or publicly available datasets become accessible.

5. Conclusions

The comparison of the results of the present paper with those in the literature highlights the validity and capability of our approach to detect BrS from a standard ECG (Fig. 5).

To the best of our knowledge, this work also represents the first attempt to develop a system to recognise spontaneous BrS as subjects with suspected syndrome before provocative testing. The final aim is to provide reliable, rapid, and accurate support for the diagnosis of BrS provided by clinicians, limiting or avoiding the need for further diagnostic techniques.

Registration of clinical trials

The BrAID trial is registered on [ClinicalTrial.gov](https://clinicaltrials.gov) with the number NCT04641585 (November 24, 2020) by Dr Federico Vozzi.

Data availability statement

The relevant datasets analysed during the current study are available from the corresponding author upon reasonable request.

Declaration of Helsinki

The authors state that their study complies with the Declaration of Helsinki, that the locally appointed ethics committee has approved the research protocol and that informed consent has been obtained from the subjects (or their legally authorised representative).

CRedit authorship contribution statement

Federico Vozzi: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Luca Pedrelli:** Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. **Giovanna Maria Dimitri:** Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. **Alessio Micheli:** Conceptualization, Data curation, Investigation, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. **Elisa Persiani:** Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Marcello Piacenti:** Conceptualization, Data curation,

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Federico Vozzi reports financial support was provided by Tuscany Region.

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Appendix A. Supplementary data

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