Malaysian Journal of Medicine and Health Sciences (eISSN 2636-9346)

ORIGINAL ARTICLE

Optimal Paired Features from the O'Hara Rudy Dynamic (ORd) Ventricular Cell Model for Predicting Drug-Induced Cardiotoxicity

Vilinaa Murali[1], Asnida Abdul Wahab[1,2], Nor Nisha Nadhira Nazirun[1], Ali Ikhsanul Qauli[3,4], Ki Moo Lim[3,5]

[1] Department of Biomedical Engineering and Health Sciences, Faculty of Electrical Engineering, Universiti Teknologi Malaysia, Skudai 81310, Johor, Malaysia
[2] Medical Device Technology Center (MEDITEC), Universiti Teknologi Malaysia, 81310 UTM Johor Bahru, Johor, Malaysia
[3] Computational Medicine Lab (CML), Department of IT Convergence Engineering, Kumoh National Institute of Technology, 39177 Gumi, South Korea
[4] Department of Engineering, Faculty of Advanced Technology and Multidiscipline, Universitas Airlangga, 60115 Surabaya, Jawa Timur, Indonesia
[5] Department of Medical IT Convergence Engineering, Kumoh National Institute of Technology, 39177 Gumi, South Korea

ABSTRACT

Introduction: Sudden cardiac death, often triggered by ventricular tachycardia and fibrillation, is a significant public health concern. Due to cardiotoxicity, a major issue in pharmaceutical research is drug-induced Torsades de Pointes (TdP). The O'Hara-Rudy dynamic (ORd) model, a popular in silico ventricular cell model, is used to assess TdP risk from drugs, but relying on a single in silico biomarker may inaccurately classify drug risk. This study aims to find the optimal paired features from the ORd model to improve predictions of torsadogenic drug effects. **Materials and methods:** Utilizing a dataset of 12 drugs (24,000 samples, 14 features), leading to 91 feature pairs, their performance was evaluated using ordinal logistic regression (OLR). Accuracy and the area under the curve (AUC) were used to assess the discriminative power of the identified feature pairs. **Results:** *Catri and qInward* were found to be the most influential in determining drug risk categories, indicating these features as the optimal pair. Achieving an accuracy of 70% with excellent AUC values across risk categories, the pair demonstrates its efficacy in predicting torsadogenic risk. **Conclusion:** This finding can enhance the management of torsadogenic drug adverse effects through better preventive and treatment strategies. By focusing on the combined effects of the optimal feature pair, researchers can improve drug safety assessments and reduce the incidence of TdP in clinical settings.

Malaysian Journal of Medicine and Health Sciences (2025) 21(SUPP11): 95-101.doi:10.47836/mjmhs.21.s11.14

Keywords: ORd ventricular cell model, *In-silico* paired features, TdP risk, Drug-induced cardiotoxicity, Ventricular tachycardia

Corresponding Author:
Asnida Abdul Wahab, PhD
Email: asnida.aw@utm.my
Tel : +607-555 8452

INTRODUCTION

Sudden cardiac death poses a significant public health concern, primarily attributed to ventricular tachycardia (VT) and ventricular fibrillation (VF), resulting in an estimated 300,000 deaths annually in the United States alone (1). VT is strongly linked to coronary artery disease, affecting approximately 15% of patients with this condition. Long-QT syndrome, characterized by prolonged ventricular repolarization, contributes to VT, with Torsades de Pointes (TdP) emphasizing the severity of the condition (2,3). TdP is frequently induced by torsadogenic drugs, necessitating their withdrawal from the market. The issue of drug-induced TdP has become a major worry in this clinical setting, demanding a critical evaluation of pharmaceutical research and development initiatives. Cardiotoxicity is one of the main causes of drug termination during clinical trials due to its adverse effects (4,5). Concerning cardiotoxicity, a critical marker for events leading to sudden cardiac death, which also happens to be a persistent challenge in the drug developmental phase, is avoiding compounds that have a tendency to initiate TdP.

A new cardiac safety paradigm, known as the Comprehensive In Vitro Proarrhythmia Assay (CiPA), has the potential to improve drug research and development efforts as well as overcome the limitations of traditional assessment guidelines. It is based on an entirely novel set of nonclinical proarrhythmia evaluations, along with *in silico* predictive modeling of cellular electrophysiological effects (6). As part of the CiPA project, numerous researchers have proposed evaluation methods and TdP metrics to assess the proarrhythmic risk of drugs through *in silico* simulations.

In an effort to assess drug-induced TdP risk, Li et al. (7) proposed a methodology categorizing the risk level into high and low by employing a logistic regression model. This approach involved modifying the O'Hara-Rudy dynamic (ORd) ventricular cell model initially proposed by Dutta et al. (8), where human Ether-a-go-go-Related Gene (hERG) dynamics were integrated to generate *qNet* (7,8). The ORd model was primarily chosen for its exceptional ability to accurately simulate various aspects of action potential duration, such as early afterdepolarizations (EADs), action potential (AP), and calcium transient alternans. The significance of the ORd model lies in its ability to precisely replicate EADs and alternans, which are crucial processes in arrhythmogenesis. Additionally, it accurately reproduces the ionic currents within the human body.

Previous investigations mostly relied on deriving a single feature that was deemed highly correlated with TdP risk and obtained favourable results through binary classification methods (10). Despite these advancements, the reliance on a single *in silico* feature for categorizing drugs into the three TdP risk levels was acknowledged as a limitation, as it may not fully encompass the diverse factors contributing to TdP risk (7). Single biomarkers may be unable to capture the complex relationship of several parameters of cardiac electrophysiology (9). When considering just one biomarker, the interdependencies and complicated connections between numerous biomarkers must be handled thoroughly. This shortcoming can lead to an inaccurate understanding of drug-induced TdP risk, which can result in inaccurate and invalid classifications (10).

Moreover, current regulatory guidelines, including the S7B nonclinical evaluation and E14 clinical evaluation, primarily rely on two key biomarkers. These biomarkers are used to assess the risk of drug-induced TdP, which includes the blockage of the hERG channel and the prolongation of the QTc interval in humans (11). However, these biomarkers are considered unreliable indicators of TdP risk, as hERG channel blockage can be affected by interactions with other cardiac ion currents. Additionally, certain drugs, such as amiodarone, prolong the QTc interval but have a low risk of causing TdP. Following these guidelines requires complex testing, which increases sensitivity but reduces specificity in drug risk classification (6). Consequently, drugs that do not induce TdP may still face stringent regulations, market withdrawals, or halted development (12).

Therefore, this study aims to identify the optimal paired features derived from the ORd ventricular cell model to enable more accurate predictions and better management of torsadogenic drug-associated adverse effects. In particular, electrophysiological characteristics of the ORd Ventricular cell model, such as action potential duration, peak calcium influx, and repolarization dynamics, are paired and then trained using ordinal logistic regression (OLR) to enhance prediction accuracy for TdP risks.

MATERIALS AND METHODS

Identifying optimal paired features involves data pre-processing, paired feature selection, and performance evaluation, as shown in Figure 1.

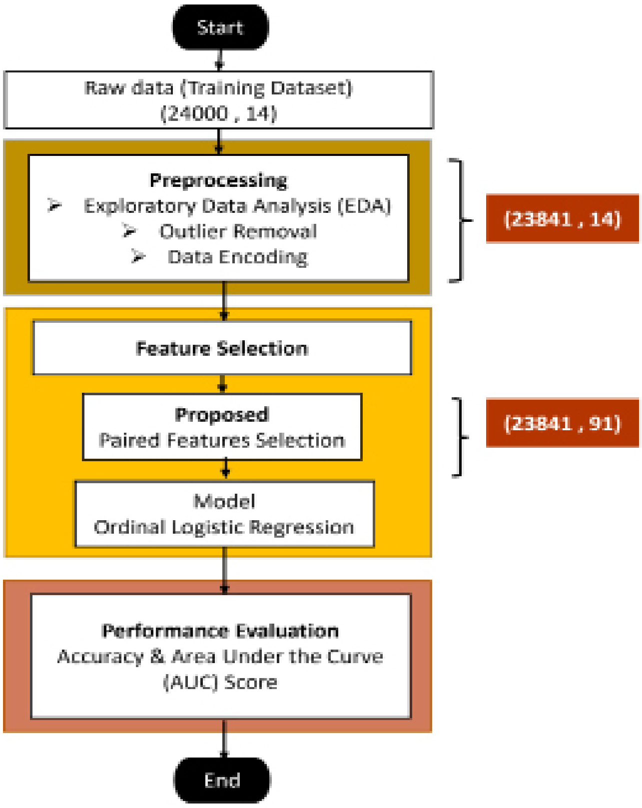


Figure 1: Overall flow of in silico **study protocol.**

Dataset description

Data pertaining to the ORd ventricular cell model, sourced from the Computational Medicine Laboratory at Kumoh National Institute of Technology (KIT), South Korea, was collected. This study utilizes 12 drugs aligned with the CiPA paradigm, each comprising 2000 samples, resulting in 24,000 data samples. The training dataset of 12 drugs was previously subdivided from CiPA by a team of clinical cardiologists and electrophysiologists. Following the data collection process, the training dataset is organized in a Microsoft Excel Comma-separated Values (CSV) file format. After selecting the best-paired feature, the model is trained with the 12 training drugs listed in Table I. The drugs have been classified into their respective risk categories, which are the high, intermediate, and low target classes.

Table I: CiPA training drugs and their respective risk categories.

CiPA training drugs	Risk categories
Bepridil	High
Dofetilide	
Quinidine	
Sotalol	
Chlorpromazine	Intermediate
Cisapride	
Ondansetron	
Terfenadine	
Diltiazem	Low
Mexiletine	
Ranolazine	
Verapamil	

Data Preprocessing

Previous machine learning (ML) approaches have faced challenges primarily due to their classifications being either (a) directly applied to raw data without feature extraction, (b) performed on raw data without outlier removal, (c) lacking the addition of replacement values for missing data, or (d) involving the simplistic filling of missing values with the mean value (13). Therefore, several data preprocessing techniques are implemented to ensure the quality and integrity of the dataset. These include conducting exploratory data analysis (EDA), handling missing values, removing outliers, and data encoding.

As a foundational analytical approach, EDA is an essential preliminary step in any data analysis endeavour that unveils inherent patterns in data, identifying outliers and unexpected features. In pandas, the .info() and .describe() command functions were used to understand and analyze data effectively. The .info() function provides a concise summary of a DataFrame, including the number of non-null entries, data types of each column, and memory usage while .describe() function generates simple summary statistics for numerical columns, including measures such as count, mean, standard deviation, minimum, and various percentiles. This allows for a quick assessment of the distribution of the data. Based on the EDA, no missing values are present in the data; thus, handling missing values is unnecessary.

Outliers, characterized as objects deviating from typical data, can be a representative of critical information crucial for applications like fraud detection and network intrusion, impacting statistical conclusions derived from significance tests (14,15). One commonly employed method for outlier detection involves visualization techniques using a scatter plot to identify any abnormal behavior between two or more variables in a dataset. If the observation data point does not fit the pattern, it is considered an outlier. By setting a cut-off threshold, data points outside the threshold are removed.

Data encoding converts textual or categorical information into a numerical representation that algorithms can process. Since the majority of ML algorithms only work with numerical variables, this step is essential to allow the model to understand and extract useful data. In this instance, the label column has been encoded such that "low" is assigned a value of 0, "intermediate" a value of 1, and "high" a value of 2.

Paired Feature Selection

The ORd ventricular cell model incorporates a comprehensive set of 14 features, encompassing crucial aspects such as dVm/dt_repol, Max_dVm/dt, Vm_Peak, *Vm_Resting*, APD90, APD50, APDtri, Ca_Peak, Ca_Diastole, CaD50, CaD90, *Catri*, *qNet*, and *qInward*. Table II tabulates the features derived from the ORd ventricular cell model.

Table II: Features derived from the ORd ventricular cell model.

Features	Descriptions
dVm/dt_repol	The rate at which the membrane potential decreases during the repolarization phase of an action potential.
Max_dVm/dt	The maximum rate of change of the membrane potential during the upstroke of the action potential.
Vm_Peak	The peak membrane potential reached during the action potential.
Vm_Resting	The resting membrane potential of the cell when it is not actively firing an action potential.
APD90	The duration from the start of the action potential to the point where the membrane potential has repolarized to 90% of its peak value.
APD50	The duration from the start of the action potential to the point where the membrane potential has repolarized to 50% of its peak value.
APDtri	The triangulation of the action potential duration, often defined as the difference between the action potential duration at 90% repolarization (APD90) and the duration at 50% repolarization (APD50).
Ca_Peak	The peak intracellular calcium concentration reached during a calcium transient
Ca_Diastole	The baseline intracellular calcium concentration during diastole, when the cell is at rest
CaD50	The duration from the start of the calcium transient to the point where the calcium level has decreased to 50% of its peak value
CaD90	The duration from the start of the calcium transient to the point where the calcium level has decreased to 90% of its peak value

CONTINUE

Table II: Features derived from the ORd ventricular cell model. (CONT.)

Features	Descriptions
Catri	The triangulation of the calcium transient duration, defined as the difference between the duration at which the calcium transient has decayed to 90% of its peak value (CaD90) and the duration at which it has decayed to 50% of its peak value (CaD50).
qNet	The amount of ionic charge crossing the six ionic channels which are INaL, ICaL, IKr, IKs, IK1and Ito
qInward	The amount of ionic charge that moves inward through INaL and ICaL

These 14 features derived from the ORd Ventricular cell model were paired to select the best-paired features, resulting in 91 possible pairs. Figure 2 illustrates the correlation map revealing the intricate relationships between these features. The first pair, for example, which consists of dVm/dt_repol (Feature 1) and Max_dVm/dt (Feature 2), was trained using OLR to assess the risk of TdP. The training process was repeated for the subsequent 90 pairs.

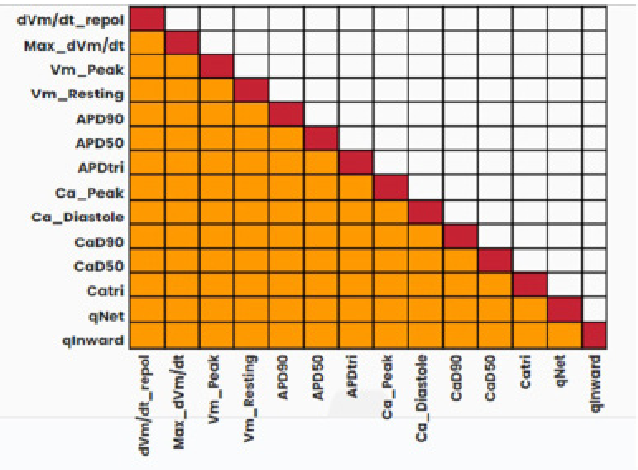


Figure 2: 91 paired features of the ORD ventricular cell model.

Various supervised ML classification algorithms were examined to categorize torsadogenic drugs into three risk levels: high, intermediate, or low. Techniques such as Random Forest, XGBoost, k-Nearest Neighbors (KNN), and Convolutional Neural Networks (CNN) were evaluated for their respective strengths in handling non-linear relationships, ensemble learning, and pattern recognition. Additionally, Uncertainty Quantification (UQ) was applied to improve the robustness of the models by assessing variability in predictions. Among these methods, OLR emerged as the most suitable approach due to its ability to model ordered categorical outcomes effectively.

In logistic regression, establishing thresholds is crucial for assessing TdP risk categories associated with drugs. Two significant threshold values, denoted as Eq. (1) and Eq. (2), are identified through OLR models. These thresholds contribute to nuanced differentiation across three proarrhythmic risk levels, relying on paired *in silico* features. Mathematical analysis inspired by a study by Li et al. (7) delves into calculating classification thresholds from training data, initially focused on a single *in silico* feature. The adaptation of the sigmoid function is tailored to accommodate the unique considerations of using paired *in silico* features for predicting drug-induced cardiotoxicity.

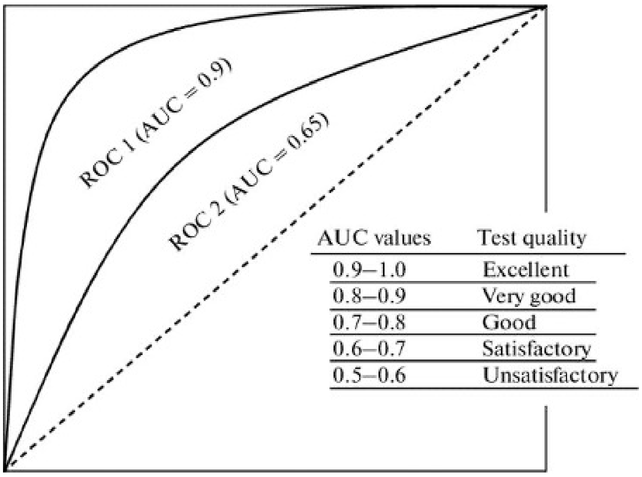
$$P\,(risk \leq Low) = \frac{1}{1+e^{-(I_1 - \beta_1 x_1 - \beta_2 x_2)}} \quad (1)$$

$$P\,(risk \leq Intermediate) = \frac{1}{1+e^{-(I_2 - \beta_1 x_1 - \beta_2 x_2)}} \quad (2)$$

Performance Evaluation

The performance of the developed OLR model was evaluated based on accuracy and Area Under Curve (AUC). Accuracy is defined as the ratio of the total number of correctly calculated predictions, as depicted in Eq. (3). Meanwhile, Figure 3 illustrates the categorization of Receiver Operating Characteristics (ROC) curves based on AUC values, representing the overall performance of a classification model. The ROC curve provides a visual depiction of the trade-off between sensitivity and specificity at different threshold settings. Evaluating model performance through ROC curves and AUC values is crucial for assessing a model's performance.

$$\text{Accuracy} = \frac{\text{Number of correct predictions}}{\text{Total number of predictions}} \times 100\% \quad (3)$$



AUC values	Test quality
0.9–1.0	Excellent
0.8–0.9	Very good
0.7–0.8	Good
0.6–0.7	Satisfactory
0.5–0.6	Unsatisfactory

Figure 3: Categorisation of ROC Curves based on AUC values (Trifonova et al., 2014).

RESULTS

Evaluation of paired features

Table III highlights the best nine paired features out of the 91 pairs, based on accuracy greater than 60% and their respective AUC values. The top pair, *Vm_resting*, and *Catri*, achieved an accuracy of 73%, with AUC values of 0.97 for low risk, 0.72 for intermediate risk, and 0.83 for high risk, indicating excellent test quality for low-risk cases and good to above-average performance for intermediate and high-risk cases. The second-best pair, *Catri*, and *qInward*, demonstrated an accuracy of 70%, with AUC values of 0.94 for low risk, 0.74 for intermediate risk, and 0.90 for high risk, reflecting good to excellent test quality across all risk categories. These results suggest that the selected feature pairs are highly effective in distinguishing different drug risk categories. It can be observed that both pairs consistently achieved a training accuracy of 70% or higher, consisting of *Catri*. *Catri* is the distinct feature that presents in both pairs with the highest accuracy. *Catri* involves the calcium channels, the sodium-calcium exchanger, and intracellular calcium handling, which are crucial for cardiac rhythm. Disruptions in calcium homeostasis can prolong action potential duration and promote EADs, triggering TdP. Excessive intracellular calcium increases sodium-calcium exchanger activity, generating a depolarizing current that prolongs the QT interval and increases TdP risk (16,17).

Table III: Accuracy and AUC values of the best nine paired features.

No	Feature 1	Feature 2	Accuracy	AUC score (low-risk)	AUC score (intermediate-risk)	AUC score (high-risk)
1	Max dVm/dt	qInward	0.66	0.92	0.69	0.90
2	Vm_Peak	Catri	0.67	0.93	0.77	0.76
3	Vm_Peak	qInward	0.67	0.95	0.73	0.91
4	Vm_Resting	CaD90	0.64	0.84	0.74	0.90
5	**Vm_Resting**	**Catri**	**0.73**	**0.97**	**0.72**	**0.83**
6	Vm_Resting	qInward	0.69	0.90	0.77	0.91
7	CaD90	qInward	0.65	0.91	0.75	0.91
8	CaD50	qInward	0.60	0.90	0.70	0.87
9	**Catri**	**qInward**	**0.70**	**0.94**	**0.74**	**0.90**

In comparison to single features

In the study conducted by Jeong et al. (18), 12 single *in silico* features were evaluated to determine their effectiveness in assessing drug-induced TdP risk. Among these features, *qInward* demonstrated the highest accuracy and consistently good AUC values across the three risk categories, indicating its strong predictive capability. Table IV presents the accuracy and AUC values for the 12 single features, highlighting the superior performance of *qInward*. Towards comparing paired features with single features, *qInward* is compared to a pair that includes *qInward*. In this case, the pair achieving the highest accuracy is chosen, which is *Catri* and *qInward*. Although the single *qInward* achieves a slightly 3% higher accuracy than the *Catri* and *qInward* pair, the pair displayed excellent AUC values of more than 0.9 for low-risk and high-risk. However, it is important to note that this is an indirect comparison. The results of the single features were obtained using the validation dataset, while the paired features were obtained using only the training dataset.

Table IV: Accuracy and AUC values of 12 single in silico features (adapted from Jeong et al. (2022).

No	Feature 1	Accuracy	AUC score (low-risk)	AUC score (intermediate-risk)	AUC score (high-risk)
1	dVm/dt_repol	0.68	0.67	0.53	0.75
2	Max_dVm/dt	0.59	0.58	0.52	0.58
3	Vm_Peak	0.64	0.56	0.56	0.62
4	APD90	0.68	0.68	0.57	0.75
5	APD50	0.69	0.68	0.59	0.75
6	APDtri	0.66	0.64	0.57	0.75
7	Ca_Peak	0.53	0.61	0.42	0.42
8	CaD50	0.54	0.44	0.50	0.62
9	CaD90	0.55	0.44	0.39	0.71
10	Catri	0.51	0.56	0.52	0.33
11	qNet	0.70	0.67	0.55	0.75
12	**qInward**	**0.73**	**0.70**	**0.65**	**0.71**

DISCUSSION

Optimal paired features

Based on the comparison, another prominent feature identified besides *Catri* was *qInward*. Analysis of the nine best pairs revealed that six pairs included *qInward*, achieving an accuracy of 60% or higher. This indicates that *qInward*, when paired with another significant feature, has a better tendency to predict TdP. The prominence of *qInward* in most pairs can be attributed to its demonstrated superiority in classifying TdP risk, as highlighted by Jeong et al. (18). This study examined *qInward* variability and found it to be more effective than other *in silico* features for this purpose. As stated in Table

II, *qInward* represents the amount of ionic charge moving inward through the late sodium current (INaL) and the L-type calcium current (ICaL), focusing on the sodium and calcium channels. This supports the importance of *Catri* as another crucial feature, given its involvement in calcium regulation, further emphasizing the role of calcium handling in cardiac electrophysiology. *qInward* is highly correlated with TdP risk and has been utilized as a biomarker to predict proarrhythmic drugs using binary classification methods (18,19).

Moreover, Yoo et al. (19) emphasized that *qInward* was the index most significantly affecting the classification performance of the intermediate-risk group. Additionally, the Food and Drug Administration (FDA) has proposed *qInward* and *qNet* as promising TdP risk metrics, derived from *in silico* simulations, for categorizing the proarrhythmic risk of drugs into high, intermediate, and low categories (7,20,21). These endorsements underscore the critical role of *qInward* in TdP risk assessment and its potential utility in predictive modeling. As evidenced by prior studies, this distinctive capability allows *qInward* to outperform certain feature pairs, highlighting its value in evaluating proarrhythmic risk.

Although the *Vm_resting* and *Catri* pair achieved the highest accuracy among the various *in silico* features computed using the OLR model, *qInward* also emerged as one of the most influential in determining TdP-risk levels. Therefore, the second-best pair underscores the significance of *Catri* and *qInward* in classifying TdP-risk levels, highlighting their potential utility in predictive modeling. Further testing and validation of the model using *qInward* are essential to determine its reliability in assessing TdP risk. Comprehensive validation will provide insights into the effectiveness of *qInward* as a predictor and its interaction with other variables in the model. The performance of models incorporating *qInward* as a feature was particularly notable for distinguishing between low-risk and high-risk groups in the ORd dataset.

CONCLUSION

This study shows that the best two pairs, consisting of *Catri*, achieved an accuracy of 73% and 70% when trained with the OLR model, with excellent AUC values. Additionally, *qInward* is found to be more influential than the other *in silico* features. These findings emphasize that *Catri* and *qInward* have the potential to be the optimal pair. However, the study is limited to utilizing the training dataset to identify optimal paired features in assessing TdP risk. Further testing and validation of the developed model are recommended to determine the reliability of the optimal paired features. The future work of this study will be extended to evaluate the performance of the developed model further using the optimal paired feature obtained on an unseen CiPA-based validation dataset.

This study advances drug safety assessment by offering a more precise and reliable approach to evaluating cardiac toxicity, particularly in addressing the risk of drug-induced TdP. By integrating advanced computational methods, it enhances predictive accuracy, enabling better-informed decisions throughout the drug development and regulatory process. This approach not only supports safer drug approval and monitoring but also reduces the likelihood of late-stage failures or market withdrawals. Ultimately, it contributes to a paradigm shift toward more proactive and cost-effective cardiac safety evaluations, reinforcing patient safety and improving healthcare outcomes.

ACKNOWLEDGEMENT

This work was financially supported by Universiti Teknologi Malaysia under the Industry Grant Vot: R.J130000.7623.4C704. The authors sincerely thank Kumoh National Institute of Technology (KIT), South Korea, and Universiti Teknologi Malaysia (UTM), Malaysia, for contributing to this work. This research is partially supported by the Ministry of Food and Drug Safety (22213MFDS3922), the NRF (National Research Foundation of Korea) under the Basic Science Research Program (2022R1A2C2006326), and the MSIT (Ministry of Science and ICT), Korea, under the Grand Information Technology Research center support program (IITP-2022-2020-0-01612) supervised by the IITP (Institute for Information & communications Technology Planning & Evaluation).

REFERENCES

1. Tang PT, Shenasa M, Boyle NG. Ventricular Arrhythmias and Sudden Cardiac Death. Card Electrophysiol Clin. 2017 Dec;9(4):693–708.
2. Patel R, Aggarwal S, Athwal PSS, Randhawa S, Kahlon S. Long QT-Syndrome With Torsades de Pointes Managed Considering Financial Constraints Faced by the Patient. Cureus. 2021 Jun 24;
3. Lankaputhra M, Voskoboinik A. Congenital long QT syndrome: a clinician's guide. Intern Med J. 2021 Dec 22;51(12):1999–2011.
4. Olson H, Betton G, Robinson D, Thomas K, Monro A, Kolaja G, et al. Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals. Regulatory Toxicology and Pharmacology. 2000 Aug;32(1):56–67.
5. Stevens JL, Baker TK. The future of drug safety testing: expanding the view and narrowing the focus. Drug Discov Today. 2009 Feb;14(3–4):162–7.
6. Colatsky T, Fermini B, Gintant G, Pierson JB, Sager P, Sekino Y, et al. The Comprehensive in Vitro Proarrhythmia Assay (CiPA) initiative — Update

on progress. J Pharmacol Toxicol Methods. 2016 Sep;81:15–20.

7. Li Z, Ridder BJ, Han X, Wu WW, Sheng J, Tran PN, et al. Assessment of an *In Silico* Mechanistic Model for Proarrhythmia Risk Prediction Under the CiPA Initiative. Clin Pharmacol Ther. 2019 Feb 27;105(2):466–75.
8. Dutta S, Chang KC, Beattie KA, Sheng J, Tran PN, Wu WW, et al. Optimization of an *In silico* Cardiac Cell Model for Proarrhythmia Risk Assessment. Front Physiol. 2017 Aug 23;8.
9. Jeong DU, Danadibrata RZ, Marcellinus A, Lim KM. Validation of *in silico* biomarkers for drug screening through ordinal logistic regression. Front Physiol. 2022 Oct 6;13.
10. Fuadah YN, Qauli AI, Marcellinus A, Pramudito MA, Lim KM. Machine learning approach to evaluate TdP risk of drugs using cardiac electrophysiological model including inter-individual variability. Front Physiol. 2023 Oct 4;14.
11. Sager PT, Nebout T, Darpo B. ICH E14: A New Regulatory Guidance on the Clinical Evaluation of QT/QTc Internal Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs. Drug Inf J. 2005 Oct 30;39(4):387–94.
12. Llopis-Lorente J, Gomis-Tena J, Cano J, Romero L, Saiz J, Trenor B. *In Silico* Classifiers for the Assessment of Drug Proarrhythmicity. J Chem Inf Model. 2020 Oct 26;60(10):5172–87.
13. Bashir S, Qamar U, Khan FH. IntelliHealth: A medical decision support application using a novel weighted multi-layer classifier ensemble framework. J Biomed Inform. 2016 Feb;59:185–200.
14. Mramba LK, Liu X, Lynch KF, Yang J, Aronsson CA, Hummel S, et al. Detecting potential outliers in longitudinal data with time-dependent covariates. Eur J Clin Nutr. 2024 Jan 3;
15. Yang J, Rahardja S, Fr∆nti P. Outlier detection. In: Proceedings of the International Conference on Artificial Intelligence, Information Processing and Cloud Computing. New York, NY, USA: ACM; 2019. p. 1–6.
16. Weiss JN, Garfinkel A, Karagueuzian HS, Chen PS, Qu Z. Early afterdepolarizations and cardiac arrhythmias. Heart Rhythm. 2010 Dec;7(12):1891–9.
17. Eisner DA, Caldwell JL, Kistamбs K, Trafford AW. Calcium and Excitation-Contraction Coupling in the Heart. Circ Res. 2017 Jul 7;121(2):181–95.
18. Jeong DU, Qashri Mahardika T N, Marcellinus A, Lim KM. *qInward* variability-based in-silico proarrhythmic risk assessment of drugs using deep learning model. Front Physiol. 2022 Dec 14;13.
19. Yoo Y, Marcellinus A, Jeong DU, Kim KS, Lim KM. Assessment of Drug Proarrhythmicity Using Artificial Neural Networks With *in silico* Deterministic Model Outputs. Front Physiol. 2021 Dec 10;12.
20. Li Z, Dutta S, Sheng J, Tran PN, Wu W, Chang K, et al. Improving the *In Silico* Assessment of Proarrhythmia Risk by Combining hERG (Human Ether-a-go-go-Related Gene) Channel–Drug Binding Kinetics and Multichannel Pharmacology. Circ Arrhythm Electrophysiol. 2017 Feb;10(2).
21. Chang KC, Dutta S, Mirams GR, Beattie KA, Sheng J, Tran PN, et al. Uncertainty Quantification Reveals the Importance of Data Variability and Experimental Design Considerations for *in Silico* Proarrhythmia Risk Assessment. Front Physiol. 2017 Nov 21;8.