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Interpretable Fuzzy Rule-Based System for Fatal Ventricular Arrhythmia Risk Level Estimation due to QT-Prolonging Treatments*

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Abstract— **This COVID-19 pandemic is impacting the world in health and economic terms since 2020 with more than 200 million confirmed infected people and more than 4 million deaths across 190 countries. Treatment used against COVID-19 disease has initially been based on the combination of several medicaments, such as hydroxychloroquine/chloroquine, azithromycin and kaletra, each of which can individually delay the ventricular depolarization and repolarization processes through morphological changes in the patient's electrocardiogram. These changes can produce serious arrhythmias that lead to the sudden death of the patient.**

This paper presents an interpretable fuzzy rule-based system for fatal ventricular arrhythmia risk level estimation due to COVID-19 treatment, whose decisions are made on the basis of the evolution of electrocardiogram morphology and certain patient's clinical information. For the risk level estimation, the proposed fuzzy rule-based system considers three different risk levels (High, Moderate and Low) which are indicated by means of three different colors (Red, Orange and Green). Decisions made by the fuzzy rule-based system present a reliable behavior in comparison with cardiologist's decision. To be precise, the obtained accuracy, when comparing both decisions, reaches the 96.43%, which, joint to the high measured interpretability of the decision making system, result in a powerful tool in order to avoid death in patients, even in health centers without specialized clinical staff, and to reduce the stress in medical centers by reducing reaction times in critical patient situations.

I. Introduction

The World Health Organization declared the outbreak of COVID-19 a public health international concern in January 2020, and a pandemic in March 2020. According to data obtained from John Hopkins University on 6th August 2021 at https://coronavirus.jhu.edu/map.html, this pandemic has been impacting the world since 2020 with more than 200 million confirmed infected people and more than 4.2 million deaths worldwide. Despite the absence of clinic trails, the treatment used against COVID-19 disease has initially been based on the combination of several medicaments, such as hydroxychloroquine/chloroquine, azithromycin and kaletra. All of them can delay the ventricular depolarization and repolarization processes, resulting in electrocardiogram (ECG) morphological changes in terms of a prolonged QT interval, which can produce serious arrhythmias that lead to the death of the patient [1, 2]. This circumstance has put the focus on these kind of drugs and has conditioned the protocol of the clinical staff in COVID-19 patients in such a way that the duration of the QT interval of all patients with the aforementioned treatment has been being permanently analyzed, which implied an additional overload for the clinical staff in hospitals.

In this regard, artificial intelligence (AI) is rapidly evolving into applicable solutions for clinical practice in different areas of medicine [3], such as atrial fibrillation [4] and epilepsy seizures [5], among many other. Indeed, its inclusion into the health care systems [6] is not only changing dynamics, such as the role of health care providers, but is also creating new potential to improve patient safety outcomes [7] and the quality of care [8]. In particular, some efforts have been made using fuzzy systems to deal with ECG. In this sense, neuro-fuzzy and fuzzy systems have been used for classifying ECG and diagnosis purposes [9, 10, 11].

Nevertheless, there are currently limited examples of such AI applications being successfully deployed into clinical practice [12]. In many cases, despite the impressive practical successes achieved by AI. This circumstance can be explained in terms of absence of capability to "explain" the decision-making in an understandable way [13], even when we understand the underlying mathematical principles of such models. Therefore, this is potentially problematic for medical applications, where there is particular demand for approaches that are not only well-performing, but also trustworthy, transparent, interpretable and explainable [14]. In this sense, explainable artificial intelligence (XAI) is a relatively new approach to AI with special emphasis to the ability of machines to give sound motivations about their decisions and behavior [15]. This relevant feature comes to give answer not only to the European General Data Protection Regulation (GDPR) that took effect in 2018, which emphasizes the "right to explanation" expressed in art. 22, but also to one of the challenges that AI must face in order to success in clinical applications: Interpretability [12].

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In this context, one of the most powerful tool of AI in terms of interpretability are fuzzy rule-based systems (FRBSs), which include human knowledge into its knowledge bases in order to make interpretable decisions [16, 17, 18, 19]. Therefore, FRBS well suited for both questions: the *accuracy*, capability to faithfully represent the real system, and the *interpretability*, capability to express the behavior of the real system in an understandable way because decisions are made following a human-like reasoning and can be understood easily by humans. As a consequence of that, the application of FRBS in medicine for different purposes can be very beneficial.

Bearing in mind the above mentioned ideas, this paper depicts a FRBS for fatal ventricular arrhythmia risk level estimation regarding the QT interval, its evolution from a basal ECG, and some relevant clinical information related to other risk factors worth considering, which could affect the QT interval prolongation. It is important to highlight that the proposed FRBS has been designed bearing in mind the criteria of specialist (three cardiologists and one pulmonologist) from four different Spanish hospitals (Hospital Universitario QuironSalud de Madrid, Hospital Universitario General de Elda, Hospital San Agustín de Linares and Complejo Hospitaliario de Jaén).

The rest of the paper is organized as follows. Section II depicts some important aspects related to ECGs, from which the QT interval is going to be obtained, emphasizing the relevance of QT interval. Section III depicts the proposed fuzzy rule-based system for fatal ventricular arrhythmia risk levels estimation. the features of the proposed FRBS in terms of interpretability is presented in section V. Section IV includes some experimental results in terms of interpretability and accuracy. Finally, conclusions and future actions are shown in section V.

II. Electrocardiogram and QT Interval

An ECG is a well-used method for examination and diagnostics in today's emergency medical services, which ultimately is of benefit to the patient's life and health. It remains one of the most widely used and readily available diagnostic tests in modern medicine [20]. In fact, the ECG is sometimes the only and most efficient way of detecting life-threatening conditions, thus allowing a timely delivery of emergency care. To be precise, a 12-lead ECG depicts the heart electrical activity from several points of view called "leads" by means of electrodes located on the skin, which detect the different small electrical changes according to both, cardiac muscle depolarization and repolarization.

The typical heartbeat of an ECG of a normal sinus rhythm is shown in Fig. 1. In addition, the different waves and the different segments and intervals involved in the morphology of a heartbeat are also presented. The QT interval on the surface ECG is given by the measured from the beginning of the QRS complex to the end of the T-wave, which represents the electrocardiographic manifestation of ventricular depolarization and repolarization. Nevertheless, current methods of measurement have not been standardized. Since the QT interval is prolonged when slower heart rates and shortened when faster heart rates, several formulas have been proposed to adjust for these kind of variations

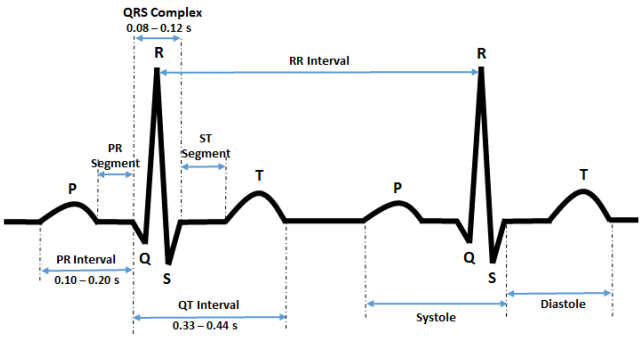

Figure 1.Typical Heartbeat of an ECG of a normal synus rhythm.

In this work, Framingham correction [21] has been used because it is based on empirical data from a large population sample rather than on hypothetical reasoning:

$$QT_C = QT + 0{,}154(1 - RR) \quad (1)$$

A. Relevance of QT Interval

The Estimation of QT interval from the ECG has gained relevance because its elongation could predispose to a potential fatal ventricular arrhythmia [22, 23, 24]. Recently, due to COVID-19 pandemic produced by the pathogen Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), this issue has raised relevance due to the different medications initially used against the illness. In fact, despite the absence of clinic trails, treatment used against COVID-19 disease has originally been based on the combination of several medicaments, such as hydroxychloroquine/chloroquine, azithromycin and kaletra [1, 2]. All of them can delay the ventricular repolarization process, resulting in a prolonged QT interval, which can produce serious ventricular arrhythmias that lead to the death of the patient. Therefore, improper use of QT prolonging medications plays and important role and deserve special attention. A list of medicaments with *known risk of sudden death*, can be accessed at https://crediblemeds.org/.

Nevertheless, although the use of QT-prolonging medications can predispose to potential fatal ventricular arrhythmia, there is a relative paucity of information that can help clinicians and patients make optimal informed decisions about how best to minimize the risk of this serious complication. In this sense, this paper presents a FRBS for risk estimation of fatal ventricular arrhythmia based on QT interval estimation from ECGs, not only for COVID-19 patients, but also for patients with QT-prolonging treatment.

III. Proposed FRBS for Fatal Ventricular Arrhythmia Risk Level Estimation

FRBS are well-known to have attracted the medicine community attention for their application to diagnosis issues [3, 4, 5, 6, 7, 8, 11]. A major advantage of FRBS is related to their ability to cope with noisy or uncertain information presented in highly dynamic systems. In addition, another interesting feature is related to the interpretability of its decisions, which are made following a human-like reasoning and can be understood easily by humans. Therefore, the application of FRBS in medicine for different purposes can be very beneficial. Next, the main features of the proposed FRBS are presented.

A. *General structure of the proposed FRBS*

The general outline, (including inputs, core and output), of the proposed fuzzy rule-based system is shown in Fig. 2.

The proposed FRBS considers three different inputs, two of them are used for the FRBS: corrected QT interval, and some relevant clinical information about the patient. The other one input, the corrected QT interval Evolution from the basal ECG, is used to select the appropriate base of rules of the expert system. It is important to highlight that the corrected QT interval and the corrected QT interval evolution are going to be obtained from the ECG.

Since the successful operation of a FRBS is strongly related to the quality of its knowledge or fuzzy Rule Bases (RB), the knowledge has been acquired from different experts on the issue (three cardiologists and one pulmonologist) and is represented in Fig. 3.

The output of the proposed FRBS is just the risk level estimation of fatal ventricular arrhythmia. The obtained risk level estimation is given in a quantitatively way by mean of an index in the interval [0,1]. In addition, this estimation is also given in a qualitative way by means of three different color (similar to traffic lights): Red Color, to indicate a high-risk level; yellow color, to indicate a moderate level; and finally, green color, when a low risk is estimated.

B. *Input and output variables of the FRBS*

The risk level estimation of fatal ventricular arrhythmia is based on several input variables obtained from the patient: QTc Interval, the QTc evolution from the basal ECG, and contextual information about the patient.

B.1. Input 1: Corrected QT Interval (QTc).

QTc is calculated according to Framingham formula (1) from the QT interval and RR interval. This parameter is absolutely relevant in this work since its evolution determines the morphological changes and its elongation could predispose patients to a potential fatal ventricular arrhythmia also known as “torsades de pointes”.

B.2. Input 2: Clinical information from the patient (CI).

There are other several risk factors worth considering that could affect the prolongation of QTc interval. In [25], a QTc interval prolongation risk score has been created, in which, for each independent variable, a weighted point score (1, 2, or 3 points) has been assigned. To arrive at a risk score for QTc interval prolongation, the sum of all points must be calculated for each patient. To determine cutoff points for low, moderate, and high risk of QTc interval prolongation, patients are stratified by total point scores.

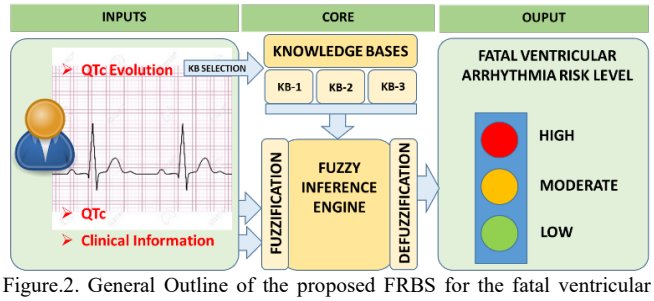

Figure.2. General Outline of the proposed FRBS for the fatal ventricular arrhythmia risk level estimation.

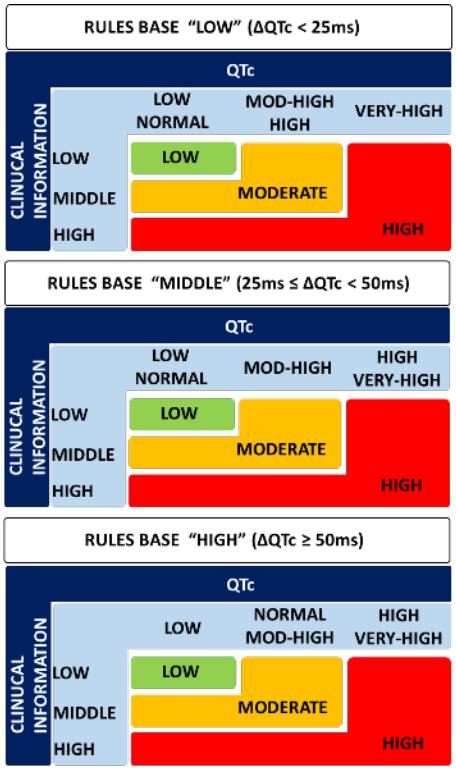

Figure 3. RBs for the making decision process.

Independent risk factors for QTc interval prolongation are presented in table II, including: ≥ 68 years of age, female sex, administration of a loop diuretic, serum K^{+}≤3.5 mEq/L, admission QTc ≥ 450 ms, diagnosis of myocardial infarction, administration of more than 1 QTc interval–prolonging drugs, sepsis left ventricular systolic dysfunction, heart failure, and administration of 1 QTc interval–prolonging drug. Table I also presents the score assigned to each and every risk factor.

Finally, based on total points calculated for every single patient, the risk score has been further categorized into low, moderate, and high risk, according to [25]. This further taxonomy is depicted in table II.

Nevertheless, in order to make easy the understanding of these scores for clinical staff, this work has changed the scale in order to use a full scale of 5 instead of 21. Therefore, the score assigned to each and every risk factor has accordingly been scaled.

B.3. Input 3: Corrected QT interval Increment from the basal ECG (ΔQT_C).

The increment of the corrected QTc interval consists of the difference between the QTc interval, obtained from the current ECG, and the QTc interval obtained from a basal ECG, which has previously obtained in the beginning of the pharmacological treatment.

$$\Delta QT_C = QT_{C\ CURRENT\ ECG} - QT_{C\ BASAL\ ECG} \qquad (2)$$

The relevance of this input variable is remarkable because it provides some information on the possible repercussions of the treatment. It is worth mentioning, that this variable is used by the FRBS to select the appropriate knowledge base depending on its value, as it is shown in table III.

TABLE I. INDEPENDENT RISK FACTORS FOR QTC INTERVAL PROLONGATION

RISK FACTORS	Points
Age ≥ 0 68 years	1
Female sex	1
Loop diuretic	1
Serum $K^+ \leq 3.5$ mEq/L	2
Admission $QT_C \geq 450$ ms	2
Acute Myocardial Infarction	2
≥2 QTc-prolonging drugs	3
Sepsis	3
Heart failure	3
One QTc-prolonging drug	3
MAXIMUM RISK SCORE	**21**

TABLE II. QTC INTERVAL RISK SCORE

RISK SCORE CATEGORIES	RISK SCORE
LOW	<7
MODERATE	7-10
HIGH	>10

TABLE III. RULES BASE SELECTION

ΔQT_C	Selected Rules Base
$\Delta QT_C < 25$ ms	RB1 (LOW)
25 ms $\leq \Delta QT_C <$ 50 ms	RB2 (MIDDLE)
$\Delta QT_C \geq 50$ ms	RB3 (HIGH)

B4. Output. Risk Level Estimation.

The output of the FRBS is the fatal ventricular arrhythmia risk level estimation. This variable is going to be represented by the use of colors: Red, when a high arrhythmia risk level is estimated; orange, when a moderate arrhythmia risk level is estimated, and finally, green, when a low arrhythmia risk level is estimated. In order to obtain the output of the FRBS, the defuzzification system converts the output sets of every rule into an overall output fuzzy set and an overall crisp value y_o for the whole RB (just a single output is considered here). Therefore, a defuzzification operator calculates the value of y_o from the overall output fuzzy set B′, regarding the "center of gravity" defuzzification method, which has been considered since it is extensively used in literature:

$$y_0 = \frac{\int_Y y \cdot \mu_{B'}^{(y)} dy}{\int_Y \mu_{B'}^{(y)} dy} \quad (3)$$

Hence, output y_o reflects fatal ventricular arrhythmia risk level estimation according to values indicated in table IV.

In Fig. 4, the input and output variables used by the expert system are depicted. As it has already been indicated, the input related to the evolution or increment of the QTc is not used by FRBS. Instead, this variable is used the select the knowledge base used by the expert system.

TABLE IV. OUTPUT – ARRHYTHMIA RISK LEVEL ESTIMATION

OUTPUT	QUALITIATIVE RISK LEVEL
$y_o < 0.25$	LOW (GREEN)
$0.25 \leq y_o < 0.75$	MODERATE (ORANGE)
$y_o \geq 0.75$	HIGH (RED)

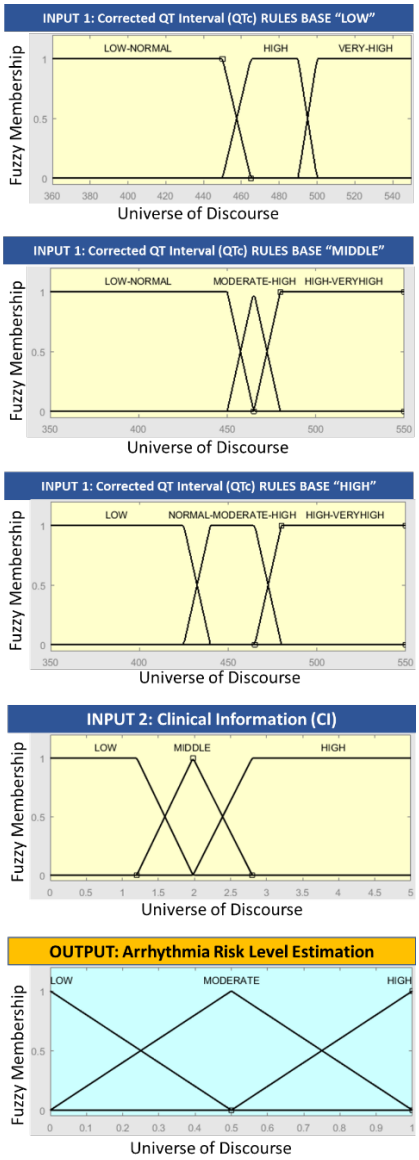

Fig.4. Membership function of variables used by the FRBS.

IV. EXPRIMENTAL RESULTS

In order to present experimental results, which have been obtained using MATLAB, both interpretability and accuracy are going to be analyzed.

A. Interpretability Analysis

Bearing in mind the afore-mentioned ideas, it is worth mentioning that one of the most remarkable features of the FRBS is related of the interpretability in the decision-making process. In fact, the structure of the FRBS has strongly been conditioned by clinician criteria in order to favor the interpretability. Furthermore, this interpretability has been measured taking into account several aspects like semantic and complexity by means of a hierarchical fuzzy system which provides an interpretability index for every single KB used by the expert system [16, 17, 18, 19] and whose input and output variables are shown in Table V, where N is the number of labels. These variables are taken as inputs of a hierarchical fuzzy system and they are grouped according to the information they convey. Therefore, the Interpretability

Index is computed as the result of inference of a hierarchical fuzzy system that is broken down in four linked KBs. A first rule base, called "Rule Base Dimension", makes an estimation of the rule base dimension taking into account as inputs the total number of rules and premises. At the same time, a second rule base, called "Rule Base Complexity," assesses the rule base complexity bearing in mind the number of inputs used by the rules (one input, two inputs three or more inputs). Additionally, a third rule base, called "Rule Base Interpretability", combines the rule base dimension and the complexity, through its outputs, and it yields a rule base interpretability index.

Finally, a rule base integrates the rule base interpretability with the evaluation of interpretability for the system variables, considering the total number of labels per input and assuming that the fuzzy rule-based systems to be evaluated only include strong fuzzy partitions. Additional explanation, including the rule bases used, on this hierarchical fuzzy system for the interpretability assessment can be found in [16, 17, 18, 19]. The obtained value for the interpretability index is 0.71, which is the same for every single knowledge base used by the expert system for the fatal ventricular arrhythmia estimation depicts how good is the interpretability in the decision-making process of the developed application. It is important to point up that this is a remarkable index that give relevance to the interpretability of the different knowledge bases used by the FRBS, and that has been checked by clinicians involved in this work.

B. *Results Validation*

It is important to point out that in order to know how good the made decision is, the outputs of the FRBS have been compared to the estimations carried out by specialist doctors. Regarding to this comparison, it is important to point out that a scenario with 84 examples, every single one with three different values for the input variables, has been considered. Results of this comparison are shown in table VI in form of a confusion matrix.

From this matrix, it can be inferred that the 96.43% of the decision made by the FRBS are the same the made by specialist doctors.

TABLE V. INPUT AND OUTPUT VARIABLES FOR THE HIERARCHICAL FUZZY SYSTEM USED FOR THE INTERPRETABILITY INDEXES OBTAINING

VARIABLE	UNIVERSE OF DISCOURSE	NUMBER OF LABELS
Total number of rules	[N,8 x N]	3
Total number of premises	[N,16 x N]	2
Number of rules with one input	[0,8 x N]	2
Number of rules with two inputs	[0,8 x N]	2
Number of rules with three or more inputs	[0,8 x N]	2
Average number of labels by input	[2,9]	2
Rule base dimension	[0,1]	3
Rule base complexity	[0, 1]	3
Rule base Interpretability	[0, 1]	5
Interpretability index	[0, 1]	5

TABLE VI. CONFUSION MATRIX

CONFUSION MATRIX				
		FRBS DECISIONS		
		GREEN	ORANGE	RED
DOCTORS DECISIONS	GREEN	9	0	0
	ORANGE	1	19	1
	RED	0	1	53

TABLE VII. STUDY CASES

	INPUTS			OUTPUT
	QTc (ms)	CI	ΔQT_C (ms)	y_o
Patient 1	476	0.24	55	**0.93**
Patient 2	450	1.91	30	**0.50**
Patient 3	455	0.48	15	**0.08**

TABLE VIII. ACTIVATED RULES AND OUTPUTS

Activated Rules for Patient 1	Output
If (QTc is NORMAL-MODERATE-HIGH) and (CI is not HIGH) then (RISK is ORANGE) If (QTc is HIGH-VERYHIGH) then (RISK is RED)	
Activated Rules for Patient 2	**Output**
If (QTc is LOW-NORMAL) and (CI is MIDDLE) then (RISK is ORANGE) If (CI is HIGH) then (RISK is RED)	
Activated Rules for Patient 3	**Output**
If (QTc is LOW-NORMAL) and (CI is LOW) then (RISK is GREEN) If (QTc is HIGH) and (CI is not HIGH) then (RISK is ORANGE)	

C. *Study Cases*

In order to show how the proposed FRBS works, several examples, one per every single fatal ventricular arrhythmia risk level, are going to be depicted. For this purpose, three different patients' situations are considered, whose inputs variables are presented in table VII.

- **Patient 1.** Bearing in mind the ΔQT_C, RB3 must be selected. In this case, two different rules have been activated, see table VIII, and the output is y_0=0.93 which means a high arrhythmia risk level.
- **Patient 2.** According to ΔQT_C, RB2 must be selected. In this case, two different rules have been activated, see table VIII, and the output is y_0=0.5 which means a moderate arrhythmia risk level.
- **Patient 3**. Taking into account ΔQT_C, RB1 must be selected. In this case, two different rules have been activated, see table VIII, and the output is y_0=0.08 which means a low arrhythmia risk level.

V. CONCLUSIONS AND FUTURE ACTIONS

This work presents a FRBS for fatal ventricular arrhythmia risk level estimation, which has been developed taking into account the experience of several cardiologist and pulmonologist who are with four (private and public) different hospitals in Spain. Due to the followed criteria of specialist doctors during the design and implementation phase, the proposed FRBS for fatal ventricular arrhythmia risk level estimation, presents a reliable behavior in terms of comparison with specialist doctors decision (96.43% accuracy). In addition, the proposed FRBS presents a highly interpretable decision-making process (0,71 interpretability

index), which give answer to the European General Data Protection Regulation and to one of the key challenges of AI so that it can success in clinical applications. Furthermore, related to clinical issues, this FRBS has been aimed to patients who undergo with QT prolonger (combined or not) treatment against illnesses like COVID-19, for instance. Among the main features of this FRBS, it is worth mentioning the capability of avoiding deaths in patients with QT prolonger treatment, regardless if they are in health center with or without specialized clinical staff, and the high interpretability by clinicians of the decision-making process, which make easy the deployment of applications. Regarding future actions, authors are already working on several issues such as the developing of a real free real-time web application, which will provide access to the presented FRBS in a convenient way, and the improvement in the QT interval calculation from ECG signals, which has a relevant impact on the performance of the developed FRBS. Additionally, authors are working on the acquisition of knowledge bases by machine learning algorithms [26, 27, 28] trying not to compromise the interpretability.

REFERENCES

[1] Sinkeler FS, Berger FA, Muntinga HJ, Jansen MMPM. The risk of QTc-interval prolongation in COVID-19 patients treated with chloroquine. *Neth Heart J*. 2020;28(7-8):418-423. doi:10.1007/s12471-020-01462-6

[2] Saleh M, Gabriels J, Chang D, et al. Effect of Chloroquine, Hydroxychloroquine, and Azithromycin on the Corrected QT Interval in Patients With SARS-CoV-2 Infection. *Circ Arrhythm Electrophysiol*. 2020;13(6):e008662. doi:10.1161/CIRCEP.120.008662

[3] Briganti Giovanni, Le Moine Olivier. Artificial Intelligence in Medicine: Today and Tomorrow. Frontiers in Medicine. Vol.7, 2020. DOI=10.3389/fmed.2020.00027

[4] Zachi I Attia, Peter A Noseworthy, et all. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction, The Lancet, Volume 394, Issue 10201, 2019, Pages 861-867, ISSN 0140-6736,

[5] Regalia G, Onorati F, Lai M, Caborni C, Picard RW. Multimodal wrist-worn devices for seizure detection and advancing research: focus on the Empatica wristbands. Epilep Res. (2019) 153:79–82. doi:10.1016/j.eplepsyres.2019.02.007

[6] Choudhury Aand Asan O. Role of artificial intelligence in patient safety outcomes: systematic literature review. JMIR Med Informatics 2020 ; 8 (7): e18599.

[7] Macrae C. Governing the safety of artificial intelligence in healthcare. BMJ Qual Saf 2019 Jun;28(6):495-498. [doi:10.1136/bmjqs-2019-009484] [Medline: 30979783]

[8] Grossman L, Choi S, Collins S, Dykes P, O'Leary K, Rizer M, et al. Implementation of acute care patient portals: recommendations on utility and use from six early adopters. J Am Med Inform Assoc 2018 Apr 01;25(4):370-379. [doi:10.1093/jamia/ocx074] [Medline: 29040634]

[9] Neagoe V-, Iatan I-, Grunwald S. A neuro-fuzzy approach to classification of ECG signals for ischemic heart disease diagnosis. AMIA Annu Symp Proc. 2003;2003:494-8. PMID: 14728222; PMCID: PMC1480049.

[10] Mahapatra, Sakuntala et al. "A Neuro-fuzzy Based Model for Analysis of an ECG Signal Using Wavelet Packet Tree." Procedia Computer Science 92 (2016): 175-180.

[11] Grauel A. Fuzzy Logic System for ECG Interpretation. In: Szczepaniak P.S., Lisboa P.J.G., Kacprzyk J. (eds) Fuzzy Systems in Medicine. Studies in Fuzziness and Soft Computing, vol 41. (2000). Physica, Heidelberg. https://doi.org/10.1007/978-3-7908-1859-8_11

[12] Kelly, C.J., Karthikesalingam, A., Suleyman, M. *et al.* Key challenges for delivering clinical impact with artificial intelligence. *BMC Med* **17,** 195 (2019). https://doi.org/10.1186/s12916-019-1426-2.

[13] Core MG, Lane HC, van Lent M, Gomboc D, Solomon S, Rosenberg M. Building Explainable Artificial Intelligence Systems. IAAI'06 Proceedings of the 18th conference on Innovative Applications of Artificial Intelligence. Volume 2; 2006. p. 1766–73.

[14] Holzinger A, Biemann C, Pattichis CS. What do we need to build explainable AI systems for the medical domain? arXiv. 2017; https://arxiv.org/abs/1712.09923.

[15] Mencar C., Alonso J.M. (2019) Paving the Way to Explainable Artificial Intelligence with Fuzzy Modeling. In: Fullér R., Giove S., Masulli F. (eds) Fuzzy Logic and Applications. WILF 2018. Lecture Notes in Computer Science, vol 11291. Springer, Cham. https://doi.org/10.1007/978-3-030-12544-8_17

[16] J. M. Alonso and L. Magdalena, HILK++: an interpretability-guided fuzzy modeling methodology for learning readable and comprehensible fuzzy rule-based classifiers, Soft Computing, 15(10):1959-1980, 2011.

[17] M. J. Gacto, R. Alcala, F. Herrera, "Interpretability of linguistic fuzzy rule-based systems: An overview of interpretability measures", *Inf. Sci.*, vol. 181, no. 20, pp. 4340-4360, 2011.

[18] S. G. Galán, M. Seddiki, R. J. P. de Prado, E. M. Expósito, A. Marchewka and N. R. Reyes, "Relevance of Using Interpretability Indexes for the Design of Schedulers in Cloud Computing Systems," *2020 IEEE International Conference on Fuzzy Systems (FUZZ-IEEE)*, Glasgow, United Kingdom, 2020, pp. 1-8,

[19] J.M. Alonso, S. Guillaume, L. Magdalena, A hierarchical fuzzy system for assessing interpretability of linguistic knowledge bases in classification problems, in: IPMU 2006, Information Processing and Management of Uncertainty in Knowledge-Based Systems, Paris, France, July 2–7, 2006, pp. 348– 355.

[20] Baranchuk A, Chiale PA, Green M, Caldwell JC. Editorial: surface electrocar-diogram remains alive in the XXI century. Curr Cardiol Rev. 2014;10(3):173-174. http://www.ncbi.nlm.nih.gov/pubmed/24856069. Accessed January 4, 2017.

[21] Gupta A, Vijay J, Agstam S. Which QTc correction formulae (Bazett, Framingham, or Fridericia) to use for Hydroxychloroquine induced QTc prolongation? Indian Pacing Electrophysiol J. 2020 Sep-Oct;20(5):208. doi: 10.1016/j.ipej.2020.06.008. Epub 2020 Jul 1.

[22] Al-Khatib SM, LaPointe NMA, Kramer JM, Califf RM. What Clinicians Should Know About the QT Interval. *JAMA*. 2003;289(16):2120–2127. doi:10.1001/jama.289.16.2120

[23] El-Sherif, N, Turitto, G, Boutjdir, M. Acquired long QT syndrome and torsade de pointes. *Pacing Clin Electrophysiol*. 2018; 41: 414– 421. https://doi.org/10.1111/pace.13296

[24] El-Sherif, N, Turitto G., Boutjdir M. (2020) Acquired Long QT Syndrome and Electrophysiology of Torsade de Pointes. In: El-Sherif N. (eds) Cardiac Repolarization. Springer, Cham. https://doi.org/10.1007/978-3-030-22672-5_11

[25] Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, Kovacs RJ. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. Circ Cardiovasc Qual Outcomes. 2013 Jul;6(4):479-87. doi: 10.1161/CIRCOUTCOMES.113.000152. Epub 2013 May 28. Erratum in: Circ Cardiovasc Qual Outcomes. 2013 Nov;6(6):e57.

[26] S. García-Galán, R. P. Prado and J. E. M. Expósito, "Swarm Fuzzy Systems: Knowledge Acquisition in Fuzzy Systems and Its Applications in Grid Computing," in *IEEE Transactions on Knowledge and Data Engineering*, vol. 26, no. 7, pp. 1791-1804, July 2014, doi: 10.1109/TKDE.2013.118

[27] R. P. Prado, S. García-Galán, J. E. Muñoz Expósito and A. J. Yuste, "Knowledge Acquisition in Fuzzy-Rule-Based Systems With Particle-Swarm Optimization," in *IEEE Transactions on Fuzzy Systems*, vol. 18, no. 6, pp. 1083-1097, Dec. 2010, doi: 10.1109/TFUZZ.2010.2062525

[28] S. García-Galán, R.P. Prado, J.E. Muñoz Expósito, Rules discovery in fuzzy classifier systems with PSO for scheduling in grid computational infrastructures, Applied Soft Computing, Volume 29, 2015, Pages 424-435, https://doi.org/10.1016/j.asoc.2014.11.064.