Using fuzzy logic for improving clinical daily-care of β-thalassemia patients

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***Abstract*—The domain of medical decision making process is heavily affected by vagueness and uncertainty issues and – for copying with them – different type of Clinical Decision Support System (CDSS)s, simulating human expert clinician reasoning, have been designed in order to suggest decisions on treatment of patients.**

In this paper, we exploit fuzzy inference machines to improve the knowledge-based CDSS actually used in the day-by-day clinical care of β-thalassemia patients of the Rare Red Blood Cell Disease Unit (RRBCDU) at Cardarelli Hospital (Naples, Italy). All the designed functionalities were iteratively developed on the field, through requirement-adjustment/development/validation cycles executed by an interdisciplinary research team comprising doctors, clinicians and IT engineers. The paper shows exemplary results on the on-line evaluation of Iron Overload during the health status assessment and care management of β-Thalassemia patients.

I. Introduction and Motivation

In recent decades, technological advances coupled with research efforts have made possible to develop very complex CDSS, defined as computer programs assisting physicians and other medical officials in taking clinical decision [1], able to exhibit highly sophisticated reasoning capabilities in order to improve clinical decision-making, and, thus, promote more efficient care practices. In particular, a knowledge-based CDSS allows the provision of person-specific information that is intelligently filtered, prioritized and presented at the right time to clinicians, patients, staff, and others [2]–[4]. Early CDSSs were designed from researchers on expert systems, with the aim of programming the computers with rules that would allow it to “think” like an expert clinician when confronted with a patient.

Nowadays, there is a growing recognition that fuzzy-based CDSS may be used, beyond the research activities, to assist clinicians in practice, e.g. by taking over some routine tasks, by warning the clinicians of potential problems, or by providing suggestions for clinician considerations. It is well recognized that fuzzy logic formalism is suitable to deal with the imprecision and vagueness that are intrinsic to many medical problems, offering a more realistic interpretation for the clinical decision. Many fuzzy-based methodical approaches have been proposed in literature for the treatment and management of chronic diseases. A number of fuzzy-based DSS have been proposed in literature for specific diseases. An innovative and extensible approach, implementing a fuzzy-based Decision Support System (DSS)s for diagnostic applications, has been proposed by d’Acierno et al. [5], demonstrating the capability of fuzzy logic to overcome such critical issues in medical applications and decision support. In De Brito et al. [6] a DSS based on fuzzy model was developed to measure distress levels in cosmetic surgerypatients. In Papageorgiou et al. [7] a decision support module is produced by using a flexible approach called Fuzzy Cognitive Maps (FCMs) to handle with uncertainty and missing information during the treatment of uncomplicated Urinary Tract Infection (uUTI) treatment. In Esposito et al. [8] is described a fuzzy-based DSSs implemented for assessing the health status of subjects affected by multiple sclerosis during the disease progression over time. To this purpose five prototypes of DSSs have been built, each of them being associated to a different database, in order to compare their results against those provided by a set of widely used machine learning methods on the same set of databases. Successively, the approach has been specifically applied to build an evolutionary-fuzzy DSS for assessing MS patients health status. However it is obvious that the possibility of guaranteeing effective and appropriate services, that play an important role within the wider and complex course of patient’s treatment, will depend on resources, technologies and knowledge used to implement the CDSS [9], [10].

In this paper, in accordance to recent research trends in the care of the thalassemia [11]–[15], we focus our attention on a study related to the daily-care of β-thalassemia patients. More precisely, we improve the CDSS adopted by the RRBCDU at Cardarelli Hospital for the monitoring and management of β-thalassemia patients with fuzzy inference machines. Thalassemia syndromes are a group of hereditary blood disorders that are characterized by reduced, or absent, beta globin chain synthesis and anemia. This pathology represents, from a clinical point of view, an interesting model of multidisciplinary management where cardiologist, nephrologist, pneumologist, radiologist, endocrinologist, and many other specialists are involved in the follow-up of these patients coordinated by an hematologist or pediatrician, as historically it happens in all thalassemia units of the

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world. The possible advantages coming from the adoption of fuzzy-CDSS in outpatient care increase the hopes that this tool could also improve key outcomes of thalassemic patients and the related clinical conditions too. The expected impacts of the proposed fuzzy-based CDSS, on the thalassemia care outcomes, can be summarized as follow: i) improvement of thalassemia-related parameters control, such as the control of serum ferritin, iron overload or blood consumption, that actually can be done only in marginal way by exploiting common Electronic Health Record (EHR) systems; ii) improvement of complications control; iii) reduction of costs of care. In particular, the fuzzy-based CDSS, in conformity with the guidelines recommended at national level, leverages available data on the status of complications of about 450 patients treated at the RRBCDU of the Cardarelli Hospital (Napoli, Italy). To allow the use of inferential analysis tools, the system offers an easy-to-use Graphical User Interface (GUI) for summarizing, analyzing and processing large amounts of heterogeneous clinical data related to thalassemic patients.

The rest of the paper is organized as follows. Sec. II briefly describes the CDSS main features and the data used in the study. In Sec. III we present the fuzzy inference machine, by describing both knowledge representation and reasoning. In Sec. IV we first illustrate the fuzzy reasoning structure deployed for the specific case of the Liver Iron Overload evaluation and then we present some exemplary results on the practical use of the CDSS. Sec. V ends the paper with concluding remarks.

II. System and Data

The fuzzy-based thalassemia-related CDSS presented in this work is designed to be used from every device (computer, smart-phone tablet etc.) equipped with a browser and an Internet connection. The CDSS has been engineered as a system based on a three tier architectural model.

As of today, more than 450 patients have been treated at the RRBCDU of Cardarelli Hospital, counting for more than 400000 database records. Data of thalassemic patients are collected in different forms, such as time series, digital images, indexes (e.g., expressed in percentage), boolean variables, yes/no questions and can be related to:

- Personal information of the patients in treatment in the Cardarelli RRBCDU (name, surname, date of birth etc..);
- Information related to the performed transfusions of a patient with specific derived quantitative measures (Hb value pre and post transfusion, time interval, number of donor blood units etc.);
- Information obtained from the clinical tests executed to assess the blood iron stores (serum iron, ferritin, transferrin);
- Information obtained from heart and liver Magnetic Resonance Imaging (MRI) which patients regularly undergo with related data (T2*, iron in mg, heart function, Liver Iron Concentration (LIC), image path, etc.);
- Information obtained from the patient Cell Blood Count with all related values (Hb, Ht, red blood cells data, white blood cells data, etc.);
- Complication information: In the case a complication occurs – e.g. endocrine, cardiac, hepatic, iron-related, transfusion-transmitted infections etc. – information related to further secondary diseases is also acquired and stored.

All acquired information are transferred to the server, where relevant fields pertaining each patient are stored into the database. In order to protect the patient privacy during clinical trials, the patient name and other identifiers are correctly replaced with a unique numeric ID, so that all patients remain anonymous within the database structure [16].

III. Fuzzy Inference Machine

A. Knowledge representation

The design of a Fuzzy Inferential System (FIS) requires, first of all, the definition of the domain knowledge in cooperation with clinical experts by means of interviews, questionnaires and observation of their day-by-day clinical practice [8]. The domain of knowledge embedded into the decision mechanism of the system has been described in terms of linguistic variables, linguistic values and membership functions. A linguistic variable is a variable whose values are words or sentences in a natural or artificial language that can be used to ease a gradual transition between states, so as to naturally express vagueness in measurements, unlike crisp variables.

Definition 1. *Linguistic Variable [17]. A linguistic variable (also named fuzzy variable) can be characterized by a quintuple* $(\mathrm{L}, \mathrm{F}(\mathrm{L}), \mathrm{U}, \mathrm{R}, \mathrm{M})$ *in which* L *is the name of the variable;* $\mathrm{F}(\mathrm{L})$ *is the term-set of* L*, that is, the collection of its linguistic values;* U *is a universe of discourse;* R *is a syntactic rule which generates the terms in* $\mathrm{F}(\mathrm{L})$*; and* M *is a semantic rule which associates to every linguistic value* X *its meaning,* $\mathrm{M}(\mathrm{X})$*, where* $\mathrm{M}(\mathrm{X})$ *denotes a fuzzy subset of* U.

Definition 2. *Fuzzy Variable [17]. A fuzzy variable is characterized by a triple* $(\mathrm{L}, \mathrm{U}, \mathrm{F}(\mathrm{L}; \mathrm{u}))$*, in which* L *is the name of the variable;* U *is a universe of discourse (finite or infinite set);* u *is a generic name for the elements of* U*; and* $\mathrm{F}(\mathrm{L}; \mathrm{u})$ *is a fuzzy subset of* U *which represents a fuzzy restriction on the values of* u *imposed by* L. $\mathrm{F}(\mathrm{L}; \mathrm{u})$ *will be referred to as the restriction on* u *or the restriction imposed by* L*. The assignment equation for* L *has the form*

$$\mathrm{x} = \mathrm{u} : \mathrm{F}(\mathrm{L}) \tag{1}$$

and represents an assignment of a value u *to* x *subject to the restriction* $\mathrm{F}(\mathrm{L})$.

In the universe of discourse U a fuzzy set $F(L; u)$ is characterized by a membership function $\mu(F)$ that assigns a membership value to elements u, within a predefined range of U, as follows: $F = \{(u, \mu_F) | u \in U \text{ and } \mu_F : U \rightarrow [0, 1]\}$. In practice, a membership function is a curve that defines how each element in the input space is mapped to a membership value (or degree of membership) between 0 and 1.

In order to grant a simple interpretation of the knowledge modeled via linguistic variables, linguistic values and membership functions have been designed following the approach presented by Gariabaldi et al. [18].

To perform the fuzzy inference, the knowledge about the medical decision-making has been formalized in terms of fuzzy "if-then rules" relying on the structure defined for the domain of knowledge. In so doing, fuzzy inference relies on rules, defined as conditional statements written in the form "if antecedent then consequent", where antecedent is a fuzzy-logic expression composed of one or more simple fuzzy expressions connected by fuzzy operators, and consequent is an expression that assigns linguistic values to the output variables [8]. Indeed, fuzzy logic provide a tool that enables to approximate an inference process i.e. the mental process by which human reach a conclusion based on specific evidence.

B. Knowledge Reasoning

To create the inferential engine, for the evaluation of some clinical aspect related to the patients' status, all clinical variables have been linked in a Mamdani-style fuzzy inference system according to different rules and membership functions [19], [20]. The Mamdani scheme is a type of fuzzy relational model where each rule is represented by an "if antecedent then consequent" relationship. Mamdani method is widely accepted for capturing expert knowledge. It allows us to describe the expertise in more intuitive, more human-like manner [21].

In the following is described the Mamdani method and basic knowledge implemented into the system. At this stage of the implementation of the fuzzy inference engine, we refer to a multi-inputs single-output decision model.

Definition 3. *Given* m *"if antecedent then consequent" fuzzy rules* $\mathrm{R} = \{\mathrm{R_1}; \ldots; \mathrm{R_m}\}$*, with* n *continuous input variables* $\mathrm{u_i}$*,* $\mathrm{i} = 1, \ldots, \mathrm{n}$*, and the output variable* y*, the formulation of the fuzzy rules is defined as follows:*

$$\begin{aligned} &\mathrm{if}(\mathrm{u_1}, \mathrm{A_{1,1}})\mathrm{AND}(\mathrm{u_2}, \mathrm{A_{1,2}})\mathrm{AND}\ldots\mathrm{AND}(\mathrm{u_n}, \mathrm{A_{1,n}})\mathrm{THEN}(\mathrm{y}, \mathrm{B_1}) \\ &\vdots \\ &\mathrm{if}(\mathrm{u_1}, \mathrm{A_{m,1}})\mathrm{AND}(\mathrm{u_2}, \mathrm{A_{m,2}})\mathrm{AND}\ldots\mathrm{AND}(\mathrm{u_n}, \mathrm{A_{m,n}})\mathrm{THEN}(\mathrm{y}, \mathrm{B_m}) \end{aligned} \tag{2}$$

where u_i *are the input variables,* y *is the output variable,* A_{ij} *and* B_i *are fuzzy sets of the associated universes of discourse.*

Now to perform inference, the first step is to evaluate the "antecedent", which involves fuzzyfying the input and applying any necessary fuzzy operators to each rules in R.

Definition 4. *Given the information input* $\mathrm{u} = \{\mathrm{u_1}, \ldots, \mathrm{u_n}\}$*, the strength level or membership* α_i *of the rule* $\mathrm{R_i}$ *is calculated in terms of the degrees of membership* $\mu_{\mathrm{A_{ij}}}$*. If the antecedent clause (the* if *part) are connected with* AND *then:*

$$\alpha_\mathrm{i}(\mathrm{u}) = \min(\mu_{\mathrm{A_{i,1}}}(\mathrm{u_1}), \ldots, \mu_{\mathrm{A_{i,n}}}(\mathrm{u_n})). \tag{3}$$

Else if the antecedent clause are connected with OR *then:*

$$\alpha_\mathrm{i}(\mathrm{u}) = \max(\mu_{\mathrm{A_{i,1}}}(\mathrm{u_1}), \ldots, \mu_{\mathrm{A_{i,n}}}(\mathrm{u_n})). \tag{4}$$

Each fuzzy rule yields a single number that represents the firing strength of that rule. The second step is "implication", or applying the result of the antecedent to the consequent. Indeed, the strength level is then used to shape the output fuzzy set that represents the consequent part of the rule.

Definition 5. *The operator of implication for the rule* $\mathrm{R_i}$ *is defined as the shaping of the "consequent" (the output fuzzy set), based on the "antecedent". The input of the implication process is a single number given by the "antecedent" (i.e.* α_i *computed as in Definition 4), and the output is a fuzzy set:*

$$\mu_{\mathrm{B_i}}(\mathrm{y}) = \min(\alpha_\mathrm{i}(\mathrm{u}), \mu_{\mathrm{B_i}}(\mathrm{y})) \tag{5}$$

where y *is the variable that represents the support value of output the membership function* $\mu_{\mathrm{B_i}}(\cdot)$*.*

Now, in order to unify the outputs of all the rules, we need to *aggregate* the corresponding output fuzzy set into one single composite set. The inputs of the *aggregation* process are represented by the clipped fuzzy sets obtained by the implication process. The *aggregation* method we exploited in our application is the $max(\cdot)$ one. Finally the defuzzification process has been performed starting from the output fuzzy set resulting from the *aggregation* process.

Definition 6. *The operations of defuzzification is computed as the center of gravity (*COG*) of the strength levels*

$$\mathrm{COG}(\mathrm{y}) = \frac{\sum_{\mathrm{i}=1}^{\mathrm{m}} \mathrm{y}\mu_{\mathrm{B_i}}(\mathrm{y})}{\sum_{\mathrm{i}=1}^{\mathrm{m}} \mu_{\mathrm{B_i}}(\mathrm{y})}. \tag{6}$$

IV. Results

In this section, we provide an overview of one of the fuzzy-based functionalities implemented into CDSS for the practical use on the field.

A. Fuzzy reasoning structure for the evaluation of Iron Overload

In what follows we describe, as exemplar case, the implementation of the FIS for the evaluation of the liver and heart status of a patient. In this scenario, the crucial parameters for the assessment of Iron Overload in the liver and heart [22] are LIC and $T2^\star$ [23]. Specifically, LIC (sometimes also referred as HIC - Hepatic Iron Concentration) results from a test that gives a complete picture of how much iron is in the liver (the test is performed by a non-invasive procedure leveraging magnetic resonance imaging, or MRI). Moreover, since MRI signals darken more quickly in regions of increased iron concentration this darkening process can be described by a half-life, similar to radioactive decay. The half-life for a spin-echo image is known as $T2$ and the half-life for a gradient echo is known as $T2^\star$ (the greater the tissue iron, the smaller the T2 and the $T2^\star$ become). The goal of the FIS is to synthesize on

a colored based scale the different grades of severity related to the Iron Overload for liver and heath of the thalassemic patient.
The fuzzification of the inputs (i.e. $T2^\star$ and LIC) has been here achieved by using triangular and trapezoidal membership functions defined in accordance with threshold values provided by medical researcher, doctors, and clinicians of the RRBCDU of Cardarelli Hospital, in Naples, Italy.
In particular, for LIC (see Fig. 1a) we have: DAnger Lic (DAL), ALlarm Lic (ALL), SUfficient Lic (SUL), GOod Lic (GOL). While for $T2^\star$ (see Fig. 1b) we have: DAnger $T2^\star$ (DAT), SUfficent $T2^\star$ (SUT), GOod $T2^\star$ (GOT). The membership functions related to the fuzzy sets have been generated according to the indication of the clinicians, as described below:

$$\mu_{DAL}(LIC) = \begin{cases} (LIC-14)/3 & \text{if } 14 < LIC < 17 \\ 1 & \text{if } LIC \geq 17 \end{cases}$$

$$\mu_{ALL}(LIC) = \begin{cases} (LIC-5)/6 & \text{if } 5 < LIC \leq 11 \\ (-LIC+11)/6+1 & \text{if } 11 < LIC < 17 \end{cases}$$

$$\mu_{SUL}(LIC) = \begin{cases} (LIC-2)/3 & \text{if } 2 < LIC \leq 5 \\ (-LIC+5)/3+1 & \text{if } 5 < LIC < 8 \end{cases}$$

$$\mu_{GOL}(LIC) = \begin{cases} 1 & \text{if } 0 \leq LIC \leq 1 \\ (-LIC+1)/3+1 & \text{if } 1 < LIC < 4 \end{cases}$$

$$\mu_{DAT}(T2^\star) = \begin{cases} 1 & \text{if } 0 \leq T2^\star \leq 7 \\ (-T2^\star+7)/4+1 & \text{if } 7 < T2^\star < 11 \end{cases}$$

$$\mu_{SUT}(T2^\star) = \begin{cases} (T2^\star-8.67)/6.33 & \text{if } 8.67 < T2^\star \leq 15 \\ (-T2^\star+15)/6.67+1 & \text{if } 15 < T2^\star < 21.67 \end{cases}$$

$$\mu_{GOT}(T2^\star) = \begin{cases} (T2^\star-19)/4 & \text{if } 19 < T2^\star < 23 \\ 1 & \text{if } T2^\star \geq 23 \end{cases}$$

Starting from the membership functions, the set of rules (defined according to Definition 3) – synthetically reported in Tab. I and graphically represented in Fig. 2 – have been derived. The fuzzy rules will be optimized after further field tests.

Note that in our approach the fuzzy reasoning block for the liver and heart status evaluation incorporates 12 standard rules.

The associated output function has been constructed by using 12 triangular membership functions [24], [25] as reported in Fig. 1c. Each color is associated to a grade of severity of the liver and heart status, in particular we have: Red (R), Red Orange (RO), Orange (O), Yellow Orange (YO), Yellow (Y), Yellow Green (YG), Green (G), Blue Green (BG), Blue (B), Blue Violet (BV), Violet (V), Red Violet (RV). In our

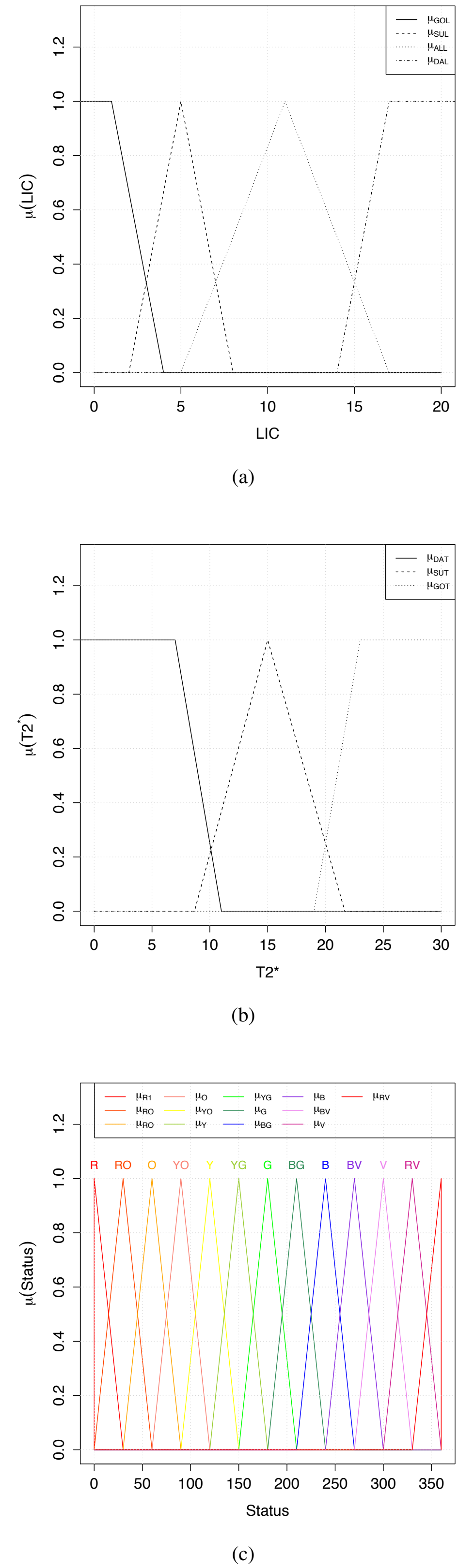

Figure 1. Membership functions. (a) Fuzzification of the LIC variable; (b) Fuzzification of the $T2^\star$; (c) output membership function for the evaluation of the liver and heart status.

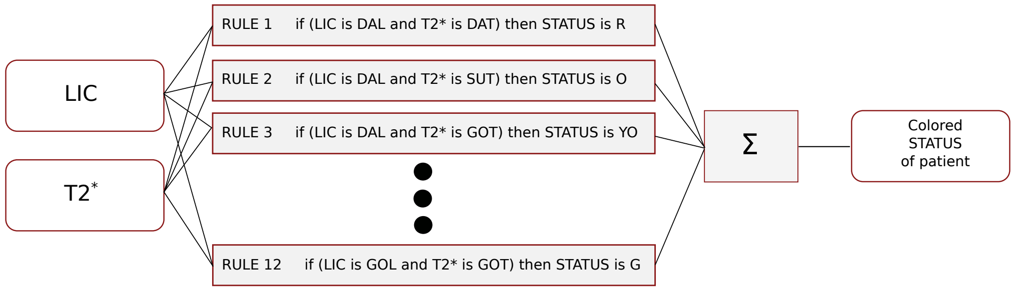

Figure 2. Logic flow of the fuzzy inference system of the *Liver Status* example.

Table I
FUZZY TUNING RULES.

		LIC DAL	ALL	SUL	GOL
$T2^\star$	DAT	R	RV	O	YO
	SUT	O	B	Y	YG
	GOT	YO	BG	YG	G

application a Green (G) output in associated to a good status while a Red (R) output is associated to a dangerous situation.

The fuzzy implication operator, implemented by the inference engine, has been computed according to Definition 5. The aggregation method to combine the output fuzzy sets into a single fuzzy set (in order to make a decision) is the $\max(\cdot)$ operator. The defuzzification process – through which the combined fuzzy set from aggregation process will output a single scalar quantity (i.e., the output color) – is based on Definition 6.

B. Results from the field: evaluation of Iron Overload

To provide an usage example on the field, among the more than 450 patients treated at the RRBCDU of Cardarelli Hospital (counting for more than 400000 database records), here we present exemplary results on the automatic evaluation of the Iron Overload – and its trend – for two given patients (namely ID 44 and ID 225). It is worth noticing that here we do not stress specific conclusions regarding the application domain, we are just presenting the features and the functionalities using an usage example. Evaluation done with patients with ID 44 and ID 225 is generalizable and applicable to the entire set of 450 patients and then medical and clinical conclusions can be easily provided.

In recent years, nuclear MRI techniques for assessing Iron Overload in the liver and heart have been introduced [26]. Indeed, it is possible to evaluate the clinical status of patients by leveraging on the inference machine and accounting for different measurements at the same time, $T2^\star$ for heart and LIC for liver [27].

Fig. 3 reports a screen shot of the “patient interface” for the evaluation of the liver and heart Iron Overload. Here the “liver and heart status” column represents the output of the fuzzy logic decision mechanism (see Sec. IV-A) that supports clinicians to evaluate the effectiveness of the medical therapy helping them to lead the patient’s clinical status in a safe zone (indicated by the color green). Clinicians can intuitively compare the patient’s clinical status with the “Color Scale” column, that reports a colored scale related to the several levels of severity.

Fig. 3a confirms that the care of the patient with ID 44, with respect to the Iron Overload, has been successful; indeed the patient’s status moves in the ranking from the red level (high risk situation) to the green one (no-risk, therapeutic goal met) and then shows a slight deterioration moving in the cyan level.

Fig. 3b reports a screen shot of the patient interface for the evaluation of iron overload in the liver and heart for the patient with ID 225. In this case is possible to observe that the treatment is ineffective, indeed the patient’s status doesn’t follow the ideal sequence. This situation may be due to a patient’s negative response to the treatment or to an unsuitable clinical choice.

V. CONCLUSIONS

In this paper, we illustrated a study on the use of fuzzy logic in the CDSS of the RRBCDU at Cardarelli Hospital (Napoli, Italy) for the monitoring and management of clinical status of β-thalassemic patients. The study has been executed in an interdisciplinary research team comprising doctors, clinicians and engineers and in this paper we have shown preliminary exemplary results on the on-line evaluation of Iron Overload. Thanks to the fuzzy-based features is possible to evaluate the clinical evolution of β-thalassemic patients and to give indications on the effectiveness of therapeutic process, thus reducing errors and time.

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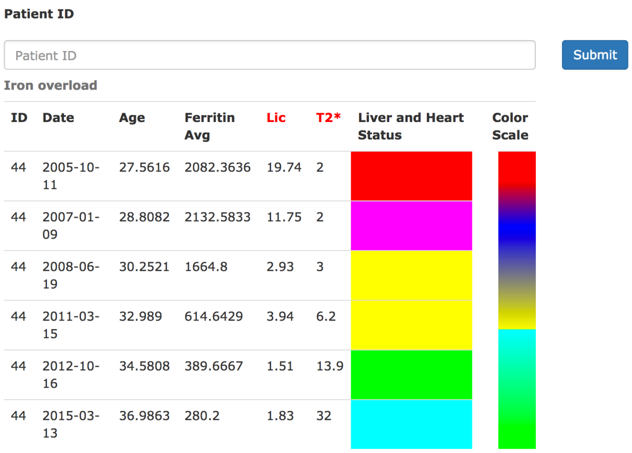


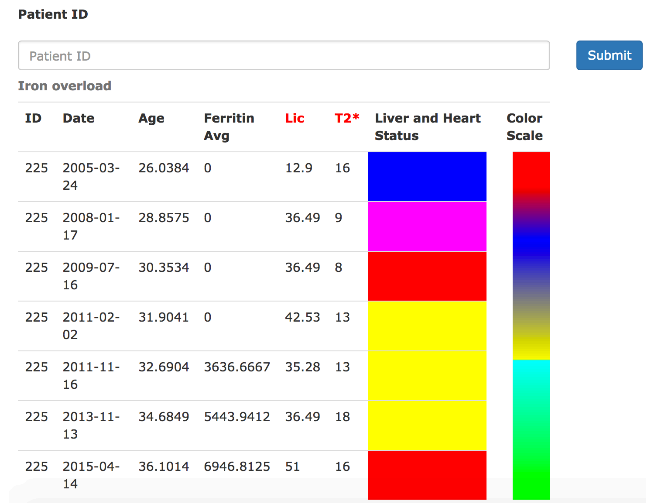
Patient ID

Patient ID | Submit

Iron overload

ID	Date	Age	Ferritin Avg	Lic	T2*	Liver and Heart Status	Color Scale
44	2005-10-11	27.5616	2082.3636	19.74	2		
44	2007-01-09	28.8082	2132.5833	11.75	2		
44	2008-06-19	30.2521	1664.8	2.93	3		
44	2011-03-15	32.989	614.6429	3.94	6.2		
44	2012-10-16	34.5808	389.6667	1.51	13.9		
44	2015-03-13	36.9863	280.2	1.83	32		

(a)



Patient ID

Patient ID | Submit

Iron overload

ID	Date	Age	Ferritin Avg	Lic	T2*	Liver and Heart Status	Color Scale
225	2005-03-24	26.0384	0	12.9	16		
225	2008-01-17	28.8575	0	36.49	9		
225	2009-07-16	30.3534	0	36.49	8		
225	2011-02-02	31.9041	0	42.53	13		
225	2011-11-16	32.6904	3636.6667	35.28	13		
225	2013-11-13	34.6849	5443.9412	36.49	18		
225	2015-04-14	36.1014	6946.8125	51	16		

(b)

Figure 3. The "Color Scale" column reports a colored scale related to the several levels of severity (from high risk (red level) toward no-risk, or therapeutic goal met (green level). The "Liver and Heart Status" column shows the real iron overload status evaluated at every MRI. (a) Evaluation of the iron overload status for patient with ID 44. (b) Evaluation of the iron overload status for patient with ID 225.

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