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Nonalcoholic Steatohepatitis Diagnosis - A Model-Related Personalized Medicine Approach

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Abstract. Nonalcoholic fatty liver disease (NAFLD) is a clinical syndrome, and pathologically characterized by diffuse macro-vesicular fatty change in the hepatocytes. NAFLD includes simple nonalcoholic fatty liver disease, nonalcoholic steatohepatitis (NASH) and hepatic cirrhosis. NASH is a disease evolving under the influence of various stimuli still poorly understood, but where insulin resistance is prominently. In this paper, we present a new diagnosis model to predict NASH.

Keywords. Nonalcoholic fatty liver disease, liver disease, clinical decision support system, knowledge representation, artificial intelligence, fuzzy logics

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in the world [1]. NAFLD is a clinical syndrome and pathologically characterized by diffuse macro-vesicular fatty change in the hepatocytes. NAFLD includes simple nonalcoholic fatty liver disease, nonalcoholic steatohepatitis (NASH) and hepatic cirrhosis [2]. NAFLD is a recently recognized entity related to modern lifestyle and with expanded clinical importance because of the rising incidence of obesity and diabetes. NAFLD is an increasingly recognized cause of liver-related morbidity and mortality, and it is frequently associated with insulin resistance. While insulin resistance and hyperinsulinemia are, in large part, metabolic consequences of obesity, the basis of diversity in severity and progression of inflammation and fibrosis is not known [3].

The presence of fat in the liver means the accumulation of triglycerides. This accumulation determines the evolution of the disease. Infiltration of 30% of hepatocytes is an incipient form, the moderate form means that 60% of hepatocytes were infiltrated, and the severe form induces over 60% of infiltration hepatocytes [4]. NASH is a disease evolving under the influence of various stimuli still poorly understood. However, in this disease, it is well know that insulin resistance is largely implied [5]. Risk factors for NASH/ Fibrosis are: Age over 45 years; Obesity; Diabetes/Insulin resistance; low platelets; low albumin; AST > ALT; and imaging signs of hyper portal hypertension.

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Several biological Nash prediction tests have been developed [6-7]. The evolution of NAFLD and NASH is variant for each patient, and it is important to use all relevant information to diagnose the disease such as clinical information, biological test, genomic information, and imaging. In this paper, we describe a new diagnosis support system based on validated knowledge from scientific literature and clinical practice guidelines (CPG) to diagnose NASH. We tested our diagnostic model with database of 36 patients generated randomly.

1. Methods

We have developed a framework for interacting with patient's heterogeneous data (omics, clinical and biological information) and formalizing medical knowledge.

1.1. CPG Formalization:

In the present work, we used not only clinical practice guideline [8] CPGbut also scientific literature as sources of knowledge. We have developed a Fuzzy Semantic Web Reasoning approach using the RDF/N3 language to express the rules from the knowledge sources [9]. This approach was previously tested for Infectious diseases diagnosis decision support [10].

1.1.1. Case Based Fuzzy Cognitive Maps (CBFCM)

Case Based Fuzzy Cognitive Map (CBFCM) is a hybrid decision-making computing technique [9]. CBFCM is represented as nodes (concepts) that illustrate the different aspects of the system's behavior. Concepts may represent variables, states, events, inputs and outputs, which are essential to model a system. The value of each node (concept) is represented as Fuzzy Set. Figure 1 is a graphical representation of CBFCM method. A patient N is described by a set of clinical parameters (C1, C2, and Cn). Those clinical

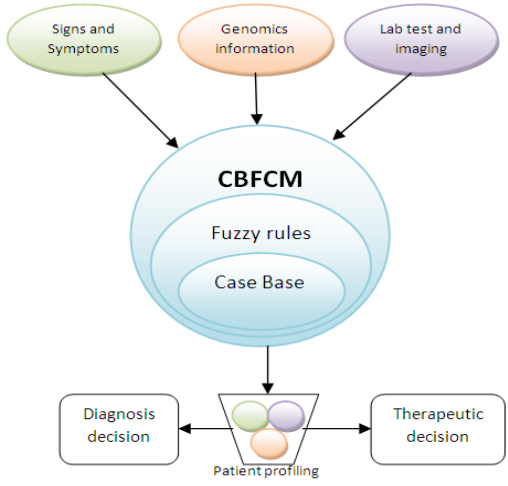

Figure 1. Diagram representing the CBFCM method

parameters can be clinical signs, age, gender, genetic profile, or biological results. D1 represents the decision concept, here the diagnosis of NASH, and W_{ij} represent the strengths of the relationships between concepts.

The construction of CBFCM [10] is consisting of three parts: (a) to determine concepts and (b) to determine the strength of cognitive relationships between concepts (c) to explicit fuzzy control rules.

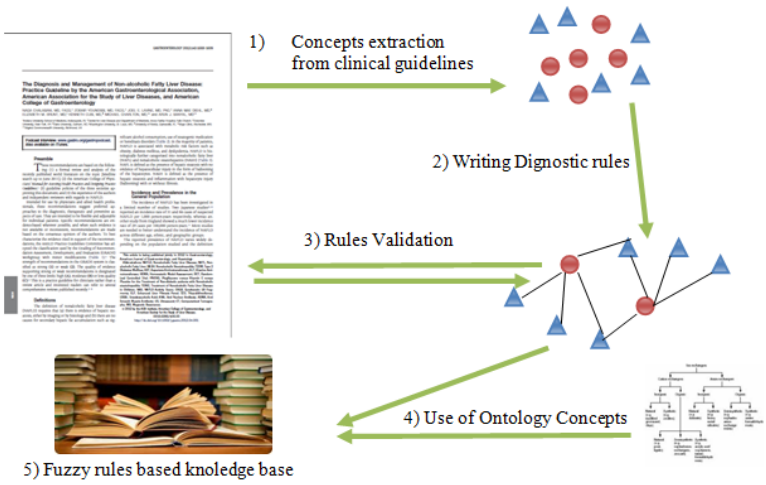

Figure 2. CPG fuzzy formalization method

In the Semantic Web N3 formalism, the weights W_{ij} are in the range (0,1), each weight (concepts' influences) presents a degree of influence from 0 to 1 [10, 11].

1.1.2. Information Model

The Semantic Web framework based on CBFCM integrate heterogeneous data: Clinical data (signs, symptoms, …); Biological data (lab test, ...); Imaging and omics data. To create a patient clinical profile, we need to use all these types of data. These data are annotated with SNOMED CT concepts. We extracted a related part of SNOMED CT using UMLS.

2. Results

We extracted 18 clinical concepts and these concepts are annotated with SNOMED CT concepts (Table 1).

Table 1. Clinical concepts of NASH diagnosis model

Clinical concepts	Label Description	SNOMED CT Concepts ID
C1	Hyperglycemia	80394007
C2	Hypertriglyceridemia	302870006
C3	HDL	9422000
C4	Hypertension	38341003
C5	BMI	60621009
C6	Waist circumference	276361009
C7	Fasting insulin	252251004
C8	Index HOMA-IR	237650006
C9	Alcohol consumption	160580001
C10	ALT	250637003
C11	AST	250641004
C12	Apolipoprotein	259599001
C13	GGT	60153001
C14	Haptoglobin	85294008
C15	α -fetoprotein	16236008
C16	Adiponutrine gene profil	413451007
C17	Old-Age	70753007
C18	Sex	263495000
D1	NASH	197321007

We tested our diagnostic model with database of 36 patients. We have a performance of 91%. Figure 3 is an example of result rules. The output are N3 triples: PatienIdxxx is the ID of our patients, snomedct:266468003 is a decision concept (NASH), and fl:pi is the confidence degree of the rule.

```
48 (:PatientId0328 snomedct:266468003) fl:pi 0.999959699696969.
49 (:PatientId0329 snomedct:266468003) fl:pi 0.999912345521133.
50 (:PatientId0330 snomedct:266468003) fl:pi 0.998752019938721.
51 (:PatientId0331 snomedct:266468003) fl:pi 0.997674901812091.
52 (:PatientId0329 snomedct:266468003) fl:pi 0.988729171911901.
```

Figure 3. Example of decision rules

3. Discussion and Conclusion

The CBFCM approach allowed us to integrate heterogeneous clinical data to perform a personalized patient profile. This method can identify causal relationships between clinical, biological, genetic concepts and decision concept (Diagnosis of NASH). The use of CBFCM enables to incorporate several sources of knowledge (several CPGs, knowledge from literature), which is of great advantage since all knowledge is rarely

embedded in a unique CPG. Indeed, knowledge of a medical field is usually broad, complex and closely related to other areas so that several knowledge sources are needed to cover and modeled the medical domain in question.

We have implemented the knowledge bases, rules and databases in the same environment (RDF, N3, Euler...) without compatibility constraints; this is one of the advantages of using Semantic Web tools. The success rate of 91% shows the functionality of the model and its future usefulness in clinical practice.

The conducted study allowed us to test cognitive approaches reasoning to enable personalized medicine. The advantage of this approach is to enable the sharing and reuse of knowledge and simplify maintenance. This work represents a preliminary step in developing a CDSS and we'll use a clinical database to test this system and to compare it with others statistic reasoning methods.

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