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ORIGINAL ARTICLE

Analysis and decision based on specialist self-assessment for prognosis factors of acute leukemia integrating data-driven Bayesian network and fuzzy cognitive map

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Abstract

The purpose of the present study is to analyze the prognostic factors of acute leukemia and to construct a decision model based on a causal relationship between the factors of this disease to assist medical specialists. In medical decisions, to reach effective, quick, and reliable results, there is a need for a simple decision-making model based on a specialist's self-assessment. It may help the medical team before final diagnosis by costly and time-consuming procedures such as bone marrow sampling and pathological test as well as provide an appropriate prognosis and diagnosis tool. Because of the complex and not the well-defined structure of medical data, the use of intelligent methods must be considered. For this purpose, first, a data-driven Bayesian network (BN) and Greedy algorithm are employed to determine causal relationships and probability between nodes using the real set of data. Then, these causal relationships will form based on the fuzzy cognitive map (FCM). Finally, according to scenarios defined, the results are analyzed. These analyses are also repeated for each type of acute leukemia including acute lymphocytic leukemia (ALL) and acute myelocytic leukemia (AML).

Keywords Data-driven Bayesian network · Fuzzy cognitive map · Decision-making based on self-assessment · Medical data · Prognosis factors · Acute leukemia

Abbreviations

ALL	Acute lymphocytic leukemia
AML	Acute myelocytic leukemia
ADR	Adverse drug reaction
ANN	Artificial neural network
ASD	Autism spectrum disorder
BHMM	Bayesian hidden Markov model
BN	Bayesian network
BF	Bootstrap forest
CBFCM	Case-based fuzzy cognitive maps
CSONN	Cat swarm optimization neural network
CNS	Central nervous system
CXR	Chest X-ray
CLL	Chronic lymphocytic leukemia
CML	Chronic myelogenous leukemia
CBC	Complete blood count
CT	Computed tomography
DEA	Data envelopment analysis
DSS	Decision support system
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
ESR	Erythrocyte sedimentation rate
EBP	Evidence-based practice
FCM	Fuzzy cognitive map
HSCT	Hematopoietic stem cell transplant
Hb	Hemoglobin
HIV	Human immunodeficiency virus
LDH	Lactate dehydrogenase
LSTM	Long short-term memory network
MRI	Magnetic resonance imaging
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MDSS	Medical decision support system
NHL	Nonlinear Hebbian learning
PSO	Particle swarm optimization

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Plt	Platelet
PC	Prototypical constraint-based
RNN	Recurrent neural network
RBC	Red blood cell count
SVM	Support vector machine
TAN	Tree augmented naïve
UTI	Urinary tract infection
WBC	White blood cell

1 Introduction

Medical data analysis is one of the areas of interest to researchers in the recent decade. The main purpose of medical data analysis is to help medical specialists make quick and accurate decisions about diseases. It leads to earlier treatment, which is vital in medicine. On the other hand, the nature of medical data, which is a very complex and not well-defined data structure, makes the analysis difficult. Furthermore, many medical diagnostic methods are costly and time consuming. For this reason, it is important to provide simple, automatic, and intelligent methods that can help specialists before the final diagnosis and provide an appropriate prognosis and diagnosis. One of these diagnostic methods is bone marrow sampling and its pathological result.

New methods of decision-making in complex systems are presented using existing knowledge, human experience, learning capabilities, and advanced features. Fuzzy cognitive map (FCM) has been presented as a way of modeling and controlling complex systems. The concepts in FCM are influenced by specific rules and the operation of complex systems is simulated. In other words, FCMs are symbolic representations for describing and modeling complex systems. They are made up of concepts that represent different aspects of the behavior of the system, their effectiveness, and their impact on each other also indicate the dynamics of the system. On the other hand, a Bayesian network (BN) is a non-circular directed graph showing a set of random variables and their independent relation. For example, a BN may indicate a link between the cause of the disease and the disease itself. So, with the help of factors, it is possible to diagnose a particular disease in a patient.

The present study provides a self-assessment approach of acute leukemia for specialists by integrating data-driven BN and FCM. After determining the factors affecting acute leukemia, data on the disease are collected and causal relationships are identified based on BNs. In our proposed approach, a data-driven BN is used for this purpose. In data-driven BNs, causal relationships and probability between nodes use the real set of data and employ intelligent algorithms. Then, these causal relationships will form based on FCM. Afterward, using the experts' opinion, the relationships will be quantified and finally, the network is trained using the learning algorithm. Finally, according to scenarios defined, the results are analyzed. These analyses are also repeated for each type of acute leukemia including acute lymphocytic leukemia (ALL) and acute myelocytic leukemia (AML).

The hybrid approach presented in the present study was performed for the first time for acute leukemia. Not only determining the significance of each symptom affects any type of leukemia but also combining it with the BN is one of the contributions of this research. Applications of FCMs are based on expert knowledge. According to a hybrid approach performed in this research, the provided cognitive map is just based on clinical and paraclinical data and performed as a BN's output. BNs are incapable to analyze and determine the significance of each symptom. In other words, they are useful tools to specify conditional probabilities. It is important to mention that different symptoms can be a different behavior for each type of disease. Considering the reviewed literature, the proposed prioritization approach is another new application of cognitive mapping presented in the present paper.

The rest of the present paper is organized as follows. Section 2 focuses on the research background that has been done using the BN and the FCM approach in medicine. Then, in Section 3, BN and FCM used in this research are introduced. In Section 4, the proposed approach of this research is introduced and decision-making based on specialist self-assessment method for acute leukemia is explained. In Section 5, the proposed approach is implemented in acute leukemia and the results and scenarios analysis are presented. Finally, the conclusion of the research is given in the last section.

2 Literature review

2.1 Bayesian network

BNs are useful tools for reasoning about casual issues. Lappenschar et al. have used multi-layer BNs as an appropriate alternative method for multi-layer regression of analyzing hierarchical healthcare information [1]. Oniśko et al. have studied the accuracy of BNs for the diagnosis of liver disorders [2]. Results show that the accuracy of BNs does not reduce with decreasing parameter accuracy. Constantinou et al. used BNs in forensic medical science which can help the decision-maker to reach better outcomes [3]. Another application of BNs in medical cases is decision-making based on the questionnaire and experts' opinions in addition to using the information on complex systems [4]. One of the recent studies of using BNs about causality evaluating adverse drug reactions for reducing the assessment time done by Rodrigues et al. [5]. The goal of the present study is to increase the efficiency of health centers. In another study, the effect of one-carbon metabolism in colorectal cancer by applying multi-variable BNs was accomplished [6]. This is the first study of using BNs in one-carbon metabolism context.

Table 1 Summary of reviewed studies used FCM and BN

Authors	approach	Case study	Results
Lappenschaar et al. 2013 [1]	Multilevel BN	Disease prediction (cardiovascular disease, diabetes mellitus)	Improvement of reclassification
Oniśko and Druzdzel. 2013 [2]	BN	Medical diagnostic systems (liver disorders, acute inflammation, single-photon emission CT heart, cardiotocography, hepatitis, lymphography, primary tumor)	Diagnostic accuracy
Constantinou et al. 2016 [3]	BN	Forensic medicine	Applicable to interventional and counterfactual BN, amendment consideration
Constantinou et al. 2016 [4]	BN	Forensic psychiatry	Applicable to cases with complex data, accuracy of prediction, data and knowledge consideration
Rodrigues et al. 2017 [5]	BN	ADR	Decrease assessment time, causality detection
Myte et al. 2017 [6]	BN	Colorectal cancer	Method's effectiveness in assessing complex biological systems
Manogaran et al. 2018 [7]	HMM, Gaussian mixture clustering	Cancer diagnosis	Effectiveness of model
Xu et al. 2018 [8]	BN	Breast cancer	Interrelations between symptoms, decrease overfitting, robustness, strong tool for cancer symptom studies
McNally et al. 2017 [9]	Regularized partial correlation network, BN	Childhood sexual abuse (posttraumatic stress disorder)	Considering participants with interpersonal stressors, defining correlations among symptoms, considering causal relationships
Papgeorgiou 2006 [10]	Decision Tree-FCM	Urinary bladder cancer	Hybrid application to various kinds of data
Giles et al. 2007 [11]	FCM	Diabetes	The capability of comparing different knowledge systems
Papgeorgiou 2011 [12]	Augmented FCM decision support system based on fuzzy rule–extraction methods	Medical decision-making (radiothera-py and prostate cancer)	Improvement of knowledge-based system, managing uncertainty, simplicity, fuzzy rule base generation
Douali et al.2011 [13]	Case-based FCMs	Urinary tract infection	CBFCM's superiority
Subramanian et al. 2015 [14]	Two-level FCM	Medical decision support system (breast cancer)	Screening mammogram, risk level prediction
Büyükavcu et al. 2016 [15]	Rule-based FCMs	Breast cancer	Considering modifiable and non-modifiable risk factors, weight determination of risk factors, different scenarios
Sarabai and Arthi 2016 [16]	FCM, cat swarm optimization neural network (Csonn)	Breast cancer	Reducing errors by using the optimization algorithm
Amirkhani et al. 2017 [17]	FCM	Medical decision support systems, disease diagnosis, medicine	A review study of FCM application in medical concepts
Bevilacqua et al. 2018 [18]	FCM	Adverse drug event	Identifying relevant risk factors, effective knowledge-modeling tool
Chakraborti and Nandi. 2018 [19]	FCM	HIV infection	A useful tool in complex and dynamic systems, Identifying HIV related disease
Rezaee et al. 2018 [20]	FCM, multi-group data envel-opment	Hospital	Group evaluation of hospitals, considering cause and effect between inputs and outputs
Rahimi et al. 2018 [21]	FCM	Health technology adoption (elderly women)	Useful for decision-makers, improve analyzing ability
Topuz et al. 2018 [22]	SVM, ANN, BF, BN	Kidney transplant	Examining variable interactions, multiple features, improve the accuracy of prediction
Shree and Sheshadree. 2018 [23]	Naïve Bayes	Alzheimer disease	Accuracy evaluation of classification
Amirkhani et al. 2018 [24]	Probabilistic Fuzzy C-means	Celiac disease	Good transparency, interpretable
Liu et al. 2018 [25]	Self-adaptive FCM, Bayesian theory and PSO algorithm	Pulmonary nodules segmentation	Cluster center accuracy, better performance in segmentation and efficiency
Leclerc et al. 2018 [26]		Pediatric HSCT	

Table 1 (continued)

Authors	approach	Case study	Results
	TAN Bayesian network, logistic regression, naïve Bayes, SVM, random forest		TAN Bayesian illustrate best characteristics, decreasing adverse effects risks, simulation and determining dosing regiment
Duneja et al. 2019 [27]	RNN, LSTM, genetic algorithm, adaptive FCM	Prostate cancer, epileptic seizure recognition, EEG eye state	The dependency of parameters, strength of dependencies, improvement in results, person (patient)centric approach of treatment
Puerto et al. 2019 [28]	Multilayer FCM	ASD	Diagnosing of ASD, more robustness, versatility
Cypko and Stoehr. 2019 [29]	BN	Laryngeal cancer	Validation of model
Leng et al. 2020 [30]	BN	Dementia	Non-pharmacological interventions effectiveness

Hidden Markov Bayesian method and Gaussian mixture clustering is a new approach in detecting the changes of DNA and its effects on causing diseases like cancer [7]. Xu et al. addressed about problems of breast cancer patients in a three-time frame of before chemotherapy, end of cycle 4 of chemotherapy, and 1 year after the start of chemotherapy process [8]. The goal of the present study is to find the relation of the sign of fatigue, depression, and sleep, and the effects of them on function and life quality of breast cancer patients. Childhood abuse and its effects on a person's life quality is one of the important issues in human societies. Posttraumatic stress disorder symptoms of patients with childhood abuse experience are taken into consideration by applying a BN to illustrate the connection of symptoms [9].

2.2 Fuzzy cognitive maps

Several applications of FCMs have been reported by researches. Papageorgiou et al. are the pioneers of using FCMs [10]. In the mentioned study, a new model of medical decision-making is presented by combining the decision tree and FCMs in the case of different input data. FCMs are one of the applications of comparing and integrating conventional scientific methods with Canadian aboriginal communities' treatment on diabetes [11]. FCMs are also used in medical radiotherapy treatment based on the fuzzy rule–extraction [12]. Another application of using FCMs is to design decision support systems. For this purpose, Douali et al. used case-based FCMs for medical decision support systems [13]. Furthermore, breast cancer is one of the prevalence of diseases of women that early diagnosis can save patients. One of the works in the breast cancer field is done which is aimed at predicting risk factors of breast cancer by proposing the FCM model [14]. Another study focused on detecting dangerous and risky factors of breast cancer based on rule-based FCMs [15]. Results show that social class and pregnancy at a late age than normal population are important amendable factors, as well as benign breast problems, family history, and breast density, which are non-amendable factors of breast cancer. In one other work, breast cancer was classified by improved FCM [16]. Amirkhani et al. reviewed the importance of applying efficient medical decision support systems in reducing medical errors [17]. Comparison of fuzzy logic, neural networks, and FCMs in the present study shows that FCMs are one of the most practical and efficient methods for medical decision support system (MDSS). In one recent study of drug administration and management, the field has been researched with the FCM approach. The goal of work was to improve the quality of a patient's life by reducing errors [18]. Furthermore, FCMs are useful methods for modeling the effects of deadly diseases and infections on the health of patients who are suffering from HIV infection [19]. Rezaee et al. used FCMs and multi-group DEA for categorizing 27 hospitals to performance evaluation [20]. Finally, FCMs apply to health technology planning decisions [21]. Table 1 summarizes the studies used by FCM or BN including approach, case study, and results. These studies depict the integrated FCM and BN is rarely used specially in medical data analysis.

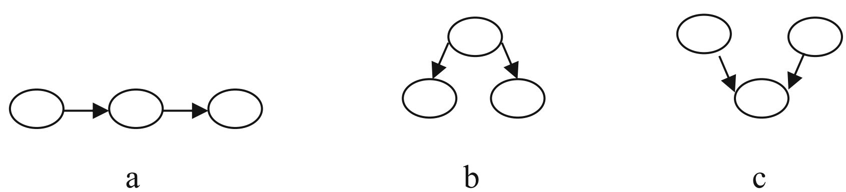

Fig. 1 Three types of causal chain: **a** sample of causal chain, **b** sample of common cause, **c** sample of common effect

3 Methodology

3.1 Bayesian approach

Bayesian theory is formed based on the probability of occurrence of an event based on considering primary knowledge of its condition. The importance of this theory is to determine the probability of occurrence or non-occurrence of another event based on posterior probability distribution. In most cases, directly calculating the probability of an event is difficult. Based on using Bayesian theory, calculating the conditional probability is much easier. The posterior probability is calculated as follows:

$$\mathbf{P}\left(\boldsymbol{\theta}|X\right) = \frac{\mathrm{P}(\mathrm{X}|\theta\ \left.\right)P(\theta)}{\mathrm{P(X)}} \tag{1}$$

where P(x) is defined as marginal distribution, P(θ) is prior distribution and P(X|θ) is considered as likelihood function of information. One of the most important tools based on Bayesian theory is BNs. BNs are widely used in probability reasoning and they are developed to a tree on reasoning probability. The BN is usually distributed among variables with acceptable primary values and relations. On the other hand, BNs are a way to represent a large continuous probability distribution exponentially and compactly, which allows for efficient calculation of probabilities. These networks use a graphic model structure for independent principles and criteria among random variables. BNs are often used for probabilistic model conditions and help to reason under indeterminate conditions such as probable conditions or uncertainty. A BN represents probable cause and effect relations in a group of random variables, conditional dependence, and also their probable shared distribution [31].

A BN is a graphical structure consisting of a random variable ($X = x_1, x_2, x_3,\ldots, X_n$) in the form of a node. Arrows show direct dependence among variables which is determined from conditional probability distribution among them. The only limitation in BNs is the impossibility of forming a circle. In other words, any conditional probability distribution in one node is calculated and defined for cause and effect outputs of previous nodes. The previous nodes are considered as parents and subsequent nodes are considered as children. Figure 1 shows a sample of a BN structure [32]:

3.2 Fuzzy cognitive maps

FCMs are a method to reveal the structure and mental content of individuals. By providing a simple model, this method controls individuals' understanding of the decision-making process at the individual level. FCMs were defined as an extension of cognitive maps by Kosko in 1986 [33]. Kosko expanded cognitive maps by giving real numbers in [−1, 1] or [0, 1] to causal relations. The structure of FCMs is derived from engineering knowledge which requires experts in that system. An expert establishes fuzzy maps by defining existing concepts in the system and type and relations of these concepts with each other. The main steps in this process are: identifying concepts, identifying cause and effect relations, and estimating the strength of relationships. In general terms, FCMs are a combination of fuzzy logic and cognitive maps.

The main components of the cognitive map are nodes and arcs between the nodes as well as the arc mark. Nodes represent concepts that describe the system and arrows represent cause and effect relationships between concepts and arc marks represent the type of cause between concepts. The relationship between two arrows has a definite weight which is a matrix of weights obtained from interviews with experts. In a calculation-based FCM method, time-series data are used as inputs and a neural network is used to estimate the weights. This perspective can be divided into pseudo-automatic and automatic categories. In a pseudo-automatic category which is often used, the input obtained from the expert's knowledge and experience on study subject is needed to draw a Fuzzy Cognitive ap. Based on this input, concepts and cause and effect relationships can be drawn. In drawing an automatic cognitive map, numerical vectors are converted to fuzzy sets, and the degree of similarity between vectors and the type of communication between them is determined by using fuzzy logic.

After drawing the cognitive map, the model is analyzed and modeled through a mathematical formula. By obtaining the value of one node, values of other nodes which have a relationship with this node can be obtained from the following equation:

$$A_i^{k+1} = f\left(A_i^k + \sum\nolimits^{N}_{\substack{i\neq j\\ j=1}}\ A_i^k w_{ji}\right) \tag{2}$$

Where $A_{\mathrm{i}}^{(k+1)}$ is the value of c_i in $K+1$ repetitions. A_i^k is the value of c_i in k-repetition. w_{ji} is the weight of the connection from concept c_j to concept c_i. N is the number of concepts (nodes). F(x) is a transformation function which returns the multiplication of 2 matrices out of defined range into the defined range. Finally, a variety of cognitive maps include cognitive-taxonomic fuzzy maps, dynamic cognitive networks, gray FCM, randomized dynamic FCM, fuzzy cognitive networks, evolutionary FCM, and cognitive maps with fuzzy times.

In this research, we introduce a new approach combining FCMs and BNs with a fuzzy inference system. The FCM approach used in this research is a powerful tool for modeling dynamic systems to illustrate and present a model based on expert knowledge. FCM can successfully demonstrate the knowledge and experience of professionals by defining important elements as concepts, the cause, and effect of the relationship between these concepts, to successfully understand the system's behavior. To create a causal relationship, we use the conversion of linguistic expressions to numerical values and determine the initial weight matrix by combining business networks, experience, expertise, and expert viewpoints. For executing BN, the Bayesian research and GeNIe 2.0 software method has been used to determine the relationships between the concepts. The Essential Graph Search structure learning algorithm is based on a combination of the constraint-based search (with its prominent representative being the PC algorithm) and the Bayesian search approach. The algorithm performs a search for essential graphs using the PC algorithm and scores the various essential graphs using the Bayesian search approach [34].

To provide scenario analysis and to propose preventive and protective measures against the disease, with changing the weight of the factors, the behavior of the system is determined. The benefits of this approach are to reduce the role of humankind and human error as well as building intelligence in decisions. The proposed approach is summarized in Figure 2.

In the present study, a self-assessment DSS is proposed to utilize the key symptoms of acute leukemia for distinguishing the type of the disease based on the clinical as well as paraclinical documents. This method is a hybrid approach based on BNs and FCM. A set of data for confirmed cases of acute leukemia (including two types) are collected. In the first stage of this approach, the BN is implemented for two main purposes: (1) extracting the EBP relationships between attributes and their impact probability in the independent and combined modes; (2) extracting the EBP relationships between attributes inside the type of diseases developing FCM. First, the Bayesian search algorithm has been utilized to learn BN. This algorithm uses background knowledge which can apply the experts' opinion in the network and this characteristic has been used in the present study. In the learning phase of BN, relations between attributes are defined based on the conditional probability and the related algorithm. The Bayesian search algorithm generates an acyclic directed graph that designates the maximum score. The score is proportional to the probability of the data given the structure. It considers that the same prior probability has been specified to any structure, which is proportional to the probability of the structure given the data. It should be mentioned that illogical relations as a background knowledge between attributes are removed. For instance, WBC cannot have any effect on the age of a patient, and consequently, this relation should be eliminated. In the second stage, the FCM is constructed based on the extracted EBP relationships by BN. The symptoms of the disease have been considered as the main concepts of the FCM and the disease is the goal node of the FCMs.

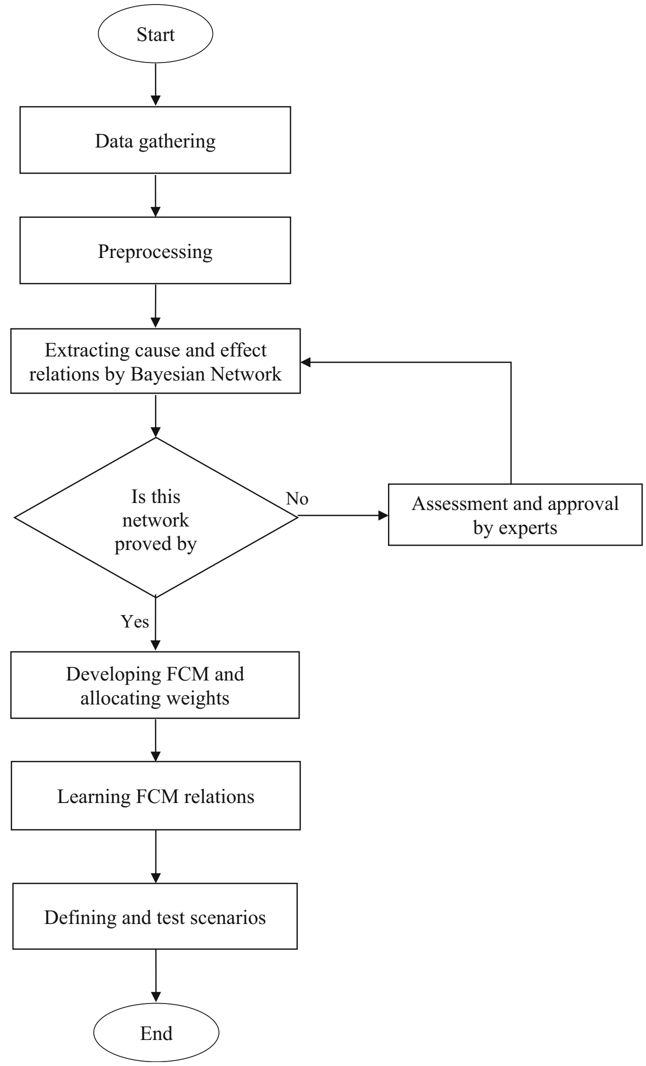

Fig. 2. A schematic view of the proposed approach

Developing FCM is based on the defining scenario for every symptom and achieving the impact of each symptom on the goal node. For this purpose, every symptom is activated and the rest of the symptoms are deactivated and the FCM is developed. After developing FCM for every symptom and severity level, the amount of the goal node is picked out. In the present study, due to the high importance of extracting the weights of EBP relationships between symptoms, a learning algorithm has been utilized to train FCM.

4 Case study

4.1 Problem statement

Leukemia and lymphoma are the most common malignant hematopoietic neoplasm in childhood [35]. Leukemia is divided into four subgroups: ALL, AML, chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML). ALL with 70% incidence is the common one and AML with 15% up to 20% is the second one in terms of incidence. The clinical manifestation, diagnosis, and treatment of each subtype are different from each other. In the case of a sibling, the risk of leukemia in the children is 2 to 4 times that of the normal population. The maximum age of ALL in children is between 2 and 5 years, and it occurs in males more than in females also in causations more than blacks. On average, annually, 2500 to 3500 new cases of leukemia are reported in children from the USA. The incidence of disease in children less than 15 years is 40 in 1 million. The maximum incidence of AML is in the neonatal period, and with an increase in age, the incidence rate decreases. According to an investigation, the incidence rate of AML in men is equal to women. Although the certain cause of the disease is unknown, a combination of genetic and environmental factors is effective in terms of incidence. For example, a translocation between (9,22) chromosomes is seen in CML subtype. Some of the environmental factors are ionizing radiation and chemotherapy drugs. Signs and symptoms of acute leukemia are according to the infiltration of malignant cells into normal tissues that cause bone marrow insufficiency. Signs and symptoms of malignant leukemia and lymphoma are nonspecific in children. In some cases, the patient may not have any signs and symptoms of the disease. Common presentations are fatigue, pain, fever, lack of appetite, abnormal mass, bleeding, headache, weakness, nausea and vomiting, easy bruising, paleness,

Table 2 Description of CBC and related range for pediatric acute leukemia

CBC attribute	Description	CBC range of ALL		CBC Range of AML		Number of levels for discretization
		Minimum	Maximum	Minimum	Maximum	
Gender	Every patient's gender	Male and female		Male and female		2
Age	Every patient's age	0<	12	0<	12	4
Hb	Hemoglobin is a substance that gives color to the red blood cells. Red blood cells contain hemoglobin (Hb)	1.88	23.0	2.9	13.2	3
RBC	Red blood cells are the most important parts of blood. These cells are agents of the red color of blood. Normal amounts: between 4.7 and 6.1 million per gram of blood. This amount in children is slightly more than normal	0.81	13.4	1.16	5.09	4
WBC	These three words are the abbreviation of white blood cells and represent white globules. Measuring the number of white globules is one of the basic methods of determining the presence of infection in the body. Since these cells are part of the body's immune system, these cells show different reactions under infectious and non-infectious conditions. Normal amounts: in adults and children over 2 years old the number of white globules is between 5000 and 10,000 per milliliter. Risk range: less than 2500 and more than 30,000 each represent the illness that can sometimes be dangerous	0.18	480.0	0.34	437.0	4
Plt	It represents the number of platelets per milliliter of blood, and the related number is usually the largest number of blood test plates. Apart from controlling the blood coagulation system, the platelet count is also used to check the progression of bone marrow impairment and blood disorders. Natural amounts: platelets are between 150,000 and 400,000/ml of blood for normal adults. In babies, this is slightly higher. Risk factors: platelet below 50A thousand or more than a million is abnormal and requires special attention	2.0	740.0	1.0	547	4
MCV	Defined as average amount of red blood cells	28.2	105.0	68.6	107.8	4
MCH	Shows average cell hemoglobin	19.21	1482	20.8	35.8	2
LDH	An enzyme found in various tissues, including the heart, and is widely found throughout the body	4.69	21,337	328	11,852	3
ESR	Shows the sedimentation rate of red blood cells in the stationary state of the body	2.0	159.0	2.0	155.0	3
Uric acid	In this test, the amount of uric acid is measured. Uric acid arises from the break of normal cells	0.5	22.0	0.0	16.0	4

bone pain, weight decrease, and night sweats. In physical examinations, lymphadenopathy, liver, and spleen enlargement are observed. The test is the most common extra bone marrow site of involvement. Commonly, cervical lymphadenopathy, spleen and liver enlargement, and central nervous system involvement are signs of ALL. The first step in diagnosis is according to abnormal findings in complete blood count (CBC) and immature cells in a peripheral blood smear. Commonly, decreases in the count of RBC, WBC, and platelets are seen in patient's laboratory results. Even in some cases, laboratory results may be normal. Also, in situations where tumor growth is rapid, it can cause an increase in the level of serum LDH and blood uric acid. Liver and kidney function tests must be evaluated in patients. Chest X-ray (CXR) as a first imaging modality must be used for certain diagnoses in all suspicious patients. Also, sonography, CT scan, MRI, and bone scan can be used as supplemental paraclinical modalities in diagnosis. Lumbar puncture for evaluation of central nervous system (CNS) involvement must be done in all cases. Finally, for certain diagnoses, bone marrow biopsy is recommended [36].

Identification and prognosis of diseases like leukemia are very important for saving human life. The present study contributes experts to analyze clinical concepts of leukemia for achieving better results of diagnosis of this illness.

4.2 Proposed approach

4.2.1 Clinical concepts of leukemia

Clinical concepts are extracted from medical records and laboratory CBC of 246 patients of Shahid Motahari Hospital of Urmia province and Tehran Specialized Child Hospital in Iran. Concepts and descriptions have been shown in Table 2. The patient's medical record review covers CBC test results in addition to clinical information. The aforementioned records and information are considered in three main segmentations: before the treatment, before any drug injection, and before gathering bone tissue samples. More specifically, a total of 246 samples were determined, of which 172 samples related to ALL, and the remaining 74 samples are affected by

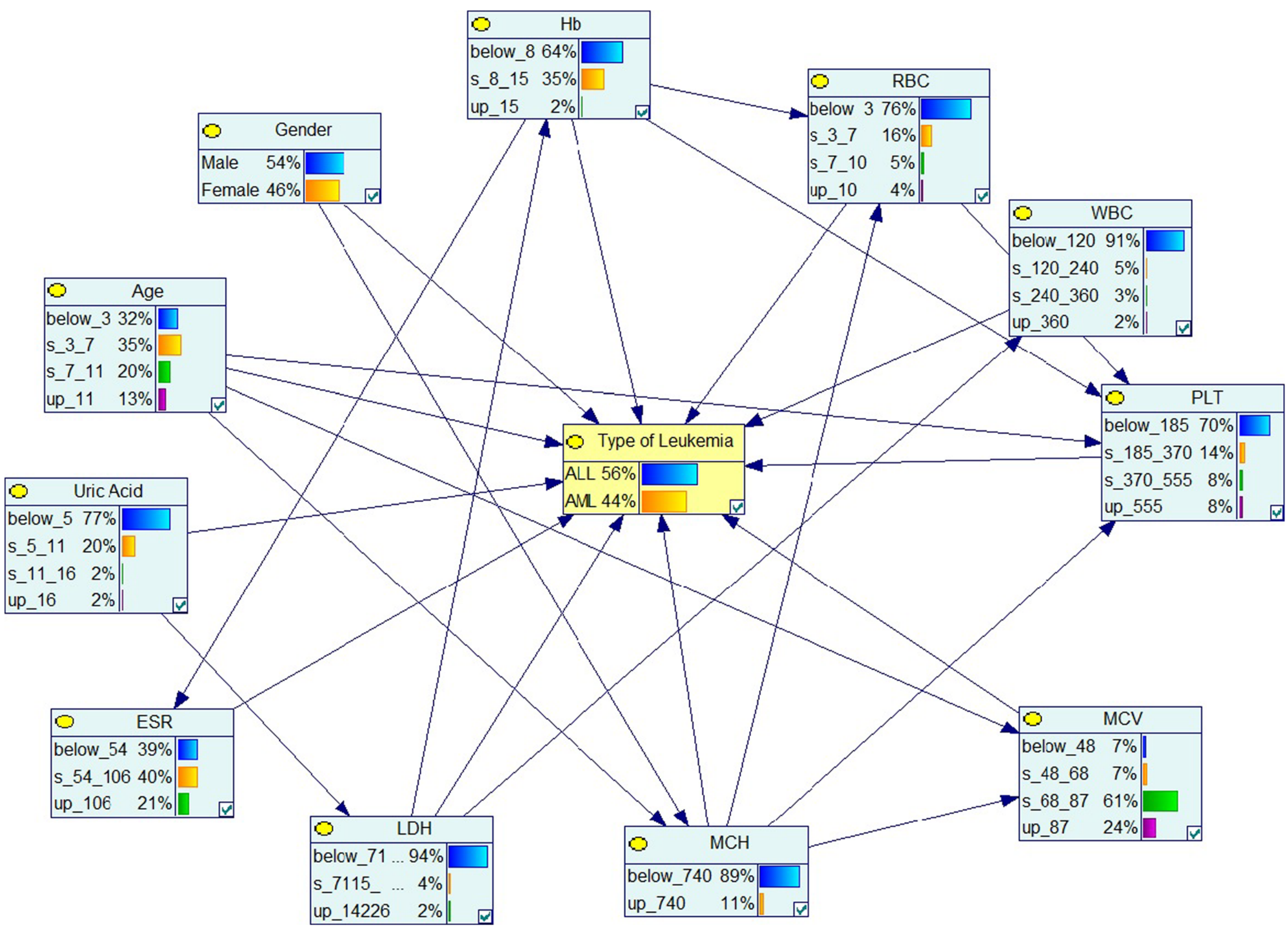

Fig. 3 Final data-driven Bayesian network for acute leukemia

Table 3 Probability of getting any type of leukemia (ALL or AML) based on the single evidence

	Evidence	Level of related evidence	Type of leukemia	
			ALL	AML
1	Gender	Male	0.56	0.44
		Female	0.56	0.44
2	Age	Below 3	0.54	0.46
		3 to 7	0.61	0.39
		7 to 11	0.52	0.48
		Up 11	0.50	0.50
3	Hb	Below 8	0.58	0.42
		8 to 15	0.51	0.49
		Up 15	0.50	0.50
4	RBC	Below 3	0.57	0.43
		3 to 7	0.51	0.49
		Other	0.50	0.50
5	WBC	Below 120	0.56	0.44
		Others	0.50	0.50
6	Plt	Below 185	0.58	0.42
		185 to 370	0.51	0.49
		Other	0.50	0.50
7	MCV	68 to 87	0.59	0.41
		Other	0.50	0.50
8	MCH	Below 740	0.56	0.44
		Up 740	0.50	0.50
9	LDH	Below 7115	0.56	0.44
		Other	0.50	0.50
10	ESR	Below 54	0.54	0.46
		54 to 106	0.54	0.46
		Up 106	0.59	0.41
11	Uric acid	Below 5	0.57	0.43
		5 to 11	0.57	0.43
		Other	0.50	0.50

AML. In addition, the ages of samples are between 1 and 12 years. The total and most important features that should be investigated by specialists are as follows: hemoglobin (Hb), red blood cells (RBC), white blood cell (WBC), platelet (Plt), mean corpuscular volume (MCV) (the average volume of red cells), mean corpuscular hemoglobin (MCH), lactate dehydrogenase (LDH) (an enzyme involved in energy production that is found in almost all of the body's cells, where the highest levels are found in the cells of the heart, liver, muscles, kidneys, lungs, and blood), and erythrocyte sedimentation rate (ESR) (a faster-than-normal rate may indicate inflammation in the body). Also, blood uric acid levels may be higher in people with leukemia which are summarized in Table 2 (also see [37]).

4.2.2 Definition of causal relationship for leukemia

Input data has been achieved from clinical reports of 246 leukemia patients. Input data is being trained by using the Greedy algorithm several times and final causal relationships are shown in Fig. 3. Irrational relations in this figure are pruned according to experts' opinions. For example, concepts of age and gender can only be root concepts, not target concepts, i.e., age and gender can affect other concepts, yet receiving no effects from others. Therefore, the relations in which other concepts had effects on gender and age were removed. The resulted network is seen after pruning and removing irrational relations. The concepts of age and gender are removed due to not having any relations with each other.

The evidence-based examinations have been provided based on two modes: independent evidence and hybrid evidence. According to Table 3, in the first mode, when the evidence is considered independent, the probability of developing any type of leukemia does not differ significantly except for a few cases. For instance, by observing the Hb level below 8, the probability of occurring ALL is 0.58, which is 0.42 for

Table 4 Probability of getting any type of leukemia (ALL or AML) based on the hybrid evidence

	Hybrid evidence	Type of leukemia	
		ALL	AML
1	Age (3 to 7), Hb (below 8), RBC (below 3), Plt (below 185)	0.67	0.33
2	ESR (up 106), MCH (below 740), MCV (68 to 87)	0.63	0.37
3	ESR (below 54), LDH (below 7115), MCH (below 740), MCV (up 87)	0.48	0.52
4	ESR (up 106), uric acid (below 5), LDH (below 7115)	0.6	0.4
5	Age (below 3), uric acid (below 5), ESR (below 54)	0.55	0.45
6	RBC (up 106), MCH (below 740), MCV (68 to 87)	0.61	0.39
7	RBC (up 106), Hb (below 8), LDH (below 7115)	0.60	0.4
8	Age (3 to 7), uric acid (below 5), LDH (below 7115), MCV (68 to 87), RBC (below 3), Hb (below 8)	0.74	0.26
9	Age (3 to 7), uric acid (below 5), ESR (below 54), MCV (68 to 87), Plt (below 185), Hb (below 8)	0.72	0.28
10	Age (3 to 7), uric acid (below 5), ESR (54 to 106), MCV (68 to 87), Plt (below 185), WBC (below 120), Hb (below 8), gender (female)	0.82	0.18

Table 5 Primary weight matrix for the causal map of acute leukemia

	Hb	RBC	WBC	Plt	MCV	MCH	LDH	ESR	Uric acid	Leukemia
Hb	0	0.66805	0	0.28870	0	0	0	−0.48842	0	0.5
RBC	0	0	0	0.30028	0	0	0	0	0	0.5
WBC	0	0	0	0	0	−0.11111	0	0	0	0.5
Plt	0	0	0	0	0	0	0	0	0	0.5
MCV	0	0	0	0	0	0	0	0	0	0.5
MCH	0	0.23727	0	−0.009	−0.36828	0	0	0	0	0.5
LDH	0.1869	0	0.43524	0	0	0	0	0	0	0.5
ESR	0	0	0	0	0	0	0	0	0	0.5
Uric acid	0	0	0	0	0	0	0.40398	0	0	0.5
Leukemia	0	0	0	0	0	0	0	0	0	0

AML type. Also, if the Hb level is between 8 and 15, the probability is 0.51 and 0.49, respectively. Likewise, if the Hb level grows above 15, the probability of any type of leukemia will be 0.5. In the second mode, the examinations are considered as hybrid evidence and Table 4 presents some of the observations. Consequently, it is obvious that by considering hybrid evidence, the probability of occurrence of each type of leukemia will be significantly different from the previous case. For example, according to the 10th row of the table and based on the observations of this case, the risk of ALL disease increases to 0.82. Generally, by considering Table 4 and the observations mentioned in this table, ALL diagnosis by using this approach will be more effective. It is worth mentioning that if the data size becomes larger, these values may change.

4.2.3 Weight allocation to cause-and-effect relations for leukemia

The step after drawing the cognitive map for leukemia is allocating weights to relations. In this stage, the correlation coefficient between the two concepts is used. The resulted primary weight matrix is provided in Table 5.

4.2.4 Processing FCM and the obtained output for leukemia

Processing FCM in this research is performed with gain values in the range of [−1, 1]. The primary weight matrix which is obtained for leukemia is introduced in the program as the input of the nonlinear Hebbian learning (NHL) algorithm. After processing the input by the NHL algorithm, the solutions are not convergent after three iterations. For more convergence, an evolutionary differential algorithm is used. The algorithm is converged after 30 iterations. The matrix of the primary weight matrix is provided in Table 6.

5 Results and scenarios analysis

5.1 Analyzing results for leukemia

After analyzing the system, results showed that MCH, uric acid, and WBC are the most important effective factors on

Table 6 Final weight matrix after employing the learning algorithm

	Hb	RBC	WBC	Plt	MCV	MCH	LDH	ESR	Uric acid	Leukemia
Hb	0	0.426641	0	0.277617	0	0	0	−0.43496	0	0.736425
RBC	0	0	0	0.232249	0	0	0	0	0	0.677174
WBC	0	0	0	0	0	−0.0401	0	0	0	0.803855
Plt	0	0	0	0	0	0	0	0	0	0.506213
MCV	0	0	0	0	0	0	0	0	0	0.726981
MCH	0	0.272399	0	−0.02975	−0.25486	0	0	0	0	0.98642
LDH	0.127668	0	0.366785	0	0	0	0	0	0	0.53388
ESR	0	0	0	0	0	0	0	0	0	0.739178
Uric acid	0	0	0	0	0	0	0.300917	0	0	0.971042
Leukemia	0	0	0	0	0	0	0	0	0	0

Table 7 Order of concepts affecting leukemia according to data-driven map

Concept name	Leukemia
MCH	0.98642
Uric acid	0.971042
WBC	0.803855
ESR	0.739178
Hb	0.736425
MCV	0.726981
RBC	0.677174
LDH	0.53388
Plt	0.506213

leukemia (shown in Table 7). According to the definition, MCH is the average amount of cell hemoglobin, and hemoglobin causes blood cells to become red. As it was said about leukemia, in this disease, the blood cells become transgenic. Thus, based on the results obtained from the algorithm, hemoglobin is the most important factor with the strongest effect on leukemia. In general, the increase in uric acid in the body is due to protein decomposition and sudden increase in cell productions in cancers. Consequently, the increase in the effect of uric acid is the second most important factor in diagnosing leukemia. Due to this transfusion, the number of healthy white blood cells decreases, and the number of immature white blood cells increases. Due to an increase in immature white blood cells by bone marrow and entry of the blood cells in the bloodstream, blood concentration increases which is defined as high ESR. Table 8 shows the order of concepts affecting leukemia.

Because of the production of immature RBCs in the bone marrow, there should be a problem, which is due to infections in the bone marrow cells. To clarify the issue, we need to know the cause of the infection. We know that the LDH hormone is naturally present in the cell crust. By lowering this hormone in the shell, the field of infection of the cells and the glands of the body is provided and the bone marrow is infected. Because the bone marrow has the task of producing other blood cells, including platelets, bone marrow infections will reduce platelet production and will be accompanied by a severe reduction in this blood cell. The same problem causes the coagulation of blood in the internal and external bleeding of the body. This problem in the cerebral capillaries or internal bleeding will lead to death. In general, the number of healthy blood cells is associated with a severe decrease, so it is normal that the size of the red blood cells decreases and the MCV also decreases. The next step is scenario analysis which leads to better results.

5.2 Scenario 2

When the MCH, the average amount of red blood cells and Hb, decreases, the number of red blood cells as well as the number of platelets also decreases. Meanwhile, MCV means that the average volume of the cells in the blood increases, which is due to the production of immature white blood cells, which is more voluminous than healthy ones, and this increases the average volume of the blood cells. The results of the second scenario are shown in Table 8.

5.3 Scenario 3

When we increase the number of white blood cells (WBC), we encounter a decrease in Hb, which is responsible for the red color of blood. Therefore, as shown in Table 8, the number of red blood cells decreases. Furthermore, the number of platelets has increased, and finally the average volume of blood cells and MCH has decreased. Because MCH is the average number of red blood cells and Hb in the blood, it decreases with decreasing hemoglobin. Table 8 shows the results of the third scenario.

Table 8 Results of the mentioned scenarios for determining the effect of each concept

Concepts	No changes (scenario 1)	Scenario 2	Scenario 3	Results—no changes (scenario 1)	Results—scenario 2	Results—scenario 3
Hb	1.00			0.70	0.70	0.7012016
RBC	1.00			0.8094419	0.8174828	0.8094566
WBC	1.00			0.8174981	0.8174981	0.8176876
Plt	1.00			0.7701634	0.7703161	0.770172
MCV	1.00			0.5785675	0.5558707	0.5785681
MCH	1.00	0.90		0.7105271	0.9	0.7105216
LDH	1.00			0.8098125	0.8098125	0.8122969
ESR	1.00			0.552271	0.552271	0.5522512
Uric acid	1.00		0.800000	0.766018	0.766018	0.8
Leukemia	1.00			0.968723	0.971340	0.969292

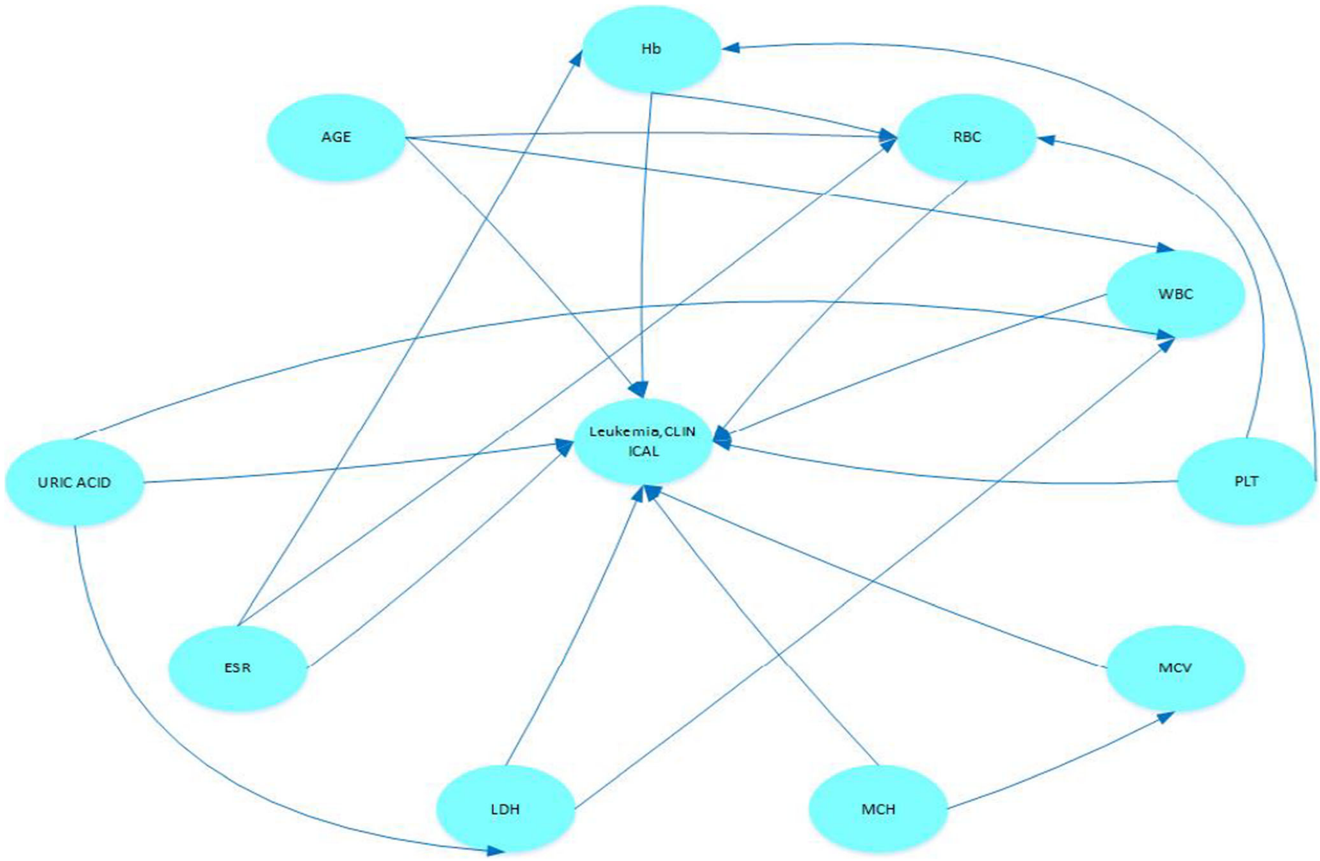

Fig. 4. Final data-driven cognitive map for ALL-type leukemia

5.4 Results of ALL-type leukemia

A distinct study of ALL-type leukemia shows that this type of cancer is common among children aged 3 to 15 years. A review of 172 ALL-type leukemia patients and the output of relationships was conducted using GeNIe 2.0. According to experts' opinions, relations in which the concept of age and gender are target nodes are removed since age and gender can only be target concepts. Therefore, the final cognitive map is seen in Fig. 4.

To allocate weights to relations in ALL-type leukemia, the correlation coefficient is used between two concepts. The obtained weight matrix is shown in Table 9.

This matrix is the result of the initial weight matrix during processing the NHL learning algorithm, which did not converge after three iterations. To this end, the differential

Table 9 Initial weight matrix for ALL-type leukemia

	Age	Hb	RBC	WBC	Plt	MCV	MCH	LDH	ESR	Uric acid	ALL
Age	0	0	0.03318	0.06258	0	0	0	0	0	0	0.5
Hb	0	0	0.68282	0	0	0	0	0	0	0	0.5
RBC	0	0	0	0	0	0	0	0	0	0	0.5
WBC	0	0	0	0	0	0	0	0	0	0	0.5
Plt	0	0.35190	0.30677	0	0	0	0	0	0	0	0.5
MCV	0	0	0	0	0	0	0	0	0	0	0.5
MCH	0	0	0	0	0	−0.4570	0	0	0	0	0.5
LDH	0	0	0	0.33673	0	0	0	0	0	0	0.5
ESR	0	−0.5267	−0.4854	0	0	0	0	0	0	0	0.5
Uric acid	0	0	0	0.33869	0	0	0	0.39096	0	0	0.5
ALL	0	0	0	0	0	0	0	0	0	0	0

Table 10 Final weight matrix after employing learning algorithm for ALL-type leukemia

	Age	Hb	RBC	WBC	Plt	MCV	MCH	LDH	ESR	Uric acid	ALL
Age	0	0	0	0	0	0	0	0	−0.0126	−0.3136	0.42869
Hb	0	0	0.58305	0	0	0	0	0	−0.5155	0	0.58098
RBC	0	0	0	0	0.34612	0	0	−0.1459	−0.2942	0	0.62718
WBC	0	0	0	0	0	0	0	0.09388	0	0.06334	0.42869
Plt	0	0	0	0	0	0	0	0	0	0	0.46633
MCV	0	0	0	0	0	0	0	0	0	−0.2292	0.42869
MCH	0	−0.3902	0	0	0	−1.6635	0	0	0	0	0.42869
LDH	0	0	0	0	0	0	0	0	0	0	0.44539
ESR	0	0	0	0	0	0	0	0	0	0	0.46109
uric acid	0	0	0	0	0	0	0	0.21569	0	0	0.42869
ALL	0	0	0	0	0	0	0	0	0	0	0

evolution learning algorithm has been used for convergence of the algorithm. This algorithm stabilized the system after 30 iterations and with a population of 100. In this case, instead of using the sigmoid function, the hyperbolic tangent function is used. The results are presented in Table 10.

According to the results of the present study, the Hb and RBC matrices have the highest effect on ALL-type leukemia. This is quite reasonable because Hb is the same substance that causes the red blood cells to be red, which means they have a direct relationship with each other, and as the number of red blood cells increases, the amount of Hb also increases. With the increase in the number of red blood cells in the blood, especially when this unconscious increase occurs, the risk of ALL-type leukemia is also increased. As we have seen in the results of this type of cancer, age is also one of the important factors in this type of cancer; we know that this type of cancer is common in children aged 5 to 10 years. Therefore, the lower the age is, the greater the likelihood of ALL-type leukemia. The results are shown in Table 11.

Table 11 Value of concepts affecting ALL-type leukemia according to data-driven map

Concept name	ALL
Age	0.428688
Hb	0.580984
RBC	0.627183
WBC	0.428688
Plt	0.466333
MCV	0.428688
MCH	0.428688
LDH	0.445395
ESR	0.46109
Uric acid	0.428688

5.5 Results of AML-type leukemia

This type of cancer is common among adults. Based on the report of 74 patients with AML and developing relationships using the GeNIe 2.0, results have been shown in the final cognitive map in Fig. 5.

To allocate weights to relations in AML-type leukemia, like the previous type, correlation coefficient is used between two concepts. The obtained weight matrix is shown in Table 12. This matrix is the result of the initial weight matrix during processing using the NHL learning algorithm, which did not converge after three iterations. To this end, we used the metaheuristic differential evolution learning algorithm for convergence of the solutions. This algorithm stabilized the system after 30 iterations and with a population of 100. In this case, instead of using the sigmoid function, the hyperbolic tangent function is used. The results are shown in Table 13.

According to the results obtained in this case, as seen in the matrix of Table 14, MCH is the most important factor affecting AML-type leukemia. With an increase in the average hemoglobin in the blood, the number of red blood cells increases, and as a result, the blood concentration will increase, directly affecting the increase in ESR, which is the red blood cell sedimentation rate. Therefore, with increasing MCV and ESR, the risk of AML increases. We can see that age and gender factors also have a significant effect on the disease, as we have said that the disease occurs in adults and is more common in men than women.

6 Conclusion

The present study aims to define endangering factors in leukemia considering each factor's weight, which leads to a supportive model. This model promotes the complete determination of preventing measurements for public health. In medical

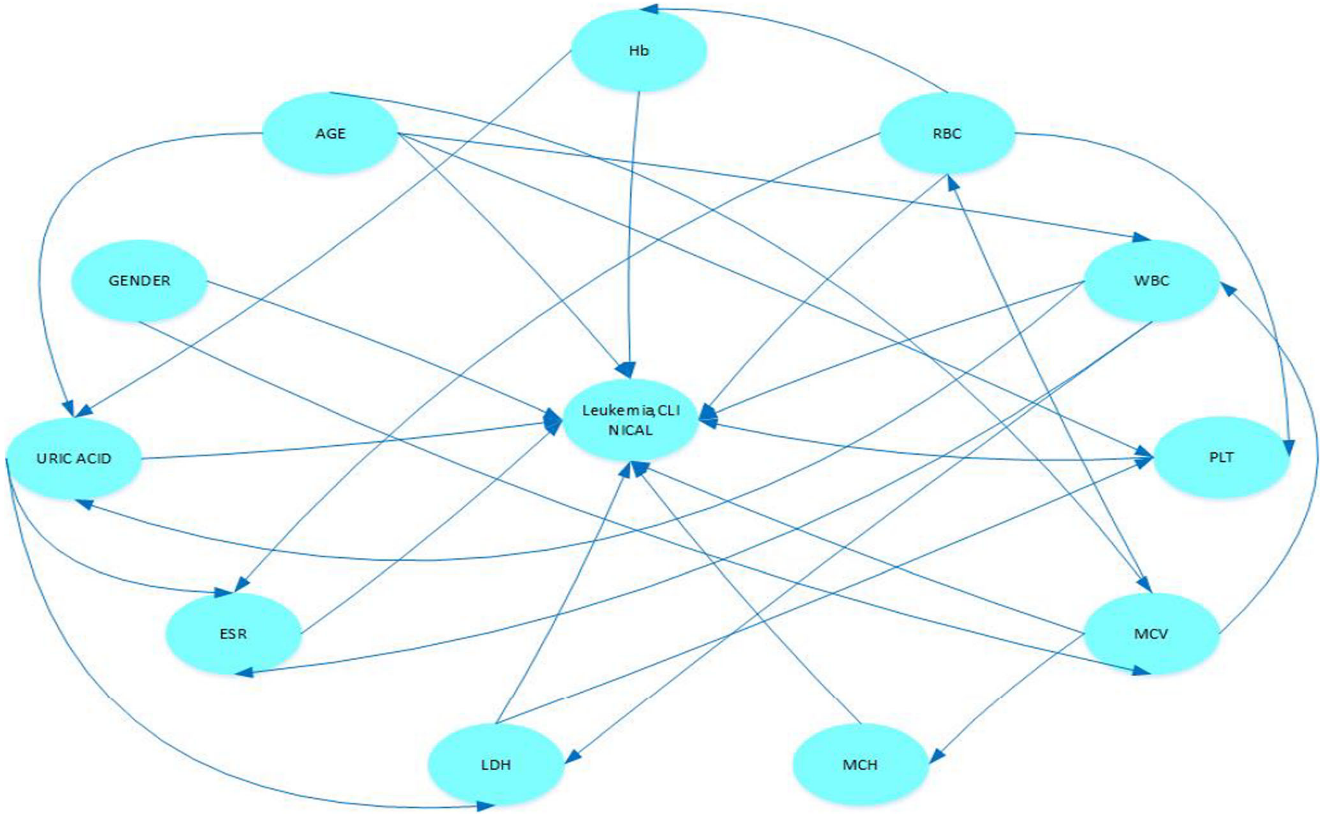

Fig. 5 Final data-driven cognitive map for AML-type leukemia

decisions, to reach effective, quick, and reliable results, there is a need for simple decision-making models based on self-assessment. Therefore, in the present study, a combination of cognitive maps and BNs with the advantages of modeling and stimulating are used. The present paper has two main parts. First, clinical concepts of leukemia are introduced, and then cause-and-effect relations are determined through BNs. Next, FCM is used for better analysis and results. In the case of leukemia and many other diseases like this, it is important to change the weights of factors and realize the system's behavior. Some important contributions of this model include using smart and data-driven based decision-making methods without human intervention, which decreases errors and mistakes. It can be stated that the cognitive maps approach is a powerful tool for dynamic modeling. This method can demonstrate the knowledge and experience of professionals by defining

Table 12 Initial weight matrix for AML-type leukemia

	Gender	Age	Hb	RBC	WBC	Plt	MCV	MCH	LDH	ESR	Uric acid	AML
Gender	0	0	0	0	0	0	0.1463	0	0	0	0	0.5
Age	0	0	0	0	0.0126	−0.246	0.3035	0	0	0	0.0677	0.5
Hb	0	0	0	0	0	0	0	0	0	0	0.0100	0.5
RBC	0	0	0.6800	0	0	0.2984142	0	0	0	−0.423	0	0.5
WBC	0	0	0	0	0	0	0	0	0.5186	−0.250	0.1361	0.5
Plt	0	0	0	0	0	0	0	0	0	0	0	0.5
MCV	0	0	0	−0.694	−0.058	0	0	0.5854672	0	0	0	0.5
MCH	0	0	0	0	0	0	0	0	0	0	0	0.5
LDH	0	0	0	0	0	−0.052	0	0	0	0	0	0.5
ESR	0	0	0	0	0	0	0	0	0	0	0	0.5
Uric acid	0	0	0	0	0	0	0	0	0.4424	−0.061	0	0.5
AML	0	0	0	0	0	0	0	0	0	0	0	0

Table 13 Final weight matrix after employing learning algorithm for AML-type leukemia

	Gender	Age	Hb	RBC	WBC	Plt	MCV	MCH	LDH	ESR	Uric acid	AML
Gender	0	0	0	0	0	0	0.1742	0	0	0	0	0.7675
Age	0	0	0	0	0.0305	−0.265	0.333	0	0	0	0.1665	0.8158
Hb	0	0	0	0	0	0	0	0	0	0	0.2	0.73623
RBC	0	0	0.5848	0	0	0.3462	0	0	0	−0.3633	0	0.76105
WBC	0	0	0	0	0	0	0	0	0.4098	−0.157	0.1589	0.57398
Plt	0	0	0	0	0	0	0	0	0	0	0	0.46819
MCV	0	0	0	−0.4734	−0.0086	0	0	0.5091	0	0	0	0.70256
MCH	0	0	0	0	0	0	0	0	0	0	0	0.8256
LDH	0	0	0	0	0	−0.072	0	0	0	0	0	0.4193
ESR	0	0	0	0	0	0	0	0	0	0	0	0.77473
Uric acid	0	0	0	0	0	0	0	0	0.3668	−0.102	0	0.73796
AML	0	0	0	0	0	0	0	0	0	0	0	0

important elements in the concepts, like the cause and effect of the relationship between concepts to understand the system's behavior. This combined method covers gaps of other used methods by using artificial intelligence strength. Although preventing all effects of factors is impossible, controlling some important factors can decrease effects. The results obtained show the effectiveness of the method used which provides decision-making based on self-assessment for specialists before doing and receiving the pathological test. Also, it helps experts to rank the risk factors and note them in their diagnosis. The method used in the present paper can be used in other fields in which factors and concepts have an important part in the final condition of the system. Finally, for further studies, other algorithms can be used instead of the NHL learning algorithm. In clinical trials, in addition to clinical concepts, clinical factors can be used to get cognitive maps. The NHL algorithm can be used to compute weights from functions other than sigmoid and tangent functions. To weigh the relationships in the FCMs, methods other than linguistic expressions and correlation coefficients can be used.

Table 14 Value of concepts affecting AML-type leukemia according to data-driven map

Concept name	AML
MCH	0.8255954
Age	0.8158307
ESR	0.7747326
Gender	0.7674504
RBC	0.7610553
uric acid	0.7379573
Hb	0.7362313
MCV	0.7025592
WBC	0.5739784
Plt	0.4681953
LDH	0.4193376

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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