Diseases Diagnosis Using Fuzzy Logic Methods: A Systematic and Meta-Analysis Review

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Highlights

- Diseases diagnosis systems using fuzzy logic methods are reviewed.
- PRISMA is used for systematic reviews and meta-analyses.
- The results showed the effectiveness of fuzzy methods in diseases diagnosis process.

Diseases Diagnosis Using Fuzzy Logic Methods: A Systematic and Meta-Analysis Review

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Abstract

Background and Objective: Diagnosis as the initial step of medical practice, is one of the most important parts of complicated clinical decision making which is usually accompanied with the degree of ambiguity and uncertainty. Since uncertainty is the inseparable nature of medicine, fuzzy logic methods have been used as one of the best methods to decrease this ambiguity. Recently, several kinds of literature have been published related to fuzzy logic methods in a wide range of medical aspects in terms of diagnosis. However, in this context there are a few review articles that have been published which belong to almost ten years ago. Hence, we conducted a systematic review to determine the contribution of utilizing fuzzy logic methods in disease diagnosis in different medical practices. **Methods:** Eight scientific databases are selected as an appropriate database and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was employed as the basis method for conducting this systematic and meta-analysis review. Regarding the main objective of this research, some inclusion and exclusion criteria were considered to limit our investigation. To achieve a structured meta-analysis, all eligible articles were classified based on authors, publication year, journals or conferences, applied fuzzy methods, main objectives of the research, problems and research gaps, tools utilized to model the fuzzy system, medical disciplines, sample sizes, the inputs and outputs of the system, findings, results and finally the impact of applied fuzzy methods to improve diagnosis. Then, we analyzed the results obtained from these classifications to indicate the effect of fuzzy methods in decreasing the complexity of diagnosis. **Results:** Consequently, the result of this study approved the effectiveness of applying different fuzzy methods in diseases diagnosis process, presenting new insights for researchers about what kind of diseases which have been more focused. This will help to determine the diagnostic aspects of medical disciplines that are being neglected. **Conclusions:** Overall, this systematic review provides an appropriate platform for further research by identifying the research needs in the domain of disease diagnosis.

Keywords. Fuzzy logic, Disease diagnosis, Uncertainty, Fuzzy methods, PRISMA

1. Introduction

The study of disease is one of the key concepts in medical sciences. Disease, like other health issues is not exclusively scientific concept. Absolutely everyone has a memory or an intuitive comprehension of the disease and it has long been one of the major human concerns [1]. In medical science, disease or illness is defined as any impairment or disability of ordinary physiological condition or function of the human body that is characterized by broadly sign and symptoms [2, 3]. In fact, the disease is a set of observable sign and symptoms that should be interpreted by physicians. This interpretation process has to be done by diagnosis process. Disease diagnosis like many terms in a medical context cannot be indicated with the clear definition; however, in general medicine, it refers to the complicated process of decision making leading to an accurate understanding of patient's health problem [4]. Since disease diagnosis is the fundamental in clinical decision making, it involves with different subjective and objective factors. Therefore, the accurate and timely diagnosis has the most important role in determining disease or disorder. Hence, until a definitive diagnosis is not determined, the treatment plan cannot be formulated [5]. Diagnosis is recognized as a complex and difficult process for healthcare professionals because the physicians have to simultaneously consider the various factors and circumstances with regard to medical evidence [6]. Due to the complexity of clinical diagnostic process as one of the main task of physicians, all health professionals try to reduce uncertainty in diagnosis by means of collecting empirical data to manage a patient's problems. In fact, disease diagnosis is a clinical reasoning process in which advantageous information are provided to improve healthcare quality [5, 7]. But with all these considerations, disease diagnosis may be performed with unwanted errors for its vague nature and complexity. In other words, since each patient might show the different degree of suspicion to various diseases, disease diagnosis is always established with uncertainty. This uncertainty can be originated from the vague nature of the disease, patient's data, and complicated medical diagnosis process. In addition, this ambiguity is related to inherent nature of medicine [8, 9].

Since getting the right diagnosis is a key aspect of healthcare subjects, many researchers applied several computer aided methods to improve disease diagnosis for helping physicians to make the most accurate decisions [10-15]. To overcome the uncertainty of disease diagnosis, researchers tried to describe the medical process in Boolean or binary format. Although it is very difficult to define all the real world details in binary logic or crisp value, a new method is required to model this vague and nonlinear nature of clinical subjects. As a result, fuzzy logic was introduced as a robust method to model uncertainty in medicine [7]. Fuzzy logic is a kind of logic system which can define realities with more than a true and false statement and its final approach to compute based on the degrees of truth. Additionally, fuzzy logic has the capability to deal with truth values between 0 and 1 which should be considered as degrees of truth. For example, with using fuzzy logic, we can assign different logic values to each disease, ranging from 0 to 1, according to the severity of disease. Since 1965, when fuzzy logic was introduced by Zadeh [16], numerous computerized systems were developed with the concept of fuzzy logic [8, 17]. Fuzzy logic is being applied in many sciences and even in medicine. According to continuous nature of disease and symptoms in medicine and its complexity, it is useful to utilize fuzzy logic in medicine to overcome this internist uncertainty in all medical disciplines from diagnosis to treatment [18]. Zadeh [17] believes that fuzzy set theory can be used effectively in developing computerized decision supporting tools to improve medical diagnosis [19, 20].

Fuzzy logic can model the human thinking process and as a result, it can stimulate the interpretation phase in disease diagnosis [8, 18, 21-23]. Hence, for its usability, various studies have been published in the context of diagnosis for different diseases. Thus, the main objective of this paper is to investigate the studies in which fuzzy methods have been employed with respect to various medical fields and diseases for determining its trend and effectiveness in disease diagnosis, through conducting a systematic review.

The rest of the paper is organized as follows. Section 2 presents a literature review of fuzzy methods which were applied in disease diagnosis studies. Section 3 proposes a general description of our proposed method. Thus, in the research methodology section, we explained our research questions, inclusion and exclusion criteria, search strategy, and applied tools with details. Section 4 represents a complete report of our systematic review results, while Section 5 discusses the results and analyses that we obtained based on our objectives. The last section of this paper outlines the conclusion, future research and limitation.

2. Literature review

2.1 Fuzzy nature of disease and diagnosis process

Throughout this paper, the term fuzzy refers to confused and not clear, however, fuzziness should not be interpreted as vagueness [18, 24, 25]. Since all of the reality in the world involves the degree of vagueness and uncertainty, no one can make decision confidently with incomplete knowledge about the reality. That is to say, medicine is part of our real world with a high rate of uncertainty in the context of human healthiness and diseases [8]. The nature of the disease in medicine is complex and in many cases is overlapped. In light of modern medicine, many diseases are classified as a complex disease caused by a combination of various factors such as cancers and autoimmune diseases [26, 27]. This view is similar to the theoretical concept of the notions of fuzzy health and fuzzy diseases, represented by Sadegh-Zadeh [28]. The author defined the disease in the context of an individual health status with series of a linguistic variable. Furthermore, Sadegh-Zadeh changed the current concept and definition of disease by defining it as "disease to a certain degree" to a fuzzy concept [27]. The author also believes that this concept can be considered as a preliminary stage in the diagnosis of the disease [28, 29].

In medicine, the outcome of clinical reasoning based on the investigation of gathered information is known as disease diagnosis [30]. Since disease diagnosis is the core of medical science, it has different steps. In other words, each step of diagnosis process can be a source of uncertainty. The initial step of diagnosis starts with data acquisition through patient's medical history and physical examination, accompanied by the data obtained from laboratory tests or any medical diagnostic methods [6, 9, 31]. In spite of emerging new various diagnostic methods and equipment, not only the inherent ambiguity was not decreased but also the complexity and uncertainty of final diagnosis is augmented because of the high volume of data. Hence, physicians often have to decide based on this collected information as soon as possible in the iterative hypothetic deductive process [32, 33]. Insufficient time for gathering information might be the greatest obstacle to make accurate decisions. Besides that, diagnostic errors are inevitable. However, these errors can occur in result of inadequate knowledge, misdiagnosis, deficiency of data gathering and clinical cognitive processes that underlie diagnostic thinking of clinician [32, 34, 35].

In fact, nowadays well-defined diagnosis for all diseases is difficult since patient might manifest the symptoms and signs of two or more diseases. Therefore, diagnosis process usually involves making one or more possible hypotheses to obtain the high possibility disease. Several methods in the context of artificial intelligence have been utilized to minimize the complexity of the diagnosis process and to improve diagnostic accuracy. Dealing with uncertainty and errors in disease diagnosis is very important which can help to control diseases by healthcare professionals. Due to a lack of comprehensive knowledge and also lack of time and fuzzy nature of disease diagnosis, the fuzzy logic method was introduced as the most effective method to model the diagnosis uncertainty [16, 22, 28]. In this regard, with applied fuzzy logic, the disease can be described with a degree of memberships to diagnose. Contrary to classical logic, in which the reality can only be defined with true and false value, in fuzzy logic, the disease can be described with partial truth values between right and wrong as a result of the diagnosis [7, 36, 37].

2.2 Applied fuzzy methods in disease diagnosis

Computational intelligence techniques are widely used in several medical fields. Significantly, the key role of integration regarding the computational methods with medical diagnostic methods have been of interest among medical researchers to decrease the complexity and improve the accuracy of diagnosis for last decades [38-40]. The capability of fuzzy logic to represent the knowledge and a quantitative result in form of linguistic expression can be useful, because most of the diagnoses usually have been performed based on the probability of clinical findings [22, 37, 41]. Coupled with the literary evidence, another advantage of using a fuzzy approach is about fuzzy theory with using simulating human thinking and decision making which can implement medical evidence-based theory to improve diagnosis [42].

Due to the proven effectiveness of applying fuzzy methods in the world of medicine to model uncertainty, it has been utilized in diagnosis process with different applications according to the type of disease and objective of the researchers [43]. One of the first systems developed in terms of disease diagnosis was provided by Sadegh-Zadeh [27] with considering clinical sign and symptoms as inputs and the probability of diagnosis as output. The author developed the system with the aim of clarifying the effectiveness of applying fuzzy methods in disease diagnosis [24, 28]. Various studies have been performed in this context with different methods. Accordingly, the authors in this systematic review, survey the significant applications on the disease diagnosis [7]. Generally, the process of applying fuzzy logic in disease diagnosis is described in Fig. 1 with its different steps. In the following sections, we will briefly discuss the most common fuzzy logic methods used within the context of disease diagnosis.

In the following, we described about some common methods that have been applied in medical studies. The notion of a fuzzy set provides a basis for fuzzy logic systems [7]. According to Alayón et al. [44] Fuzzy Rule-Based System (FRBS) is one of the most common fuzzy set methods applied in medicine which belongs to Fuzzy Inference Systems (FIS) in general [16]. FRBS refers to fuzzy systems that apply “IF-Then” rules for knowledge representation [41]. Fuzzy clustering and classifying are the most interested methods used in medical domain too. In addition to fuzzy sets and fuzzy clusters, in the following FIS and FDSS are also described as the most common methods in the field of medicine.

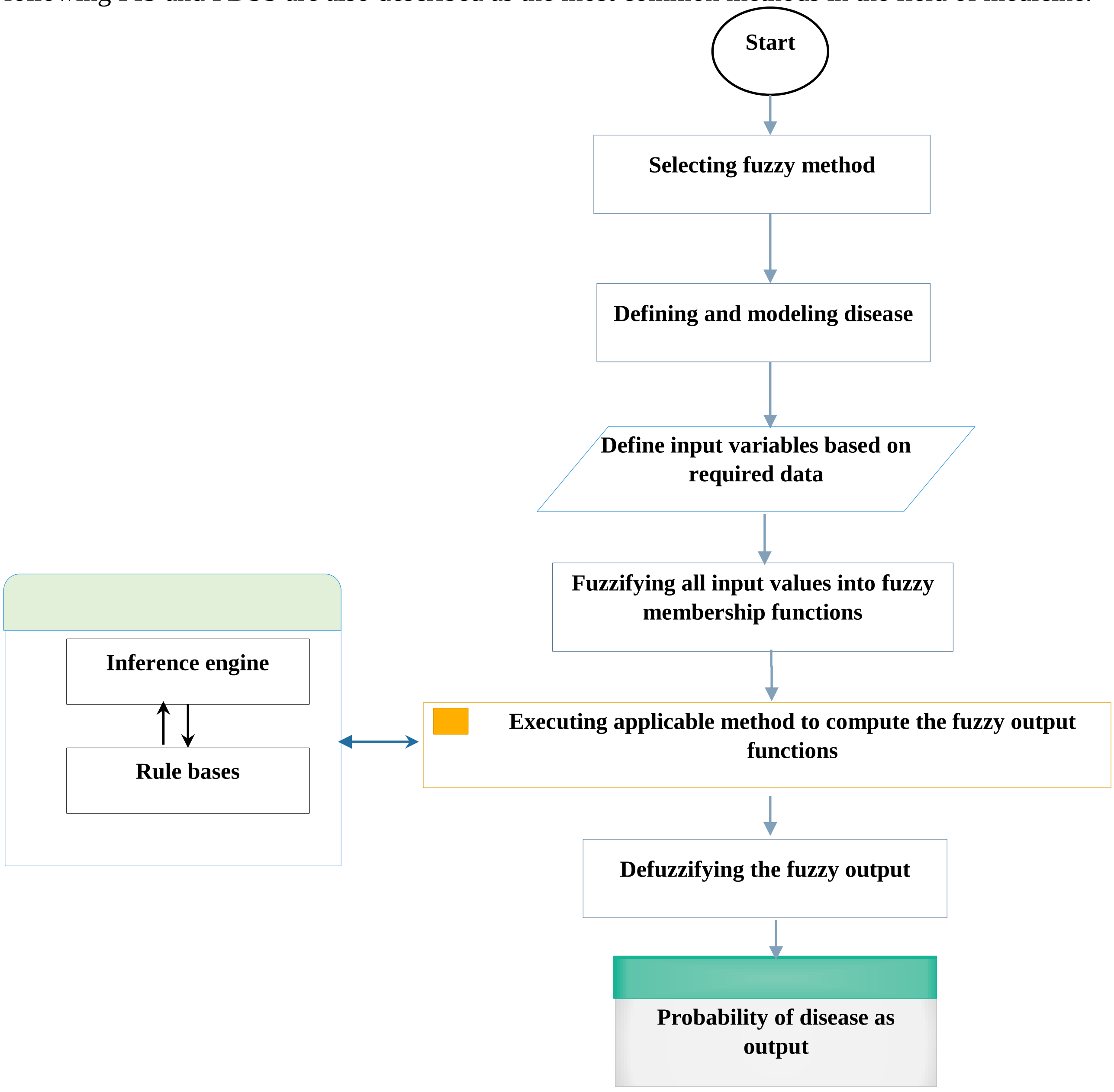

Fig. 1. The process of applying fuzzy logic in disease diagnosis

2.2.1 Fuzzy set theory and fuzzy memberships

Fuzzy set theory is known as the basis of all fuzzy logic methods. With using fuzzy sets, crisp values can be defined with degree of memberships to predefine sets, mathematically [8, 25]. The scores of 1 and 0 are assigned to true and false in a set, respectively [16, 41]. Any vague reality can be clarified by applying fuzzy sets, therefore the researchers can utilize it to determine any uncertain situation in medicine such as the severity of disease, the probability of disease, the degree of sign and symptoms and any vague or incomplete knowledge [7, 16]. In addition, with an effectiveness of this method to determine the nature of disease with fuzzy sets, decision making can be facilitated in diagnosis process [8]. Hence, we can imply that fuzzy set theory might be a suitable tool to develop a computerized diagnosis system. Based on the fuzzy sets, health and disease have complementary relations, but they are not opposite [37]. One of the earliest method concerning the fuzzy set memberships was implemented by Sanchez [45]. The author formulated three fuzzy sets consisting of the symptoms as *S* sets, diagnosis as *D* sets, and patients as *P* sets to describe disease diagnosis process. Thus, physicians based on the clinical experience create a relationship with the patient to disease diagnosis according to the set of symptoms [24, 37, 46].

2.2.2 Fuzzy logic in decision support systems

Medical diagnosis and treatment are usually accompanied by decision making process. Timely and accurate decision making based on clinical knowledge and patient information to diagnosing, treating and managing the diseases, is complex [47, 48]. In the most recent studies, Decision Support Systems (DSSs) are one of the early computerized systems that were developed in medicine with trying to suggest the best recommendation to assist the physicians in decision making [49]. By applying fuzzy logic to model physician diagnosis decisions, the more accurate mathematical model can be developed in the context of DSS. One of the important parts of DSS is knowledge representation, where fuzzy logic can provide an effective way to dealing with the problem of knowledge representation with uncertainty and imprecision [10]. Unlike classic methods, fuzzy logic can represent vague knowledge in a set of fuzzy based rules [50]. In addition, with the similarity of fuzzy logic to natural language, it can stimulate how the medical expert makes a decision in the best way [51]. Hence, DSSs are recognized as easy-to-use applications, because of their high accuracy and low complexity.

2.2.3 Fuzzy inference systems

Fuzzy Inference System (FIS) is one of the main categories of fuzzy methods. FIS is the process of formulating the mapping from a given input to an output using fuzzy logic and it involves all of the membership functions, fuzzy logic operators and if-then rules [52, 53]. Therefore, FES as one of the most popular fuzzy methods can be included to fuzzy inference systems. As medical knowledge has benefited from the use of fuzzy logic, FES for disease diagnosis was developed to detect diseases more accurate and quicker. FES utilizes a collection of different fuzzy methods such as fuzzy membership sets and fuzzy rule-based reasoning to develop relations between input and output data. Generally, to date, various systems have been developed using FES methods which are applied for diagnosis of different diseases [36, 54].

2.2.4 Fuzzy clustering and classifying

Both clustering and classifying are data mining techniques, but they are completely different methods. Clustering is used for splitting the data into groups (called as clusters) to find hidden patterns according to its objective. In each cluster, the objects have similar properties and objects of different clusters, while in classification, each data is labeled. One of the most clustering techniques which is used in diagnosis methods is fuzzy c-means clustering [55, 56].

Fuzzy classification has been used to extract a predictive model in different medical fields. Classification technique can improve disease diagnosis to support physicians in the decision making process. Importantly, fuzzy classifying is used in image processing, laboratory data, and the degree of disease and the severity of sign and symptoms. Despite this, the fuzzy clustering method is more used in image segmentation and signal processing; for example, to measure tumor size in the response to chemotherapy treatment [18, 55, 57].

2.3 The benefits of using fuzzy logic in diseases diagnosis

Over the past decade, most researches in disease diagnosis have emphasized on the use of computer-aided diagnosis methods which can improve decision making by healthcare professionals [19, 41]. To date, various computational methods have been developed and introduced in this regard. These kinds of tools can simulate the thinking process of experts to solve the problem of the complicated process of diagnosis [38, 40, 58, 59].
It is obvious that we can map a quantitative medical result to linguistic expression with a fuzzy method for better comprehension [60]. Furthermore, due to easy mapping, it has been used in diagnosis process to improve decision making over 20 years ago [18, 42]. Various systems, applications, and algorithms are being developed by utilizing fuzzy logic in the context of disease diagnosis, showing that it is advantageous in accurate diagnosis in chronic disease, cancers and acute disorders [8, 41, 61] such as lung cancers, fever, diabetes mellitus, electrolyte disorders, heart failure, and cancers with high accuracy [18, 21]. However, it has some advantages and disadvantages in comparison with other artificial intelligent methods. Due to the fact that inherent of medicine and diagnosis process are uncertain and ambiguous, fuzzy logic can describe disease definition and its severity, clearly [42, 62]. Accordingly, it seems that disease diagnosis almost relies on a form of “fuzzy logic” [7]. Perhaps the most serious disadvantage of this method is that fuzzy outputs might have a different meaning in view of different experts, therefore, using fuzzy systems could be difficult for physicians and medical students [22]. Gürsel et al. [18] identified several disadvantages of the fuzzy methods. They believed that developing fuzzy systems is difficult and it needs mathematical knowledge. Furthermore, they emphasized that such systems need to be defined and fine-tuning before they are implemented [24].

3. Research methodology

This systematic review was done based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) method which was introduced by Moher et al. [63]. PRISMA is one of the best methods that can help authors doing the systematic reviews and meta-analyses properly and also help them to move in a structured way as a road map [63-65]. The systematic reviews are valuable high evidence source, that summarize and analyze scientific reliable literature with the use of a structured procedure based on predefined questions which can be utilized by different researchers [66]. In systematic review with accurate and comprehensive investigation, different ideas can be analyzed which are published in form of traditional articles by different researchers. One of the important parts is defining the eligible criteria which should be selected carefully to describe hypothesis [66, 67]. This can play an important role in solving problems by describing, synthesizing, and assessing quantitative or qualitative evidences.
A systematic review includes a statistical analysis called meta-analysis [68]. PRISMA is the most common method used in a considerable amount of literature. According to guidance provided by the PRISMA, the following sections include literature search, study selection and eligible papers, and data extraction and summarizing [64, 65]. Hence, to improve the quality of our study process, we selected the PRISMA checklist with 27 items. This checklist was designed in response to increase the accuracy of all reviewed articles in this study. Currently, this is known as one of the best standards for reviewers when reporting their results [63].

3.1. Literature search

In this step, eight famous scientific electronic databases were selected as appropriate databases which were searched to find relative articles based on our research question. The search for systematic reviews was performed on PubMed, Google Scholar, IEEE, Science Direct, Web of Science, Taylor & Francis, Wiley Online Library, and Emerald publishers. According to our defined research question and our final objective, the literature search was done by utilizing the keywords including “fuzzy logic”, “fuzzy methods”, “disease diagnosis” and “diagnostic”. Published studies were searched and identified using a search strategy developed by reviewers. The search strategy was written for each database separately which is shown in Table 1. The articles were searched from January 2005 until Jun 2017. As a result, based on our search strategy, 242 records were retrieved. The results of each database are shown in PRISMA diagram. All search result citations were entered into EndNote™ bibliographic software. By conducting PRISMA method, in the next step the duplication removal was done automatically by the software. Duplication removals in results were checked by the researchers, where 38 duplicated studies were removed. Finally, 204 relative articles remained. The results of each phase are summarized in PRISMA diagram in Fig. 2.

Table 1. Search strategy in different databases

Database	**Search Strategy**
PubMed	((“Diagnosis”[Mesh]) AND (“Fuzzy logic”[Mesh] OR “Fuzzy logic”[Majr])) AND ("Fuzzy logic"[TIAB] AND (("Diagnosis"[TIAB] OR “Diagnostic” [TIAB]))
IEEE	((Fuzzy Logic) AND (disease diagnosis))
Science Direct	pub-date > 2004 and TITLE-ABSTR-KEY(fuzzy logic) and TITLE-ABSTR-KEY(disease diagnosis)
Web of Science	TS= (“Fuzzy logic”) AND TS= (“Disease diagnosis”) AND PY= (2005-2017)
Taylor & Francis	Fuzzy method in Abstract AND Disease diagnosis in Abstract
Willey Online Library	[All: “fuzzy logic”] AND [All: “disease diagnosis”] AND [Publication Date: (01/01/2005 TO 12/31/2017)]
Emerald	[Anywhere “Fuzzy logic”] AND [Anywhere “diagnosis”] AND [Type (articles/chapters)]
Google Scholar	“Fuzzy logic methods” AND “disease diagnosis” anywhere in articles

3.2. Study selection and eligible papers

Since eligibility criteria are required to select appropriate articles, the academic papers were screened based on inclusion and exclusion criteria which have been represented in Fig. 3. According to exclusion criteria, eligible articles were selected, and the book chapters, thesis, letters to the editor, brief reports and non-English papers were removed. In other words, only journal and international conference papers were considered according to inclusion criteria. In this regard, 25 academic papers were removed and 180 articles remained.

The abstracts and titles of all remained articles were screened based on relevancy of their subject to disease diagnosis. But since diagnosis covers a wide range of diagnostic process such as prognosis, differential diagnosis, image diagnosis, and autopsy diagnosis [4, 69], it is essential to determine the exact meaning of “disease diagnosis” in this study. Hence, we selected the ontological definition represented by Scheuermann et al. [4], as the main criteria for eligibility study. According to this definition, diagnosis is redefined as a result of an interpretive process which its input is patient with its clinical description and its output is the declaration of patient’s disease and type of disease. The output of disease diagnosis should be considered as a specific health problem or specific disease. Additionally, the reviewers investigated titles and abstracts to see whether or not the articles are matched with the defined criteria. During this phase, the irrelevant review articles were removed. Likewise, during the data extraction, we also had to remove any academic papers that did not meet our criteria in terms of disease diagnosis. Overall, 89 articles matched our inclusion criteria that are relevant to the question of this systematic review research.

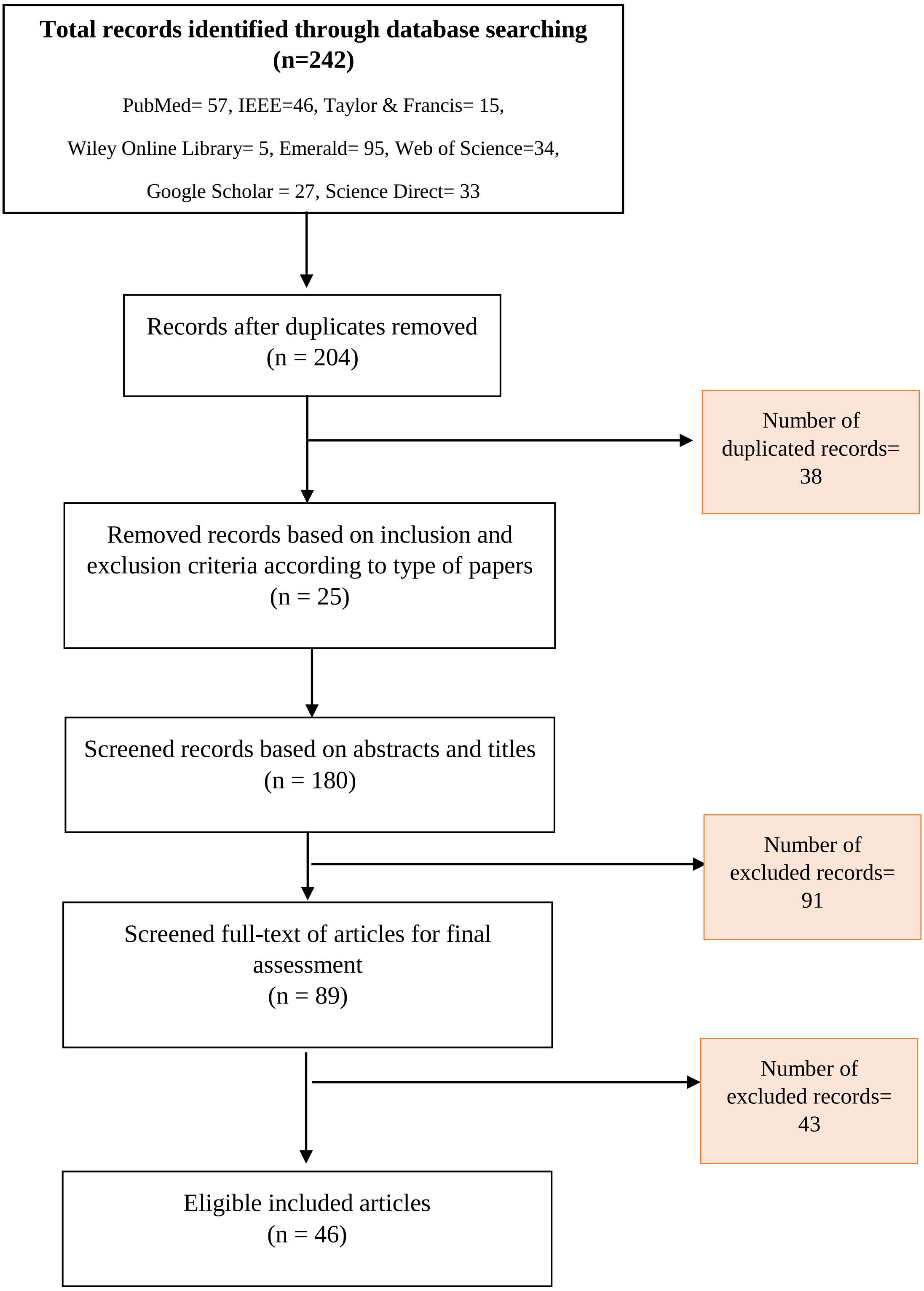

Fig. 2. PRISMA diagram for the identification, screening, eligibility and included articles

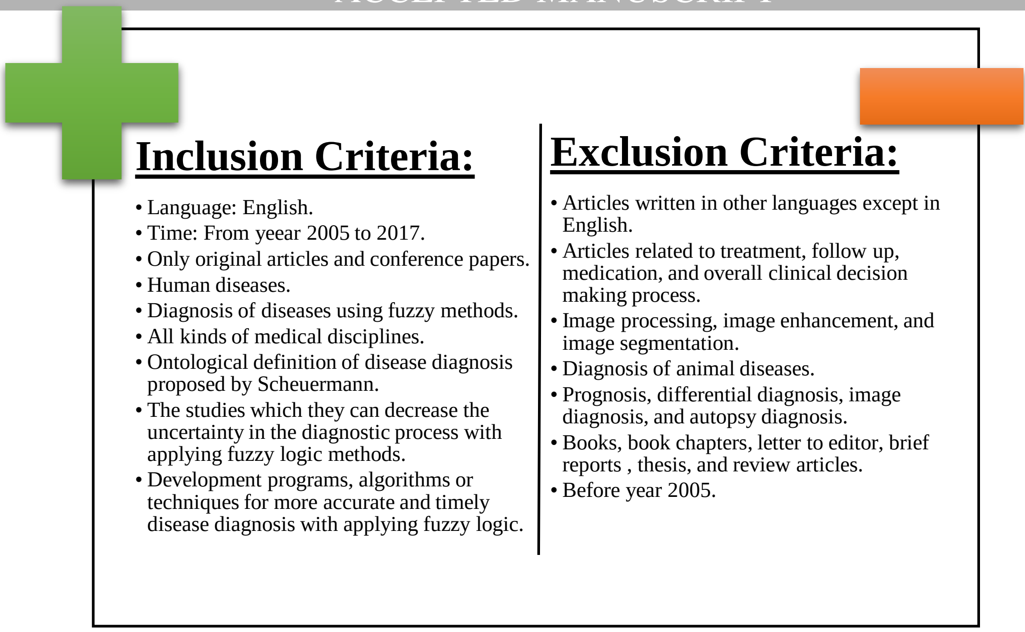

Fig. 3. Inclusion and exclusion criteria for selecting eligible articles

3.3. Extraction and summarizing of data

Finally, in the last step, reviewers examined the full-text of 89 articles to achieve the final collection of studies that will contribute to our review. The included articles were completely scrutinized to extract and summarize importantly the required information with the aim of answering the main research question. Based on the required information, we consider some classifications and criteria according to our objectives. Data extraction form was designed to classify, analyze and synthesize the eligible articles based on the imperative defined criteria. Then, based on our analysis of data extraction form, we could achieve the best results and recommendations. The criteria included the author, year of publication, type of article, journal or conference, type of disease, problem, medical disciplines, objective, research gap, applied fuzzy method, findings and results, inputs, outputs, and positive impact on diagnosis. The classification chart has been shown in Fig. 4. After reviewing and summarizing the collected full-texts, 46 academic papers from 38 scientific international journals and 13 conferences between 2005 and 2017, matched our inclusion criteria that were recognized as suitable articles to be analyzed and interpreted, in this systematic review. Four full texts were not found, and hence, we did our analysis and interpretation based on 46 included articles. Reviewers read full texts, deeply with considering their details to select the articles related to applying fuzzy logic in disease diagnosis. However, moving according to the PRISMA method and choosing the proper articles took a lot of time but because of the specific structured nature of this method, we ensured that the most suitable and relevant articles related to the subject of this systematic review, have been selected.

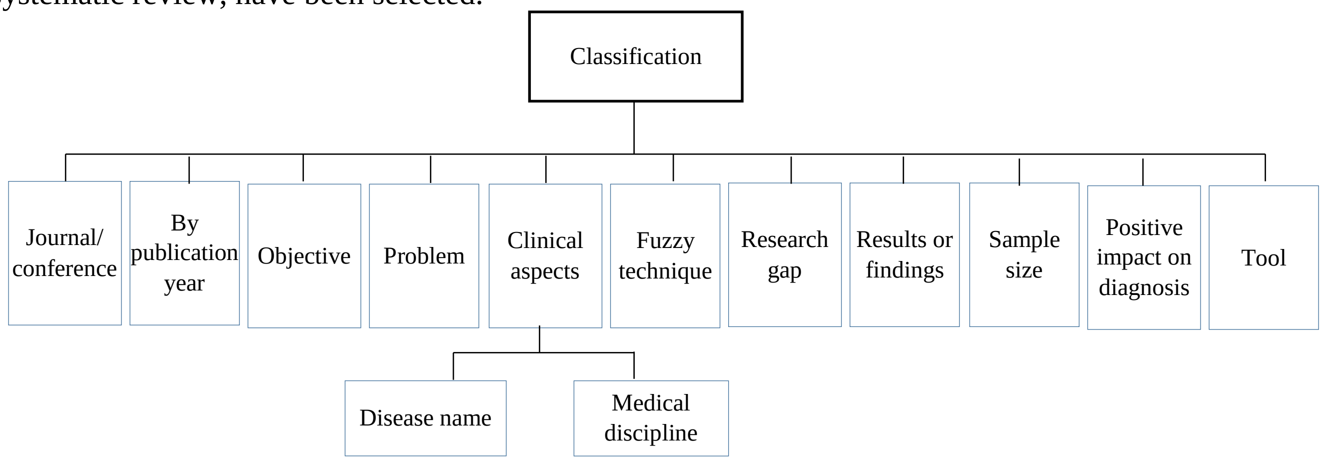

Fig. 4. The classifications of research questions

4. Results

The findings and results of analysis and synthesis of related articles are represented in this section. With conducting this systematic review and the outcomes of meta-analysis data, we can anticipate the efficacy of different fuzzy methods which have been applied in disease diagnosis. To that end, first, eligible published studies regarding the application of employed fuzzy methods in disease diagnosis were summarized and classified in the following. These are based on the different categories that were considered in relation to our research questions and objectives. Second, we examined the impact of different fuzzy methods in various medical disciplines.

4.1 The frequency of published articles over the past years

The final distribution of papers includes 46 academic papers which met our inclusion criteria. They included 17.22% of total papers, retrieved through the databases searching in the first step. The frequency of published articles in the time period between 2005 and 2017 are shown in Fig. 5. In fact, the graph indicates that there has been a significant increase in published articles from 2005 up to now. In this regard, almost 20% of included articles were published in 2016. However, from the graph below, we can see that over the first 5 years between 2005 and 2010, researchers were not interested in studying the context of utilizing fuzzy methods in disease diagnosis; and hence, a little research has been conducted. On the other hand, significant progress has been made over the last 5 years by achieving 8 work papers in 2016. Hence, it is apparent that the researchers have shown an increased interest in applying fuzzy methods in disease diagnosis, recently.

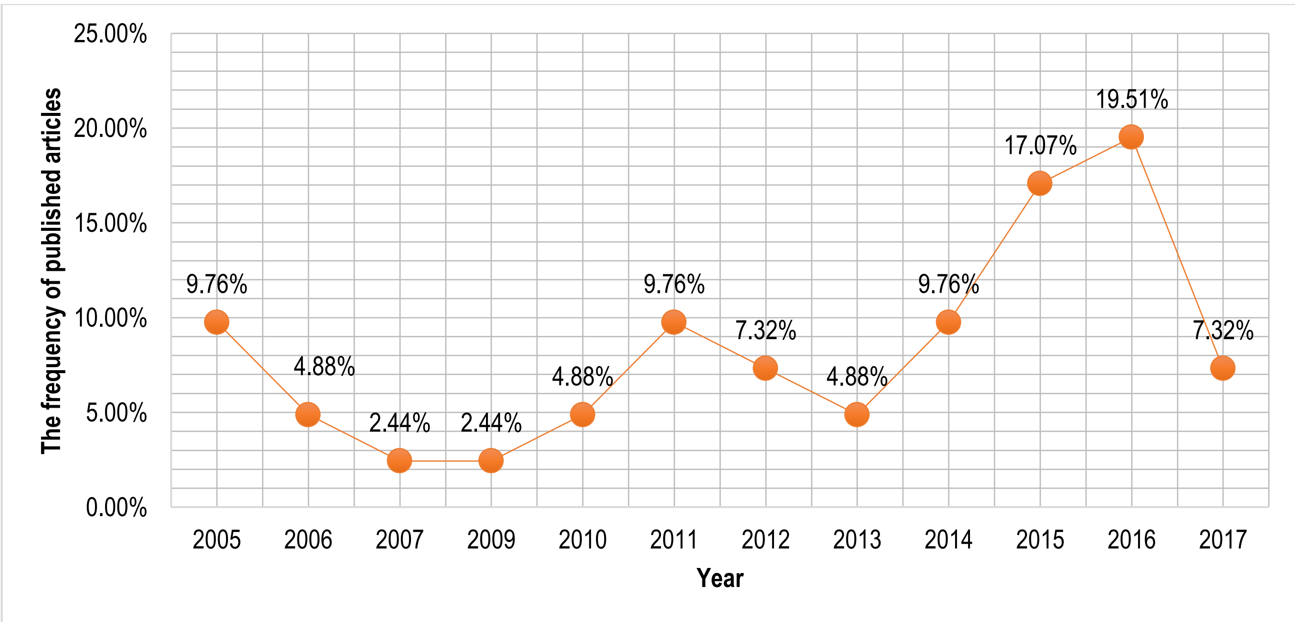

Fig. 5. The distribution of papers by publication year

4.2 Distribution of academic papers by journal and conference type

The included academic papers in this review were retrieved from 38 different scientific journals and international conferences between 2005 and 2017. The frequency of included articles by their publication type is presented in Fig. 6. As shown in this figure, the articles published in journals were significantly more than the articles presented in the international conferences. What is interesting in this chart is that the academic papers published in conference proceedings are related to using the fuzzy logic concept in disease diagnosis, increased notably, which reached to the peak of six publications in 2015.

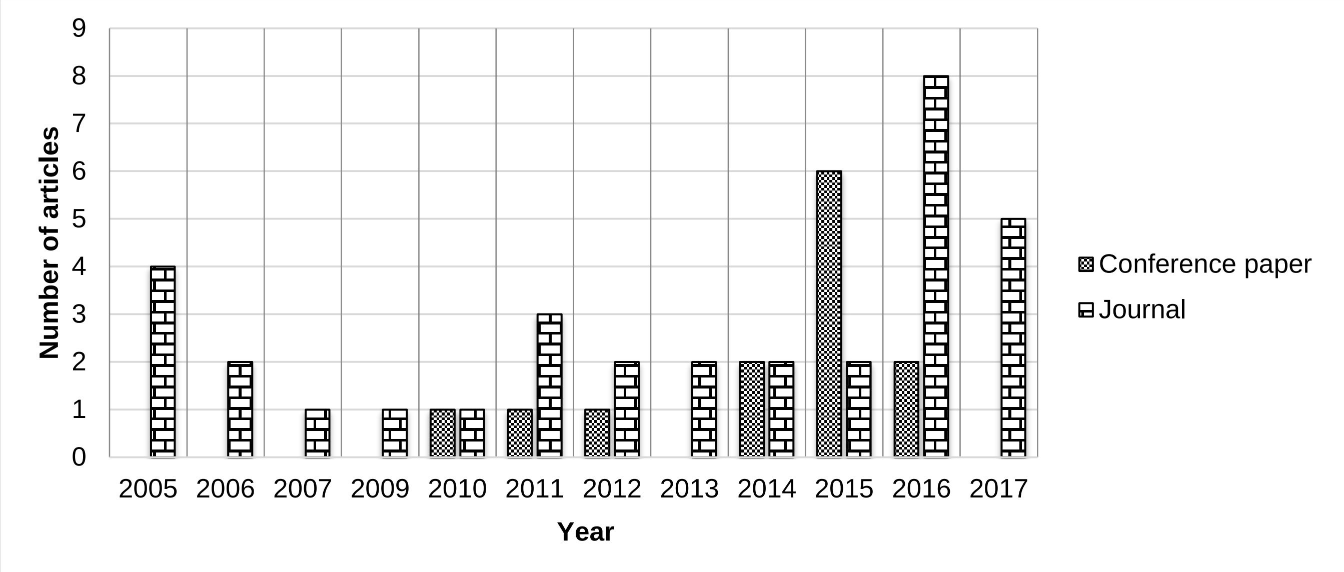

Fig. 6. The distribution of papers by publication year and type

Distribution of academic papers by journals and conferences is shown in Tables 3 and 4, respectively. As we can see, all reviewed articles have been categorized into journals and conferences categories. Almost 71% of academic papers were published in different journals and 28% was represented in international conferences. The largest number of articles were published in the journals that can be found in journals including “Computer Methods and Programs in Biomedicine”, “Computers in Biology and Medicine”, “Journal of Medical Systems”, and “Applied Soft Computing” with three publications (6.52%). The mean rate of publication rate in each journal was 2.17%.

Among the journal category based on the results, Elsevier had the second rank (10.87%) among the publishers presented in this table, while Springer was ranked third (8.70%) among 25 journals from 14 publishers considered in this review. But overall, IEEE had the first rank (28.26%) with 13 academic papers among the publishers of publishing articles and conference papers related to applying fuzzy methods in disease diagnosis. Furthermore, Hindawi publisher was in fourth place with the percentage of 4.35%. The rest of the publishers were ranked next to the same percentage. The frequency and percentage of published articles are given below.

Table 2. The frequency of published articles by publishers

Publisher	Articles	Percentage
BioMed Central	1	2.17%
BMC	1	2.17%
CISIM	1	2.17%
De Gruyter	1	2.17%
Elsevier	5	10.87%
Hindawi	2	4.35%
IEEE	13	28.26%
IOSPress	1	2.17%
SciElo	1	2.17%
Springer	4	8.70%
Wiley Online Library	1	2.17%
Wolters Kluwer Health	1	2.17%
World Scientific	1	2.17%
Nature	1	2.17%

Table 3. Distribution of papers based on journals name and publisher

Journal	Count	Percentage	Publisher
Australasian physical & engineering sciences in medicine	1	2.17%	Springer
Biomed Eng Online	1	2.17%	BioMed Central
BMC Bioinformatics	1	2.17%	BioMed Central
Brazilian journal of medical and biological research	1	2.17%	SciElo
Computational and mathematical methods in medicine	1	2.17%	Hindawi
Computer methods and programs in biomedicine	3	6.52%	Elsevier
Computers in biology and medicine	3	6.52%	Elsevier
Computers, informatics, nursing: CIN	1	2.17%	Wolters Kluwer Health
Expert Systems with Applications	1	2.17%	Elsevier
Gait & posture	1	2.17%	Elsevier
IEEE transactions on systems, man, and cybernetics	1	2.17%	IEEE
Informatics in Medicine Unlocked	1	2.17%	Elsevier
International Journal of Intelligent Systems	1	2.17%	Wiley Online Library
Journal of Biomedical Informatics	1	2.17%	Elsevier
Journal of biomedicine & biotechnology	1	2.17%	Hindawi
Journal of Circuits Systems and Computers	1	2.17%	World Scientific
Journal of Intelligent Systems	1	2.17%	Walter de Gruyter GmbH
Journal of King Saud University - Computer and Information Sciences	1	2.17%	King Saud University
Journal of medical systems	3	6.52%	Springer
Measurement	1	2.17%	Elsevier
Studies in health technology and informatics	1	2.17%	IOSPress
Telematics and Informatics	1	2.17%	Elsevier
Applied soft computing	3	6.52%	Elsevier
Scientific Reports	1	2.17%	Nature
Computers and chemical engineering	1	2.17%	Elsevier
Total	**33**	**71.74%**	**-**

Table 4. Distribution of papers based on conferences name and publisher

Conference Paper	Count	Percentage	Database Provider
2010 International Conference on Computer Information Systems and Industrial Management Applications (CISIM)	1	2.17%	IEEE
2011 5th International Conference on Application of Information and Communication Technologies (AICT)	1	2.17%	IEEE
2012 Federated Conference on Computer Science and Information Systems (FedCSIS)	1	2.17%	IEEE
2014 International Conference on Engineering and Technology (ICET)	1	2.17%	IEEE
2015 18th International Conference on Computer and Information Technology (ICCIT)	1	2.17%	IEEE
2015 IEEE Conference on Computational Intelligence in Bioinformatics and Computational Biology (CIBCB)	1	2.17%	PubMed
2015 IEEE International Conference on Computational Intelligence and Computing Research (ICCIC)	1	2.17%	IEEE
2015 International Conference on Electrical Engineering and Informatics (ICEEI)	1	2.17%	IEEE
2015 Signal Processing Symposium (SPSympo)	1	2.17%	IEEE
2015 XXV International Conference on Information, Communication and Automation Technologies (ICAT)	1	2.17%	IEEE
2016 IEEE Global Humanitarian Technology Conference (GHTC)	1	2.17%	IEEE
2016 International Conference on Microelectronics, Computing and Communications (MicroCom)	1	2.17%	IEEE
The 8th International Conference on Software, Knowledge, Information Management and Applications (SKIMA 2014)	1	2.17%	IEEE
Total	**13**	**28.26%**	**-**

4.3 Distribution of papers by database providers

We selected 8 databases to search articles. We can see the contribution of eligible articles by database providers in Table 5. The PubMed was ranked first with almost 30.43% percentage. Furthermore, Science Direct was ranked second with almost 28% percent of our selected databases. Additionally, IEEE was ranked third with 26.90%. Finally, PubMed is the most frequently scientific resource in which over 18 million citations related to biomedical research are available from 1984 to present [70].

Table 5. The frequency of published articles by database providers

Database Provider	Count of Papers	Percentage
IEEE	12	26.09%
PubMed	14	30.43%
Science Direct	13	28.26%
Taylor & Francis	1	2.17%
Web of Science	5	10.87%
Wiley Online Library	1	2.17%
Total	**46**	**100%**

4.4 The distribution of fuzzy methods applied in published articles

The main aim of this study is to investigate the use of fuzzy methods in diagnosis and the distribution of applying fuzzy methods to improve accurate diagnosis. This improvement can be due to the ability of fuzzy logic to define partial truth between true and false that is very useful in diagnosis process [7]. With considering no human being to be totally healthy or completely ill, health and illness are defined with a degree of being sick or healthy. In other words, partial healthy and illness can be described to some degree, therefore, the status of all persons is explained with the following formula [8, 28, 29]:

$$Healthy + Illness = 1 \tag{1}$$

This means that health and illness could be defined between 0 and 1 as the partial degree of health. This definition implies the fuzzy nature of diseases obviously. That is to say, a crisp value can be defined by degree of membership or can be described by this function: $\mu: X \rightarrow [0,1]$. It means that $\mu(x)$ represents the degree of x belonging to the subset [71]. For example, Adeli et al. [72] define tachycardia or maximum heart rate disorder with fuzzy definition with a set of predefined terms including low, medium, and high fuzzy sets (low means less than 111 beat per second; medium means between 111 and 149 beat per second; and high means more than 152 beat per second) [73].
After the medical concepts are defined with membership function $\mu(x)$ as fuzzy properties, their connections are determined as rules of knowledge based on logical operations [19, 24, 28, 37, 41]. In fact, the fuzzy set operations are defined via their membership functions, however, these operatives are similar to crisp sets [74]. In this regard, Sadegh-Zadeh [28] based on fuzzy logic theory defined the state of health with aid of linguistic variables as a set of terms which are shown in the following [19]:

$$T_{State\ of\ Health}=\{well,\ not\ well,\ very\ well, not\ ill, very\ ill, \ldots\} \tag{2}$$

In a nutshell, the author believed that the concept of disease and illness have a fuzzy nature where he created the term “fuzzy diseases”, trying to describe this notion in fuzzy theory with fuzzy sets [24, 28]. After representing this notion by Sadegh-Zadeh [28] in year 2000, numerous academic papers were published in this context with utilizing different fuzzy methods in medicine.
Another key fact to remember is that some of these published studies were related to improving disease diagnosis by applying different fuzzy methods. Thus, the distribution and frequency of various methods in academic papers based on the published year were investigated to show the most common fuzzy methods in each year. For this reason, first of all, we should indicate the common fuzzy methods applied in disease diagnosis.
Based on literature review section, we can generally categorize all of the articles in four categories based on applied fuzzy methods: fuzzy inference systems, fuzzy set theory and fuzzy set memberships, fuzzy-based DSSs and fuzzy clustering and classifying as represented in Table 6.

Table 6. The frequency of general fuzzy methods related to disease diagnosis

Fuzzy Method	Frequency	Percent (%)
Fuzzy set theory and fuzzy set memberships	5	10.87%
Fuzzy-based DSSs	4	8.70%
Fuzzy inference systems	30	65.22%
Fuzzy clustering and classifying	7	15.22%
Total	**46**	

Fuzzy inference systems have multidisciplinary nature, and it associated with different fuzzy methods such as fuzzy-rule-based systems, fuzzy expert systems, fuzzy decision tree, fuzzy logic controllers, and simply ANFIS methods [53, 75-79]. Since fuzzy decision tree generates fuzzy rules, thus, it should belong to "fuzzy rule-based method system". Then, it should also be included to "fuzzy inference system" groups. "Fuzzy neural networks" associated with neural network classification techniques. Therefore, fuzzy neural networks should belong to fuzzy classification methods [80]. "Fuzzy analytic method" is used for classifying, thus it should belong to fuzzy classification methods too [81]. Therefore; to classify these methods with details to describe which method has been used in articles, we categorized fuzzy methods in the context of diagnosis in different 13 categories with their distribution and frequency. The classification of the fuzzy methods represented in this article is based on the method that authors stated in the method sections in their articles. These are listed in Table 7. The evidence presented that the FES, an Adaptive Neuro-Fuzzy Inference System (ANFIS), and rule-based fuzzy logic have been the most popular fuzzy methods for improving disease diagnosis with almost 15.22%. The FIS and the fuzzy set theory were ranked second with 5 published articles (10.87%). FDSS were ranked third (8.70%) among thirteen fuzzy methods. Weighted fuzzy rules, Fuzzy Cognitive Map (FCM), Fuzzy Logic Control (FLC), and fuzzy AHP were allocated the lowest number of articles in this review with 2.17%.

Table 7. The frequency of applied fuzzy methods related to disease diagnosis

Fuzzy Method	Frequency	Percent (%)	The Code of References
FES	7	15.22%	1-5-6-7-8-9-10
Fuzzy set theory	5	10.87%	17-18-19-20-21
FIS	5	10.87%	3-38-39-40-41
Fuzzy AHP	1	2.17%	45
ANFIS	7	15.22%	22-23-24-25-26-27-28
FDSS	4	8.70%	34-35-36-37
FDT	3	6.52%	31-32-33
FLC	1	2.17%	46
Fuzzy classification	2	4.35%	4-42
Fuzzy neural networks	2	4.35%	29-30
Fuzzy cognitive maps	1	2.17%	43
Rule based fuzzy logic	7	15.22%	2-11-12-13-14-15-16
Weighted fuzzy rules	1	2.17%	44
Total	**46**	**100.00%**	*** These codes are defined based on the tables represented in Appendix B.**

As one of our research questions was about which fuzzy methods have been more used among researchers in each year, therefore we summarized the distribution of different fuzzy methods by year in Fig. 7. As shown in the Table 5, the most common fuzzy method used to diagnose diseases is FES. From 17% of published articles in relation to FES, 7 percent of articles were published in 2016. About the rule-based fuzzy logic in diagnosis, almost 4% of articles in this category were published in 2017. The articles that utilized FIS method were published only in 2015 and 2016. Furthermore, in 2005, a large number of articles used ANFIS method to improve disease diagnosis. In the following, we have represented complementary information that we achieved with this review according to applied fuzzy methods.

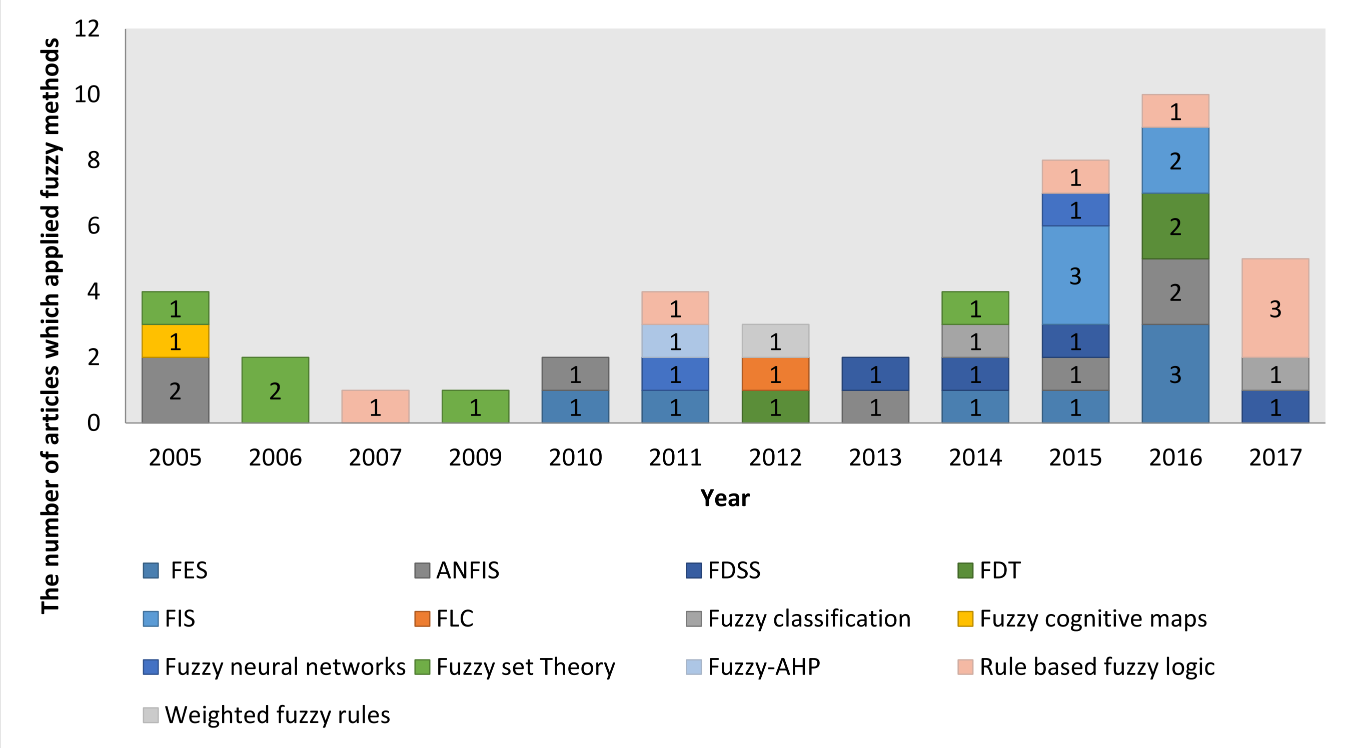

Fig. 7. The distribution of fuzzy methods by year

4.4.1 FES method

Fuzzy Expert Systems (FES) are defined as systems that utilize a collection of fuzzy membership theories and complicated rules, instead of using Boolean logic to reasoning about data. In performed studies, there are differences of fuzzy methods used to design rules in such systems [57]. It is significant to note that 6 out of 7 studies which published upon FES, can improve the diagnosis of complicated diseases and their positive impact on diagnosis was reported [79, 82-88]. Because of importance and remarkable success of developing a fuzzy expert system in the context of diagnosis, the book entitled “Fuzzy Expert Systems for Disease Diagnosis” has been published in 2015 [36].

Uncu [83] designed a new diagnosis expert system with fuzzy logic approach to facilitate interpretation of pulmonary function tests with a high level of confidence. This expert system by applying fuzzy set theory in combination with fuzzy rule-based methods can calculate the risk of Chronic Obstructive Pulmonary Disease (COPD) in patients. This system uses FEV1 and FVC values as inputs which are measured by PFT tools and it generates the interpretation of the test and the probability of COPD risk as outputs. The researchers concluded that the developed system can be effective in the early and accurate diagnosis of pulmonary diseases. In this regard, Oluwagbemi et al. [84] by applying fuzzy methods designed an expert system to aid the physicians in early diagnosis of Ebola Virus (EVD) disease. The EVD can cause an acute, serious, and fatal infectious which was a major public health problem during 2014-2016 [89]. This expert system programmed with C# language and its knowledge base was designed with adopting fuzzy sets to provide early diagnosis and best recommendation from patient’s data. The evaluation of this system indicated that it can improve the early diagnosis of EVB. In addition, it can be used in training medical students to practice accurate diagnosis of this fatal infectious disease.

Reshmalakshmi and Sasikumar [79] developed an expert system to detect osteoporosis and thereby assist the physicians to make a better diagnosis. In their study, the risk factor of osteoporosis was modeled by defining fuzzy membership based on input variables. Furthermore, the evaluation shows that the researchers succeed to represent an efficient osteoporosis detection framework with developing this system.

Meza-Palacios et al. [85] developed a fuzzy expert system to assess the nephropathy in patients who suffer Type 2 diabetes mellitus. This system was developed by 432 fuzzy rules which was created based on fuzzy sets. This fuzzy expert system can be effective to aid experts and non-specialists to assess nephropathy with reducing errors in diagnosis. Moreover, Putra and Munir [86] implemented application

upon the expert system with applying FIS for skin disease diagnosis in children. 21 fuzzy rules were utilized in this system based on scientific academic papers and experts' experience to design inference engine to diagnose measles, German measles and chickenpox. The application was implemented by C# programming language. The built on FIS was constructed based on fuzzy variables such as body temperature, rash, and number of symptoms of each skin disease as inputs.
Due to the difficulty of determining the healthiness of a kidney, Ahmed et al. [87] provided an application to evaluate whether or not a kidney is healthy. The system was designed based on a fuzzy rule-based inference method with utilizing the Mamdani approach. The authors concluded that the expert system can be used by physicians to determine the health status of the kidneys. Importantly, the system can be used by patients to test their status.
As periodontal dental disease needs a long time to diagnose and its timely treatment is vital, Allahverdi and Ackan [88] proposed fuzzy expert system to formulating each rule by Mamdani approach and analyzing diagnosis to determine the severity of the disease. This system was able to speed up diagnosis of periodontal dental disease with using analysis of possible diagnoses.

4.4.2. Fuzzy rule-based method

Fuzzy rule-based systems are an increasingly important area in applied fuzzy set theory where 14.6% of included articles are related to this method. FRBS can be defined as a type of rule-based system in which fuzzy sets in combination with the fuzzy logic, are used to describe an expert knowledge based on the goal of the study and modeling the relations between input and output variables with the aim of overcoming the existing inherent uncertainty in knowledge [90-93].

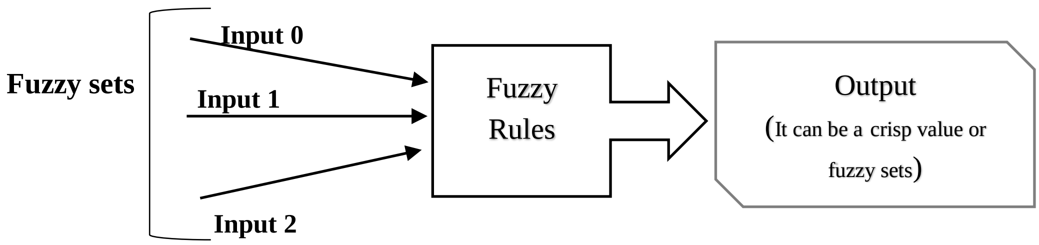

Fig. 8. The performance of fuzzy rule-based systems

The rules are usually represented in form of "IF . . . THEN" statement and each rule can be described as a fuzzy conception [94]. Generally, the process of applying fuzzy rule-based systems is shown in Fig. 8. For instance:

IF temperature >38^{C} THEN patient has fever

If problem has dimensional pattern, the fuzzy rule is formed as following:

Rule R_i: If $x_1$is A_{i1} and … and x_n is A_{in} Then Class C_i with CF_i , i= 1... N (3)

In a mentioned equation, N can be considered as the total number of fuzzy rules in form of if-then statement and X set (X={$x_1, x_2, \dots, x_n$}) is reprehensive of dimensional pattern, C_i represents a consequent class and $CF_i$is a degree of the fuzzy rule of R_i [17, 90, 91, 95, 96].
In this regard, fuzzy rules with utilizing reasoning ability will simulate the deciding process of the human mind thinking to make a decision in an uncertain environment. In the above equation, x represents the crisp inputs to the rule and A and C are linguistic variables. The operator in this equation can be AND, OR and XOR to generate fuzzy rules.
Fuzzy rule-based systems were developed in two types of approach namely Mamdani and Sugeno. Output and results in Mamdani approach appear as a fuzzy set while in Sugeno approach the crisp output is appeared in form of fuzzy value [52]. Mamdani type of fuzzy rules and Sugeno type of fuzzy rules are presented in Eqs. (4) and (5).

If a is x_1 and b is x_2, then c is x_3 (x_1,x_2, x_3 are fuzzy sets) (4)

If a is x_1 and b is x_2 then c = ax_1+bx_2+ c (a, b, and c defined as constant value) (5)

In disease diagnosis, this method can be utilized to predict and improve diagnosis based on a complex characteristic of the disease. Additionally, this method was applied in six reviewed articles of this study to improve diagnosis of different diseases. The diseases were considered with utilizing rule-based method including Fibromyalgia [97]; diagnosing the disorders is seen in critical care units [98], CVD [99], breast cancer [100], aphasia [101] and thyroid disease [102].

Leite et al. [98] developed a fuzzy medical system to classify the vital signs with the acquisition of data from hospitalized patients to provide pre-diagnosis of the disorders to help physicians and sending alerts via mobile devices. This model with 96% accuracy, monitored vital signs and sent alarms as early as it can. This means that only 4% of alarms which were generated by fuzzy system were false and it might be due to various external causes such as equipment fault. However, development of fuzzy systems could facilitate the management of critically ill patients in intensive care units. In another study conducted by Reddy and Khare [99], a new system was represented to assist the physicians to diagnose the probability of heart disease automatically. Thus, they have used optimal rule generation using Opposition Based Algorithm (OFBAT) to produce the fuzzy rules for classification of heart disease data. FBAT is kind of algorithms in which two feature of BAT and Firefly techniques have been combined to optimize the fuzzy logic performance.

Nilashi et al. [100] applied Triangular and Gaussian MFs to define heuristic and expert rules to develop a fuzzy system to classifying breast cancer with using classification and rule-based techniques. They described the relationship between different input variables to calculate the probability of breast cancer. Additionally, the combination of PCA, EM, and fuzzy rule-based data mining techniques were utilized in their study.

Because of complex and difficult diagnosis of Fibromyalgia Syndrome (FMS), Arslan et al. [97] developed fuzzy rule-based system for the purpose of accurate diagnosis and FMS severity. Some clinical sign and symptoms were used as the basis for developing fuzzy rules to classify the severity of diseases, final diagnosis, and probability of FMS. This system was notably improved diagnosis of fibromyalgia with high accuracy.

Akbarzadeh-T and Moshtagh-Khorasani [101] applied hierarchical fuzzy rule-based structure with considering statistical analysis in its construction to determine the type of aphasia. Aphasia diagnosis is very complex and difficult. The authors developed a fuzzy system to improve complex aphasia diagnosis with considering fewer features in comparison with artificial neural networks [93].

Thyroid disease has a high prevalence worldwide and negligence of thyroid disorders will cause irreparable events. Biyouki et al. [102] developed a new computational system for diagnosing thyroid disease when endocrinologist experts are not available. Authors applied Gaussian membership function with Sugeno inference method to develop fuzzy rules based on different inputs.

Nowadays, data mining becomes the most interesting field among researchers in fields of medical science and diagnosis. In this context, Nilashi et al. [11] invented a new method consists of CART method and fuzzy logic theory to develop a system based on medical data sets. They applied this new method to generate fuzzy rules utilized in early diagnosis of diseases, and also provide disease prediction based on machine learning techniques.

4.4.3. Fuzzy set theory

As we described in the last section, fuzzy sets are assigned to the degree of membership. It is one of the best solutions to model uncertainty in disease and diagnosis. Among the articles that were under-surveyed in this review, fuzzy set theory ranked third with 5 academic papers. Fuzzy sets define the rating of membership of x in A as following; however, fuzzy sets are completely different from crisp sets [73].

$$\mathrm{A}=\{x, \mu_x(x) | x \epsilon\, X\} \tag{6}$$

Linguistic variables can be utilized in fuzzy sets to define medical concepts. Fuzzy sets are defined with uncertain boundaries against classical collections with sharp and crisp boundaries, therefore, fuzzy sets are determined with membership function which are compatible with medical decision making process in disease diagnosis [16, 19, 25, 103]. Thus, fuzzy sets can define the medical entity in an appropriate way by considering different classes for diseases diagnosis. A certain symptom can be assigned by many diseases. Considering that, various diseases might appear in a manner that is accompanied by other diseases. Therefore, Sadegh-Zadeh [28] invented "fuzzy disease" term to define the complicated nature of the disease. According to this concept, the disease can be considered a fuzzy set of disease that consists of individual disease entities in which each member represents disease with a different degree [24, 29, 104]:

$$D = \{(D_1, \mu_D(D_1)), \ldots, (D_q, \mu_D(D_q))\} \quad (7)$$

Furthermore, for diagnosis, we can define symptoms and patients with fuzzy sets. Then, with using operation such as max-min composition calculation, the membership function with fuzzy relation can be defined by T=Q*R [24, 29, 73, 103, 105, 106]:

$$\mu_T(p_k, d_j) = \mathrm{Max}\left(\mathrm{Min}\{\mu_Q(p_k, s_i), \mu_R(s_i, d_j)\}\right), s_i \in S, d_j \in D, p_k \in P, \quad (8)$$

where *S* indicates a set of symptoms and *P* means a set of patients. This method was applied in 5 articles, considering different diseases such as Urinary Incontinence (UI), diagnosis the cardiac care unit diseases, coronary artery disease, and cardiomyopathy to improve diagnosis. In this regard, 3 out of 5 articles were related to cardiology discipline.

Sacco et al. [107] in their research determined problems in the patient's legs, whom previously had diabetic foot ulcers by examining the pressure to different points of the foot and categorizing them to fuzzy sets. As many cases of UI remain undiagnosed because of different reasons, De Moraes Lopes et al. [108] designed fuzzy model to improve nursing diagnosis; the max-min composition of fuzzy sets was applied to develop the system.

Kannathal et al. [109] utilized fuzzy set theory to discover hidden abnormalities based on the clinical information such as data from the Multi-Channel Electrocardiogram (ECG), Arterial Blood Pressure (ABP) and respiration rate. In this system, fuzzy logic has succeeded to show patient status with the fuzzified probability. Duarte et al. [110] in their study proposed a model for Myocardial Perfusion Scan (MPS) to select appropriate patient with applying fuzzy sets theory. The authors concluded that the system was designed based on fuzzy set theory that can assist GP to select the appropriate patients for MPS with 100% sensitivity by calculating the risk point degree in patients suffered from Coronary Artery Disease (CAD).

Tsai and Kojima [111] represented a fuzzy system to optimize the classifying of echocardiographic images with using fuzzy sets theory, namely, normal and abnormal cases. In this study, fuzzy reasoning utilized 8 Gaussian-distributed membership functions. They reported that with developing the fuzzy model, an average of 96% accuracy can be achieved.

4.4.4. ANFIS method

In this review, it was found that ANFIS method has been employed by 7 articles in which ranked third with almost 15.22% of 46 articles. ANFIS can be defined as a kind of neuro-fuzzy network system that was introduced by Jang [78] for the first time. A Sugeno type system with using fuzzy IF-THEN rules were applied in ANFIS to represent expert knowledge with learning capability to model nonlinear concepts. In terms of the ANFIS architecture, we can represent it with two fuzzy if-then rules [78, 112, 113] as following:

Rule 1: If (*x* is *A*1) and (*y* is *B*1) then (*f*1 = *p*1*x* + *q*1*y* + *r*1)
Rule 2: If (*x* is *A*2) and (*y* is *B*2) then (*f*2 = *p*2*x* + *q*2*y* + *r*2) (9)

In formula that we represented, *x* and *y* should be considered as the inputs where *Ai* and *Bi* have been defined as fuzzy sets. *fi* is the outputs that were determined by the fuzzy rules while *pi*, *qi*, and *ri* are the parameters that are specified during the training. With applying this method, symptoms and signs can be considered as inputs and diagnosis as output [75, 112, 114, 115]. ANFIS method has been successfully applied to diagnosing different diseases over the past few years.

Yilmaz et al. [116] developed a system to decrease the lung cancer death risk with calculating the risk of getting lung cancer and the impact of stress on disease condition. This system with high accuracy could perform early diagnosis for the people with the possibility of getting cancer. Most of the times anesthetist may be overloaded by patient data and intuitive decision making might fail to achieve the optimal decision. In this regard, Mansoor Baig et al. [117] attempted to improve clinician performance to design

a diagnostic alerting system for early detection of critical events during anesthesia. They reported that with applying this system, the levels of hypovolemia can be detected accurately with 95% confidence.
Ubeyli and Guler [118] to notably improve diagnosis of erythema squamous disease, applied ANFIS method in their research. With different ANFIS classifiers, system can detect a different kind of erythema squamous diseases with predefined clinical inputs to generate an accurate diagnosis. In this study, the researchers showed that the proposed ANFIS method in comparison with neural network model has high capability to diagnose the erythema-squamous diseases. In another study conducted by Ubeyli and Guler [119], a new method was invented to diagnose internal carotid artery stenosis and occlusion. The ANFIS method applied in the study, achieved almost 92.65% accuracy to classify patients suffered from stenosis and occlusion that its accuracy was higher than neural network model.
Shariati and Haghighi [120] designed a system to detect hepatitis and thyroid diseases. The researchers compared the result of ANFIS method with other methods that include Support Vector Machine (SVM) and artificial neural networks. Finally, they reported that this system had shown a 1.2% improvement in accurate diagnosis in comparison with other methods.
Unfortunately, esophageal cancer might not be detected until advanced stages, due to the absence of signs. With this in mind, Wang et al. [121] decided to invent a new system for early diagnosis of esophageal cancer to improve survival of esophageal cancer. They applied ANFIS method to develop their system to help clinicians to improve cancer detection and predicting the survival of patients at an early stage of cancer.
Due to difficulty and complexity of Parkinson's disease and to control and prevent the disease progress, Nilashi et al. [122] invented a new intelligent computational method to improve the diagnosis and control the disease with utilizing ANFIS method. The results indicated the impact of this system on improving the diagnosis of Parkinson and the precision of this method in anticipating the progression of the disease; in addition, to helping the physicians to detect the disease timely.

4.4.5. Fuzzy neural network method

Fuzzy Neural Network (FNN) is a kind of fuzzy logic method which is created from the combination of neural networks with fuzzy logic. In FNN, crisp data or fuzzy set of data can be utilized as training data [80]. In this method, neural network is utilized to determine the different parts of the fuzzy system such as fuzzy rules or membership functions of fuzzy sets. In fact, fuzzy logic in FNN is applied to improve the performance of the neural network. In the reviewed articles, FNN was utilized in two of the articles. One of them is related to pediatrics discipline and the second study is about utilizing the fuzzy neural network to improve diagnosis of electrolyte disorder in terms of critical care.
The process of diagnosing Hypoxic-Ischemic Encephalopathy (HIE) in newborns, usually is very complex. Hence, Li et al. [123] established a system for early detection of HIE in infants. Developing such systems could overcome the difficult diagnosing with using fuzzy logic in a combination of neural networks. This system was based on clinical indicators which could provide early diagnosis of HIE with high accuracy.
Beganovic and Avdagic [124] developed an intelligent system to classify acid-base disorder. They model a hybrid fuzzy-neural voting system to give information to clinicians about the percentage presence of acid-base disorders. This fuzzy subsystem includes three fuzzy models, and giving fuzzy IF-THEN rules for diagnosis.

4.4.6. FDT

Fuzzy Decision Tree (FDT) is used to represent a complicated problem with classification techniques to overcome uncertainty. The knowledge represented with FDT can stimulate human thinking successfully [125, 126]. Thus, FDT described as the best tool to classify fuzzy sets in medicine. Using fuzzy logic in constructing FDT to generate fuzzy rules can improve the understanding of researchers about disease diagnosis process according to medical classifications [7, 127, 128].
Kadi and Idri [129] conducted a research to compare the results, obtained from crisp decision tree with FDT in terms of diagnosis of heart disease. These two methods were utilized to improve Chronic Vascular Disease (CVD) diagnosis. This study has shown that FDT classifiers are more efficient than

crisp decision tree in diagnosis CVD and FDT, encountering low error rates in comparison with crisp DT.
Due to the fact that huge amount of clinical data, caused the decision making and disease diagnosis difficult and complex, Levashenko and Zaitseva [130], to decrease this complexity decided to develop FDT technique. This technique was designed based on the use of a fuzzy notion for each numerical feature. They found that constructing an automatic method to generate a set of fuzzy values automatically for each numerical value in disease diagnosis, can be useful, therefore, they applied this technique to find patterns in medical data to calculate the possibility of breast cancer in patients, which improves breast cancer diagnosis.
As diabetes are now recognized as a worldwide health problem with high prevalence, Kamadi et al. [131] represented new Computational Intelligence (CI) technique for early diagnosis of diabetes to improve disease control. With applying FDT, researchers succeed to develop a new model to diagnose diabetes with high accuracy in comparison to previous models.

4.4.7 FDSS

In medicine, Fuzzy Decision Support System (FDSS) is developed to convert knowledge from experts based on fuzzy rules to improve decision making. Clinical Decision Support System (CDSS) can facilitate diagnosing “fuzzy diseases” based on symptoms and test results as input with utilizing different fuzzy methods [132]. Furthermore, FDSS can minimize diagnosis errors and assist healthcare providers in disease diagnostic process with high accuracy.
Predicting the risk level of heart disease is a challenging topic in cardiology. To optimize this problem, Paul et al. [133] represented FDSS to improve the accuracy of heart disease diagnosis with learning the optimum rules from training data with automating the membership functions. D'Acierno et al. [51] tried to propose a general technique to create fuzzy DSSs automatically in terms of disease diagnosis. Since the process of disease diagnosis in many diseases can be considered as a decision, they could describe a methodology to design FDSS to improve diagnosis of various kinds of diseases, easily.
The diagnosis of fibromyalgia is very complicated due to its uncertain symptoms, thus, most of the time it remains undiagnosed. Therefore, Romero et al. [27] developed new CDSS to improve diagnosis in a set of fuzzy diseases that related to fibromyalgia with applying fuzzy deformable prototype. They concluded that such system can enhance fibromyalgia diagnosis.
Kunhimangalam et al. [82] to improve peripheral neuropathy, have developed CDSS to diagnose neuropathy in an effective time period. The inputs of the system include clinical symptoms obtained from Electronic Medical Record (EMR) to generate a diagnosis. With applying Mamdani type of fuzzy inference technique, accurate diagnosis is provided when a neurologist is not available.

4.4.8. FIS

Fuzzy Inference System (FIS) can map the input variables such as a sign, symptoms, and clinical data to an output via fuzzy logic methods including IF-THEN rules, membership functions and other fuzzy methods to model expert decision making in terms of disease diagnosis [134-136]. Generally, FIS consists of fuzzifier, inference engine, defuzzifier, and a knowledge base. Two kinds of models which were defined as Mamdani-type and Sugeno-type, are applicable to all types of FIS frameworks which can be implemented via fuzzy logic toolbox [53, 137]. However, in disease diagnosis, Mamdani type of FIS has been widely applied [138, 139].
Peritonitis is one of the most complex diseases in terms of diagnosis that can lead to unrecoverable complications if the late diagnosis occurred. Dragovic et al. [76] decided to design FISs with the aid of fuzzy membership to estimate the likelihood of having peritonitis by patients when medical experts are not available. Gynecology encountered inherent uncertainty, therefore, Sardesai et al. [140] endeavored to invent a solution to minimize the complexity of gynecological disease with fuzzy logic. They could apply Mamdani-type FIS in their study to confirm the single disease diagnosis.
Since Alzheimer Disease (AD) has a slow progress with different stages, Krashenyi et al. [141] applied FIS to classify AD to improve diagnosis. The notable finding of their approach is assigning membership

to a patient in three classes including Normal, MCI or AD class based on the features obtained from the MRI images.
Saikia and Dutta [142] developed a fuzzy system to improve dengue fever diagnosis with applying both trapezoidal and triangular membership functions and Mamdani type of FIS. Dengue fever is one of the fatal infectious diseases with the high risk level of death. Using fuzzy inference to prevent the development of dengue fever and selecting the appropriate treatment, in addition to diagnosing the disease based on symptoms, the likelihood of developing a disease is calculated. Additionally, the model of Gayathri and Sumathi [77] assisted in determining cancerous or non-cancerous tumor with developing Mamdani fuzzy inference. Hence, by applying fuzzy logic, they calculated the risk of breast cancer with lesser attributes.

4.4.9. Fuzzy classification

Classification framework provides an automated analysis of data, assigning a degree of membership for each instance or it can be accompanied by grouping fuzzy data sets process [143, 144]. In terms of disease diagnosis, in most studies fuzzy classification tries to classify patients based on the information acquired from medical data in combination with various artificial intelligence techniques to overcome uncertainty in diagnosis [145].
Elshazly et al. [146] developed a fuzzy system to diagnose a kind of chronic eye disease in the early stage to prevent its complications. The authors in this research, have attempted to timely and accurately diagnose glaucoma by comparing decision tree, fuzzy classification, and ROC. The study was the only research applying fuzzy logic methods that did not show any improvement in disease diagnosis in comparison with other methods. Furthermore, Cheruku et al. [147] with the aid of fuzzy logic theory presented a new type of fuzzy classification rules to generate high accuracy and comprehensible fuzzy rules to diagnose diabetes. These fuzzy rules were generated based on the inputs in which this new model showed high accuracy in early diagnosis of diabetes in comparison with previous algorithms.

4.4.10. Fuzzy cognitive maps

Fuzzy Cognitive Map (FCP) is one of the effective tools to modeling complex concepts in artificial intelligence. It is the most used algorithm in fuzzy clustering [148, 149]. FCP can represent expert knowledge with graphical representation based on the cognitive map. Thus, it can be utilized in disease diagnosis effectively [150].
To overcome the vague knowledge about a linguistic nature in terms of different diseases, researchers used various fuzzy methods for disease classification. In this regard, John and Innocent [50] applied Type-2 fuzzy sets to implement FCP for diagnosing influenza. The authors indicated that the objective of their study was to investigate the possibility of determining the phase of the disease in addition to diagnosing the disease by using a fuzzy system.

4.4.11. Weighted fuzzy rules

Weighted fuzzy rules are usually used to design DSS to generate a set of fuzzy rules. With the generated fuzzy rules by using the relationships of input variables based on training data, the weight of each input variable in this technique was calculated with the generated fuzzy rules by the relationships of input variables based on training data. In other words, this method was developed based on learning [151, 152]. According to systematic investigation of our study, this method was applied only in one study conducted by Anooj et al. [153] in terms of diagnosing heart diseases. The authors applied weighted fuzzy rules to develop decision support system to diagnose heart diseases automatically. This system was designed based on Mamdani fuzzy inference system to be able in determining the risk level of heart disease in patients with 68.75% specificity.

4.4.12. FAHP

Fuzzy Analytic Hierarchy Process (FAHP) is applied by many researchers in medical sciences since FAHP has the capability to model linguistic entity [154]. FAHP with utilizing fuzzy logic has the ability to make a comparison between different decision elements in addition to model uncertainty to determine their important role of the decision making process in terms of disease diagnosis [81, 155].
In the article represented by Uzoka et al. [155] to verify the diagnosis level of malaria, the authors tried to compare FAHP with other intelligent methods. In this system, physicians can assure that the patient suffers from malaria based on the clinical information entered into the system as the input. The researchers concluded that fuzzy logic can be considered as one of the most powerful tools in terms of best performance in malaria diagnosis process.

4.4.13. FLC

Fuzzy Logic Control (FLC) method was born simultaneously with the introduction of fuzzy logic. FLC is a methodology in which a method is provided for representing expert's knowledge and how human reason is operated for controlling systems [156]. It can be described as the method to control by sentences rather than equations. It means that the fuzzy control is performed by fuzzy rules and is developed based on fuzzy sets that can control system with no human intervention [157].
The FLC method was applied by Singh et al. [158] to diagnose the degree of disease severity in osteoarthritis and arthritis rheumatoid. With the late arthritis diagnosis, the patient might encounter with a higher risk of disease progression. Thus, they applied the FLC to create fuzzy system for diagnosing arthritis and severity of the disease to aid physicians in selecting the best treatment before the severity of disease increases.

4.5 Distribution of fuzzy methods applied in published articles based on clinical aspects

One of the main research questions to conduct this systematic review is about which disciplines of medical sciences are more interested in previous research. Additionally, we would like to know what diseases were being considered more in relation to applying fuzzy logic methods to improve diagnosis. This question can provide a clear synthesis and interpretation of the most common diseases that were studied by the researchers in the context of disease diagnosis. Therefore, we classified the articles selected in this study by diseases and application of fuzzy methods. The frequency of diseases applied in the reviewed articles by year is presented in Table 8 and the distribution of different diseases by applying fuzzy methods is shown in Table 9. As we see in Table 8, diabetes with 8.27% was ranked first with 4 out of 46 articles. Breast cancer was ranked second with 3 articles (5%). Besides, heart diseases after breast cancer were ranked third with 4.35% of all reviewed articles. The frequency of other diseases that are named in the table, was almost similar.

Table 8. The distribution of diseases by year

2005	2006	2007	2009	2010	2011	2012	2013	2014	2015	2016	2017
Cardiomyopathy	Cardiac care unit diseases	Aphasia	Urinary Incontinence (UI)	Hepatitis and thyroid diseases	Hypoxic ischemic encephalopathy	Arthritis	General medicine	Diabetes	Alzheimer	Gynecological diseases	Breast cancer
Erythematous-squamous diseases	Coronary Artery Disease (CAD)	-	-	Pulmonary diseases	Intensive care disease	Breast cancer	Hypovolemia	Glaucoma	Breast cancer	Cardiovascular disease, ANS	CVD
Influenza	-	-	-	-	Malaria	Heart disease	-	Kidney diseases	Children skin disease	Dengue fever	Fibromyalgia
Internal carotid artery stenosis and occlusion	-	-	-	-	Periodontal disease	0	-	Neuropathy	Electrolytes disorder	Two cases of diabetes	General disease
-	-	-	-	-	-	-	-	-	Heart disease	Ebola	Diabetes
-	-	-	-	-	-	-	-	-	Peritonitis	Fibromyalgia	-
-	-	-	-	-	-	-	-	-	Thyroid disease	Lung cancer	-
-	-	-	-	-	-	-	-	-	-	Parkinson	-
-	-	-	-	-	-	-	-	-	Esophageal cancer	Osteoporosis	-
4	**2**	**1**	**1**	**2**	**4**	**3**	**2**	**4**	**8**	**9**	**5**

Table 9. The distribution of diseases by fuzzy methods

FES	Rule based fuzzy logic	Fuzzy set	FIS	ANFIS	FDSS	Fuzzy-AHP	FDT	Classification	FLC	Fuzzy neural networks
Periodontal disease	Aphasia	Urinary Incontinence (UI)	Peritonitis	Lung cancer	Neuropathy	Malaria	Cardiovascular disease, ANS	Glaucoma	Arthritis	Hypoxic ischemic encephalopathy
Pulmonary diseases	Fibromyalgia	Cardiac care unit diseases	Gynecological diseases	Erythematous-squamous diseases	Heart diseases	-	Breast cancer	Diabetes	-	Electrolytes disorder
Ebola	Intensive care disease	CAD	Alzheimer	Hypovolemia	General disease	-	Diabetes	-	-	-
Diabetes	CVD	Cardiomyopathy	Dengue fever	Internal carotid artery stenosis	Fibromyalgia	-	-	-	-	-
Osteoporosis	Breast cancer	Diabetes	Breast cancer	Hepatitis and thyroid diseases	-	-	-	-	-	-
Children skin disease	Thyroid diseases	-	-	Parkinson disease	-	-	-	-	-	-
Kidney diseases	General medicine	-	-	Esophageal cancer	-	-	-	-	-	-

As shown in Table 8 and Table 9, in relation to the subject of our paper, distribution of diseases in various studies is very diverse, therefore, the analysis of fuzzy methods applied in various diseases will not have beneficial results. Thus, we conducted the analysis of applied fuzzy methods in disease diagnosis by medical disciplines, instead as we can see in Fig. 9.

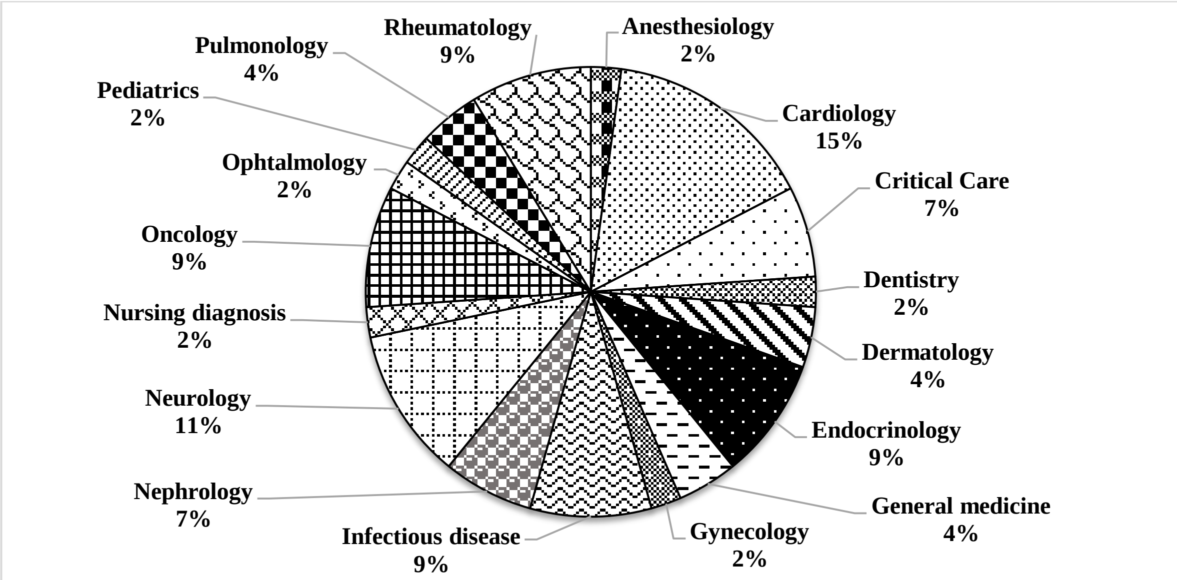

Fig. 9. The frequency of medical disciplines

The pie chart showed in Fig. 9 presents the summary statistics for medical disciplines. From the data in this chart, it is apparent that a high percentage of studies have been allocated to cardiology (15%). Although this may be due to the fact that this field includes a wide range of different cardiovascular diseases. The neurology was ranked second with 11% percentage. Oncology, endocrinology, rheumatology and infectious diseases were ranked second with 9% percentage. In following, critical care and nephrology were ranked third (7%) among 17 different medical disciplines. The lowest proportion of studies based on medical disciplines belongs to anesthesiology, pediatric medicine, ophthalmology, gynecology, dentistry and nursing diagnosis with 2% of total articles. Additionally, the distribution of medical disciplines by applied fuzzy methods is show in Table 1 of Appendix A. The table can provide valuable information for researchers in the context of applying different fuzzy methods based on medical disciplines.

4.6 The distribution of fuzzy methods in published articles based on the applied tools

In this study, we reviewed some fuzzy logic methods based on the articles published in terms of disease diagnosis in different medical disciplines. Regarding the process of designing fuzzy logic systems, it seems that researchers need software or tools which have the ability to implement the fuzzy set theory for designing and implementing such systems. Since fuzzy systems have been used widely in the last decades, different software existed to implement a wide range of fuzzy logic methods. In this section, our main focus is on applied tools which were used in research in the context of disease diagnosis to determine the most popular tools among fuzzy logic researchers. The frequency of tools utilized in reviewed articles to model fuzzy logic, have been shown in Fig. 10.
According to the results, the most favorable tool used in the reviewed articles is MATLAB software. However, 34.1 % of studies did not mention the tools they used. On the other hand, 52.4% of the studies utilized MATLAB in their studies. Additionally, MATLAB software is one of the most popular engineering computational packages. The functions in Fuzzy Logic Toolbox in MATLAB is provided to design fuzzy logic system [159]. Other tools that were used in the articles are related to using fuzzy logic to improve disease diagnosis which are shown with their frequency in Fig. 10.

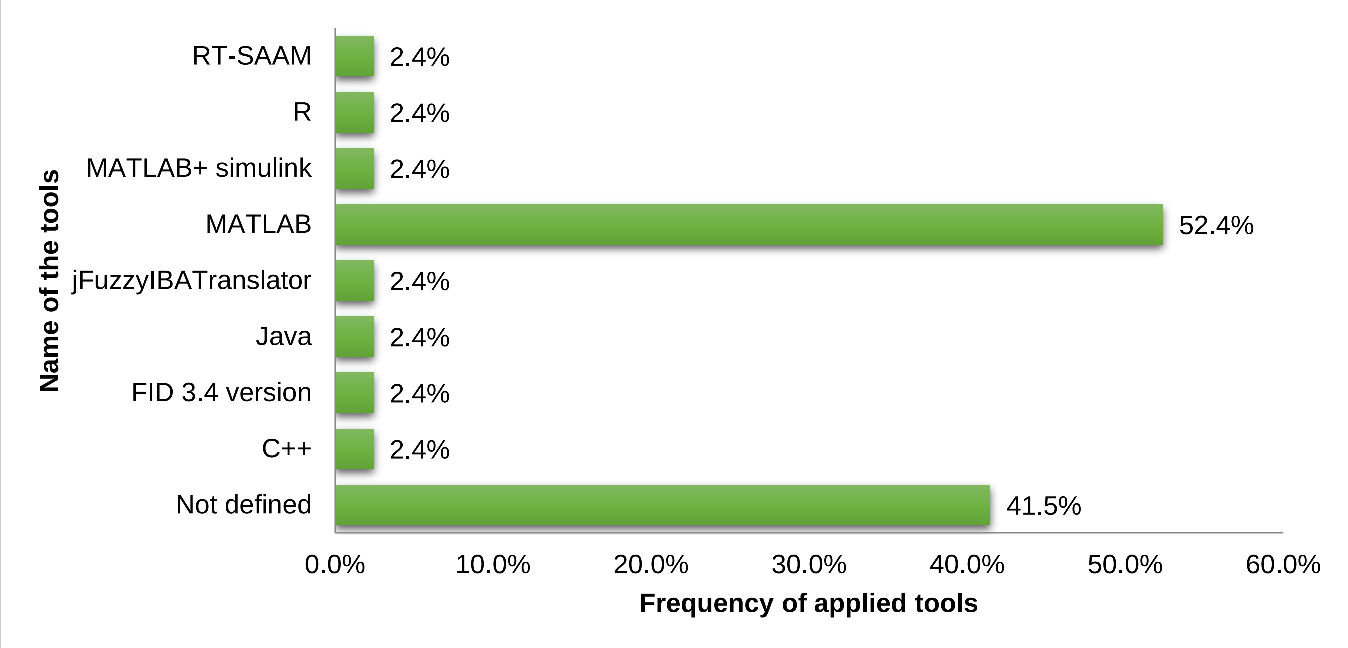

Fig.10. The frequency of applied tools in included articles

4.7 The distribution of fuzzy methods applied in published articles based on the sample size

In this section, sample size and frequency of data sets, numerical size and the summary of the statistical description of data sets used in various papers have been surveyed. In this survey, a considered data set is composed of both the number of data sets that were utilized to model fuzzy logic (training data) and the data sets applied in evaluating and testing the accuracy of the fuzzy model. The summary of the statically description of data sets is shown in Table 10 and the graphical distribution of sample size in articles by year is represented in Fig. 11.

Table 10. Statistical descriptions of sample size

Variable	Valid N	Mean	Minimum	Q1	Median	Q3	Maximum	No Sample Size Reported
Sample Size	26	598.57	20	103.00	197.50	488.50	5875	20

In articles reviewed in this study, their sample size is reported, the mean is calculated 598.5 and the range of sample size is between 20 and 5875. The median of reported sample sizes from 26 articles, is 197.5. The quartiles of sample sizes are also calculated.

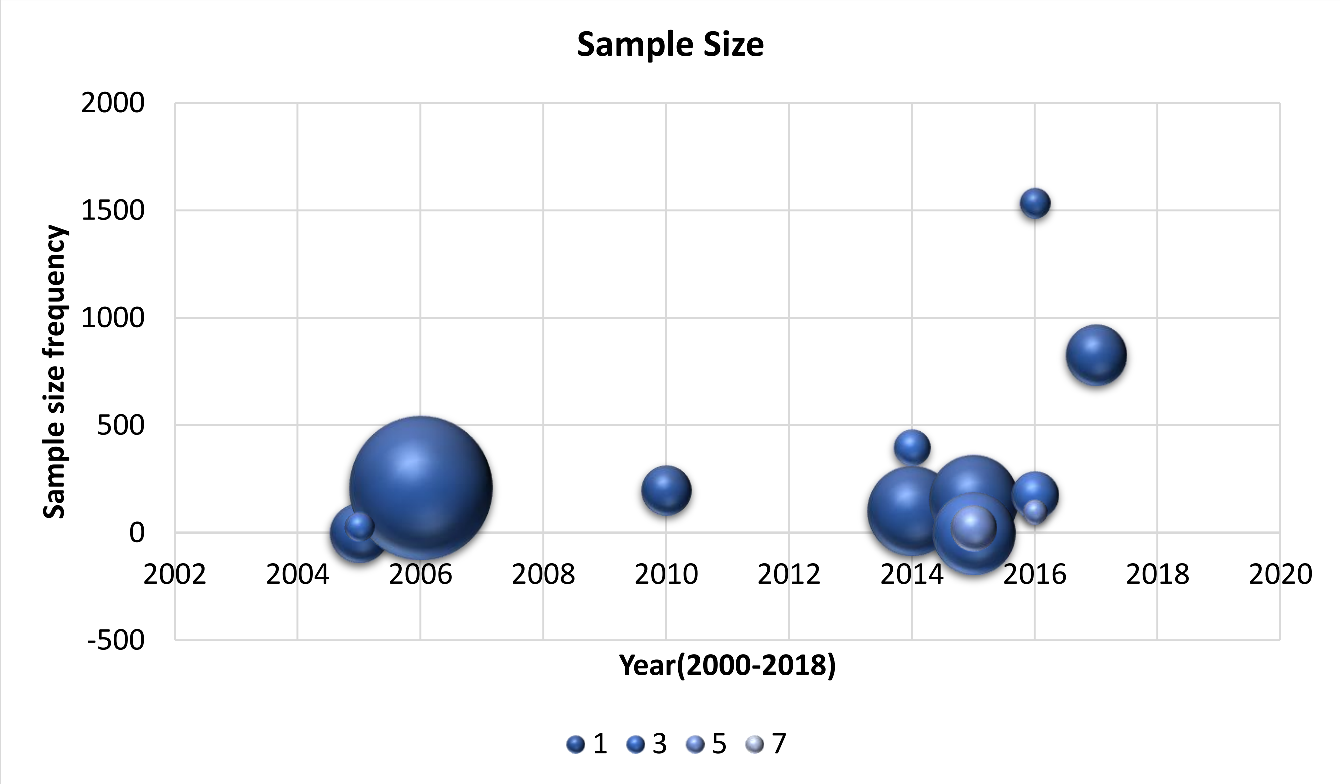

Fig. 11. Distribution of sample size in articles by year

4.8 The distribution of fuzzy methods on diagnosis in published articles based on positive effect

The key research question of this study was whether or not the fuzzy method can improve disease diagnosis. Hence, we examine the reported effect of fuzzy methods on diagnosis by different articles that were surveyed in this review. The percentage of the positive impact of fuzzy methods to improve diagnosis is indicated in Table 11. It is apparent from this table that in few studies no positive impact was reported. However, almost 90% of articles described the positive effect of applying fuzzy methods in improving disease diagnosis. However, these results were limited to articles selected in this study and therefore they cannot be a representative of the total effect of the fuzzy methods on disease diagnosis.

Table 11. The frequency of positive effect of fuzzy logic methods

Positive impact	**Frequency**	**Percent (%)**
Yes	42	91.30
No	2	4.35
To some degree	2	4.35
Total	46	100.0

In order to show the use of applied fuzzy methods to what extent they have shown their positive effects on the diagnosis of diseases, the effect of fuzzy methods according to each fuzzy method in terms of diseases diagnosis is shown in Fig. 12. According to our analysis, ANFIS has the highest proportion among other methods in improving disease diagnosis and all of the studies that applied this method to develop their models or systems, succeed to meet their objectives with high accuracy. It means that all of the studies which employed ANFIS method can diagnose the disease with no error. In addition, as we see in Fig. 12, FES and rule-based fuzzy logic methods have the second rank among other methods to improve disease diagnosis (15.22%). However, we should also take into account a combination of different fuzzy methods which might usually be employed to develop a system. That is to say the combination of different fuzzy methods might be more effective than utilizing single method, however this hypothesis will need further research. Only in two studies conducted in the context of dermatology and neurology, researchers reported the fuzzy expert system has improved diagnosis to some degree.

The studies conducted by Krashenyi et al. [141] and Elshazly et al. [146] in the domains of ophthalmology and neurology, respectively, have not mentioned any positive impact of applying fuzzy logic to improve diseases diagnosis. Among the studies that have reported the positive effects of fuzzy methods in improving the diagnosis of diseases, we can mention the studies conducted by Kunhimangalam et al. [82], Uncu [83], Oluwagbemi et al. [84], Meza-Palacios et al. [85], Reshmalakshmi and Sasikumar [79], Ahmed et al. [87], and Allahverdi and Ackan [88] to diagnose Ebola, diabetes, osteoporosis, kidney diseases, and periodontal disease, respectively. In this regard, the details of articles in each category are described in Table 2 of Appendix B (to some degree of impact regarding the fuzzy method on disease diagnosis), Table 3 of Appendix B (no positive impact of the fuzzy method on disease diagnosis), and Table 4 of Appendix B (positive effects and improvements in the diagnosis of diseases).

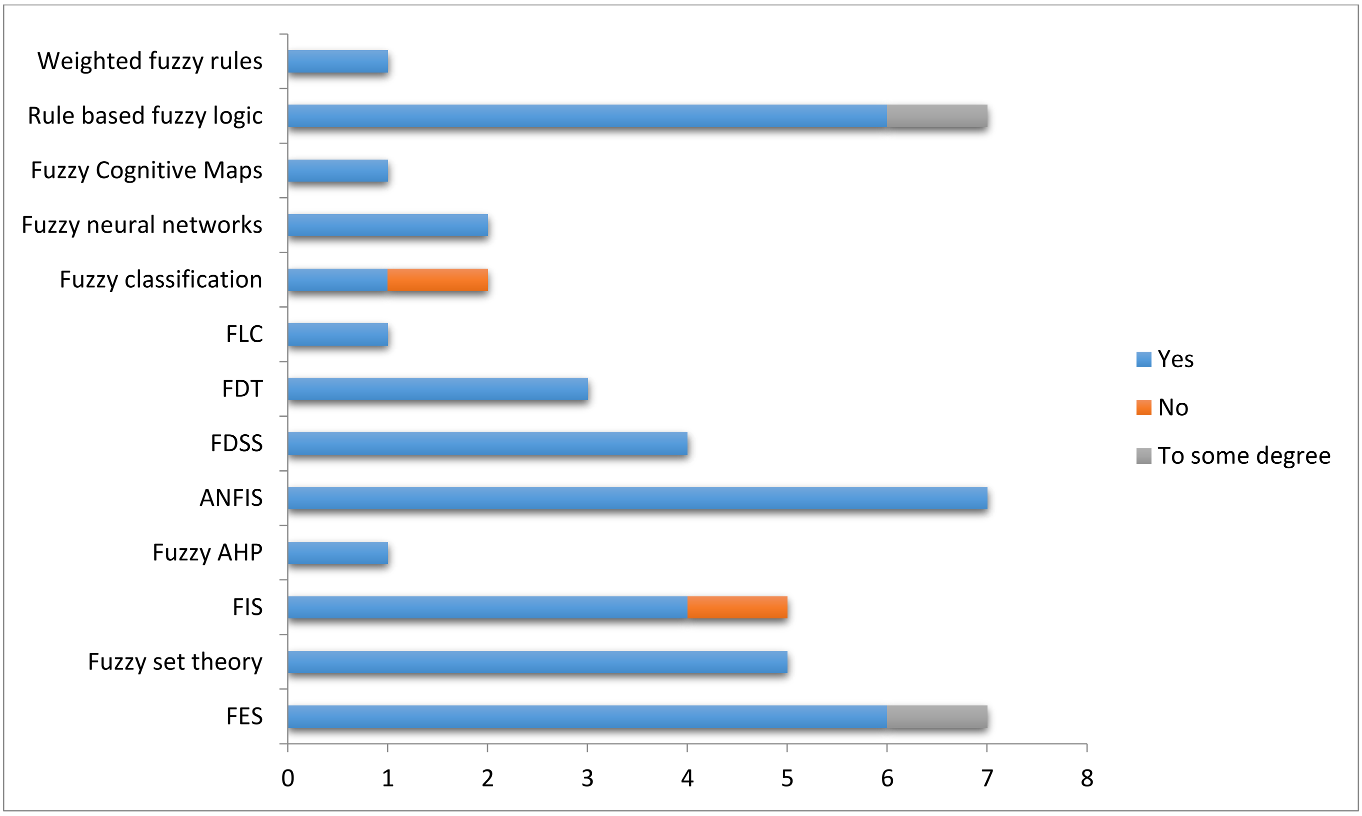

Fig. 12. The frequency of fuzzy methods impact

5. Discussion

This research was designed to review the impact of fuzzy logic methods in disease diagnosis. Previous studies have noted the importance of fuzzy methods, but there are very few review articles which have been published to systematically scrutinize the extent to which fuzzy logic is applied in each of the medical disciplines and diseases. As a result, this study can be seen as one of the most valuable studies in reviewing the fuzzy methods that are being used to improve diagnosis of diseases and also to assess the impact of these methods. In this study, we were able to identify and review 46 articles that applied different fuzzy logic techniques in diagnosing various diseases from 2005 to 2017. Because at the time of writing this article, we were in the mid-2017, so we could not accurately determine the number of articles retrieved in this year, but those articles that were retrievable until the time of writing, were also reviewed. Since the first question in this study is to determine which methods have had the most impact on the diagnosis of diseases with respect to medical disciplines, we investigated the studies based on this objective. Therefore, we considered suitable classifications to survey on the fuzzy methods. One of this classification is about classifying a number of articles published each year. In the recent years, the increasing interest in studying the application of fuzzy methods in diseases diagnosis is evident from the results of papers analysis in our research. This shows that the extent rate of published articles from 5% in 2005 reached to 21% of all reviewed articles in 2016. This escalation in the popularity of fuzzy techniques among researchers is likely to be due to beneficial results in improving diagnosis and helping physicians to identify the disease in early-stage which can lead to select the best treatment plan.

Based on our analysis, 13 different fuzzy methods have been applied in reviewed articles which were under survey. Therefore, we considered these 13 methods as the basis of widely used fuzzy methods in the diagnosis of diseases in order to present the results of this research based on them. However, these classifications are restricted to this study and we cannot generalize to other studies on the application of fuzzy methods in the medical fields. ANFIS, FES, and fuzzy logic rule-based methods have the high rate among other fuzzy methods. The results show that the degree of utilizing these methods have been more augmented in disease diagnosis because of their applicability. On the other hand, the results might indicate that researchers have more tended to use fuzzy methods in their studies, recently.

From a clinical point of view, the included articles were examined based on the type of diseases. In addition, the specialized medical field has also been investigated in order to find out the most favorable field of the fuzzy logic. The most studied medical disciplines were related to cardiology, neurology, oncology, and nephrology, respectively, in terms of fuzzy methods application in disease diagnosis. It is apparent that fuzzy logic was the most used method in medical disciplines which has the high complexity and vagueness. Another important finding was that reviewed articles are very diverse in terms of the type of disease. As a result, by analyzing the studies based on the type of disease, we cannot reach the conclusion about the most favorable diseases in which fuzzy methods have been effective in their diagnosis. A possible explanation for this might be the fuzzy nature of all diseases. The most obvious finding to emerge from this study is that we can apply fuzzy logic methods in any diseases and it might be effective to improve diagnosis in all diseases.

On the question of the positive impact regarding the fuzzy methods in the diagnosis of diseases in different studies, through analysis we found that approximately 90% of the reviewed studies believed that the use of this method can improve the diagnosis of diseases. The most interesting finding was that among the different applied methods of fuzzy logic in the reviewed articles, all seven studies applied the ANFIS method, where have been able to show the positive impact of fuzzy logic in the diagnosis of various diseases. This indicates the positive impact of ANFIS as one of the most commonly used fuzzy logic methods to improve disease diagnosis and ambiguity reduction in diagnosis due to the complex nature of the disease. According to the analysis of reviewed articles, among other widely used methods in this study, ANFIS and fuzzy rule-based methods showed the similar results with regard to the positive effect of these methods on disease diagnosis process. In each of these methods, 26% of the studies from the 14 studies that applied these two methods have reported a positive effect on fuzzy logic, and four percent of the studies have considered the effect of a fuzzy method to some degree.

From the distribution of reviewed articles which reported a positive impact of fuzzy methods, we can imply that fuzzy methods are more effective in diagnosing complex diseases that can be considered as a critical health problem or in which a late diagnosis, causes a serious health problem or even death. Since the importance of this method in our systematic review study, different methods in various studies were also investigated based on the clinical disciplines. As a result, the most frequent method was related to utilizing fuzzy set theory in the field of cardiovascular diseases or cardiology. This can be partly due to the fact that cardiology involves a wide range of cardiovascular diseases, where fuzzy set theory is considered as the basis of fuzzy logic theory. However, as we discussed in the previous section about the disadvantage of this method, the fuzzy method has shown less efficiency in some of the complex diseases such as the diagnosis of Alzheimer’s degree and the classification of glaucoma severity compared to other methods.

Another noticeable finding was that one of the most widely used tools in these studies is MATLAB software which is due to its ability to analyze the fuzzy variables as a favorite of researchers, in this domain. Based on the analysis of the results, about 90% of the studies used this tool for modeling and designing their fuzzy systems or their fuzzy models. This shows that MATLAB is particularly useful for researchers to conduct research regarding the application of fuzzy logic to improve disease diagnosis.

This research extends our knowledge about the effectiveness of fuzzy methods in disease diagnosis. Thus, the present study provides additional evidence for researchers who work in health technology domains. In addition, with using the results of this study, we can find out which areas and diseases associated with the use of fuzzy methods and which have been neglected.

6. Conclusion

This review has argued about prior studies that were conducted about applying fuzzy methods in disease diagnosis. In this investigation, the main goal was to assess the effect of fuzzy methods and their frequency on improving diagnosis to decrease errors in misdiagnosis, with meta-analysis systematic review. Therefore, we designed search strategy based on our main goal. In this regard, eight scientific databases include PubMed, Google Scholar, IEEE, Science Direct, Web of Science, Taylor & Francis, Wiley Online Library, and Emerald were selected to retrieve the published scientific papers in a period of 2005 to 2017. In order to meet the goals of this study, all found papers were classified by authors, the publication year, journals or conferences type, the fuzzy methods, main objectives of the research, problems and research gaps, tools utilized to model fuzzy system, medical disciplines, sample size, the inputs and outputs of the system, findings, results and finally the impact of applied fuzzy method to improve diagnosis. Additionally, we classified our results based on their publishers and the databases with reviewing relevant articles which have been retrieved by the search strategy. The results showed that the rate of publishing articles in this domain has been increased. In this study, more favorable journals and conferences related to our issue were determined with their frequency and percentage. Another goal in this review was to determining the most utilized fuzzy methods among researchers. Returning to the question posed at the beginning of this study, it is now possible to state that the use of fuzzy logic is a beneficial way to improve the accurate diagnosis of diseases, because most of the studies declared positive impact of fuzzy methods in diagnosing various diseases. The most obvious finding to emerge from this study is that applying the fuzzy method, in addition to improve the diagnosis of diseases, can provide an early detection of the disease in order to prevent the progression of complex diseases. Another key point to remember is that we identified 13 fuzzy methods which are the most used in recent studies and we represented our results based on this classification. In addition, the impact of each fuzzy method based on the degree of effects reported by articles, was investigated. Hence, we hope that this review will serve as a base for future studies; a summary of the articles reviewed based on the impact of the applied fuzzy method along with their classification are also provided in the Appendix B in order to be used by researchers in future research. Moreover, we can conclude that different fuzzy methods have been applied to solve the problems in terms of disease diagnosis, however, some fuzzy methods were reported to have more effective result compared to others. Overall, when more than 90% of the studies reported positive impacts of using fuzzy methods to improve disease diagnosis, the effectiveness of this method in the diagnosis of diseases cannot be ruled out. In this regard, the most medical areas that utilized fuzzy methods in this context were also surveyed. Another major finding in this study is that researchers tend to use MATLAB for implementing fuzzy methods in this context, thus it can be a proper tool for designing fuzzy systems.

The generalizability of the aforementioned results is subject to certain limitations. This systematic review investigated the studies in the defined period of time to survey the studies published in terms of fuzzy methods in diagnosis. As a result, only articles published between year 2005 and Jun 2017 were reviewed. It is unfortunate that this study did not include scientific papers which have been published after Jun 2017, because the search strategy of this review only includes scientific papers which published by mid-2017. However, the upward trend of the published articles was visible in consecutive years. Consequently, for further research, we can extend our period of time to obtain more generalized results. Another limitation of this study was that we excluded the studies that applied hybrid methods with fuzzy methods such as genetic algorithm because we conducted a survey of the studies applied only within the context of fuzzy methods to investigate its impact on improving diagnosis. Therefore, in the future study, we can consider hybrid methods in terms of disease diagnosis with a more extensive view. Although this study has successfully conducted a systematic review about applying fuzzy methods in disease diagnosis, it has certain limitations in terms of “diagnosis of diseases” definition. In light of the ontological definition of “diagnosis”, we considered disease diagnosis which has an input, called a disease and an output, called diagnosis. In addition, we considered only studies in which the fuzzy method is used solely to improve the proper diagnosis. Hence, many of the studies which diagnosis contains another meaning, were excluded from our reviewed studies. As a result, studies that were related to the processing of images, signal processing, or other fields of medical diagnosis were excluded from the results, according to criteria defined by reviewers. In future studies, we advise to consider the diagnosis in a broader sense to indicate the applicability of fuzzy methods.

Although the authors carefully reviewed all of the restored studies but only the papers published in the journals or represented at the conferences, were considered in this study. With this in mind, there might be still valuable resources, such as books, theses, and other scientific sources which have been neglected. As a result, we can consider further resources for upcoming studies.

Appendix A

Table 1. The Distribution of fuzzy methods by medical disciplines

	FES	***Fuzzy rule-based***	***Fuzzy set theory***	***FIS***	***ANFIS***	***FDSS***	***Fuzzy neural network***	***FDT***	***FLC***	***Fuzzy classification***	***Fuzzy cognitive map***	***Fuzzy AHP***	***Weighted fuzzy rules***
Anesthesiology	**-**	**-**	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Cardiology	**-**	**1**	**3**	**-**	**1**	**1**	**-**	**1**	**-**	**-**	**-**	**-**	**1**
Critical care	**-**	**1**	**1**	**-**	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**-**	**-**
Dentistry	**1**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Dermatology	**1**	**-**	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Endocrinology	**-**	**1**	**-**	**-**	**1**	**-**	**-**	**1**		**1**	**-**	**-**	**-**
General medicine	**-**	**1**	**-**	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Gynecology	**-**	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Infectious disease	**1**	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**-**	**-**	**1**	**1**	**-**
Nephrology	**2**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Neurology	**1**	**1**	**1**	**1**	**1**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Nursing diagnosis	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Oncology	**-**	**2**	**-**	**1**	**1**	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**-**
Ophthalmology	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1**	**-**	**-**	**-**
Pediatrics	**-**	**-**	**-**	**-**	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**-**	**-**
Pulmonology	**1**	**-**	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Rheumatology	**1**	**1**	**-**	**-**	**-**	**1**	**-**	**-**	**1**	**-**	**-**	**-**	**-**

Appendix B

Table 2. Articles reported the positive impact of fuzzy method on disease diagnosis to some degree

#	Author	Year	Disease	Fuzzy method	Research objective	Input variables	Output	Problem and research gap	Finding and results
1	Putra and Munir, [86]	2015	Skin disease	FES	To develop fuzzy inference system for skin disease diagnosis.	Clinical data: A cough; A runny nose; A sore throat; Conjunctivitis; Koplik's spot; Diarrhea; A headache; Swollen neck/ear; Loss of appetite; Malaise; Pimples/crust skin; Joint pain.	Skin disease diagnosis.	Each sign or symptom is weighted with fuzzy variables and the scale of this weighting affects the accuracy of the inference system.	The program was able to detect 19 of the 25 cases correctly during the test.
2	Leite et al., [98]	2011	Diagnose critically ill patients	Rule based fuzzy logic	The main goal of this study was to classify hospitalized patients based on their vital signs by developing a fuzzy system to send alert to the physicians according to the systems pre-diagnosis.	Clinical data: Partial oxygen saturation; Pressure (Systolic/Diastolic); Heart rate; Body temperature; Respiratory rate.	Status diagnosis and determining the urgency levels of hospitalized patients.	1- The developed system required a wireless connection to send alerts and information. 2- Before implementing this system, model validation in the real situation was needed.	The fuzzy model was able to monitor and classify the condition level of vital signs of hospitalized patients successfully, in addition to sending alerts with 96% accuracy.

Table 3. Articles reported no positive impact of fuzzy method on disease diagnosis

#	Author	Year	Disease	Fuzzy method	Research objective	Input variables	Output	Problem and research gap	Finding and results
3	Krashenyi et al., [141]	2015	Diagnose Alzheimer's disease	FIS	To develop fuzzy inference system as a classifier in an AD for better diagnosis.	Image features.	K-fold cross-validation.	These methods allow only classifying the patient which has an AD or not and there is no clarity of its stages.	For this system, the specificity, sensitivity, accuracy and positive predictive value for AD vs. normal classification were calculated almost 91%, 86%, 88% and 88%, respectively, for overall performance estimation.
4	Elshazly et al., [146]	2014	Glaucoma diagnosis	Fuzzy classification	To design a diagnostic system to generate early and accurate detection of glaucoma by comparing three methods: DT, fuzzy logic and ROC.	Not defined.	Not defined.	In order to evaluate the system's performance, more tests are needed with larger datasets.	The authors concluded that ROT classifier had a high accuracy in comparison with other methods in disease diagnosis.

Table 4. Articles reported the positive impact of fuzzy method on disease diagnosis

#	Author	Year	Disease	Fuzzy method	Research objective	Input variables	Output	Problem and research gap	Finding and results
5	Uncu [83]	2010	COPD	FES	To design fuzzy diagnosis to improve PFT interpretation to be more reliable.	Clinical data: FEV1 and FVC level.	The risk of COPD.	Real FVC and FEV1 values and a large number of datasets are required to evaluate diagnosis results.	The results of the study indicated that applying fuzzy logic can be utilized for classifying spirometric FVC graphs with high accuracy.
6	Oluwagbemi et al., [84]	2016	Ebola	FES	The main goal of this research is to design a fuzzy system for the purpose of diagnosing Ebola with useful recommendations.	Clinical data: Bleeding Eyes; Bloody cough; Bleeding gums; Bleeding mouth; Backache; Breathing difficulty; Chest Pain; Fever; Fatigue; Living or visiting any Ebola-affected country in the last 3 months.	Degree of possibility of having Ebola.	Ebola is a very contagious and deadly disease. Since one of the problems associated with the disease is lack of proper knowledge in diagnosing and managing the disease, developing such systems are necessary but the accuracy of the system should be calculated.	The success of Ebinformatics illustrates the potentials of applying an informatics tool as a means of fostering critical tasks such as patient diagnosis, prediction, and appropriate recommendations.
7	Reshmalakshmi and Sasikumar, [79]	2016	Osteoporosis	FES	To propose a fuzzy system to diagnose osteoporosis to assist the physician efficiently.	Demographic and Clinical data: Age, Sex, Heredity, BMI, pain, Calcium level, Height, Weight, Alcohol, Years of menopause, Stress.	Osteoporosis risk.	To choose the best treatment, it is necessary to diagnose it properly and timely.	The use of different membership functions and Fuzzy Edge Directed Image Interpolation (FEDI) technique helps to design an efficient osteoporosis detection framework.
8	Meza-Palacios et al., [85]	2016	Nephropathy diagnosis	FES	The objective of this research is to develop a fuzzy expert system to aid physicians in nephropathy controlling in patients with T2DM.	Clinical data: GFR; Serum creatinine; Uric acid; Dyslipidemia; Blood glucose; Hypertension; Duration of T2DMA.	Nephropathy control.	Nephropathy is usually diagnosed late and accurate diagnosis is very important. Thus, the errors of FES could be more serious.	The authors concluded that the developed system can aid clinical experts and non-specialists in the nephropathy assessment.
9	Ahmed et al., [87]	2014	Diagnosing kidney status	FES	Developing a fuzzy expert system to provide diagnosing kidney condition to determine whether a kidney is in good or bad condition.	Demographic and Clinical data: Nephron functionality; Age; Weight; Serum creatinine; Blood sugar; Alcohol intake; Diastolic blood pressure; Systolic blood pressure.	Kidney condition.	Due to the difficulty of determining the kidney condition, developing such systems is vital to determine the exact condition of the kidney but in this study, some features were not considered such as electrolyte disorder, water consumption level or other serious diseases.	This system can be used in disease diagnosis process to help experts in clinical decision making with high accuracy. Additionally, the system can be used by patients because of its simplicity.

#	Author	Year	Disease	Fuzzy method	Research objective	Input variables	Output	Problem and research gap	Finding and results

10	Allahverdi and Ackan, [88]	2011	Dental disease	FES	To develop a Fuzzy Expert System to improve periodontal dental disease diagnosis to select the best treatment methods.	Clinical data: Gingival index; Alveolar bone loss; Probing packet Depth; Mobility; Attachment loss.	Severity of the disease.	This study is the first work of applying fuzzy logic in periodontal dental disease domain and it should be evaluated with real data to recognize its performance.	The authors indicated that this system increases the time of diagnosis and it can determine the severity of disease as output.
11	Reddy and Khare, [99]	2017	Heart diseases	Rule based fuzzy logic	To predict heart disease with using computing techniques.	Not defined.	Predicting heart disease.	Because of the importance of CVD, management of such disease is necessary. Thus, more data and different cases were needed to achieve high performance in this system.	From the result, this system can predict heart diseases with the maximum accuracy of 78%.
12	Nilashi et al., [100]	2017	Breast cancer	Rule based fuzzy logic	To develop a new knowledge-based system to classifying breast cancer with using classification and rule-based techniques.	Demographic and Clinical data: Age; BI-RADS assessment; Margin; Density; Shape from mammographic dataset.	Breast cancer diagnosis.	Breast cancer has become a common disease around the world. The authors developed the method using non-incremental data mining techniques, therefore it would be fascinating to develop the proposed knowledge-based system for incremental learning.	The results of experiments on two different datasets indicated that the proposed method achieved good prediction accuracy (94.4%) for breast cancer.
13	Arslan et al., [97]	2016	Fibromyalgia	Rule based fuzzy logic	To achieve accurate diagnose and severity of FMS (Fibromyalgia syndrome) with the fuzzy method.	Clinical data: Fatigue severity (FS), Sleep disturbance (SD), Level Tender Point (TP) count, Chronic widespread pain (CWP) duration, Pain severity (PS).	Diagnosis classification result.	Because of complex and difficult nature of FMS diagnosis, examing the ACR criteria to classifying the severity of disease was not possible in this research.	This fuzzy model was remarkable for its ability to diagnose fibromyalgia with a high accuracy of 92.2%.
14	Akbarzadeh-T and Moshtagh-Khorasani, [101]	2007	Diagnose aphasia type	Rule based fuzzy logic	To represent hierarchical fuzzy rule-based structure for accurate aphasia diagnosis by using statistical analysis in its construction.	Clinical data: Communicative behavior, Articulation, and prosody, Automatized language, Semantic structure, Syntactic structure.	Aphasia type.	Increasing sample is required to evaluate the model because of the difficulty of detecting aphasia.	With using statistical analysis, the authors can conclude the model to determine aphasia type with fewer features in comparison with artificial neural networks with 92% accuracy.

#	Author	Year	Disease	Fuzzy method	Research objective	Input variables	Output	Problem and research gap	Finding and results
15	Biyouki et al., [102]	2015	Thyroid disease	Rule based fuzzy logic	Designing a system to detect thyroid disease in a situation where an expert is not available.	Clinical data: T4; T3; TSH; Maximal absolute difference of TSH; T3-resin uptake test.	Diagnosis of thyroid disease.	No research gap was reported.	This expert system can act as a consulting system to determine thyroid's function disease like an endocrinologist expert.
16	Nilashi et al., [11]	2017	General disease	Rule based fuzzy logic	To design a new knowledge-based system for diseases prediction based on fuzzy logic and CART technique.	Demographic and Clinical data: Age, Diastolic blood pressure, Triceps skin fold thickness, 2-hour serum insulin, Body mass index, diabetes pedigree function, Number of times pregnant, Plasma glucose.	Class of a disease.	Large data sets from various sources are required to invent new methods.	Researchers found out that the combination of fuzzy rule-based and CART techniques can improve disease diagnosis and help physicians to predict disease.
17	Sacco et al., [107]	2014	Diabetic foot ulcer	Fuzzy set theory	To ascertain the hypothesis that with investigating the greater magnitude of pressures in patients suffering from DM and defining them with fuzzy sets, diabetic foot ulcer can be prevented.	Not defined.	Not defined.	A lack of comparison between a diabetic and non-diabetic population can be considered as a limitation.	The treatment should begin in the early stage of disease to prevent diabetic neuropathy.
18	De Moraes Lopes et al., [108]	2009	Urinary infection	Fuzzy set theory	To design a model to improve UI diagnosis.	Clinical data: Urge UI, functional UI, total UI, and urinary retention, stress UI, reflex UI.	Diagnosing UI.	1) The need for nurses' knowledge and also their knowledge of fuzzy logic to accurately assess the system. 2) Different data from different populations are needed to design decision support systems.	The system is designed in a way to handle fuzzy relationships with ease of use with 79% concordance.
19	Kannathal et al., [109]	2006	Cardiovascular diseases	Fuzzy set theory	To improve critical care diagnosis based on clinical test results with fusion determination.	Clinical data: Two variables related to heart rate measurements, one variable related to respiratory rate, blood pressure systolic, diastolic and mean pressures and one SpO2 measurement.	Diagnosis of cardiovascular condition.	For more accurate diagnosis, testing with more data will be required.	The findings of this study showed that applying fuzzy logic improves the diagnosis of patient's condition.
20	Duarte et	2006	Myocardial	Fuzzy	To develop a model	Demographic and	Degree of risk	The complexity of using	The authors concluded that the

al., [110]	disease	set theory	for Myocardial Perfusion Scan (MPS) to select appropriate patient with applying fuzzy sets theory.	Clinical data: Age, sex, diabetes, blood cholesterol level, chest pain characteristics, systolic blood pressure, history of smoking.	points.	fuzzy model for physician are considered an obstacle to implementing such system.	system was designed based on fuzzy set theory to assist GP to select appropriate patients for MPS with 100% sensitivity.

#	Author	Year	Disease	Fuzzy method	Research objective	Input variables	Output	Problem and research gap	Finding and results
21	Tsai and Kojima, [111]	2005	Diagnose cardiomyopathy	Fuzzy set theory	To optimize the classification of echocardiographic images with defining two fuzzy sets: normal and abnormal cases.	Clinical data: An end-diastole and an end-systole features of the clinical image.	Diagnosis type of cardiomyopathy.	Further work is required to improve the evaluation of this method.	The proposed method enabled the classification of the results reached to 96% accuracy.
22	Yilmaz et al., [116]	2016	Lung cancer	ANFIS	To decrease the lung cancer death with calculating the risk of getting lung cancer and the effect of stress on disease condition to eliminate it.	Not specified.	Risk result based on stress-cancer model.	The death as the result of late diagnosis is the main problem, and it can be decreased with the proposed method.	With this system, pre-diagnosis of lung cancer can be provided in patients who might have the risk of getting cancer due to their clinical and social condition with 94.64% performance.
23	Mansoor Baig et al., [117]	2013	Hypovolemia diagnosis	ANFIS	Designing the fuzzy system to improve hypovolemia assessment during surgery.	Clinical data: Vital signs: HR; BP; MAP; Pleth; SVP.	Possibility of Hypovolemia.	The overall performance and efficacy of this system should be validated through more tests in the real environment and in a clinical process.	This system succeeds to detect more accurately the levels of hypovolemia with 95% confidence.
24	Ubeyli and Guler, [118]	2005	Erythema squamous diseases	ANFIS	To achieve notable improvement in the diagnosis of erythema-squamous by applying ANFIS model compared to neural network method.	Clinical data: Erythema; Polygonal papules; Follicular papules; Oral mucosal involvement; Knee and elbow involvement; Clubbing of the rete ridges; Scaling; Definite borders; Itching; Koebner phenomenon.	Diagnosis of erythemato-squamous diseases.	To diagnose erythema to-squamous diseases in a real-world domain, more features should be considered in different levels.	Comparing the result of ANFIS model with neural network indicated that proposed model has high accuracy in detecting the erythematous-squamous diseases with 96.4% sensitivity and 98.4% specificity.
25	Ubeyli and Guler, [119]	2005	Internal carotid artery stenosis	ANFIS	To present new approach based on ANFIS method to detect internal carotid artery stenosis and occlusion	Clinical data: Carotid arterial Doppler signals.	Internal carotid artery stenosis and occlusion detection.	No research gap was reported.	The proposed model was designed by ANFIS method to detect internal carotid artery stenosis and occlusion higher than the neural network model.

#	Author	Year	Disease	Fuzzy method	Research objective	Input variables	Output	Problem and research gap	Finding and results

26	Shariati and Haghighi, [120]	2010	Hepatitis	ANFIS	Developing a system to recognize the type and phase of the disease with ANFIS method and comparing the accuracy of different methods to select the best method in terms of hepatitis and liver diagnosis.	Not specified.	Diagnosis of diseases.	No research gap was reported.	The results showed that the accuracy of hepatitis and liver diagnosis were improved notably in comparison with applying other methods.
27	Wang et al., [121]	2015	Esophageal cancer	ANFIS	To invent a new system for early diagnosis of esophageal cancer to improve survival.	Clinical data: Pretreatment serum C-reactive protein CRP, Pretreatment albumin value, Albumin values after treatment, Survival time (months), and sensor status (patient died or was censored).	Hazard (probability of event occurrence).	Since esophageal cancer usually remained undiagnosed in the early stage, and it usually reached to advanced stages but with this system with calculating survival, early diagnosis is improved.	This method can assist clinicians to improve esophageal cancer diagnosis and predicting cancer survival to select the best treatment.
28	Nilashi et al., [122]	2016	Parkinson disease	ANFIS	Providing a new computational intelligence method to reduce the progression of Parkinson disease and improving prediction of disease.	Clinical data: 16 vocal attributes based on traditional measurement and nonlinear dynamical theory.	A score on the two outputs of UPDRS, Total-UPDRS and Motor-UPDRS.	No research gap was reported.	The proposed method improved Parkinson's diagnosis and the precision in anticipating the progression of the disease, in addition to helping physicians to detect disease timely.
29	Li et al., [123]	2011	Hypoxic-Ischemic Encephalopathy (HIE)	Fuzzy Neural Networks	To develop a fuzzy system for early diagnosing and management of Hypoxic-Ischemic Encephalopathy (HIE) in newborns.	Clinical manifestations that included awareness, muscle tension, embrace reflex, sucking reflex, convulsions, central respiratory failure, pupil changes, and anterior fontanel tension.Lac/cr (basal nuclei), NAA/Gr (basal nuclei), DWI (ADC value); (lenticular nuclei), lactic acid/creatinine in urine (the first day), S100B protein C (the third day), fetal distress (absent, mild, severe), and neonatal asphyxia (absent, mild, severe).	Recognition of Hypoxic-Ischemic Encephalopathy (HIE).	More data are required for accurate results because the study was done by limited training data.	This system can improve the existence problems associated with defining the fuzzy nature of variables and clinical knowledge using fuzzy logic.

#	Author	Year	Disease	Fuzzy method	Research objective	Input variables	Output	Problem and research gap	Finding and results
30	Beganovic and Avdagic, [124]	2015	Diagnosing acid-base disorders	Fuzzy neural networks	To create and compare more fuzzy systems trained by ANFIS method with using fuzzy neural networks to find the best method to manage and detect electrolytes disorder.	Demographic and Clinical data: Age, PH, pCO2, HCO3,BE.	Electrolyte disorder.	Acid-base level has the important effect on the functioning of all body's enzyme systems and it depends on many variables but in this study, small numbers of input variables were considered.	This fuzzy system could give clinicians valuable knowledge about the presence of acid-base disorders.
31	Kadi and Idri, [129]	2016	Cardiovascular dysautonomias diagnosis	FDT	Comparison between the results obtained by using crisp DTs and FDTs.	Clinical data: Deep Breathing; Hand Grip; Mental stress; Orthostatic; HR; BP.	Diagnosis result.	The number of nodes and leafs was higher in FDTs than crisp DTs while the depths of FDTs and DTs were slightly the same.	The results of this study indicated the effectiveness of the FDT classifier method to achieve low error rates in comparison with crisp DT with 94.98% accuracy.
32	Levashenko and Zaitseva, [130]	2012	Breast cancer	FDT	To develop a new technique for improving the prognosis of complex diseases such as breast cancer.	Clinical data: A1 (Gynecological history), A2 (Tumor), A3 (Heredity), and A4 (Age).	Breast cancer possibility.	No research gap was reported.	Since clinical data have a fuzzy nature, applying FDT can be defined as a useful technique to find a hidden pattern to improve diagnosis.
33	Kamadi et al., [131]	2016	Diabetes	FDT	The researchers represented Computational Intelligence (CI) techniques for early diagnosis of diabetes.	Demographic and Clinical data: Pregnant, Glucose, 2-Hour serum insulin, Body mass index, Age, Positive diabetic test, Diastolic blood pressure, Triceps skinfold thickness.	New classification accuracy in context of PID data set.	No research gap was reported.	The authors indicated that the proposed model achieved high accuracy for early diagnosis of diabetes in comparison to previous models.
34	Paul et al., [133]	2015	Heart diseases	FDSS	To improve the quality of heart diagnosis with training rules and defining the membership functions in optimal mode.	Demographic and Clinical data: Age, sex, max heart rate achieved, exercise induced angina, ST depression, slope of the peak exercise ST segment, number of major vessels, chest pain type, resting blood pressure, serum cholesterol in mg/dl, fasting blood sugar, resting electrocardiographic results.	Diagnosis of heart disease.	To achieve the best performance, larger dataset is required.	Based on the results of this study, it can be said that the FDSSs can provide more reliable results than traditional methods.

#	Author	Year	Disease	Fuzzy method	Research objective	Input variables	Output	Problem and research gap	Finding and results
35	D'Acierno et al., [51]	2013	General disease	FDSS	To provide a method for designing decision support systems to extract fuzzy knowledge from data automatically.	Not defined.	Not defined.	A knowledge of fuzzy decision making systems is required to design such systems.	The proposed method is very flexible and does not depend on the type of study and its objective, and it is designed in a way that designing fuzzy decision systems with any kind of information make it possible.
36	Romero et al., [27]	2017	Fibromyalgia	FDSS	To develop a CDSS to determine fuzzy diseases such as fibromyalgia.	Clinical data: TSH, Fever, Pain.	Diagnosis of the Fibromyalgia.	No research gap was reported.	The developed system can improve the disease diagnosis in patients with fibromyalgia.
37	Kunhimangalam et al., [82]	2014	Peripheral neuropathy	FDSS	Developing an expert system with using fuzzy logic methods to improve the diagnosis of peripheral neuropathy based on clinical symptoms.	Clinical data: Motor ulnar latency (msec); Motor Ulnar Amplitude; Motor Ulnar Nerve Conduction Velocity (m/s); Sensory Median latency (msec); Sensory Median Amplitude; Motor Median latency (msec); Motor Median Amplitude; Motor Median Nerve Conduction Velocity (m/s).	Sensory demyelinating type.	An accurate and rigorous evaluation of the system is essential before its implementation in the real environment.	The results showed that the diagnosis was improved with 93.26% accuracy when neurologists are not accessible.
38	Dragovic et al., [76]	2015	Peritonitis	FIS	To enable patients to calculate the risk of their disease in order to help clinicians in early diagnosis of peritonitis.	Clinical data: F: fever, L: number of leukocytes, AP: abdominal pain, CE: cloudiness of effluent, MC: number of microorganisms.	PL: peritonitis likelihood.	If the peritonitis is not recognized in time, or if inadequately treated, it can lead to serious complications and even death. On the other hand, medical experts are not close at hand all of the time.	The main advantage of an improved Boolean FIS is that it preserves the transparency and interpretability inherent regarding the fuzzy inference systems.

#	Author	Year	Disease	Fuzzy method	Research objective	Input variables	Output	Problem and research gap	Finding and results
39	Sardesai et al., [140]	2016	Gynecological diseases	FIS	To investigate the possibility of using fuzzy logic in medical decision making in terms of disease diagnosis.	Demographic and Clinical data: Age, backache; painful menstruation; irregular menses; heavy bleeding between periods; the frequency of micturition; pain in lower abdomen; vaginal bleeding; burning micturition; abdominal swelling; bowel/bladder complaints; clots passage; painful intercourse; weakness; white discharge; vaginal itching.	Diagnosis of disease.	The exponential growth of gynecological diseases across the globe is high, hence, exhaustive user-friendly software should be developed.	Fuzzy logic could help to diagnose most of the patients correctly to confirm the single disease diagnosis.
40	Saikia and Dutta, [142]	2016	Dengue fever	FIS	To develop a fuzzy logic system for early diagnosis of dengue infection.	Clinical data: Clinical symptoms/signs such as: a) Fever; b) Gastro Intestinal symptoms (Nausea, Diarrhea, Vomiting); c) Headache; d) Pains (Myalgia, Arthralgia, Bone pain); e) Skin Rash; f) Eye Ball Pain; 2) Laboratory findings: a) Leucopenia (WBC<4000/mm3);)Thrombocytopenia (PLT<100,000/mm3); c) Liver dysfunction (AST/ALT>30U/L); d) C-Reactive Protein (CRP<20mg/L); e) Partial Thromboplastin Time (PTT<38sec).	Predicting the markers involved in early diagnosis of dengue infection.	The parameters undertaken can be more strengthening if more detail about the dengue disease to be found and embedded in the training module.	This decision making system helps a dengue patient to take proper therapeutic measure timely in addition to the early diagnosis of patients with a probability of dengue fever.
41	Gayathri and Sumathi, [77]	2015	Breast cancer	FIS	To determine the risk of breast cancer with the fuzzy approach.	Clinical data: Single Epithelia Cell size; Bare nuclei; Bland chromatin; Normal Nucleoli; Mitosis ; Class of Benning or Malignant; Clumpthickness;	Cancerous or non-cancerous.	Because of the high rate of breast cancer, a large number of features is required to diagnose breast cancer.	This methodology can be implemented in clinical environment successfully to diagnose breast cancer with considering fewer attributes.

						Uniformity cell size, Uniformity cell shape; Marginal Adhesion.			

#	Author	Year	Disease	Fuzzy method	Research objective	Input variables	Output	Problem and research gap	Finding and results
42	Cheruku et al., [147]	2010	Diabetes	Fuzzy classification	To present a new type of fuzzy classification rules to generate high accuracy and comprehensible fuzzy rules to diagnose diabetes.	Clinical data: Pima Indians diabetes, Cleveland heart Disease, Iris, Wine, Glass, Wisconsin Breast cancer.	Reducing sets for generating rules.	This method should be tested with more data to verify the accuracy of this method.	The new approach (FRBCS) was represented to show its high accuracy in comparison with another algorithm.
43	John and Innocent, [50]	2005	Influenza	Fuzzy cognitive maps	To decrease inherent uncertainty and vague knowledge in diagnosis process with applying fuzzy methods.	Clinical data: Fever, cough, headache, muscle pains, collapse, running eyes, running nose, vertigo, chills, back pains and sore throat.	Diagnosis of disease.	Determining the stage of the disease is one of the important parts of diagnosis but it was neglected in this study.	New method was designed for estimation of diagnosis in different diseases with their probability.
44	Anooj, [153]	2012	Heart disease	Weighted fuzzy rules	To develop CDSS based on fuzzy logic to generate fuzzy rules automatically.	Demographic and Clinical data: Age, sex, smoking history, hypertension, total cholesterol level, HDL, LDL, and reeclampsia.	Risk level of heart patients.	Large training datasets are required.	The results and accuracy of the fuzzy system were compared with neural network where they succeeded to show the better performance of the fuzzy system.
45	Uzoka et al., [155]	2011	Malaria	Fuzzy AHP	Comparing the fuzzy model with the AHP methodology to determine malaria.	Clinical data: A cough, loss of appetite, nausea, vomiting, fever, rigors, pain, sweating, tiredness, abdominal pain, and diarrhea.	Diagnosis of Malaria.	More data and different cases are needed to compare two methods because of vague nature of malaria diagnosis.	Fuzzy logic was considered as a powerful tool to diagnose malaria.
46	Singh et al., [158]	2012	Arthritis	FLC	To develop a fuzzy system for arthritis diagnosis with using a FLC.	Clinical data: Rest pain; ESR; Morning stiffness; Symmetry of joint infection; Redness; Anticcp; RF; Body pain; Swelling.	Severity of Arthritis.	The accuracy of the developed system should be approved by physicians in terms of undiagnosed arthritis rheumatoid which late diagnosis may cause severe risk.	Fuzzy system was useful to assist physicians in arthritis diagnosis timely.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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