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# Diagnosing rheumatoid arthritis disease using fuzzy expert system and machine learning techniques

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**Abstract**. Rheumatoid Arthritis (RA) is a very common autoimmune disease that causes significant morbidity and mortality, and therefore early diagnosis and treatment are important. Early diagnosis of RA and knowing the severity of the disease are very important for the treatment to be applied. The diagnosis of RA usually requires a physical examination, laboratory tests, and a review of the patient's medical history. In this study, the diagnosis of RA was made with two different methods using a fuzzy expert system (FES) and machine learning (ML) techniques, which were designed and implemented with the help of a specialist in the field, and the results were compared. For this purpose, blood counts were taken from 286 people, including 91 men and 195 women from various age groups. In the first method, an FES structure that determines the severity of RA disease has been established from blood count using the laboratory test results of CRP, ESR, RF, and ANA. The FES result that determines RA disease severity, the Anti-CCP level that is used to distinguish RA disease, and the patient's medical history were used to design the Decision Support System (DSS) that diagnoses RA disease. The DSS is web-based and publicly accessible. In the second method, RA disease was diagnosed using kNN, SVM, LR, DT, NB, and MLP algorithms, which are widely used in machine learning. To examine the effect of the patient's history on RA disease diagnosis, two different models were used in machine learning techniques, one with and one without the patient's history. The results of the fuzzy-based DSS were also compared with the diagnoses made by the specialist and the diagnoses made according to the 2010 ACR / EULAR RA classification criteria. The performed DSS has achieved a diagnostic success rate of 94.05% on 286 patients. In the study of machine learning techniques, the highest success rate was achieved with the LR model. While the success rate of the model was 91.25 % with only blood count data, the success rate was 97.90% with the addition of the patient's history. In addition to the high success rate, the results show that the patient's history is important in diagnosing RA disease.

Keywords: Fuzzy expert system, rheumatoid arthritis, decision support system, machine learning, diagnosis of disease

## 1. Introduction

Rheumatoid arthritis (RA) is a chronic, multisystemic, and inflammatory rheumatic disease with unknown etiology, which can lead to erosion and deformities in joints and surrounding tissues, showing non-joint organ involvements (Fig. 1). The incidence of the disease varies by approximately 0.5–1%. While the disease can be seen at any age, it is most common between the ages of 30–50. The disease is approximately 2-3 times more common in women than in men [1].

Although the etiopathogenesis of RA is not clearly known, it is defined as a disease that occurs when immunological and environmental factors come

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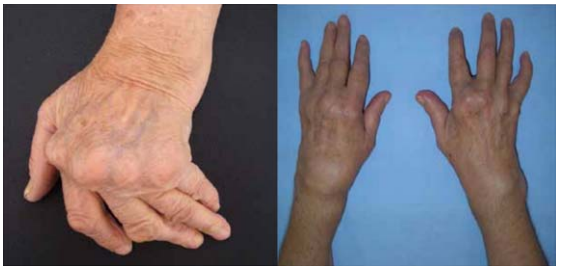

Fig. 1. Symptom of Rheumatoid arthritis disease [3].

Table 1
2010 ACR/EULAR rheumatoid arthritis classification criteria

| | | Score |
|---|---|---|
| **A** | Joint involvement | |
| | One large joint | 0 |
| | 2–10 large joints | 1 |
| | 1–3 small joints | 2 |
| | 4–10 small joints | 3 |
| | >10 joints (at least one small joint) | 5 |
| **B** | Serology (at least one test result required for classification) | |
| | Negative RF and negative Anti-CCP | 0 |
| | Low positive RF or low positive Anti-CCP | 2 |
| | High positive RF or high positive Anti-CCP | 3 |
| **C** | Acute phase reactant (at least one test result is required for classification) | |
| | Normal CRP and normal ESR | 0 |
| | Abnormal CRP or Abnormal ESR | 1 |
| **D** | Symptom duration | |
| | <6 weeks | 0 |
| | >6 weeks | |

together in individuals with a genetic predisposition. RA is a chronic polyarticular disease that can hold all synovial joints symmetrically. Although clinical findings of joints are in the foreground, most patients also have systemic symptoms. These symptoms may be nonspecific symptoms such as weakness, fatigue, fever, as well as non-joint findings that cause serious organ damage such as pulmonary, cardiovascular, neurological, renal, and eye involvement [2].

Although the etiopathogenesis of RA is not clearly known, it is defined as a disease that occurs when immunological and environmental factors come together in individuals with a genetic predisposition [2, 4]. RA is a chronic polyarticular disease that can hold all synovial joints symmetrically. Although clinical findings of joints are in the foreground, most patients also have systemic symptoms. These symptoms may be nonspecific symptoms such as weakness, fatigue, fever, as well as non-joint findings that cause serious organ damage such as pulmonary, cardiovascular, neurological, renal, and eye involvement [2].

Typical joint involvement in RA is seen as swelling, pain, sensitivity, and loss of function in many joints simultaneously and bilaterally. Morning stiffness accompanying joint pain indicates that the pain is inflammatory. Prolonged morning stiffness is a typical finding of RA. Deformities caused by inflammation may develop over time in untreated patients [2, 5].

Diagnosis of RA patients; it is determined by the evaluation of clinical, laboratory, and medical imaging. Laboratory evaluation carries great importance in both diagnosis and disease follow-up [6]. Since the laboratory findings of RA are not specific to RA, they are not sufficient in the diagnosis of the disease alone but they are used to support the diagnosis made according to clinical signs and findings [7]. Laboratory findings are important in monitoring RA disease severity activity and evaluating response to treatment, as well as diagnosis [5]. A non-specific acute phase response can be seen in patients with RA, showing inflammation associated with disease severity. An increase in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which are positive acute phase reactants, are the most common findings. The most frequently used autoantibody tests in the diagnosis of RA are RF and Anti-CCP. It is known that these antibodies can be positive years before RA findings appear. The presence of these autoantibodies in high titer is related to the poor progression of the disease [6].

To classify RA cases, classification criteria were developed with the cooperation of ACR and EULAR (European Union for Combating Rheumatism) in 2010 (Table 1). These criteria should be applied to patients who were clinically diagnosed by a specialist as having active synovitis in at least one joint and who do not have any other disease to explain this synovitis. In this score-based algorithm, the total score of all categories must be greater than six to be diagnosed with RA [8].

RA is a difficult disease to diagnose, despite the fact that certain criteria exist to help with the diagnosis. Therefore, expert systems and machine learning techniques can be benefited to assist doctors in diagnosing the RA disease. Expert systems are knowledge-based systems, and are an application area of artificial intelligence that aims to imitate human intelligence in its solution, examining problems in a wider framework [9]. On the other hand,

machine learning is a system that can learn as a structural function and investigate the work construction of algorithms that can make predictions over data [10].

The diagnosis of RA includes uncertainty and complexity. When the literature is reviewed, it is seen that fuzzy logic, expert systems, and machine learning techniques can be successfully applied in the diagnosis of RA. In this study, RA was diagnosed using two different methods: a fuzzy-based DSS and machine learning techniques. In addition to the decision support systems previously developed for RA diagnosis, the main aim of the developed comprehensive fuzzy-based DSS is to improve the accuracy of RA diagnosis. The study was designed as a web-based software which is carried out in accordance with the recommendations given in the literature, to increase the ease of access to the system and to quickly diagnose the disease. Access to the designed DSS is publicly available and accessible at https://www.tf.selcuk.edu.tr/rad/. In addition, RA disease was also diagnosed by making a classification with kNN, SVM, LR, DT, NB, and MLP algorithms, which are widely used in machine learning. Two different models were used in machine learning techniques. In the first model, a classification was made according to seven features in the data set (age, gender, CRP, ESR, RF, ANA, Anti-CPP). In the second model, RA disease was detected by making a new classification by adding the patient's history to these features.

The rest of this study is organized as follows; In the second chapter, information about the studies in the literature related to the study subject is given. In the third chapter, the materials and methods used in the study are given. The creation of the dataset, the designed decision support system, the disease diagnosis unit, machine learning methods and performance metrics are explained in this section. In the fourth chapter, the experimental results are given. Chapter 5 includes conclusions and recommendations.

## 2. Related works

There are studies in which expert systems and machine learning techniques are extremely successful and widely used in medicine [11].

Singh et al. performed a fuzzy inference system for the diagnosis of RA disease. They used six physical symptoms and three laboratory findings in the system they developed. It was stated that for the efficiency of the developed system, the system could be made public on the internet and the system could be developed with the recommendations of specialist doctors [12].

Pandey et al. have developed a decision support system with a fuzzy approach for the diagnosis of arthritis pain for rheumatic fever patients. They divided arthritis pain into different stages using fuzzy logic in their work. This system they developed helps to determine whether existing arthritis pain is associated with rheumatic fever [13].

Morita et al. tried to determine the erosion given by RA to finger joints from X-ray images by using support vector machines one of the machine learning techniques [14].

Siddiqui et al. diagnosed RA by using 12 input parameters with a two-layered fuzzy expert system they designed in their study [15].

Hairani et al., aim to develop an expert system that uses forward chaining inference and certainty factor methods to diagnose rheumatic disease types in their study, Types of rheumatic disease under investigation in this study cover Gout Arthritis, Rheumatoid Arthritis, and Osteoarthritis. The success rate of this study conducted in Indonesia is 80 percent. The accuracy value of this system is 80%, which means the combination of forward chaining inference and certainty factor method to diagnose types of rheumatic diseases has a good performance [16].

Samridhi et al., aim to design a cheap and easily accessible system for the early diagnosis of arthritis by using fuzzy logic and artificial intelligence in their study. The results of the system designed in MATLAB were checked by a specialist doctor and the success of the system was approved [17].

More and Singla aimed to make an early diagnosis of rheumatoid arthritis with magnetic resonance images in their study. Fuzzy and various machine learning algorithms were used in the study. The paper further explores the common classification methods for the diagnosis of rheumatoid arthritis. This analysis aims to explain new advances to increase the rate of identification and diagnosis of rheumatoid arthritis [18].

Kaur et al. present a new technique for estimating arthritis based on the arthritis dataset in their study. The kNN algorithm was used in the study. The success rate of the study for the diagnosis of arthritis was 83.3%.This study involves the methodology by which we can predict that a person is Arthritis-positive or Arthritis-negative [19].

Köse et al. in their study it is aimed to prioritize the factors causing Rheumatoid Arthritis by

using Spherical Fuzzy AHP and to select the best treatment alternative based on Spherical Fuzzy Sets. Furthermore, this study will provide a general and an analytical view to medical doctors for how to plan a treatment process for the patients having RA [20].

Medical disorder classification based on RA was made with ensemble methods in the study of Sundaramurthy et al. The dataset consists of 750 patients with RA and 250 people without RA. Three ensemble algorithms, like SVM, Ada-boosting, and random sub-space, were used in this investigation. These ensemble classifiers use k-NN and Random forest for baseline measurements of the classifier. Data classification is performed with 10-fold cross-validation, in which evaluation is done with performance metrics like Accuracy, Precision, and ROC. The SVM-based Random Forest algorithm was 94 percent successful in classifying and predicting RA [21].

The diagnosis of RA is discussed the usefulness of machine learning methods for monitoring patients and predicting the response of patients to treatment in the study of Kedra et al. ML methods have the potential to revolutionize RA-related research and improve disease management and patient care. Nevertheless, these models are not yet ready to contribute fully to rheumatologists' daily practice. Indeed, these methods raise technical, methodological, and ethical issues, which should be addressed properly to allow their implementation. Collaboration between data scientists, clinical researchers, and physicians is therefore required to move this field forward [22].

Pandit and Radstak aimed to find the classification, early diagnosis and treatment response prediction of RA by using clinical data and molecular data with machine learning algorithms in their study. The data set consists of 1,892 patients with RA. In addition, the designed system has been tested on 680 people.This study shows that genetic heterogeneity, along with robust clinical assessment, can together be used for improving treatment strategies for patients with RA [23].

In the study of Hügle et al provide an overview of current machine learning applications in rheumatology, mainly supervised learning methods for e-diagnosis, disease detection and medical image analysis.In the future, machine learning will be likely to assist rheumatologists in predicting the course of the disease and identifying important disease factors. Even more interestingly, machine learning will probably be able to make treatment propositions and estimate their expected benefit (e.g. by reinforcement learning). Thus, in future, shared decision-making will not only include the patient's opinion and the rheumatologist's empirical and evidence-based experience, but it will also be influenced by machine-learned evidence [24].

Besides, logistic regression, artificial neural networks, and algorithm-based expert system approaches are available for RA diagnosis [25]. When the literature review is examined, it is seen that laboratory results and traditional machine learning methods are frequently used in the diagnosis of RA disease. However, there is still a need to investigate the necessary parameters in the diagnosis and treatment, such as the patient's medical history and the severity of the RA disease.

## 3. Material and methods

### *3.1. Rheumatoid arthritis data set*

The data set that was created to be used in the design and validation of the system to be performed for the diagnosis of RA was prepared with the permission (Permission Number:2017/27) of the Non-Invasive Clinical Research Ethics Committee of the Faculty of Medicine of Selcuk University, and the studies were carried out in the Department of Rheumatology at Selcuk University Faculty of Medicine. The data set consists of nine characteristics and sample data of 91 males and 195 females, totally 286 individuals from various age groups who applied to the Rheumatology clinic. While 166 of the people in the dataset have RA, 120 of them do not have RA. Of the patients, 23 (14%) have mildly RA, 84 (51%) have moderately RA, and 59 (35%) have severely RA.

A specialist doctor collected the data set during the clinical examination, and the data set consists of nine features.

- Gender (Male, Female)
- Age of the patient
- ESR (mm/s)
- CRP (mg/l)
- RF (u/ml)
- ANA (1 titer)
- Anti-CCP (Positive, Negative)
- The patient's history (%)
- Diagnosis (0: Not RA, 1:RA)

Gender, Anti-CCP, and Diagnosis are binary properties. The patient's history value is a numeric value

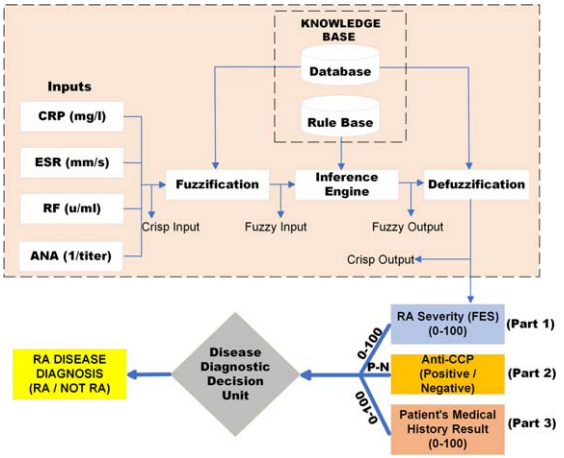


Fig. 2. Developed decision support system structure.

obtained by the Likert scale. Statistical information of the numeric features is given in Table 2.

### 3.2. Designed decision support system

The fuzzy-based DSS is a multi-layered system that provides performance enhancement by integrating different expert system structures into a single framework to solve a complex problem. The DSS has substantial advantages since they combine different structures. In addition, their accuracy performances are high [26, 27]. Each of the resulting values from laboratory tests, physical examination, and the patient's medical history (Anamnesis) are important in diagnosing RA. The study is based on the development of a hybrid system that can take all these three basic phenomena into account. On this basis, three basic facts have been taken into consideration. These facts;

- Determining FES based RA severity,
- Anti-CCP result,
- The result of the physical examination and the patient's medical history.

The structure of the fuzzy-based DSS created by bringing these basic facts together is given in Fig. 2. As can be seen in the figure, this developed DSS consists of three main parts: FES-based RA severity, Anti-CCP outcome, and the patient's history. By using these three results obtained, designed DSS makes the diagnosis of the disease based on the disease diagnosis decision unit evaluation table given in attachment prepared with the help of an expert.

The components of this three-part structure are given separately in the following sections. First of all, the working structure of FES, which is based on laboratory results and determines the severity of RA disease, is explained. In the next section, the definition of Anti-CCP, one of the antibodies that have an important role in the differential diagnosis of the disease, and its use in the study are explained. Then, the questions asked to find the patient's medical history and the calculations used to convert this question into a numerical value are included. Finally, according to the information obtained from these three separate parts, the working structure of the disease diagnosis decision unit is given in detail.

#### 3.2.1. Determining FES-based RA Severity (Part 1)

The goal of this part is to obtain a result related to the severity of RA by using the laboratory results used as the basis for RA disease diagnosis. As inputs, four laboratory test data sets were used: C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), Rheumatoid factor (RF), and Antinuclear antibodies (ANA). The descriptions and effects of the input parameters used in this part can be briefly summarized as follows.

C-reactive protein (CRP) measures the C-reactive protein level in the blood. CRP is a protein that indicates whether there is inflammation in the body, but it does not give an idea of where the inflammation is. It can be found up to 0.5 mg/dl in a healthy person's serum. The serum level begins to rise only 6 hours after the occurrence of the inflammatory event. When the inflammation ends, it quickly returns to normal because its half-life is short. It correlates with the severity of the RA disease [28, 29].

Erythrocyte sedimentation rate (ESR) is a test that indirectly indicates the increase in acute phase proteins and the severity of inflammation. Calculation with a rough formula is as follows; ESR values which are half of the value of their age in men and half of the value found by adding ten to the age in women can be accepted as normal. When ESR is compared to the increase and normalization of CRP, ESR increases and normalizes more slowly than CRP. Although ESR is highly sensitive to changes in RA activity, it is affected by various factors such as age, gender, pregnancy, satiety, and erythrocyte count [29, 30].

Rheumatoid factor (RF): Autoantibody, which is mostly in the structure of IgM and is called a rheumatoid factor, is found in 85% of patients with RA. RF positivity is observed in 70–80% of RA patients with

Table 2
Descriptive statistics of numeric features

| | Age | CRP (mg/l) | ESR (mm/s) | RF (u/ml) | ANA (1/titer) | The patient's history (%) |
|---|---|---|---|---|---|---|
| Frequency (n) | 286 | 286 | 286 | 286 | 286 | 286 |
| Mean | 50.06 | 15.86 | 27.96 | 100.30 | 132 | 53.90 |
| Minimum | 18 | 1 | 2 | 6.33 | 40 | 7.50 |
| Maximum | 76 | 139 | 120 | 2770 | 1000 | 100 |
| Std. Deviation | 11.60 | 21,76 | 23,27 | 283,07 | 131,34 | 29,50 |

advanced RA. The standard value of the rheumatoid factor is < 20 u/ml [31, 32].

Anti-nuclear antibodies (ANA) are the name given to antibodies that occur against various structures in human cell structure (e.g., DNA, histone, centromere, etc.). The ANA is a test used in the diagnosis of systemic or organ-specific autoimmune diseases and is done to check whether the relevant antibodies are produced. When the results of the analysis are positive, they are reported as titers. It is considered normal that the ANA titer is 1/40 or less. In autoimmune rheumatological diseases, the ANA test is mostly positive, but ANA positivity is not diagnostic, and the test should be evaluated with clinical findings. Briefly, ANA positivity alone has no meaning without the symptoms of the disease; if there is a high titer positivity, the person is informed and followed up [29, 33].

Two basic laboratory tests that are closely related to the severity of the disease in RA are ESR and CRP levels. High CRP and ESR are important factors that determine the severity of RA. In addition, RF positivity was observed in 70–80of the disease is more severe and the incidence of extra-articular manifestations increases in patients with a high rate of positive RF. Anti-CCP positivity and high titer ANA positivity are also two important antibodies in determining the severity of RA.

In Part 1, FES determines the severity of the RA disease. It is designed to consist of four inputs (CRP, ESR, RF, and ANA) and one output (RA severity), and its general structure is given in Fig. 2 [34]. In Table 3, the linguistic expressions and numerical ranges of the input and output parameters determined by the help of a specialist in FES are given.

The crisp values of input are fuzzified and converted to Low (L), Normal (N), High(H) linguistic variables, as shown in Table 3. The triangular membership function was used in the fuzzification of these linguistic expressions.

Linguistic expressions for the CRP input parameter were created with triangular membership functions. Membership degrees of fuzzy sets are given in Equations 1–3. Here x is a member of the fuzzy set and determines the degree of membership in the $\mu(x)$. Similarly, fuzzy sets and linguistic expressions were created for other input parameters.

$$\mu_L(x) = \begin{cases} x \leq 2;\ 1 \\ 2 \leq x \leq 5;\ \frac{5-x}{3} \\ x > 5;\ 0 \end{cases} \quad (1)$$

$$\mu_N(x) = \begin{cases} x < 2 \text{ or } x > 8;\ 0 \\ 2 \leq x \leq 5;\ \frac{x-2}{3} \\ 5 \leq x \leq 8;\ \frac{8-x}{3} \end{cases} \quad (2)$$

$$\mu_H(x) = \begin{cases} x < 5;\ 0 \\ 5 \leq x \leq 8;\ \frac{x-5}{3} \\ x \geq 8;\ 1 \end{cases} \quad (3)$$

FES modeling was made with MATLAB Fuzzy Logic Toolbox software. Membership function graphs of the input parameters are given in Fig. 4.

For the RA disease severity output parameter, four different linguistic expressions were identified, ranging from 0–100% Not RA (N), Low RA (L), Normal

Table 3
Membership value ranges of input-output parameters for FES

| | Membership value ranges of input parameters | | | | Membership value ranges of the output parameter |
|---|---|---|---|---|---|
| | CRP (mg/l) | ESR (mm/s) | RF (u/ml) | ANA (1/titer) | RA Level |
| High | >5 | >20 | >20 | >160 | >60 |
| Normal | 2–8 | 10–30 | 10–30 | 120–200 | 40–80 |
| Low | <5 | <20 | <20 | <160 | 20–60 |
| Not RA | | | | | <40 |

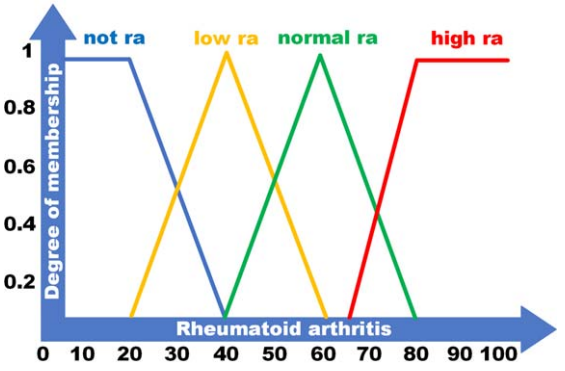


Fig. 3. RA disease severity membership function graph.

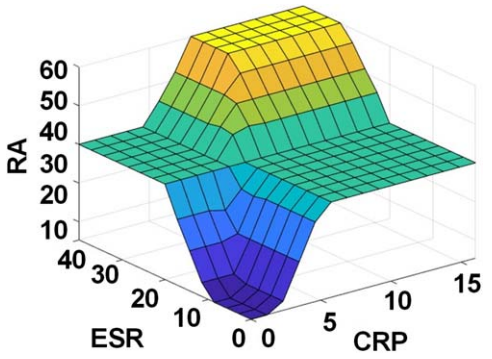


Fig. 5. RA disease severity change according to CRP and ESR.

RA (N), and High RA (H). RA disease severity membership function is shown in Fig. 3.

Depending on the input parameter values, one or more rules can be fired. The inference mechanism determines the result of the fired rules. In this study, fuzzy output values were obtained by using the Mamdani inference mechanism and max-min method. The severity of the RA disease was found by using the "Centroid - Center of Gravity" method to rinse the turbid output values obtained.

The changes in RA disease severity according to CRP and ESR are given in Fig. 5.

### 3.2.2. *Anti-CCP antibody (Part 2)*

Anti-CCP is the name given to antibodies formed against citrullinized proteins such as flagrin and its circular form. When used with RF, anti-CCP increases its specificity to 98% for RA diagnosis and is an essential antibody in the distinctive diagnosis of RA disease. In the early stages of the disease, it was found that serum levels increased in 79% of the patients. If the Anti-CCP level is < 5 ru/ml, the result is negative, and if the Anti-CCP level is > 5 ru / ml, the result can be considered positive. If there are no clinical signs and symptoms, it is insufficient to diagnose alone. The positive anti-CCP and RF test results indicate that the patient has a high probability of having RA and severe disease activity [35]. The positive or negative Anti-CCP result obtained in this section is transferred to the decision-making unit.

Table 4
Anamnesis form applied to patients

| No | Anamnesis Questions |
|---|---|
| 1 | Do you feel that joint function is decreasing, are there any restrictions on your movements? |
| 2 | Is there any pain in the joint? |
| 3 | Do you have any swelling in your joints? |
| 4 | Is there a rash on the joints? |
| 5 | Is there a symmetrical eclipse in your joints, i.e., an eclipse on both sides? |
| 6 | Is there morning stiffness that is defined as morning passion around the joints and joints after a long period of sleep and long rest? |
| 7 | Does your pain decrease with movement? |
| 8 | Do painless lumps (nodules) occur on the elbow, on hand or in different parts of the body? |
| 9 | Is there any deformation in the joints? |
| 10 | How often do you have complaints in MKF, PIF, wrists, knees, shoulders, toes, and ankles? |

### 3.2.3. *Patient's medical history (Part 3)*

Since there is no definite cause of RA, several factors need to be reviewed before reaching a diagnosis. One of these factors, symptoms, is an important tool in diagnosing RA. Doctors first examine symptoms to begin the diagnostic process. RA symptoms inform the doctor about the process of RA.

An anamnesis form containing ten questions specific to RA was prepared to evaluate the patient's condition. The anamnesis questions determined with the help of the specialist doctor are given in Table 4.

In this section, the Likert scale method, which is widely used in computer-based diagnostic systems, is used. The responses given by the patients to all questions were prepared according to the Likert scale such as Never (0 points), Rarely (1 point), Occasionally (2 points), Often (3 points), Always (4 points). Evaluation is made on the total value of the answers given by the patients to all questions. Finally, the percentage obtained from the patients' answers to all questions is calculated according to Equation 4, and the patient's history value is obtained.

$$\textit{Patient's medical history result}\ (\%)$$

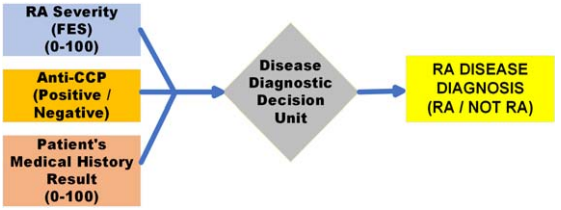


Fig. 6. Disease diagnostic decision unit.

$$= \frac{100 * \left(Patient's\ score\ \ from\ the\ story\right)}{40} \quad (4)$$

The results obtained from this equation are used to determine the patient's medical history. At which stages of the models are used at the results of the medical history are shown at Fig. 2 and Fig. 6. In addition, the medical history results of the patients are given in Table 6 and Table 7.

### 3.3. Disease Diagnostic Decision Unit

The Disease Diagnostics Decision Unit (Fig. 6) is designed to evaluate RA disease severity (0–100) and the patient's medical history result (0–100) and the Anti-CCP result (positive/negative). Firstly, RA severity and disease medical history, which contain numeric values, were subjected to discretization. As a result of this procedure, thirty-two different RA conditions including diagnosis of RA disease, probability of occurrence, severity, and activity were obtained. The detailed form of this structure, which constitutes the inference system of the DSS, is given in the attachment [36].

### 3.4. Development of machine learning models

In this study, two different models were designed for the diagnosis of RA with the kNN, SVM, LR, DT, NB, and MLP algorithms, as shown in Fig. 7. In the first model, while seven features in the data set (Age, Gender, CRP, ESR, RF, ANA, Anti-CPP) were determined as input parameters, the number of features was increased to eight features by adding the patient's history to the second model, and the disease was diagnosed by making a new classification. Thus, the effect of the patient's history on the diagnosis of the disease was examined.

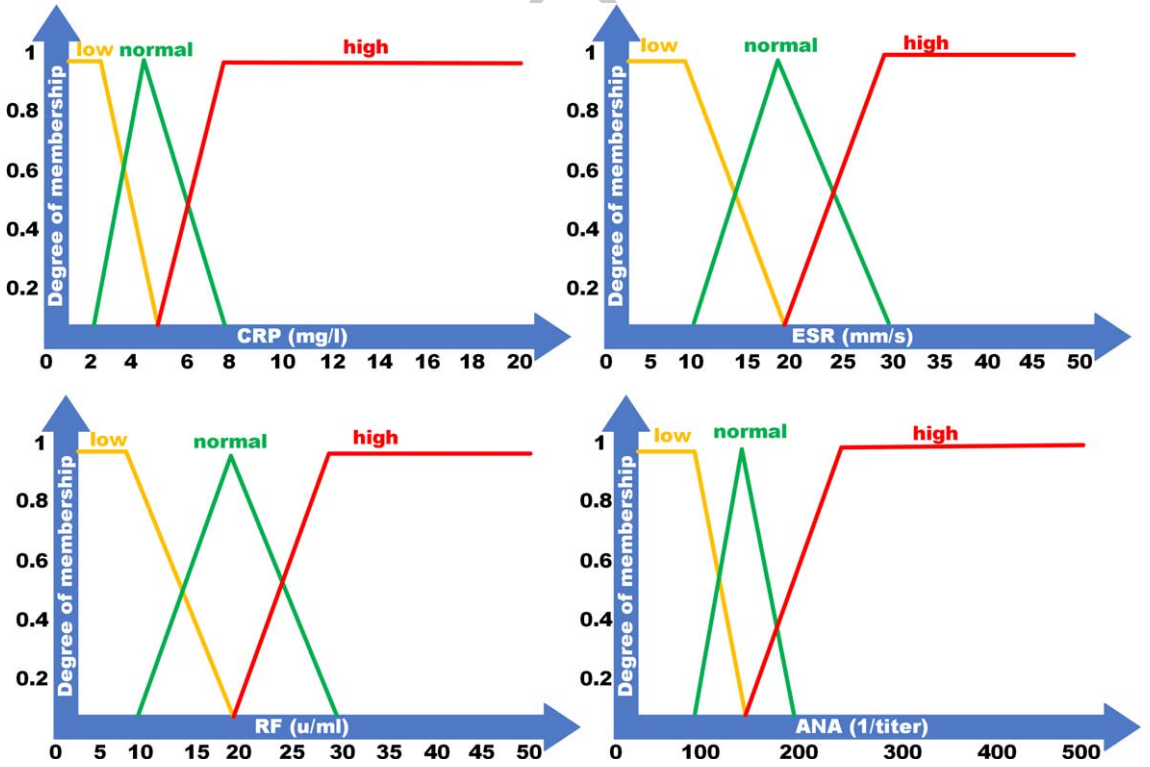


Fig. 4. Membership functions of input parameters.

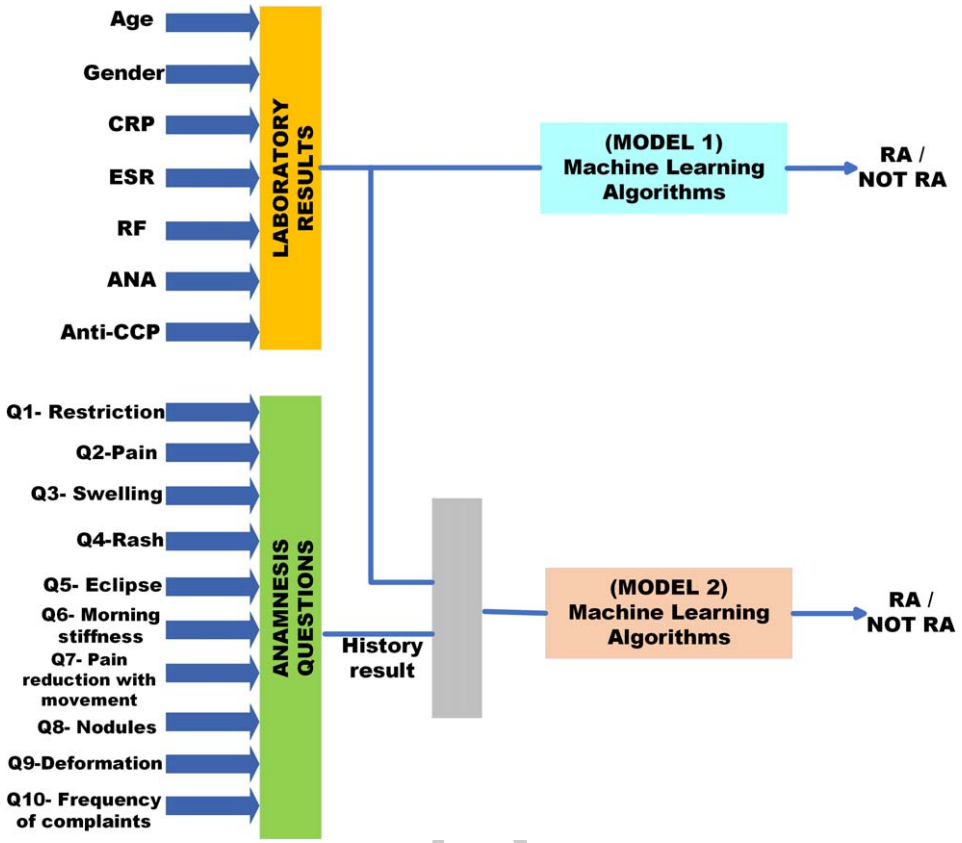


Fig. 7. Machine learning models used in the study.

Table 5
Performance measurement formulas

| Performance Metric | Formula |
|---|---|
| Accuracy | (TP + TN) / (TP + FP + FN + TN) |
| Error Rate | (FP + FN) / (TP + FP + FN + TN) |
| Specificity | TN / (TN + FP) |
| P: Precision | TP / (TP + FP) |
| R: Recall | TP / (TP + FN) |
| F1-Score | (2 * P * R) + (*P*+ R) |

### 3.5. Performance evaluation methods

To measure the performance of a classification algorithm, evaluation measures are used such as accuracy, specificity, sensitivity, recall, and F1-Score calculated by using a confusion matrix. The confusion matrix is a table consisting of four parameters, in which the performance of the classification model is evaluated, and the predictions and actual values of the target attribute are compared. These parameters are TP (True Positives), TN (True Negatives), FP (False Positives), and FN (False Negatives). The performance measurement formulas calculated based on the confusion matrix are given in Table 5 [37].

Evaluation Focus [38]:

*Accuracy:* It is used to measure the ratio of accurately estimated samples to the total number of samples. It can be considered that the model is the best if there is high accuracy in the model used.

*Error Rate:* It is used to measure the ratio of the values of incorrectly estimated samples to the total number of samples.

*Specificity:* It is used to measure the proportion of negative values classified as true.

*Precision:* The ratio of correctly classified positive samples to estimated total positive samples. This is also called a Positive Predictive Value.

*Recall:* It is used to measure the proportion of positive values classified as true.

*F1-Score:* It is the harmonic mean of sensitivity. Therefore, it takes into account both false positives and false negatives. Especially in cases of irregular class distribution, looking at the F1-score may be more useful than looking at the accuracy.

### 3.6. Cross Validation

Cross-validation is a method developed to evaluate the success of machine learning classification models and to increase the security of the classification. It is known as k-fold cross-validation in the literature. Cross-validation is the division into the determined number of k sub-groups, as data set including training and test sets. The system is trained with the remaining clusters while one of the subgroups is used as a test set. The test set is shifted one step at a time and this process is repeated for the specified number of k. The error or success metric of the model is determined by averaging the successes in all k trials. In this study (k) was determined as 10 [39].

## 4. Results

In this study, the diagnosis of RA disease was provided with the designed and implemented fuzzy-based DSS and machine learning techniques. The factors that encourage us to do this study are: the lack of a comprehensive study on this subject in the literature, the involvement of human errors and the insufficiency of laboratory data being the sole data in the diagnosis of the disease, the early diagnosis of the disease being very decisive for the treatment method to be applied and confusing the disease with other rheumatic diseases during diagnosis, and also the difficulties encountered in the diagnosis and treatment of the disease. In the study, firstly the diagnostic results made by the DSS and then the results of the machine learning models were included.

### 4.1. Disease diagnosis results made with the DSS

The DSS performed evaluates the most basic factors in laboratory tests and physical examination on separate systems. Furthermore, a disease diagnosis for RA is created by combining all of these evaluations diagnosis by taking into account not only the patient's laboratory results but also the patient's history.

The DSS developed was applied to a total of 286 patients, 91 males, and 195 females, in Selcuk University Medical Faculty Rheumatology Department. The disease diagnosis was made by entering the data obtained in the polyclinic processes of the patients into the web-based fuzzy expert system. The diagnostic results of the developed system were compared with the diagnostic results given by the doctor.

Table 6
Records and results of patients' medical histories (Part III)

| PATIENT NO | Question 1 | Question 2 | Question 3 | Question 4 | Question 5 | Question 6 | Question 7 | Question 8 | Question 9 | Question 10 | *MEDICAL HISTORY* RESULT *(PART III)* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***1*** | Often | Often | Occasionally | Occasionally | Often | Often | Rarely | Never | Never | Occasionally | ***%47.5*** |
| ***2*** | Often | Always | Often | Rarely | Often | Always | Occasionally | Never | Never | Occasionally | ***%55*** |
| ***3*** | Often | Often | Often | Never | Often | Always | Occasionally | Never | Never | Occasionally | ***%50*** |
| ***4*** | Never | Occasionally | Never | Never | Rarely | Never | Rarely | Rarely | Never | Rarely | ***%15*** |
| ***5*** | Often | Always | Often | Never | Always | Often | Occasionally | Never | Never | Rarely | ***%50*** |
| ***6*** | Rarely | Often | Occasionally | Rarely | Often | Often | Often | Never | Never | Often | ***%47.5*** |
| ***7*** | Often | Rarely | Often | Often | Often | Always | Rarely | Never | Occasionally | Often | ***%65*** |
| ***8*** | Rarely | Often | Rarely | Rarely | Often | Often | Rarely | Never | Never | Often | ***%40*** |
| ***9*** | Often | Often | Often | Occasionally | Often | Often | Always | Never | Rarely | Rarely | ***%57.5*** |
| ***10*** | Occasionally | Often | Rarely | Rarely | Occasionally | Occasionally | Rarely | Never | Rarely | Rarely | ***%35*** |

Table 7
Comparative representation of the results of the DSS

| PATIENT NO | RA DISEASE SEVERITY (PART I) | | | | | | | ANTI-CCP (PART II) | MADICAL HISTORY RESULT (PART III) | DSS | DOCTOR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | INPUTS | | | | FES (ONLINE) | FES (MATLAB) | DIFFERENCE | | | | |
| | CRP | ESR | RF | ANA | | | | | | | |
| 1 | 12.4 | 4 | 56.8 | Negative | 60.00 | 60.0 | 0 | Positive | %47.5 | RA | RA |
| 2 | 10.8 | 25 | 19 | Negative | 46.85 | 46.9 | 0.8 | Negative | %55 | RA | RA |
| 3 | 3.9 | 12 | 218 | 100 | 35.39 | 35.4 | 0.01 | Positive | %50 | RA | RA |
| 4 | 2 | 15 | 10 | Negative | 17.36 | 17.4 | 0.06 | Negative | %15 | Not RA | Not RA |
| 5 | 5.4 | 23 | 19 | Negative | 40.53 | 40.5 | 0.56 | Negative | %50 | RA | RA |
| 6 | 23 | 19 | 17 | Negative | 31,99 | 32.0 | 0.1 | Negative | %47,5 | Not RA | Not RA |
| 7 | 14 | 15 | 311 | 100 | 72.67 | 72.7 | 0.3 | Negative | %65 | RA | RA |
| 8 | 21.7 | 29 | 67.2 | Negative | 84.32 | 83.7 | 0. 62 | Positive | %40 | RA | RA |
| 9 | 12. 2 | 34 | 21.8 | Negative | 65. 04 | 65.0 | 0.04 | Negative | %57.5 | RA | RA |
| 10 | 3.6 | 19 | 20.9 | Negative | 39.40 | 36.4 | 3 | Positive | %35 | Not RA | RA |

Questions were given to determine the patients' stories in Table 4. In Table 6, ten patient data were included to show different patient types and the patients' responses to these questions are presented.

DSS diagnosis results, obtained by using the patient's stories results determined in Table 6 and other laboratory findings, are given in Table 7. FES and patient's history results in Table 7 were obtained through the online website (https://www.tf.selcuk.edu.tr/rad/).

Table 7 lists the components that make up the system's basic structure as well as their results. RA disease severity value is obtained by using CRP, ESR, RF, and ANA inputs in Part 1. The values of the FES, which is coded as web-based, and the MATLAB Fuzzy Logic Toolbox are also compared in this part. It is seen that the results obtained are compatible with each other.

Some of the diagnostic results made by DSS and specialist doctors are given in Table 7. As a result of using the Fuzzy-based DSS in all patient records, an overall success rate of 94.05% was achieved in diagnosing the RA disease. DSS correctly diagnosed 269 of the 286 people.

The 2010 ACR/EULAR RA classification criteria, as seen in Table 1, are another widely used criterion in the classification of RA disease. The total score in this score-based algorithm must be greater than 6 for a patient to be diagnosed with RA [6]. Table 8 shows the classification of the patient data collected in this study according to the 2010 ACR / EULAR criteria, and a comparison of the diagnoses.

The evaluation criteria of A, B, C, and D sections and the results obtained from each criterion are specified separately in Table 8. The results obtained based on the total score in Table 6 were compared with the DSS and the expert's diagnoses. The DSS results appear to be in line with the 2010 ACR/EULAR evaluation criteria.

### 4.2. Disease diagnosis results made using machine learning techniques

While Model 1 classified the data set based on seven features (age, gender, CRP, ESR, RF, ANA, Anti-CPP), Model 2 classified the data set based on eight features by adding the patient's history. MATLAB software is used to build machine learning models. The 10-fold cross-validation method has been used to get a robust result in this study performed with machine learning models.

The complexity matrices of the algorithms used in the study were extracted and performance measurements were calculated. The confusion matrix of each algorithm is shown in Table 9.

The confusion matrix was used to calculate the accuracy, error rate, specificity, precision, recall, and F1-Score of the algorithms that classify the data set, and performance metrics are shown in Table 10.

In Model1, the LR, DT, SVM, NB, and MLP algorithms have classification success rates of 87.06%, 90.20%, 91.95%, 91.95%, 88.46%, and 92.65%, respectively. In Model2, the LR, DT, SVM, NB, and MLP algorithms have classification success rates of 88.81%, 97.90%, 97.90%, 97.90%, 97.20% and 97.20% respectively. As the table clearly shows, the patient's history is extremely important in the diagnosis of RA. In Model 2, where the patient's history is used as the input parameter, it is seen that the success of all algorithms except the kNN algorithm is over

Table 8
Comparison of patients' diagnostic according to RA 2010 ACR/EULAR classification criteria

| PATIENT NO | 2010 ACR/EULAR CRITTERS | | | | | | | | | Diagnostic | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | | | B | | C | | D | | | | |
| | CRP | ESR | SCORE (CRP & ESR) | RF (Positive/ Negative) | ANTI-CCP (Positive/ Negative) | SCORE (RF & ANTI CCP) | JOINT INVOLVEMENT | SCORE (Joint involvement) | SYMPTOM DURATION (<6 Weeks &>6 Weeks) | SCORE (Symptom duration) | 2010 ACR / EULAR TOTAL SCORE | Result | DSS | Doctor |
| 1 | 12.4 | 4 | 1 | 56.8 P | P | 3 | 3 small joints | 2 | >6 | 1 | 7 | RA | RA | RA |
| 2 | 10.8 | 25 | 1 | 19 N | N | 0 | >10 joints (2 small) | 5 | >6 | 1 | 7 | RA | RA | RA |
| 3 | 3.9 | 12 | 0 | 218 P | P | 3 | 4–10 small joints | 3 | >6 | 1 | 7 | RA | RA | RA |
| 4 | 2 | 15 | 0 | 10 N | N | 0 | 1–3 small joints | 2 | <6 | 0 | 2 | Not RA | Not RA | Not RA |
| 5 | 5.4 | 23 | 1 | 19 N | N | 0 | >10 joints (4 small) | 5 | >6 | 1 | 7 | RA | RA | RA |
| 6 | 23 | 19 | 1 | 17 N | N | 0 | >10 joints (4 small) | 5 | >6 | 1 | 7 | RA | RA | RA |
| 7 | 14 | 15 | 1 | 311 P | N | 3 | 8 small joints | 3 | >6 | 1 | 8 | RA | RA | RA |
| 8 | 21.7 | 29 | 1 | 67.2 P | P | 3 | 4–10 small joints | 3 | >6 | 1 | 8 | RA | RA | RA |
| 9 | 12.2 | 34 | 1 | 21.8 P | N | 1 | >10 joints (6 small) | 5 | >6 | 1 | 8 | RA | RA | RA |
| 10 | 3.6 | 19 | 0 | 20.9 P | P | 2 | 4–10 small joints | 3 | >6 | 1 | 6 | Not RA | Not RA | RA |

97%. It has been observed that the success of the second model in the diagnosis of RA is quite high. In terms of the F1-Score, which is another measure of the classifier's performance, LR can be used as the most efficient classification algorithm in the diagnosis of RA disease, due to both its accuracy rate and F1-Score success.

The LR algorithm and other machine learning algorithms do not provide information about the severity of the insipite of their success in classification. These algorithms are used to determine whether the disease is or not.

In addition, shown in Fig. 8 ROC curve, also known as the AUC, is one of the most commonly used metrics for evaluating binary classifiers. The bigger the value of the AUC, the better the performance of the classifier.

Table 11 summarizes the results of several studies on the diagnosis of RA disease in the literature and this study.

## 5. Conclusions

This study aims to develop a model for diagnosing RA. For this purpose, models were formed using both expert systems and machine learning methods used in the diagnosis of RA in the literature, and evaluations were made on these models. In the first expert system-based design, similar factors were evaluated together as in the 2010 ACR / EULAR criteria system in addressing the RA diagnosis problem, and the results obtained were combined with an inference system. In the second design, machine learning methods were used to build models and laboratory results were evaluated alone and together with the patient's history.

This study has shown that artificial intelligence-based systems can be successfully applied in the diagnosis of RA. The second major finding is that machine learning methods achieve better results in data sets where the patient's history results are included in the laboratory results.

Furthermore, the web-based system developed within the scope of this study contributed positively to data collection and sharing of results by experts. The fact that the developed system is web-based and accessible to researchers, experts, and patients has been important in terms of obtaining and analyzing more patient data about RA.

Moreover, radiological images are used in the diagnosis of RA disease. The absence of radiological

Table 9
Confusion matrices of the models used in the study

| | Predicted | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | kNN | | SVM | | LR | | DT | | NB | | MLP | |
| **Model 1** | **N** | **P** | **N** | **P** | **N** | **P** | **N** | **P** | **N** | **P** | **N** | **P** |
| **N** | 107 | 12 | 112 | 7 | 111 | 8 | 108 | 11 | 113 | 6 | 113 | 6 |
| **P** | 25 | 142 | 21 | 146 | 15 | 152 | 14 | 153 | 27 | 140 | 15 | 152 |
| | **Predicted** | | | | | | | | | | | |
| | kNN | | SVM | | LR | | DT | | NB | | MLP | |
| **Model 2** | **N** | **P** | **N** | **P** | **N** | **P** | **N** | **P** | **N** | **P** | **N** | **P** |
| **N** | 111 | 8 | 115 | 4 | 117 | 2 | 116 | 3 | 118 | 1 | 114 | 5 |
| **P** | 24 | 143 | 2 | 165 | 4 | 163 | 3 | 163 | 7 | 160 | 3 | 164 |

Table 10
Performance measurements of the algorithms used in the study

| | | Acc | Error | Spec. | Prec | Recall | F1-Score |
|---|---|---|---|---|---|---|---|
| **MODEL 1** | kNN | 87.06 | 12.94 | 85.03 | 81.06 | 89.91 | 85.25 |
| | SVM | 90.20 | 9.80 | 87.42 | 84.21 | 94.11 | 88.88 |
| | LR | 91.95 | 8.05 | 91.01 | 88.09 | 93.27 | 90.61 |
| | DT | 91.25 | 8.75 | 91.61 | 88.52 | 90.75 | 89.62 |
| | NB | 88.46 | 11.54 | 83.83 | 80.71 | 94.95 | 87.25 |
| | MLP | 92.65 | 73.42 | 91.01 | 88.28 | 94.95 | 91.49 |
| **MODEL 2** | kNN | 88.81 | 11.19 | 85.62 | 82.22 | 93.27 | 87.40 |
| | SVM | 97.90 | 2.10 | 98.80 | 98.29 | 96.63 | 97.45 |
| | **LR** | **97.90** | **2.10** | **97.60** | **96.69** | **98.31** | **97.50** |
| | DT | 97.90 | 2.10 | 98.20 | 97.47 | 97.47 | 97.47 |
| | NB | 97.20 | 2.80 | 95.80 | 94.40 | 99.15 | 96.72 |
| | MLP | 97.20 | 2.80 | 98.20 | 94.43 | 95.79 | 96.61 |

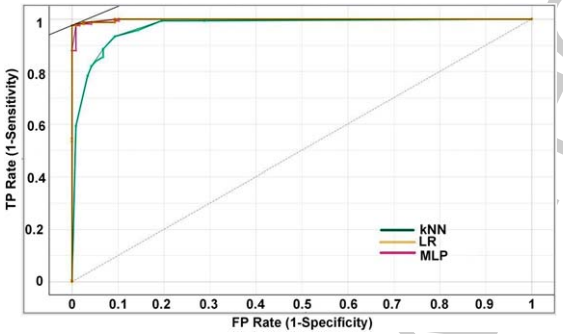


Fig. 8. ROC curves for kNN, LR and MLP.

images used in the diagnosis of RA disease is one of the study's limitations. This limitation makes it difficult to distinguish the disease from other rheumatic diseases, and this is one of the main factors limiting success.

The main benefits of this DSS include helping experts in disease diagnosis, increasing the possibility of early diagnosis in the treatment process of the disease, serving as a basis for medical expert systems for this disease, and using in the education of medical students. On the other hand, the designed system is web-based; it provides many advantages in terms of informing patients, minimizing communication issues between patient and doctor, and saving time, space, and effort due to remote access.

The system's success demonstrates that similar systems can be developed for other rheumatic dis-

Table 11
Comparison with existing studies in RA diagnosis

| Author | Year | Method | Acc. |
|---|---|---|---|
| Shiezadeh et al. **[40]** | 2015 | Machine Learning Methods (Ensemble Learning) | % 85.00 |
| Zhou et al. **[41]** | 2016 | Machine Learning Methods | % 92.29 |
| Morita et al. [14] | 2017 | Machine Learning Methods (Support Vector Machine) | % 81.40 |
| Siddiqui et al. [15] | 2019 | Mamdani Fuzzy Type-1 Expert System | % 95.60 |
| Sundaramurthy et al. **[42]** | 2020 | Grey Wolf Optimization (GWO) Particle Swarm Optimization (PSO) | % 84.00 |
| This Study | – | Fuzzy Based Decision Support System | % 94.05 |
| This Study | – | Machine Learning Methods | % 97.90 |

eases. With advanced machine learning methods, it would be possible to build a medical expert system framework capable of handling all rheumatic diseases. In addition, it will be possible to achieve better results in the success of the diagnosis of the disease by adding radiological images of patients using image processing techniques to this designed system.

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