BioMed Research International

# Precision Medicine and Big Data Research Progress in Inflammatory Diseases

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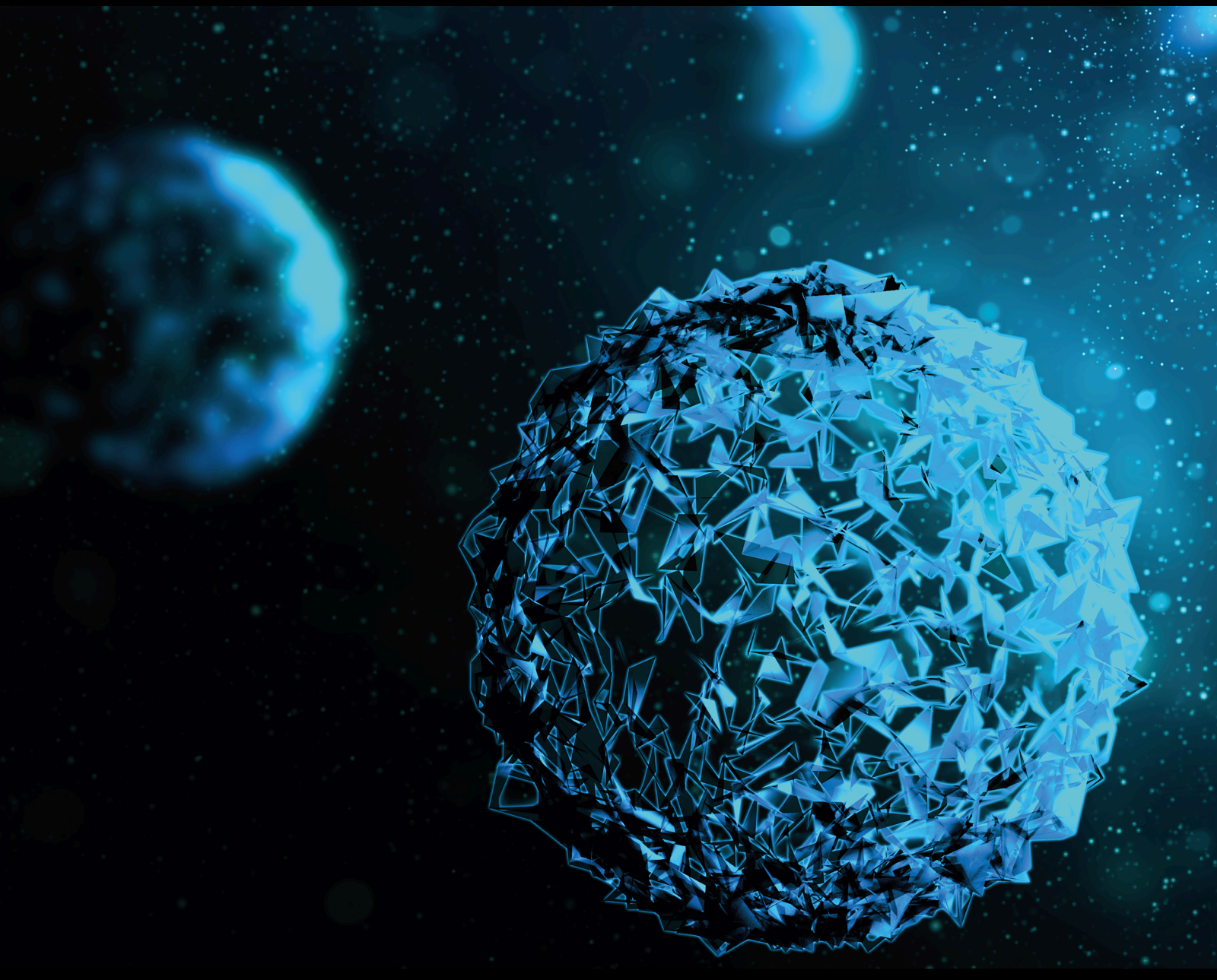

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*Research Article*

# Machine Learning-Based Model to Predict Heart Disease in Early Stage Employing Different Feature Selection Techniques

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Almost 17.9 million people are losing their lives due to cardiovascular disease, which is 32% of total death throughout the world. It is a global concern nowadays. However, it is a matter of joy that the mortality rate due to heart disease can be reduced by early treatment, for which early-stage detection is a crucial issue. This study is aimed at building a potential machine learning model to predict heart disease in early stage employing several feature selection techniques to identify significant features. Three different approaches were applied for feature selection such as chi-square, ANOVA, and mutual information, and the selected feature subsets were denoted as SF1, SF2, and SF3, respectively. Then, six different machine learning models such as logistic regression (C1), support vector machine (C2), K-nearest neighbor (C3), random forest (C4), Naive Bayes (C5), and decision tree (C6) were applied to find the most optimistic model along with the best-fit feature subset. Finally, we found that random forest provided the most optimistic performance for SF3 feature subsets with 94.51% accuracy, 94.87% sensitivity, 94.23% specificity, 94.95 area under ROC curve (AURC), and 0.31 log loss. The performance of the applied model along with selected features indicates that the proposed model is highly potential for clinical use to predict heart disease in the early stages with low cost and less time.

## 1. Introduction

Nowadays, machine learning algorithms are vastly used all over the world. In the healthcare industry, machine learning is widely used for predicting disease at an early stage. It saves a lot of people's lives worldwide by predicting their disease at an early stage. Even then, every year, thousands of people are affected and died from heart disease. If machines can predict the early stage of the disease, then, this prediction should reduce the death risk of heart disease. The heart is a significant limb of the human body, and heart disease is the major reason for death in the present world. When it is unable to perform properly, various limbs are obstructed, and then, the brain and several limbs do not work, and a person will die within a few seconds. It is one of the foremost diseases that most commonly affects middle or old-aged people and creates severe complications in the human body [1]. It is difficult to diagnose heart disease because of the number of risk factors. The main

symptoms of heart disease are body physical weakness, chest pain, shortness of breath, and rapid or irregular heartbeat [2]. The incidence of heart disease is much higher in the United States (US), and every 34 seconds, one person died due to heart disease [3]. Approximately, almost 26 million people all over the world are affected by heart disease [4]. Every year, 17.9 million people are affected by heart disease, and the worldwide death rate of heart disease is 32% [5]. From 2005 to 2015, India lost up to $237 billion, due to heart-related diseases, estimates made by the World Health Organization (WHO) [5]. Both males and females suffer from heart disease (HD) [6]. Heart diseases are also revealed in older age and middle life, because of exposure to unhealthy lifestyles for many years. After finishing this research, we can predict heart disease at an early stage. This prediction will help millions of heart disease patients worldwide, and millions of lives will be saved. We see heart disease causes a huge loss in the global economy, and predicting it in the early stage will save billions of dollars. For prediction, six machine learning algorithms are used to find the best accuracy. Then, come to the latest conclusion as to which algorithm is better among them.

## 2. Related Work

In this section, previous heart disease-related study using machine learning methods is discussed, which motivated this work. In this paper, according to Ramalingam et al. [7], a machine learning approach has been employed on some medical datasets and experiments of numerous data. This paper contributes to various model-based algorithms and techniques. Using some supervised algorithms such as Naive Bayes, random forest (RF), decision trees (DT), support vector machine (SVM), and K-nearest neighbor (KNN) are found in these researchers. Based on the accuracy, the implementation of various techniques used in the research was compared. The results accuracy of NB was 84.1584% with SVM-RFE (recursive feature elimination) selected in the 10 most significant features. According to Pouriyeh et al. [8] using 13 attributes, in this research, the NB algorithm has performed an accuracy of 83.49%. In 1951, Fix and Hodges [9] proposed a nonparametric method for pattern classification which is popularly known as the KNN rule. Accuracy of DT and KNN was 82.17% and 83.16%, respectively. Palaniappan and Awang [10] predict the intelligent heart disease prediction in ML algorithms. The algorithms are collectively proposed to achieve accuracy. Using DT, NB, and NN technique to perdition HD, the accuracy of the DT, NB, and NN was 80.4%, 86.12%, and 85.68%. Rabbi et al. [11] used Cleveland standard heart disease dataset and classified the three-technique to prove the accuracy. Predicting the accuracy of the computer-based prediction algorithm, SVM, KNN, and artificial neural network (ANN) are used. In the accuracy, KNN (82.963%) and ANN (73.3333%) are used. They proposed SVM as the best classification algorithm with the highest accuracy to predict heart disease. In the paper, Haq et al. [12] used the UCI dataset to develop using popular algorithms, the cross-validation method, three feature selection (FS) algorithms, and seven classifier performance evaluation metrics such as classification accuracy, specificity, Matthews' correlation, sensitivity, and execution time. Impact on classifier's performance terms to accuracy and execution time is featured. Three feature selection algorithms, mRMR, relief, and LASSO, were used to select the important features, to develop performance, specificity, sensitivity, and accuracy.

Above all those previous studies [7], Ramalingam et al. did a survey which is heart disease prediction using machine learning techniques. The best data will give the best performance of each algorithm [8]. This author worked on the UCI data set with a comprehensive investigation on the comparison of machine learning techniques on heart disease domain. However, the performance of those techniques depends on feature selection algorithms [9]. Palaniappan and Awang use data mining techniques to predict heart disease; this work was done on 909 patients' data. However, data mining is much more effective with big amounts of data [10]. According to Rabbi et al., this paper is done by the same techniques using several algorithms which are given less than 90% accuracy, and those algorithms are applied on MATLAB, and using Python for feature selection techniques, it could be performed better [11]. Haq et al. use much better techniques. But it is not given more than 90% accuracy [12]. If it can handle data more carefully, it may give the best accuracy. Finally, it can be said that they tried to find the best accuracy for predicting heart disease from the UCI dataset's clinical information of patients and correctly predicted below the average of 80% of heart disease patients. They tried to find the best accuracy using all of the features or use some specific feature selection algorithm for a specific machine learning algorithm, and they do not visualize any correlation between features. Also, every other study only shows the prediction score of any algorithm, and they do not describe other performance evaluation matrices like sensitivity, specificity, log loss, and others.

In this study, heart disease (HD) datasets from UCI Machine Learning repository [13] are used. This work is related to the supervised problem of machine learning. Although there has been a lot of research on heart disease, they have tried to solve it using different algorithms. However, it is a complex problem that cannot be solved with a simple machine learning algorithm. This project will be solved by some algorithms such as linear regression (LR) and decision tree (DT). For these analyses, some feature selection methods were applied to the datasets. Several classifiers show the best accuracy in heart disease. In addition, machine learning algorithms play vital roles to predict various health-related diseases in the early stages. The visual representation of the sequential steps for predicting heart disease analysis workflow used in this study is shown in Figure 1.

## 3. Methodology

In this study, Python 3.8 was used to perform the experiment because it is more accessible to everyone, and it makes it easier to perform rapid testing of algorithms. The workflow of the study is mentioned in Figure 1. The following subsections briefly describe the research methods used in this study.

*3.1. Dataset.* In this study, the UCI Cleveland dataset [13] is used. This dataset was used in so much research and analysis. We use it for predicting heart disease. The UCI heart disease dataset contains 303 patient records, and each record

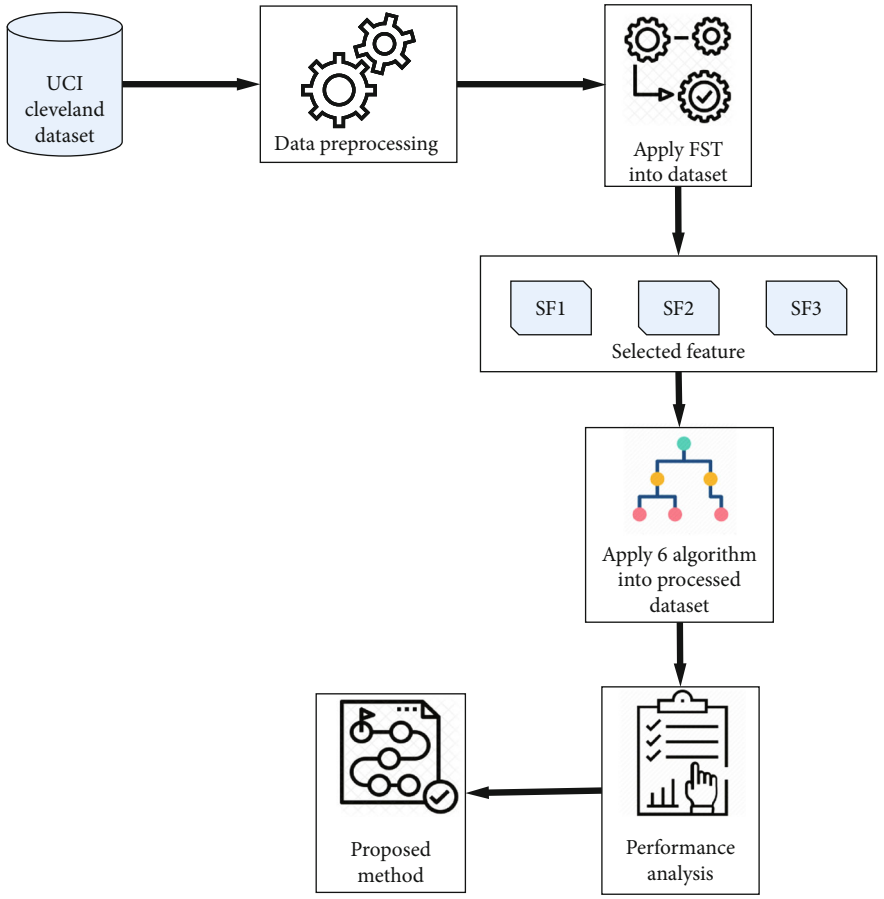


Figure 1: Workflow of predicting heart disease.

Table 1: Heart disease dataset description.

| Serial no. | Feature name | Code | Description |
|---|---|---|---|
| 1 | Age | AGE | The patient's age in years. |
| 2 | Sex | SEX | The patient's sex: male = 1, female = 0 |
| 3 | cp | CPT | Chest pain type: 0 = typical angina,1 = atypical angina, 2 = nonanginal pain, 3 = asymptomatic |
| 4 | trestbps | RBP | Resting blood pressure (in mm) |
| 5 | chol | CM | The patient's cholesterol measurement in mg/dl |
| 6 | fbs | FBS | The patient's fasting blood sugar > 120 mg/dl. 1 = true, 0 = false |
| 7 | restecg | REC | Resting electrocardiographic results: 0 = nothing to note, 1 = having ST-T wave abnormality, 2 = possible or definite left ventricular hypertrophy |
| 8 | Thalach | MHR | Maximum heart rate achieved |
| 9 | exang | EIA | Exercise-induced angina: 1 = yes, 0 = no |
| 10 | Oldpeak | OP | ST depression induced by exercise relative to rest checks the stress of the heart during exercise. The weak heart will stress more. |
| 11 | Slope | PES | The slope of the peak exercise ST segment: 0 = up sloping, 1= flat sloping, 2 = down sloping |
| 12 | ca | NMV | Number of primary vessels (0-3) colored by fluoroscopy. |
| 13 | thal | TS | Thallium stress result: 1, 3 = normal, 6 = fixed defect, 7 = reversible defect |

Table 2: Brief description of different feature selection techniques.

| FST | Description | Code |
|---|---|---|
| ANOVA *F* value | Calculate analysis of variance (ANOVA) between features for classification algorithms. | FST1 |
| Chi-square | Calculate the chi-squared score, which is used to select the highest valued feature between each nonnegative feature. | FST2 |
| Mutual information (MI) | Calculate mutual information between the attributes, which measures the relation between the features. | FST3 |

Table 3: Feature score using FST1.

| Order | Feature | Feature name | Code | Scores |
|---|---|---|---|---|
| 1 | 9 | exang | EIA | 70.95 |
| 2 | 3 | cp | CPT | 69.77 |
| 3 | 10 | Oldpeak | OP | 68.55 |
| 4 | 8 | Thalach | MHR | 65.12 |
| 5 | 12 | ca | NMV | 64.05 |
| 6 | 11 | Slope | PES | 40.90 |
| 7 | 13 | thal | TS | 31.80 |
| 8 | 2 | Sex | SEX | 25.79 |
| 9 | 1 | Age | AGE | 16.12 |
| 10 | 4 | trestbps | RBP | 6.46 |
| 11 | 7 | restecg | REC | 5.78 |
| 12 | 5 | chol | CM | 2.20 |
| 13 | 6 | fbs | FBS | 0.24 |

Table 4: Feature score using FST2.

| Order | Feature | Feature name | Code | Scores |
|---|---|---|---|---|
| 1 | 8 | Thalach | MHR | 188.32 |
| 2 | 10 | Oldpeak | OP | 72.64 |
| 3 | 12 | ca | NMV | 70.89 |
| 4 | 3 | cp | CPT | 62.60 |
| 5 | 9 | exang | EIA | 38.91 |
| 6 | 5 | chol | CM | 23.94 |
| 7 | 1 | Age | AGE | 23.29 |
| 8 | 4 | trestbps | RBP | 14.82 |
| 9 | 11 | Slope | PES | 9.80 |
| 10 | 2 | Sex | SEX | 7.58 |
| 11 | 13 | thal | TS | 5.90 |
| 12 | 7 | restecg | REC | 2.98 |
| 13 | 6 | fbs | FBS | 0.20 |

has 13 features. Two classes represent heart patients or normal cases in our target label. The dataset matrix information is given in Table 1.

*3.2. Data Preprocessing.* In this study, data were preprocessed after collection. There are 4 records on NMV and 2 records on TS that are incorrect in the Cleveland dataset. All those records with incorrect values are replaced with optimal values. Next, StandardScaler is used for ensuring that every feature has mean 0 and variance 1 and bringing all the features to the corresponding coefficient.

*3.3. Feature Selection.* Feature selection plays an important role in the machine learning process because sometimes, the dataset contains many irrelevant features that are affecting the accuracy of the algorithms. Feature selection helps to reduce those unconnected features and improve the performance of the algorithms [14]. It used different feature ranking techniques [15] to rank the most important feature based on their relevance. In this study, three well-known feature selection algorithms are used to identify important features based on their score.

*3.3.1. ANOVA F Value.* ANOVA test is a prediction technique to measure similarity or pertinent feature and to reduce the high dimensional data and identify the important feature by feature space and improving the classification accuracy. Here, the formula [16] is used:

$$F = \frac{\sum_{j=1}^{i} N_j \left(\underline{x}_j - x\right)^2 / (J-1)}{\left(\sum_{j=1}^{i} \left(N_j - 1\right)^{s^2} j / (N-1)\right)}. \quad (1)$$

*3.3.2. Chi-Square.* This test is a statistical hypothesis testing system, and also, it is written as $x^2$ test. It is calculated between the observed value and the expected value. This formula [17] is given below.

$$X^2 = \sum \frac{\left(o_j - e_j\right)}{e_i}. \quad (2)$$

*3.3.3. Mutual Information (MI).* A couple of decennial mutual information has acquired considerable attention for its application in both machine learning. MI is calculated between two variables and features [18], and this is the mathematical equation for calculating mutual information between the features.

$$I(X;Y) = H(Y) - H\left(\frac{Y}{X}\right). \quad (3)$$

As previously mentioned in this experiment, ML algorithms were used such as LR, SVM, KNN, RF, NB, and DT.

*3.4. Classification and Modeling.* The models used for predicting heart disease are described sequentially. Each algorithm is applied following that sequence. Various types of classification algorithms are available for data analysis. In

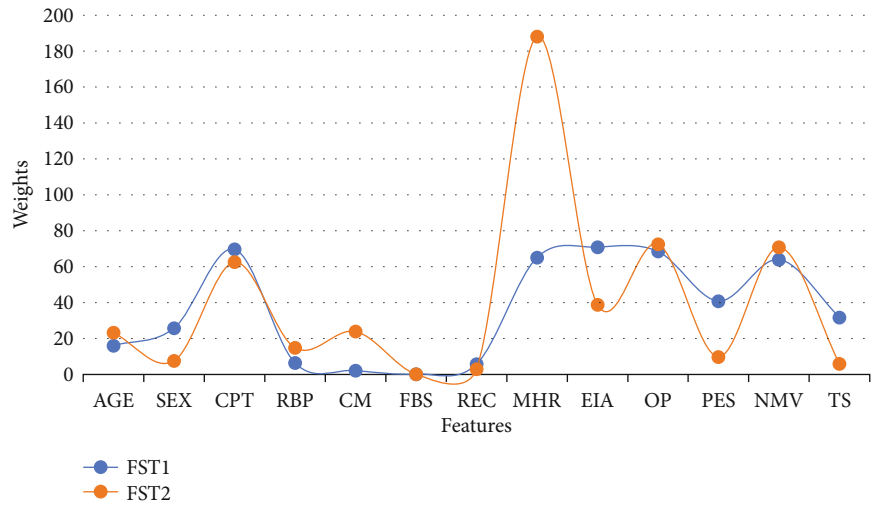


Figure 2: Feature score by FST1 and FST2.

Table 5: Feature score using FST3.

| Order | Feature | Feature name | Code | Scores |
|---|---|---|---|---|
| 1 | 3 | cp | CPT | 0.17 |
| 2 | 13 | thal | TS | 0.14 |
| 3 | 12 | ca | NMV | 0.11 |
| 4 | 9 | exang | EIA | 0.10 |
| 5 | 8 | Thalach | MHR | 0.10 |
| 6 | 10 | Oldpeak | OP | 0.09 |
| 7 | 5 | chol | CM | 0.08 |
| 8 | 11 | Slope | PES | 0.08 |
| 9 | 2 | Sex | SEX | 0.05 |
| 10 | 4 | trestbps | RBP | 0.03 |
| 11 | 1 | Age | AGE | 0.01 |
| 12 | 6 | fbs | FBS | 0.00 |
| 13 | 7 | restecg | REC | 0.00 |

this study, six types of classification algorithms are used. A brief discussion of each algorithm is given below.

*3.4.1. Logistic Regression.* Logistic regression model, the probabilities for classification problems with two possible outcomes, can be regarded as $y$ when $y \in [0, 1]$, 0 is a negative class and 1 is a positive class [12], and a hypothesis is designed based on it $h(\theta) = (\theta^n A)$. Consider that the hypothesis value is $h\theta(a) \geq 0.5$, then predict value $y = 1$. Consider that the hypothesis value is $h\theta(a) \leq 0.5$, then predict value $y = 0$. Here, the logistic regression sigmoid function is written:

$h\theta(a) = m(\theta^n \mathrm{A})$, where

$$f(y) = \frac{1}{1 + a^{-y}}, \qquad h(a) = \frac{1}{1 + a^{-y}}. \tag{4}$$

*3.4.2. Support Vector Machine.* SVM creates an effective decision boundary (hyperplane) between the two classes [19]. The main focus when drawing a decision boundary is centered on the maximum distance of the nearest data point of both classes. Although the radial base function is used as a kernel, SVM automatically determines centers, mass, and doorstep and reduces the upper limit of the expected test error. In the case of the study, we consider the support vector function as a radial base function. Here, $p$ is the length of the vector. It clarifies as

$$R\left(p, p'\right) = \text{expexp}\left(-\frac{\left\|p - p'\right\|^2}{2\sigma\text{^}2}\right). \tag{5}$$

Here, $\|p - p'\|^2$ is identified as the squared Euclidean distance between vector and $\sigma$.

*3.4.3. K-Nearest Neighbor.* KNN uses a training set directly for classifying the test data. Which refers to the number of KNN. To test each data, it calculates all the training data and the distance between them. Then, test data will be assigned to be used by multiplicity voting and class label. The Euclidean distance measure equation is given below:

$$W_e = \sqrt{\sum_{i=1}^{n} (a_i - b_i)^2}. \tag{6}$$

*3.4.4. Random Forest.* Random forest is the most powerful algorithm of supervisory machine learning algorithms. It is principally used for classification problems. As we see, a forest is made up of many trees, which means almighty forest. This algorithm similarly builds a decision tree based on data samples. Here, we use it for efficient heart disease results.

*3.4.5. Naive Bayes.* In potential, the Bayes theorem is used for calculating probability and conditional probabilities. A patient may have certain symptoms (side effects). The possibility of the proposed conclusion being true may be due to the use of the Bayes hypothesis. Here, $M$ = target variable

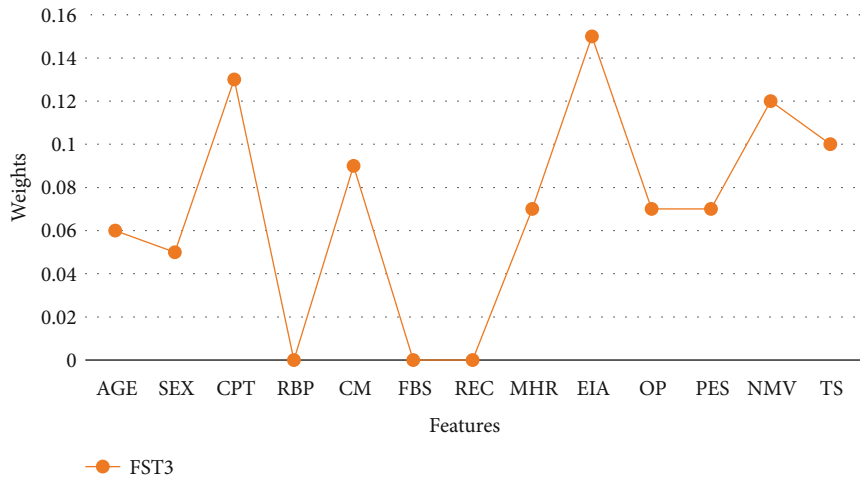


Figure 3: Feature score by FST3.

Table 6: Selected features.

| Selected feature | Selected features |
|---|---|
| SF1 | Age, sex, CPT, RBP, CM, FBS, REC, MHR, EIA, OP, PES, NMV, TS |
| SF2 | Age, sex, CPT, CM, MHR, EIA, OP, PES, NMV, TS |
| SF3 | Age, sex, CPT, MHR, EIA, OP, PES, NMV, TS |

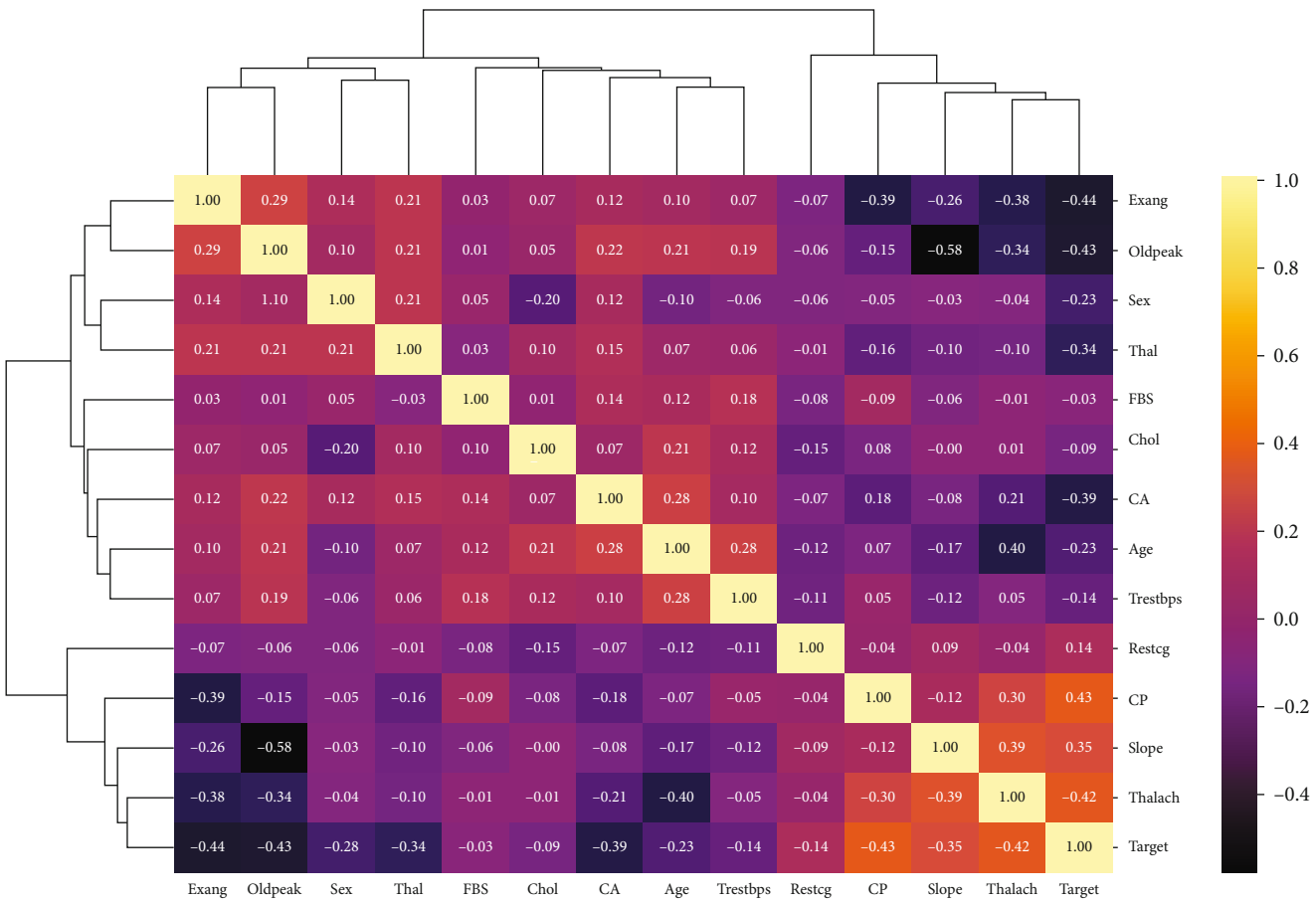


Figure 4: Correlation matrix heat map.

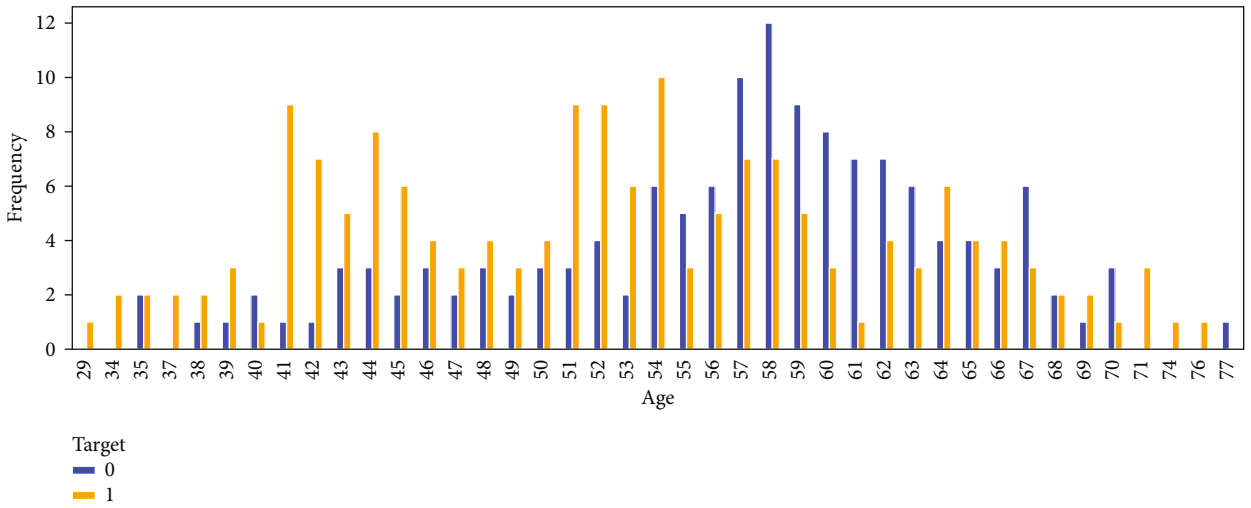


Figure 5: Correlation between patients' age with the disease.

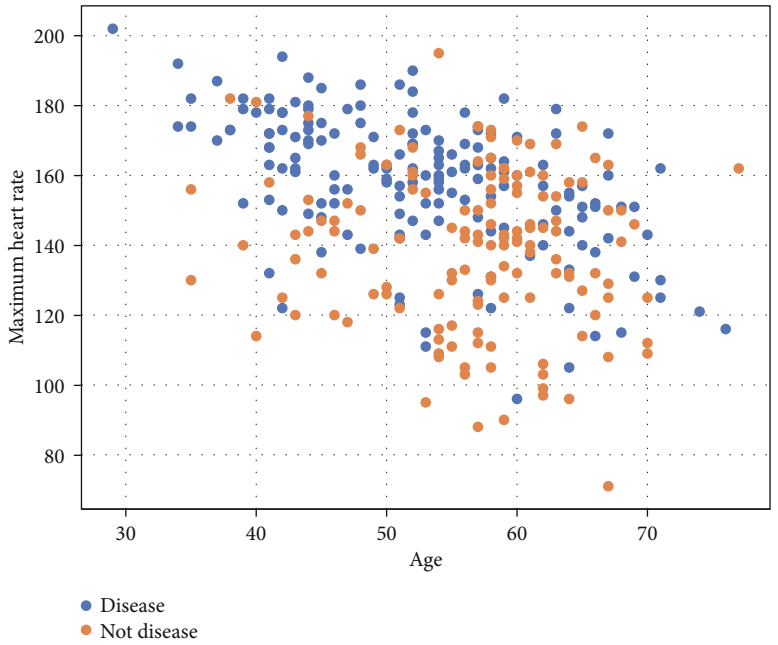


Figure 6: Correlation between patients' maximum heart rate with the disease.

Table 7: Accuracy of different algorithms.

| | Selected features | C1 | C2 | C3 | C4 | C5 | C6 |
|---|---|---|---|---|---|---|---|
| Dataset | SF1 | 93.41 | 78.02 | 87.91 | 90.11 | 89.01 | 83.52 |
| | SF2 | 93.41 | 76.92 | 86.81 | 89.01 | 90.11 | 92.31 |
| | SF3 | 93.41 | 75.82 | 84.61 | 94.51 | 90.11 | 91.21 |

and $N$ = attributes. The formula is given below:

$$P\left(\frac{M}{N}\right) = \frac{P(N/M)P(M)}{P(N)}. \tag{7}$$

*3.4.6. Decision Tree.* Decision trees are the most powerful way to classify problems. In this method, the entropy for each property is calculated in two or more similar sets based on more predictive values, and then, the data set is divided on the basis of minimum entropy or maximum data gain.

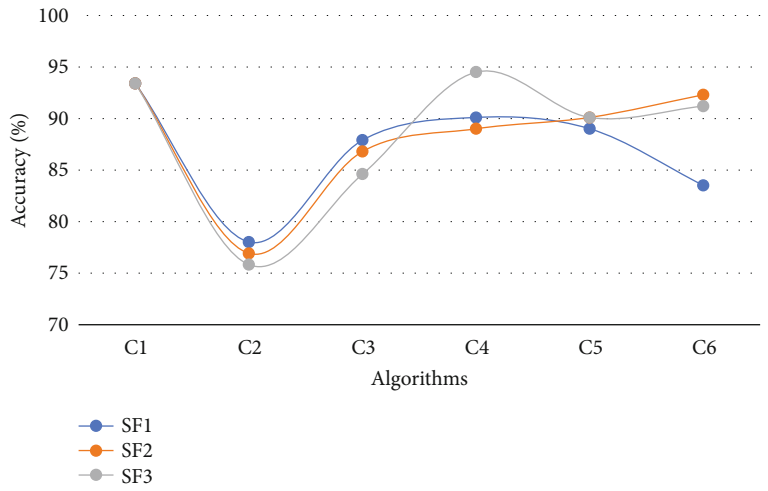


Figure 7: Accuracy of different algorithms.

Table 8: Sensitivity of different algorithms.

| | Selected features | C1 | C2 | C3 | C4 | C5 | C6 |
|---|---|---|---|---|---|---|---|
| Dataset | SF1 | 94.74 | 70.83 | 87.18 | 94.28 | 87.5 | 80.49 |
| | SF2 | 94.74 | 69.38 | 83.33 | 91.66 | 87.8 | 94.6 |
| | SF3 | 94.74 | 71.42 | 80.95 | 94.87 | 87.8 | 92.1 |

The entropy and information gain formula are given as follows:

$$\text{Entropy}(E) = \sum_{i=1}^{c} - q\, iq_i,$$

$$\text{Info} - \text{gain}(E, G) = \text{Entropy}(E) - \sum_{v \in \text{Values}(G)} \frac{|Gv|}{|E|}(Sv). \tag{8}$$

Multiplex evaluation metrics such as accuracy, sensitivity, specificity, AUROC, and log loss were evaluated to present the results of different algorithms and comparison performance based on these metrics. These matrices were represented by calculating the true positive (TP), false positive (FP), true negative (TN), and false negative (FN) values. The below section describes more about these metrics. After completing the analysis, the best algorithm is represented which achieves the highest outcomes.

*3.4.7. Performance Evaluation Matrices*

*(1) Accuracy*. The accuracy is determined by the matrices called confusion matrices. The confusion matrices are $N \times N$ matrices, which are used for assessing the performance of the classification model. The formula used to calculate the accuracy is

$$A_{cc} = \frac{(TP + TN)}{(TP + TN + FP + TN)}. \tag{9}$$

*(2) Sensitivity*. It is the measurement of the proportion of true positive cases and predicts that all values are positive. For calculating sensitivity, the used formula is

$$S_{en} = \frac{(TP)}{(TP + FN)}. \tag{10}$$

*(3) Specificity*. It calculates the proportion of true negative cases and predicts that all values are negative. The formula used to calculate the specificity is.

$$Sp_{ec} = 1 - \left(\frac{FP}{FP + TN}\right). \tag{11}$$

*(4) AUROC*. This evaluation matrix is used for checking classification model performance. For calculating AUROC, the used formula is

$$TPR = \left(\frac{TP}{TP + FN}\right),$$
$$FPR = 1 - \left(\frac{FP}{FP + FN}\right). \tag{12}$$

*(5) Log loss*. This is a classification loss function used to evaluate the performance of machine learning algorithms. The closer to zero will be the value of the log loss model and will become more accurate. For calculating log loss, the used formula is

$$Lg = \frac{-\sum_{y=1}^{j}\sum_{x=1}^{n} f(x, y) \log\,(p()x, y)}{n}. \tag{13}$$

## 4. Experimental Setting

In this analysis, Jupyter notebook is used to perform heart disease prediction of the dataset. It helps to create documents with live codes and easy to visualize various data relation diagrams of the dataset. In this analysis, firstly, the UCI

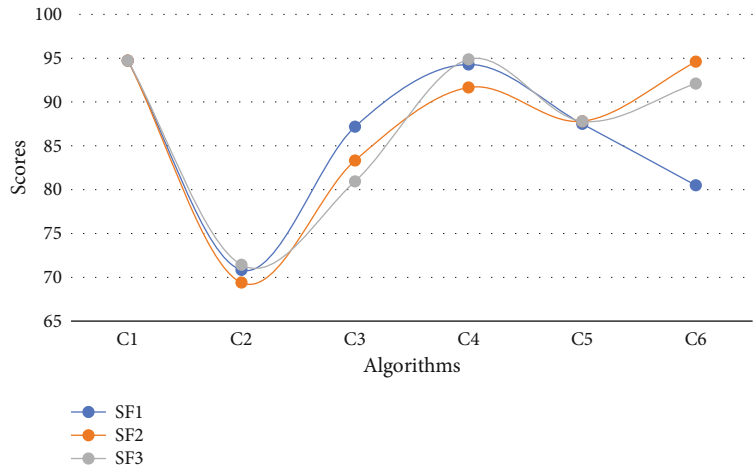


Figure 8: Sensitivity of different algorithms.

Table 9: Specificity of different algorithms.

| | Selected features | C1 | C2 | C3 | C4 | C5 | C6 |
|---|---|---|---|---|---|---|---|
| Dataset | SF1 | 92.45 | 86.05 | 88.46 | 87.5 | 90.2 | 86.0 |
| | SF2 | 92.45 | 85.71 | 89.79 | 87.27 | 92.0 | 90.70 |
| | SF3 | 92.45 | 79.59 | 87.75 | 94.23 | 92.0 | 90.57 |

HD dataset is cleaned using Pandas 1.1 and NumPy 1.19.0 libraries of Python and then preprocessed it using the StandardScaler algorithm from Scikit-learn [20] library of Python. Secondly, some feature selection algorithm is applied to find the feature importance, then made three different selected feature (SF) sets. Thirdly, the dataset was split into train and test sets, 70% of the data is used as a train set, and the rest is used as a test set. In the last, this 70% test data was used to train six different machine learning algorithms. The algorithm with the highest performance was used for predicting heart disease. The used PC for performing all the computations is Intel(R) Core(™) i5-7200U @ 2.50GHz.

*4.1. Experimental Results.* In this study, the Scikit-learn package of Python [20] is used for feature selection and classification tasks. First, different algorithms, logistic regression, decision tree, random forests, support vector machine, Gaussian NB, and K-nearest neighbor (denoted as C1, C2, C3, C4, C5, and C6, respectively), were applied to the processed dataset using all the feature and have checked the performance. In the second, Matplotlib and seaborn library of Python are used to visualize correlation matrix heat map and other correlations between different features. Third, different feature selection methods of univariate selection algorithm ANOVA *F* value, chi-square, and mutual information (MI) that are given in Table 2 (denoted as FST1, FST2, and FST3, respectively) were applied. Fourth, different algorithm performances were evaluated for the selected features. Accuracy, sensitivity, specificity, AUROC, and log loss were used to prove the results of those analyses. All features were standardized using StandardScaler before applying them to the algorithms.

*4.2. Result of Different Feature Selection Techniques.* ANOVA *F* value method calculates the *F* value between features based on the weights of the features. The score of ANOVA *F* value is given in Table 3. In this score, the three most important features are EIA, CPT, and OP, and the less important features are RES, CM, and FBS, respectively. Another method is chi-square, which calculates the chi-square score between every feature and the target. The scores of chi-square are given in Table 4. In this method, the three most important features are MHR, OP, and NMV, and the less important features are TS, REC, and FBS, respectively. The rank of features in the FST1 and FST2 methods are shown in Figure 2. The third method used in FST3 is mutual information (MI), which calculates the mutual information between each feature, which measures dependency between the features. If the score is zero, then, two features are independent, and the more score will increase, the more the features will be dependent. The scores of mutual information are given in Table 5. Here, the three most dependent features are CPT, TS, and NMV, and the independent features are fbs and restecg. The rank of the feature in FST3 method is shown in Figure 3. Those three tables present significant features for the prediction of heart disease. Besides, FBS, REC, RBP, and CM have an overall lower score for all three FSTs, and in this study, those features are not used in the different algorithms. From all those features, three different sets of features are selected based on their score. Each of the three sets of features was denoted by SF1, SF2, and SF3, respectively. Those selected feature sets are shown in Table 6.

*4.3. Visualizing Correlation between Features.* Firstly, a clustered heat map is visualized that is shown in Figure 4. This heat map shows the correlation amongst the different features of the dataset. The correlation values show that almost all of this dataset's features are significantly less correlated with each other. This implies that only a few features can be eliminated. In this heat map, CPT, MHR, and PES

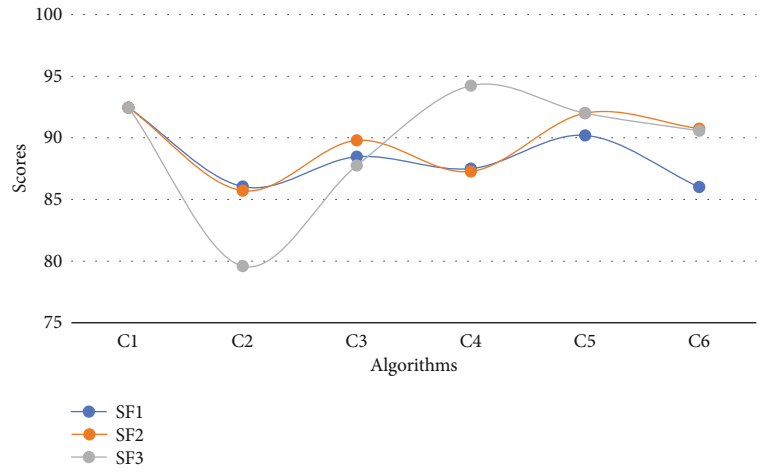


Figure 9: Specificity of different algorithms.

Table 10: AUROC of different algorithms.

| | Selected features | C1 | C2 | C3 | C4 | C5 | C6 |
|---|---|---|---|---|---|---|---|
| Dataset | SF1 | 94.56 | 76.54 | 94.09 | 93.77 | 95.05 | 91.89 |
| | SF2 | 96.03 | 76.27 | 93.43 | 94.41 | 95.54 | 91.81 |
| | SF3 | 96.08 | 79.48 | 93.87 | 94.95 | 95.49 | 93.8 |

show the highest positive correlation between the target, and EIA, OP, and NMV show the highest negative correlation between the target attribute. However, FBS, CM, RBP, and REC show the lowest correlation score between the target. This is similar to the other feature selection technique feature score, and these features are eliminated in different SF.

Secondly, a relation is shown between age and the target attribute that is shown in Figure 5. It shows that around nine patients aged 41, 51, and 52 and 11 patients, aged 54 suffered from heart disease. It suggests that between the ages of 41 to 54 and mostly the mid-aged people suffered from heart disease.

Thirdly, a relation between MHR and target is shown in Figure 6. It shows that older people have a lower heart rate than young aged. And higher heart rate slightly increases the possibility of heart disease.

*4.4. Experimental Analysis of Accuracy.* The processed dataset was analyzed using different algorithms, and Table 7 shows the accuracy of each algorithm. Relevant to the accuracy of each algorithm, the highest accuracy (94.51%) was calculated by C4 for SF3; C4 also gave (90.11% and 89.01%) accuracy for SF1 and SF2. The second highest accuracy (93.41%) was calculated by C1 for all three SFs. On the other hand, the poor accuracy (75.82%) was calculated by C2 for SF3. C4 also gave low accuracy (78.02% and 76.92%) for SF1 and SF2. The other algorithm's accuracy was between 84.61 and 92.31%. In addition, the result shows that the best algorithm for the dataset is C4 for SF3. All the accuracies of different algorithms for different SFs are shown in Figure 7.

*4.5. Experimental Analysis of Sensitivity.* In this analysis, the sensitivity was analyzed for all those algorithms. The score of the sensitivity for all those algorithms was shown in Table 8. The poorest sensitivity (69.38) was given by C2 for SF2. C2 also gave (70.83 and 71.42) scores for SF1 and SF2. And the highest sensitivity was 94.87 given by C4 for SF3 also; the second-highest sensitivity was 94.74 given by C1 for all the SFs. The other algorithm's sensitivity was between 80.49 and 94.6. In addition, the result shows that C4 gave the best score for SF3. All the sensitivity scores of different algorithms for different SFs are shown in Figure 8.

*4.6. Experimental Analysis of Specificity.* The specificity was explored for all of those algorithms, and the scores of specificity for different algorithms are shown in Table 9. During analysis, C2 gave the most inferior score (79.69) for SF3, and C4 gave the highest score (94.23) for SF3. C4 also gave sensitivity scores (87.50 and 87.27) for SF1 and SF2. C1 gave the second highest score (92.45) for all those SFs. The other algorithms gave scores between 87.27 and 92.0. In addition, the result shows that C4 gave the best score for SF3. All the specificity scores of different algorithms for different SFs are shown in Figure 9.

*4.7. Experimental Analysis of AUROC.* AUROC were analyzed to evaluate the predictions made for the heart disease dataset. The scores of AUROC for different algorithms were shown in Table 10. In this analysis, the poorest AUROC score (76.27) was given by C2 for SF2. C2 also gave scores (76.54) and (79.48) for SF1 and SF3. C1 gave the highest score (96.08) for SF3. C1 also gave AUROC scores (94.56 and 96.03 for SF1 and SF2. C5 gave the second highest score (95.54) for SF2. The other algorithms gave AUROC scores between 91.81 and 95.49. In addition, the result shows that C1 gave the best score for SF3. All the AUROC scores of different algorithms for different SFs are shown in Figures 10–12.

*4.8. Experimental Analysis of Log Loss.* In this analysis, log loss was explored. The results given by different algorithms are shown in Table 11. In this experiment, C2 gave the highest

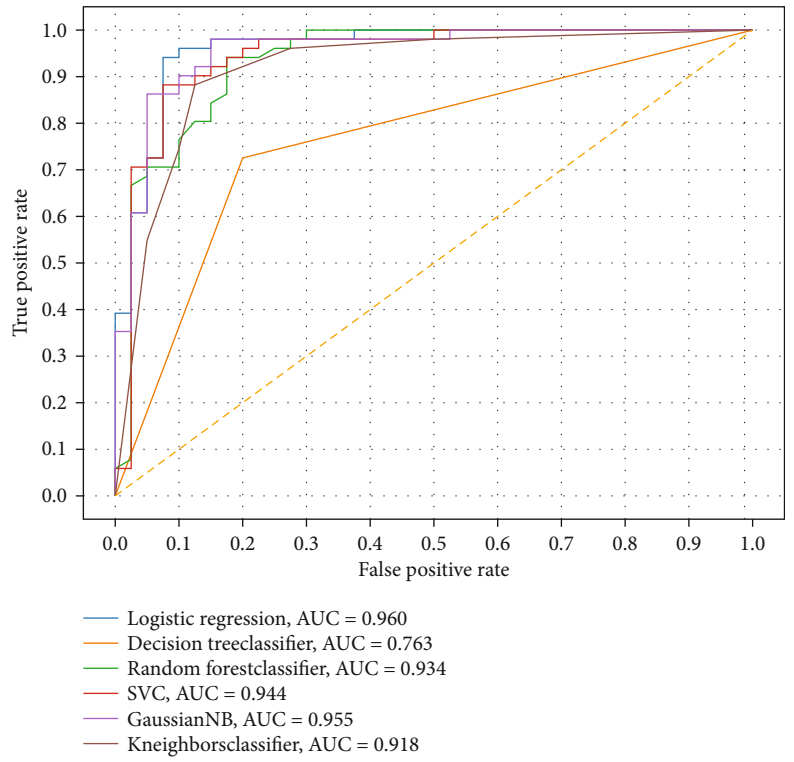


Figure 10: AUROC for SF1.

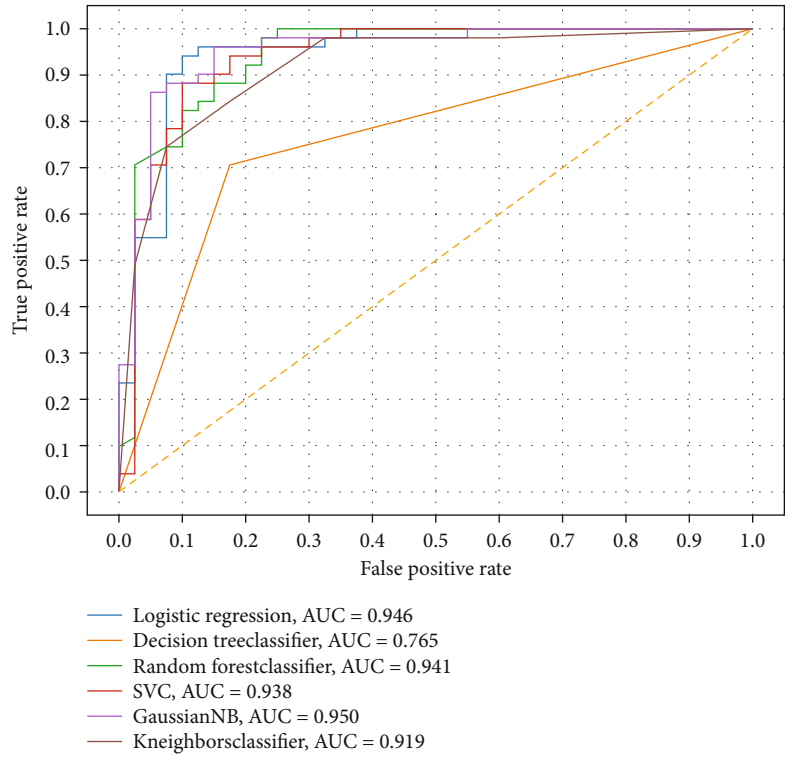


Figure 11: AUROC for SF2.

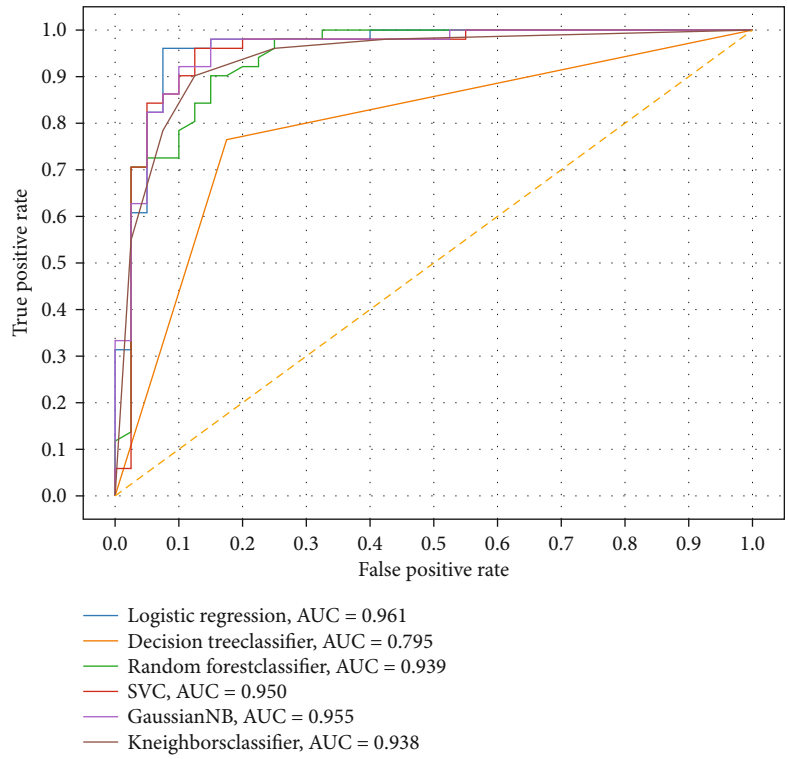


Figure 12: AUROC for SF3.

Table 11: Log loss of different algorithms.

| | Selected features | C1 | C2 | C3 | C4 | C5 | C6 |
|---|---|---|---|---|---|---|---|
| Dataset | SF1 | 0.29 | 7.59 | 0.35 | 0.33 | 0.31 | 1.02 |
| | SF2 | 0.27 | 7.97 | 0.36 | 0.32 | 0.29 | 0.67 |
| | SF3 | 0.27 | 8.35 | 0.34 | 0.31 | 0.29 | 0.62 |

score (8.35) for SF3. C2 also gave scores (7.59 and 7.97) for SF1 and SF2. Therefore, the lowest log loss value (0.27) was given by C1 for SF2 and SF3 both. The other algorithms gave log loss scores between 0.29 and 1.02. All the log loss scores of different algorithms for different SFs are shown in Figure 13.

## 5. Discussion

In this research, various machine learning algorithms were used for the early detection of heart disease, and the UCI Cleveland dataset was used for training and testing purposes. Specifically, six well-known algorithms such as LR, DT, RF, SVM, Gaussian NB, and KNN were used with different selected features. And univariate selection algorithms, ANOVA *F* value, chi-square, and mutual information (MI) are used to classify significant features which are more important for predicting heart disease. To check the performance of the different algorithms, different evaluation metrics which are accuracy, sensitivity, specificity, AUROC, and log loss were used. The experimental result shows that the algorithm C4 achieves the highest accuracy (94.51%) for SF3, and C1 achieved the second highest accuracy (93.41%) for all three SFs shown in Table 7. In terms of sensitivity and specificity, C4 also achieved the highest sensitivity (94.87) and specificity score (94.23) for SF3 shown in Tables 8 and 9. Then, for AUROC, C1 gave the highest AUROC score (96.08) for SF3 as shown in Table 10. Then, for log loss, C1 gives the lowest log loss value (0.27) for SF2 and SF3 both, as shown in Table 11. Because of the highest performance of C4 with SF3, it is the best predictive model in terms of accuracy, sensitivity, and specificity. And for AUROC and log loss, C1 is the better predictive model for SF2 and SF3, which is the second-best predictive model overall. In this analysis, we find that SVM has given the best performance for accuracy, sensitivity, and specificity, and LR is given the best performance for AUROC and log loss. Consequently, it is authorized to judge that the support vector machine is an efficient algorithm for heart disease prediction. If compressing between several machine learning algorithms, it was performing above 90 percent accuracy most of the time.

*5.1. Comparisons with Other Work.* Comparing our analysis with previous studies we found, Mohan et al. [21] developed a heart disease prediction model by using the HRFLM method. Their model predicted (88.47%) accuracy, (92.8%) sensitivity, and (82.6%) specificity for the UCI heart disease dataset, and they used all thirteen features. Amin et al. [22] predicted heart disease 87.41% accurately using Naive Bayes and logistic regression algorithm. A previous study [23] has 56.76% accuracy using J48 with reduced error pruning algorithm. There are more previous studies shown in Table 12, where their overall accuracy is between 87.41 and 83.70%. Besides, no study has evaluated the heart disease prediction

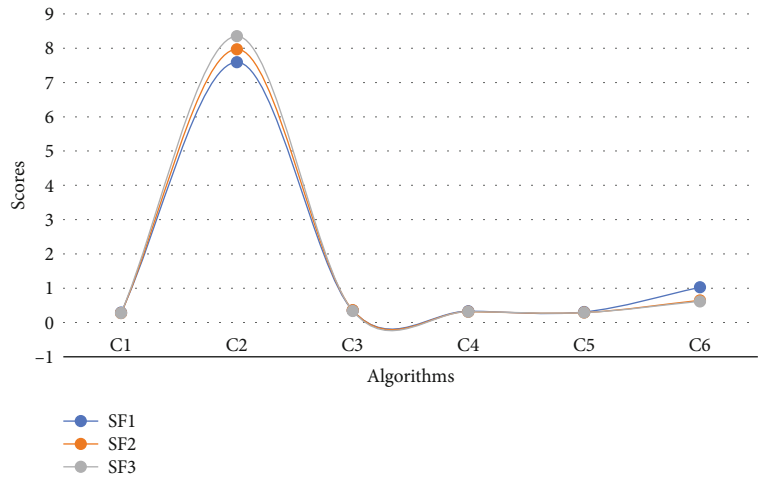


Figure 13: Log loss of different algorithms.

Table 12: Compare our predictive results with the previous results.

| Authors | Methods | Acc.(%) | Sens. (%) | Spec. (%) | AUROC (%) | Log loss |
|---|---|---|---|---|---|---|
| Our study | SVM and LR | 94.51 | 94.87 | 94.23 | 96.08 | 0.27 |
| Mohan et al. [21] | HRFLM | 88.47 | 92.8 | 82.6 | - | - |
| Amin et al. [22] | Naïve Bayes and Logistic Regression | 87.41 | - | - | - | - |
| Latha & Jeeva [24] | NB, BN, RF, and MP | 85.48 | - | - | - | - |
| Patel et al. [23] | J48 with ReducedErrorpruning Algorithm | 56.76 | - | - | - | - |
| Tomar & Agarwal [25] | Feature selection-based LSTSVM | 85.59 | 0.8571 | 0.8913 | - | - |
| Buscema et al. [26] | TWIST algorithm | 84.14 | - | - | - | - |
| Subbulakshmi et al. [27] | ELM | 87.5 | - | - | - | - |
| Srinivas et al. [28] | Na¨ıve Bayes | 83.70 | - | - | - | - |
| Polat & Gunes [29] | Combining of RBF kernel F-score feature selection and LS-SVM classifier | 83.70 | 83.92 | 83.54 | 0.831 | - |
| Kahramanli & Allahverdi [30] | Hybrid neural network method | 86.8 | - | - | - | - |

in detail; while in our study, a range of metrics (accuracy, sensitivity, specificity, AUROC, and log loss) is evaluated, and different feature selection algorithms are used for selected important features that also improve the performance of algorithms.

## 6. Conclusion

In summary, we implemented different feature selection techniques and found the most significant features which are highly valuable for heart disease prediction, then applied six different machine learning algorithms for those selected features. Every algorithm performed a separate score using different selected features. SVM and LR performance were more significant among all other algorithms. However, the amount of heart disease data available was not large enough for a better predictive model. This experiment will be more accurate if the same analysis is performed in a large real-world patient's data. In future, more experiments will be performed to find more efficient algorithms like deep learning algorithms, for this prediction to achieve better performance of the algorithms using more effective feature selection techniques.

## Data Availability

The data are available by contacting the corresponding author upon reasonable request.

## Conflicts of Interest

The authors declare no conflict of interest.

## Authors' Contributions

K.A. and M.A.M. provided the idea and designed the experiments; N.B., M.M.A., M.A.R., M.R.M., M.I., and K.A. analyzed the data and wrote the manuscript. N.B., M.M.A., M.A.R. M.I., F.M.B., S.A., F.A.A., and M.R.M. helped perform the

experimental analysis with constructive discussions. F.M.B. and F.A.A. supported the funding. All authors discussed the results and contributed to the manuscript.

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*Review Article*

# The Diagnostic Value of Neutrophil to Lymphocyte Ratio as an Effective Biomarker for Eye Disorders: A Meta-Analysis

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The neutrophil to lymphocyte ratio (NLR) reflects a dynamic relationship between the innate (neutrophils) and adaptive (lymphocytes) cellular immune response. This systematic review and meta-analysis was conducted to critically evaluate the literature regarding the use of the NLR as a reliable means to detect several ocular disorders. Our study was registered with the PROSPERO (ID: CRD42022314850). Three databases, including PubMed, Embase, Scopus, and the Web of Science, were searched on September 9, 2022, with no restrictions on the article's language. Finally, 32 articles were recognized as eligible for our meta-analysis. We found that patients with eye diseases had significantly elevated levels of NLR in comparison to healthy controls (SMD =0.53, 95% CI =0.35-0.71, $P < 0.001$). In subgroup analysis, patients with keratoconus (SMD =0.69; 95% CI =0.33-1.05, $P < 0.001$), glaucoma (SMD =0.56, 95% CI =0.25-0.87, $P < 0.001$), pterygium (SMD =0.14; 95% CI =0.01-0.26, $P < 0.001$), and idiopathic epiretinal membrane (SMD =0.14; 95% CI =0.01-0.26, $P < 0.001$) had higher levels of NLR compared to healthy controls. However, NLR levels of patients with dry eye disease were similar to healthy controls (SMD =0.32, 95% CI = -0.49-1.13, $P = 0.435$). It can be said that NLR is a valuable marker of systemic inflammation, which is significantly increased in many eye disorders, suggesting that inflammation plays a key role in the pathophysiology of these diseases.

## 1. Introduction

In recent decades, many studies revealed that numerous inflammatory responses are implicated in a variety of eye diseases [1, 2]. Such inflammatory disorders of the eye are one of the most frequent illnesses that cause permanent blindness across the globe. Much of the current literature on the role of inflammation in eye disease focuses on simple hematological biomarkers such as neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) due to their low cost and accessibility [3–31]. NLR reflects online dynamic relationship between the adaptive (lymphocytes)

and innate (neutrophils) cellular immune response. The diagnostic and prognostic value of NLR as an affordable, novel, and widely accepted marker has also been discussed in several human disorders including eye diseases such as glaucoma, dry eye disease (DED), idiopathic epiretinal membrane (iERM), retinal vein occlusion, keratoconus (KC), pterygium, and diabetic retinopathy [3–35]. This ratio is critical to early detection as a lot of patients with eye diseases were previously healthy and asymptomatic.

KC is an ectatic corneal condition that causes myopia and irregular astigmatism, and leads to vision loss due to stromal scarring, protrusion, and thinning in the cornea. Systemic inflammatory indicators such as PLR, monocyte/high-density lipoprotein cholesterol ratio, and red blood cell distribution width have also been demonstrated to be higher in individuals with KC [5, 11, 13, 15]. However, to date, there has been little agreement on the importance of NLR level in these patients [5, 11, 13, 15, 23, 27].

Glaucoma is a neurodegenerative disease that causes progressive atrophy of the optic disc leading to visual field defects. This disorder is often linked with high intraocular pressure (IOP), which is an established risk factor for disease development and permanent blindness [36]. In the literature focused on glaucoma, the relative importance of NLR has been subject to debate, because some studies reported significant differences in NLR levels between glaucoma patients and healthy control patients [3, 4, 9, 14, 18, 20, 25, 26, 29, 31, 37, 38].

Pterygium is a fibrovascular tissue growth on the cornea that leads to persistent irritation in the eye and astigmatism [39]. Recently, the literature has emerged that offers contradictory findings about the NLR level in pterygium patients compared to healthy individuals [12, 16, 17, 19, 22, 35].

Dry eye disease or DED is characterized by the symptoms such as foreign body sensation, discharge, and even obscured vision. The most updated classification subdivides DED into two types: tear-deficient and evaporative DED. In the tear-deficient DED subtype, malfunctioning lacrimal glands are often diagnosed, and this deficiency is strongly associated with an autoimmune response that may target the body's salivary and lacrimal glands (Sjögren's syndrome). Many studies have shown increased amounts of proinflammatory mediators such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-$\alpha$) in tear fluid of DED patients [6]. With respect to NLR level in DED, some studies reported that NLR level is higher in DED in comparison to healthy controls [21, 24, 28]. Vice versa, one study reported different results [6].

In addition, iERM is a relatively prevalent macular disorder among older people due to an abnormal vitreomacular interface [40]. It may cause decreased visual acuity, metamorphopsia, monocular diplopia, macropsia, and micropsia [40]. Several researchers have reported that NLR levels were higher in iERM patients than healthy controls [7, 8, 10, 30].

Eye disorders are characterized by some degree of inflammatory burden [41]. On the other hand, NLR is associated with increased inflammation in various conditions such as type 2 DM [42], autoimmune conditions [43], stroke [44, 45], thyroid disorders [46], functional bowel disease [47], and even COVID-19 infection [48]. In addition, there has been an increase in the number of papers related to the role of NLR in several eye diseases [3–31, 35, 37, 38], and it has gained prominence as an early predictive marker for several eye diseases that were mentioned earlier. However, much uncertainty still exists about this relationship, because most studies have only been carried out on a small sample size. In addition, the literature has emerged that offers inconsistent findings about these interesting topics. Existing accounts fail to resolve these discrepancies since much of the research up to now has been original except in the case of retinal vein occlusion [49], age-related macular degeneration [50], and diabetic retinopathy [51]. No meta-analysis has been conducted in this regard [25]. So, a critical review of the available literature has yet to be performed regarding these important topics. This paper seeks to remedy these problems by reviewing the studies on the prognostic and diagnostic value of NLR in several ocular disorders, including KC, glaucoma, pterygium, iERM, and DED. The key is to understand what an elevated ratio might mean for a patient with eye disease to help clinicians institute early interventions and improve outcomes.

## 2. Methods

This study was conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guideline and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Our study was registered with the PROSPERO (ID: CRD42022314850).

*2.1. Search Strategy.* Three databases, including PubMed, Embase, Scopus, and the Web of Science, were searched up to September 9, 2022. In our literature search, we included a combination of keywords, such as NLR, neutrophil to lymphocyte ratio, eye disease, and ophthalmology, in the form of title/abstract words or medical subject headings. For details, please refer to supplementary appendix A (available here).

*2.2. Study Selection.* After eliminating the duplicates, one author assessed the title and abstract of the remaining articles to exclude obviously unrelated reports. The complete text of the remaining references was then separately checked for eligibility by two authors. Any other relevant studies were found in the reference lists of recognized articles. If there was a disagreement, a third author would be brought in to debate the situation and establish a consensus.

We identify eligible studies according to the PICOS (population, intervention, control, outcomes, and study design) principle in order to ensure the systematic search of available literature. The inclusion criteria were presented below:

(a) Population. Patients with KC, glaucoma, pterygium, iERM, or DED

(b) Intervention. NLR

(c) Control. Healthy controls

(d) Outcomes. The diagnostic performance of NLR in eye diseases

(e) Study Design. We expected papers to be case-control or cross-sectional. However, we did not limit our search to any particular research design

Review articles, letters to editors, animal studies, single case reports, and studies presented as conference abstracts were not considered eligible. In addition, we excluded studies on the relationship between NLR and retinal vein occlusion, age-related macular degeneration, and diabetic retinopathy, because the relevant meta-analysis in these contexts was published.

*2.3. Data Extraction and Quality Assessment.* The first author's name, year of publication, language, study location, ethnicity, study design, eye disease type, number of cases and controls, and NLR level data in cases and controls were all collected. The medication of the patients with eye disorders could potentially conceal the actual association of NLR levels with eye disorders; so the exclusion criteria based on medication use in the included studies were extracted as well.

We used the ROBINS-1 (formerly called A Cochrane Risk of Bias Assessment Tool) for assessing the quality of included studies [52].

*2.4. Publication Bias and Statistical Analysis.* The difference in means in NLR between patients and healthy controls was the primary outcome; thus, we used a quantitative synthesis to compute the difference in NLR means between two groups (meta-analysis). The difference in NLR between patients with different clinical subtypes of glaucoma and healthy controls was the secondary outcome; thus, subgroup meta-analyses for patients with primary open-angle glaucoma (POAG), secondary open-angle glaucoma (SOAG), primary closed angle glaucoma (PCAG), and secondary closed angle glaucoma (SCAG) were performed. In addition, we conducted a subgroup meta-analysis based on research location on the connection between NLR and glaucoma. STATA 12.0 was used to conduct the meta-analyses (Stata Corporation, College Station, TX, USA). When mean and standard deviation (SD) were not supplied, median and interquartile ranges were utilized to determine mean and SD using Wan, X. et al. method [53]. Because of the presumed heterogeneity across the studies due to diverse study designs, methods, and populations, a random-effects model was adopted. Cochran's $Q$ and $I^2$ were used to determine the level of heterogeneity. A Funnel plot was used to assess publication bias. Forest plots were used to show the summary measures.

## 3. Results

*3.1. Literature Search and Selection.* A total of 813 records were retrieved in the database search and manual search of citation list of articles. After the exclusion of duplicates, 32 studies [3–31, 35, 37, 38] were included in the systematic review and meta-analysis. The process of inclusion and exclusion is detailed in the PRISMA flow diagram, provided in Figure 1.

*3.2. Characteristics of the Included Studies.* Of 32 studies included in this meta-analysis, 26 studies [3–19, 22–28, 30, 35] were conducted in Turkey, four in China [20, 21, 29, 31], one study in India [37], and one in Korea [38]. Concerning document language, 31 studies were in English [3–31, 37, 38], and one study in Turkish [35]. In terms of study design, there were 11 prospective [4–6, 11, 13, 16, 21, 24, 27, 28, 30] and 21 retrospective studies [3, 7–10, 12, 14, 15, 17–20, 22, 23, 25, 26, 29, 31, 35, 37, 38]. Overall, 3242 healthy controls and 3378 patients with eye diseases were enrolled in the selected studies. The general characteristics of the selected studies and their quality score are presented in Table 1. We found six studies on KC [5, 11, 13, 15, 23, 27], six studies on pterygium [12, 16, 17, 19, 22, 35], four studies on DED [6, 21, 24, 28], and four studies on iERM [7, 8, 10, 30]. Also, the association between NLR and glaucoma was investigated in 12 studies [3, 4, 9, 14, 18, 20, 25, 26, 29, 31, 37, 38], of which four were conducted among East Asian patients [20, 29, 31, 38] and eight among Caucasian patients [3, 4, 9, 14, 18, 25, 26, 37]. Among these ten studies, we found five studies on POAG [3, 4, 14, 25, 29], six studies on SOAG [3, 9, 18, 26, 37, 38], two studies on PCAG [14, 20], and one study on SCAG [31].

Of 32 studies, 23 studies [4, 6, 7, 10–13, 15–17, 19, 21–24, 26–30, 35, 38] excluded the patients who were smoking, using alcohol, or receiving medications that could affect the ocular surface of the eye and blood parameters. These include systemic or ocular medications including topical steroids, anti-inflammatory medications, iron preparations, vitamins, and chemotherapeutic agents. Remaining studies did not declare any exclusion criteria based on the medication taking history of the patients. However, they mentioned that excluded patients with systematic disorders such as diabetes mellitus, cardiovascular diseases, arterial hypertension, chronic obstructive lung disease, malignancies, renal dysfunction, liver dysfunction, hematologic or autoimmune disorders, and chronic systemic inflammatory disorders. It can imply the exclusion of patients with a history of receiving medications with systematic effects. With these strict exclusion criteria, the effect of medication use on blood parameters was modified in included studies.

Table 2 shows the results of the publication bias and heterogeneity tests in every single outcome (KC, glaucoma, pterygium, iERM, or DED).

*3.3. The Association between NLR Levels and Overall Risk of Eye Diseases.* Overall, 3323 healthy controls and 3558 patients with several eye diseases were compared in terms of NLR levels in 32 studies [3–31, 35, 37, 38]. Patients with eye diseases had significantly higher levels of NLR in comparison to healthy controls (SMD =0.53, 95% CI =0.35-0.71, $P < 0.001$) (Figure 2).

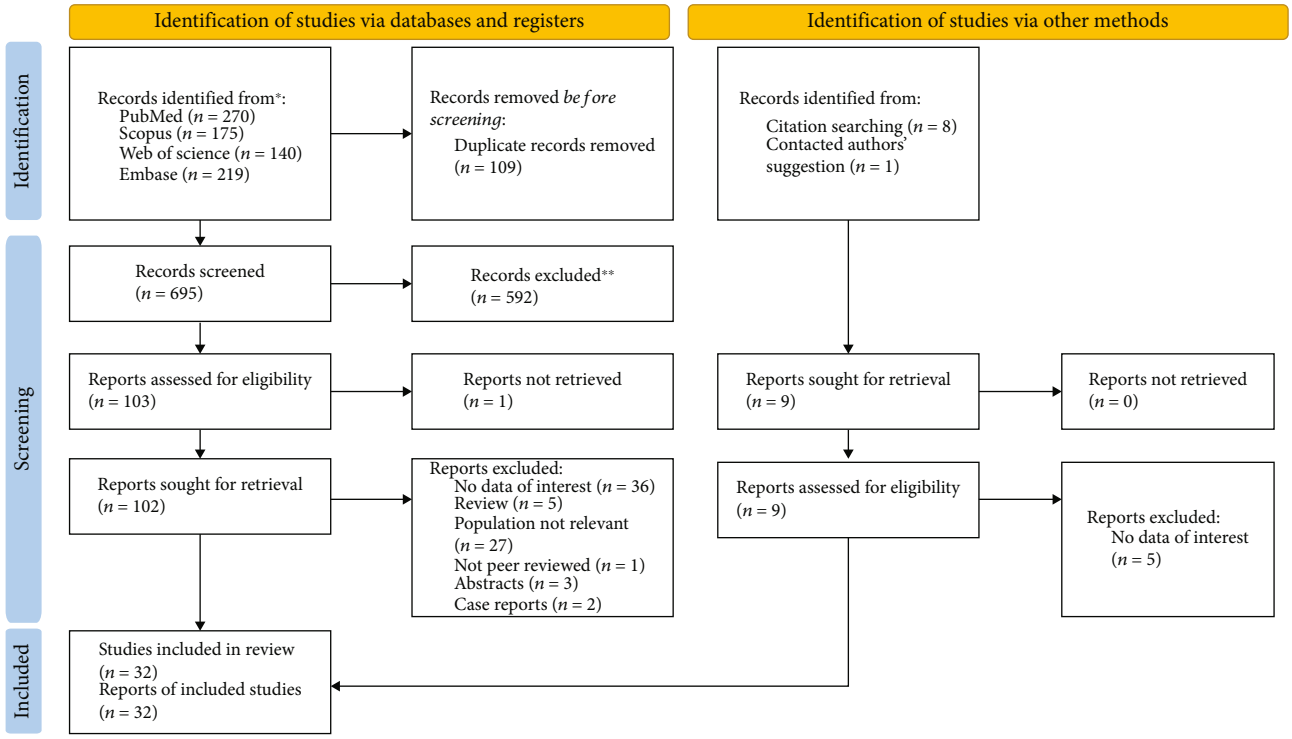


Figure 1: PRISMA 2020 flow diagram for new systematic reviews which includes searches of databases, registers, and other sources.

*3.4. Keratoconus and NLR.* NLR levels in keratoconus patients were compared with those of healthy controls in six studies [5, 11, 13, 15, 23, 27] with 245 patients with keratoconus and 211 healthy controls. Compared with the control group, the keratoconus patients' NLR levels were significantly higher (SMD =0.69; 95% CI =0.33-1.05, $P < 0.001$) (Figure 3).

*3.5. Dry Eye and NLR.* Four studies [6, 12, 16, 17, 19, 21, 22, 24, 28, 35] including 262 patients and 236 healthy controls investigated the NLR level differences between dry eye patients and healthy controls. The pooled results showed that there were no significant differences between DED patients and healthy individuals in NLR level (SMD =0.32, -0.49-1.13, $P = 0.435$) (Figure 4).

*3.6. Pterygium and NLR.* Pterygium patients' NLR levels were compared with those of healthy controls in six studies [12, 16, 17, 19, 22, 35] including 1384 patients and 1238 controls. Compared to healthy individuals, patients with pterygium had significantly higher levels of NLR (SMD =0.14; 95% CI =0.01-0.26, $P < 0.001$) (Figure 5).

*3.7. Idiopathic Epiretinal Membrane and NLR.* In four studies [7, 8, 10, 30], iERM patients' NLR levels were compared with those of healthy controls including 178 patients and 176 controls. Compared to healthy individuals, patients with iERM had significantly higher levels of NLR (SMD =0.14; 95% CI =0.01-0.26, $P < 0.001$) (Figure 6).

*3.8. Glaucoma and NLR.* The association between NLR and glaucoma was investigated in 12 studies [3, 4, 9, 14, 18, 20, 25, 26, 29, 31, 37, 38] including 1568 glaucoma patients and 1737 healthy controls. NLR levels were significantly higher in glaucoma patients compared with controls (SMD =0.56; 95% CI =0.25-0.87, $P < 0.001$) (Figure 7).

In subgroup analysis according to ethnicity, there were four studies including East Asian patients [20, 29, 31, 38], consisting of 1111 patients and 1234 controls, and eight studies including Caucasian patients [3, 4, 9, 14, 18, 25, 26, 37] including 457 patients and 483 controls. The pooled results showed that the NLR levels in Caucasian patients with glaucoma were significantly more than healthy controls (SMD =0.80, 95% CI =022-1.39, $P$ value<0.001). However, the NLR levels of East Asian patients were similar to those of healthy controls (SMD =0.23, 95% CI = -0.15-0.62, $P = 0.03$) (Figure 8).

In the next step, we categorized studies in four groups according to the type of patients' glaucoma and conducted the second subgroup intending to comparing glaucoma patients and healthy controls in each group. There were five studies on primary open-angle glaucoma [3, 4, 14, 25, 29] including 595 patients and 547 controls, six studies on secondary open-angle glaucoma [3, 9, 18, 26, 37, 38] comprising 186 patients and 376 controls, two studies on primary closed angle glaucoma [14, 20] with 793 patients and 870 controls, and one study on secondary closed angle glaucoma [31] with 59 patients and 84 controls. NLR was significantly higher in patients with SOAG (SMD =1.35, 95% CI =0.41-2.28, $P = 0.005$) and significantly lower in patients with SCAG (SMD = -0.58, 95% CI = -0.9 - -0.24,

Table 1: Characteristic of included studies.

| Author | Year | Country | Exclusion criteria based on medication taking history | Patients with eye diseases | | | Healthy controls | | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Number | NLR | | Number | NLR | | |
| | | | | | Mean | SD | | Mean | SD | |
| Keratoconus | | | | | | | | | | |
| Karaca | 2014 | Turkey | Smoking habit, current anti-inflammatory therapies | 54 | 2.59 | 0.89 | 25 | 1.86 | 0.52 | Moderate |
| Katipoglu | 2019 | Turkey | Anti-hyperlipidemic therapy or steroid use, or smoking and alcohol use | 31 | 2.30 | 0.80 | 31 | 1.70 | 0.60 | Low |
| Bozkurt | 2020 | Turkey | ND | 35 | 2.01 | 0.53 | 30 | 1.97 | 0.41 | Moderate |
| Elbeyli | 2021 | Turkey | Anti-hyperlipidemic therapy or steroid use, or smoking and alcohol use, current anti-inflammatory therapies | 42 | 2.50 | 0.80 | 42 | 1.70 | 0.30 | Low |
| Oltutu | 2021 | Turkey | Smoker, and alcohol abuse, any medication that could affect blood parameters | 43 | 2.30 | 0.87 | 43 | 1.77 | 0.61 | Critical |
| Reyhan | 2021 | Turkey | Currently receiving anti-inflammatory drugs, smoking, and alcohol use | 40 | 2.15 | 1.46 | 40 | 1.81 | 0.72 | Moderate |
| Dry eye disease | | | | | | | | | | |
| Sekeryap | 2016 | Turkey | Smoking, taking anti-inflammatory drugs | 33 | 2.80 | 1.40 | 32 | 1.60 | 0.70 | Low |
| Celic | 2017 | Turkey | Smoking, receiving ocular/systemic drug | 78 | 1.84 | 0.50 | 60 | 2.60 | 1.20 | Moderate |
| Ozcan | 2020 | Turkey | Smoking, systemic or ocular medications including topical steroids (the previous use during at least 3 months) and anti-inflammatory medications, that could affect the ocular surface of the eye and blood parameters | 47 | 2.26 | 0.55 | 47 | 1.81 | 0.55 | Moderate |
| Meng | 2021 | China | Receiving hormone medication and systemic or tropical immunosuppressant during three months | 104 | 2.59 | 1.25 | 97 | 2.20 | 1.24 | Moderate |
| Pterygium | | | | | | | | | | |
| Akcam | 2019 | Turkey | Receiving topical/systemic drug, cigarette/alcohol using | 30 | 1.86 | 0.38 | 31 | 1.76 | 0.54 | Moderate |
| Atilgan | 2019 | Turkey | Steroid use | 200 | 2.10 | 0.89 | 200 | 2.05 | 0.80 | Low |
| Gokmen | 2019 | Turkey | Smoking, using steroid, or oral contraceptive drugs | 111 | 2.53 | 2.27 | 106 | 2.04 | 1.03 | Low |
| Kilic 1 | 2019 | Turkey | Receiving antioxidant or anti-inflammatory medications or any topical or systemic drugs | 71 | 1.90 | 0.59 | 46 | 1.73 | 0.67 | Moderate |
| Kurtul2 | 2019 | Turkey | Receiving immunosuppressive treatment | 61 | 1.85 | 0.82 | 55 | 2.72 | 0.79 | Low |
| Kilic 2 | 2020 | Turkey | Past systemic medical therapy, smoking | 35 | 2.72 | 3.61 | 30 | 1.81 | 3.97 | Low |
| Idiopathic epiretinal membrane | | | | | | | | | | |
| Dilkaya | 2017 | Turkey | Any special drug use (e.g., corticosteroids iron preparations, vitamins, and chemotherapeutic agents) | 43 | 3.03 | 1.20 | 46 | 1.77 | 0.70 | Moderate |
| Cubuk | 2020 | Turkey | Any drug use | 42 | 2.85 | 0.72 | 40 | 2.18 | 0.71 | Moderate |

Table 1: Continued.

| Author | Year | Country | Exclusion criteria based on medication taking history | Patients with eye diseases | | | Healthy controls | | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Number | NLR | | Number | NLR | | |
| | | | | | Mean | SD | | Mean | SD | |
| Ulza | 2020 | Turkey | A history of systemic drug use | 57 | 2.10 | 0.90 | 51 | 1.64 | 0.46 | Low |
| Demir | 2021 | Turkey | Receiving medications affecting whole blood parameters such as corticosteroid and iron and chemotherapeutic | 36 | 2.13 | 0.43 | 39 | 1.63 | 0.28 | Low |
| Glaucoma | | | | | | | | | | |
| Arikan | 2015 | Turkey | ND | 40 | 2.30 | 0.20 | 40 | 1.70 | 0.10 | Low |
| Ozgonul1 | 2015 | Turkey | ND | 29 | 2.45 | 0.82 | 42 | 1.84 | 0.59 | Low |
| Ozgonul2 | 2016 | Turkey | Any special drug use (e.g., corticosteroids, iron preparations, vitamins, and chemotherapeutic agents) | 84 | 2.33 | 0.90 | 80 | 1.98 | 0.73 | Moderate |
| Li | 2017 | China | ND | 771 | 2.85 | 1.94 | 770 | 1.98 | 0.86 | Serious |
| Kurtul 1 | 2018 | Turkey | ND | 14 | 2.19 | 0.78 | 43 | 1.56 | 0.58 | Moderate |
| Atalay | 2019 | Turkey | Smoking | 28 | 1.82 | 0.68 | 27 | 2.21 | 0.84 | Moderate |
| Tang | 2019 | China | Any special drug use (e.g., corticosteroids, iron preparations, vitamins, and chemotherapeutic agents) | 240 | 2.59 | 1.40 | 300 | 2.08 | 1.05 | Moderate |
| Zhang | 2019 | China | ND | 59 | 2.07 | 0.88 | 84 | 2.73 | 1.30 | Low |
| Demirtas | 2021 | Turkey | ND | 22 | 3.82 | 4.28 | 71 | 4.04 | 6.47 | Serious |
| Karahan | 2021 | Turkey | ND | 200 | 5.40 | 9.28 | 100 | 3.00 | 4.91 | Moderate |
| Bashir | 2022 | India | ND | 40 | 2.06 | 0.48 | 80 | 1.49 | 0.67 | Moderate |
| Oh | 2022 | Korea | History of ocular drug use except cataracts | 41 | 1.94 | 0.60 | 100 | 1.70 | 0.56 | Moderate |

NLR: neutrophil to lymphocyte ratio; SD: standard deviation; ND: not declared.

Table 2: The results of the publication bias and heterogeneity tests.

| Outcome | Number of studies | SMD(95% CI) | Heterogeneity | | Publication bias | |
|---|---|---|---|---|---|---|
| | | | $I^2$ statistics | Q test *P* value | Egger's test *P* value | Begg's test *P* value |
| Keratoconus | 6 | 0.69 (0.33-1.05) | 70.6% | 0.004 | 0.65 | 1.00 |
| Dry eye disease | 4 | 0.32 (-0.49-1.13) | 94.6% | <0.001 | 0.30 | 0.30 |
| Pterygium | 6 | 0.14 (0.01-0.26) | 0.0% | 0.727 | 0.75 | 1.00 |
| Idiopathic epiretinal membrane | 4 | 0.14 (0.01-0.26) | 59.3% | 0.061 | 0.01 | 0.08 |
| Glaucoma | 12 | 0.56 (0.25-0.87) | 92% | <0.001 | 0.06 | 0.53 |

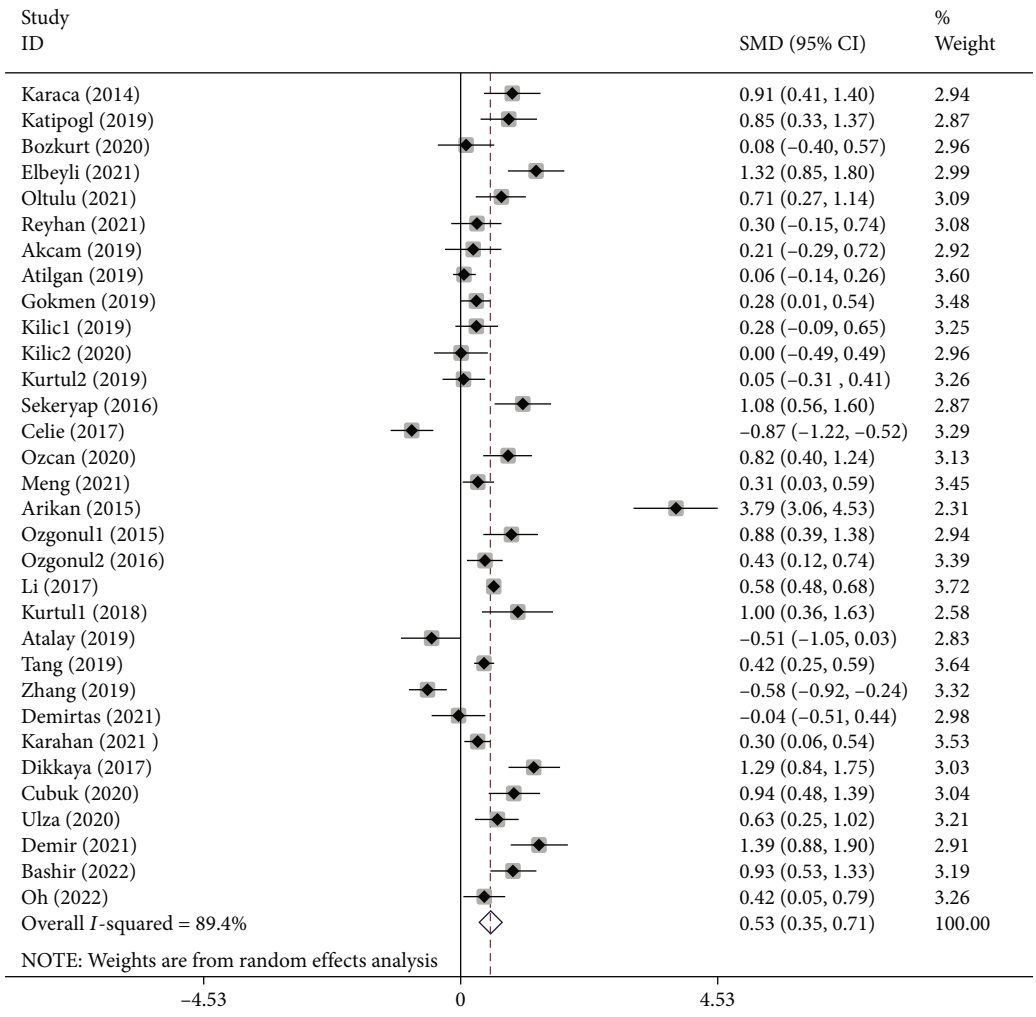


Figure 2: Meta-analysis of differences in NLR levels between patients with eye diseases and healthy controls (*P* value<0.001).

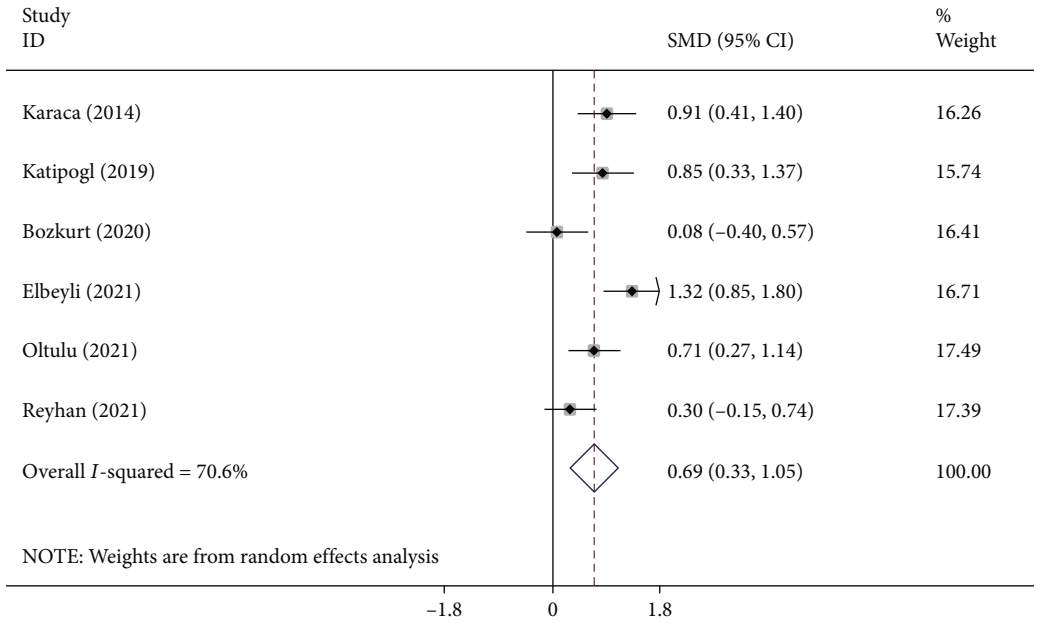


Figure 3: Meta-analysis of differences in NLR levels between KC patients and healthy controls ($P$ value<0.001).

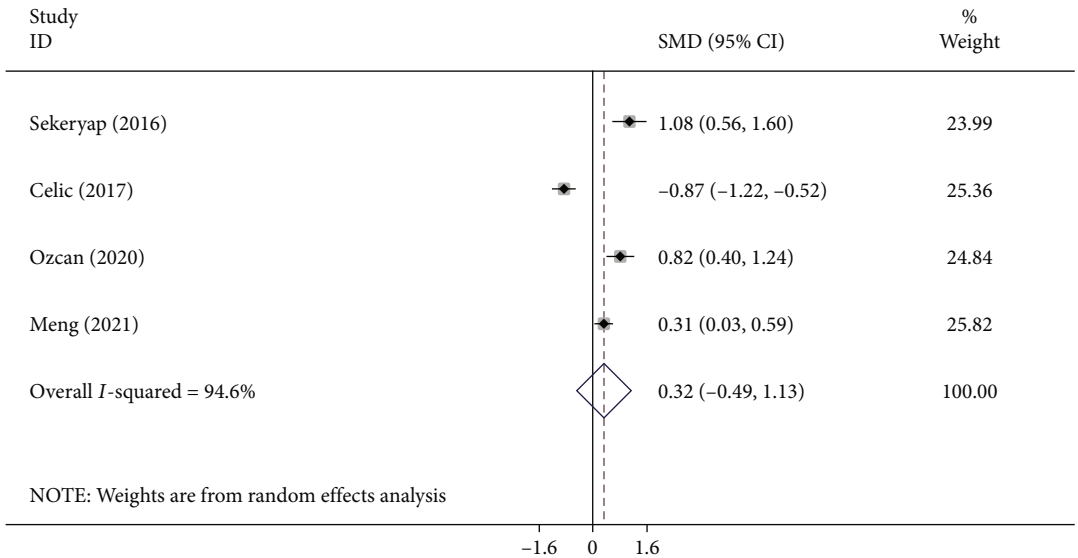


Figure 4: Meta-analysis of differences in NLR levels between DED patients and healthy controls ($P$ value =0.435).

$P = 0.42$), compared to healthy controls. However, when focusing on the differences between patients with POAG and PCAG compared to healthy controls, we found no differences (SMD =0.70, 95% CI = -0.05-1.45, $P = 0.06$ and SMD =0.27, 95% CI = -0.40-0.94, $P = 0.001$, respectively) (Figure 9).

*3.9. Publication Bias.* As presented in Figure 10, the results of studies on difference in NLR levels between patients with eye diseases and healthy controls showed no significant publication bias.

## 4. Discussion

In this systematic review and meta-analysis, we compared NLR between healthy controls and patients with a variety of eye diseases, including keratoconus, glaucoma, pterygium, iERM, and DED, to see if this marker is sensitive enough for the estimation of the severity of systemic inflammation in these patients. We found that except for patients with eye disorders, NLR levels were significantly higher in patients with these disorders than healthy controls, implying the critical role of inflammation in developing these disorders.

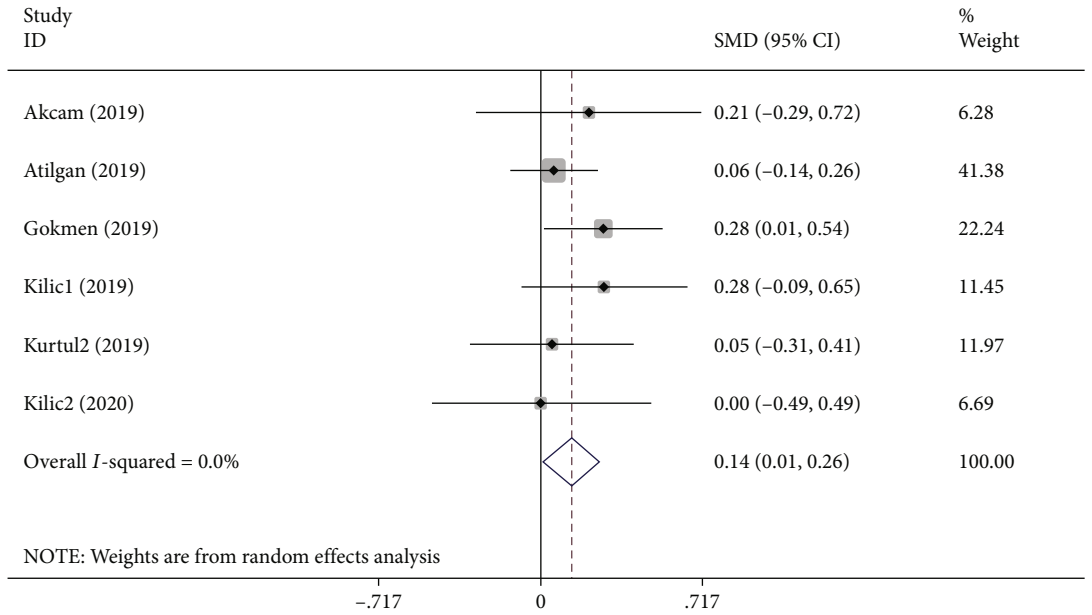


Figure 5: Meta-analysis of differences in NLR levels between pterygium patients and healthy controls ($P$ value =0.033).

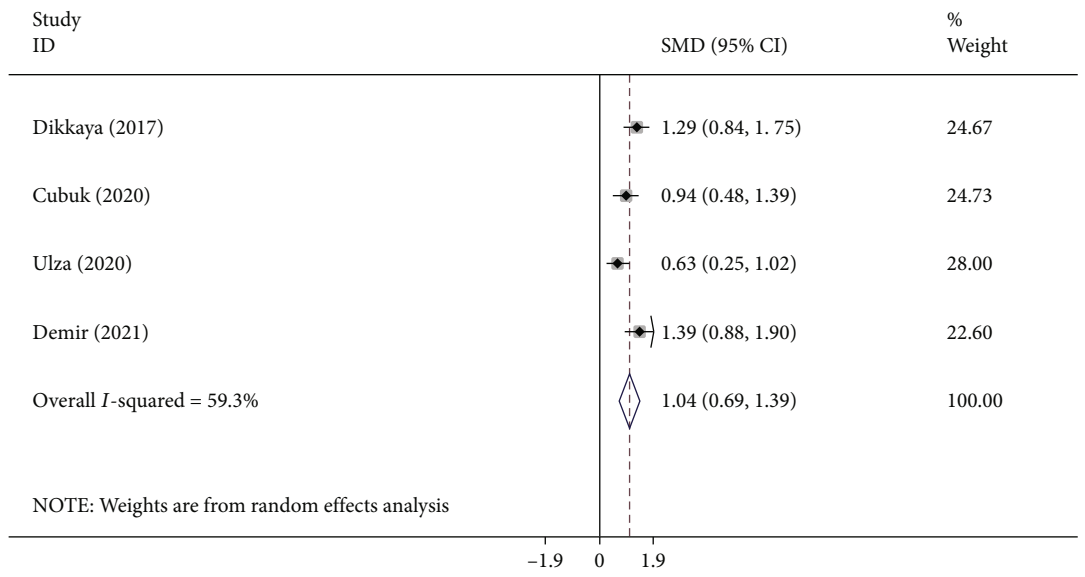


Figure 6: Meta-analysis of differences in NLR levels between iERM patients and healthy controls ($P$ value<0.001).

Neutrophils and lymphocytes are key immune system cellular components. Neutrophils are a type of innate immunity cell that can produce chemokines, cytokines, vascular endothelial growth factor, and matrix metalloproteinase to reinforce the initial line of immune system. Lymphocytes, which are adaptive immunity cells, are also fine controllers of particular immune responses [50]. As neutrophils and lymphocytes can interact with each other, their ratio and sheer numbers have an impact on the immune response's amplitude. Increased neutrophil numbers, in particular, decrease lymphocyte activity [54]. Recently, NLR has emerged as an indicator of systemic inflammation in a variety of disorders including eye diseases, and it has been used as an independent prognostic biomarker in various clinical setting, predicting major mortality, morbidity, and long-term survival [51, 55–58].

NLR was significantly higher in patients with KC compared to healthy controls. According to previous studies, pro-inflammatory cytokines (such as TNF-$\alpha$, IL-6, and matrix metalloproteinase) levels are considerably greater in tear fluid of KC patients [11, 59]. Degradation of the corneal extracellular matrix and alteration of its cellular components may occur as a result of oxidative stress and inflammation [59–62]. There are also further reports that showed immunohistochemically evidence of inflammation in the keratoconic cornea, including leukocyte deposition, macrophage infiltration, and dendritic

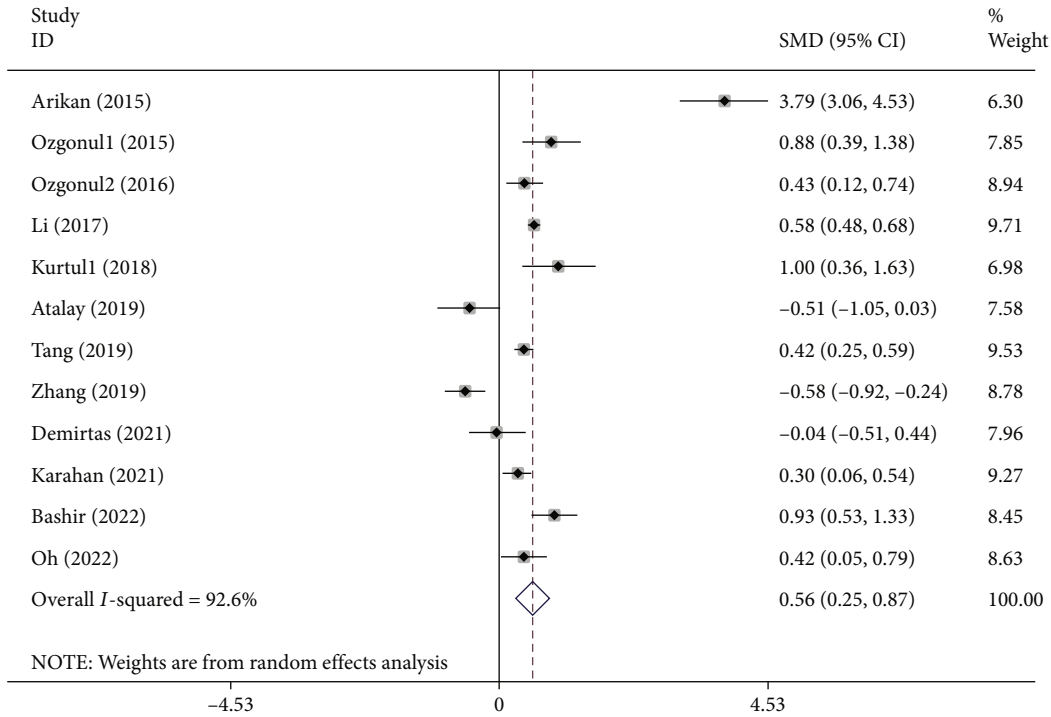


Figure 7: Meta-analysis of differences in NLR levels between glaucoma patients and healthy controls ($P$ value<0.001).

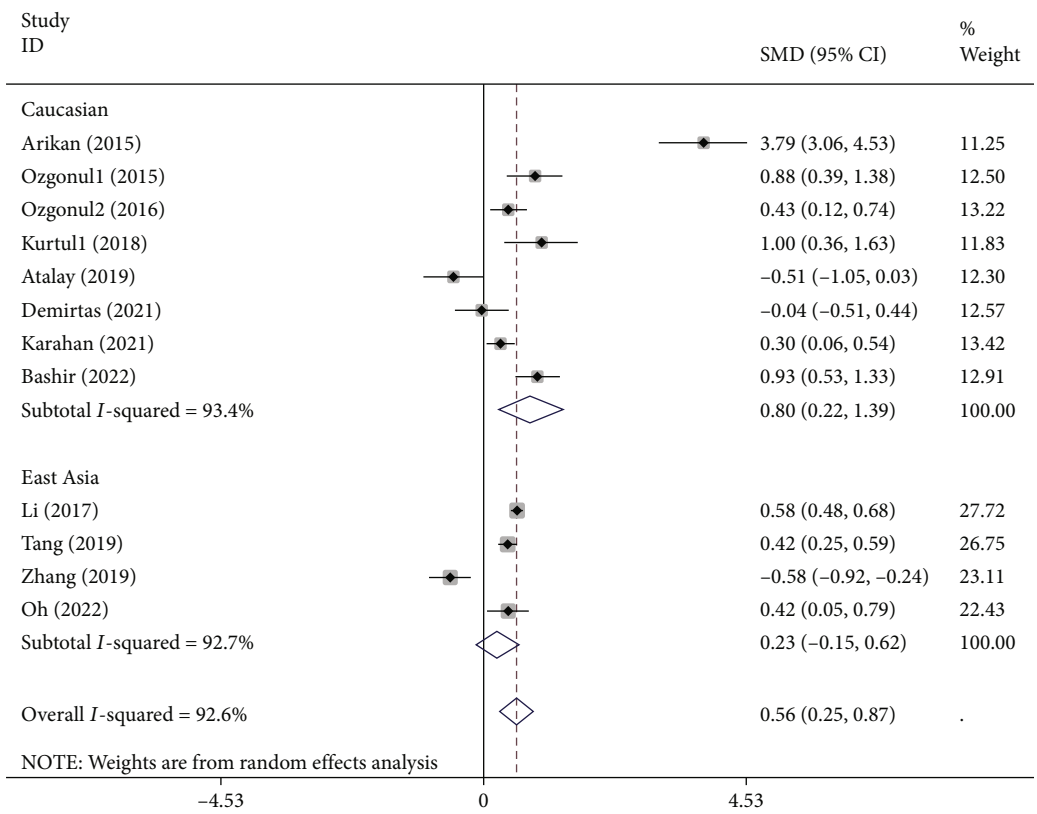


Figure 8: Subgroup analysis of the differences in NLR levels between glaucoma patients and healthy controls according to ethnicity.

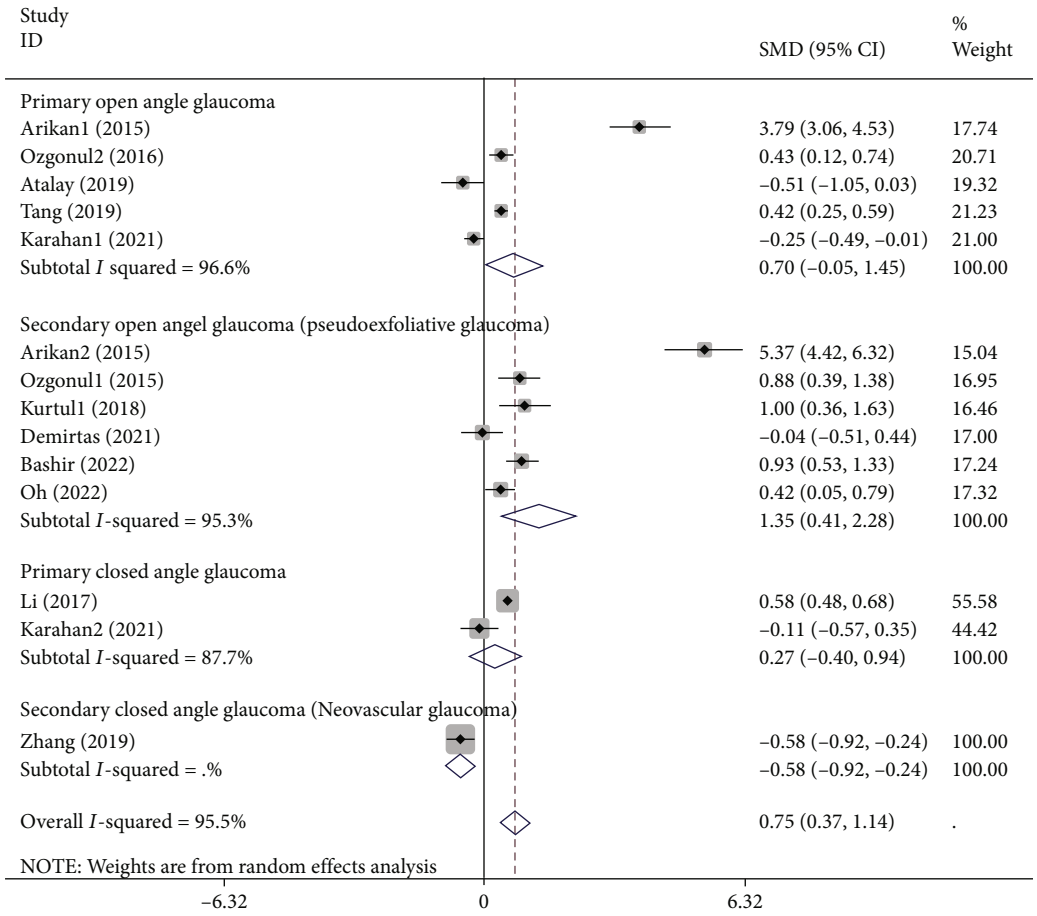


Figure 9: Subgroup analysis of the differences in NLR levels between glaucoma patients and healthy controls according to the glaucoma type.

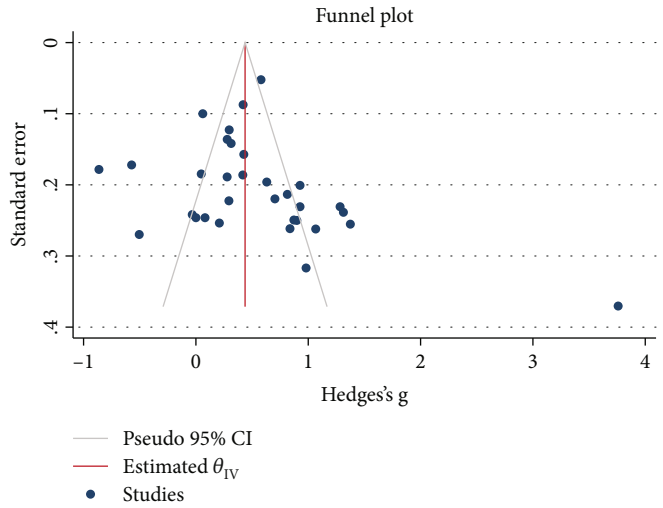


Figure 10: Funnel plot assessing publication bias across studies on NLR level in patients with eye diseases.

Langerhans cell abundance [63]. Loh et al. also investigated the cytokine profile of human keratoconic corneas. They agreed with the past evidence implicating inflammatory activation in KC and suggested that KC could be reclassified as a chronic inflammatory corneal disorder [64]. A meta-analysis by Zhang et al. revealed that tear levels of proinflammatory cytokines including IL-1, IL-6, and TNF-$\alpha$ were elevated in KC patients compared to healthy controls, suggesting that the cytokine profile is definitely altered in these patients and inflammation implicates in the pathophysiology and progression of the disease [65]. Karaca et al. studied the relationship between NLR and KC and found that NLR levels were greater in progressive patients with KC in comparison to nonprogressive patients [13]. In their research, they discovered a significant positive link between NLR and progression of the disease. Apart from NLR, systemic immune-inflammation index (SII) values were found to be considerably higher in the KC group in a study by Elbeyli et al. Furthermore, they observed that SII levels steadily increased in the severe KC subgroup [11].

In the second analysis, we found that NLR was significantly higher in patients with glaucoma compared to healthy controls. In a subgroup analysis according to the study location, NLR was significantly higher in Caucasian patients with glaucoma compared to healthy controls. However, it was not different between East Asian patients and controls. In a subgroup analysis according to the glaucoma type, NLR was significantly higher only in SOAG group compared to healthy controls. Glaucoma is a collection of progressive visual neuropathic disorders that is estimated to be one of the leading causes of permanent blindness globally [66]. While IOP is a well-established and modifiable risk factor, the actual mechanism of both POAG and PCAG is still being debated [66, 67]. Among the underlying molecular mechanisms, autoimmune processes, vascular dysfunction, oxidative stress, and inflammatory responses are the most important ones [14]. As a result, systemic inflammation may play a role in the pathophysiology of glaucoma.

Our results showed that NLR levels in patients with pterygium were higher than healthy controls. Exposure to ultraviolet irradiation and low moisture are the most prevalent recognized predisposing factors for pterygium. Aside from these factors, recent data reveals that local oxidative stress, as well as local inflammatory mediators, has a role in the initiation and growth of pterygial tissue [68, 69]. However, unlike local inflammation, the literature on the systemic inflammatory state of pterygium patients is sparse, and there is no clear agreement on the correlation between NLR and pterygium. These findings suggest that the local inflammatory response, rather than the systemic inflammation, is considerably more active in the pathophysiology of primary pterygium. However, in our meta-analysis, we found a significantly increased NLR in pterygium patients compared to healthy controls, which may imply to the fact that systemic inflammation is also correlated with incidence of pterygium.

In addition, we showed that NLR was not different between DED patients and healthy controls. The lipid layer of the tear film, which regulates the evaporation process, controls the wettability of the ocular surface. Because of the excessive evaporation and unstable lipid layer in DED, the osmolarity of tear fluid rises and therefore the release of proinflammatory cytokines is stimulated by the hyperosmotic tear fluid [70]. So, DED has been linked to increased levels of proinflammatory cytokines such as different interleukins (IL-1, IL-2, IL-6, and IL-8), TNF, transforming growth factor, and matrix metallopeptidase [71, 72]. From the many cellular components of the immune response participating in DED, lymphocytes constitute one crucial component, especially in tear-deficient type. However, in our study, the data did not show any significant difference between patients with DED and healthy controls, which may show that this marker is not sensitive enough for dry eye condition when it is evaluated in larger populations.

In addition, we found that iERM patients had elevated levels of NLR in comparison to healthy controls. In accordance with the present result, previous studies have demonstrated that vitreous of iERM patients had elevated levels of several cytokines such as vascular endothelial growth factor, nerve growth factor, fibroblast growth factor, and compared with that of healthy controls [73]. It seems possible that these results are due to the fact that local and systematic inflammations have an important role in iERM development.

*4.1. Clinical Utility of the Results.* NLR is a measure that is readily obtained on admission from a white blood cell differential and is associated with no additional cost or labor. It shows balance between innate (neutrophil) and the adaptive (lymphocyte) immune system [74]. Recent studies show that NLR can predict eye disorders with relatively high sensitivity and specificity. As evidenced by these results, restoring balance between the innate and adaptive immune system may serve as attractive therapeutic targets; so medications aimed at reducing NLR may be efficacious for treating and even preventing such disorders. Theoretically, reduction in NLR values could be used to measure therapeutic efficacy, reflecting restoration of balance within these systems. Further, our findings support NLR to be a promising biomarker that can be readily integrated into clinical settings to aid in the prediction and prevention of eye disorders. Ultimately, with the development of new biomarkers and therapeutic modalities, we can better prevent and treat eye disorders to decrease long-term morbidity and mortality.

*4.2. Limitations.* The findings of this report are subject to at least four limitations. Small sample size of included studies was the first major limitation. Second, the majority of them were retrospective. Thirdly, the studies did not evaluate these patients' NLR levels obtained from tear, due to limited number of studies. Fourthly, there were a limited number of studies on the role of NLR in DED and iERM. Meanwhile, several questions remain unanswered at present on the association between NLR and many other eye diseases, due to the lack of published

papers on them. So, there is abundant room for further progress in determining this association. In addition, the majority of studies were conducted in China and Turkey; so further work is required to establish this association. Nonetheless, there were three main strengths in the present review. First, the present study, to our best knowledge, serves as the first meta-analysis exploring the correlation between NLR and eye diseases. Second, the studies were included in the final analysis based on clear inclusion and exclusion criteria. Third, our systematic search, in conjunction with a manual review of references from resulting articles without any limitation on language or date, has ensured a thorough and reliable search of literature and serves as a notable strength of this study.

## 5. Conclusion

In summary, it can be said that NLR is a valuable marker of systemic inflammation, which is significantly increased in many eye disorders including KC, glaucoma, pterygium, and iERM, but not DED, suggesting that inflammation plays a key role in the pathophysiology of these disease.

## Abbreviations

NLR: Neutrophil to lymphocyte ratio
PLR: Platelet to lymphocyte ratio
DED: Dry eye disease
iERM: Idiopathic epiretinal membrane
KC: Keratoconus
IOP: Intraocular pressure
IL: Interleukin
TNF-$\alpha$: Tumor necrosis factor-alpha
MOOSE: Meta-Analysis of Observational Studies in Epidemiology
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
NOS: Newcastle-Ottawa scale
POAG: Primary open-angle glaucoma
SOAG: Secondary open-angle glaucoma
PCAG: Primary closed angle glaucoma
SCAG: Secondary closed angle glaucoma
SD: Standard deviation
SII: Systemic immune-inflammation index.

## Data Availability

All data generated or analyzed during this study are included in this published article.

## Conflicts of Interest

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

## Supplementary Materials

supplementary appendix A shows the exact search strategy in all databases, searched in our study. *(Supplementary Materials)*

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