



SURVEY OF LIVER FIBROSIS PREDICTION USING MACHINE LEARNING TECHNIQUES

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Abstract: *The prediction of liver fibrosis stages in Hepatitis B virus (HBV) and Hepatitis C virus (HCV) is an important issue. The gold standard for liver fibrosis stages evaluation is the liver biopsy but with a lot of drawbacks. So, it became necessary to use alternative methods to evaluate the stage of liver fibrosis. Many machine learning techniques were used as non-invasive alternative methods for doing the liver fibrosis prediction task to avoid the disadvantages of the liver biopsy. This study surveys many machine learning techniques that were applied for liver fibrosis prediction and differentiation between the stages of hepatic fibrosis on different medical HBV and HCV datasets using different blood tests and clinical parameters with applying several feature selection techniques. Also, the results and performance of classifier models are reviewed with comparison to non-invasive methods, which used for liver fibrosis prediction, such as FIB-4 index score and APRI score.*

Keywords: *HBV; HCV; machine learning techniques; FIB-4; APRI.*

1. Introduction

Liver is a main center of many physiological processes [1]. Therefore, it must be preserved from diseases or any harm that affects it. Liver diseases can be caused by different ways. One of these ways is the infection by hepatitis B and C viruses. Hepatitis B and C are popular infectious diseases in the world that lead to liver fibrosis, cirrhosis and in some cases to hepatocellular carcinoma [2][3]. Therefore, early and correct evaluation of hepatic fibrosis in patients is a very significant issue to detect the appropriate treatment in early time and get desired results.

The liver biopsy is the reference standard for detection of different liver fibrosis stages, but it has two significant drawbacks: it evaluates only a small liver area, and it is an invasive method [4][5]. Therefore, the noninvasive alternative techniques are important to avoid the drawbacks of liver biopsy.

In recent years, machine learning techniques are applied in many medical fields [6-10]. One of these fields is the prediction of hepatic fibrosis stages. Several models were built to classify the different stages of liver fibrosis using clinical laboratory parameters such as Gamma-Glutamyl Transpeptidase (GGT), Aspartate Aminotransferase (AST), Alanine Transaminase (ALT), Platelet, White Blood Cell (WBC), White Blood Cell (RBC), Cholinesterase (CHE), Total Serum Bilirubin (TBIL), Hemoglobin (HGB), Red Cell Distribution Width (RDW) and Prothrombin Time (PT), Body Mass Index (BMI), Alpha-Fetoprotein (AFP), Creatinine (Cre), International Normalized Ratio (INR), Hepatitis B virus DNA quantitative level (HBV-DNA) and Baseline Histological Staging (BHS). This paper is organized as follows: Section 2 introduces machine learning techniques, section 3 presents feature selection methods, section 4 introduces a review of existing literature, section 5 provides the challenges that were encountered while building the classification models and section 6 presents the conclusion.

2. Machine Learning Classification Techniques

There are many classification models that were built using blood tests clinical parameters to predict the liver fibrosis stages and differentiate between them with different medical dataset [26][27][30- 39]. Examples of these classification models are:

- a. **Decision Tree (DT) [11]:** It constructs classification models in the tree structure form. It divides a dataset into smaller subsets and at the same time an associated decision tree is incrementally developed. The final tree consists of decision nodes and leaf nodes. A decision node has two or more branches. Leaf node presents a decision. It handles both numerical and categorical data. The aim is to create a model that predicts the target variable value based on many input variables.
- b. **Random Forest (RF) [12]:** It is one of an ensemble learning methods for classification that works by constructing a number of decision trees at training. The output is the class selected by most trees. It overcomes the over-fitting of decision tree classifier.
- c. **Gradient Boosting (GB) [13]:** It consists of group of machine learning algorithms that combine many weak learning models together to create a strong predictive model. Decision trees are usually used when doing gradient boosting, which are typically decision trees. It shows a good performance in classifying complex datasets.
- d. **Naïve Bayes (NB) [14]:** It is a probabilistic classifier, which means that it predicts based on the object probability, based on applying Bayes' theorem (the probability of an event occurring given the probability of another event actually occurring).
- e. **Logistic Regression (LR) [15]:** It is a statistical analysis method for prediction a binary

outcome based on previous observations of dataset (probability of a target variable). It predicts a dependent data variable by analyzing the relationship between one or more independent variables.

- f. **k-Nearest Neighbor (kNN) [16]:** k-Nearest Neighbor is a non-parametric supervised learning classifier, which uses a distance between each individual data point and all the example in the data to make classifications or predictions about the grouping of it.
- g. **Support Vector Machine (SVM) [17]:** Support Vector Machine depends on creating the best line or decision boundary that can separate n-dimensional space into classes. There are two kinds of SVM, linear (can be categorized by using straight line to separate data) and non-linear (cannot be classified by using straight line to separate data).
- h. **Neural Network (NN) [18]:** Neural Network, also known as Artificial Neural Network (ANN), is a machine learning process type that called deep learning that uses interconnected nodes in a layered structure to model the relationships between input and output data. It contains three different type layers (input layer, hidden layers and output layer).

3. Feature Selection Methods

There are different feature selection methods that were applied to reduce the dimensionality of datasets. Examples of these methods are:

- a. **Genetic Search-Based Strategy [19]:** It depends on the Genetic Algorithm (GA) that uses the principles of evolution such as reproduction, selection, crossover and mutation to determine the optimal set of features.
- b. **Correlation-Based Feature Selection (CFS) [20]:** It evaluates the worth of a subset of attributes by considering the individual predictive ability of each feature along with the degree of redundancy between them.
- c. **Information Gain Attribute Evaluation [21]:** It evaluates the worth of an attribute according to the information gain of each attribute.
- d. **Gain Ratio Attribute Evaluation [21]:** It evaluates the worth of an attribute according to gain ratio of each attribute.
- e. **SVM [21]:** SVM is used to evaluate the worth of an attribute. Attributes are ranked according to the square value of the weight assigned by the SVM.
- f. **Genetic Wrapper [22]:** It is used to evaluate attribute sets with using cross-validation to estimate the learning scheme accuracy for a set of attributes.
- g. **Single Accuracy [23]:** It uses ten Cross-validation using IBK (Instance Based learning with parameter K) classifier to evaluate a worth of an attribute and evaluates classification overall accuracy based on a single attribute.
- h. **Relief Feature Scoring [24]:** It is a filter-method approach for feature selection. It is based on the feature value identification differences between nearest neighbor instance pairs.

4. Literature Review

There are a lot of researches in the field of predicting the liver fibrosis degree and differentiation between them. Sections 4.1 and 4.2 review researches for predicting of liver fibrosis stage using HBV and HCV datasets, respectively. The datasets, classification models and results were achieved were summarized in both Table (1) and Table (2) for HBV and HCV, respectively.

4.1. Prediction of liver fibrosis stage in HBV dataset:

Danan Wang et al. [26] collected HBV dataset that contained 455 patients (329 without significant fibrosis and 126 with significant fibrosis) from China. They constructed three layers of Neural Network (Bayesian learning) based on numerous routine and serum markers (Age, GGT, AST, ALT, Platelet, WBC, RBC, CHE and TBIL) for predicting the significant hepatic fibrosis stage. The AUROC were 0.883 in training set (226 patients), 0.884 in validation set (113 patients) and 0.920 in testing set (116 patients).

Yuan Cao et al. [27] collected a total of 239 subjects, containing 124 liver cirrhosis patients with CHB and 115 non-liver cirrhosis patients with CHB from China. The Genetic Search-based strategy in WEKA was used as feature selection method to decrease the parameter numbers. A multilayer perceptron (MLP) classifier to differentiate between non-liver cirrhosis (non-LC) and liver cirrhosis (LC) cohort was built using seven parameters (age, AST, ALT, PLT, HGB, RDW and PT) on training set (120 patients) with accuracy of 82.2%, sensitivity of 80.6% and AUROC of 0.9. Then, the performance of the classifier was evaluated by testing set (119 patients) and the results were accuracy (87.4%), sensitivity (85.5%) and AUROC (0.942). By comparing their classifier with two widely used noninvasive methods, which are FIB-4 (scoring system uses a combination of patient age, platelet count, AST and ALT for the liver fibrosis assessment) [28] and ARBI (scoring system is based on the amount of AST and platelets in body for liver fibrosis assessment) [29], it achieved better results.

Runmin Wei et al. [30] collected a dataset included a total of 490 HBV infected subjects from China (discovery dataset), which divided into training set (70%) and testing set (30%). Three classification models (random forest (RF), decision tree (DT), and gradient boosting (GB)) were constructed using four clinical parameters (age, AST, ALT and Platelet counts) of FIB-4 index score to predict the advanced liver fibrosis stages (distinguishing between (F0 – F2) and (F3, F4)) and liver cirrhosis (distinguishing between (F0 – F3) and (F4)). Gradient boosting model was achieved the best AUROC result, then it was compared with FIB-4 index using discovery dataset and validation dataset (contained 86 HBV infected subjects) For differentiation between early and advanced liver fibrosis, AUROC of GB model was 0.918, while FIB-4 was 0.841, and for differentiation between non-cirrhosis and cirrhosis, GB model achieved AUROC of 0.871, while FIB-4 was 0.830. The GB classifier was rebuilt using six parameters by adding albumin and GGT to previous four parameters, and showed similar results. The GB model (using four parameters) and FIB-4 were applied on two HCV validation datasets. The GB model and FIB-4 in first HCV cohorts achieved AUROC of 0.797 and 0.816, respectively, and in second HCV cohorts achieved AUROC of 0.849 and 0.795, respectively.

NAIPING LI et al. [31] collected 920 cases with chronic HBV infection from China (262 cases

with no fibrosis and portal fibrosis without septa (S0, S1), 285 cases with portal fibrosis with few septa (S2), 186 cases with numerous septa (S3), 187 cases with cirrhosis (S4)), with 24 parameters. Four machine learning classification techniques (Decision Tree Classifier, Logistic Regression Classifier, Random Forest Classifier and Support Vector Classifier), with different combination of 24 parameters, were used for assessment of hepatic fibrosis severity ($\geq S2$, $\geq S3$ and S4). The dataset divided into training set (50%) and testing set (50%). The results showed that the Random Forest based classifier using nine parameters (ALT, Age, GGT, AST, WBC, Cre, lymphocyte, Platelet and INR) achieved the best performance in assessment the severity of liver fibrosis (especially for stages of $\geq S2$ and $\geq S3$) and better than other existing 19 models.

Eslam Sharshar et al. [32] collected 235 patients dataset with hepatitis B from Egypt with parameters (age, sex, AST, ALT, TLC, platelet and PCR), which divided into 80% training set and 20% testing set. Two feature selection techniques were implemented in WEKA, which were Gain Ratio and Information Gain Attribute Evaluation. For differentiation between the moderate stage (F0-F2) (166 patients) and advanced stage of fibrosis (F3 and F4) (69 patients), three machine learning techniques (Logistic Regression (LR), Random Forest (RF) and Vote classifier (combination between LR and RF)) were implemented to construct classifier models using all seven parameters and only four parameters. The best two models were LR with seven parameters which achieved accuracy of 93.61% and AUROC of 0.991, and LR with four parameters which achieved accuracy of 95.74% and AUROC of 0.971, which were better than FIB-4 score. For differentiation between non-cirrhosis (F0-F3) (197 patients) and cirrhosis (F4) (38 patients) of liver, for dealing with imbalanced dataset, the Cost Sensitive classifier with different penalty values (2,3 and 5) and two machine learning techniques (LR and RF) were implemented to construct classifier models using all seven parameters and only three parameters. The best classifier model was the Cost Sensitive Classifier model with LR and seven parameters using penalty value (2) which achieved accuracy of 91.49% and AUROC of 0.936, which were better than FIB-4 score.

4.2. Prediction of liver fibrosis degree in HCV dataset:

Somaya Hashem et al. [33] collected 39,567 patients dataset with chronic hepatitis C from Egypt (classified as mild to moderate fibrosis stages (F0 – F2) or advanced fibrosis stages (F3 – F4)). Two models of Alternative Decision Tree (merges a number of weak hypotheses to induce a boosted one) were constructed on training set (22,690 patients). First model was constructed using six variables which showed highest statistically significant relationship and accepted correlation with fibrosis (age, AST, BMI, AFP, albumin and platelets count). Second model was constructed using four variables (age, AST, AFP and platelet count). These features were similar to FIB-4 index features except AFP instead of ALT, and then the two models were evaluated on testing set (16,877 patients). Model number two showed highest accuracy of 85.7% in training set and 84.8% in testing set, and achieved ROC area of 0.78 in both training and testing set. It also achieved highest negative predictive value of 87.3% in training set and 86.2% in testing set, which is better than FIB-4

Tomasz Orczyk et al. [34] collected records of 290 patients infected with a hepatitis C with 26 features. The dataset was divided into three classes low (F0-F1) (129 patients), medium (F2-F3) (102

patients) and high advancement of the liver fibrosis (F4) (59 patients). Seven feature selection algorithms were implemented (Single-Separate using IBK classifier (14 features), Single-Accuracy using IBK classifier (14 features), CFS (7 features), SVM (10 features), Genetic Wrapper using IBK algorithm (9 features), Genetic Wrapper using C4.5 algorithm (9 features) and ReliefF (10 features)). Five popular classification algorithms have been tested (J48 decision tree classifier, IBk k-nearest neighbors classifier, Random Forest classifier, OneR classifier (One Rule) and Decision-Table classifier) using features taken out from each feature selection method and also using all features in dataset. The best three classifiers (the accuracy near to 70 %) were: J48 with using CFS feature selection, Random Forest with using ReliefF feature selection and IBk with using Single-Separate feature selection method in differentiate between the three hepatic fibrosis classes.

Somaya Hashem et al. [35] collected 39,567 patients dataset with chronic hepatitis C from Egypt (33549 patients have mild to moderate fibrosis stage (F0 – F2), and 6018 patients have advanced fibrosis stage (F3 – F4)). Feature selection method was used (P-value and Pearson correlation coefficients) to remove the redundant features. Four machine learning approaches were developed (Particle swarm optimization (PSO), Alternative decision tree (ADT), multi-linear regression (MReg) and genetic algorithm (GA)) for predicting of advanced hepatic fibrosis using four features (age, AST, platelets count and albumin) that showed significant relationship with fibrosis stages. By comparing the different models, ADT model achieved best result on accuracy (84.4%) and AUROC (0.76).

Mahzabeen Emu et al. [36] used a dataset consisted of 1385 patients infected with the Hepatitis C Virus from Egypt. Three machine learning methods (Random Forest, Multilayer Perceptron (MLP) and Logistic Regression) were developed to predict the degree of liver fibrosis using the reduced feature set after implementing of feature selection method and full feature set. For the validation process, the 5-fold cross-validation was used and the best classifier was MLP with full features (accuracy of 97.831%). And also, the Decision tree classifier was built to generate rules for prediction of staging of liver fibrosis, and 28 rules were produced with accuracy of 97.45%. The results also point out that ALT enzyme parameter is more significant for Portal Fibrosis (F1) and Few Septa (F2) stages, and AST enzyme parameter is more significant for the stages of Many Septa (F3) and Cirrhosis (F4).

Taher M. Ghazal et al. [37] used previously available dataset contained 1385 patients infected with the hepatitis C virus with 29 features from Egypt to build machine learning model for prediction of advanced fibrosis stage, which called (Hep-Pred). Gaussian support vector machine (SVM) algorithm was used to construct the prediction model after applying feature selection technique to reduce the parameters number. The model achieved 97.9% accurate result with 5 cross-validation, that was better than accuracy of other models (Decision Tree model) of other researchers' work (achieved accuracy of 84.8%).

Table (1): Prediction of liver fibrosis Stage using HBV patients’ dataset.

Authors	Year	Dataset	Classifier	Results
Eslam Sharshar et al. [32]	2022	235 HBV patients (Egypt)	<ul style="list-style-type: none"> - Logistic Regression (LR). - Random Forest (RF). - Vote classifier (combination of LR and RF). - Cost Sensitive classifier with logistic regression using three penalty values. - Cost Sensitive classifier with random forest using three penalty values. 	<ul style="list-style-type: none"> - For prediction of hepatic fibrosis: the Logistic regression classifier model achieved the best performance with both seven and four parameters, and better results than FIB-4. - For prediction of hepatic cirrhosis: the Cost Sensitive Classifier (with LR) using penalty (2) achieved the best performance with seven parameters, and better results than FIB-4
NAIPING LI et al. [31]	2019	920 HBV patients (China)	<ul style="list-style-type: none"> - Decision Tree. - Logistic Regression. - Random Forest. - Support Vector Machine. 	<ul style="list-style-type: none"> - The Random Forest with nine parameters achieved the best results and better than other existing 19 models.
Runmin Wei et al. [30]	2018	490 HBV patients (China) / HCV patients (validation set)	<ul style="list-style-type: none"> - Decision Tree (DT). - Random Forest (RF). - Gradient Boosting (GB). 	<ul style="list-style-type: none"> - GB model achieved the best results. - GB model was better than FIB-4.
Yuan Cao et al. [27]	2013	239 HBV patients (China)	<ul style="list-style-type: none"> - A Multilayer Perceptron (MLP). 	<ul style="list-style-type: none"> - An MLP model achieved accuracy of 87.4% and AUROC of 0.942. -MLP showed better result than FIB-4 and APRI.
Danan Wang et al. [26]	2010	455 HBV patients (China)	<ul style="list-style-type: none"> - Three layers of Neural Network (Bayesian learning). 	<ul style="list-style-type: none"> - AUROC were: 0.883(in training set) 0.884 (in validation set) 0.920 (in testing set)

Table (2): Prediction of liver fibrosis Stage using HCV patients’ dataset.

Authors	Year	Dataset	Classifier	Results
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Michael Onyema Edeh et al. [39]	2022	HCV patients (UCI Machine Learning Repository)	<ul style="list-style-type: none"> - Multi-layer perceptron (MLP). - Bayesian network. - Quest Decision Tree. <p>- Ensemble Learning model was built by mixing the three models (MLP, Bayesian network and Quest).</p>	- The Ensemble Learning model achieved the best accuracy (95.59%).
Aravind Akella et al. [38]	2021	1385 HCV patients (Egypt)	<ul style="list-style-type: none"> - Naïve Bayes. - Logistic Regression. - Extreme Gradient Boosting. - Ensemble Method. - Decision Tree. - Random Forest. - k-Nearest Neighbor. - Support Vector Machine. - Neural Networks. 	- Extreme Gradient Boosting (XGB) achieved the best results (accuracy of 0.81) and (AUROC of 0.84). Also, the results of this model were better than other eight laboratory tests.
Taher M. Ghazal et al. [37]	2021	1385 HCV patients (Egypt)	-Gaussian support vector machine (SVM).	- Accuracy was 97.9%.
Mahzabeen Emu et al. [36]	2020	1385 HCV patients (Egypt)	<ul style="list-style-type: none"> - Random Forest. - Multilayer Perceptron (MLP). - Logistic Regression. <p>- Decision tree classifier was built to generate rules.</p>	<ul style="list-style-type: none"> - MLP with full features achieved the best results (accuracy of 97.831%). - Decision Tree model generated 28 rules were produced with accuracy of 97.45%.
Somaya Hashem et al. [35]	2017	39,567 HCV patients (Egypt)	<ul style="list-style-type: none"> - Particle swarm optimization (PSO). - Alternative decision tree (ADT). - Multi-linear regression (MReg). - Genetic algorithm (GA). 	- ADT model achieved the best results (Accuracy (84.4%) and AUROC (0.76)).
Tomasz Orczyk et al. [34]	2016	290 HCV patients	<ul style="list-style-type: none"> - J48 decision tree. - IBk (k-nearest neighbors). - Random Forest. - OneR (One Rule). - Decision-Table. 	- The best three classifiers were: J48 with using CFS. Random Forest with using ReliefF. IBk with using Single-Separate (the accuracy near to 70 %).
Somaya Hashem et al. [33]	2016	39,567 HCV patients (Egypt)	- Two Alternative Decision Tree models.	- Alternative Decision Tree using four parameters achieved best results (accuracy of 84.8% and ROC area of 0.78), which also is better than FIB-4.

Aravind Akella et al. [38] used available dataset contained 1385 patients infected with the hepatitis C virus from Egypt (336 patients (F1), 332 patients (F2), 355 patients (F4) and 362 patients (F4)). Nine Machine Learning algorithms (Naïve Bayes, Logistic Regression, Extreme Gradient Boosting, Ensemble Method, Decision Tree, Random Forest, k-Nearest Neighbor, Support Vector Machine and Neural Networks) were applied on three experiments using only six features (age, BMI, platelet count, AST, ALT, and BHS). In first experiment, the classifier models were built to distinguish between non-significant fibrosis stage that contained (F1) and the significant fibrosis stage that contained (F2, F3 and F4). But in second experiment, the classifier models were built to distinguish between non-significant fibrosis stage that contained (F1) and the significant fibrosis stage that contained (F3 and F4), and In third experiment, the classifier models were constructed to differentiate between non-significant fibrosis stage that contained (F1) and the significant fibrosis stage that contained only (F4). Due to class imbalance in first and second experiments, the oversample technique was used by randomly duplicating the minority class. The performance of all models was evaluated and the best model was Extreme Gradient Boosting (XGB) in first experiment, which achieved accuracy of 0.81 and AUROC of 0.84. Also, the results of this model were better than other eight laboratory tests.

Michael Onyema Edeh et al. [39] collected data from UCI Machine Learning Repository of patients suffering from Hepatitis C. Three machine learning models were built to predict the advanced liver fibrosis. These models were Multi-layer perceptron (MLP), the Bayesian network and Quest Decision Tree, and their accuracy results were 94.10%, 94.47% and 94.63% respectively. Then, the proposed Ensemble Learning model was built by mixing the three models (MLP, Bayesian network and Quest) to improve the performance and obtain more accurate prediction, and the accuracy became 95.59%.

5. Challenges

There are many challenges when applying machine learning techniques and data mining on medical datasets, and this applies on the liver fibrosis disease. The followings are some of the challenges:

- Data always needs updates as new symptoms and new blood tests emerge.
- It is a difficult task to collect data of patients from hospitals and liver institutes, due to widerange of data sources and the lack of clarity some of them.
- Inconsistent data representation due to problems or errors in the entry of data.
- Missing and incomplete data is one of the main problems in medical dataset and dealing with this issue is very important.
- The amount of data that is used to build the classifier model is very small. Therefore, it is difficult to generalize a specific classifier model to all datasets for all patients around the world.

6. Conclusion

In this study, several machine learning techniques for the prediction of the hepatic fibrosis stages and differentiating between them have been surveyed such as Random Forest (RF), Decision Tree (DT), Gradient Boosting (GB), Naïve Bayes (NB), Logistic Regression (LR), k-Nearest Neighbor (KNN), Support Vector Machine (SVM) and Neural Networks. All classification models were constructed using different clinical parameters, blood tests and different datasets (HCV and HBV patients) from different regions. Also, different feature selection methods were used to reduce the parameter numbers and for dimensionality reduction. Many classification models achieved good results in the hepatic fibrosis stages, and showed better performance than another non-invasive methods as FIB-4 and ARBI score.

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