Applied Medical Informatics
Original Research Vol. 46, No. 4 /2024, pp: -

Machine Learning-Based Classification and Statistical Analysis of Liver Cancer: A Comprehensive Study of Model Performance and Clinical Significance

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Received: 16 August 2024/Accepted: 26 November 2024 / Published online: 10 December 2024

Abstract

Background: The liver is an internal organ located in the upper right section of the abdomen, just beneath the diaphragm, and near the stomach. It performs numerous functions that are essential for metabolism, digestion, detoxification, and nutrient storage. Several types of liver cancers are known, with the most common being hepatocellular carcinoma (HCC), which is the main type of liver cell called hepatocytes. Another less common typeis cholangiocarcinoma, which originates in the bile ducts the liver. This study aimed to evaluate and compare machine-learning-based models for the early detection of liver cancer to improve diagnostic accuracy. *Method*: In this study, various models, such as SVM, decision tree, random forest, logistic regression, K-neighbor, Gaussian NB, AdaBoost classifier, MLP classifier, passive aggressive, ridge classifier, extra tree, bagging classifier, extra trees, gradient boosting, SGD classifier, linear SVC, voting classifier, and stacking classifier were used. Five performance metrics (accuracy, precision, recall, F1 score, and Cohen's kappa) were used to evaluate the performance of the proposed methods. Results: The dataset comprised 12 instances, and across all the models tested, we utilized the extra tree classifier for the early detection of liver cancer, achieving a notable accuracy of 85.8%. The model demonstrated a precision of 75.5%, while it achieved a high recall of 92.2%, and the F1 score of 83.2% underscored its robust performance, suggesting significant potential for enhancing diagnostic accuracy and necessitating further investigation. These performance metrics highlight the potential of the extra tree classifier to improve early detection strategies for liver cancer. *Conclusion*: After performing the complete process, we conclude that the extra tree classifier out of 17 models is the most suitable machine learning algorithm for liver cancer prediction.

Keywords: Hepatocellular Carcinoma (HCC); Machine Learning (ML); Multilayer Perceptron (MLP); Stochastic Gradient Descent (SGD); Area Under Receiver Operating Characteristic Curve (AUROC); Shapley Additive exPlanations (SHAPs)

Introduction

Liver cancer is a common malignant tumor of the digestive system. According to the 2018 World Cancer Report, there are approximately 18 million new cases of liver cancer and 9.6 million deaths, with these numbers continuing to rise becomes to 19.9 million fresh new cases and 9.7 million deaths by 2022 [1]. Hepatocellular carcinoma (HCC), the main type of liver cancer, is the leading cause of cancer-related

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deaths worldwide [2]. The prognosis of patients with HCC is strongly related to the clinical tumor stage, which is essential for guiding clinical treatment. Despite advancements in diagnosis and treatment, liver cancer is associated with a high mortality rate, which will increase by 77% by 2050 with limited therapeutic options, particularly in the advanced stages, making it challenging for clinicians [1, 3, 4]. Addressing challenges such as late-stage diagnosis, treatment resistance, and recurrence necessitates continued research into innovative therapeutic strategies, early detection methods, and personalized medicine approaches [5]. Therefore, improving the accuracy of clinical HCC staging will help to determine a patient's tumor status, establish treatment, and further improve patient prognosis.

Clinical studies have also shown that incorporating more variables can improve staging accuracy [6]. In this study, we propose a new liver cancer staging and detection model based on various numbers of forefront ML models and clustering of functional embeddings. The aim of developing and evaluating a machine learning-based model for the early detection of liver cancer is multifaceted, and focuses on improving diagnostic accuracy, personalizing treatment, optimizing healthcare resources, and ultimately enhancing patient outcomes. As technology advances, the integration of machine learning into clinical practice holds promise for the transformation of liver cancer diagnosis and management.

Materials and Methods

Database

This study extracted a comprehensive dataset of liver cancer data from the GitHub. The liver dataset has 10 feature parameters, including patient demographics (age and sex) and different blood tests (total bilirubin count, direct bilirubin count, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein counts, albumin, albumin, and globulin ratio), and the end parameter was categorized with binary classification, that is, 0: immortal rate and 1: mortality rate. The dataset contains a total of 584 case instances in which both male and female cases reside together (Table 1). The dataset was retrieved from a source on 9th of March of 2024 (https://github.com/shinjinighosh/liver-cancer-pred/blob/master/datasets_2607_4342_indian_liver_patient_labelled.csv). Using the train_test split methodimported from the sklearn library, we split the data into an 80:20 ratio to implement the ML models.

Table 1. Liver cancer dataset with complete feature descriptions

Features	No. of features	Mean	Standard deviation	Min	Max	Description
Id	5			1	583	-
Age	72	44.74	16.18	4	90	A chronological number based on the number of months or years since a person's birth.
Sex	2			0	1	Male (0) or Female (1)
Total Bilirubin (mg/dL)	113	3.29	6.20	0.4	75	A combination of direct and indirect bilirubin.
Direct Bilirubin (mg/dL)	80	1.4	2.80	0.1	19.7	The form of bilirubin which has been conjugated with glucuronic acid and is excreted in the bile.
Alkaline Phosphatase (U/ml)	263	290.57	242.93	63	2110	A group of isoenzymes located on the outer layer of the cell membrane.
Alanine Aminotransfe	152	80.71	182.62	10	2000	An important enzyme in the intermediary metabolism of glucose and protein catalyzing

rase (U/L)						the reversible transamination between alanine and 2-oxoglutarate to form pyruvate and glutamate.
Aspartate Aminotransfe rase (mU/mL)	177	109.91	288.91	10	4929	An enzyme that is found mostly in the liver, also in muscles and other organs of body.
Total proteins (g/dL)	58	6.48	1.08	2.7	9.6	It measures the amount of proteins in your blood. It provides clinical information about a person.
Albumin (g/dl)	40	3.14	0.79	0.9	5.5	A protein made by the liver. Regulating osmotic pressure and facilitating the binding and transport of substances such as hormones and drugs in the blood.
Albumin and Globulin Ratio (g/dl)	70	0.94	0.32	0	2.8	The normal range for albumin/globulin ratio is over 1, usually approximately 1 to 2.
Cancer	2			1	2	Inactive: 0, Active: 1

Importance of Dataset Features

In Figure 1, the Python library panda using the corr() method to draw the Pearson correlation heatmap on the given data represents the relationships between various liver functions, such as test results, and the presence or absence of a particular disease. For example, the correlation coefficient between direct bilirubin and total bilirubin was 0.87, indicating a strong positive correlation, as direct bilirubin was most likely associated with total bilirubin count. Similarly, alanine aminotransferase and aspartate aminotransferase levels had the second-best strong positive correlation (0.79). The correlation coefficient between the serum ALB concentration and total protein concentration was 0.78, indicating a strong positive correlation. These parameters were statistically significant, indicating a strong correlation between them. The features of age and ALB concentration had a strong negative correlation (i.e., -0.27. This means that older age is associated with a lower likelihood of albumin levels.

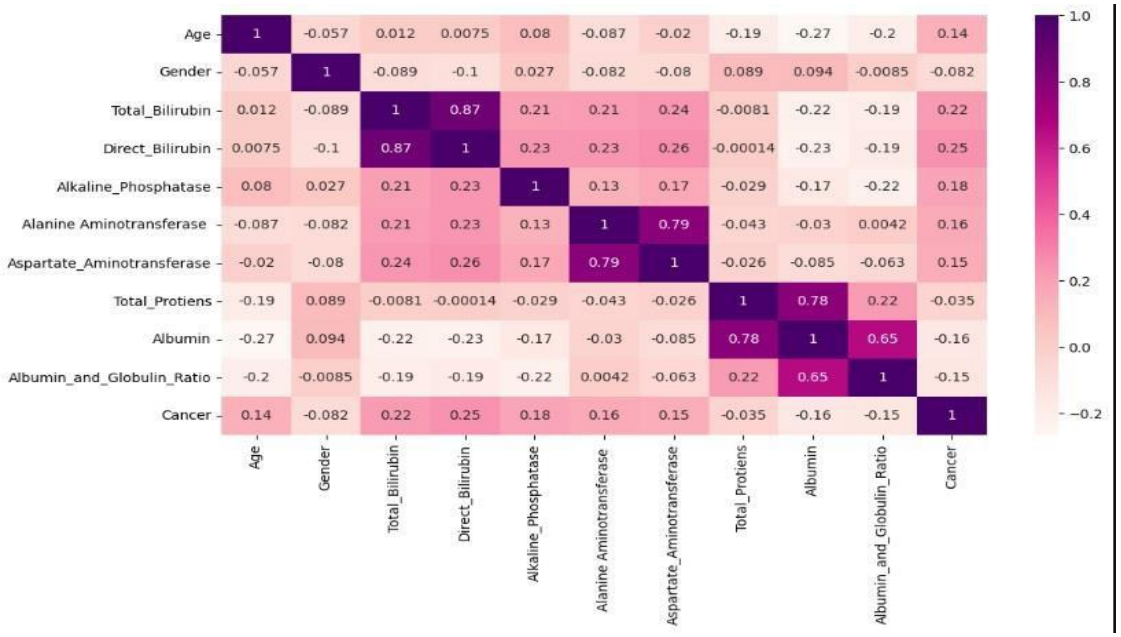

Figure 1. Heatmap showing the correlation between the dataset features

In Figure 2 (a), a Beeswarm plot consists of individual data points plotted along an axis corresponding to the continuous variable, with each point representing a single observation in the dataset. The points are spread horizontally to avoid overlapping, resembling the arrangement of a swarm of bees. The horizontal axis specifies the predicted value of individuals in the positive (right) or negative (left) directions. Categorical features, such as total bilirubin and direct bilirubin, are indicated in blue (0) and red (1). In the above plot, there was a large distribution of alanine aminotransferases, i.e., -0.4--0.6, in the dataset. In Figure 2 (b), the absolute mean values are represented as bars with each feature along the y-axis, and the magnitude of the absolute mean is represented along the x-axis. Dataset features with higher absolute mean values had longer bars, indicating their greater importance in the model's decision-making process.

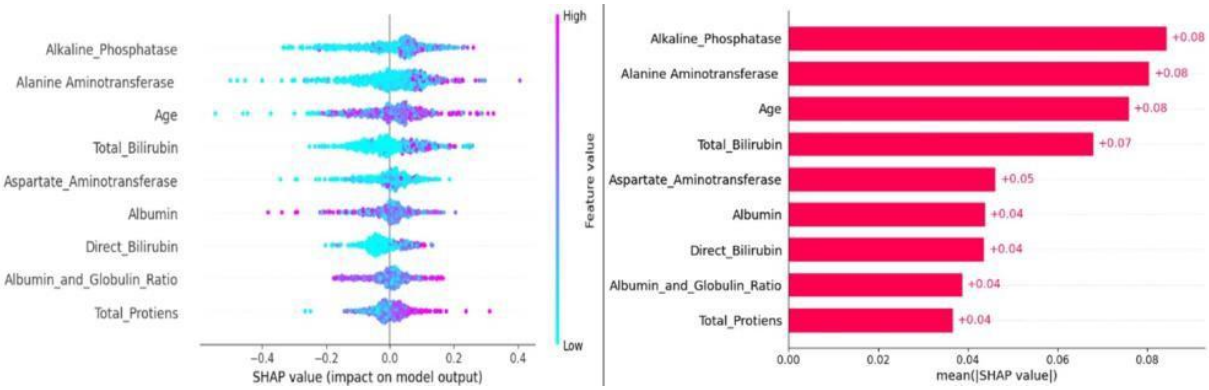

Figure 2. (a) SHAP beeswarm plot showing feature importance in the liver dataset. 2 (b) Absolute SHAP value across all instances in the liver dataset.

Machine Learning

In the machine learning preprocessing step, the dataset was normalized to improve consistency and then divided into two subsets: training set and testing set. The 17 ML models were fitted over the training set, whereas predictions were made for the testing set. This final assessment step allows for a comparison of performance across performance metrics. Figure 3 shows the complete study scenario.

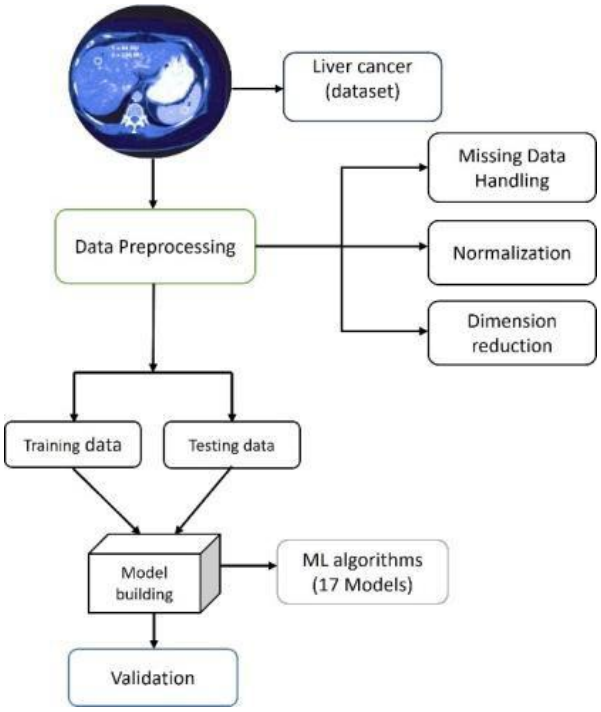

Figure 3. Principle diagram of the implementation of machine learning algorithms on the liver cancer dataset.

Data Preprocessing

Preprocessing in data analysis and machine learning involves a series of steps aimed at preparing raw data for further analysis or modelling. In this step, numerical features were scaled or normalized and categorical variables were encoded into a suitable format for analysis. Data were normalized to values between 0 and 1.

$$X_{normalized} = \frac{X - X_{min}}{X_{max - X_{min}}} \quad (1)$$

where X_{min} indicates the minimum value considered in the dataset and X_{max} is the maximum value considered in the dataset.

Machine Learning Algorithms

Machine learning algorithms are computational procedures or methods used to train models and generate predictions or decisions from data. Machine learning algorithms come in many forms, each tailored to specific tasks and data types. This study focused on an enhanced comparison of model performance involving various types of algorithms, that is, neural networks, bagging, boosting, regressors, classifiers, and hybrid approaches, which were chosen for statistical analyses. These algorithms have excellent prediction power, operate on large datasets, and achieve the best performance in classification tasks. The performance and analysis of these models are presented in the Results section.

Five performance measures were used in our study:

- **Accuracy** is a measure used to ensure that the classification models are accurate. It is determined by dividing the sum of the true positives and true negatives by the total number of samples.

$$Accuracy = \frac{True\ Positive + True\ Negative}{True\ Positive + True\ Negative + False\ Positive + False\ Negative} \quad (2)$$

- **Precision** is an indicator of the performance of a machine learning model. Quality prediction using the model. Precision was defined as the ratio of true positives to the total number of positive predictions.

$$Precision = \frac{True\ Positive}{True\ Positive + False\ Positive} \quad (3)$$

Precision can also be expressed as TP/(TP + FP), which increases the number of positively predicted results.

- **Recall** is a metric that measures how often a machine learning model correctly identifies positive instances (true positives) from all actual positive samples in the dataset. Recall can be calculated by dividing the number of true positives by the number of positive instances.

$$Recall = \frac{True\ Positive}{True\ Positive + False\ Negative} \quad (4)$$

where TP + FN is the number of actual positives, which does not depend on the classifier threshold. This means that reducing the value of the classifier threshold may improve recall because it increases the number of true positives.

- The **F1 score** was the harmonic mean of the precision and recall of the classification model.

$$F1\ score = 2 * \frac{Precision * Recall}{Precision + Recall} \quad (5)$$

- **Cohen-kappa score**: A statistical measure used to assess the effectiveness of machine-learning classification models. Its formula, which is based on the conventional 2 × 2 confusion matrix, is used to assess the binary classifiers in statistics and machine learning.

$$Cohen\text{-}kappa = \frac{2 * (TP * TN - FN * FP)}{(TP + FP) * (FP + TN) + (TP + FN) * (FN + TN)} \quad (6)$$

To evaluate the performance of the binary classification model, the area under the receiver operating characteristic curve (AUROC) metric was used. The receiver operating characteristic (ROC) curve is a graphical representation of the true positive rate (also called the sensitivity) against the false positive rate (which is 1 minus the specificity) for various threshold values. This curve plots these two parameters.

$$\text{True Positive Rate (TPR)} = \frac{True\ Positive}{True\ Positive + False\ Negative} \quad (7)$$

$$\text{False Positive Rate (FPR)} = \frac{False\ Positive}{False\ Positive + True\ Negative} \quad (8)$$

The area under the precision-recall curve (AUPRC) is a measure used to determine the performance of a binary classification model. Precision is the proportion of true-positive predictions from all positive predictions, whereas recall is the proportion of true-positive predictions from all actual positive instances. The AUPRC ranges between 0 and 1, with higher values indicating better performance of the model.

Results

Table 2 shows the mean values with standard deviations (Std dev). for the accuracy, precision, recall, F1 score, and Cohen's kappa score obtained over 50 independent simulations for each algorithm, as we used 17 ML models for the liver cancer dataset. In Table 3, the Wilcoxon signed-rank test is applied with a confidence level of 95%, and the best model for a performance measure is compared with the remaining models to obtain the statistically conditional values, with a worse (−) or equivalent (≈) model with respect to the corresponding best model.

Figure 4 (a) shows the ROC curve that illustrates the relationship between TPR and FPR for the 17 machine learning classification algorithm thresholds. Lowering the threshold classifies more items as positive, thereby increasing both the FP and TP. AUROC evaluates a model's ability to differentiate between two classes. An ideal model would have an AUROC of 1.0, whereas an entirely random model would have an AUROC of 0.5. In general, the higher the AUROC, the better is the model's performance in separating the two classes. In Figure 4 (b), a PR plot is drawn for recall against the precision score in response to the 17 ML algorithms.

Table 2. Means and standards of the ML algorithms, including performance measures, on the liver dataset

Models	Accuracy Mean±Std. Dev	Precision Mean±Std. Dev	Recall Mean±Std. Dev	F1 score Mean±Std. Dev	Cohen-kappa Mean±Std. Dev
SVM	0.7264	0.735	0.8473	0.8473	0.2528
DT	0.7094±0.0321	0.7519±0.019	0.8958±0.046	0.8169±0.0232	0.0866±0.097
RF	0.7692±0.0156	0.7564±0.0106	0.9195±0.0162	0.83±0.0096	0.1199±0.056
LR	0.7264	0.7414	1	0.8515	0.0467
KNN	0.6666	0.7444	0.7791	0.7614	0.0387
GNB	0.5982	**1**	0.4884	0.6563	0.3359
ADB	0.7606	0.8298	0.907	**0.8667**	**0.4260**
MLP	0.7265	0.735	**1**	0.8473	0.2657
PA	0.7264±0.1	0.8263±0.0941	0.7772±0.2582	0.7573±0.148	0.2492±0.1241
RC	0.7264	0.7414	1	0.8515	0.0467
ET	0.7606±0.0392	0.7791±0.0265	0.7888±0.0437	0.7834±0.029	0.1685±0.095
BC	0.844±0.0194	0.7666±0.0140	0.9109±0.0207	0.8324±0.0121	0.1675±0.0705
ETC	**0.858±0.0163**	0.7554±0.01	0.9226±0.0179	0.8324±0.0104	0.1159±0.0543
GB	0.7606	0.7835	0.8837	0.8306	0.2327
SGD	0.7435±0.0494	0.83±0.0712	0.8267±0.1507	0.8131±0.065	0.2900±0.1149
LSVC	0.7350	0.735	1	0.8473	0.1877±2.8043
VC	0.7606	0.8684	0.9186	0.8571	0.1644±0.0884

Table 3. Wilcoxon signed-rank test results on the liver cancer dataset considering five performance measures

Models	Accuracy	Precision	Recall	F1 score	Cohen-kappa score
SVM	−	−	−	−	−
DT	−	−	−	−	−

RF	–	–	–	–	–
LR	–	–	–	–	–
KNN	–	–	–	–	–
GNB	–	NA	–	–	–
ADB	–	–	–	NA	NA
MLP	–	–	–	–	–
PA	–	–	–	–	–
RC	–	–	–	–	–
ET	–	–	–	–	–
BC	–	–	–	–	–
ETC	NA	–	NA	–	–
GB	–	–	–	–	–
SGD	–	–	–	–	–
LSVC	–	–	–	–	–
VC	–	–	–	–	–

Discussion

The results indicate that an ML model can be selected based on certain parameters. This study highlights the potential of machine learning techniques for predicting HCC patient outcomes, with the random forest model achieving the highest accuracy (i.e., 80.64%) in choosing certain parameters. [6] Our study demonstrated the effectiveness of the extra tree classifier out of 17 models for early liver cancer detection. It surpassed the study performance by achieving a higher accuracy score of 85.8%, precision, and recall.

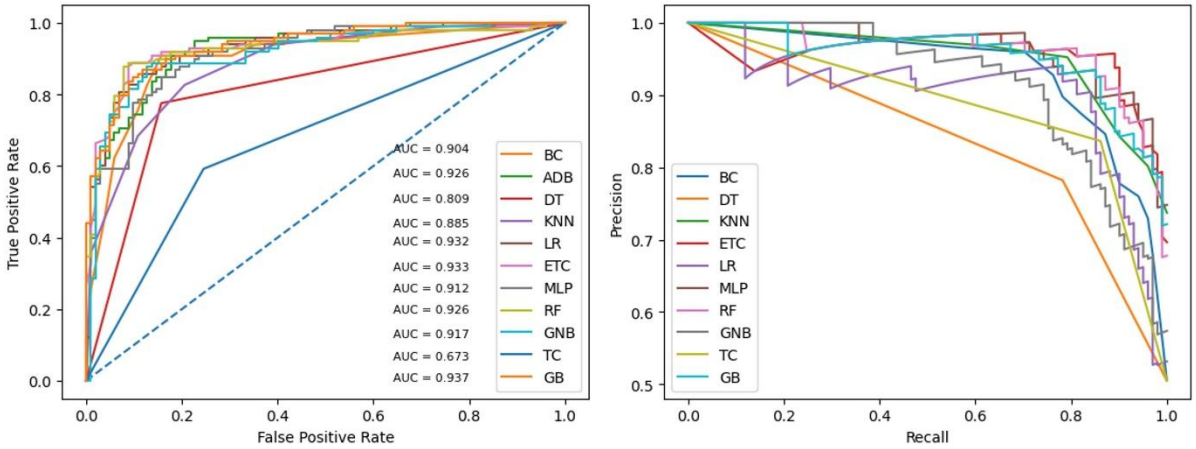

Figure 4. (a) AUC calculated for the ROC curve of the models showing the true positive and false positive rates to distinguish among the trained models. 4(b) Area under the precision-recall curve showing the (sensitivity) against (1-specificity) for different threshold values of 17 ML models.

According to the accuracy performance measure, the extra tree classifier achieved the highest performance, that is, 0.858 (Table 2). Similarly, in terms of the precision performance measure, GNB had the best score, that is, 1, and in terms of the recall performance measure, MLP, LR, LSVC, and RC achieved the highest performance score, 1. For the F1 score, ADB had the highest score, which is 0.866). Finally, the Cohen's kappa measure, ADB, achieved the highest performance score i.e., 0.426).

In Figure 4 (a), the curves show the highest pick in distinguishing between the true-positive and true-negative results of an algorithm. Here, the GB model achieved the highest pick in distinguishing the classes, with a score of 0.937. Consecutively, the ETC and LR curves were the second best at classifying the TPR and FPR, with scores of 0.933 and 0.932, respectively. In Figure 4 (b), the curve shows the highest increase for the MLP classifier, with a score of 0.966. Similarly, the second-best score in the precision–recall curve was for the LR model, with a value of 0.961.

This study has certain limitations in the prediction of liver cancer because the use of machine learning techniques in clinical practice has several significant problems. The work of such models critically depends on the presence of voluminous and highly accurate data; problematic or biased data supply creates problems with model reliability and the weak generality of results. Models may also have the problem of overfitting the training data and may not generalize well across different patient populations. In addition, models rely on the accuracy of the input dataset parameters, which may decrease with time and affect the significance of the models. This technique should be incorporated with the systems already in place and healthcare providers, who may be weary of new devices or gadgets because of a lack of experience or belief. The introduction of a hyperoptimization technique to ML classifiers also enhanced the performance. Similarly, applying feature selection wrapper or embedded filter methods, feature engineering (early, intermediate, and late fusion), and feature transformation (principal component analysis, t-distributed stochastic neighborhood embedding, etc.) concepts to the clinical dataset will increase the classification outcome. Artificial intelligence techniques are beneficial for analyzing large patterns within a shorter span than the human mind, and can enhance the level of accuracy of diagnosing liver cancer. This makes it possible to detect characteristics and their relationships, which cannot be detected when other approaches are used, allowing for earlier diagnostic accuracy. High-quality data improves the generalizability of the model to different patient populations, thus increasing the likelihood that the classification technique will be equally relevant in different clinical settings. This approach is essential for treatment planning and improving patient care. It also assists in the diagnosis, where the workload is offloaded to the machine and results in a quicker output for radiologists and pathologists. The implementation of machine learning in clinical liver diagnosis is important. In addition, it is important to routinely validate and update the model to conform to changes in medical knowledge and technological developments.

In liver cancer, in terms of prediction, the extra tree classifier, multilayer perceptron, and random forest effectively affect all the performance measures. For certain types of datasets, the algorithms work accordingly and differently, and one algorithm or more is specified to one dataset. This study provides a comprehensive overview of various methods in which machine-learning algorithms can be employed to assist medical providers and enhance the care of patients with HCC. Despite the valuable insights gained from this study, several limitations of this study should be acknowledged. First, the sample size of the dataset was relatively small, limiting the generalizability of our findings to a broader population. Second, not all ML algorithms were effective in predicting HCC using five performance measures. The small sample size in our dataset indicated fewer features and instances that may have limited the statistical power of our analyses, potentially affecting the reliability of our findings and increasing the uncertainty of the results regarding cancer risk. To address these limitations, future studies should use larger and more varied datasets to improve the generalizability of the results. Despite some important limitations to overcome, the application of state-of-the-art AI technologies such as ML for the care of patients with HCC is no longer a futuristic idea but is rapidly becoming a reality. Some of the studies covered in this review were published within the past few years, and the number of studies utilizing ML continues to increase exponentially. In the future, we anticipate that machine learning algorithms will soon play a vital role in the diagnosis, prognosis, and treatment of patients with liver cancer (HCC) and will focus on implementing feature selection and feature engineering techniques with these ML algorithms for the acute classification of liver cancer.

List of Abbreviations: HCC- Hepatocellular carcinoma; SVM, Support Vector Machine; MLP, Multi-Layer Perceptron; SGD, Stochastic Gradient Descent; LSVC, Linear Support Vector Classifier; GNB, Gaussian Naïve Bayes; SHAP, SHapley Additive exPlanations; AUC- Area Under the Curve; AUPRC- Area Under the Precision-Recall Curve; ROC- Receiver Operating Characteristic; ETC- Extra Trees Classifier; LR- Logistic Regression; ML- Machine Learning; ADB- AdaBoost; RC- Ridge Classifier

Author Contributions: P.K.N. defined the research strategy and final review of the manuscript.

T.K.B. helped design and carry out the experiments. P.K.M. performed the analyses and drafted the manuscript. All authors have read and approved the final manuscript.

Funding: This research received no external funding.

Ethics Statement: Not applicable.

Data Availability Statement: Raw data used in this study are available at https://github.com/shinjinighosh/liver-cancer-pred/blob/master/datasets_2607_4342_indian_liver_patient_labelled.csv

Conflict of Interest: The authors declare no conflicts of interest.

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