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Acute-on-Chronic Liver Failure Mortality Prediction using an Artificial Neural Network

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Abstract

Acute-on-chronic liver failure (ACLF) is a clinical syndrome affecting patients with chronic liver disease characterized by abrupt hepatic decompensation and associated with high short-term mortality. It is characterized by intense systemic inflammation, organ failure, and a poor prognosis. Using certain liver-specific prognostic scores, and organ failures, it is possible to triage and prognosticate the outcome of patients with ACLF. This work investigates the role of the artificial neural network (ANN), which functionally mimics biological neural systems, in predicting 90-day liver disease-related mortality. This study evaluated ANN among patients with ACLF. An accuracy of 94.12% was noticed at predicting 30-day mortality and 88.2% at predicting 90-day mortality, with an area under the curve of 0.915 and 0.921, respectively. ANN plays a very important role in predicting short term mortality patients with a high accuracy. Its application in patients of ACLF is promising as it automates and eases the method of identifying those patients at a higher risk of mortality. The application of ANN in this field has a vast potential for assisting clinicians in decision making, triaging of patients requiring emergent liver transplantation, and predicting mortality and complications.

Keywords: Acute-on-chronic liver failure (ACLF); Child turcotte pugh (CTP); Artificial neural network (ANN); Biological neural systems; Gastroenterology.

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1. Introduction

Acute-on-chronic liver failure (ACLF) is a clinical syndrome of sudden hepatic decompensation observed in patients with pre-existing chronic liver disease. ACLF is associated with one or more extrahepatic organ failures and increases short-term mortality. A characteristic feature of ACLF is its rapid progression, the requirement for multiple organ supports, and a high incidence of short and medium-term mortality.[1] The term ACLF was first coined in 1995 to include acute hepatic insult in the background on chronic liver insult.[2] The current worldwide mortality rate as per the European Association for the Study of Liver-Chronic-Liver Failure (EASL-CLIF consortium) is 30% to 50%.[1] In a multicentre study from India, the in-hospital mortality was 42% among patients with ACLF.[3]

When compared to the most common causes of hospitalization in the United States, the healthcare burden per patient is much higher in patients with ACLF. The mean cost of hospitalization for patients with ACLF is three times more than the cost of patients hospitalized with cirrhosis.[4] ACLF is defined by The Asian Pacific Association for the Study of the Liver (APASL) as acute hepatic insult manifesting as jaundice (serum bilirubin 5 mg/dL (85 micromol/L)) and the International Normalized Ratio (INR) of coagulopathy is 1.5 or prothrombin activity (40%) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with high 28-day mortality.[5,6]

Various predictive scoring systems have been developed for ACLF and include MELD (model for end-stage liver

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disease) score, MELD-Na (MELD- sodium), CTP (child-pugh-turcotte) scores to predict the outcome and prognosis.[7] These scores were originally developed for cirrhosis of the liver while later validated for ACLF. However, they have limited accuracy as they do not consider the existence of organ failures that also impact the prognosis of patients. Recently various newer scoring systems like Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA),[8] APASL ACLF Reseach Consortium Score (AARC),[9] and quick-Sequential Organ Failure Assessment (q-SOFA)[10] were developed specifically for ACLF and validated for the short-term prognosis of patients with ACLF. However, all the scoring systems lack a predictive accuracy.[7]

Artificial neural network (ANN) is a computer-based modeling technique that uses non-linear statistical analysis to identify the relationship between input variables and an outcome variable by using pattern recognition techniques.[11] The artificial neural networks (ANNs), structurally and functionally mimicking biological neural systems, have been widely used to manage nonlinear complex biological systems. It has been revealed that the ANN models are more accurate than multiple logistic regression and multiple linear discriminant analysis models.[12] There have been few studies that evaluated ANN in predicting short-term mortality in patients with cirrhosis of the liver,[13,14] Hepatitis B associated ACLF.[15,16] With this background, we conducted this analytical study to evaluate the role of ANNs in predicting 30 and 90-day mortality among patients with ACLF.

2. Materials and Methods

2.1 Study Design

Clinical details of all the patients who were admitted to the Department of Gastroenterology with a diagnosis of acute-on-chronic liver failure from March 2019 up to Dec. 2020 were collected retrospectively. Patients were diagnosed with acute chronic liver failure after initial basic evaluation based on the presence of cirrhosis of the liver and those qualifying into the ACLF according to the APASL definition given above.[6] Cirrhosis of the liver was diagnosed based on clinical, biochemical, radiologic, or histopathologic evidence with F4 changes (wherever available). All the patients who were followed prospectively for up to 90 days or up to death (whichever was earlier) were included in the study. Those patients with incomplete or missing data, those patients where the diagnosis of ACLF was in doubt, and those with malignancy were excluded from the study. 111 patients were included in the study. Mortality at 28 and 90 days after index admission was recorded from patients' medical records.

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2.2 Ethical Consideration

The ethical consideration procedure of this study was approved by the Institutional Ethics Committee (IEC: 173/2021) and registered under the Clinical trial registry of India (2021/05033425). Patients' data regarding demographics, presence of decompensating events at presentation including ascites, encephalopathy, Gastrointestinal (GI) bleed, acute kidney injury, and infections were recorded in a predesigned proforma. Relevant Blood investigations including complete blood count, bilirubin, albumin, INR, renal functions, and lactate levels were recorded. Various standard prognostic scoring systems like Child-Turcotte-Pugh (CTP) score, Model For End-Stage Liver Disease (MELD), CLIF-SOFA, AARC, and quick-Sequential Organ Failure Assessment (qSOFA) scores were recorded.

3. Computational Techniques - Artificial Neural Network

An ANN is made up of nodes modeled after neurons in the human brain. It is composed of intricate layers of artificial neurons linked by edges. Each edge has a weight or a bias based on how much each node contributes to the outcome. These biases are computed by the neural network while training the model on the training data set. The input travels from the first layer to the outermost layer and produces an output by a self-adapting process. The result calculated is compared to the actual output. If there is a difference between these two values, the ANN sends a signal to adjust the value of the bias in such a way that the difference between them is minimized with the help of the back propagation algorithm. During the training process, the difference between the predicted outputs and the known outputs is gradually decreased till it reaches a minimum value, beyond which it remains constant. The model accuracy and speed depend on the input sanitization, the number of hidden layers, the number of neurons, the activation function, and other hyper-parameters.

3.1 Network Architecture

In this study, a multi-layer perceptron model was used in the architecture. It is a feed-forward model, where signals traverse in one direction from the input layer to the output layer. Each neuron in a layer is connected to all the other neurons in the adjacent layers through acyclic arcs. Each node receives data in the form of external input and produces an output using its learning algorithms. This model is made of an input layer, a hidden layer, and an output layer. The input layer consists of 27 neurons as the dataset has 27 parameters. The output layer consists of 2 neurons as it has 2 outputs- mortality at 30 days and 90 days; and 9 neurons in the hidden layer are chosen with the help of evolutionary optimization methods. Fig. 1 refers to the neural network model to predict the acute-on-chronic liver failure mortality.

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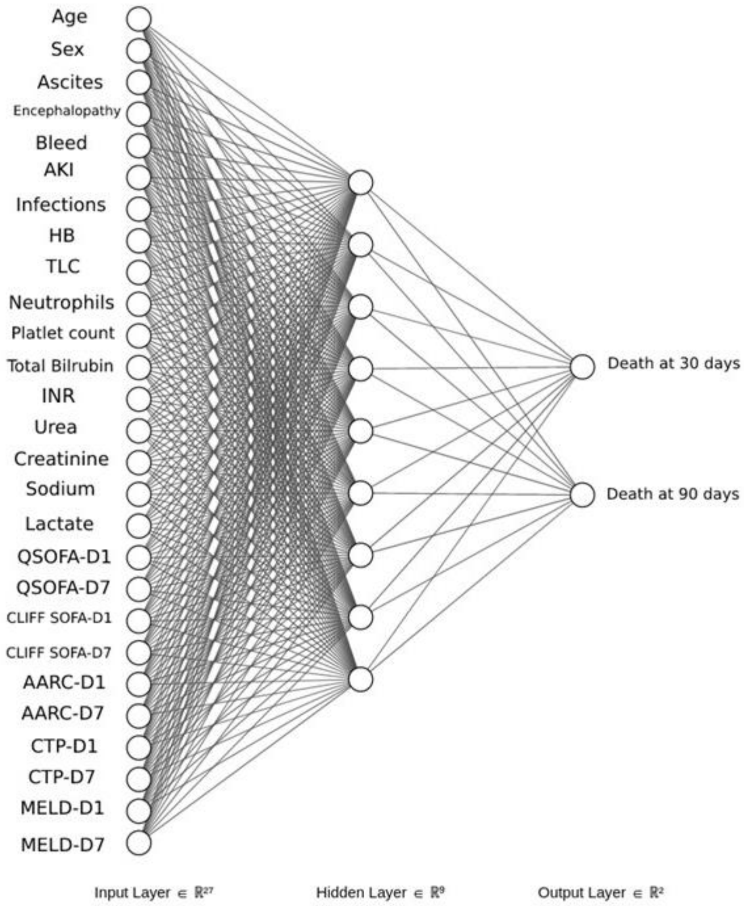

Fig. 1 Neural Network Model with an input layer, a hidden layer, and an output layer to predict Acute-on-Chronic Liver Failure Mortality.

3.2 Network Training and Validation

The model was trained with the help of python libraries in jupyter notebook ide. Keras is an open-source software library that provided a Python interface for ANN model. Similarly, Sklearn was used for randomly splitting the data set and finding Receiver Operating Characteristic (ROC), Area Under the Cover (AUC) scores and confusion matrix. The input matrix was randomly divided in a ratio of 70:15:15, where 70% was reserved for the training set, 15% for the validation set, and 15% for the training set. This research used a sequential model with a kernel regularizer, which was used to apply a penalty to a layer's kernel. Binary cross-entropy loss function as it predicts maximum likelihood estimation leads to well-calibrated probabilities and reduces the exponential behavior of most activation functions.[17-19] Evolutionary optimization was used to optimize hyper parameters such as hidden layers, number of neurons, and batch size. The adaptive moment estimation (Adam) optimization algorithm was used instead of the classical stochastic gradient descent optimization algorithm as it combines gradient descent with momentum and RMSprop and also requires less memory and it is found to be the best and most suitable model for this study.[20] For the dataset (n=111 patients), it was critical to achieving a high precision while avoiding overfitting the data during training. Ridge Regression (L2 regularization) and early stopping were found to be the most successful methods for avoiding this impact. The activation function used in the first layer was Rectified Linear Unit (ReLu) as it accelerates the convergence and its gradient does not saturate and sigmoid function in the second layer as it works as a classifier, respectively.[21] The batch size was set to 7, regularization constant to 0.01, and a patience value to 25 for an early stopping with a minimum variation of 0.001.

3.3 Model Prediction

The binary cross-entropy loss is used to calculate the performance of the neural network and it is given by Equation (1).[22]

$$J(w) = \frac{1}{N}\sum_{n=1}^{N} H(p_n, q_n) = -\frac{1}{N}\sum_{n=1}^{N}[y_n \log \hat{y} + (1 - y_n)\log(1 - \widehat{y_n})] \quad (1)$$

It is used when the output is either 0 or 1. If y=0, we need calculate only the 2nd term $(1\text{-}y_n)\log(1\text{-}y\hat{}_n)$ and if y=1, we need calculate only the 1st term $y_n \log y\hat{}_n$. Adam optimizer (Adaptive Moment Estimation) uses an adaptive learning method. It can be considered as a combination of Stochastic Gradient Descent (SGD) with momentum and RMSprop. It uses the first and second moments of gradients to adjust each

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bias according to the learning rate. It has huge performance gains in the form of speed of training, however, in some cases, it can lead to a poor generalization compared to SGD.[23]

Other performance metrics used to check the correctness of the model were the accuracy, confusion matrix results, and ROC AUC score. The confusion matrix, which was calculated by scikit-learn library and plotted with the help of the seaborn library, helps to describe the performance of the model on test, validation, training data in a simple way, which is very easy to understand and read and it brings to notice the true positives, true negatives, false positives, and false negatives in the result. The AUC of the ROC curve highlights the performance of the model at different threshold settings by differentiating between positive and negative classes.

4. Results

Confusion matrix is useful in representing the performance measurement of a machine learning classification and the model is developed considering the training group and validation group. The confusion matrix shows four combinations of predicted and actual values. The commonly used diagnostic evaluation tool is the ROC curve. The true positive rate (sensitivity) is plotted in a function of the false-positive rate (100 - specificity) at various threshold settings as shown in Fig. 2(a) and 2(b) highlighting the ROC scores for 90-day and 30-day, respectively, with an area under curve >0.9 in both the settings.

The confusion matrix gives us the following data and Equation (2) highlights the accuracy. The accuracy for test after 90 days and 30 days are 88.24% and 94.12%, respectively.

$$Accuracy = \left(\frac{True\ Positive + True\ Negative}{Total}\right) \tag{2}$$

The misclassification rate has been mentioned in Equation (3) and the misclassification rates for test after 90 days and 30 days are 11.76% and 5.8%, respectively.

$$Missclassification\ rate = \left(\frac{False\ Positive + False\ Negative}{Total}\right) \tag{3}$$

The precision has been mentioned in Equation (4) and the precision for test after 90 days and 30 days are 85.71% and 100%, respectively.

$$Precision = \left(\frac{True\ Positive}{Predicted\ True}\right) \tag{4}$$

The true positive rate (Sensitivity/recall rate) has been mentioned in Equation (5) and true positive rate for test after 90 days and 30 days are 85.71% and 83.33%, respectively.

$$True\ Positive\ Rate\ \left(\frac{Sensitivity}{recall}rate\right) = \left(\frac{True\ Positive}{Actual\ True}\right) \tag{5}$$

The true negative rate has been mentioned in Equation (6) and true negative rate for test after 90 days and 30 days are 90% and 100% respectively.

$$True\ Negative\ Rate\ (Specificity) = \left(\frac{True\ Negative}{Actual\ Negative}\right) \tag{6}$$

The accuracy of the model using ANN is around 88% in the case of 90-day mortality while close to 94% for 30-day mortality is observed. Fig. 3 and Fig. 4 indicate the confusion matrix for 90-day and 30-day mortality, respectively.

The correlation matrix is used to summarize the input data and output data in an advanced manner to help understand, analyze and diagnose it better and shows the relation between two variables. Fig. 5 refers to the correlation matrix for the Pearson Correlation method used in the study. It was found out that factors like CLIF SOFA, MELD, lactate, creatinine, CTP, AARC had a high positive correlation and were directly proportional to the mortality rate amongst patients. Among factors like sodium, Bleed, Acute Kidney Injury (AKI), sodium showed a negative correlation with the mortality rates. Factors like sex, age, ascites, platelet count, and QSOFA were found to have little significance on the mortality rates.

5. Discussion

ACLF is a recently described syndrome that is characterized by abrupt hepatic decompensation in patients with chronic liver disease and has a high short-term mortality. In a multi-centric study from India among 1049 patients, the in-hospital mortality was found to be42.6%.[3] Among such patients, where conventional prognostic scores like CTP and MELD

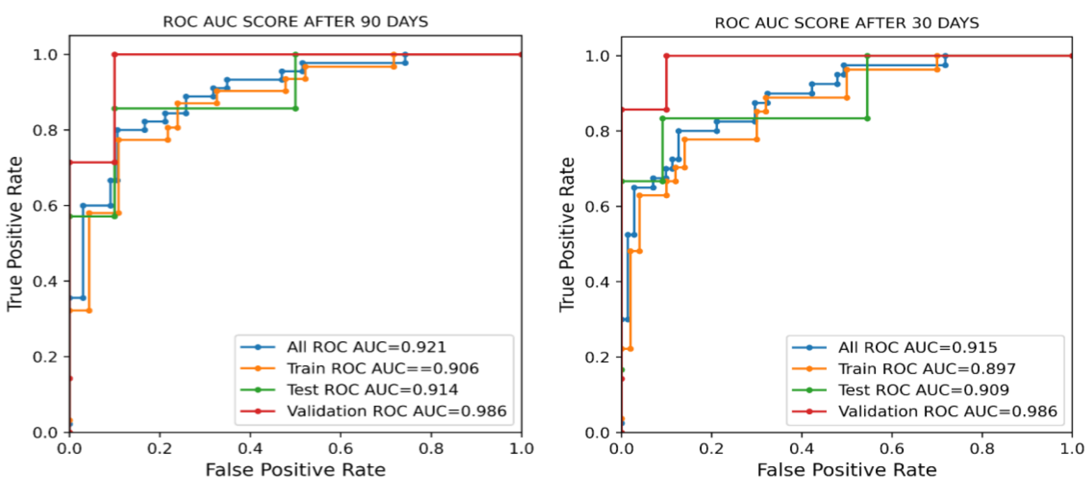

Fig. 2 The diagnostic evaluation tool highlights the performance of the model at different threshold settings by differentiating between positive and negative classes (a) ROC-AUC plot for testing after 90 days (b) ROC-AUC plot for testing after 30 days.

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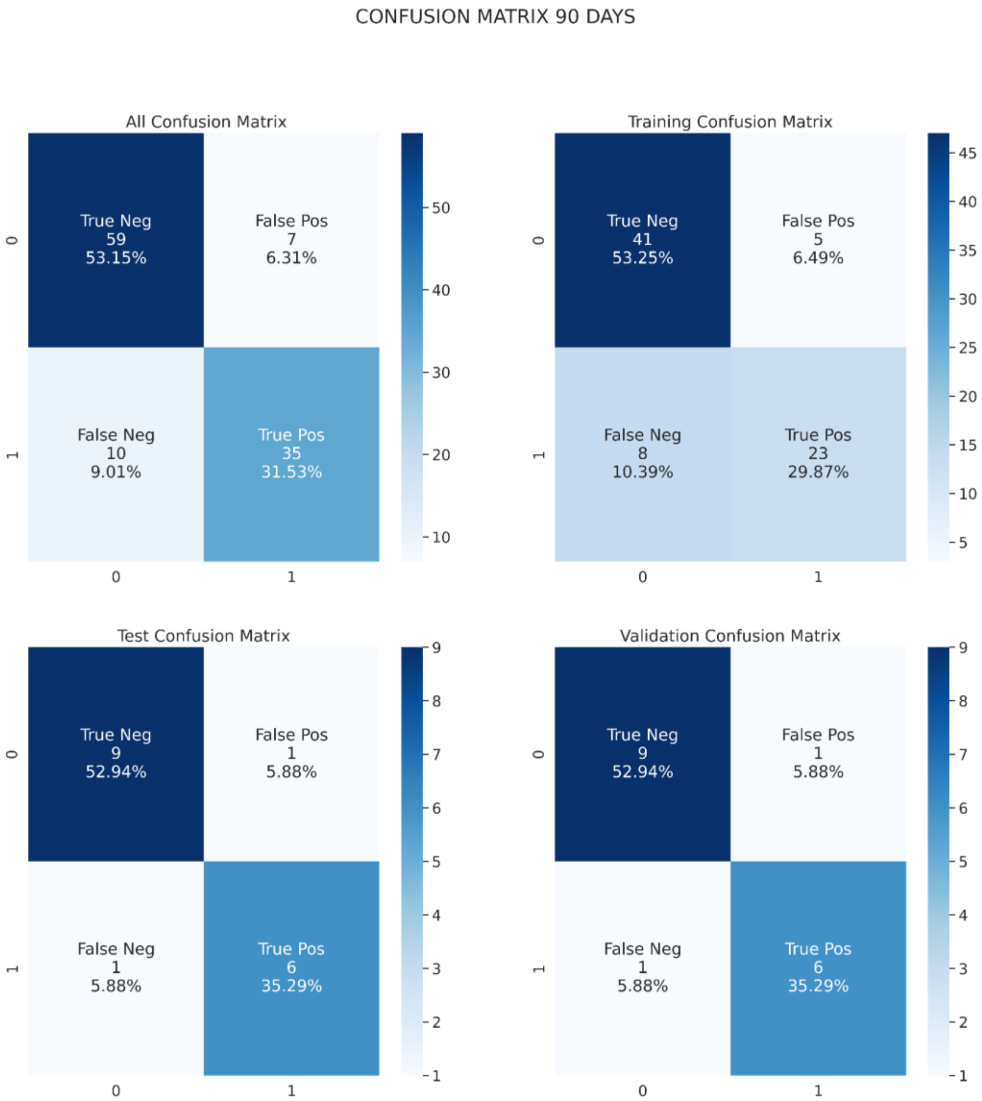

Fig. 3 Confusion matrix for 90 days acute-on-chronic liver failure mortality prediction.

are not robust in predicting the mortality, there is an urgent need for further prognostic indicators that accurately predict the risk of mortality. Liver transplantation has been the option of choice, in those with three or more organ failures, the one-year post-transplantation survival rates are higher compared to those who do not undergo transplantation.[24] Since in ACLF, inflammation is likely a critical early event and can progress to multiple organ failures, liver-specific scoring systems such as CTP and MELD scores are suboptimal. This has led to a search for better prognostic scores, few of which have been validated including CLIF-C ACLF score[25] and AARC score.[9]

Several studies have used ANN as a tool, in various domains of cirrhosis of the liver to predict mortality, to predict readmission rates, and to diagnose liver cirrhosis.[26-30] However, very few studies have evaluated the role of ANN in patients with ACLF. In the present study, the role of ANN in predicting the short term mortality among this special group of patients with ACLF, who had a significantly higher mortality rate, is evaluated. The study included clinical, biochemical, and prognostic scores among such patients. The clinical parameters included the presence or absence of decompensating events like ascites, encephalopathy, infections, bleed and AKI, biochemical parameters including complete blood counts, renal functions, bilirubin, INR, and prognostic scores including CTP, MELD, AARC, CLIF-C-SOFA among all the patients.

1) In a retrospective study done in Taiwan among patients with end-stage liver disease using 1214 patients as training set and 689 patients as the validation set using supervised machine-learning models, the concordance statistics of ROC curves reached 0.852 for the random forest model and 0.833 for an adaptive boosting model in predicting the mortality.[26]

2) In the USA, machine learning (ML) models were used to predict 30-day and 90-day readmission rates among patients with cirrhosis. They found that various ML models (Logistic regression, Kernel support vector machine, and random forest classifiers) had an AUC of 0.62 for 90-day re-admission rate and 0.67 for mortality, which was comparable to conventional

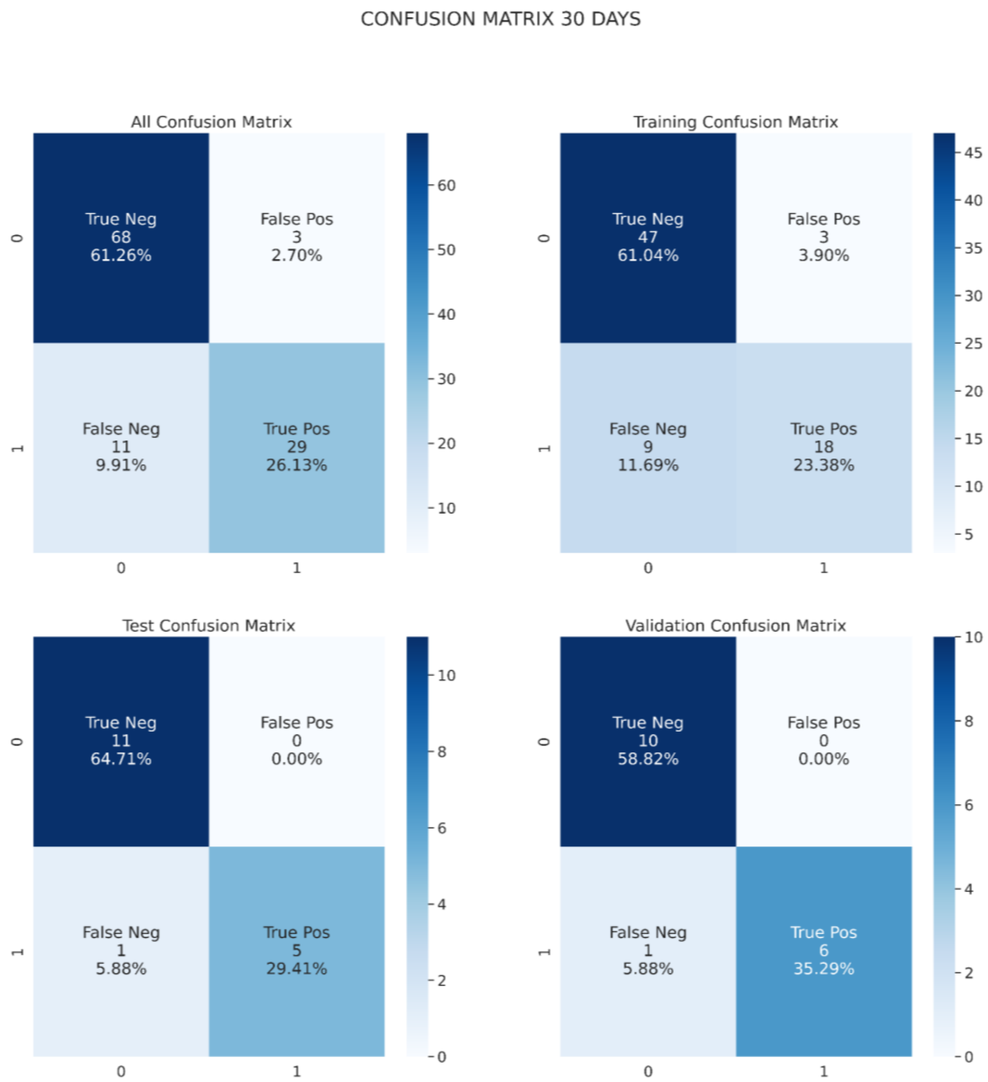

Fig. 4 Confusion matrix for 30 days acute-on-chronic liver failure mortality prediction.

MELD-Sodium scores.[27]
3) Similarly, the ANN model was evaluated in the diagnosis of liver cirrhosis among patients who were under hepatectomy for Hepatitis B-related hepatocellular carcinoma, which had a higher predictive accuracy compared to the logistic model and other conventional models including CTP, MLED scores for the diagnosis of cirrhosis of the liver.[28]

An ANN based study that used clinical and laboratory data of Indian patients had achieved an accuracy of 90% in predicting mortality, thus suggesting that this model could be used to identify the candidates for liver transplantation.[13] Another study in the USA developed and validated ML model based on clinical, laboratory, and histological data of chronic hepatitis C patients to identify those at risk of disease progression.[29] Similarly, ANN fared superior to MELD in predicting 3-month mortality among cirrhotic patients awaiting liver transplantation and suggesting the utility of ANN in prioritizing liver transplant candidates.[30] Among the patients who underwent liver transplantation, ANN was used to predict 5-year survival and had an Area Under the Receiver Operating Characteristic (AUROC) of 86.4% compared to 80.7% for Cox proportional hazard regression models.[31]

Hou *et al*.[15] and Zheng *et al*.[16] developed prognostic models among patients with Hepatitis-B associated ACLF and found that it had more accuracy in predicting 90-day mortality. To our knowledge, this is probably the first study from the Indian subcontinent evaluating the role of ANNs among patients with ACLF. The study utilized clinical and laboratory parameters including prognostic scores in ANN. Experiments involved data from 77 patients as a training cohort, 17 as a testing cohort, and 17 as a validation cohort. It showed an accuracy of 94.12% in predicting 30-day mortality, with lower misclassification rates of 5.8%. Similarly, in predicting 90-day mortality, its accuracy was 88.2% and misclassification rate of 11.76%. It had a significant AUROC area of >0.9. Also, it has been found that CLIF-SOFA and AARC score at day 7 had a high correlation with mortality. This was similar to earlier studies done elsewhere.[9,25]

As the study is retrospective in nature, it may bring about a selection bias. ANN has an innate advantage over other

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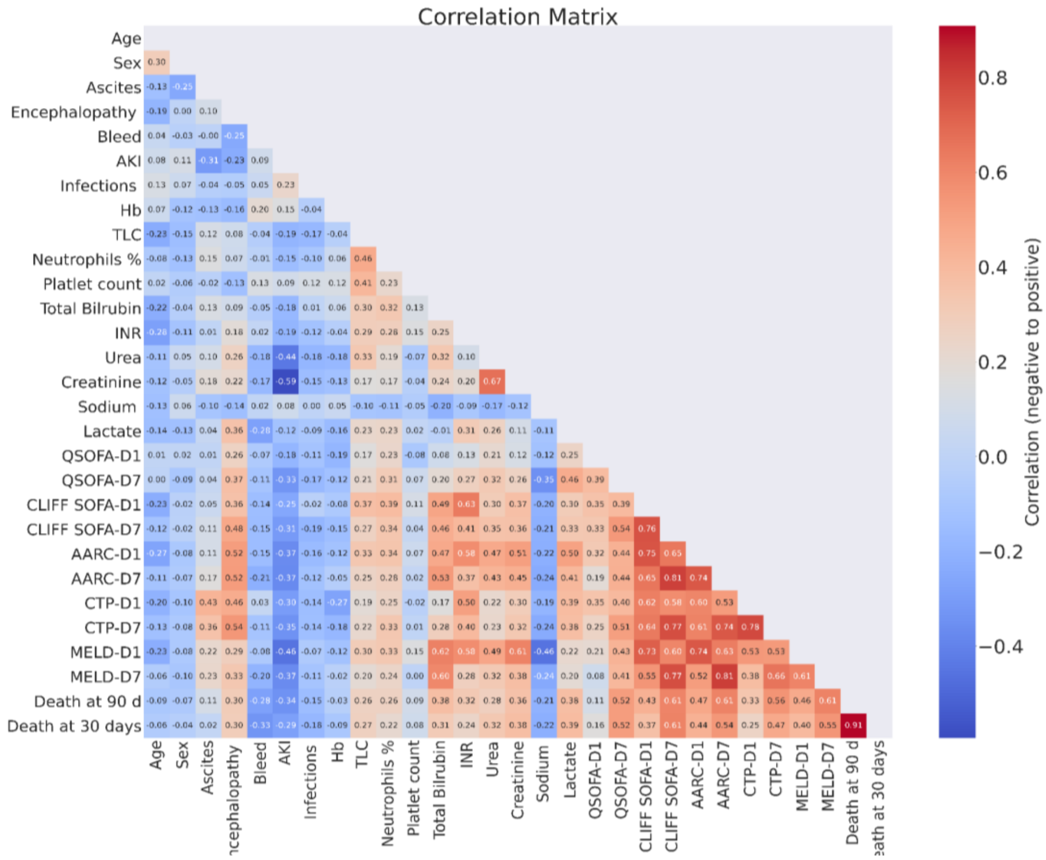

Fig. 5 The correlation matrix for the Pearson correlation method used for prediction of acute-on-chronic liver failure mortality using an artificial neural network.

models, in that ANN is a dynamic model. It can analyze and use new data, and with each new patient, the model back propagates and checks the data with an error-minimization function and re-adjusts hidden weights to improve the accuracy; thus predicting better by ‘crunching’ huge data. We have used clinical and biochemical variables including predictive scores in assessing the utility of ANN. More studies including only clinical and biochemical parameters, and with more sample size are required to further analyze its accuracy.

In the present multi-cloud era, where large data will be shared between various centers, there is an urgent need for utilizing such technology and integrating it into the medical field helping in clinical decision making, especially in critically ill patients with a short beneficiary window, where the multi-modality approach may be beneficial for the patients. ANN-based models have a huge utility among patients with ACLF, helping in prioritizing the therapy options.

6. Conclusions

ACLF is a clinical syndrome affecting patients with chronic liver disease characterized by abrupt hepatic decompensation and associated with high short-term mortality. Artificial neural network (ANN) plays a very important role in predicting 90-day liver disease-related mortality. The accuracy of 88% and 94% is achieved for 90 and 30 days, respectively. A Multi-Layer Perceptron model has been used in the architecture. This model has been made of an input layer, a hidden layer, and an output layer. It is a feed-forward model where signals traverse from the input layer to the output layer. Each neuron in a layer is connected to all the other neurons in the adjacent layers through acyclic arcs. Each node receives data in the form of external input and produces an output using its learning algorithms.

The correlation matrix highlights the factors like CLIF SOFA, MELD, Lactate, Creatinine, CTP, and AARC, that have a high positive correlation to the mortality rate. Acute-on-chronic liver failure is a clinical syndrome that affects patients with chronic liver disease and is associated with increased short-term mortality. ANN plays a very important role in predicting short term mortality patients with a high accuracy. Its application in patients of ACLF is promising as it automates and eases the method of identifying those patients at a higher risk of mortality. The application of ANN in this field has a vast potential for assisting clinicians in decision making, triaging of patients requiring emergent liver transplantation, and predicting mortality and complications.

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Supporting information

Not Applicable.

Conflict of interest

There are no conflicts to declare.

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