Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Design of an artificial neural network to predict mortality among COVID-19 patients

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ABSTRACT

Introduction: The fast pandemic of coronavirus disease 2019 (COVID-19) has challenged clinicians with many uncertainties and ambiguities regarding disease outcomes and complications. To deal with these uncertainties, our study aimed to develop and evaluate several artificial neural networks (ANNs) to predict the mortality risk in hospitalized COVID-19 patients.

Material and methods: The data of 1710 hospitalized COVID-19 patients were used in this retrospective and developmental study. First, a Chi-square test ($P < 0.05$), Eta coefficient ($\eta > 0.4$), and binary logistics regression (BLR) analysis were performed to determine the factors affecting COVID-19 mortality. Then, using the selected variables, two types of feed-forward (FF) models, including the back-propagation (BP) and distributed time delay (DTD) were trained. The models' performance was assessed using mean squared error (MSE), error histogram (EH), and area under the ROC curve (AUC-ROC) metrics.

Results: After applying the univariate and multivariate analysis, 13 variables were selected as important features in predicting COVID-19 mortality at $P < 0.05$. A comparison of the two ANN architectures using the MSE showed that the BP-ANN (validation error: 0.067, most of the classified samples having 0.049 and 0.05 error rates, and AUC-ROC: 0.888) was the best model.

Conclusions: Our findings show the acceptable performance of ANN for predicting the risk of mortality in hospitalized COVID-19 patients. Application of the developed ANN-based CDSS in a real clinical environment will improve patient safety and reduce disease severity and mortality.

1. Introduction

Since March 11, 2020, the coronavirus disease 2019 (COVID-19) pandemic has remained a worldwide public health concern [1]. With the widespread outbreak of COVID-19, the healthcare systems of many countries have failed to meet the growing needs of patients for diagnosis, treatment, and care [2,3]. Due to the weakness of many healthcare industries in dealing with the overwhelming demands during the pandemic, the need to use advanced intelligence and computing technologies has increased [4,5]. In addition, due to the lack of a definitive and approved treatment and the increasing number of infected cases and deaths, artificial intelligence (AI) techniques have become essential to identifying and triaging patients and predicting disease severity and outcome detection [6–8]. Using AI-based prediction models for the early prognosis of the illness and forecasting patients' clinical deterioration can diminish the adverse outcomes of the COVID-19 pandemic [9,10], maintain treatment efficiency, and improve resource utilization [11].

Machine learning (ML) is a branch of AI that can play an essential role in the prognosis, diagnosis, and treatment of various diseases, especially chronic and complex conditions [12,13]. ML techniques extract applied knowledge to support decision-making by exploring cumulative datasets [14,15]. The ML process involves several phases, e.g., data gathering, visualization, and extracting applicable and informative patterns from massive raw datasets. It combines computational, statistical, and database sciences [16]. By training valid and qualitative predictive models, ML techniques are critical to effective triaging and improvement of treatment outcomes [17].

Artificial neural networks (ANN), as a subclass of ML, are adaptive, tutorial, and computational functions that mimic the structure and

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Abbreviations

1- COVID-19 Coronavirus disease 2019
2- AI Artificial intelligence
3- ML: Machine learning
4- CDSS Clinical decision support systems
5- ANN Artificial neural network
6- BLR Binary logistic regression
7- BP Back-propagation
8- DTD Distributed time delay
9- FF Feed-forward
10- MSR Mean squared error
11- RMSE Root mean square error
12- AUC Area under the ROC curve

behavior of neurons in the human brain [18,19]. This method can be trained to discriminate and classify intricate patterns of diseases through an iterative learning process. Once proper training is executed, ANNs can predict with higher accuracy than traditional statistical models. Due to their ability to detect multifaceted nonlinear relations among predictors and outcomes, ANNs have been effectively applied in clinical decision support systems (CDSS) [20–24]. Thus, the current study first selected the most influential variables on COVID-19 mortality at the time of admission, then compared different ANN architectures, and finally established a CDSS based on the best-selected ones to predict COVID-19 mortality.

2. Materials and methods

2.1. Study design and setting

This was a retrospective and developmental study conducted in 2022. The records of 1980 COVID-19 patients were analyzed. The patients had been referred to the Ayatollah Taleghani Hospital (COVID-19 hub center), southwest of Khuzestan Province, Iran, from August 2021 to January 2022. Of these, 1221 and 759 cases were female and male, respectively.

The methodology of this study is shown in Fig. 1 in brief. Its included dataset preparation, feature selection, model development, and evaluation.

2.2. Predictor and outcome variables

A total of 58 features were selected and classified into four main categories: demographic, clinical manifestations, epidemiological, and hospitalization indicators (see Table 1). The output variable was life status characterized by two values: surviving (code 0) and deceased (code 1).

2.3. Dataset preprocessing

The dataset was normalized before ANN implementation. This step was performed to achieve maximum performance and have a more straightforward ANN implementation. For this purpose, the normalization process was carried out in three phases:

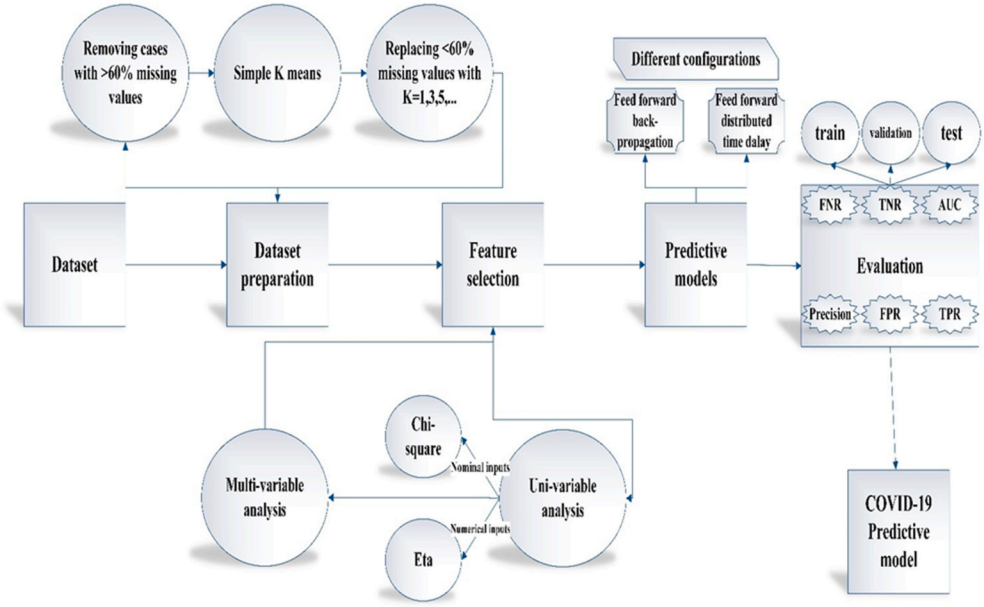

Fig. 1. The study's roadmap.

1) Scrutinizing the database for outliers, duplicates, or a high percentage of missing values: Two Health Information Management experts (M–SH and H–KA), in consultation with two Infectious Diseases specialists, screened all the data samples. Outlier values were deleted from the dataset by the authors. Case records with more than 60% missing values were also excluded from the analysis.
2) Replacing the missing values for the case records with less than 60% missing data:

The simple K-means algorithm with specific Euclidean distances of K = 1, 3, and 5 was used to impute the missing values. In this method, the missing values are filled with the same feature value belonging to the nearest case. This closest case is very similar to the cases having missing values in terms of all attribute values. The algorithm uses the value of the feature belonging to this case to fill the missing value for the incomplete data case. Moreover, imputation was evaluated via the root mean square error (RMSE) in different algorithm iterations.

3) Choosing the most important factors affecting COVID-19 mortality using the feature selection (FS) process:

Table 1
Characteristics associated with COVID-19 mortality.

NO.	Variable category	Variable name
1	Demographic factors	Age (year), Height (cm)[1], Weight (Kg)[2], Blood type (AB^+, AB^-, O^+, O^-, A^+, A^-, B^+, B^-), Sex (male, female)
2	Hospitalization factors	Length of hospitalization (Day), ICU hospitalization (Yes, No)
3	Clinical manifestations, including symptoms and signs	Contusion (Has, Does not have), Headache (Has, Does not have), Body temperature, Fever (Has, Does not have), Dyspnea (Has, Does not have), Loss of taste (Has, Does not have), Rhinorrhea (Has, Does not have), Muscular pain (Has, Does not have), Cardiac disease (Has, Does not have), Loss of smell (Has, Does not have), Lung consolidation (Has, Does not have), Cough (Has, Does not have), Gastrointestinal manifestation (GI) (Has, Does not have), Chill sensation (Has, Does not have), other underlying diseases (Has, Does not have), pneumonia (Has, Does not have), Nausea (Has, Does not have), Vomiting (Has, Does not have), Blood pressure (Has, Does not have), Diabetes (Has, Does not have), Sore throat (Has, Does not have)
4	Therapy	Oxygen therapy (Has, Does not have)
5	Laboratory data	Hypersensitive troponin (ng/L)[3], White cell count (Cells/mL)[4], Erythrocyte sedimentation rate (mm/hr)[5], C-reactive protein (mg/L)[6], Alkaline phosphatase (Units/L)[7], Prothrombin time (s)[8], Activated partial thromboplastin time (s)[8], Lactate dehydrogenase (Units/L)[7], Blood glucose (mg/dL)[9], Serum albumin (g/dL)[10], Alanine aminotransferase (units/L)[7], Aspartate aminotransferase (units/L)[7], Total bilirubin (mg/dL)[9], Blood urea nitrogen (mg/dL)[9], Blood potassium (mEq/L)[11], Blood phosphor (mg/dL)[9], Blood magnesium (mEq/L)[11], Blood sodium (mEq/L)[11], Blood calcium (mg/dL)[6], Absolute neutrophil count (10^3Cells/μL)[12], Absolute lymphocyte count (10^3 Cells/μL)[12], Platelet count (Cells/μL)[12], Hemoglobin rate (g/dL)[10], Hematocrit (L/L)[13], Red cell count (mc/mL)[13], Blood creatinine (mg/dL)[9]
6	Epidemiological factors	Smoking (Yes, No), Alcohol addiction (Has, Does not have)

1- Centimeters, 2- Kilograms, 3- Nanograms per liter, 4- Cell per microliter, 5- Millimeters per hour, 6- Milligrams per liter, 7- Units per liter, 8- Seconds, 9- Milligrams per deciliter, 10- Grams per deciliter, 11- Milliequivalents per liter, 12- Number of cells per microliter, 13- Million cells per microliter.

FS means reducing the dataset features in data preprocessing [25]. This process was undertaken in order to 1- reduce the dataset dimension for a better understanding of the data, 2- enhance the data mining algorithm's performance, 3- prevent algorithm overfitting, 4- accelerate algorithm development, and 5- simplify data visualization [26–29]. This study used the Chi-square test and Eta coefficient method to determine the best factors affecting mortality in COVID-19 patients. The $P < 0.05$ was considered for significant relationships between determinant factors and mortality among COVID-19 patients. For the Eta, a coefficient of more than 0.4 was considered the most critical factor. We applied the multivariate analysis of binary logistic regression (BLR) to determine the factors having a computational correlation with the dependent variable; we used the multivariate analysis of BLR with the forward LR method. We also considered the variable entering the model at $P < 0.05$ as the highly hybrid correlated factor predicting COVID-19 mortality to form the ANN model.

2.4. Implementing the artificial neural network

ANN is the abstraction of the human brain structure and attempts to mimic its performance [30]. It consists of three layers: the input layer, the calculation or hidden layer, and the output layer [31,32], (see Fig. 2). Each layer includes neurons in ANN and performs different tasks in its layers [33]. The input layer receives elements such as data, images, or signals from the environment and turns them into normalized pieces suitable for mathematical calculations in the output layer. The calculation process occurs in the hidden layer(s) which has the highest number of neurons and performs the calculation operation through proper communication between neurons. In the output layer, the neurons receive the results of the processing layer calculations and present them to the user [34–36]. In the ANN, there are weights between the neurons to transfer information between nodes in the computation process [37]. Based on the adjusted weight during ANN training, the computation process results in previous nodes reaching the common next node to continue the process in the next node and present the results [38,39]. Another critical parameter in ANN is the activation function that describes neurons' processing results in the spanned amounts in nonlinear connections between neurons. This function increases the nonlinear learning in ANN and makes it amplified for a sophisticated computational process [40]. In this study, we used the feed-forward (FF) ANN in MATLAB 2013-a to train and test our algorithm based on the dataset of COVID-19 patients. FF, also known as multi-layered perceptron (MLP), is the most understandable and popular ANN configuration adaptable with the non-linearity forward connection between neurons [41]. To simulate the non-linearity connection between neurons, we used the tansig activation function method because of its rapid performance during the training process [42]. The Levenberg Marquardt (LM) algorithm with its high running speed was applied in MATLAB to train the ANN and adjust the weight connected with the neurons during this process [43]. We also set the training iterations to 1000 and the training time to unlimited due to the high speed of the LM algorithm.

2.5. Evaluating the artificial neural network

This study used the two FF types of back-propagation (BP) and distributed time delay (DTD) to implement the model predicting COVID-19 mortality. In evaluation phases, performance was assessed in two steps. First, we separately implemented each FF-type of the ANN. To compare and evaluate each ANN configuration, the confusion matrix metrics (Table 2) such as the accuracy (Equation (1)) and F-score (Equation (2)) were assessed. The true positive (TP) and true negative (TN) are deceased and surviving cases correctly classified by model. The false negative (FN) and false positive (FP) are the same cases incorrectly classified. 70% of the COVID-19 sample was used to train and 30% to test the ANN algorithms by default. We also split our dataset into 50% and 50% of train and test samples, 60% of train samples and 40% of test samples, 80% of train samples and 20% of test samples to better investigate dataset splitting to build the predictive model. We set the number of neurons in the input and output layers to the number of input and output research variables. To determine the number of nodes in the hidden layer, we started from one neuron, added one neuron, and compared each ANN step to obtain the best configuration. After achieving the best structure of each FF-type of the ANN, in the second step, we compared the selected design of the FF to assess the validation process of two FF types of the ANN during fitting and achieve the best model predicting COVID-19 mortality. In this step, we used the mean squared error (MSE) and area under the ROC curve (AUC-ROC) to compare the various FF types. We investigated the capability of classifying the selected model using the confusion matrix and the error histogram diagram.

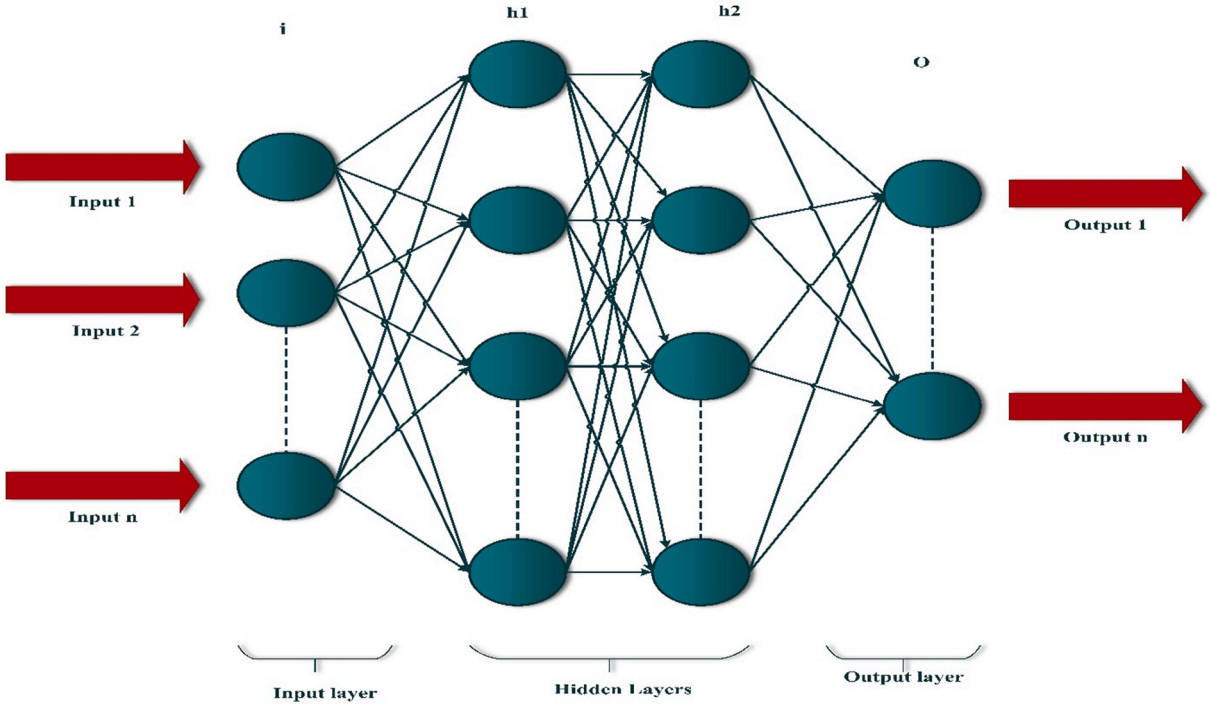

Fig. 2. The overall schema of ANN configuration.

Table 2
Confusion matrix.

Real Model	+	−
+	True Positive (TP)	False Negative (FN)
−	False Positive (FP)	True Negative (TN)

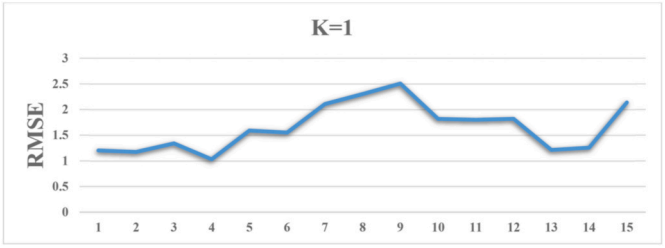

Fig. 3. The RMSE of simple K-means in K = 1 for 15 epochs.

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FN + FP} \quad (1)$$

$$F - \text{Score} = \frac{2(TP)}{2(TP) + FP + FN} \quad (2)$$

3. Results

After applying the exclusion criteria such as non-hospitalized COVID-19 cases, patients who were less than 18 years of age, incomplete case records (missing more than 60%), and admission time before January 9, 2020, or after January 20, 2021, 270 patient records were excluded. Out of the 1710 eligible records, 1121 (63.6%) and 589 (34.4%) records belonged to surviving and deceased cases, respectively, with a mean age of 61.62 ± 17.6 years. Evaluation of the simple K-means clustering algorithm in imputing the missing values for different iterations (up to 15 epochs) of the algorithm and specific K = 1, K = 3, and K = 5 is shown in Figs. 3–5.

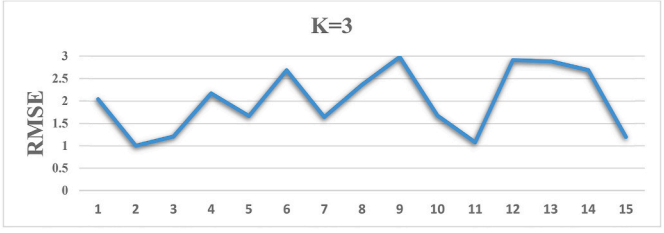

Fig. 4. The RMSE of simple K-means in K = 3 for 15 epochs.

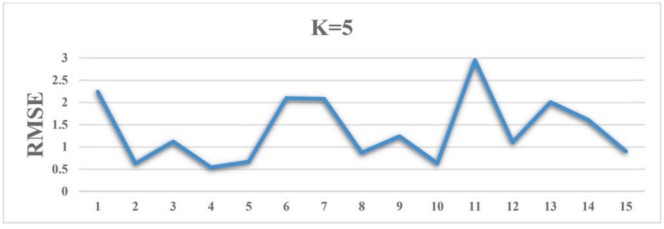

Fig. 5. The RMSE of simple K-means in K = 5 for 15 epochs.

Based on Figs. 3 and 4, for K = 1 and K = 3, the simple K-means gained the error value rates between RMSE of 1–3. In K = 5, these interval amounts were increased to 0.5–3 for 15 iterations. The results of clustering the cases and filling missing values by the simple K-means showed no significant difference between the actual and predicted values by the algorithm [0.5–3], which indicated the desirable performance of the algorithm.

The results of selecting each variable that had a significant relationship with COVID-19 mortality at $P < 0.05$ or Eta>0.4 are presented in Table 3.

Based on the information represented in Table 3, 31 variables had a significant relationship with COVID-19 mortality at $P < 0.05$ or $\eta > 0.4$. They were then considered as the important factors affecting mortality.

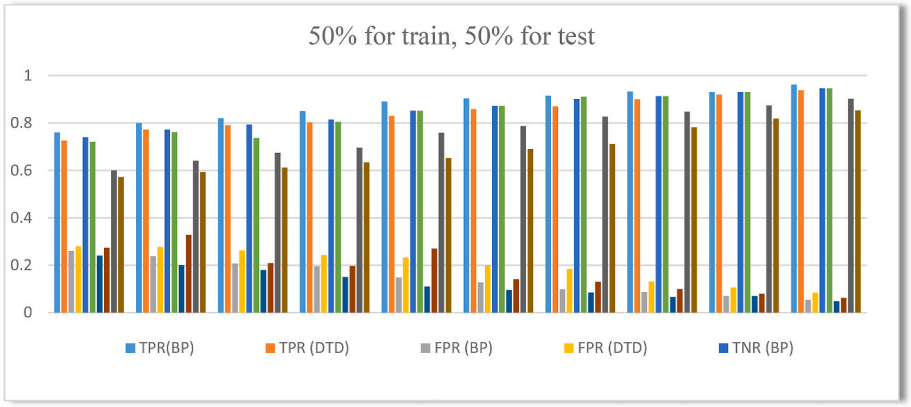

Fig. 6. Different performance criteria of two selected ANN modes (1–10 neurons from left to right).

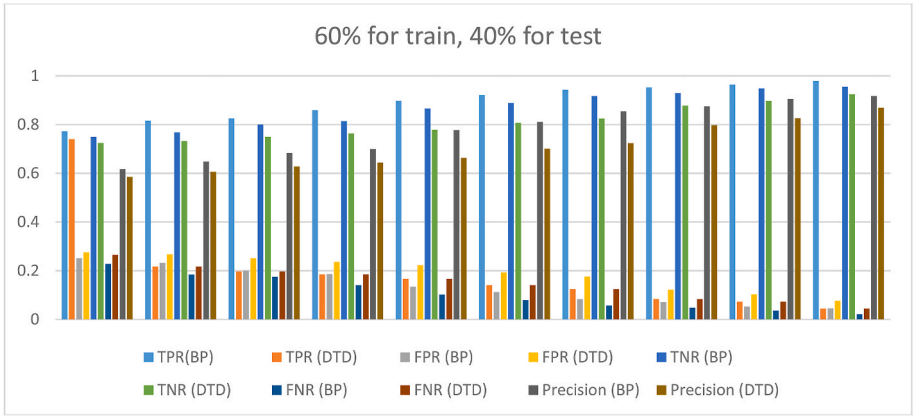

Fig. 7. Different performance criteria of two selected ANN modes (1–10 neurons from left to right).

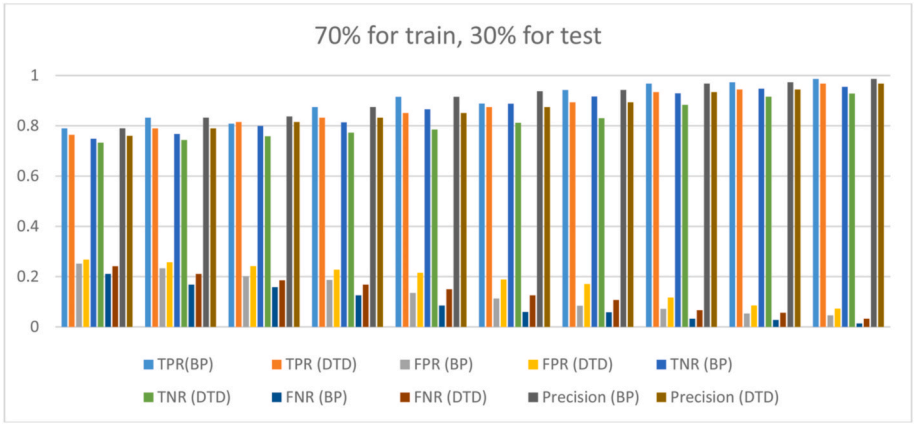

Fig. 8. Different performance criteria of two selected ANN modes (1–10 neurons from left to right).

The 18 variables of blood calcium ($\eta = 0.25$), blood phosphor ($\eta = 0.12$), blood magnesium ($\eta = 0.01$), blood sodium ($\eta = 0.17$), blood potassium ($\eta = 0.12$), total bilirubin ($\eta = 0.11$), blood albumin ($\eta = 0.26$), prothrombin time ($\eta = 0.25$), C-reactive protein ($P = 0.201$), height ($\eta = 0.16$), weight ($\eta = 0.14$), blood type ($P = 0.155$), sex ($P = 0.123$), headache ($P = 0.244$), gastrointestinal manifestation ($P = 0.10$), muscle pain ($P = 0.36$), chill sensation ($P = 0.55$), fever ($P = 0.48$), body temperature ($\eta = 0.163$), pneumonia ($P = 0.115$), diabetes ($P = 0.12$), smoking ($P = 0.06$), alcohol consumption ($P = 0.11$), red cell count ($\eta = 0.12$), hematocrit ($\eta = 0.113$), hemoglobin rate ($\eta = 0.153$), and serum albumin ($\eta = 0.121$) with $P > 0.05$ or $\eta < 0.4$ were excluded from the study. After entering the significant variables into the BLR model, we obtained the results shown in Table 4.

Based on the information given in Table 4, 13 variables of vomiting ($P < 0.001$), oxygen therapy ($P < 0.001$), loss of taste ($P < 0.001$), loss of smell ($P < 0.001$), rhinorrhea ($P < 0.001$), white cell count ($P = 0.014$), platelet count ($P = 0.005$), absolute neutrophil count ($P < 0.001$), erythrocyte sedimentation rate ($P = 0.003$), pleural fluid ($P < 0.001$), ICU hospitalization ($P < 0.001$), length of hospitalization ($P = 0.002$), and age ($P < 0.001$) were entered into the forward LR of the BLR at 13 steps at $P < 0.05$. Comparing the Log-likelihood (LL) size of the 13th step and 1st step demonstrated that the LL rate of BLR in the 13th step (3.57)

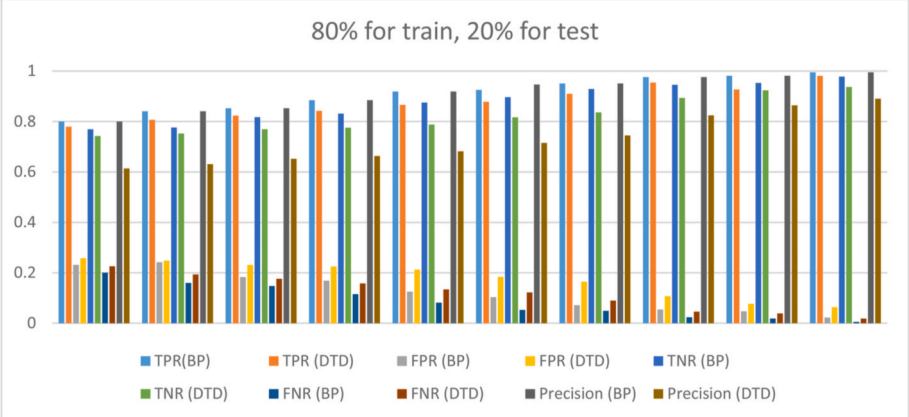

Fig. 9. Different performance criteria of two selected ANN modes (1–10 neurons from left to right).

was reduced compared to the 1st step (LL = 216.347) by entering these variables. With this reduction, the BLR capability for predicting COVID-19 mortality in the 13th step markedly increased more than in the 1st step. Therefore, we considered these 13 highly correlated variables for developing the ANN predicting COVID-19 mortality. To compare different ANN configurations of BP and DTD, we presented the performance results of adding 10 neurons to the ANN hidden layer using the accuracy, F-score, and AUC-ROC. The results of the different datasets partitioning up to 10 nodes in the hidden layer are depicted in Table 5.

Based on the results shown in Figs. 6–9, we observed that by using 80% of the data to train the ANN and 20% for the test, the performance was enhanced compared to other data splitting types. The BP of this ANN type in this state of data splitting with TPR = 0.994, FPR = 0.022, TNR = 0.977, FNR = 0.005, and precision = 0.994 had the best performance for predicting the mortality of COVID-19 patients. Fig. 10 displays the selected configurations of each FF type with the best total performance.

The results of comparing the two selected architectures of FF during training, testing, and validation to assess the ANN's validation during ANN training are given in Figs. 11 and 12 by investigating the MSE and error histogram diagram.

Evaluating the validation process of the BP-ANN (left side of Fig. 11) showed this rate reached less than 10^{-1} during the training and fitting of the ANN. In the 9th step of ANN fitting iterations for BP, we obtained the validation rate as the best (validation = 0.055). Moreover, measuring the validation process during the training of the DTD type of the ANN showed that the validation rate dropped to 10^{-1} during ANN fitting. The precise value of validation in the 4th step of the ANN fitting was 0.089. Therefore, comparing the two selected architectures of the ANN demonstrated that the BP-ANN achieved a lower error rate than the DTD during the ANN fitting using the validation evaluation in the MSE diagram. The results of evaluating the two selected configurations of the ANN using the error histogram diagram with 20 bins showed that the BP-ANN (left side) classified the 250 training and less than 100 validation and test samples of the study in the bin = −0.049 and approximately 30 samples in the bin = 0.05 (the bins near-zero error). The DTD categorized about 110 training, 25 validation, and 20 test samples in bin = −0.053 and about 50 training, less than 10 validation, and 10 test samples in bin = 0.036. The rest cases were also located in other bins during the DTD fitting. Comparing the two modes of FF using the error histogram diagram showed that the BP-ANN had a lower error rate than the DTD during the fitting of the two ANN methods. Fig. 13 depicts the comparison of the two selected configurations of the ANN in 80% of data for the model train and 10% for the test, and 10% for validation using the ROC curve in each state of training, validation, and test modes in each form of training, validation, and test modes. The vertical and horizontal vertices present true-positive rates (TPR) and false-positive rates (FPR).

Based on Fig. 13, in the training mode, the BP algorithm with $AUC\text{-}_{train}$ = 0.926 had a slightly better performance than the DTD with $AUC\text{-}_{train}$ = 0.896. In the validation mode of ANN, the BP with $AUC\text{-}_{validation}$ = 0.873 obtained better capability than the DTD with $AUC\text{-}_{validation}$ = 0.791, but in the test mode, DTD with $AUC\text{-}_{test}$ = 0.881 gained slightly better ability than BP with the $AUC\text{-}_{test}$ = 0.853. In general, the BP with the AUC = 0.901 had better potential in categorizing deceased and surviving COVID-19 cases than DTD with AUC = 0.866. Based on the comparison of the two selected ANN architectures during the fitting process using the MSE, error histogram, and ROC curve, we concluded that the BP architecture of the FF obtained better performance in classifying the training, validation, and test samples. Based on the BP of the FF, we designed the CDSS user interface for COVID-19 mortality (Fig. 14). The users, such as physicians, entered the 13 essential factors, and then the CDSS suggested the predictive results about the high or low risk of mortality of the COVID-19 patients.

4. Discussion

The adoption of ML-based CDSSs to support clinical decisions about COVID-19 is on the rise [10]. Such technologies can improve treatment outcomes for patients with COVID-19 [10,11]. Proactive prediction of COVID-19 mortality using ML models can help promote the survival chances of hospitalized patients [11,44]. This study aimed to predict mortality among hospitalized COVID-19 patients based on the best configuration of the ANNs. To this end, we used the data of 1710 hospitalized COVID-19 patients to achieve the most important factors affecting COVID-19 mortality.

To detect the most important predictive factors influencing COVID-19 mortality, we applied the chi-square test and Eta coefficient as univariate and BLR as multivariate analysis. Using the univariate analysis, 31 features were selected as the most influential factors on COVID-19 mortality at $P < 0.05$ and $\eta > 0.4$. After using the BLR, 13 variables were determined as the most critical predictors for COVID-19 mortality. To develop the model, we used two architectures of ANN, including the BP and DTD of the FF.

The results indicated that the design of 13–10-1 (10 neurons in the hidden layer) with TP = 586, FN = 3, FP = 25, and TN = 1096 associated with the BP, and 13-10-1 (10 neurons in DTD's hidden layer) with TP = 578, FN = 11, FP = 71, and TN = 1050 belonging to the DTD presented the best ability in each architecture. Thus, the BP-ANN with an AUC of 0.901 was considered the best ANN architecture to predict COVID-19 mortality.

In previous studies, different ML methods were trained to predict COVID-19 outcomes such as disease progression and deterioration [45,46], ICU hospitalization [46–50], and mortality [47,48,51–56]. The

Table 3
The essential variables at P < 0.05 or Eta>0.4

Variable name	Variable type	Variable feature With code	Variable frequency or mean (SD)	P_{-value} or Eta coefficient
Cough	Nominal	No (0) Yes [1]	No (779) Yes (931)	<0.001
Contusion	Nominal	No (0) Yes [1]	No (729) Yes (981)	<0.001
Nausea	Nominal	No (0) Yes [1]	No (983) Yes (798)	0.001
Vomiting	Nominal	No (0) Yes [1]	No (839) Yes (871)	0.001
Oxygen therapy	Nominal	No (0) Yes [1]	No (926) Yes (784)	<0.001
Dyspnea	Nominal	No (0) Yes [1]	No (830) Yes (880)	0.001
Loss of taste	Nominal	No (0) Yes [1]	No (758) Yes (952)	<0.001
Loss of smell	Nominal	No (0) Yes [1]	No (930) Yes (780)	<0.001
Rhinorrhea	Nominal	No (0) Yes [1]	No (789) Yes (921)	<0.001
Sore throat	Nominal	No (0) Yes [1]	No (739) Yes (971)	0.001
Other underlying diseases	Nominal	No (0) Yes [1]	No (660) Yes (1050)	<0.001
Cardiac disease	Nominal	No (0) Yes [1]	No (829) Yes (881)	0.001
Blood pressure	Nominal	No (0) Yes [1]	No (850) Yes (860)	0.001
White cell count	Numeric	–	9223.52 (6223)	0.9
Platelet count	Numeric	–	212318.59 (658.2)	0.9
Absolute lymphocyte count	Numeric	–	21.54 (8.432)	0.6
Absolute neutrophil count	Numeric	–	75.22 (4.3)	0.6
Blood urea nitrogen	Numeric	–	53.52 (6.663)	0.6
Aspartate amino transferase	Numeric	–	55.5 (12.3)	0.6
Alanine aminotransferase	Numeric	–	48.32 (5.2)	0.7
Blood glucose	Numeric	–	135.40 (41.2)	0.7
Lactate dehydrogenase	Numeric	–	604.22 (41.6)	0.9
Activated partial thromboplastin time	Numeric	–	28.6 (6.7)	0.9
Alkaline phosphatase	Numeric	–	255 (150.9)	0.7
Erythrocyte sedimentation rate	Numeric	–	33.24 (19.3)	0.7
Hypersensitive troponin	Nominal	Negative (0) Positive [1]	Negative (1224) Positive (486)	0.001
Lung consolidation	Nominal	No (0) Yes [1]	No (437) Yes (1273)	<0.001
Pleural fluid	Nominal	No (0) Yes [1]	No (410) Yes (1300)	<0.001
ICU hospitalization	Nominal	No (0) Yes [1]	No (875) Yes (935)	<0.001
Length of hospitalization	Numeric	–	4.83 (3.2)	0.6
Age	Numeric	–	58.8 (7.6)	0.6

most important of these algorithms can be listed as ANN [57–64], ensemble models (boosting algorithms) [65–69], decision trees, in particular random forests (RF) [6,58,61,70,71], support vector machine (SVM) [58,61], and Naive Bayes (NB) [72]. According to the literature, the ANN model [57–64] has the greatest performance in predicting COVID-19 mortality. The results of other reviewed studies also showed that ensemble ML (hybrid) models [65–69] and RF [58,61,70,71]

Table 4
The results of entering the variables into the BLR.

Model if Term Removed					
Variable		Model Log-Likelihood	Change in −2 Log-Likelihood	df	Sig. of the Change
Step 1	ICU hospitalization	−216.347	199.209	1	.000
Step 2	Pleural fluid	−116.742	131.975	1	.000
	ICU hospitalization	−123.828	146.145	1	.000
Step 3	Absolute neutrophil count	−50.755	19.260	1	.000
	Pleural fluid	−109.997	137.745	1	.000
	ICU hospitalization	−93.544	104.838	1	.000
Step 4	Vomiting	−41.125	22.932	1	.000
	Absolute neutrophil count	−42.350	25.382	1	.000
	Pleural fluid	−105.400	151.482	1	.000
	ICU hospitalization	−83.648	107.979	1	.000
Step 5	Vomiting	−136.164	22.659	1	.000
	Absolute neutrophil count	−38.497	27.325	1	.000
	Pleural fluid	−99.083	148.496	1	.000
	ICU hospitalization	−79.791	109.913	1	.000
	Length of hospitalization	−29.659	9.649	1	.000
Step 6	Vomiting	−31.591	21.789	1	.000
	Loss of taste	−24.835	8.276	1	.000
	Absolute neutrophil count	−33.224	25.055	1	.000
	Pleural fluid	−89.802	138.210	1	.000
	ICU hospitalization	−73.150	104.906	1	.000
	Length of hospitalization	−25.903	10.413	1	.000
Step 7	Vomiting	−27.255	21.951	1	.000
	Loss of taste	−20.757	8.955	1	.000
	Loss of smell	−20.697	8.835	1	.000
	Absolute neutrophil count	−28.461	24.364	1	.000
	Pleural fluid	−81.758	130.959	1	.000
	ICU hospitalization	−65.344	98.131	1	.000
	Length of hospitalization	−21.648	10.737	1	.000
Step 8	Vomiting	−19.608	16.955	1	.000
	Loss of taste	−16.899	11.535	1	.000
	Loss of smell	−17.389	12.515	1	.000
	Rhinorrhea	−16.279	10.296	1	.000
	Absolute neutrophil count	−23.352	24.441	1	.000
	Pleural fluid	−76.071	129.880	1	.000
	ICU hospitalization	−55.328	88.394	1	.000
	Length of hospitalization	−16.641	11.021	1	.000
Step 9	Vomiting	−15.966	18.051	1	.000
	Loss of taste	−12.084	10.288	1	.000
	Loss of smell	−13.482	13.083	1	.000
	Rhinorrhea	−12.862	11.843	1	.000
	Absolute neutrophil count	−17.749	21.618	1	.000
	Pleural fluid	−71.503	129.125	1	.000
	ICU hospitalization	−47.948	82.016	1	.000
	Length of hospitalization	−12.410	10.940	1	.000
	Age	−11.131	8.382	1	.000
Step 10	Vomiting	−10.197	17.564	1	.000
	Oxygen therapy	−6.940	11.049	1	.000
	Loss of taste	−7.432	12.032	1	.000
	Loss of smell	−8.983	15.135	1	.000
	Rhinorrhea	−8.524	14.218	1	.000
		−11.581	20.330	1	.000

(continued on next page)

Table 4 (*continued*)

Model if Term Removed					
Variable		Model Log-Likelihood	Change in −2 Log-Likelihood	df	Sig. of the Change
	Absolute neutrophil count				
	Pleural fluid	−65.568	128.304	1	.000
	ICU hospitalization	−40.117	77.403	1	.000
	Length of hospitalization	−6.783	10.734	1	.000
	Age	−6.475	10.119	1	.000
Step	Vomiting	−7.137	17.168	1	.000
11	Oxygen therapy	−4.804	12.502	1	.000
	Loss of taste	−4.415	11.725	1	.000
	Loss of smell	−6.159	15.213	1	.000
	Rhinorrhea	−5.221	13.337	1	.000
	Absolute neutrophil count	−8.051	18.997	1	.000
	Erythrocyte sedimentation rate	−1.416	5.726	1	.000
	Pleural fluid	−60.513	123.920	1	.000
	ICU hospitalization	−38.927	80.749	1	.000
	Length of hospitalization	−3.528	9.951	1	.000
	Age	−4.725	12.344	1	.000
Step	Vomiting	−3.057	15.997	1	.000
12	Oxygen therapy	−1.216	12.314	1	.000
	Loss of taste	−1.902	13.687	1	.000
	Loss of smell	−3.445	16.772	1	.000
	Rhinorrhea	−1.574	13.031	1	.000
	Platelet count	−8.552	6.988	1	.000
	Absolute neutrophil count	−5.947	21.776	1	.000
	Erythrocyte sedimentation rate	−9.360	8.604	1	.000
	Pleural fluid	−59.973	129.829	1	.000
	ICU hospitalization	−35.363	80.609	1	.000
	Length of hospitalization	−0.095	10.073	1	.002
	Age	−1.038	11.959	1	.001
Step	Vomiting	−2.386	16.588	1	.000
13	Oxygen therapy	−1.159	12.135	1	.000
	Loss of taste	−1.695	13.205	1	.000
	Loss of smell	−2.814	17.444	1	.000
	Rhinorrhea	−1.766	13.348	1	.000
	White-cell count	−5.059	1.933	1	.001
	Platelet count	−7.992	7.801	1	.005
	Absolute neutrophil count	−1.093	20.003	1	.000
	Erythrocyte sedimentation rate	−9.572	8.960	1	.003
	Pleural fluid	−1.511	128.839	1	.000
	ICU hospitalization	−1.126	80.067	1	.000
	Length of hospitalization	−9.026	9.868	1	.002
	Age	−1.257	12.331	1	.000

algorithms are the most widely used and effective models for predicting COVID-19 mortality. So far, most efforts have targeted the application of ANNs and their comparison with other techniques for mortality prediction in patients with COVID-19. Accordingly, Gao et al. (2020) conducted a retrospective study on the data of 2520 hospitalized COVID-19 patients. The result showed that the ANN model with an AUC of 0.9760 was the most successful algorithm for mortality prediction [51]. Vaid et al. (2020) analyzed the data of 4029 positive COVID-19 patients. Their results showed that the MLP-ANN classifier gained the best performance to predict COVID-19-related mortality [73]. The results of one study conducted by Zhao et al. (2020) on 313 COVID-19 patient data showed that the ANN achieved the best performance in predicting mortality with an AUC of 0.75 [74]. Asteris et al. (2022) trained four ML techniques on the data of 10,237 patients, and finally implemented and evaluated the ANN model to predict mortality in COVID-19 patients with an accuracy of 89.47% [75]. The ANN model developed by Lin et al. (2021) predicts the mortality risk of COVID-19 patients with an AUC of 0.96 [76]. Adib et al. (2021) also compared three ML models' performance for mortality analysis of pregnant women with COVID-19. The results showed the ANN technique yields significantly higher prediction performance (precision of 100% and accuracy of 95%) [77]. Accordingly, Naseem et al. (2021) applied several ML methods for predicting mortality in confirmed COVID-19 patients. They found that the deep neural network (DNN), with an accuracy of 99.53% and AUC of 88.5%, gained the highest performance [78]. Similarly, Xiaoran et al. (2020) proposed a DNN model based on the clinical data of 5766 individuals to predict the likelihood of ICU admission and mortality among hospitalized COVID-19 patients with an AUC of 0.780 [79]. Furthermore, Hoon et al. (2020) implemented a DNN-based prediction model with a database containing the data of 361 COVID-19 patients to predict the mortality of COVID-19 patients. The developed model provided 100% sensitivity, 91% specificity, and 92% accuracy [80]. Alsuwaiket et al. (2020) proposed an ANN-based prediction method to predict COVID-19 mortality, and the proposed model attained appropriate performance with an MAE of 0.053 and an MSE of 0.032 [81]. In addition, Sankaranarayanan et al. (2021) compared the performance of four ANN models on 1025 patients' data to predict the mortality risk among hospitalized COVID-19 patients. The most successful performance was obtained by using the recurrent neural network (RNN) with an AUC-ROC of 0.938 [82]. Schiaffino et al. (2021) also assessed the performance of four ANN models using a dataset (n = 1541) to predict COVID-19 mortality. The model developed with the MLP-ANN yielded the best performance in predicting mortality in COVID-19 cases (AUC = 0.844) [83]. Finally, Karthikeyan et al. (2021) designed an ANN-based model for predicting COVID-19-related mortality with an AUC of 0.90 [11].

In the present study, given the superiority of the ANN model, we attempted to identify the most effective configuration to predict COVID-19 mortality. Hence, the current retrospective study aimed to develop and validate two ANN models based on 13 variables to predict mortality among hospitalized COVID-19 patients. Based on the findings, the BP-ANN obtained the best performance with an AUC-ROC of 0.901. Implementing a CDSS interface based on the best ANN configuration creates more added value.

FS is an effective prerequisite to improving the performance of ML models. The selected variables were used as inputs to the ML models. In the reviewed studies [11,17,44,74,83–87], the most important clinical factors for COVID-19 mortality prediction were old age, chronic underlying diseases, oxygen saturation, loss of taste/smell, pleural fluid, ICU hospitalization, length of stay (LOS), lymphocyte count, CRP rate, and D-dimer level. In the current study, after feature selection, the variables of age, vomiting, oxygen therapy, loss of taste, loss of smell, rhinorrhea, white-cell count, platelet count, absolute neutrophil count, erythrocyte sedimentation rate, pleural fluid, ICU hospitalization, and length of hospitalization were introduced as the top predictors. We applied nominated features as inputs to train different ANN models for the mortality prediction of COVID-19 patients. The ANN algorithm implementation in previous studies and our study demonstrated optimal performance for most indicators.

5. Limitations and implications

The CDSS designed herein seems to predict the mortality risk of hospitalized COVID-19 patients with acceptable accuracy. However, the implementation of the proposed system has several limitations that must be addressed. The most significant limitation of the present study was the retrospective and single-center nature of the selected dataset. The dataset contained inconsistent, erroneous, and abnormal data fields, affecting the quality of modeling and limiting the comprehensiveness

Table 5
Comparing different configurations of the ANN.

BP (50% train, 50% test)					DTD (50% train, 50% test)				
Configuration	TP	FN	FP	TN	Configuration	TP	FN	FP	TN
13-1-1	450	139	297	824	13-1-1	428	161	320	801
13-2-1	477	112	267	854	13-2-1	455	134	311	810
13-3-1	483	106	233	888	13-3-1	466	123	295	826
13-4-1	502	87	219	902	13-4-1	473	116	273	848
13-5-1	527	62	167	954	13-5-1	489	100	261	860
13-6-1	533	56	144	977	13-6-1	501	88	225	896
13-7-1	539	50	112	1009	13-7-1	513	76	208	913
13-8-1	550	39	98	1023	13-8-1	534	55	146	975
13-9-1	548	41	79	1042	13-9-1	542	47	119	1002
13-10-1	567	22	61	1060	13-10-1	553	36	95	1026
BP (60% train, 40% test)					BP (60% train, 40% test)				
Configuration	TP	FN	FP	TN	Configuration	TP	FN	FP	TN
13-1-1	455	134	282	839	13-1-1	436	156	309	812
13-2-1	481	108	261	860	13-2-1	461	128	300	821
13-3-1	486	103	225	896	13-3-1	473	116	281	840
13-4-1	506	83	209	912	13-4-1	480	109	265	856
13-5-1	529	60	151	970	13-5-1	491	98	249	872
13-6-1	543	46	126	995	13-6-1	506	83	216	905
13-7-1	550	39	94	1027	13-7-1	516	73	197	924
13-8-1	561	28	80	1041	13-8-1	540	49	137	984
13-9-1	568	21	59	1062	13-9-1	546	43	115	1006
13-10-1	577	12	51	1070	13-10-1	563	26	85	1036
BP (70% train, 30% test)					BP (70% train, 30% test)				
Configuration	TP	FN	FP	TN	Configuration	TP	FN	FP	TN
13-1-1	465	124	282	839	13-1-1	450	142	300	821
13-2-1	490	99	261	860	13-2-1	465	124	288	833
13-3-1	476	93	225	896	13-3-1	480	109	271	850
13-4-1	515	74	209	912	13-4-1	490	99	255	866
13-5-1	539	50	151	970	13-5-1	501	88	241	880
13-6-1	523	35	126	995	13-6-1	515	74	211	910
13-7-1	555	34	94	1027	13-7-1	526	63	191	930
13-8-1	570	19	80	1041	13-8-1	550	39	131	990
13-9-1	573	16	59	1062	13-9-1	556	33	95	1026
13-10-1	581	8	51	1070	13-10-1	570	19	81	1040
BP (80% train, 20% test)					BP (80% train, 20% test)				
Configuration	TP	FN	FP	TN	Configuration	TP	FN	FP	TN
13-1-1	471	118	259	862	13-1-1	459	133	289	832
13-2-1	495	94	271	870	13-2-1	475	114	278	843
13-3-1	502	87	205	916	13-3-1	485	104	259	862
13-4-1	521	68	189	932	13-4-1	496	93	252	869
13-5-1	541	48	140	981	13-5-1	510	79	238	883
13-6-1	545	31	116	1005	13-6-1	517	72	206	915
13-7-1	560	29	80	1041	13-7-1	536	53	184	937
13-8-1	575	14	61	1060	13-8-1	562	27	120	1001
13-9-1	578	11	53	1068	13-9-1	546	23	86	1035
13-10-1	586	3	25	1096	13-10-1	578	11	71	1050

Based on comparing the different architectures of two selected configurations of the ANN using the confusion matrix, we obtained BP-ANN with the structure of 13–10-1 with TP = 586, FN = 3, FP = 25, and TN = 1096. DTD with the design of 13–10-1 with TP = 578, FN = 11, FP = 71, and TN = 11,050 gained the best performance compared to other configurations in 80% data for train and 20% data for test. The results of measuring the TPR, FPR, TNR, TPR, and the precision of two selected ANN configurations for various dataset splittings are depicted in Figs. 6–9.

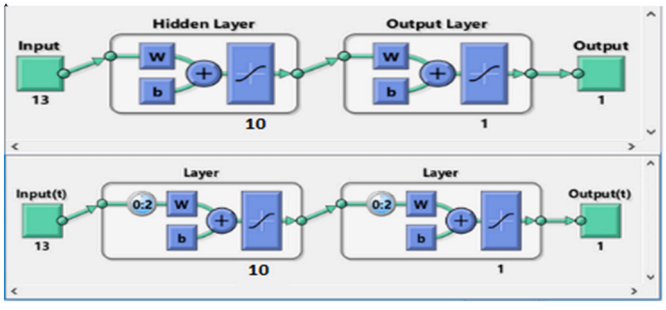

Fig. 10. The best configuration of BP (above) and DTD (below).

and generalizability of data. Therefore, an attempt was made to minimize this challenge by referring to the responsible physician. In addition, to solve the problem of incomplete fields, the cases with more than 60% missing data were excluded from the analysis. In other instances, empty values were replaced with the values predicted by the simple K-means algorithm with specific values of K. The selected dataset lacks some essential variables, such as imaging data. However, as our study aimed to predict mortality at the time of admission, the available clinical and administrative data were sufficient. Finally, we only used two ANN algorithms in different configurations. In the future, the performance of our proposed model can be enhanced if more ML techniques are tested on larger, prospective, and multicenter datasets. Finally, future studies should concentrate on more external validations to improve the modeling quality and alleviate the bias.

6. Conclusions

Timely and accurate prediction of COVID-19 patients' outcomes, especially determining their mortality risk, is critical to optimal use of limited hospital resources and supporting clinical decisions. Using the ANN-based CDSS developed in our study in real clinical environments will promote patient safety and reduce COVID-19 severity and mortality.

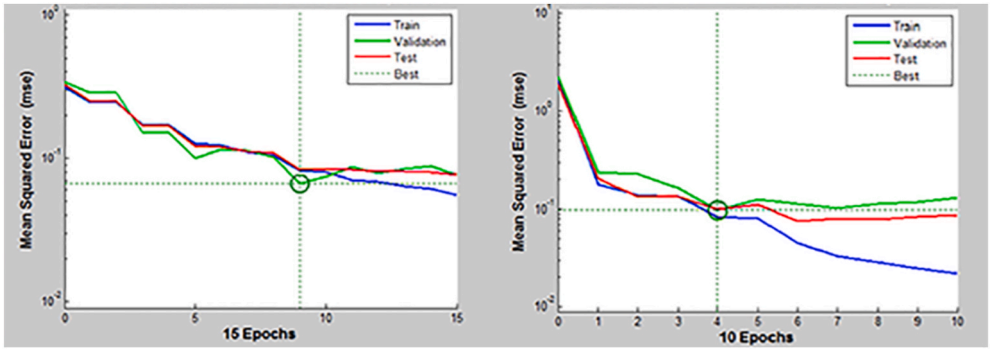

Fig. 11. Comparing the two selected configurations using the MSE.

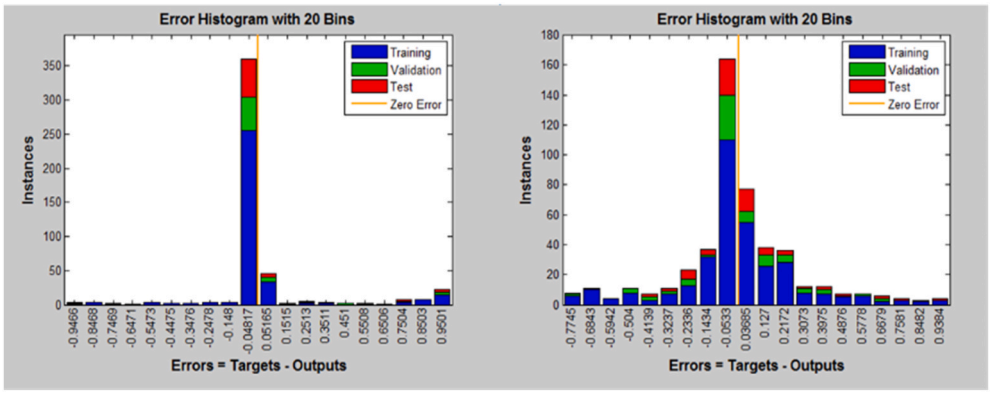

Fig. 12. Comparing the two selected configurations using the error histogram.

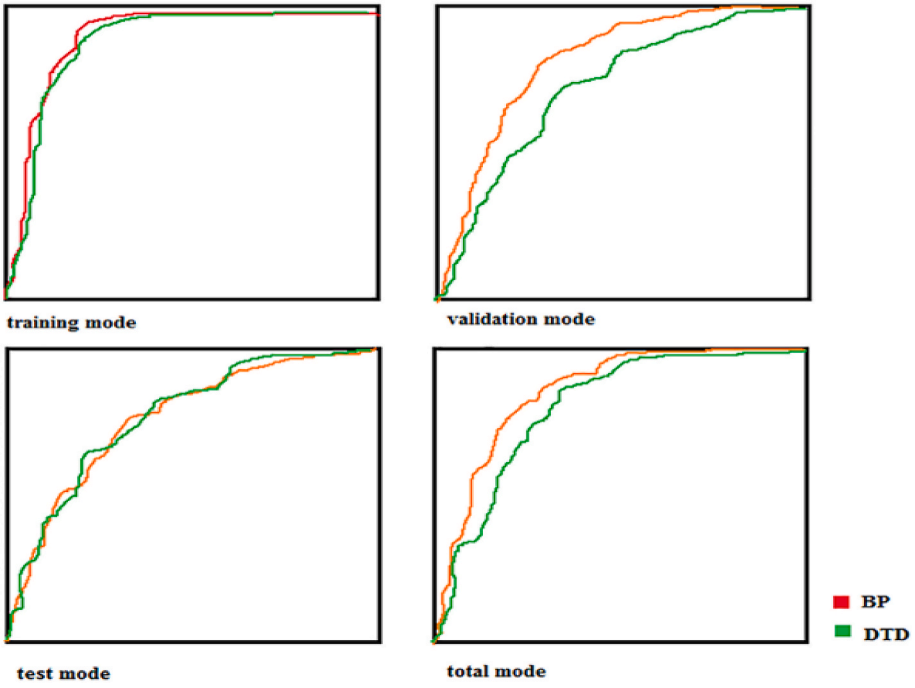

Fig. 13. All ROC modes of the two FF of the ANN.

Still, further external validation studies are required to validate our findings.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

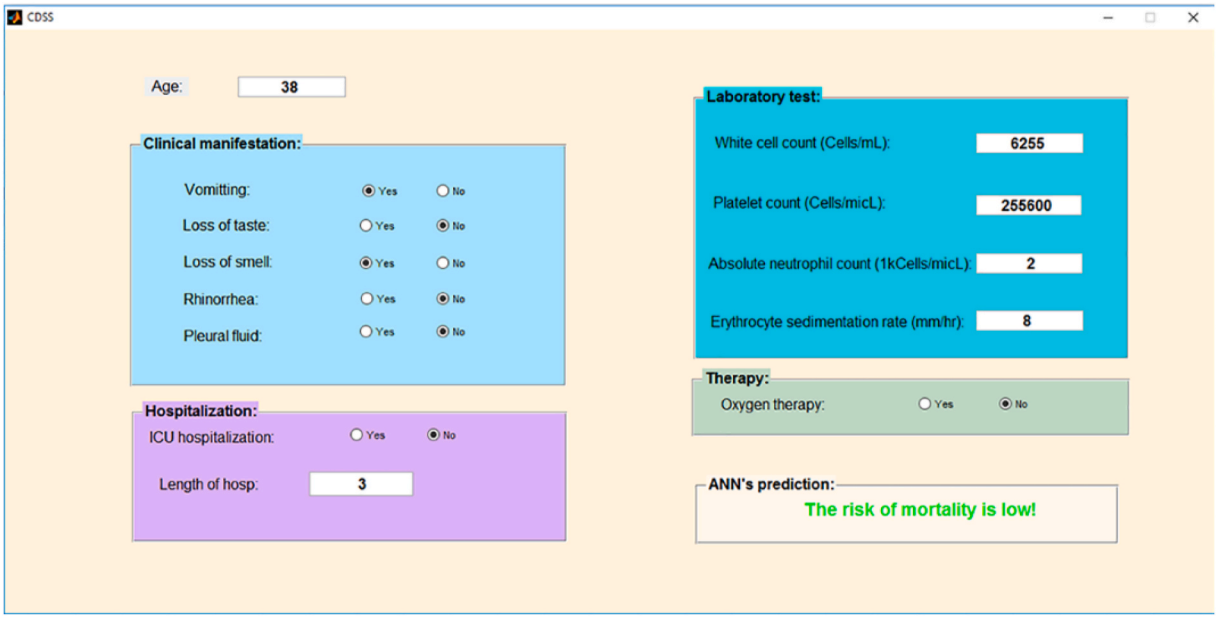

Fig. 14. The CDSS to predict COVID-19 mortality based on ANN.

the work reported in this paper.

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