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AI-Enhanced Prediction of Multi Organ Failure in COVID-19 Patients

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***Abstract*—The occurrence of multi-organ failure (MOF) in COVID-19 patients constitutes a critical complication, markedly elevating the mortality risk compared to patients without MOF. Consequently, early identification and timely intervention for these patients are crucial. In this research, we utilized a substantial dataset derived from the multicenter observational study "Coagulopathy associated with COVID-19 (CA-COVID-19)," covering 26 UK NHS Trusts and involving 8,032 COVID-19 patients aged 18 years and older. Previously, numerous analyses have been conducted to assess clinical outcomes and their predictive factors, utilizing data from the CA-COVID-19 study through standard statistical methods. However, Artificial Intelligence (AI) models have not been used on this data for predicting clinical outcomes. This paper introduces an AI driven approach to predict the onset of multi-organ failure (MOF) in patients diagnosed with COVID-19. We implemented six AI models including (i) Artificial Neural Network with Backpropagation, (ii) XGBoost, (iii) Support Vector Classifier, (iv) Stochastic Gradient Descent Classifier, (v) Random Forest, and (vi) Logistic Regression. The models underwent evaluation through a 5-fold cross-validation technique, employing various metrics for assessment. The findings revealed that the Support Vector Classifier surpassed all other models in terms of overall performance, consistently achieving a score of 0.98 across accuracy, precision, F1 score, and recall metrics. Additionally, this model attained the lowest loss score at 0.082 and the highest AUC score of 0.951, outperforming all competing models. Leveraging a distinctive feature selection method, we identified that certain factors such as major bleeding, thrombosis, prior malignancy, lung disease history, smoking status, Asian ethnicity, and elevated levels of platelets, D-dimer, LDH, and Troponin I, significantly contribute to the development of multi-organ failure in COVID-19 patients. The insights garnered from this study could enable clinicians to promptly identify patients at heightened risk of developing multi-organ failure, facilitating timely interventions that may enhance clinical outcomes.**

Keywords—Artificial Intelligence; Machine Learning; Deep Learning; Malti Organ Failure; COVID-19

I. INTRODUCTION

Corona virus disease (COVID-19) was first declared as a global pandemic in early 2020 [1]. It was associated with an unprecedented increase in mortality and other complications such as thrombosis (blood clots), multi organ failure (MOF) and major bleeding. This unexpected pandemic exerted significant pressure on the already limited health care resources [2] and it was particularly pressing in relatively resource-scarce settings, such as low or middle-income countries [3,4]. To prevent human efforts of disease containment from being overwhelmed, it was required to have tools that can streamline the diagnosis, predict clinical outcome and treatment of COVID-19 [5]. As an attempt to minimise the pressure on available medical facilities and resources, there were attempts to deploy artificial intelligence (AI) at various levels of the health care system. In general, AI has been applied to COVID-19 in four main areas: diagnosis, public health, clinical decision making, and therapeutics [6].

In a study by Liang et al, a deep learning model was used to predict the risk of developing critical illness for COVID-19 patients [7]. The model was able to predict low, medium, and high risk of critical illness with 95% sensitivity and 95% specificity respectively. In another study by Li et al, machine learning techniques were used to predict the mortality in patients with COVID-19 [8]. They used five models including (i) an Autoencoder model, (ii) logistic regression, (iii) random forest, (iv) Support Vector Machine, and (v) Isolation Forest. They reported that autoencoder model outperformed the other models with specificity and accuracy above 90% [8]. Wu et al, also used four logistic regression models with different set of features for severity risk prediction during the admission process at hospital [9]. They achieved AUC score of 0.86 on training dataset and 0.90 on the validation dataset [9].

Moreover, Mushtaq et al, [10] used initial chest radiographs and a set of Convolutional Neural Networks to predict clinical outcome for COVID-19 patients. They trained the models with 2.3 million Chest X Rays (CXRs) to detect several specific abnormalities on frontal CXRs. They stated that the AUC score

for the detection of the specific abnormalities varied from 0.89 to 0.98. Additionally, a deep neural network, Support Vector Machine (SVM), and random forest models were used in a study by Fang et al [11] to predict ICU admission and mortality for COVID-19 patients. They were able to achieve AUC score of 0.813 in predicting ICU admission and AUC score of 0.741 in predicting mortality.

Furthermore, Zandehshahvar et al, used a two-stage transfer learning technique to train a convolutional neural network (CNN) to analyse chest-X-rays and predict severity of illness in patients with COVID-19 [12]. They were able to classify four classes of disease severity (normal, mild, moderate, and severe) with AUC score of 0.93 [13] and also used XGBoost and Support Vector Machine (SVM) classifiers for predicting severity of illness. XGBoost outperformed SVM with 97% accuracy, 98% precision, 95% recall, 96% f1-score.

In addition to predicting clinical outcomes for COVID-19 patients, machine learning models have also been used for COVID-19 diagnosis. For instance, Jin et al used CT scans from 9025 patients consisting of COVID-19, CAP, influenza, and non-pneumonia, and they developed deep learning models to predict COVID-19 diagnosis [14]. They achieved AUC score of 0.9745, sensitivity score of:0.8703, and specificity score of 0.9660 in predicting COVID-19. A Squeeze Net Convolutional Neural Network with Bayesian optimization additive was also used by Ucar et al [15] to analyse X-ray images and predict COVID-19 diagnosis. This model achieved an accuracy of 98.3%.

Machine learning models were also used to predict the death or recovery of the COVID-19 patients based on their treatment plan. In a study by Shahid et al. [16], four machine learning models (1. Autoregressive integrated moving average [ARIMA], 2. support vector regression [SVR], 3. long short-term memory [LSTM], 4. bidirectional long short-term memory [Bi-LSTM]) were used to predict the death or recovery of the COVID-19 patients. They reported that Bi-LSTM model had the best performance with lowest MAE and RMSE values of 0.0070 and 0.0077 respectively.

AI prediction models developed by most of these studies are mainly to predict the development of critical illness or mortality. Moreover, most of the studies are limited to small number of patients and there are no models in predicting the MOF as a clinical outcome on its own. Robustness of these machine learning and deep learning models can also be considered a limitation, as clinical datasets may contain various types of noise, perturbations, and adversarial examples. Thus, a proper data cleaning and pre-processing is required and testing a model requires several aspects that go beyond testing itself. Some of these aspects relate to how the model reacts to different inputs when they are unexpected [23, 24].

In this study, we built models to predict MOF in patients with COVID-19 admitted to hospitals using the data obtained from Coagulopathy associated with COVID-19 (CA-COVID-19) which is a multicentre observational study across 26 UK NHS Trusts. The study included 8032 COVID patients with age >= 18 years and it was approved by the Health Research Authority (HRA), Health and Care Research Wales (HCRW) and received local Caldicott Guardian support in Scotland (reference number: 20/HRA/1785) [17,18].

The data used in this research has already been used to assess clinical outcomes such as thrombosis, major bleeding, MOF and mortality and their association with patient demographics, comorbidities and on admission laboratory data using standard statistical methods [17,18]. However, the previous studies that used this data, only used traditional statistical analysis and machine learning models have not been used on this data.

One of the previous analyses of the data from CA-COVID-19 [17] included 5883 patients admitted to hospitals between 1 April 2020 and 31 July 2020. Of these 5883 patients, 194 patients developed MOF during the hospital admission equating to incidence of 3.3%. They assessed the impact of oral anticoagulation (OAC) in developing MOF prior to admission with COVID-19 and of the 194 patients who developed MOF, 10/194 (5.2% were on oral anticoagulant and 184/194 (94.8%) were not on OACs, corresponding to a 3.64-fold increased risk (95% CI 1.93–6.90) prior to adjusting the analysis with Fine and Gray model for the multivariate setting and death in the absence of the secondary outcome was considered the competing event. They observed significant reduction of developing MOF in patients on oral anticoagulant prior to admission disappear following adjusted multivariate analysis (HR 1.86, 95% CI 0.98–3.61) and adjusted propensity score (for patients not on anticoagulant analysis) (HR 1.53, 95% CI0.70–3.33).

Another sub-group analysis from CA-COVID-19 included 152 consecutive patients who had severe COVID-19 requiring veno-venous extracorporeal oxygenation (ECMO) from four UK commissioned centres during the first wave of the COVID-19 pandemic (1 March to 31 May 2020) [19]. This study [19] found that there were 96 thrombotic events consisting of venous 44·7% [of which 66·2% pulmonary embolism (PE)], arterial 18·6% and extracorporeal membrane oxygenation (ECMO) circuit thrombosis 9·9%]. Authors found that raised lactate dehydrogenase (LDH) at the initiation of ECMO was associated with an increased risk of thrombosis. Major bleeding was associated with 3·87-fold increased risk of mortality and PE with a 2-fold risk of mortality [19].

Another sub-analysis of patients from CA-COVID-19 supported with VV-ECMO during the first and second waves of the pandemic found that Age >55 years and an elevated creatinine level were associated with increased mortality and the development of major bleeding during ECMO had a 3-fold risk of mortality [20]. In another sub-analysis of patients with history of autoimmune disease (AD) who develop COVID-19 found that patients with severe rheumatologic AD had significantly higher mortality [21].

To address the existing knowledge gap, this study used a large-scale dataset and a machine learning approach for the first time, to predict multi organ failure (MOF) in patients with COVID-19 admitted to hospitals.

II. METHODOLOGY

Data collected from CA-COVID-19 was used to build machine learning (ML) and deep learning (DL) models for predicting possible development of MOF in COVID-19 patients.

To build a quality dataset, fully anonymised source data of the study was passed through couple of stages. During data preprocessing, we removed outliers and invalid data and treated missing data by data imputation with K Nearest neighbour algorithm using fancy impute library.

By feature engineering, we extracted new features for example, patient body mass index group ('less than 18.5', '18.6 to 24.9', '25 to 29.9', '30 to 39.9', 'above 40'), and patient age group ('18 to 29 years', '30 to 49 years', '50 to 69 years', '70 to 89 years', 'over 90 years'). There were 44 features at the end of feature engineering stage, and it included 17 laboratory blood test results, 17 demographic factors and 10 historical or present clinical conditions of the patient.

Moreover, the categorical clinical and demographic features were encoded using one-hot encoding technique and created binary columns for each category. Numerical features such as laboratory test results were passed through standard scaler to scale the values to standard range.

In the feature selection stage, we used four methods including (i) statistical T test, (ii) Pearson pairwise feature correlation, (iii) feature ranking with recursive feature elimination with logistic regression, and (iv) feature ranking with recursive feature elimination with random forest classifier, to find features which have an impact on developing multi organ failure of COVID-19 patients. Table 1 shows the significant features which have been identified using each feature selection method.

TABLE I. SIGNIFICANT FEATURES FOR MULTI ORGAN FAILURE CLINICAL OUTCOME OF COVID-19 PATIENTS

Feature Selection Method	Significant features
T test (SciPy Stats)	Thrombosis ($p<0.001$) Major bleeding ($p<0.001$) Asian ethnicity ($p=0.03$) History of malignancy ($p=0.02$)
Pearson pairwise feature correlation	Thrombosis Major bleeding History of malignancy History of lung disease Raised levels of fibrinogen CRP Age group 70 to 89
Feature ranking with recursive feature elimination (Logistic Regression)	Thrombosis Major bleeding Smoking Ethnicity Asian History of bleeding disorders BMI over 40
Feature ranking with recursive feature elimination (Random Forest Regressor)	Raised levels of Platelets D-dimer LDH Troponin I Ferritin Lactate CRP Major bleeding Thrombosis

Considering common features identified in above feature selection methods (Table 1) and already published literature on COVID-19, we selected the presented features in Table II, for model training stage for predicting multi organ failure clinical outcome.

TABLE II. SELECTED FEATURES FOR MODEL TRAINING

Feature Name
Presence of major bleeding
Thrombosis (blood clots)
History of malignancy
History of lung disease
Smoking
Asian ethnicity
Levels of platelets
D-dimer
Lactate dehydrogenase (LDH)
Troponin I

Following feature selection step, six binary classification AI models were developed to predict risk of developing multi organ failure of the COVID-19 patient. The models include (i) ANN with backpropagation using binary cross entropy loss function and activation functions (rectified linear unit and sigmoid), (ii) XGBoost, (iii) Support Vector Classifier (SVC), (iv) Stochastic Gradient Descent classifier (SGDClassifier), (v) Random Forest, and (vi) Logistic Regression.

In addition, Grid Search and Random Search hyper parameter tuning techniques were used to find the best possible parameters for each of the models to optimise predicting power. Table III shows the selected optimum values for each parameter and each model.

TABLE III. HYPER PARAMETER TUNING OUTCOMES

Model	Modified parameters and extra details
ANN	keras sequential API with optimizer function = adam data batch size = 32 number of times to run the model (epochs) = 10 compilation with binary cross entropy loss function, rectified linear unit, and sigmoid activation functions
XGBoost	Learning rate = 0.01 maximum tree depth = 8 minimum child weight = 1
SVC	Strength of the regularization (C) = 3.4067 gamma=0.331 probability estimates = True
SGDClassifier	Regularization constant (alpha) = 0.000774 Elastic Net mixing parameter (l1_ratio) = 0.06 Loss = log penalty (regularization term) = elasticnet
Random Forest	Minimum number of samples at a leaf node = 50 Maximum depth of the tree = 4 Function to measure the quality of a split = entropy
Logistic Regression	Inverse of regularization strength (C) = 10

Furthermore, a 5-fold cross validation technique was used during model training and evaluation. In our experiment, 33% of the original dataset (records of 2649 COVID patients out of 8032 COVID patients) was used for testing the performance of trained models.

III. Results and Discussion

The six developed AI models were evaluated on the test dataset including records of 2649 COVID-19 patients using a 5-fold cross validation technique. Figure 1 shows the generated confusion matrices for each model.

The confusion matrices presented in figure 1 show true postives (sensitivity - correctly predicting patients developing MOF), true negatives (specificity - correctly predicting patients not developing MOF), false postives (wrongly predicting patients developing MOF), false negatives (wrongly predicting patients not developing MOF).

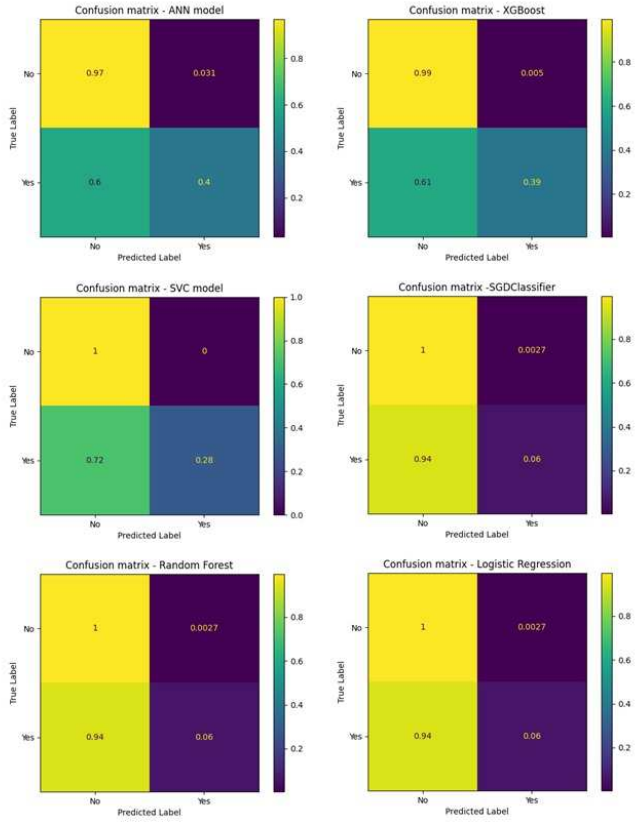

Figure 1. Confusion matrices for each classifier

Moreover, Table IV presents the results of model performance evaluation based on four evaluation metrics including (i) accuracy, (ii) F1 score, (iii) precision and (iv) recall, which were calculated based on the generated confusion matrices after performing 5-fold cross validation.

TABLE IV. Performance evaluation based on Accuracy, F1 score, precision, and recall scores

Model	Accuracy	Precision	Recall	F1 Score
ANN	0.96	0.97	0.96	0.96
XGBoost	0.98	0.98	0.98	0.98
SVC	0.98	0.98	0.98	0.98
SGDClassifier	0.97	0.96	0.97	0.96
Random Forest	0.97	0.96	0.97	0.96
Logistic Regression	0.97	0.96	0.97	0.96

Accoring to Table IV, XGBoost and SVC classifiers had the best performance with the accuracy of 0.98 and outperformed all other models. These models also achieved the same score (0.98) for percision, F1 score and recall evaluation metrics. SGDClassifier, Random Forest, and Logistic Regression models were the second best performing models with accuracy score of 0.97 for prediction. These three models achieved the same score of 0.96 for percision and F1 score, and 0.97 for recall evaluation metric. ANN model with backpropagation had the worst performance out of all these six models with the accuracy score of 0.96, precision score of 0.97 and F1 score and recall score of 0.96.

In order to perform a more in-depth evaluation and to identify the best performing model, in addition to confusion matrices and accuracy, F1 score, precision, and recall evaluation metrics, ROC diagrams were generated to illustrate the performance of the classifiers across different classification thresholds. The ROC curve visualises the true positive rate against the false positive rate at various threshold settings. Figure 2 shows the ROC diagrams for each model.

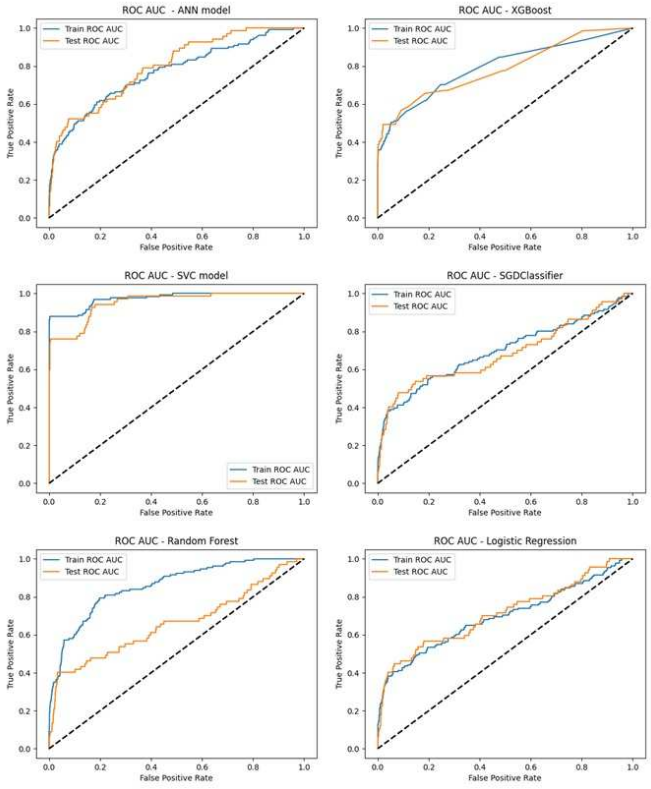

Figure 2. ROC diagram for each classifier

Accordingly, models were evaluated using Loss score (penalty for failing to meet the projected output) and AUC (Area Under the Receiver Operating Characteristic Curve) score and the results are presented in Table V.

TABLE V. PERFORMANCE EVALUATION BASED ON LOSS AND AUC SCORES

Model	Loss Score	AUC Score
ANN	0.097	0.798
XGBoost	0.143	0.786
SVC	0.082	0.951
SGDClassifier	0.116	0.684
Random Forest	0.104	0.659
Logistic Regression	0.103	0.712

The Loss Score provides insights into how well the models are minimizing their errors during training. Lower Loss Scores generally indicate better model convergence and improved fitting to the training data. Moreover, the AUC Score is a critical metric for assessing the model's ability to discriminate between positive and negative instances. Higher AUC Scores indicate superior discriminatory power.

Table V shows that Loss score for SVC model was less than all other models (0.082), suggesting effective model training and minimal error during the learning process. ANN model follows closely with a Loss score of 0.097, indicating a relatively low level of training error. Other models including Logistic Regression, Random Forest, and SGDClassifier also demonstrate competitive Loss scores, signifying reasonable convergence during training.

Regarding AUC score, SVC model achieved a remarkably high score of 0.951, signifying excellent discrimination between positive and negative classes. ANN follows with an AUC Score of 0.798, demonstrating a good ability to distinguish between classes, though not as high as SVC model. Logistic Regression and XGBoost models also display respectable AUC Scores, indicating solid performance in terms of classification accuracy. Considering both Loss score and AUC score, SVC model emerges as a top performer in this comparison, showcasing strong convergence during training and exceptional discriminatory power.

After considering all evaluation metrics including accuracy, precision, recall, F1 score, Loss score, and AUC score, we identified that SVC model has the best overall performance in predicting multi organ failure in patients diagnosed with COVID-19 and outperformed all other models.

IV. CONCLUSION

This study pioneers the use of machine learning techniques, diverging from conventional statistical methods, to predict the likelihood of multi-organ failure in COVID-19 patients upon hospital admission. By leveraging patient demographic data, comorbidities, and initial laboratory findings, our approach offers a novel and potentially more effective means of identifying at-risk individuals.

Six machine learning and deep learning models including (i) Artificial Neural Network (ANN) with Backpropagation, (ii) XGBoost, (iii) Support Vector Classifier (SVC), (iv) Stochastic Gradient Descent classifier (SGDClassifier), (v) Random Forest, and (vi) Logistic Regression, were developed and evaluated in this research. Table IV and Table V provide the summary of the performance in these models and figures 1 and 2 show individual model behaviour.

Moreover, a unique feature selection approach was used in this research to identify the most influential features for predicting multi organ failure in COVID-19 patients. In this approach, four feature selection methods including (i) statistical T test, (ii) Pearson pairwise feature correlation, (iii) feature ranking with recursive feature elimination with logistic regression, and (iv) feature ranking with recursive feature elimination with random forest classifier were used. The most influential features for prediction were selected based on already published studies in COVID-19 and the common features identified by each one of the feature selection methods. The selected features are presented in Table II.

During the feature selection phase, it was realized that development of major bleeding, thrombosis during admission, history of malignancy, history of lung disease, Smoking, Asian ethnicity, raised levels of platelets, D-dimer, LDH, and Troponin I are the features that significantly contribute to higher risk of developing MOF in patients with COVID-19.

In addition, k-fold cross validation (k =5) technique and six evaluation metrics including (i) accuracy, (ii) F1 score, (iii) precision, (iv) recall, (v) Loss score, and (vi) AUC score were used to evaluate the performance of the models. Grid search and random search methods were also used for hyper parameter tuning and to build models with optimum performance. 33% of the overall dataset (8032 COVID-19 patients) was used for testing the trained models.

The results show that the SVC model outperformed all other models in the overall performance with 0.98 accuracy, precision, F1 score, and recall evaluation metrics. This model also achieved the lowest Loss score of 0.082 and the highest AUC score of 0.951 among all other models. The findings from this research may assist clinicians to identify patients at risk of developing MOF early and intervene promptly to improve the clinical outcomes.

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