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Combined machine learning and finite element simulation approach towards personalized model for prognosis of COVID-19 disease development in patients

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Abstract

INTRODUCTION: Machine learning algorithms and in silico models for the COVID-19 have been used to classify infectious people and predict their condition in time.
OBJECTIVES: This study aims at creating a personalized model that combines machine learning and finite element simulation approach in order to predict development of COVID-19 infection in patients.
METHODS: The methodology combines several aspects (1) classification of patients into several classes of clinical condition (2) segmentation of human lungs in X ray images (3) finite element simulation to investigate the spreading of SARS-COV-2 virion in the lungs.
RESULTS: The findings show accuracy larger than 90% in all aspects of methodology. FE simulation has revealed that the distribution of airflow in the lung changes in time with the infection.
CONCLUSION: The key benefit of our proposed method is that it combines several methods that will be further improved in order to create a truly unique combined methodology for predictive models in patients infected with COVID-19.

Keywords: COVID-19, machine learning, personalized model, U-net, classification, predictive models, finite element simulation

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1. Introduction

Since December 2019, global health issues have been caused by the outbreaks of the COVID-19 disease of SARS-CoV-2 virus. SARS-CoV-2 triggers wide spectrum of heterogeneous clinical manifestation, from asymptomatic cases through acute respiratory distress syndromes to multiple organ failure and death [1, 2, 3, 4]. Therefore, researchers all over the world have been looking to define and stratify predictors of the severity of COVID-19 disease in an attempt to properly guide medical management. Basic knowledge of diseases and methods of discerning and assessing infection with COVID-19 have been established. Common blood hematology and clinical biochemistry tests are cheap, simple and widely-accessible biomarkers. As such, they became the most common method of tracking and predicting disease effects and forecasts it [5]. In addition to blood biomarkers, some indications show that COVID-19 can be better diagnosed using radiological imaging, so doctors all around the world decided to make an additional diagnosis based on chest CT or X-ray images

[6, 7, 8]. X-rays are more often chosen because of their advantages, such as less radiation dose and cost than CT. Also, X-ray machines are more frequent in hospitals and easier to clean than CT scanners.

Research is focused on all areas which could help to uncover key things that would prevent fatal outcomes. Scientists are examining the haematology and biochemistry data as well as the mentioned X-rays in order to obtain valuable results. Some studies have shown that serious, often fatal cases of COVID-19 disease are associated with elevated white blood cell counts, creatinine, blood urea nitrogen, markers of liver and kidney function, C-reactive protein (CRP), lower lymphocyte and platelet counts [9, 10, 11]. These research results provided an initial insight into how COVID-19 disease manifests, but after a more comprehensive study, it can be concluded that the results based on blood data show inconsistency. Blood biomarkers that have been shown to be good predictors of a patient's condition often differ from study to study and sometimes are contradictory [12]. Therefore, in order to obtain a better insight into prognostic biomarkers, it is desirable to explore other strategies, such as the machine learning (ML) methods.

The machine learning algorithms have been investigated in the field of COVID-19 for many purposes including epidemiological and clinical issues such as timely detection of disease outbreaks, fast diagnosis, classification and segmentation of radiological images, risk factors analysis, as well as prediction of final clinical outcomes [13, 14, 15]. For example, Yan and co-workers [16] conducted a research that used a blood sample database of 404 infected patients to classify important biomarkers of the disease seriousness in support of decision-making and logistical planners of health systems. To achieve this, three biomarkers have been selected using ML which had accuracy of more than 90%: LDH, lymphocyte and high sensitivity CRP (hs-CRP). The main drawback of this study is that their classification is binary – survival/death, which may not be the best type of classification in situations where the healthcare systems are overloaded. Same group of researchers lead by Yan employed supervised XGBoost model classification to predict the outcomes of individual patients (death/survival) using a sample blood test database. Same biomarkers (features) as in previous study were experimentally chosen with strong predictive degradation values or fatality of disease, also matching those in other literature [2, 17, 18, 19]. As in the previous paper, the classification was binary and except predicting survival, does not help in reducing the burden put on healthcare system, as severity of clinical condition is not predicted. Also, all previous research include only blood biomarkers and as mentioned, sometimes for setting up a diagnosis for COVID-19 patients, radiological images are of greater importance. For that purpose, we investigate X ray images in order to segment the lung. Lung segmentation can help not only in helping setting up diagnosis, but also in creating accurate 3D human airway in order to investigate airflow changes in COVID-19 infected patients.

The first step in processing medical images is segmentation. It indicates areas of interest or infected regions on X-ray and CT images. However, research is more oriented to CT segmentation in the case of COVID-19 disease. The most frequently used segmentation networks for CT scans include the classic U-Net network and some of its variations [20, 21, 22]. However, segmentation of chest X-ray images is more challenging, due to the confusing contrast of the image. The problem with image contrast is because the ribs are located over the soft tissue of the lungs [23]. To overcome these limitations, we have considered different deep learning methods, but in general, most of the papers are classification-based.

In some cases, for the detection task, YOLO algorithm was used in combination with deep neural networks [24, 25]. For example, Ozturk et al. used mentioned methodology and achieved an accuracy of 98.08% for binary classes and 87.02% for multi-class classification [25]. The main drawback of this study is that their multi-class is focused on 3 target classes (COVID-19, no-findings and pneumonia), which may not be the best type of classification in situations where it is better to have a more distinct classification into clinical conditions, in order to determine which patients will develop critical condition and therefore should stay at the hospital, and which could be discharged and treated at home, having only mild condition.

However, our goal is not to classify and assess the clinical condition, but to consider the best method to segment the lungs on X-rays in order to prepare images that will enable lung reconstruction with COVID-19. Instead of the YOLO algorithm, for detection mostly deep neural networks were used, such as VGG [26], ResNet [27], etc. Also, in these research papers, the emphasis is not on detection, but on classification, so we conclude that there are not many studies that aim only at lung detection and segmentation.

In addition to analysis of X ray imaging, CT/MRI images are also convenient for use, in order to create in silico models suitable for further examination. There has been a large increase in the number and complexity of in silico respiratory models in recent years. Latest airway models have integrated geometry based on images [28], realistic respiration manoeuvres [29] and lung mechanics [30, 31]. Reconstruction of human airway system is a complex task. Although segmentation and automated segment marking is an industry norm for two generations above the segmental airways, some user manual verification and corrections remain [32]. In contrast, the key challenge of automatic airway segmentation is to prevent false positive detections, as many algorithms appear to “leak" into the lung parenchyma [33]. A variety of methods are applied in order to detect and avoid leakage [34, 35].

Although there are many papers that deal with implementing ML in proposing valid prognostic

biomarkers and predictors of survival several days in advance, unsatisfied needs still remain. Furthermore, there is a limited research in the field focused on classification of patient in more subtle severity-of-illness categories (e.g. mild, moderate, severe, critical) during the hospital stay. Such knowledge could help physician and hospital managers in decision-making process aiming to avoid not only patient's final unfavourable outcome but also to improve other important secondary treatment endpoints and institutional performances which are deteriorated by inappropriate measures such as unnecessary prescription of adjunctive drugs (e.g. wide-spectrum antibiotics, immune-modulatory biologics), over-utilization of sophisticated and invasive diagnostics and inappropriate allocation of intensive care beds. Therefore, in this paper we propose a methodology based on ML to classify patients into several categories and predict the outcome in advance (change of severity of clinical condition). The main objectives and contributions of this paper are:

- examine rule-based algorithms which are more suitable for implementation in clinical practices rather than black box models (i.e. neural networks)
- classify patients into 4 distinct categories (mild, moderate, severe and critical) of COVID-19 disease
- predict disease progression (mild to moderate, moderate to severe, severe to critical clinical condition)
- work with a limited dataset, but implement different methods to overcome the drawbacks of small datasets
- implement U-net to perform segmentation of lungs with pneumonia in X-ray images coming from COVID-19 patients, all in order to create a unique combined blood biomarker and image analysis personalised model
- create in silico model of lungs and investigate the spreading of CORS-COV-2 virion using finite element computer simulation

2. Materials and methods

2.1. Dataset

Blood analysis data of the patients from two hospitals were used. The dataset from the Clinical Center of Kragujevac, Serbia consists of 45 patients and the dataset from the Clinical Center of Rijeka, Croatia consists of 60 patients. In total, the results of hematology and biochemistry analysis of 105 COVID-19 positive patients were collected. Dataset consisted of 44 female and 61 male patients, and when it comes to the age distribution of the patients in the form mean ± standard deviation was 52.77 ± 16.63.

For most patients, there are multiple blood samples in the dataset. We considered the first day (hospital admission) and days 2, 5, 7, 9, 11, and 14 after admission to the hospital. To deal with the missing data and to include values of analysis of the days that are not directly included in the prediction, we used the data imputation method. For filling each missing value, we used the mean of values of 2 days before and 2 days after.

Also, there some additional information about patients such as symptoms. In 83% of cases, fever was the most frequent symptom and in 74.6% cases it is followed by a cough. In Table 1 all the data about patients in the form of subgroups are given.

Table 1. Available data of COVID-19 patients for blood biomarker prediction.

demographic data
• gender and age
symptoms
• fever, cough, fatigue, chest pain, muscle pain, headache, dyspnea, loss of taste or smell
blood analysis
• Complete blood count (CBC): *erythrocytes* (red blood cells (RBC)) – red cell indices: hemoglobin (HGB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW); *leucocytes (white blood cells (WBC))* – white cell differentials: neutrophils, lymphocytes, monocytes, eosinophils (EOS) and basophils (BASO), *platelet indices*: platelets (PLT) platelet distribution width (PDW), mean platelet volume (MPV)
• Coagulation: prothrombin time (PT), international normalized ratio (INR), D-dimer
• Kidney function: urea, creatinine (CREA)
• Hepatic function: bilirubin - direct and total, alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyltransferase (also γ-glutamyltransferase, GGT), albumin
• Enzymes: creatine kinase (CK), also known as creatine phosphokinase (CPK) or phosphocreatine kinase; lactate dehydrogenase (LDH)
• Electrolytes: Sodium (Na), potassium (K)
• Oxygenation and acid-base balance: arterial blood gas (ABG) analyses/tests: partial pressure of oxygen (pO2), arterial partial pressure of oxygen (PaO2) partial pressure of carbon dioxide (pCO2), arterial partial pressure of carbon dioxide (PaCO2), SpO2 (peripheral oxygen saturation s. oxygen saturation as measured by pulse oximetry), pH:
• Inflammation indices: C-reactive protein (CRP), procalcitonin (PCT)
• Carbohydrate metabolism (glycemia): GLUC –

glucose

Additionally, regarding the analyses of images, dataset available resulted in 196 radiological images from 25 patients diagnosed with COVID-19. It should be emphasised that these patients were the same as in the original 45 patients from Serbian database, however not all 45 patients had X ray images for analyses, thus resulting in images from 25 patients. Gender distribution is given as follows: 7 female patients and 18 male patients. Age of patients in the form of mean ± standard deviation was 60.2 ± 12.7 years. One example of a patient's images of three consecutive days after hospital admission is given in Figure 1.

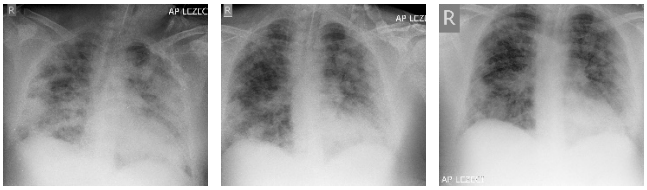

Figure 1. A patient's chronologically taken chest X-ray images

2.2. Machine learning based blood biomarker analysis

The system for analysis of blood biomarkers based on machine learning aims to determine the severity of the clinical condition (mild, moderate, severe and critical). This is possible on the basis of predicted several blood analyses (in days). To perform these tasks, methods of supervised learning, regression and classification were used.

Pre-processing data

To evaluate which biomarkers are crucial for determination of the severity of clinical condition, through a feature selection process we chose five features that had the greatest influence in making effective model. Also, another importance of considering 5 features instead of 44 original ones reduces the computational complexity. In addition to the missing values in the blood tests, there are also some missing values in the output labels. To solve that problem, missing labels were filled in based on the outcomes of clustering method. We have applied the simplest and most commonly used k-means algorithm. One should choose a number of clusters so that adding another cluster in the analysis does not give much better variance explanation. The optimal number of clusters that was found in this paper was 4, which is in accordance with the manually marked target outputs (doctor's categorization of the patients into 4 categories (mild, moderate, severe and critical)). This confirms the right use of such ML methodology. As a result, the dataset was divided in four clusters with expected distribution (31.80% of total data belongs to cluster with mild, 50.90% belongs to cluster with moderate, 13.88% belongs to cluster with severe, 3.42% of total data belongs to cluster with critical medical condition).

Regression

One of the main tasks is to predict the change of biomarkers values in time. The aim is to predict the patient's clinical condition 14 days after hospital admission based on blood analysis from previous days, starting from the day of admission and ending on the 11th day. The main limitation was the lack of data for biomarkers in time, full blood analysis on the admission day was available for all 105 patients, but for example, on 7th day, the data was available for only 68 patients. Due to the small number of patients' data available in time, in order to predict blood biomarkers values, we decided to select 34 patients with a full blood analysis for all days. In this case, blood biomarkers were used as targets, and for our regression model, we created new features such as the same blood biomarker in the previous moment (the previous day observed) and the difference between values of the biomarker in the current and previous recorded moment (Figure 2). In such a way, we have created time dependencies between a patient's blood analysis throughout time and expand the dataset for the regression problem.

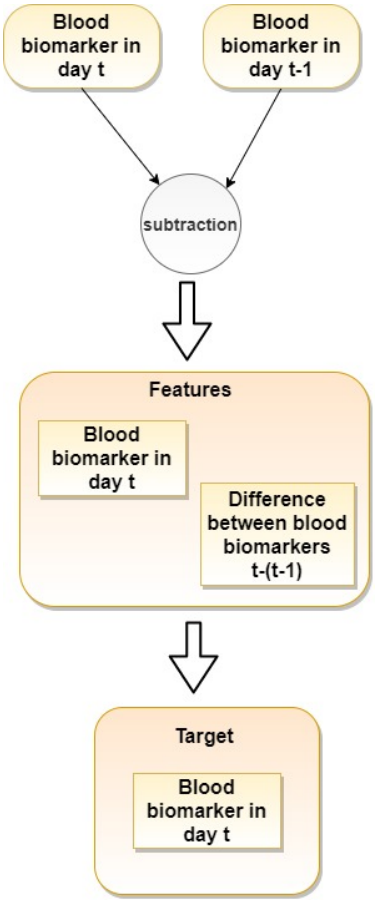

Figure 2. Schematic representation of the method used to organize the database

After establishing the database for the regression task, we divided data into training and test set, training set consists of data from days 2,5,7,9 and 11, therefore day 14 belongs to the test set. For the prediction of each blood biomarker was used Gradient boosting regressor (GBR). This model was trained with optimal hyperparameters settings based on the grid search method.

Classification

The key task of this paper is to examine how COVID-19 progresses in patients over time, in particular to decide the progress of the patient's condition 14 days after hospital admission. First, it is important to evaluate the importance of biomarkers using the methods explained in the previous part, and then group them into one of four groups (mild, moderate, severe and critical). For classification purposes, the original dataset has been modified, including all patients for which we had blood analysis on a specific day. This would suggest that inside this dataset, the same patients are replicated several times without any dependency between days. This alteration is justified, since it is not necessary to track the same patient over time in this situation, but to build as many separate instances as possible in order to extend the dataset and plan for the process of classification. The goal of the mentioned classification task was to create a simplified, rule-based decision model and, for that reason, an extreme gradient boosting model (XGBoost) was used [36, 37]. The key benefit of rule-based algorithms, such as XGBoost, is that internal model methods can be easily interpreted. The importance of these algorithms in clinical prediction is also expressed in the fact that decision-making features are established, unlike black box models whose rules and methods are difficult to understand. XGBoost has been trained with optimal hyperparameters using grid search.

2.3. Machine learning based image segmentation

A standard U-net neural network was applied with its paths encoder and decoder. The encoder path included two 3x3 convolutional layers and 2x2 max pooling with stride 2 for downsampling. The decoder included consecutive 2x2 up-convolution layers and two 3x3 convolutional layers. After each up-convolution layer, there is the concatenation of feature maps [38]. This helps in providing localization information from the encoder to the decoder path. Cross-over connections are used to recover some fine-grained features. For this U-net model, an input image with resolution 128×128 pixels was used and the output was a 128×128 binarized image. For the purpose of training process, the available dataset was divided into subsets for training, validation, and testing. Training and validation subsets consisted of 144 and 37 X-ray images with masks for lungs, respectively. The implemented model of U-net was tested on 15 unknown X-ray images. The training process lasted about 60 iterations with 128 X-ray scans in each batch and a learning rate of 0.01. Also, it is tried to perform training with smaller batch sizes, but in those cases, the model tends to overfit. As an accuracy metric of segmentation, we have used the dice coefficient – D [39]. This coefficient calculates the overlapping between automatically segmented region - S and the ground truth region - G:

$$D = \frac{2|S \cap G|}{|S| + |G|} \quad (1)$$

2.4. Finite element analysis of 3D reconstructed lungs

We have developed finite element model of lung airway, using optimized material and friction parameters, from CT image using functional residual capacity (FRC) to total lung capacity (TLC). In our previous work, we have analysed predicted displacement field for lobe sliding and continuum-based using average landmark error and correlation with the lobe-by-lobe deformable image

registration results [40]. Lungs are divided into units called lobes that are not mechanically attached and can slide with respect to one another. The human left lung contains two and right lung contains three lobes. Our model is the airway coupled to a parenchyma model (Figure 3). Upper airways geometry is segmented from a CT scan. This framework is used to mimic virus spreading from alveoli to other airway geometry. We have been used around 500,000 finite elements to model both airway and lobes [40, 41, 42, 43] (Figure 3).

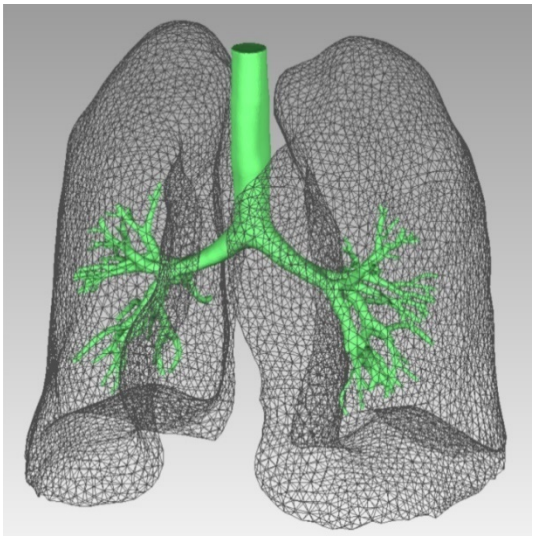

Figure 3. Finite element mesh of upper airways with the lung mesh and all lobes

3. Results and discussion

This section contains the results obtained by training the proposed Gradient boosting regressor and XGboost methods, as well as the U-net network model discussed in the previous section.

First of all, five blood biomarkers that most reliably described the development of COVID-19 disease in patients were selected as the features, according to the previously described methodology. These blood biomarkers and their values are presented in Table 2. In addition, there are normal values of biomarkers and their values from our database in the form of mean ± standard deviation.

Table 2. Ten blood analysis that had the greatest influence in COVID-19 patient's clinical condition assessment.

Blood biomarker	Mean ± standard deviation	Normal values	Units
WBC	8.25 ± 4.72	3.70 - 10.00	10^9/L
Urea	7.35 ± 5.76	3.0 - 8.0	mmol/L
Creatinine	92.46 ± 69.62	49 - 106	μmol/L
LDH	424.86 ± 239.26	220 - 450	U/L
CRP	69.11 ± 93.55	0.0 - 5.0	mg/L

For the evaluation of the importance of features, correlation of each two features was used, after which the importance scores were computed. The importance of all the best five features is shown in Figure 4. Lactate dehydrogenase (LDH) has the highest importance score, which can be due to the fact that this enzyme is widely distributed in tissues and its elevated serum levels could be caused by systemic hypoxemia [44]. Besides LDH, other parameters which mostly influence the model are urea (2nd most important), creatinine (3rd most important), CRP (4th most important) and WBC (5th most important). An explanation for the importance of urea and creatinine biomarkers could be found in the fact that both biomarkers are associated with kidney function - one research paper that included an analysis of patients with COVID-19 concluded that deaths were significantly higher in patients with elevated baseline serum creatinine levels [45]. The explanation for that is the accumulation of the virus in the kidney, which causes necrosis of the kidney cells. Furthermore, the biomarker CRP is an indicator of the level of the inflammatory process and may therefore be correlated with the severity of the clinical condition.

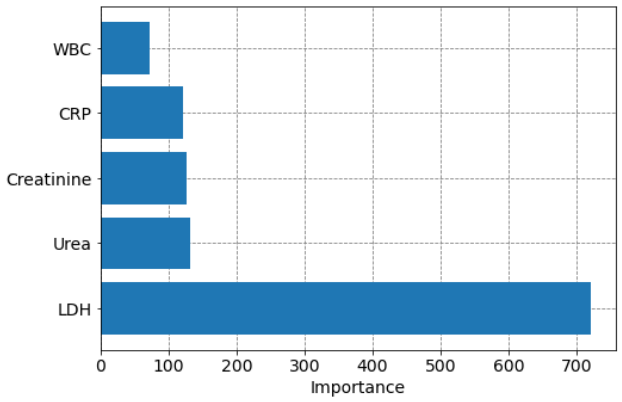

Figure 4. Importance scores of five best features

This feature selection method reduces the number of blood analyses that need to be assessed. Values of all five selected blood analyses are assessed for 34 patients on day 14 after the admission day by gradient boost regressor model. Table 3 shows the root mean square error between predicted and actual values of blood analysis.

Table 3. Root mean squared error between predicted and actual values of blood analyses.

Blood biomarker	RMSE
WBC	3.03
Urea	2.54
Creatinine	55.23
LDH	35.51
CRP	41.68

It can be seen that normal values of biomarkers such white blood cell (WBC), % lymphocytes, MCHC, RDW, urea and albumins fall under the narrower range as it is shown in Table 3, so we can expect smaller RMSE. On the other hand, Hgb, creatinine, LDH and CRP have more deviation between real and predicted values. Results for each of these four biomarkers will be discussed individually.

After evaluation of the results of the patient's blood analyses, it is possible to predict the patient's clinical condition in advance. This was accomplished by the proposed classification algorithm. The model was tested on 34 patients and achieved an accuracy of 92% in predicting the patient's condition on day 14 after the hospital admission. For the mentioned testing set, we computed the confusion matrix with normalized values which is shown in Figure 5.

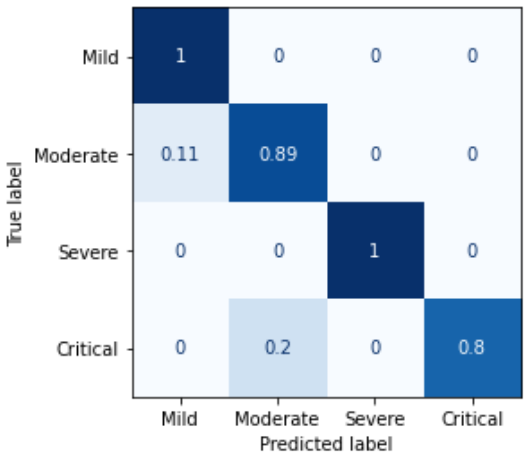

Figure 5. Confusion matrix with normalized values

In addition to classification accuracy, we considered other metrics such as precision, recall and F1-score. In Table 4, all of these metrics for each class individually are shown.

Table 4. Computed classification metrics for each class on test data.

Class	Accuracy	Precision	Recall	F1-score
Mild	1.00	0.80	1.00	0.89
Moderate	0.89	0.94	0.89	0.91
Severe	1.00	1.00	1.00	1.00
Critical	0.8	1.00	0.8	0.89

Our validated XGboost model is a rule-based model, consisting of hundreds of trees whose rules are understandable and based on if-then-else. This type of model is suitable for application in clinical practice due to its comprehensibility. Also, it should be emphasized that this analysis is automated and from a clinical point of view, the final decision is obtained within seconds.

As part of the second aspect of this study, convolutional neural network U-net was applied in order to segment the lungs in X ray images. Due to usual problem with overfitting, early stopping function is included in the training process. The loss function of training and validation for 60 epochs is given in Figure 6. We can observe that the loss function was decreasing during the first 30 epochs and then it was converging.

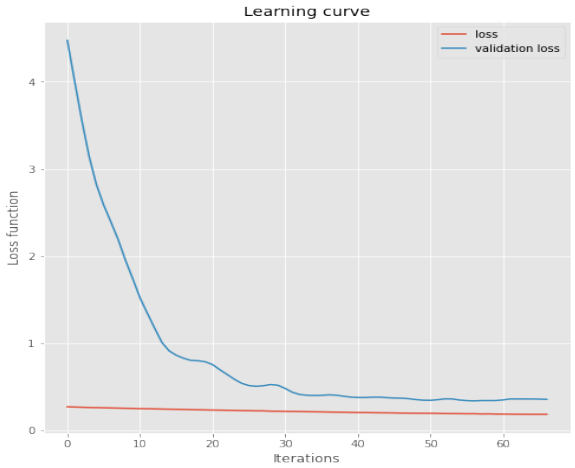

Figure 6. Loss function on training and validation process

After the training process, we evaluated the overlap between the automatic and manually created mask. The trained U-Net achieved an average Dice coefficient of 91% for 15 X-ray images of the test set. An example of segmentation of lung infected by COVID-19 from an X-ray image is given in Figure 7.

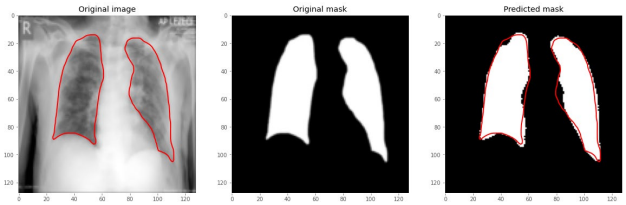

Figure 7. Lung segmentation using U-Net (best case scenario): (a) the original chest X-ray image, (b) manually segmented mask, and (c) automatically segmented mask of the lung

An example of segmentation with bad scenarios of lung infected by COVID-19 from an X-ray image is given in Figure 8. One possibility for improving the segmentation accuracy is post-processing by morphological transformations such as erosion and dilation.

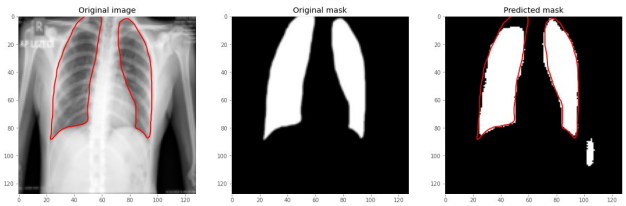

Figure 8. Lung segmentation using U-Net (worst case scenario): (a) the original chest X-ray image, (b) manually segmented mask, and (c) automatically segmented mask of the lung

Third aspect of the study, finite element simulation, has shown that it is able to distinguish virus spreading inside the lung for a specific patient. COVID-19 can induce innate inflammation by pro-inflammatory macrophages and granulocytes and makes liquid in the alveoli space and bronchi. That liquid can be detected in CT images as GGO (ground glass opacity). In our simulation dynamical growing during several days of the liquid positions can be compared. One of this comparison has been presented in Figure 9.

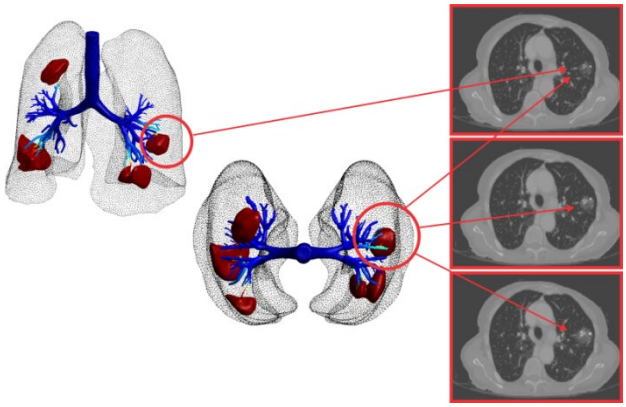

Figure 9. Virus spreading and comparison of red objects in the finite element simulation with CT images GGO positions detection

4. Conclusion

Although there are several studies examining the use of ML in the diagnosis of prognostic biomarkers and survival prediction in advance, available literature shown that only final outcome is predicted (mortality/survival). There is a lack of studies classifying the infected into severeness categories (mild, moderate, severe, etc.) that would help not only to respond in a timely manner to prevent lethal outcomes, but also to minimize the number of occupied hospital beds. This study aims at creating a personalized model that combines machine learning and finite element simulation approach in order to predict development of COVID-19 infection in patients. The methodology combines several strategies (1) novel approach for classifying patients into four distinct classes of clinical condition (mild, moderate, severe and critical) of COVID-19 disease and predicting outcomes (change in severity of clinical condition) in advance. In addition, convolutional neural network U-net is implemented for segmentation of human lungs in X ray images, only to create 3D model of human airway and investigate the spreading of SARS-COV-2 virion in the lungs using finite element (FE) simulation. The findings reveal that the XGboost classifier has reached an overall accuracy of 94%. We also derived 5 best features from the blood examination that are closely correlated with the condition of the patient and can estimate the severity of the health condition based on these features. Segmentation accuracy was 90.5%, indicating that such methodology can also be further used in creating 3D reconstructed human lungs. FE simulation has revealed that the distribution of airflow in the lungs changes in time with the infection, as well as that there is an overwhelming innate immune response that may occur if multiple areas of the lungs are simultaneously infected, resulting in a widely-distributed ‘‘cytokine storm’’.

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