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Early Detection of Mortality in COVID-19 Patients Through Laboratory Findings with Factor Analysis and Artificial Neural Networks

Selçuk ÖĞÜTCÜ[1], Melih İNAL[1,*], Cantekin ÇELIKHASI[2], Uğur YILDIZ[1], Nurettin Özgür DOĞAN[3], and Murat PEKDEMIR[3]

[1]Department of Informatics, Kocaeli University
[2]Institute of Science, Kocaeli University
[3]Department of Emergency Medicine, Faculty of Medicine, Kocaeli University
E-mails: selcuk@kocaeli.edu.tr, melih.inal@gmail.com*, cantek41@gmail.com, uguryildiz@kocaeli.edu.tr, ozgur.dogan@kocaeli.edu.tr, mpekdemir@kocaeli.edu.tr
* Corresponding author

Abstract. In this paper, some biochemical findings of patients who applied to Kocaeli University Faculty of Medicine Emergency Service with suspicion of COVID-19 are examined. The common characteristics of the cases regarding mortality status are analyzed via *factor analysis* (FA). Following the FA, blood parameters related to the severity of the cases are determined. Finally, a multi-layered *artificial neural network* (ANN) is trained with these parameters. This paper proposes a method that helps early detection of severe cases and determination of non-risk group vaccination priority. Thus, the main contribution is the creation of a decision-support system to start advanced medical support as soon as possible. The data set consists of 105 patients with 19 different input parameters. After FA, 7 parameters are found relevant to one-month mortality. These are HB, AST, BUN, LDH, pH, HCO3 and LAC. The chi-square value was 1252.9552, the p value for the significance level of 0.05 was close to zero ($7.3696 \text{x} 10^{-156}$). An ANN is accurately trained based on this subset of the data. The most successful model of ANN's training and testing errors as a *root sum squared estimate of error* (RSSE) are 0.1958 and 0.2402, respectively. This ANN model can be queried for patient data with determined parameters. This paper shows that the early detection of patients who can have the severe or fatal disease can be determined regarding COVID-19. The proposed method can be used to determine vaccination priority, for early intervention to expected severe course of treatment, and medical analysis and analytics of unknown diseases via their outcomes, enriched with numerical laboratory test results.

Key-words: Artificial neural networks; COVID-19; factor analysis; triage.

1. Introduction

As of December 2019, an increase in pneumonia cases of unknown cause have been observed in Wuhan, China. Later, with various symptoms including pneumonia, the number of patient complaints increased and as a common insurance, it was found that patients were infected with a new type of coronavirus. With the detection of the first case, the COVID-19 pandemic was announced on January 23 [1], in the reports of WHO officials, that the Chinese officials were satisfied that they had isolated the virus very well and WHO did not declare the virus as seriously as it took [1, 2]. There were 584 cases and 17 deaths at this time; 575 of these cases and all deaths were reported in China, while the rest were in Japan, Korea, Singapore, Thailand, the United States of America, and Vietnam.

The number of cases has increased rapidly throughout the world and data such as the transmission routes of the disease, the rate of spread and the severity of the disease process affecting patients have started to be acquired. On March 11, 2020, the WHO declared Pandemic with more than 118,000 cases and 4,291 deaths in 114 countries, as the spread and severity of the epidemic reached alarming levels [3]. Then, measures aimed at reducing the risk of transmission and treatments for the symptoms caused by the disease began to be investigated simultaneously. In the treatment of COVID-19 disease, drugs used in diseases with similar symptoms have been examined and experimental studies have been initiated.

In the process of developing the COVID-19 vaccine, countries have highlighted different treatment methods. There is still no treatment method with proven efficacy for the disease. Besides the effects of the applied treatment methods, the side effects are also the subject of controversy. Criticism focused on risk-benefit analysis has paved the way for addressing methods of gaining time for the body for natural antibody production through suppression of the overreacting immune system as well as treatments applied based on symptom similarity. With the analysis and conclusion work carried out, it is aimed to early detection of severe cases and to contribute to the research to be carried out as treatment methods for these cases.

In this section, the literature review is conducted on the method of transmission and effects of the virus with laboratory findings which are directly related to mortality in COVID-19 and other related studies in medical science. In Section 2, methods and materials which are used in the study are presented and are explained for FA and ANN in detail. Results are evaluated and discussed in Section 3, and finally the important findings of the study are concluded in Section 4.

1.1. The Transmission and Effects of the Virus

The coronavirus, which is the agent of COVID-19, which was originally called SARS-CoV2, uses the angiotensin converting enzyme 2 (ACE2) receptor to hold in the lower respiratory tract and thus can hold in the host [4]. Figure 1 shows the progression of the virus binding to the ACE2 enzyme [5]. Although COVID-19 causes respiratory tract infection, it leads to lung involvement, pneumonia, respiratory tract failure, multi-organ failure and mortality [6]. In addition, although the respiratory tract is prominent in terms of transmission routes of the virus, the virus can spread through droplets from all mucosal sources, including the eyes [7]. It has been observed that the virus is associated with complications such as lung, liver, nervous system and cardiovascular. These complications are shown anatomically in Figure 2 [8].

Underlying cardiovascular comorbidities such as hypertension, diabetes, and especially cardiovascular disease, have been associated with adverse effects. The emergence of cardiovascular

complications such as myocardial damage and heart failure has been associated with mortality [9]. In general, cardiac complications related to pneumonia have been observed to have an independent effect on short-term mortality rates [10].

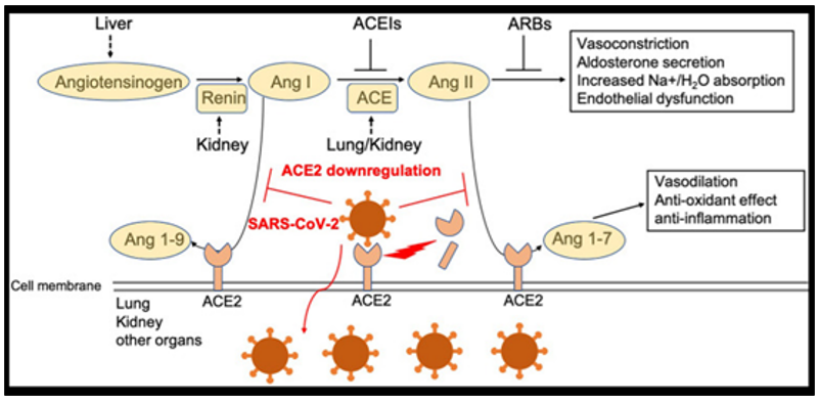

Fig. 1. The progression of the virus that binds to the ACE2 enzyme [5].

1.2. Laboratory Findings on COVID-19 in the Literature

It has been reported that patients admitted to healthcare facilities with suspected COVID-19 have lymphopenia and increased levels of neutrophils, thrombocytes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and *lactate dehydrogenase* (LDH) [11]. During the course of the disease, elevations of inflammatory markers such as LDH, CRP and IL-6 can help identify patients who may have a poor prognosis [12]. Dynamic changes in laboratory findings during the hospital stay of severe survivors and non-survivors have demonstrated a steady increase in leukocyte and neutrophil count, persistent lymphopenia and eosinopenia, progressive decrease in platelet count and elevated levels of NLR, CRP, PCT, AST, BUN and serum creatinine levels have been associated with in-hospital mortality [13].

Regarding initial laboratory studies, increased TLC, neutrophil count, urea, creatinine, sodium, and decreased lymphocyte count were all associated with disease severity and death, but in addition, factors such as immune dysregulation, secondary bacterial infections and multi-organ failure that could not be directly attributed to viral agent effects have been observed that it may be the main subject [14]. Results for *complete blood count* (CBC) testing, liver and kidney function tests, inflammatory / infection markers, serum electrolytes and glucose have been reported to significantly differ between severe and non-severe COVID-19 cases [15]. It has been reported that rhabdomyolysis caused by influenza A and B viruses, HIV, enteroviruses, and coronavirus such as SARS-CoV-1 and COVID-19 can be seen in some adults and rarely in pediatric patients [16]. Numerous prediction models have been developed in the literature and all these models are at high risk of bias mainly due to non-representative selection of control patients, exclusion of patients who did not experience the event of interest at the end of the study and overfitting the model [17]. Several cardiovascular disease biomarkers have also been reported to be higher in the non-survivor group [18]. Literature data show some evidence regarding hemoglobin (Hb) and COVID virus interaction [19].

1.3. Artificial Intelligence in Medical Science

The technology, in general, and particularly the Artificial Intelligence (AI) tools could help both of them, and it is assisted by appropriate theory regarding modeling tools. One of the most powerful mechanisms that can be used in this field is the ANNs. The Process Control group of the Politehnica University Timisoara from Romania presents some of the results obtained in the field of ANNs applied to modeling, prediction and decision-making related to medical systems. An Iterative Learning Control-based approach to batch training a feedforward ANN architecture is given; the paper includes authors' concerns in this domain and emphasizes that these intelligent models, even if they are artificial, are able to make decisions, being useful tools for prevention, early detection and personalized healthcare [20]. Lots of Artificial Intelligence research results have been reported on applications of medical and psychology sciences from prosthetic organs to decision-making, prediction, control and modeling [21-24]. In the another paper on the enhanced cellular automata with autonomous agents, in order to model the epidemic spreading of COVID-19 pandemic; the dynamics of these epidemic spreading phenomena in large populations can be controlled and even stopped efficiently if appropriate measures are taken and especially if those measures are tailored to the specificity of each population. The COVID-19 Pandemic Model including factors that influence the dynamics of the epidemic and the dynamics of the population, could be of much help for authorities and scientists in this context. The model takes into consideration specific details of the actual COVID-19 infection: the atypicality of evolution of cases, the proximity required for infection, the long gestation time [25].

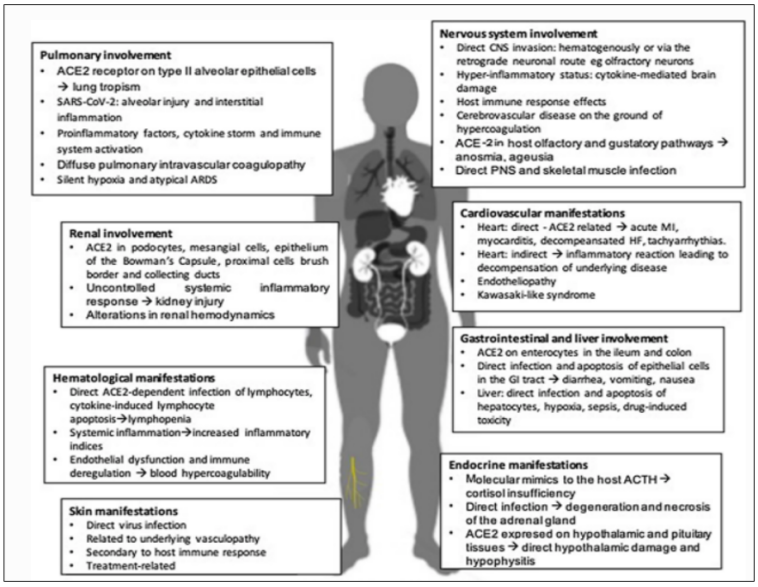

Fig. 2. Schematic overview of the systemic manifestations of COVID-19 infection and the underlying pathophysiology [8].

2. Methods and Materials

In this paper, a data set of 150 patients was considered. Of these, 105 patient data were found to be complete enough to be used in the study. In data analysis studies, there are approaches such as completing the missing data by using the column average. However, completing missing data with such methods may cause misleading results in studies that require precision. Therefore, 47 patient data whose deficiencies were detected were excluded from the analysis. Before analysis, min-max normalization was applied to data columns. Thus, data with different value ranges were scaled to 0-1 range.

2.1. Factor Analysis

In this paper, we propose an FA-based method for determining the features of a large matrix of medical parameters reduced to robust parameters for early detection of mortality. This approach can be used to identify other diseases with the goal of prediction of a desired outcome using the input data. Also, this method has been adapted to different cases such as prediction of student performances as in [26]. The combined method used here was also used in [26] to predict student scores of a course using the other courses that appear in the same factor(s). This paper expands the method by programmatically increasing the minimum required correlation that was previously preferred as a constant, due to the nature of a medical disease that shows different characteristics compared to the evaluation of a curriculum performance. Thus, we have been able to focus on a single factor to use for the prediction goal, while extracting the most mortality-relevant biomarkers. The data set of 105 patients with 19 parameters with COVID-19 cases was reduced to latent variables with the help of FA. The statistical properties of raw data of latent variables are shown in Table 1. To determine the number of factors to be formed as a result of FA, the eigenvalues of the correlation matrix of the data set were calculated and the number of eigenvalues greater than 1 was accepted as the number of factors (latent variables).

Table 1. The statistical properties of raw data of latent variables (min-max normalized)

Stat.	Hb	AST	BUN	LDH	pH	HCO3	LAC	ONE_M_M
mean	0,5755	0,0423	0,1564	0,0721	0,4903	0,5442	0,1505	0,0952
std	0,1827	0,1106	0,1377	0,1312	0,1018	0,1671	0,1471	0,2950
min	0,0000	0,0000	0,0000	0,0000	0,0000	0,0000	0,0000	0,0000
max	1,0000	1,0000	1,0000	1,0000	1,0000	1,0000	1,0000	1,0000

It was preferred that the hidden variable associated with one-month mortality be independent from other latent variables. For this purpose, the varimax method, which is one of the rotation methods of FA, was used. The main data set consists of 19 variables: Hb, WBC, NEUTROPHIL, LYMPHOCYTE, NA, K, AST, BUN, Cr, DDIMER, LDH, CRP, PCT, pH, PO2, PCO2, HCO3, LAC. The correlation base value used in determining latent variables was increased in a loop and the loop was continued until there was only one latent variable including one-month mortality. The correlation matrix of the COVID-19 severity latent variable after FA is shown in Table 2. Figure 3 shows the COVID-19 severity latent variable heatmap based on FA result. Heatmap shows the effects of Hb, AST, BUN, LDH, pH, HCO3 and LAC.

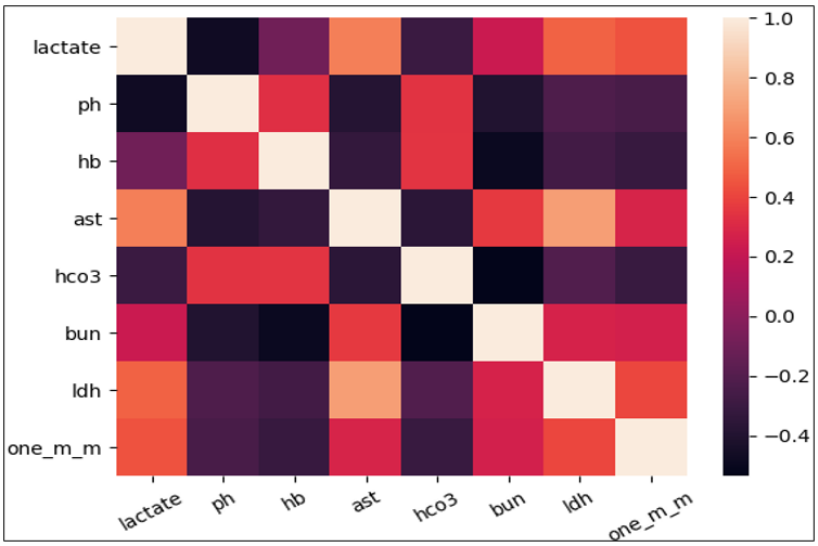

Fig. 3. COVID-19 Severity heatmap.

Table 2. COVID-19 Severity latent variable correlation matrix

Correlation Matrix	LAC	pH	Hb	AST	HCO3	BUN	LDH	ONE_M_M
LAC	1,0000	-0,4714	-0,0948	0,5868	-0,3015	0,2277	0,4950	0,4434
pH	-0,4714	1,0000	0,3294	-0,3860	0,3451	-0,4045	-0,2236	-0,2469
Hb	-0,0948	0,3294	1,0000	-0,3273	0,3467	-0,4944	-0,2704	-0,3103
AST	0,5868	-0,3860	-0,3273	1,0000	-0,3579	0,3639	0,6972	0,2836
HCO3	-0,3015	0,3451	0,3467	-0,3579	1,0000	-0,5370	-0,2112	-0,3038
BUN	0,2277	-0,4045	-0,4944	0,3639	-0,5370	1,0000	0,2736	0,2663
LDH	0,4950	-0,2236	-0,2704	0,6972	-0,2112	0,2736	1,0000	0,4097
ONE_M_M	0,4434	-0,2469	-0,3103	0,2836	-0,3038	0,2663	0,4097	1,0000

2.2. Artificial Neural Network

After confirming that the latent variable obtained from the patient data as a result of the FA provides a regression in itself, it was deemed appropriate to use this data in the training of an ANN model in order to produce a generalized result. It was observed that the ANN, which was trained with blood laboratory values in the same factor with the mortality variable, succeeded with training and testing errors as *root sum squared of error* (RSSE) are 0.1958 and 0.2402, respectively.

The RSSE between target t_i and output of ANN y_i is calculated as follows:

$$RSSE = \sqrt{\sum_{i=1}^{n} (t_i - y_i)^2}. \tag{1}$$

In the ANN, there are three hidden layers containing 100, 80 and 33 processing units (neurons), respectively. The numbers have been chosen based on trials with the data set. While these

neurons were using the *Logarithmic Sigmoid* (LogSig) activation function, a linear (PureLin) neuron was used as the output neuron. Gradient descent method was used in ANN training. ANN technique has emerged as a powerful tool which can be used for many scientific and/or engineering applications such as process control and system modelling. ANNs are inspired by the nervous biological architecture systems consisting of relatively simple systems working in parallel to facilitate quick decisions [27]. A basic neuron model is shown in Figure 4.

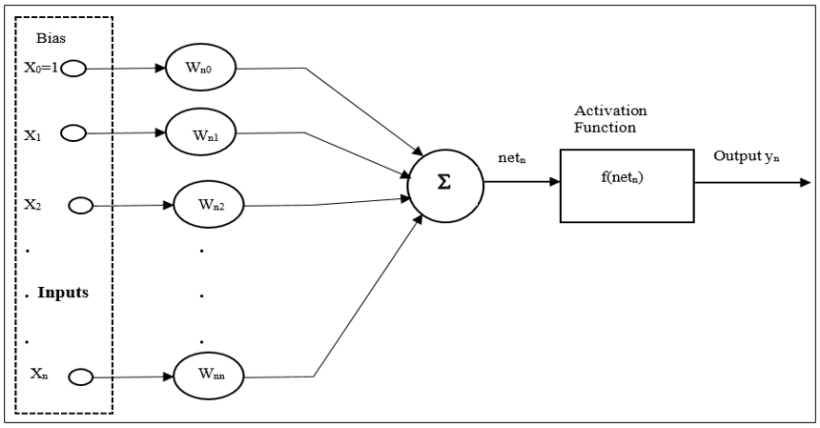

Fig. 4. An ANN neuron model.

The sum of the product of the elements of the input vector $x_1, x_2...x_n$ by the weights W_{ni} is usually passed through a nonlinear transfer function $f(net_n)$ to obtain the output of the neuron y_n:

$$y_n = f\left(\text{net}_n\right) = f\left(\sum_{i=0}^{n} W_{ni} X_i\right). \tag{2}$$

where W_{ni} are the weights of the nth neuron and W_{n0} is the weight of the bias input X_0 which usually is chosen 1.

The purpose of the bias input X_0 used in (2) is to eliminate the attenuating factors that will affect the output of the neuron. In this paper, $f(net_n)$ is chosen as a logarithmic sigmoid function:

$$f\left(\text{net}_n\right) = \frac{1}{1 + e^{(-a * \text{net}_n)}}. \tag{3}$$

The coefficient a determines the slope of the sigmoid function and is usually chosen as constant. When a coefficient is chosen large enough the sigmoid function will become the threshold transfer function. It is known that this coefficient has an accelerating effect on the learning in the training stage of ANN. In addition, it is considered that a better performance is obtained by adapting the coefficient a in the training process of the ANN [28].

The weight update equation of gradient descent with momentum is

$$\Delta W_{ni} = \left(\eta \frac{dE}{\text{dW}_{ni}}\right) + \left(\gamma \Delta W_{ni}^{(t-1)}\right), \tag{4}$$

where dE/dW_{ni} is the weight gradient of error $E = (t_i - y_i)$, η is learning rate, γ is momentum factor, AND the term $(t-1)$ on ΔW_{ni} shows the previous iteration of weight increment.

The statistical model of Factor Analysis used in this paper is expressed as

$$X = LF + M + \varepsilon, \tag{5}$$

where $X \epsilon R^{p \times n}$ is the observation matrix, $L \epsilon R^{p \times k}$ is the loading matrix, $F \epsilon R^{k \times n}$ is the factor matrix, $M \epsilon R^{p \times n}$ is the mean matrix, and $\varepsilon \epsilon R^{pxn}$ is the error term matrix.

The FA model is used to explain p observations in individuals represented with n with common factors k to support the criterion $k < p$. The best training result of the ANN trained in a 10 times loop is kept and the training of the ANN which cannot be more successful than the previous training results is terminated. With the reloading of the last best ANN model, the loop continues until the sum of training and test errors are lower than 0.5 as the stop criterion. In other words, it is confirmed according to the relevant values of all subjects in the data set according to one-month mortality result with an acceptable error value for the entire data set training. As predicted and tested, it was seen that ANN could not provide enough good performance in the data reserved for validation. Since the ANN does not have enough input-output data for validation, the data set is divided into training and test data only. Data splitting was carried out to create 80% training and 20% test data. As shown in the ANN training and testing algorithm Step 13, the training and test data are randomly shuffled in each trial cycle to avoid overfitting. Moreover, the stop criteria of the learning algorithm is defined as shown in the algorithm Step 18 through Step 20. The ANN training and testing algorithm used in this paper is

Step 1: Read the data set (df)
Step 2: Determine the target criterion (mortality)
Step 3: Remove data rows that include missing values
Step 4: Define the baseline correlation (min_corr)
Step 5: Define the correlation increment (inc_corr)
Step 6: Increase min_corr by inc_corr
Step 7: Apply FA to the data set according to (5)
Step 8: If the number of factors with criterion is more than 1, go to Step 6
Step 9: Normalize df to 0-1 range
Step 10: Define the ANN properties
Step 11: Select ANN input data from COVID-19 Severity excluding criterion
Step 12: Select criterion as ANN output data
Step 13: Randomly split ANN input and expected output data for training and testing
Step 14: Increase trial_count
Step 15: Perform training with ANN training data according to (2), (3) and (4), and calculate train_error using (1)
Step 16: Test with ANN test data, calculate test_error using (1)
Step 17: If test result is the best so far then memorize ANN, else increase num_of_unsuccessful_ANN
Step 18: If (train_error + test_error $<$ 0.5 "stop_criterion"), then break loop
Step 19: If trial_count is lower than 10, increase trial_count else restore last best ANN
Step 20: If (train_error + test_error) $>=$ 0.5 then go to Step 13

The python code and the dataset of the algorithm can be accessed via the following link: https://github.com/selcukogutcu/COVID-19. For the validation of the method, first, the algorithm has been used to efficiently reduce the number of required biomarkers for the early detection

of mortality in COVID-19 cases, based on the supplied patients' dataset. The algorithm was designed to satisfy the dimension reduction needs of big data use cases. Due to the lack of a large dataset, it shuffles the training and test partitions of the dataset following each completion of training iteration until a desired RSSE is obtained. Therefore, training of the hidden layers of the neural network does not complete the learning process of specific COVID-19 variant features before satisfying a generalization. Figure 5 shows Iteration vs. RSEE of training and testing stages until the most successful trial that satisfies the stop criterion.

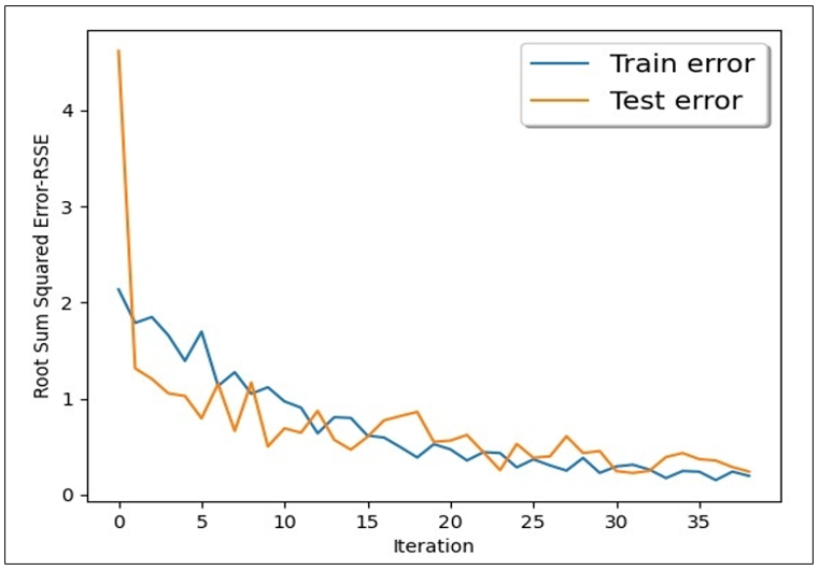

Fig. 5. RSSE of training and testing stages.

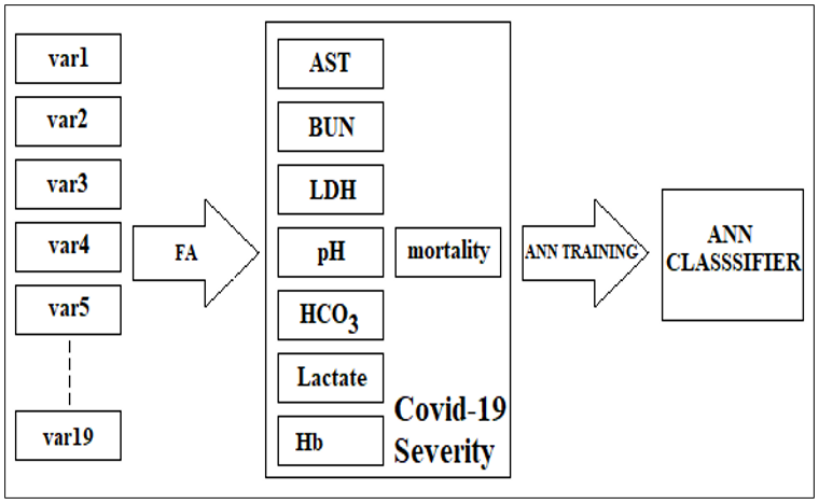

Fig. 6. Visualization of the COVID-19 decision-support system.

Figure 6 shows the visualization of COVID-19 decision-support system with all combinations of the methods. FA gives the contribution to ANN to supply an abstract dataset for designing a robust ANN classifier.

The constitute a decision-support system the data for blood samples are evaluated by FA and the seven of these parameters which are the most relevant with mortality are determined and trained for ANN Classifier. The findings are discussed in the following section.

3. Results and Discussion

In this paper, data on blood samples of patients who came to the hospital emergency service with suspicion of COVID-19 were collected. FA method was applied in order to express the multi-dimensional structure of the final table with fewer dimensions. For FA, the baseline correlation was increased until only one factor (latent variable) remained that included the one-month mortality column. Since there is no correlation between the factors provided by varimax rotation, the assumption is that the data columns constitute the only factor with the one-month mortality column expressing the COVID-19 Severity.

FA loop that increases base correlation reference to ensure mortality occurs only in one latent variable, creates seven latent variables after completing successfully. We named the first latent variable as COVID-19 severity as it is the only latent variable that includes the variable "one_m_m". The list of latent variables summarizing the data set where each row represents a latent variable is

- Hb, AST, BUN, LDH, pH, HCO3, LAC, one_m_m
- WBC, NEU, LYM, CRP
- Hb, BUN, Cr, pH, PO2, HCO3
- PO2, PCO2, HCO3
- LYM, CRP, PCT, PCO2, LAC
- DDIMER, LDH, CRP, pH, PCO2
- Hb, LYM, NA

The number of latent variables created depend on eigenvalues that are greater than 1, where computation is executed on the data set's correlation matrix. Each latent variable can be named after their corresponding fact based on medical information. Because the first row represents the severity latent variable, this paper has been focused on these variables in the data set to train the ANN model.

It can be observed in Figure 7 that the expected mortality output has been correctly classified by the ANN model. Since the ANN model has linear output, it produces an output close to the target mortality value. Therefore, the maximum value of the linear output of the ANN model below 0.5 is determined as *Dynamic Threshold Value* (DTV). DTV is calculated as 0.30. The values below the DTV are assigned as 0, while above values are 1. According to this result, the ANN model and expected mortality outputs fit with each other.

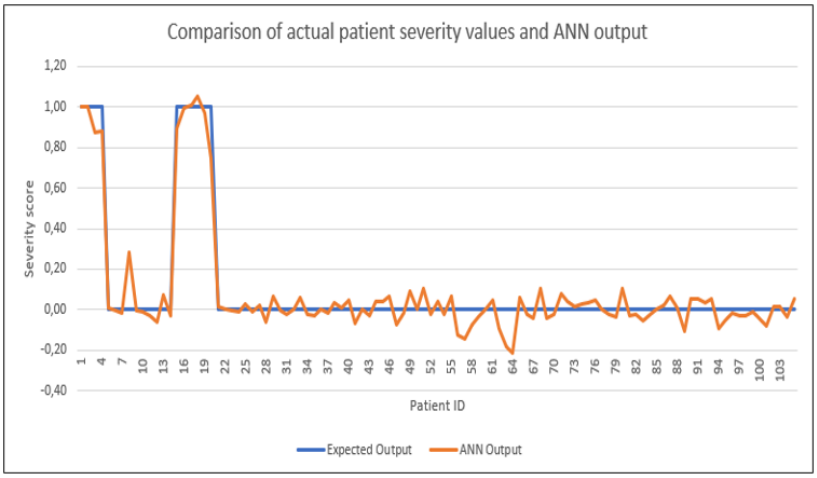

Fig. 7. Expected mortality output vs ANN output.

4. Conclusions

In this paper, triage of patients who apply to the hospital is possible in the case of COVID-19, the early detection of patients who can have severe or fatal disease can be provided in case of COVID+. Thus, it has been seen that it can create a decision-support system to start advanced medical support as soon as possible. It is considered that the results presented in this paper can be helpful in identifying patients who are not in risk groups but should be given priority in vaccination. The proposed method can be adapted for early detection of severe conditions and potentially fatal diseases based on gathered data.

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