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Prediction of sepsis for the intensive care unit patients with stream mining and machine learning

Akış madenciliği ve makine öğrenimi ile yoğun bakım hastalarında sepsis tahmini

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Abstract

Sepsis, which is known as multiple organ failure, is the primary cause of mortality for all patients in intensive care units, regardless of their other illnesses. An intensive care unit decision support system that can predict sepsis in intensive care patients early and warns the doctor has been developed. Since the COVID-19 virus, the variant and number of intensive care patients have increased, so this study has been developed as a precaution to worsen the situation with sepsis. A user-friendly interface and system have been designed to help the physician better monitor the patient's sepsis status. It has been developed in order to meet the need for a decision support system that makes sepsis estimation in accordance with the reference intervals of Turkish patients' values. For a better result of predicting sepsis early, it has been concluded how the data obtained and used in a certain period of time should be analyzed and what methods could be used to estimate higher performance. In the study, machine learning (classification and regression), deep learning algorithms have been used for estimation and the results obtained have been compared. As an impact of research, an intensive care sepsis decision support system, which consists of 122400 hourly data of 300 intensive care patients and estimates with approximately between 88% and 94% successful results in accordance with the reference intervals of Turkish patients, has been developed.

Keywords: Deep Learning, Decision Support Systems, Machine Learning, Medical Information Systems, Stream Mining

Öz

Çoklu organ yetmezliği olarak bilinen Sepsis hastalığı yoğun bakımlardaki tüm hastalar için, başka her ne hastalıklara sahip olurlarsa olsunlar, birinci mortalite sebebidir. Bu çalışmada yoğun bakım hastalarında sepsisi erken tahmin edebilen ve doktoru uyaran yoğun bakım ünitesi karar destek sistemi geliştirildi. COVID-19 virüsünün varyantı ve yoğun bakım hasta sayısı arttığından bu çalışma sepsis ile durumu kötüleştirmeye yönelik bir önlem olarak geliştirilmiştir. Hekimin hastanın sepsis durumunu daha iyi izlemesine yardımcı olmak için kullanıcı dostu bir arayüz ve sistem tasarlanmıştır. Türk hasta değerlerinin referans aralıklarına göre sepsis tahmini yapan bir karar destek sistemi ihtiyacını karşılamak amacıyla geliştirilmiştir. Sepsisi erken tahmin etmede daha iyi bir sonuç için, belirli bir süre içinde elde edilen ve kullanılan verilerin nasıl analiz edilmesi gerektiği ve daha yüksek performansı tahmin etmek için hangi yöntemlerin kullanılabileceği sonucuna varılmıştır. Çalışmada tahmin için makine öğrenmesi (sınıflandırma ve regresyon), derin öğrenme algoritmaları kullanılmış ve elde edilen sonuçlar karşılaştırılmıştır. Araştırmalar sonucunda, 300 yoğun bakım hastasına ait 122400 saatlik veriden oluşan ve Türk hastalarının referans aralıklarına göre yaklaşık %88 ile %94 arasında başarılı sonuçlar tahmin eden yoğun bakım sepsis karar destek sistemi geliştirilmiştir.

Anahtar kelimeler: Derin Öğrenme, Karar Destek Sistemleri, Makine Öğrenmesi, Tıbbi Bilişim Sistemleri, Akış Madenciliği

1 Introduction

Sepsis, septic shock, and subsequent multi-organ failure are one of the global causes of mortality affecting millions of people around the world today [1]. It has become a global health problem, especially due to high treatment costs. Sepsis has been one of the most important causes of mortality in intensive care patients as it is treated in intensive care units (ICUs). Sepsis causes death, as well as permanent organ failure. In the diagnosis of sepsis, speed, and early treatment are very important as they may reduce the patient's impact from these results.

Models created with machine learning approaches have shown higher performance than existing early diagnoses [2, 3]. The need for early diagnosis has been identified with a decision support system that can be used in the ICU and can be created from real-time data flow. To meet this need, it has been observed that creating a prediction model and establishing a decision support system can reduce the mortality rate due to sepsis [4]. Today, various machine learning algorithms provide predictions of the vital activities of the patient for the possibility of sepsis [5]. There are some early diagnosis systems used to reduce the mortality rate of patients in ICUs due to sepsis. As a result of early detection of sepsis, the patient can be intervened early, and the risk of life can be reduced. Used systems are not successful enough because they do not have the desired performance.

Since sepsis results in multiple organ failures, it is critical to examine the improvement or deterioration of the organs. Therefore, in addition to existing studies, the need to show the changes in the organ's value to the doctor has been observed. Unlike the algorithms and models that can draw conclusions from the streaming data, the studies have mostly used models created from past data. Unfortunately, sepsis and organ failure caused by new viruses cannot be detected with the data on existing infections or diseases. For instance, COVID-19 is a new virus and causes an infectious disease. It has been observed that COVID-19 is an infection affecting sepsis according to the cases observed so far. Therefore, the created model should always update itself according to the current conditions and existing

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disease values. Therefore, there is a need for a system that can eliminate existing deficiencies and reduce the death rate [6].

The areas and articles have been examined in the last four years in order to improve the study and to research the gaps. One of the motivating studies is the meta-analysis of machine learning algorithms in sepsis prediction [7]. It has been found that machine learning is a high-performance tool to reduce the diagnostic uncertainty of sepsis, select appropriate antibiotics, identify suitable sepsis patients, and predict sepsis three or four hours earlier. In addition, performance comparisons of prediction models such as Support Vector Machines, Deep Neural Networks, or Logistic Regression have been analysed by the study. It has been one of the studies that contributed to the study in terms of seeing the speed and accuracy of machine learning in the early diagnosis of sepsis [8]. As it is known in ICU, the most important issue that saves life in case of sepsis and organ failure is to detect the life-threatening as early as possible and machine learning models have a great contribution to this. Another motivating article on this subject has revealed that the flowing physiological data have been diagnosed in sepsis much earlier than clinical practice [9].

One of the most important issues in such medical decision support systems is that the study is done according to geography. Local attitudes, life habits, and routines are more valuable than global datasets concerning discovering hidden relationships in datasets in medical data analysis. According to the disease course characteristics of Turkish patients, there is no decision support system and sepsis-prediction model established so far.

The contributions in our study are that it is aimed to propose a novel neural network approach and thus, to eliminate the deficiencies in the previous studies and to reduce the mortality rates due to sepsis by using the reference intervals of the tests according to Turkish patients. The model trained for the decision support system should be trained with up-to-date data and be able to adapt to the risk of sepsis that may be caused by new infections. Therefore, it is aimed to increase the success rate in new cases by continuously training the model with the current data of patients in the ICU in a digital environment instead of past data. By means of this model, it is aimed to reduce the mortality rate by informing the physician about the possible sepsis situation beforehand. In addition, the physician is informed about the deterioration and changes in an organ which can be brain, heart, lungs, liver, or kidneys. The patient's up-to-date and historical data have been compared by the model. As a result of the comparison, the doctor may be informed about the condition of the organs and the possibility of sepsis with the estimation of the sepsis situation in the future. At the same time, the physician has been shown a future forecast of the improvement in the patient's values.

The aim of our study is to implement a decision support system that can detect the sepsis situation more successfully in advance and warn the doctor by giving the current data of the patients in the ICU to the previously trained model. In addition, the model is continuously trained with new data, and it is aimed to be successful against new infections that may cause sepsis.

The values of patients hospitalized in the ICU at Dokuz Eylül University Research and Application Hospital formed our data. These data are used with the permission of the Ethics Committee. The steps to be followed in the model development process in order of data extraction, data pre-processing, creating the model according to the machine learning classification algorithm, and evaluating the performance of the model. To use real-time data more efficiently, a prediction model is created with machine learning algorithms with the data of ICU patients. Thus, organ failure or sepsis status can be detected thanks to a better estimation.

This study to be done is a decision support system intended to be used by physicians. Physicians can make interpretations of the patient's condition by observing each of the organs from the visualized information screen that is created. The screen shows the progress in the values of each organ according to the patient's analysis results. It is aimed to give an early warning to the physician when a risk situation is observed in the values of the organs. In the system, the colour change is observed according to the current state of each organ visually displayed on the screen before a vital warning is given to the physician, so that the patient's condition can be understood in a practical way for the observing physician.

Classification algorithms have been used during the model creation phase. The performances of algorithms such as decision trees and artificial neural networks have been tested. The algorithm with the most accuracy and high performance has been selected and used in that study. The model creation process has been done through Python, Spyder has been used as an integrated development environment [10].

The data of patients in the ICU of Dokuz Eylül University Research and Application Hospital are currently stored in the Oracle Database 11g. The data to be used in our study has been extracted from the existing database. By determining the relationships of the data in the database, the data to be used has been transferred to the backend part. As a result, the study proposes a system by developing clinical guidelines and a decision support system to support diagnosis and treatment decisions in the ICUs where physicians need them. With the devices providing user convenience, it is aimed that the decision support system has been established with HIMS (Hospital Information Management System) of instantaneous data. The reports are saved according to the desired form. Deep learning and time series including vital risk data such as stream mining are used for this.

This paper details our study in six sections. In Section 2 the related works are given; in Section 3 the methodology of the proposed approach is detailed; in Section 4, the experimental studies are explained, and their accuracy results are given; in Section 5, the discussion is detailed and finally, Section 6 presents conclusions about the proposed approaches.

2 Related works

With COVID-19 being a pandemic disease, the studies on decision support systems in this area have gained momentum. For example, Saperstein et al. have implemented a clinical support system application for the newly emerging COVID-19. While this application has been developed on a mobile basis, the guidelines of organizations such as the World Health Organization (WHO) and the Society of Critical Care Medicine (SCCM) formed the decision mechanism. For ICU patients, mortality scores are obtained by evaluating sequential organ failure [11]. Also, Wu et al. show that it has been conducted to identify the severity and urgency of patients caused by COVID-19. Data of 299 patients meeting the criteria of the data to be used for model training have been selected and those meeting the conditions have been marked as serious. Of these 299 samples, 80% have been used for training and 20% for testing,

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and the features to be selected for the training of the model have been determined by the Boruta algorithm. Using logistic regression logic, 4 models have been trained for different features and the features have been fixed according to the model with the highest accuracy [12].

In these decision support systems, machine learning algorithms have been extensively preferred to detect sepsis. For example, Wernly et al. have aimed to carry out the mortality risk of septically life-threatening patients from the first 48 hours to 96 hours in ICU by looking at the arterial blood gas (ABG) data [13]. It is important to allocate ICUs in an optimized way, especially in times such as pandemics. This model, developed with the machine learning algorithm, is Recurrent Neural Networks. As a result, the use of a multi-centre approach and a Long short-term memory (LTSM)-based model provides the patients with re-triage and helps to determine the treatment method, especially in patients with poor prognosis [14]. Also, Islam et al. have focused on the meta-analysis that machine learning models can help identify potential clinical variables and outperform existing traditional low performance models, as an innovative and applicable tool for predicting sepsis is still unclear. As a result of the study findings, it has been revealed that the machine learning approach has a better performance than existing sepsis systems in predicting sepsis and decreasing the prediction time [7].

The studies about the early detection of sepsis are important to reduce the mortality rate. For example, Desautels et al. have mentioned how low the rate of early detection of sepsis is still. In the early diagnosis of sepsis, the definition of Sepsis-3 has been used instead of categorizing sepsis traditionally, and this method uses a two-stage system based on an increase in mortality (septic or non-septic). As a result, the InSight prediction model, together with electronic health records, has been found to have a higher performance than other prediction models currently in use [15]. Also, Liu et al. have mentioned many different systems for early diagnosis of sepsis are used today, but none of them have positive predictive value. In the study, a two-step framework, containing Random Forest, Neural Network models, and Kolmogorov-Smirnov tests, has been developed to apply machine learning methods to increase performance. As a result of the experiments, it has been demonstrated that it has fewer false alarms and precision with this framework compared to other methods [16].

In machine learning approaches, different applications have been encountered such as using natural language processing, different statistical methods, PDSA (plan-do-study-act) cycle, and randomized approach. For example, Giannini et al. have developed a machine learning algorithm to predict severe sepsis and septic shock, and to evaluate its effect on patient outcomes. It represents potential opportunities to improve the impact of sepsis prediction on clinical care outcomes by effectively communicating risk for patients with suspected clinical worsening by using natural language processing and improved machine learning algorithms [17]. Nemati et al. have conducted to reduce the static or the limit of previous studies to reduce the mortality and cost caused by sepsis. While the model used in the study uses a different version of the Weibull-cox proportional hazard model, different statistical methods are used for the variables given to the model. In this model, where predictions have been made with the data read from the monitor, it has been observed that the success of the predictions decreased as time increased [18]. Also, McCoy et al. have created a score because of the values used to predict severe sepsis, and accordingly, the danger of severe sepsis is warned according to the higher score. The prepared machine learning algorithm has 3 PDSA cycles. As a result of this study, hospital mortality rates and length of stay in the hospital decreased with each PDSA cycle, and costs have been reduced accordingly [19]. And, Shimabukuro et al. have aimed to test and perform the average length of stay in the hospital using a machine learning-based severe sepsis prediction system in a randomized study since no sepsis definitions have been confirmed before. As a result of the analyses, it has been observed that the average length of stay decreased, and the in-hospital mortality rate has been observed to decrease when using machine learning algorithms [20].

It has been observed that some studies have focused on parameters and signs to detect sepsis. For example, Barton et al. have validated a gradient-enhanced batch machine learning tool and among adult patient data from retrospective databases, those with at least one of six vital signs (SpO_2, heart rate, respiratory rate, temperature, systolic and diastolic blood pressure) of admitted patients without sepsis have been included in the study. In addition, it has provided higher performance for sepsis detection when the data sets have been trained and tested [21]. Tran et al. have aimed to prove that using machine learning contributes to the diagnosis of sepsis in such cases. Developed Machine Intelligence Learning Optimizer (MILO) platform enables the determination of the optimal hyperparameter value for non-automated algorithms, evaluates the performance, and produces a report. MILO determines the most optimal algorithm and features to be used to quickly determine burned sepsis [22]. Also, Ibrahim et al. have suggested that clinical heterogeneity is important both in predicting the course of the disease and in treatment. Subpopulations have been created with the Self Organization Map which is one of the machine learning methods, and neurons on the two-dimensional area are organ dysfunction records that are very similar to each other. Patterns formed in this way; 4 different organ failures have been detected. This shows that the model used, and the clusters formed have been very satisfying in the diagnosis of sepsis [23].

A study has been focused on the mobility of the decision support system. Bayrak et al. have studied the ICU Automation System and Clinical Decision Support System (ICU-CDSS) software. Analysis methods such as clustering and classification have been used with data mining. Decision Support System has been used to ensure the efficient use of data and models and to identify situations that may occur in advance. As a result of the study, a web and mobile interface suitable for the needs of ICU nurses and physicians has been developed and a data warehouse has been provided that can be used for medical research in our country. It has advised physicians to detect critical situations before they occur with the intended decision support system [24].

A study has been focused on preventing patients who should not be in ICU. Yoon et al. have recommended whether the patient must go to ICU or not by looking at the stream values. Created with the Bayesian approach, this system has been first established offline, and a threshold has been determined. It constantly updates itself with the new values of the observed patient and gives an alarm when the threshold value is reached [25].

A study has been focused on data preprocessing. Gupta et al. have developed a clinical decision support system to estimate the risk of sepsis by using a tree-reinforced Naive Bayes network by defining a set called optimal biomarkers. In the study, it has been used the following steps to build a predictive model: data extraction, data preprocessing (imputation, feature selection, and discretization), and building Tree Augmented Bayesian (TAN) Bayesian network. Comparative analysis has showed that the model in the study performed better than the alternative models [26].

Amland et al. have worked on a decision support system. For the sepsis program, a confusion matrix has been used to report predictable values such as sepsis prevalence and sensitivity, and multivariate logistic regression (MLR) has been used to determine the results. As a result, it has been determined that early diagnosis of sepsis reduces the risk of adverse outcomes. It is concluded that a multidisciplinary sepsis program has provided with a 2-stage sepsis Clinical Decision Support System (CDSS) accelerates the correct detection, stratification, and intervention of patients with sepsis [27].

Fleuren et al. have focused on right aligned models, that is, continuous flowing data. The purpose is to identify the important factors affecting early diagnosis and performance. The articles for sepsis have been filtered through the specified databases and they have been studied. The result of this meta-analysis has showed that sepsis has been detected early by machine learning on retrospective data [28].

van Wyk et al. have conducted a study with physiological data and white blood cell counts from 1161 patients hospitalized in the ICU to determine and diagnose the development of sepsis. The definition of early sepsis and non-at-risk patients with the data stream and Random Forest that occurs with specified time intervals has visibly positively affected as a result [9]. In another study by van Wyk et al., it is aimed to use artificial intelligence for high frequency and continuous data for sepsis. While predicting sepsis 82 minutes before in the first layer, the second layer can predict sepsis 178 minutes before. While the learning algorithm used for the model has been the random forest, the data used for the non-sepsis group have been used 6 hours ago, while the data that met the criteria for systemic inflammatory response syndrome (SIRS) have been used for the group with sepsis. As a result of the study, in the model created in a multi-layer structure, the second layer is more sensitive and sensitive and can make earlier predictions [29].

In recent studies, it has been seen that the usage of deep learning is increasing in the studies in ICUs. For example, Meng et al. have implemented a model containing deep learning approaches on MIMIC-IV open-source dataset for mortality estimation [30]. Hu et al. also used this open-source dataset for sepsis prediction [31]; however, the local characteristic of patients should be considered in these kinds of studies; therefore, the studies using the original datasets are encountered such as the study of Huyut and Üstündağ. They used the dataset for the patients in Erzincan in Turkiye. The aim of this study is to predict the dominant blood parameters for COVID-19 mortality [32]. Also, Chen et al. also, have used the original dataset of the UCI in Kingston Health Sciences Centre in Canada and implemented a model using deep learning for new-onset atrial fibrillation illness to predict mortality [33]. And, Jentzer et al. have researched cardiovascular ICUs about machine learning and deep learning algorithms, and they have used them in their recent study [34].

3 Methodology and implementation

A sepsis prediction decision support system is a medical information system which makes predictions about ICU patients. The system to be created in the study operated in an integrated manner with other devices in the hospital and aimed to contribute to physicians and ICU staff in predicting early sepsis in ICU patients. During the development of the study, the tests performed on the patients, the scoring values of the organs, and vital follow-up values have been used for sepsis prediction. Sepsis occurs because of at least three or more organ failures. The most important organs for sepsis prediction are acute renal failure and lung failure.

All patient information that needs to be used and evaluated has been obtained from the hospital management system and bedside monitors. Tables taken from different databases are used and have been combined. As a result of this merger, a sepsis follow-up page has been created, which enables healthcare professionals to make a decision about the patient without entering any manual information.

Healthcare personnel who log in to the system from the login page can see the patients in ICU. A sepsis follow-up page has been added to the ICU patients page that personnel can access when they need to examine the information in detail. Critical values such as test results and scoring values (Glasgow Coma Scale, APACHE II, SAPS II, and RIFLE) of organs are shown on this follow-up page, which is presented to physicians and ICU healthcare professionals. At the same time, if a different date is selected from this screen, all values belonging to that date are also shown. These values have certain critical ranges. On the sepsis monitoring page, organs and values are shown in 3 different colors in accordance with these intervals. Green indicates that an organ is in good condition, yellow expresses that it is getting worse and red means in bad condition. It is aimed to provide better visuality and prediction by coloring the organs for the doctors.

The model-controller-view architecture has been used when creating the system to be used by physicians and to predict whether the patient hospitalized in ICU has sepsis or not.

The model defines the data structure in the study. The connection of the database where the study's data source is stored is made through the model. The model transmits data that is added, updated, or deleted to the controller. In the system, data of ICU patients are kept in the hospital management system database. Vital monitoring and lab test results tables required for sepsis from this database have been combined according to individual patient IDs. This process is used as a view table in the study's Oracle database. Database functions are written, such as the necessary procedures and functions that retrieve data from different tables. All written database transactions are transmitted to the controller through the model and used in shaping the data.

The controller is the structure between the model layer and the view layer. A response is created to the request received from the user with the data received from the model and sent to the view layer. In the study, the controller layer transfers the data (sofa score, apache score, vital values) coming from the model layer to the view. In addition, it has been used for sepsis prediction to establish a connection with the backend. The data from the model layer has been sent to the machine learning model, and it has been predicted whether the patient will get sepsis in the future. Then the result generated from the

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machine learning model has been sent back to the controller. These predictions received through the controller have been transferred to the view for examination by physicians and healthcare professionals.

The view, the last step in this architecture, is the part that the user encounters. After entering the application, the page with the patients hospitalized in the ICU is displayed, the desired patient can be selected, and the sepsis follow-up page can be switched. This is also the screen where physicians can follow all the processes related to the patient's organs, from normal to critical. The model provides general information about why the patient is hospitalized in ICU, and whether the patient has a disease that triggers organ failure (chronic obstructive pulmonary disease, lung failure, and acute kidney failure). There are 5 vital organs in the human body, and it is very important to follow each one. The warning operation done on the application for this is that the coloring of the organs changes according to their condition. Again, the organ color changes according to the values taken from the model, test results, and scores because of the operations performed on the controller. Thus, a warning has been designed for the physician as to whether to experience sepsis as sudden multiple organ failures. In addition, by changing the date, the patient can be monitored vitally.

In the study, the data that must be in the Oracle database and the information sources to be used for sepsis prediction are needed. Vital monitoring, scoring values, and tests, which are important for the prediction of sepsis, have been taken from different databases and storage. The tests consisted of approximately 14 different laboratory tests. Vital monitoring values have been obtained from bedside monitors of ICUs showing the vital values of patients. Scoring values are Glasgow Coma Scale, APACHE II, SAPS II, and RIFLE which are calculated by HMS (Hospital Management System).

The aim of this study is to predict whether the processes of ICU patients that start with organ failure progress to sepsis. The prediction is made using various machine learning models with the streaming data of current patient values and the values of patients with sepsis in past records taken from the database.

The values of ICU patients to be used as descriptive features for sepsis prediction are taken through the HMS. Critical values are presented from vital monitoring, laboratory tests and scoring values about organs come to the Oracle database in a calculated form. For the incoming data to be used in classification algorithms, it must go through the necessary preliminary processes.

The data coming together from different tables in the Oracle database of HMS are integrated. From the ICU patient data set obtained, it is necessary to clean and prepare the data that may reduce the accuracy of the model. Data selection and reduction have been used on the data. Descriptive features that do not have any contribution to the target feature have been detected and eliminated by feature selection. Multiple data continuously measured on patients have been downsized and fit into one or more cells using min, max, or average. Numerical data taking up a lot of space is compressed. It has been minimized by taking samples from patients who are very similar to each other. The dataset has been cleared of missing or empty, irrelevant, duplicated, outlier, and inconsistent data. Some of these values have been filled with values such as mean or most portable values.

Since the data set consists of numerical values, these values must be brought to the same scale. Therefore, data transformations are used. Normalization methods such as Z-score, Min-Max, and Decimal Scaling have been examined to transform the numerical data into the same range.

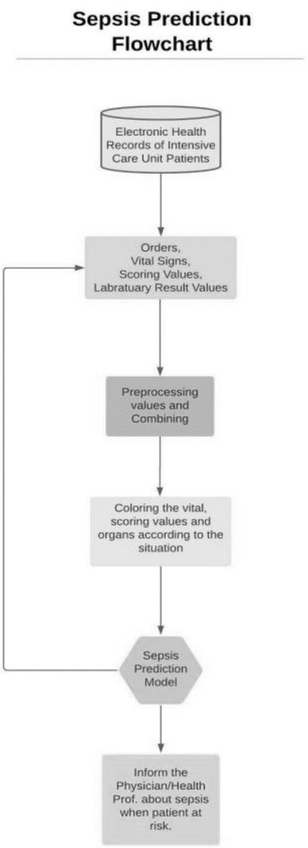

Figure 1. The flowchart of the system

All data obtained from the patient is numerical data. There is also a binary target feature, not sepsis or sepsis. Classification algorithms have been used for sepsis prediction, which is the aim of the study. They calculate the accuracy themselves using different methods and have different effects on the data. Since early detection is the most important process to be desired, high accuracy is also the greatest need. Models have been created with different machine learning algorithms such as Decision Tree, Naive Bayes, K-nearest Neighbor, Logistic Regression, Support Vector Machines, and Neural Networks, etc. The highest estimate has been chosen from among them. In addition to accuracy, it is also important to work quickly for the early detection of sepsis.

The non-functional qualities of the system that can be used to evaluate the operation of the system are determined as follows.

In the current geography, a study has been conducted on hospital software that can predict sepsis suitable for the genetic difference of Turkish patients. It is aimed to provide progressive solutions that can be reached in the field of health with the study. Early predictions have been achieved by the use of this system by physicians and patients to be less affected by sepsis results and to receive earlier and more accurate treatment.

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Sepsis prediction is vital for ICU patients, so it is very important that the prediction is done early and correctly. It is possible to make this estimation early with the model's operating performance and the correct integration with other devices. The software created has high performance in terms of time and uses ideal storage. The software to work has been integrated with the bedside monitors and HMS in the ICU. It has taken the necessary information from other hardware requirements and followed the flowing data of the patients and the old data records in parallel.

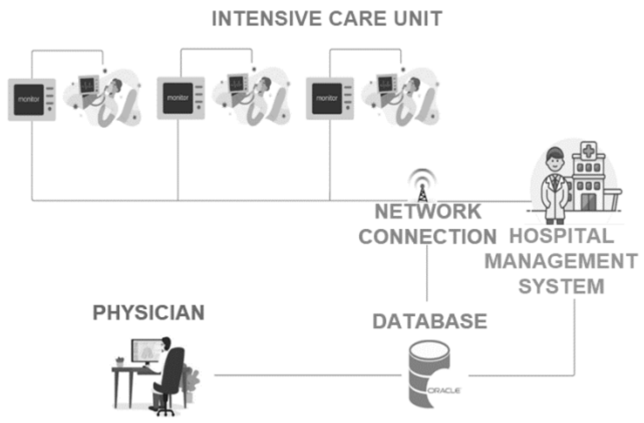

Figure 2. The architectural design of the system

The aim of the study is to establish an early diagnosis of sepsis for Turkish patients in all circumstances. Since the software has been developed to increase the survival rate of patients in ICU, this software must be maintained after it is officially used. Considering that new infections, new viruses, and various diseases emerge every day, it should be recalculated by taking these conditions into consideration in sepsis prediction. Machine learning models used in sepsis prediction need to be retrained with new values and possibilities. Currently, with the advancement of technology and research in the world, studies on the early diagnosis of early sepsis should be followed, and additions and maintenance operations should be made in this direction in the software. The processes that explain the progress of the study and help establish the system are analyzed in this chapter. According to the results of the analysis, the stages of the system are shown visually with diagrams.

A flowchart has been used to express which environment the data come from, how the problem is solved, which steps are passed, and where and how the result is used. The follow-up of these steps of the study is shown in the flowchart in Figure 1. The data in the flowchart of the system are the electronic patient records that the environment unit which has been the hospital has stored in its database. Four important subjects have been drawn for sepsis prediction from electronic records according to flow. The lab results of the patient, the medications used or the foods the patient is fed, the vital monitoring obtained from their monitors, and the scoring values of the calculated ratios. For the sepsis model to predict sepsis, these data must first be extracted from the hospital database. In addition, preprocessing stages should be applied to the data to clean the data for the prediction model, to place them according to their relationships, and to use them. These important values are displayed in three colors according to their condition to provide a better observation to the doctor on the sepsis screen. After the preprocessing, the model is created. The model to be created must constantly renew itself over stream data in order to accurately predict the patient's instant condition. Therefore, the flow repeats again at this point to review the data. If the created model finds the patient dangerous for sepsis, it offers the doctor a scoring according to the early warning and prediction from the sepsis monitoring screen. The architectural view is the diagram showing the components in the system and their connections with each other.

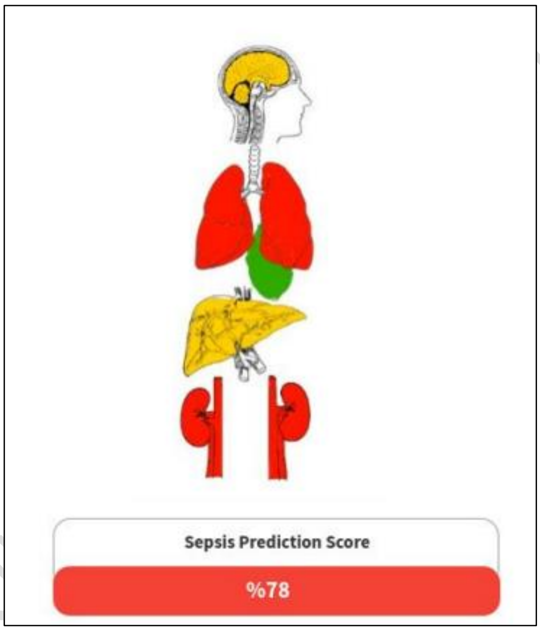

Figure 3. An example output.

In this diagram shown in Figure 2, firstly, all the values taken from the monitors next to the bed of each patient in the ICU go to a network connection. Then, all values from the network connection stream into the Oracle Database and Hospital Management System. The physician can also access every value belonging to the patients by establishing a database connection on the computer.

The design of the test interface which interacts with the user has been provided with .NET Model-View-Controller (MVC) architecture and C# programming language. Python integration has been provided for the backend side for using machine and deep learning algorithms. The predictions to be made by the model have been taken from there and displayed on the user interface. An example test output is given in Figure 3.

4 Experimental Studies and Tests

The implementation of the study consists of 3 stages. The user interface of the system, the creation and preprocessing of the dataset of the ICU patients, and sepsis prediction with machine learning algorithms. As the first stage in this study, an easy-to-use and familiar interface has been designed for physicians and ICU professionals. In the second stage of the study, a consistent and complete stream dataset has been created for ICU patients, and this dataset has been passed through some pre-processing. The last stage is to examine and analyse the prepared dataset and to test with the best fit machine learning algorithms, and to apply regression models and deep learning to predict sepsis.

The study, to understand the progress of intensive care patients going to sepsis, has been completed to create consistent and

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complete patient data and to process these data by using the SynSys method (A Synthetic Data Generation System for Healthcare Applications) [35]. Since inconsistent data on Turkish ICU patients in hospitals may affect the model, a simulation has been created that synthetically creates the data set. In this simulation, many types of synthetic patients have been created in a controlled manner based on the references in the values of Turkish patients to remain loyal to the study and lead the research. Based on the critical values that are constantly monitored in ICU patients, multiple patient stories have been included based on these values. In ICU patients, many values such as laboratory and vital values are monitored digitally every hour, every four hours or every day, and any instant change in values is important to understand the process of the patient's critical condition. It is important to monitor this course hourly and to understand whether the patient has organ failure or has more than one organ failure, sepsis. The data values to be used in the data set to examine the sepsis status in ICU patients have been determined. Critical values that are followed on an organ basis and specific to each organ are grouped and followed. Each organ has specific values which tell its situation. These values have been obtained from the decisive tests for Sepsis in given Table 1.

Table 1. Vital organs and their decisive tests for Sepsis

Organs	Decisive tests
Lung	PO2, PCO2, SPO2, ETCO2 and HCO3
Heart	SBP, DBP, Pulse, MAP and CVP
Brain	Glasgow Score
Liver	ALB, INR, BIL and Glucose
Kidney	CRE, Urine and GFR

The data is indispensable for studies involving machine learning. Some of the patient data to be used in the study come from the hospital every hour and every six hours, and therefore there is a lot of data flow. This directly affects the training of the model, increasing the learning time.

In the study, the dataset, where there are 300 patients, 17 attributes, and time series for every 24 hours, has been created. Total of 122400 values have been evaluated in the model.

The range values of the variables are very different from each other. While these values are calculated in algorithms, they can affect the models negatively. To achieve this, the critical level has been transformed into ordinal values. It has been numbered 0 with low risk and 8 with high risk like scoring approaches in the Glasgow Skala, Apache score, etc to have large numbers that doctors can more easily understand. Thus, the difference in the value ranges of the variables is prevented from adversely affecting the operation of the algorithms. The time series example of the PO_2 value of 5 patients hospitalized in the ICU, updated hourly, is shown in Figure 4. In order to prevent this, first of all, the method of statistical extraction from the data obtained has been used. In this method, a daily summary of the data of the patient has been made. Statistical data such as average, median, mean absolute deviation, variance, standard deviation, maximum and minimum values of the patient belonging to that day have been obtained. By extracting the data summary, the size of the data has been reduced and if there has been an extraordinary value, this value has been highlighted.

T1	T2	T3	T4	T5
1	2	2	4	3
0	1	2	2	2
4	4	2	2	2
3	4	5	7	7
5	6	4	3	3
...	...	...	...	...

PO_2 Median	PO_2 Min	PO_2 Max	PO_2 Mad*	PO_2 Std	PO_2 Variance	PO_2 Mean
2.0	0	7	1.738	2.216	4.910	6.475
3.0	0	8	1.609	1.992	3.969	6.400
4.0	1	8	1.408	1.783	3.179	3.100
5.5	0	8	2.516	2.773	7.692	4.875
4.0	0	8	2.130	2.482	6.164	3.650

Figure 4. Hourly values of PO_2 value of the patients hospitalized in the ICU and the statistically summerized data for PO_2 (* Mean absolute deviation)

In Phase 1, machine learning algorithms have been used to predict sepsis on the created data set. There is a rate of 70% to 30% sepsis/non-sepsis patients in the dataset respectively. Since the target attribute is a binary value, sepsis predictions have been made with classification algorithms. Python's PyCaret library has been used to understand comparisons and results. PyCaret's Classification Module is a machine learning module used to group binary or multi-class problems into groups. It uses 13 different classification algorithms to predict categorical class labels in a discrete and unordered manner.

The module itself provides several pre-processing features that prepare the data for modeling and makes comparisons easy. The stratify parameter has been used to distinguish the test and train size equally as having or not having sepsis and to prevent from memorization of the model while training the data. In this way, there has been no observation of overfitting or underfitting in the model. All steps of Phase 1 are shown in Figure 5.

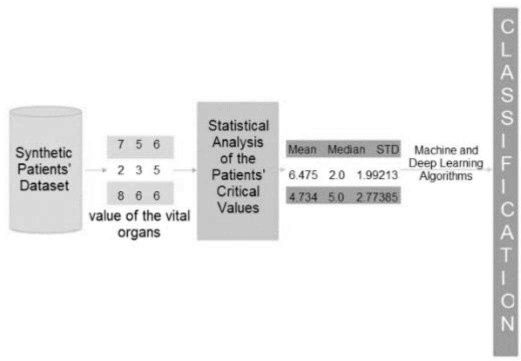

Figure 5. The steps of Phase 1

In Phase 2, an analysis has been carried out with different retrospective values on this dataset, which has been created as a time series. Considering that a critical value belonging to any organ may also affect the critical values of other organs, epoch values taken from 5 to 15 and values that give results depending on time have been created. After it has been applied to each sample, the average errors of each dataset have been compared over the regression model, and the optimal epoch value has been selected. The elbow point, epoch 7 is also shown in Figure 6.

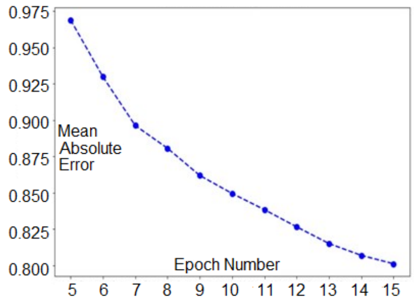

Figure 6. Mean absolute error for each epoch

Then, a new data set has been created with the weights of each value from the regression model applied to the dataset of epoch 7. The classification algorithms in the PyCaret library have been applied to the data set created with the weights, and it has been observed that the results have been not efficient enough.

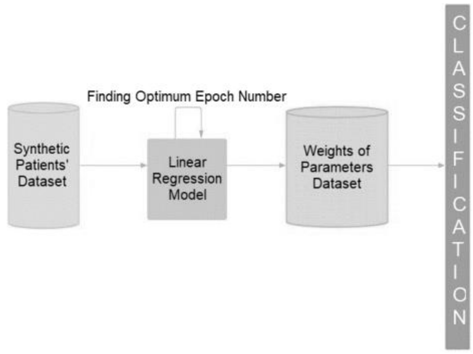

Figure 7. The steps of Phase 2

In Phase 3, a new dataset has been created by combining the weighted dataset from regression and the statistical dataset made in Phase 1. In the obtained dataset, deep learning has been used to test the success of the patients in terms of understanding and classifying the presence of sepsis and to see the success of the model. It has been observed that there is no overfit in the model with deep learning, and even the F1 score value gives better results. All steps of phase 3 are shown in Figure 8.

At this stage, epoch values have been determined by a different method. While looking at the retrospective values, a new data set has been created by obtaining the specific value of the organ in a way that gives time-dependent results in itself. As a result of the regression applied in the same way, epoch 7 has been selected as optimal again and then a new data set has been created with the weights of each value.

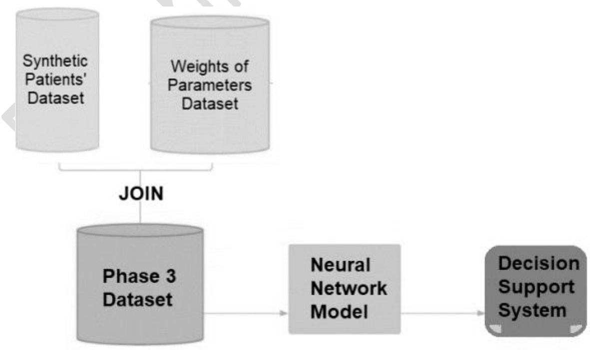

Figure 8. The steps of Phase 3

The selected epoch 7 value corresponds to 1 day and 18 hours, and the hospitalized patient at the ICU must have at least 1 day and 18 hours of data in order to make the estimation of sepsis. All steps of phase 2 are shown in Figure 6. The deep learning method neural network model has been applied to the data set obtained in the last phase. In each layer, learning is reinforced as illustrated in Figure 9 [30].

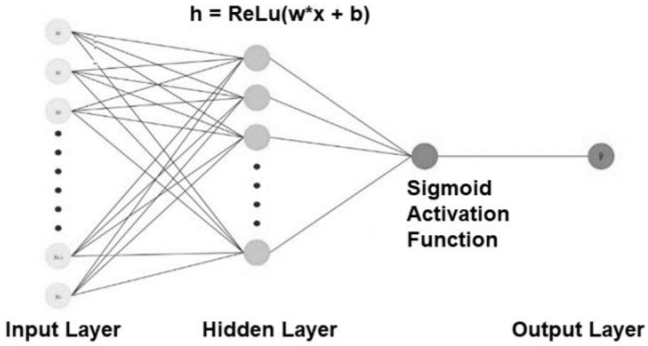

Figure 9. Illustration of the neural network

For activation function in formulization, in intermediate layers ReLu is used, and in the last layer sigmoid is used. The reason for using ReLu in the intermediate layers is that our work progresses based on weights. The derivative of ReLu becomes 0 or 1, multiplying with ReLu as the activation function prevents weights further away from the result of the loss function from suffering from the vanishing gradient problem. For the last layer, sigmoid is used because of the binary classification. As a result, the most successful result has been obtained with this combination. Testing has been performed in three different ways and their success has been compared after performing the implementation with the data of ICU patients. Many models have been tried to select the model to be used at the end of the study. The success of the models created with 3 different approaches has been compared.

In Phase 1, classical approaches have been tried on the data set created with statistical inferences. The results generated are shown in Table 2.

The confusion matrix is used to determine the accuracy of the classification. By calculating the matrix, an idea can be obtained about whether mistakes have been made in the classification model. The confusion matrix shows the values in the formulas used in the creation of the metrics analyzed.

Accuracy is one of the most used success metrics in machine learning studies. When calculating, the number of values found correctly is divided by the size of the total data set. This metric alone is not sufficient for unbalanced datasets. The formula used in the calculation is shown in the Formula 1.

Recall determines how many of the values that need to be predicted positively have been predicted positively. The formula used in the calculation is shown in the Formula 2.

Another metric, precision, determines what percentage of those predicted positively actually have a positive value. The formula used in the calculation is shown in the Formula 3.

The F1 metric makes up for the lack where the accuracy metric is insufficient. It is a metric calculated by using precision and recall values together. The formula used in the calculation is shown in the Formula 4.

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

$$\text{Recall} = \frac{TP}{TP + FN} \quad (2)$$

$$\text{Precision} = \frac{TP}{TP + FP} \quad (3)$$

$$\text{F1 Score} = 2 \text{ x } \frac{Precision \ x \ Recall}{Precision + \ Recall} \quad (4)$$

where TN is true-negative, TP is true-positive, FN is false-negative and FP is false-positive.

F1 score has been determined as the value to be considered as the success rate in the table. As shown in Table 2, when the F1 scores of the results are examined, the most successful results are at an 83% success rate. Since the study is in the field of health, this success result should be improved, and a higher success should be achieved. Patients with sepsis have been found to be highly accurate. Models have been successful in this area. However, the success rate of patients without sepsis is not good enough. Mistaking this classification may cause poor results by applying the wrong treatment to the patient who will not get sepsis.

After Phase 1, the second approach, the data set prepared with the coefficients from the Regression model, has been tested. After the trial results with different models, the results in Table 3 have been obtained. Although no obvious increase has been observed in the F1 score, an increase has been observed in the recall value. But the precision value has decreased. In this case, it has been not possible to predict whether the ICU patients would have sepsis or not.

Table 2. Comparison of Classification Algorithms for Phase 1

Model	Precision	Recall	F1-score	Accuracy
Gradient Boosting Classifier	0.7596	0.9048	0.8245	0.7333
Naive Bayes	0.8379	0.7684	0.7959	0.7292
Extra Trees Classifier	0.7282	0.9702	0.8317	0.7250
Random Forest Classifier	0.7296	0.9460	0.8233	0.7167
Light Gradient Boosting Machine	0.7546	0.8875	0.8127	0.7167
Logistic Regression	0.7929	0.7978	0.7893	0.7083
Quadratic Discriminant Analysis	0.7000	1.0000	0.8200	0.7000
Ada Boost Classifier	0.7614	0.8162	0.7842	0.6917
SVM - Linear Kernel	0.7877	0.7728	0.7540	0.6750
K Neighbors Classifier	0.7564	0.7607	0.7532	0.6667
Ridge Classifier	0.7538	0.7621	0.7530	0.6583
Linear Discriminant Analysis	0.7756	0.7085	0.7313	0.6458
Decision Tree Classifier	0.7493	0.7018	0.7231	0.6250

After Phase 2, the new data set has been used as a combination of the first two approaches. In Phase 3, The deep learning model, which is expected to be successful in larger data, has been applied to the new data set with both regression coefficients and statistical values.

Table 3. Comparison of Classification Algorithms for Phase 2

Model	Precision	Recall	F1-score	Accuracy
Gradient Boosting Classifier	0.7403	0.9173	0.8187	0.7167
Naive Bayes	0.7000	1.0000	0.8234	0.7000
Extra Trees Classifier	0.7022	0.9824	0.8188	0.6958
Random Forest Classifier	0.7005	0.9882	0.8196	0.6958
Light Gradient Boosting Machine	0.7276	0.9055	0.8057	0.6958
Logistic Regression	0.7206	0.8636	0.7826	0.6667
Quadratic Discriminant Analysis	0.7307	0.8283	0.7729	0.6625
Ada Boost Classifier	0.7231	0.8342	0.7720	0.6583
SVM - Linear Kernel	0.7398	0.7864	0.7584	0.6542
K Neighbors Classifier	0.7341	0.7794	0.7502	0.6458
Ridge Classifier	0.7509	0.6846	0.7105	0.6167
Linear Discriminant Analysis	0.7495	0.6562	0.6791	0.6042
Decision Tree Classifier	0.7142	0.6846	0.6935	0.5833

Looking at the results, a significant increase has been observed in all values. The F1 score value, which has been determined as a success metric, reached its highest value. In addition, success has been achieved in the estimation of patients without sepsis in ICU patients in Phase 2.

As seen in Figure 10, the F1 score success rate of the model established with the neural network at the end of Phase 3 is higher. Also, when Table 2 and Table 3 are also examined, it has been observed that the model created because of Phase 3 is more successful in Recall and Precision values.

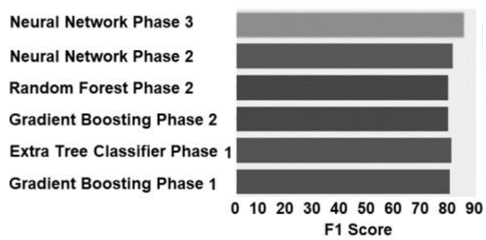

Figure 10. Comparison of the models that achieved the most successful F1 score at the End of the Phases.

5 Discussion

Many studies have been conducted on the newly emerging pandemic in the world. The decision mechanism is constantly updated with the information obtained from the organizations. Calculations are made according to the data received from the user and the risk level is determined accordingly and recommendations are made. For ICU patients, mortality scores are obtained by evaluating sequential organ failure at an accuracy between 80%-85% [10]. During the pandemic period, it is very important to determine whether the patient should be

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treated in the ICU or be in quarantine at home. Using logistic regression logic, 4 models have been trained for different features and the features have been fixed according to the model with the highest accuracy at 87.5%. Patients with severe conditions are taken to the ICU. However, as the drawbacks of the study, the different effects of the virus on patients of different ethnicity and the limited number of samples can be shown [11]. The study of Wernly et al. carried out another model by looking at the arterial blood gas (ABG) data with an accuracy of 86% [12]. It is important to allocate ICUs in an optimized way, especially in times such as pandemics. The study, developed with the machine learning algorithm, is Recurrent Neural Networks and for each step, values are taken from the patient, and the network is updated by creating a rate for the possible death situation with an accuracy of 88% [13].

In the study of Islam et al., for machine learning models, values have been calculated to predict the onset of sepsis 3 to 4 hours before and performance has been evaluated. As a result of the study findings, it has been revealed that the machine learning approach has a better performance than existing sepsis systems in predicting sepsis and decreasing the prediction time with an accuracy of 89% [14]. In one of the studies, Desautels et al. InSight machine learning algorithm is used with the Sepsis-3 standard, with minimum data and without the need for any additional data. Another advantage for Insight is that it has a very strong algorithm against the situations that may arise from the degradation by randomly deleting data with an accuracy of 88% [15]. In another study by Liu et al., the Random Forest model has been used on the physiological data, and then the same dataset has been alternatively trained with the Neural Network model because it is a flexible framework. By examining the probabilities taken from the previous stage with PhaseI-III in Stage 2, if the patient had sepsis or non-sepsis is predicted by statistical tests which are Kolmogorov-Smirnov tests. As a result of the experiments, 88% accuracy has been obtained [16]. High performance has been achieved with natural language processing algorithms applied to datasets in addition to machine learning algorithms. In the study of Giannini et al., a random forest classifier, derived and validated using electronic health record data, has been distributed with a warning to inform clinical teams of the sepsis estimate. It has been concluded that the machine learning algorithm can predict the occurrence of impending severe sepsis and septic shock with low sensitivity but high specificity with an accuracy of 88% [17].

Treatment costs of patients hospitalized in ICUs due to sepsis are quite high. In the study of Nemati et al., while the aim of the model is to determine sepsis and sofa beforehand, the most successful result is predicted 4 hours in advance. Sensitivity decreases in predictions made 6, 8, and 12 hours in advance. In this model, it has been observed that the success of the predictions decreased as the time increased with an accuracy of 85% [18]. In another study by McCoy et al., the machine learning algorithm, prepared as 3 PDSA (plan-do-study-act) cycles, has been improved by receiving feedback from the user in each cycle and the possibility of giving false warnings has been tried to be minimized with mortality rate decreased by 60.24% [19]. In some studies, missing subjects such as length of hospital stay, or randomized data have been studied and machine learning has been combined with them. In the study of Shimabukuro et al., a randomized controlled clinical study has been conducted on adult patients evaluating the primary and secondary outcomes of in-hospital mortality at specific intervals of average length of stay in two different medical-surgical ICUs. In addition to the present severe sepsis detector, the machine learning algorithm has been also used in the experimental groups with a mortality rate decrease of 58% [20]. In addition to these studies, studies have been conducted on the control of the patients' prehospitalization values, too. The study by Barton et al. has implemented a machine learning tool and its performance compared to existing methods to use machine learning systems and electronic health records to facilitate the detection of a common syndrome and costly sepsis in hospitals. The performance of the machine learning algorithm has been compared with commonly used scoring systems. The machine learning algorithm obtained the values at an accuracy of 88% for the onset of sepsis 24 and 48 hours before the onset of sepsis compared to other scoring systems [21].

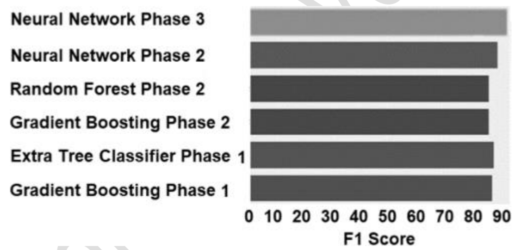

Figure 11. Comparison of the models that achieved the most Successful F1 score at the End of the Phases by using MIMIC-III database.

The Medical Information Mart for Intensive Care (MIMIC)-III database [36], which has been used in many recent publications [37, 38], has been also used for testing, except for the synthetic data we used in our study. Alternative main algorithms and the most successful Neural Network Approach Phase 3 have been also tested with this dataset. The results are shown in Figure 11. It has been observed that F1 score results are more successful in terms of all algorithms due to the larger data in this dataset. Moreover, with an F1 score of 94%, it can be deduced that the Neural Network Approach Phase 3 approach becomes more prominent in model learning as the data set grows.

In line with these studies, it can be assumed that our proposed approach has satisfying results with accuracies of 88% and 94%.

6 Conclusion and Future Works

Nowadays, with the emergence of the COVID-19 virus, the number of patients hospitalized in ICU is increasing considerably. Sepsis constitutes a very high proportion of the cause of death of patients hospitalized in the ICU. It is very important to detect organ failure caused by not only COVID-19 but also many other diseases and viruses that have emerged over the years. Since each person has different genetics and reference ranges in values it has been observed that the existing sepsis prediction decision support systems have been not successful enough in Turkish patients and that this system has been needed in the ICU due to the consequences of the COVID-19 virus. Therefore, researching a decision support system that predicts sepsis suitable for Turkish ICU patients has been beneficial in the field of healthcare. The desired result with the system has been to detect the daily changes of the patients through the flowing data so that the physicians could recognize the multi-organ failure earlier and reduce the stay of patients in the ICU. The number of patients with sepsis is also increasing with COVID-19. Therefore, it will also be ensured that the number of ICU patients rising with COVID-19 will decrease. The Sepsis prediction decision support system not only provided an easy-to-use and user-friendly interface that enables the evaluation of organs one by one with colouring, but also contributed to the early diagnosis of the physician by making predictions. With this study, it has been shown that when the data from the patients are arranged appropriately, it is possible to successfully predict the patient who will have sepsis or who may have sepsis.

As a future work, it can be turned into an API as a result of the implementation and improvement of Phase 3 studies with real data. After this process, a connection with HMS can be established. Thus, a sepsis prediction model can be performed on real patient data. After this procedure, the most similar patient to the new patient can be found and the ICU process of that patient can be shown to the physician in a report.

7 Author contribution statements

In this study, while Author 2 contributed to the creation of the idea, all authors together with Author 2 have made contributions in the titles of literature review, sourcing, establishing and validating models, performing analysis, obtaining and discussing the findings, writing the article and final checking of the article.

8 Ethics committee approval and conflict of interest statement

No need for permission from ethics committee for the article prepared. There is no conflict of interest in the article prepared.

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Düzenlenmemiş Sürüm - Uncorrected Version