PREDICTION OF SEPSIS DISEASE BY ARTIFICIAL NEURAL NETWORKS

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Abstract

Sepsis is a fatal condition, which affects at least 26 million people in the world every year that is resulted by an infection. For every 100,000 people, sepsis is seen in 149-240 of them and it has a mortality rate of 30%. The presence of infection in the patient is determined in order to diagnose the sepsis disease. Organ dysfunctions associated with an infection is diagnosed as sepsis. With the increased usage of artificial intelligence in the field of medicine, the early prediction and treatment of many diseases are provided with these methods. Considering the learning, reasoning and decision making abilities of artificial neural networks, which are the sub field of artificial intelligence are inferred to be used in predicting early stages of sepsis disease and determining the sepsis level is assessed. In this study, it is aimed to help sepsis diagnosis by using multi-layered artificial neural network. In construction of artificial neural network model, feed forward back propagation network structure and Levenberg-Marquardt training algorithm were used. The input and output variables of the model were the parameters which doctors use to diagnose the sepsis disease and determine the level of sepsis. The proposed method aims to provide an alternative prediction model for the early detection of sepsis disease.

Keywords: Sepsis, artificial intelligence, artificial neural networks, sepsis risk prediction.

1. Introduction

Sepsis is a fatal condition, which affects at least 26 million people in the world

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every year that is resulted by an infection. For every 100,000 people, sepsis is seen in 149-240 of them, with a mortality rate of 30%. Sepsis is a condition that is associated with infection and it involves a disordered reaction leading to organ system failure. For the diagnosis of infection in the patient, the presence of infection in the lungs, the detection of bacterial growth or bacterial infection in the hemoculture of the patient during bacterial screening, the presence of intraabdominal infection, new antibiotic therapy and other infections are investigated. In case of infection, the patient's QSOFA criteria are considered. QSOFA is the scoring system, which consists of the respiratory rate, altered mental status and systolic blood pressure values. A QSOFA score greater than or equal to 2 constitutes suspicion of sepsis. To confirm the diagnosis and severity of sepsis, a score named as Sepsis Related Organ Failure Assessment (SOFA) score is used, which comprises variables of respiration, coagulation, liver, cardiovascular system, brain and renal functions. An increased SOFA score is associated with increased risk of death [1, 2, 3, 4].

Third International Sepsis and Septic Shock Consensus Definitions were reorganized by the American Medical Association [5]. In this new arrangement, the SIRS criteria determined by Bone et al. [6] were used. The occurrence of two or more of the following conditions according to the specified SIRS criteria leads to the SIRS syndrome:

- If the body temperature is lower than 36 degrees or higher than 38 degrees,
- If the patient has more than 90 heartbeats per minute
- If the patient has more than 20 breaths per minute,
- If the number of white blood cells in the patient is more than 12,000 or less than 4000 at 1 mm3, or if the number of immature neutrophils is greater than 10%, the patient is diagnosed with SIRS [5]. Key concepts used in the definition of sepsis are as follows [5]:
- Sepsis is the primary cause of death due to infection, especially if it is not noticed and is not treated immediately. This requires immediate intervention in case of recognition.
- Sepsis is a syndrome that is shaped by pathogenic factors and host factors that develop over time. What distinguishes the sepsis from infection is the presence of an

abnormal or irregular host response and organ failure.

- There may be hidden organ failure due to sepsis; therefore, it should be considered to be present in any patient with an infection. However, unknown infection may be the cause of organ failure. Any unexplained organ impairment increases the likelihood of underlying infection.

- The clinical and biological phenotype of sepsis may be altered by pre-existing acute disease, prolonged ongoing additional disease, medications and interventions.

- Specific infections may result in local organ failure without producing an irregular systemic host response.

The evaluation criteria used in determining the SOFA score are shown in Figure 1 [5].

- In a way that everyone can understand, Sepsis is a life-threatening condition that occurs when the body suffers damage to its tissues and organs during an infection reaction.

Patients with septic shock can be described by clinical Sepsis with persistent hypotension requiring a mean arterial pressure of MAP <= 65 mm Hg and a serum lactate level> 2 mmol / L (18 mg / dL) despite adequate volume resuscitation. Hospital mortality exceeds 40% with these criteria.

- When SOFA is defined as consecutive or sequential organ impairment associated with Sepsis, QSOFA is expressed as rapid SOFA evaluation [5].

After these definitions, QSOFA (rapid SOFA evaluation criteria) are:

- The number of breaths per minute is equal to or greater than 22

- Changes in consciousness, i.e. mental activity.

- The systolic blood pressure is equal to or greater than 100 mm Hg.

Figure 2 shows the application of clinical criteria to identify Sepsis and septic shock patients, and septic or septic shock conditions of patients are determined according to the SOFA and QSOFA criteria used in the algorithm [5].

These updated definitions and clinical criteria should clarify the long-term use of descriptors and drafts.

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Figure 1. SOFA score evaluation criteria for sepsis [5].

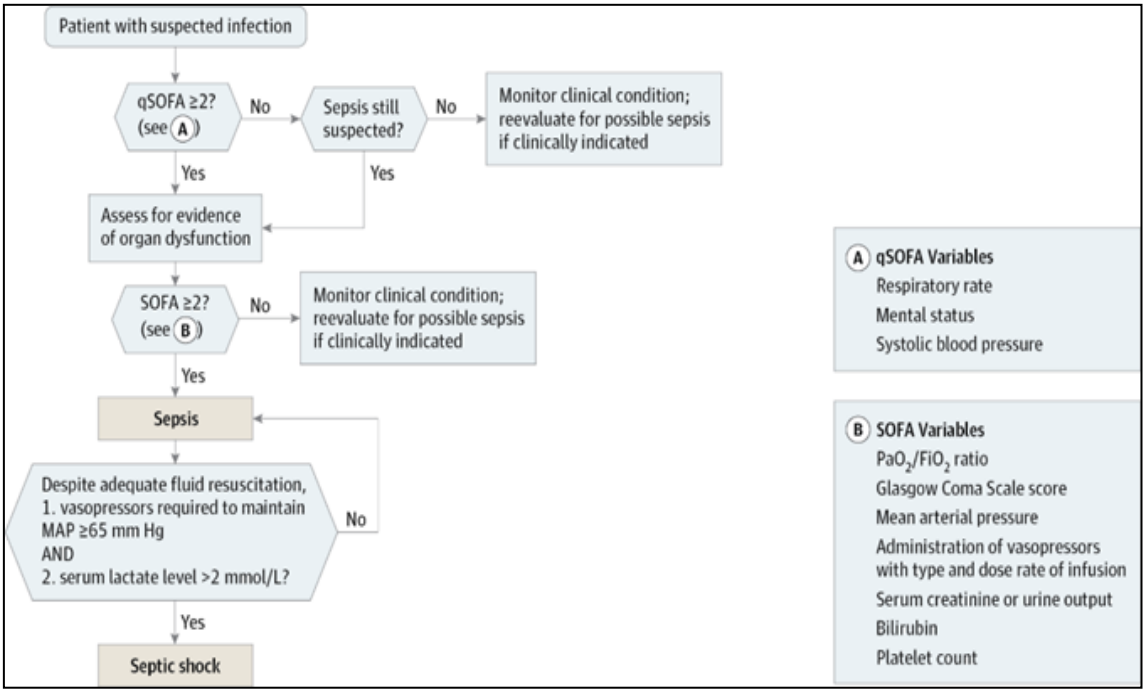

Figure 2. Sepsis and septic shock estimation algorithm using SOFA and QSOFA score criteria [5].

However, this should be an ongoing process. As with Software and other encoder updates, the next work is to distinguish future iteration requirements.

The use of artificial intelligence methods in the field of medicine provides important contributions in the early diagnosis and treatment of diseases. The use of artificial neural networks for lung cancer risk analysis [7], prediction of cardiovascular

disease risk with artificial neural networks [8] can be given as an example.

The cases of Sepsis are frequently observed in cancer patients and patients in intensive care are the leading cause of death in Turkey.

It is thought that this field will help doctors to reduce the number of death cases and to treat the disease by studies on the prediction of Sepsis disease using artificial intelligence methods. Artificial neural networks, one of the artificial intelligence methods that have the ability to learn and to decide, are tried to be obtained as an alternative early diagnosis method by using the anticipated risk of Sepsis.

2. Related Studies

The studies on Sepsis have been examined and the following studies in the literature have been given as examples.

Parente and colleagues have revealed that bio-labeling classifiers are useful for real-time diagnostic testing according to the characteristic roc curve in their study for rapid and accurate diagnostic testing of severe Sepsis cases using a nuclear classifier [9].

Ongenae et al. added time series data to the medical database with semantic information by using ontology, and used machine learning technique for the automatic classification of this time series data. By machine learning technique, they have attempted to identify a complication that indicates clinical deterioration or to suggest a new pathological condition. While explaining uncertainty by adding this classification to ontology, they have associated it with prediction.

Baldini and colleagues benefited from biomarkers to diagnose sudden Sepsis. They tried to do Sepsis analysis with the devices they put in the bed. As a result, they observed that an integrated and portable device gave better results in a very short time [11].

Ward and colleagues used a machine learning method for the CPN scoring system, which they have manually defined to determine the severity of the systemic inflammatory response syndrome and to compare objective data with other severity scoring systems and to separate Sepsis and uninfected SIRS. They found that the area under the ROK curve was significant at 0.79 level in terms of predicting the 30-day mortality rate of the created Sepsis learning model. They have also shown that the

model they produced have the ability to differentiate between Sepsis and non-infection-related SIRS [12].

Danner and colleagues studied on large data by evaluating records of 53313 emergency patients from January to June, 2015 and compared heart rate and pulse rate based on SIRS criteria for Sepsis prediction with machine learning. Among the discharged patients, 884 patients had Sepsis, severe Sepsis or septic shock. In their study, they have indicated that heartbeat, pulse (systolic blood pressure ratio), and temperature variables are primary early determinants for preferential early Sepsis prediction with an (654/884) 74% accuracy value according to the 34% (304/884) SIRS criterion ($p < 0.0001$) in approved sepsis patients. They have emphasized the importance of physiologic-based prediction for an earlier, and more accurate diagnosis in Sepsis treatment [13].

Calvert and colleagues have resorted to machine learning with the purpose of developing high-performance early sepsis prediction technology for the general patient population by using the multi-parameter smart imaging data set (in the computer aided diagnosis and on the basis of clinical decision support systems) for the retrospective analysis of adults with non-sepsis and those who apply to intensive care unit. Sepsis predictions were made three hours before the first five-hour SIRS phase of the patient with the early Sepsis warning algorithm they developed. In a previously untried test case, the early warning algorithm showed 90% sensitivity and 81% specificity. It has gained an average area of 0.83 under the ROK curve for the estimated periods of up to three hours from a continuous SIRS event. They have shown that the use of multiple risk factors in Sepsis patient risk analysis is more important than the use of isolated individual risk factors. As a result, they have declared that the Sepsis prediction performed better than current standard practice [14].

Saraiva and colleagues have applied the results on bio marker lists to many transcriptomic (copying DNA itself in an RNA) studies for the diagnosis of Sepsis. They developed Support Vector Machine classifier based mixed integer linear programming and trained them separately with different sets of data, then combined them into common property constraints. As a result of this development they have achieved, the predictive success of bio markers in datasets has increased by 42% [15].

Morales and colleagues used the conditional independent mapping method (CIM) with the aim of verifying changes in the definition of Sepsis and investigating possible causal relationships between measured variables and survival outcome in their Sepsis diagnosis study. They tried to analyze one of the most useful multicenter Sepsis databases by applying this method. They have shown that the inflammatory response plays an important role in the diagnosis of Sepsis [16].

Vieira et al. have attempted to solve the problem of feature selection by using a particle swarm optimization method in a wraparound approach to artificial neural networks, fuzzy models, and assisted vector machines. The best particle flock optimization method which they tried to predict the outcomes of Sepsis patients was compared with the method of genetic algorithms. With accuracy it was shown that the best particle flock optimization method was similar to the method of genetic algorithms, but that method needed a lower duration of simulation and fewer selected features [17].

Bui and his colleagues aimed to design and develop a remote imaging platform for Sepsis tracking indicators which they intended to increase the quality of outpatient treatment and reduce re-hospitalization and death rate. In this study which they conducted to expand outpatient criteria, they offered a remote monitoring solution solutions using high-frequency sensor devices such as temperature sensors for early detection of sepsis taking into account the difficulties of patient biometrics remotely using technology on the market [18].

Guillen and colleagues aimed to determine a new framework for estimating severe sepsis and identify early predictors using clinical laboratory values and vital findings collected from adult patients in ICU. They have attempted to explore models of logistic regression, support vector machines and logistic model trees methods by using vital findings, laboratory values, or a combination of vital findings and laboratory values. When the predictive support vector machine model, which uses vital and laboratory findings is applied to the retrospective cohort of intensive care patients, it has showed higher predictive power than the other two models with an accurate forecasting that there was severe sepsis developing in 339(%65) patients out of 3446. However, this model does not have the clinical transparency and interpretability of the other two models. Notwithstanding, the data before 24 hours to severe sepsis was used in this

model and the data which was obtained just before two hours to severe sepsis was extracted to avoid misleading (prejudice). They have shown that the models on the basis of this framework and developed can be suggested for clinical decision support in intensive care unit and in non-intensive care environment [19].

Ghalwash et al. used the data mining technique which they in their previous studies for pattern recognition in the study of early diagnosis and the advantages of sepsis for blood cleansing treatment and they have shown that these patterns can be used to help doctor to make early diagnosis. In their study, they found that it is more likely for % 52 of patients with the combine of the blood cleansing treatment and early diagnosis to survive than % 32 of patients with the standard blood cleansing procedure.

In order to provide evidence of the classification of transient observations of patients, they first extracted time series from the original time series for early classification. Then, they have shown that the MSD method they used performed better than the other methods developed for time series and univariate time series. They have applied the MSD method which they constructed for an early diagnosis of septic patients. They have shown that the hybrid therapy they applied saved more patients than the standard approach [20].

Ghasemi and Raoufy compared the last 25 hours of heart rate dynamics of the sepsis patients who survived and unable to survive in the intensive care unit by using the time series methods. Patients' RR (heart rate per millisecond) interval time series were calculated and impaired fluctuation analysis was applied to the data set every 30 minutes. For the analysis of heart rate variability, they have observed the sequential dependent fluctuation analysis algorithm (DFA) which is used for prediction of the sepsis mortality rate 9 hours before the death of sepsis patients. The exponential measurement parameter of the DFA algorithm is lower in dying patients. This parameter is more consistent in patients who survived and is closed to 1, whereas it is about 0.5 in patients who died. This parameter is further decreasing when approaching death. So, they have shown that this parameter can be used as a death alert (alarm) before 25 hours of death [21].

Jiang et al. presented the new graphical adaptive dynamic Bayesian network model which is a model calculation method as an evolutionary imaging approach that

adapts spontaneously in determining the stage of sepsis for sepsis patients to provide medical knowledge and semantic deduction with clearly defined syntax. The system, which includes the clinical research and physician information, aims to provide the early caution of suspected infection patients who have gone through the sepsis stage by semantically extracting this information [22].

In study of ward patients' optimization of sepsis risk assessment by Mitchell et al. using the newly accepted definition of sepsis and developed predictive models, they related sepsis and non-intensive care ward patients more accurately and earlier. They have obtained the early detection which determines the ward patients at risk 12-24 hours before the onset of sepsis by using the physiological data and the multivariate logistic regression and laboratory data which can always be obtained from electronic health records in the area under the receiver operating characteristic curve (AUC) with a result of 74%. When this model was applied to a separate intensive care population, the receiver operating characteristic curve showed 56% success and the model performed poorly in this environment. This study was approved by the ethics committee of the University of Virginia. The primary data source was created from patient admissions at the Virginia Medical Center between September 2010 and August 2015 [23].

In the study of Gunnarsdottir et al.'s classification of Sepsis using demographic data and physiological characteristics of time series in intensive care unit. They established a generalized linear model for the probability of patients with intractable Sepsis (GLM) as a function of bedside measurements and demography. They selected physiologic variables are heart rate variability, respiratory rate, arterial oxygen saturation variance and low and medium frequency photoplethysmography, in addition to preselected demographic characteristics. The accuracy of the demographic model was tested as; 62.5% classification accuracy in the test data, 100% sensitivity throughout the patient group and 25% specificity. The classification accuracy of the physiological model is higher than the demographic model, which is 75%. Sensitivity throughout the patient group was tested as 100% and specificity as 50% [24].

In their study, Marshall and colleagues used the discrete conditional survival model (DC-S), which is a classification component, to predict the patients' results, and survival component to predict the length of hospital stay. It was observed that the

validation data included 773 infants and 9.8% (76) of them were late-onset Sepsis patients. The revealed model has the potential to accurately estimate the length of stay of the babies and, thus, to plan their stay. Logistic regression, Bayesian nets, and Navie Bayes classifier are the methodologies used to construct the discrete conditional survival model (DC-S). They introduced the combination of classification trees within the situational component of the discrete conditional survival model. They have demonstrated the suitability of these techniques for newborn care and emphasized that the capacity planning and resource management are key to newborn care. They expect that the development of statistical models will provide effective, accurate and easy-to-implement methods for newborn care management [25].

In their study of applied autoregressive Hidden Markov models for early detection of newborn sepsis, Stanculescu and colleagues viewed late-onset premature sepsis as one of the major clinical concerns when premature infants were under intense care. The model they applied can produce real-time estimates of the onset of infection and can work with incomplete data. They evaluated the efficacy of the autoregressive hidden Markov model for the diagnosis of Sepsis through data from the Newborn intensive care unit at the Edinburgh Royal Clinic [26].

In the study which Moutzouri and colleagues defended the additional effect of severe sepsis and diabetes mellitus on the red blood cell deformation, 40 patients suffering from severe Sepsis, 12 patients suffering from diabetes, and 24 patients with severe Sepsis were enrolled. The mean intensive care disease severity score in non-diabetic and diabetic septic patients was 23.5% and 26.8%, respectively. While the mortality rate was 22.5% in diabetic Sepsis patients; 34.3% in diabetic septic patients, septic shock rate was 15% in non-diabetic patients and 20.8% in diabetic patients. Patients with septic diabetes had a higher stiffness index (17.72 + - 6.31) compared to diabetic and non-septic patients (12.26 + - 2.28, $p < 0.001$), and stiffness index in non-diabetic sepsis patients is (13.9 + - 2.86, $p < 0.01$). They stated that the presence of diabetes in septic patients is effective in deformation of red blood cells and that this deformability may lead to severe micro-circulatory dysfunction in Sepsis patients [27]

In their study, Gültepe and colleagues report that Sepsis is a serious medical condition that is caused by an irregular immune response to infection. Early diagnosis of

the Sepsis symptoms is important to prevent the progression of the disease to more severe stages that results in the death of one in every four individuals. 1492 Patient records with 233 Sepsis cases on electronic medical records were used in the clustering analysis to identify features showing signs of sepsis. The Bayesian network that they used in their study was established using criteria for systemic inflammatory response syndrome (systolic), meaning arterial pressure and lactate level in patients with Sepsis. The acquire network reveals a clear correlation between lactate level and Sepsis. It has been shown that the lactate level may be a predictor of SIRS criterion [28].

Yanes et al. and intended to compare the tendency in Sepsis outcomes of people with or without type 2 diabetes T2DM in Spain between 2008 and 2012 and reported that there is conflicting evidence between sepsis mortality and T2DM patients. They used statistical analysis in the study by using the data from national hospital records. Type 2 diabetes was found to be less related to the mortality rate in the hospital (risk ratio = 0.88, confidence interval 95%, 0.86-0.90). They noted that the annual increase in the incidence of Sepsis was high in patients with type 2 diabetes in Spain, but they stated that the risk of death with Sepsis in admission was lower in patients with type 2 diabetes [29].

Schuh did a retrospective Sepsis and septic shock analysis study on 1674 patients selected from patients with intensive care heart and thoracic patients by using artificial neural networks. In his work he used the SIRS criteria [30] that Bone and his colleagues identified. In the model using multi-layer artificial neural network, he used sigmoid transfer function and logistic regression in the outcome. He used the Conjugate Gradient algorithm to train the artificial neural network. He stated that SIRS cases in 1544 patients, hypotensive SIRS cases in 1315(SAP<90mmHg or MAP<70 mmHg, % 78.6) and serious SIRS case in 1175 of all patients were seen [31].

The difference between the work done and the previous studies in the literature is the use of criteria determined according to the definition of new Sepsis made in 2016. In the definitions made in 2012 [32], the course of the disease is expressed as SIRS, Sepsis, severe Sepsis, septic shock. However, in 2016 [5] these definitions have been abandoned and SOFA and QSOFA scores have been found to be more successful than previous methods in diagnosing Sepsis disease and determining the level of Sepsis

diseases.

It is aimed to obtain a better and more accurate Sepsis prediction by using this new Sepsis definition and the data set of SOFA and QSOFA scoring which are prominent in the diagnosis of the disease, together with other parameters.

It is known that multilayer artificial neural network models are able to learn, generalize and deduce, as well as minimize error by using a back propagation algorithm and nonlinear problems are more successful in solution than other methods in the literature. Therefore, the best, most accurate, and least error-free prediction of the disease is targeted by using artificial neural network method with Levenberg-Marquardt training algorithm with multi-layer forward feedback propagation.

3. Method

By using the data on intensive care patients aged 18-65 years in Istanbul Data on intensive care patients aged 18-65 years in Istanbul, the risk of catching Sepsis is being tried to be predicted with the help of artificial neural networks. The inputs and outputs of the patients placed in the intensive care unit and diagnosed as Sepsis are generated by the definition of Sepsis in 2017 and by examining the algorithms and variables used by the doctors were used in the modeling of the artificial neural network. The modeled inputs for the early diagnosis of Sepsis are the parameters used by physicians to diagnose Sepsis and the level of Sepsis. Input parameters were determined using the Sepsis definitions and criteria described in the Journal of the American Medical Association [5] published in 2016. All of the determined parameters were taught to network through multi-layered artificial neural networks by supervised learning which are never thought to be used in predicting Sepsis disease in Turkey and it was attempted to predict the outcome of death caused by disease or survival outcome.

3.1. Steps in Identifying Sepsis Disease and Sepsis Level

In order to determine the diagnosis and level of Sepsis disease, the following three steps are followed by doctors:

Stage 1: If the patient has SIRS or an infection, it means that infection is diagnosed.

Stage 2: If there is an infection diagnosis, the QSOFA score of the patient is

calculated. If the QSOFA score is equal to or greater than 2, the patient is diagnosed with Sepsis.

Stage 3: To determine the level of Sepsis of the patient, the SOFA score, which consists of evaluation of respiration, coagulation, liver, cardiovascular system, brain function and kidney function is looked at. If the score is high, it means that the patient's Sepsis level is at advanced stages and the patient is close to death. If the SOFA score is low, it is concluded that the patient is recovering. Below are explanations of QSOFA the parameters that play a role in determining the data set used to diagnose Sepsis. Parameters used in prediction of Sepsis disease and data set formation are shown in below:

P = Patient

Tv = Temperature value at first hospitalization (ºC)

Hv = Heart rate value at first hospitalization (min)

Bp = Number of breaths per minute (min)

PaCO2 = Arterial partial carbon dioxide pressure of the patient (mmHg)

Leu = Leukocytes count in the blood of the patient (mm3)

Ne = Neutrophil count in the patient's blood (mm3)

Pn = Diagnosis of pneumonia in the patient (infection of the lung)

Bac = The presence of bacteria in the patient's blood

Iai = Presence of intra-abdominal infection

Oi = Presence of other infections in the patient

Nat = Presence of newly started antibiotic treatment in the patient

Ams = Altered mental status (turning on / off of consciousness)

Sbp = Systolic blood pressure value of the patient (mmHg)

PaO2 = Arterial partial oxygen pressure of the patient

FiO2 = Percentage of oxygen in the air where the patient is breathing

PaO2 / FiO2 = The ratio of the patient's oxygen partial pressure to the amount of oxygen in the air that the patient breathes

Tro = The amount of thrombocyte in the blood of the patient

Bil = The amount of bilirubin in the patient

Epi = The amount of epinephrine in the patient

Nor = The amount of norepinephrine in the patient

Dob = Dobutamine supplementation to the patient

Dop = dopamine supplementation to the patient

MAP = Average arterial pressure

GCS = Patient's Glasgow Coma Score

Uri = The amount of urine output of the patient in 24 hours

Cre = The amount of creatine in the patient

Result = Diagnostic result indicating whether the patient has Sepsis.

Table 1, Table 2, and Table 3 contain examples of the parameters that make up the input of the artificial neural network model.

Parameters used in the diagnosis of Sepsis disease were normalized before they were used in the ANN model, and examples of the parameters forming the normalized ANN entries are shown in Table 4, Table 5 and Table 6.

Table 1. Input parameters of ANN used in the diagnosis of Sepsis

P	Tv	Hv	Bp	PaCO2	Leu	Ne	Pn	Bac	Iai	Oi	Nat	Ams	Sbp
1	37,6	105	16	36	12000	15500	Pos.	Neg.	Neg.	Neg.	Neg.	closed	60
2	37,8	140	20	32	7000	6000	Neg.	Pos.	Neg.	Neg.	Neg.	closed	110
3	35,7	112	40	25	10600	8400	Pos.	Neg.	Neg.	Neg.	Neg.	open	115
4	36,4	94	11	42	9200	6500	Pos.	Neg.	Neg.	Neg.	Neg.	closed	160
5	37,2	105	23	32	500	0	Neg.	Neg.	Neg.	Neg.	Pos.	closed	125

Table 2. Input parameters of ANN used in the diagnosis of Sepsis

pao2	fio2	pao2/fio2	Tro	Bil	Epi	Nor	Dob	Dop	MAP	GCS
200	1	200	111000	0,2	0	0	Neg.	0	40	3
142	0,4	355	229000	0,6	0,5	0	Neg.	0	60	3
79	0,45	175,5	341000	0,49	0	0	Neg.	0	75	15
130	0,4	325	391000	0,7	0	0	Neg.	0	115	9
91	0,28	325	30000	37	0	0	Neg.	0	83	9

Table 3. Input parameters of ANN used in the diagnosis of Sepsis

Uri	Cre	Result
1200	1,54	Sepsis-death
1200	0,67	Sepsis-death (within 24 hours)
880	0,8	Sepsis-survival
1400	0,86	Sepsis-death
1100	2,04	Sepsis-death

Table 4. Normalized ANN sample input parameters.

P	Tv	Hv	Bp	paco2	Leu	Ne	Pn	Bac	Iai	Oi	Nat	Ams	Sbp
1	0,72	0,4	0,2	0,456	0,418	0,62	1	0	0	0	0	1	0
2	0,76	0,68	0,33	0,369	0,236	0,24	0	1	0	0	0	1	0,416
3	0,34	0,456	1	0,217	0,367	0,336	1	0	0	0	0	0	0,458
4	0,48	0,312	0,033	0,586	0,316	0,26	1	0	0	0	0	1	0,833
5	0,64	0,4	0,433	0,369	0	0	0	0	0	0	1	1	0,541

Table 5. Normalized ANN sample parameters

P	pao2/fio2	Tro	Bil	MAP	Dop	Dob	Epi	Nor	Gcs
1	0,287	0,123	0,002	0,047	0	0	0	0	0
2	0,712	0,303	0,013	0,238	0	0	1	0	0
3	0,220	0,474	0,010	0,380	0	0	0	0	1
4	0,630	0,550	0,016	0,761	0	0	0	0	0,5
5	0,630	0	1	0,457	0	0	0	0	0,5

Table 6. Normalized ANN sample input parameters

P	Cre	Uri	Result
1	0,209	0,422	1
2	0,068	0,422	1
3	0,089	0,28	1
4	0,098	0,511	1
5	0,290	0,377	1

3.2. Artificial Neural Networks

Artificial neural networks are artificial intelligence methods in which the biological characteristics of nerve cells are imitated using mathematical models from the methods that enable machines to make deductions and decisions like a human being. In addition, these are structures with parallel and distributed processing capacity, in which the human brain is modeled on the working logic and each of these structures is bound with the weights of its own memory processing elements [33]. Artificial neural networks, which generalize by collecting information on samples and construct a structure that can deduce and make decisions based on information that they have learned about in the past, have been used to solve complex problems in many fields [34]. The artificial neural networks, which are the basic building blocks of neurons, are made up of the model structures which use these neurons in the entrance, hidden layer and exit layers. The components of ANN are: input-hidden-output layer, activation function, bias weight values and learning and training algorithms. In this study, artificial neural networks were preferred because of their ability to deduce, make decisions and learn.

3.3. Feed Forward Back Propagation ANN

This network structure, which consists of two different algorithms, is a back propagation that determines whether the network, which is an advanced feed and supervised training method that expresses how the network works and remembers the patterns, can determine the desired output through inputs.

Errors are calculated by comparing the outputs obtained from the network with the desired output values in back propagation. The calculated error values are taken and the input threshold and weight values of the neural network are updated to try to reduce the error [35]. Figure 3 shows an example of this network structure.

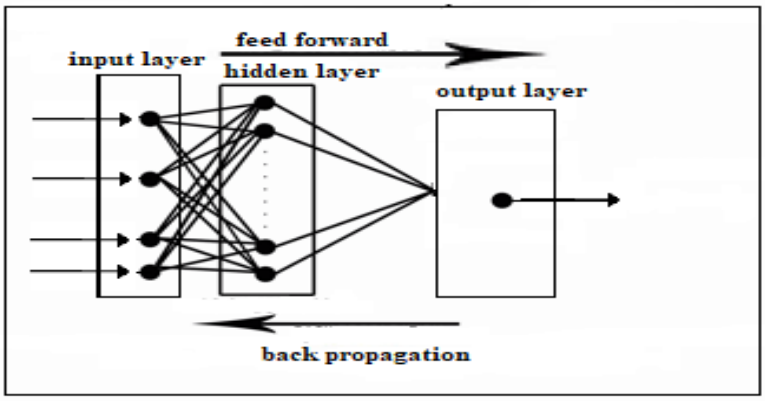

Figure 3. Feed forward back propagation artificial neural network model.

3.4. Artificial Neural Network Models Used for the Prediction of Sepsis Disease

P, Tv, Hv, Bp, PaCO2, Leu, Ne, Pn, Bac, Iai, Oi, Nat, Ams, Sbp, PaO2 / Fio2, Tro, Bil, Epi, Nor, Dob, Dop, MAP, GCS, Uri and Cre from the normalized data are determined as input parameters and the Result parameter is determined as output parameter of the system.

Multilayer artificial neural network model was created in Matlab. Entries in the model consist of 24 parameters used in the diagnosis of Sepsis. As it can be seen from the figure, by using a feed forward network model and a back-propagation network model to minimize the network computation error, it is aimed to increase the performance of the network.

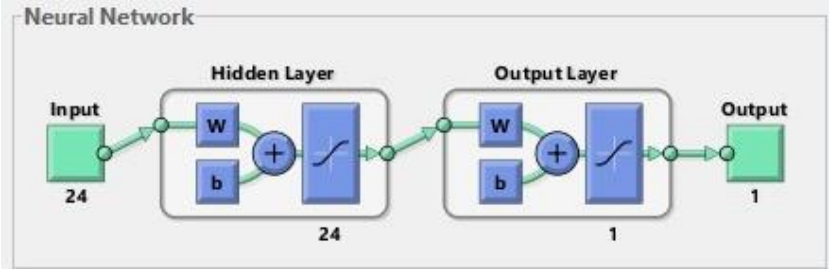

Figure 4. ANN model for Sepsis prediction.

Figure 4 shows the artificial neural network model. In the artificial neural network consisting of 24 inputs and 1 output, for the applicability in different data set successfully, data needs to be chosen randomly. Therefore, a random algorithm is chosen for training the data. For network training, The Levenberg-Marquardt algorithm which is most commonly used and known for its success in the literature is applied. For evaluation of performance, the mean square error algorithm (MSE), which is one of the most valid performance criterion used for many studies in the literature, is applied.

Finally, the default derivation algorithm is used for the derivative. As addition, the most commonly used hyperbolic tangent sigmoid function is used in the literature as a transfer function. The mean squared error performance graph (MSE) showing the training, test and verification values of the ANN network is shown in Figure 6, and it is seen that the training phase is terminated at epoch 8. At epoch 2 an increase in accuracy and at epoch 4 an increase in test value is seen. To increase the ANN performance, the training phase was repeated with the updated weights and the experiment is terminated with the lowest mean square error which gives the best result. The graphic in Figure 5 shows that the training phase is complete.

The training graph of the ANN network is shown in Figure 6. The gradient, mu, and accuracy error values on the training graph were obtained as 3.6897e-8, 1e-11 and 6 at epoch 8, respectively.

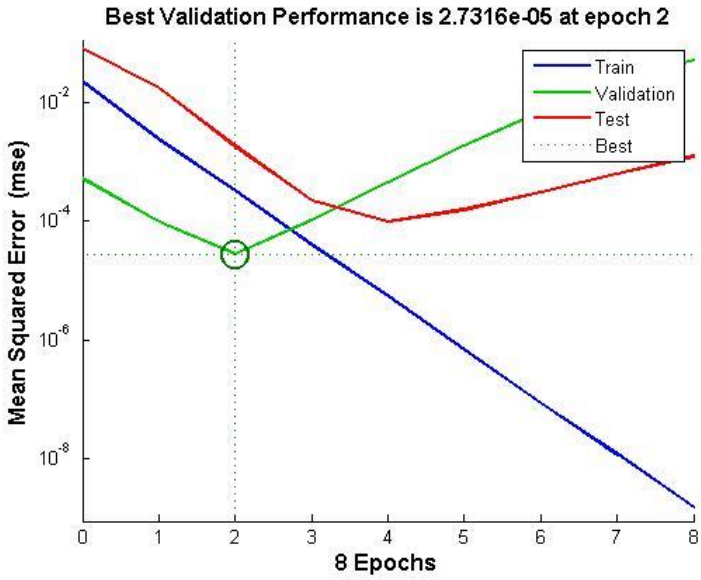

Figure 5. ANN performance graph.

The regression graph of ANN network is shown in Figure 7. According to the regression graph, the ANN model has 99.95% education, 99.76% test, 99.99% accuracy and 99.93% performance in total.

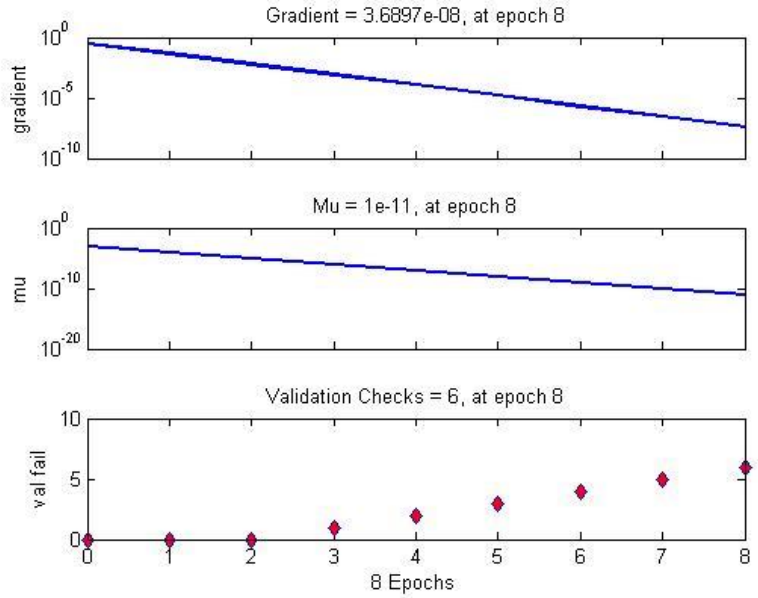

Figure 6. ANN training chart.

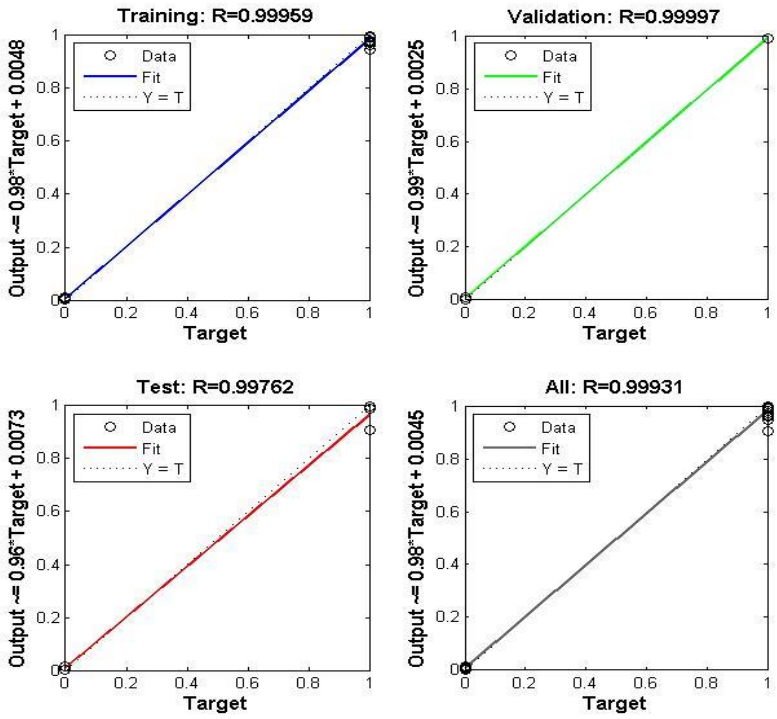

Figure 7. ANN regression graph.

The output graph of ANN network is shown in Figure 8. In this output graph (*), the actual output (+) refers to the output of the network. Accordingly, it is seen that the output obtained is close to the desired output.

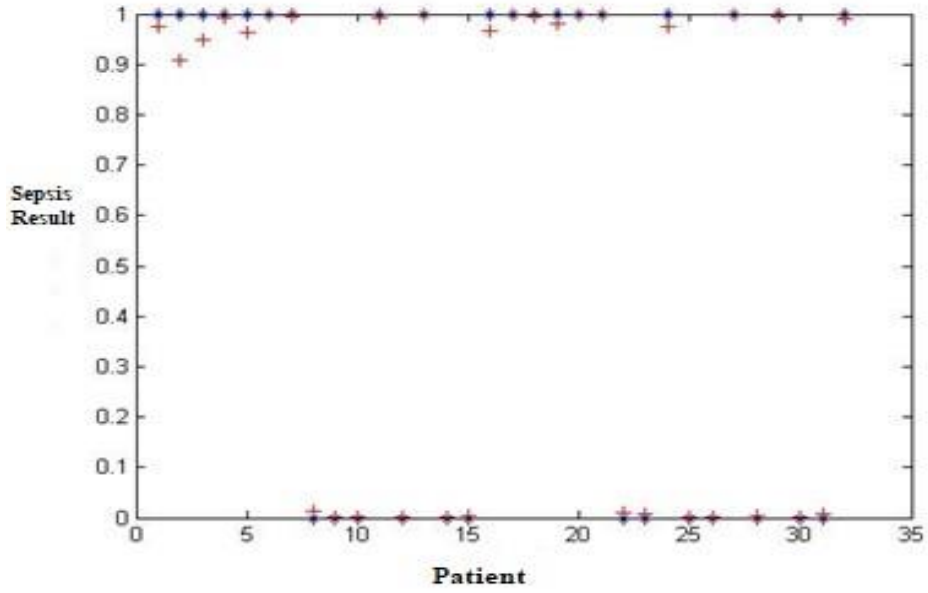

Figure 8. ANN output graph.

4. Results

24 different variables belonging to 32 patients were taken as inputs and 1 resultant variable was taken as output for the diagnosis of Sepsis by artificial neural networks. The regression graph shows that the system has reached an accuracy value of 0.99. In Table 7, the output values, error values and target values of the ANN are compared.

Table 7. Comparison of ANN sample output values, error values and target values.

Network output values	Target (Result Values)	Network Error Values
0,974	1	0,025
0,907	1	0,092
0,948	1	0,051
0,993	1	0,006
0,962	1	0,037

Table 8 shows the mean square error (MSE), root mean square error (RMSE), and root error sum (ESS) values for artificial neural network.

Table 8. ANN mean squared error, root mean squared error and root error sum values.

Mean square error(MSE)	Root mean square error(RMSE)	Error sum of squares(ESS)
$5.0781e^{-04}$	0.0225	0.0162

5. Conclusion

New Sepsis definitions [5] that were done in 2017 were used for predictive modeling of Sepsis disease with artificial neural networks. According to the new definition of Sepsis, SIRS is now out of being a decisive criterion on its own, instead, it was observed that the presence of infection was investigated primarily by providing an infection diagnosis or SIRS criteria. It was expressed in new sepsis definition that Sepsis diagnosis should be determined by calculating QSOFA scores of patients who are diagnosed with infection, and the level of sepsis should be determined by calculating SOFA scores. Considering the increase in the use of artificial intelligence in medicine, artificial neural networks were used in this study to determine the level of the disease and to determine whether the patient died or survived from the disease. In this study, a 99% training, test and accuracy values were obtained by using a feed forward back propagation artificial neural network model constructed using the Levenberg-Marquardt training algorithm. Additionally, the mean squared error (MSE) value was 5.0781e-04, the root mean square error (RMSE) value was 0.0225, and the root error sum (ESS) value was 0.0162 which were used to evaluate the performance of the artificial neural network in the literature. It is seen that the performance values obtained are better at satisfactory level when compared with the ones in literature. Why such a high accuracy level is reached can be explained by the fact that the number of patients was small according to the results obtained by expert evaluation. Besides, this interdisciplinary study was carried out according to the new sepsis criteria and it was aimed to be a pioneer in the work to be done thereafter. It is thought that this study using new definitions of Sepsis and artificial intelligence methods can guide doctors for the diagnosis of Sepsis. Furthermore, it is also expected to contribute to the reduction of the

error possibility that may arise from the doctor error. In the next studies, it is thought that in the study, much larger patient data could be used to make improvements in predictive and intuitive modeling using different methods.

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