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Analysis of Cryotherapy Treatment of Verruca by Machine Learning

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Abstract

There are several patients- and verruca-specific factors that determine treatment response to cryotherapy. A comprehensive analysis of these factors necessitates the use of a systematic and rational approach. The present study uses machine learning algorithms to analyze the clinical patient- and verruca-specific factors that affect the success of cryotherapy treatment. Machine learning algorithms were applied to the cryotherapy dataset. The best results in the prediction of treatment response to cryotherapy were achieved through the multilayer neural network classification method, with a 96,2% accuracy rate, followed by the C&R Tree, C5.0 Tree, CHAID Tree, and the adjusted J48 Decision Tree algorithms, respectively. The C&R Tree classification method revealed that the most significant factors that affected treatment response in verrucae, in the order of importance, were the time to the first session, the patient's age, the type of verruca, the number of verrucae and the region of the verruca. We believe that by identifying factors that affect treatment success and investigating the relations between variables, machine learning approaches can guide clinical treatment decisions for the more effective management of verruca treatment, which represents an important social and economic burden in public health.

Keywords: "CRISP-DM, cryotherapy dataset, machine learning, wart treatment"

1. Introduction

Human papillomavirus (HPV) infections are common around the world and cause pathologic changes to the skin and mucous membranes. Verruca (warts) are infections that are caused by HPV and are among the most common skin disorders, characterized by epithelial hyperplasia and keratin formation. So far, more than 120 HPV different species have been identified based on their DNA series [1,2]. There are only a limited number of epidemiological studies that demonstrated the link between the type of HPV and verruca, although the type of HPV is known to affect the clinical characteristics, prognosis and treatment response of the verruca [3]. The prevalence of verruca in the overall population is estimated to be around 7–12% [4], while this rate has been known to increase to 33% in school-age children [5]. A 2010 Global Burden of Disease Study showed that verruca represent a significant public health problem associated with an economic burden [6].

Verruca may appear in different clinical forms regarding their anatomic or morphological characteristics that include verruca vulgaris (common wart), verruca plantaris (plantar warts), verruca filiform is (filiform warts), verruca plana (flat warts) and condyloma accuminata (genital warts) [7, 8]. Verruca may negatively affect the quality of life by causing cosmetic and social problems, particularly when they appear on the face or hands. There is a need for an effective treatment for verruca given that they have oncogenic potential, becoming widespread and treatment-resistant as the immune system weakens, resulting in painful and contagious lesions [7, 9, 10]. Verruca can be treated with different methods, such as topical acid, cryotherapy, surgical methods, laser ablation and immunotherapy [11]. Among these treatment approaches, cryotherapy has become the most common in recent years, and is the preferred approach among dermatologists as an inexpensive and easy-to-implement method that is associated with a lower risk of complications, as well as easier post-session care and a less apparent scar formation, while also not limiting the patients' daily activities [9,12]. Furthermore, cryotherapy, performed with liquid nitrogen, ensures the recovery of 50–70% of the lesions after three to four sessions [13].

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Treatment response in cryotherapy depends upon several factors, such as factors related to the verruca, its localization and patient characteristics [14]. As cryotherapy is commonly used in clinical practice, the identification and comprehensive analysis of the factors that affect response to cryotherapy are crucially important for the treatment success and disease management. The manual analysis of the factors associated with patients and verruca may become a complex problem as a result of the increasing number of patients and variables. Moreover, as the amount of medical data to be processed increases, the use of statistical methods alone may lack the ability to demonstrate these effects and relationships. In recent years one can observe that machine learning techniques are used for processing and analysis of medical data [15,16] Also, disease diagnosis tools that are based on machine learning algorithms have become major decision support systems in healthcare. Software that makes use of machine learning algorithms can perform real-time analyses and thus support decision making by interpreting complex and vast amounts of medical data.

In the present study, factors that affect treatment response in verruca patients treated with cryotherapy were analyzed by using machine learning algorithms. To the best of our knowledge, this is the first study that uses machine learning algorithms for this purpose.

2. Related Work

A review of previous studies related to this subject identified only a limited number of clinical trials, which were conducted with limited medical data and using a limited number of statistical tests. To our knowledge, no previous study was found in the literature that analyzed the factors affecting response to cryotherapy treatment through the use of machine learning approaches. Furthermore, only one study was identified that applied machine learning approaches to compare the treatments used for verruca. In that study, Khozeimeh et al. [17] developed a specialized system that predicted treatment response to immunotherapy and cryotherapy methods in patients with two common types of verruca (plantar and common). Their study was conducted with 180 patients in total, of which 90 of them were treated with cryotherapy and 90 of them were treated with the immunotherapy method, and a fuzzy logic rule-based system was used to predict treatment response. The estimated accuracy rate was found to be 83.33% for immunotherapy and 80.7% for cryotherapy.

The literature contains many studies in which machine learning algorithms are used to support the diagnosis and treatment of melanoma, which is a common type of skin cancer that can be grouped among skin disorders as an important topic of medical research. For example, Jamil et al. [18] developed a computer-based decision support system for detection of melanoma in which classification was carried out on a PH2 dataset that consisted of dermoscopic images labeled by physicians, and involved applying k-medoids, gauss mixture models (GMM) and support vector machines (SVM). The highest rate of accuracy was found in GMM at 99.25%.

Other than melanoma, machine learning algorithms have also been used in the literature for the diagnosis, analysis and classification of skin disorders, such as psoriasis and benign skin lesions. Shrivastava et al. [19], for instance, developed a computer-based automated tool for diagnosing psoriasis, applying 10-fold cross-validation and a polynomial-based kernel function with an SVM (Support Vector Machine) learning algorithm on 540 images obtained from equal numbers of healthy controls and psoriasis patients, and achieved 99.94% accuracy rate. Shrivastava et al. [20] developed another online system that automatically classified healthy skin and psoriasis from dermatologic images using SVM as a machine learning algorithm. The accuracy of the developed system (5 layers, 10 layers and Jack Knife) in their study was shown to have a 99.66% accuracy rate for classification based on 10-fold cross-validation.

In another study, Sumithra et al. [21] developed a new method that automatically segmented and classified skin lesions. Features, such as color and texture, were extracted from the skin lesions through the use of image processing tools, and the features that were extracted from 726 samples derived from 141 dermatologic images were classified using SVM and k-nearest neighbors algorithms. In this study, the F-criterion was found to be 46.71% for SVM and 34% for k-nearest neighbors.

Bunte et al. [22] investigated the extraction of effective color features of content-based image access systems used in dermatology. To measure the effectiveness of the color characteristics, access rates were used from four classes of colors for the image in skin lesions. The limited rank matrix learning vector quantization (LiRaMLVQ) and large margin nearest neighbor (LMNN) methods were used and compared in that study, and a k-nearest neighbors search was used to assess the images from the database based on the extracted color features. Researchers found out that feature extraction by the LiRaMLVQ method provided better results in a color-based assessment of dermatologic images.

3. Materials and Methods

3.1. Cryotherapy Dataset

A cryotherapy dataset obtained from the UCI Machine Learning Repository [23] was used in this study, which provides details on the treatment outcomes and other information on 90 patients who underwent treatment of verrucae by cryotherapy. The dataset includes seven variables, one of which is the target variable. Table 1 presents a brief description of the variables, and also descriptive statistics of the numerical variables.

Table 1. Attributes of dataset

Attribute	Type	Direction	Min.	Max.	Mean	Std. Deviation
Sex	Nominal	Input				
Age	Numeric	Input	15.00	67.00	28.60	13.36
Time	Numeric	Input	0.25	12.00	7.67	3.41
Number of Warts	Numeric	Input	1.00	12.00	5.51	3.57
Type of Wart	Nominal	Input				
Area	Numeric	Input	4.00	750.00	85.83	131.73
Result of Treatment	Nominal	Output				

3.2. Data Understanding

Data understanding is an important step in each machine learning application. In this section we give a summary of the data understanding results for the dataset used in this study. The analyses were supported by a literature review and the expert opinion of a dermatologist. Any findings that were identified during the analyses that were deemed important for treatment are presented in this part.

The cryotherapy dataset provides information on 47 male and 43 female patients. The dataset has three categorical features: sex of the patient, type of wart and result of treatment. Figure 1 presents bar charts summarizing the type of wart and the result of treatment variables. These graphs show clearly that patients with the plantar wart-type are significantly smaller than the other two wart types in the data set.

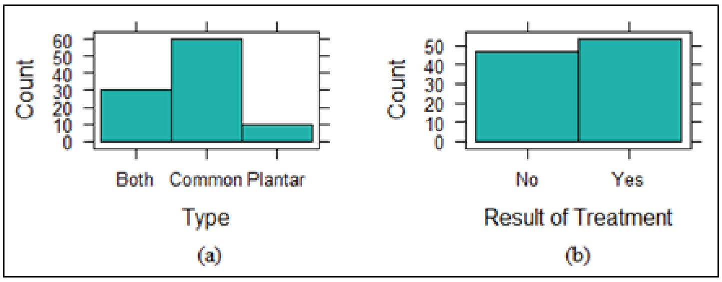

Figure 1. Bar graphs. (a) type; (b) result of treatment

Outlier and extreme values are those that are found to be inappropriate for a dataset when compared with the other data, and such values should be kept in the dataset as long as they are considered to reflect real-world data, otherwise a decision should be given as to whether they should be removed from the dataset. An abundance of extreme values can affect statistical analyses. Box-plot analyses were used to identify the outlier and extreme values in the dataset. Figure 2 shows the box-plots of the numeric variables (Age, Time, Area and Number of Warts) with respect to the target variable.

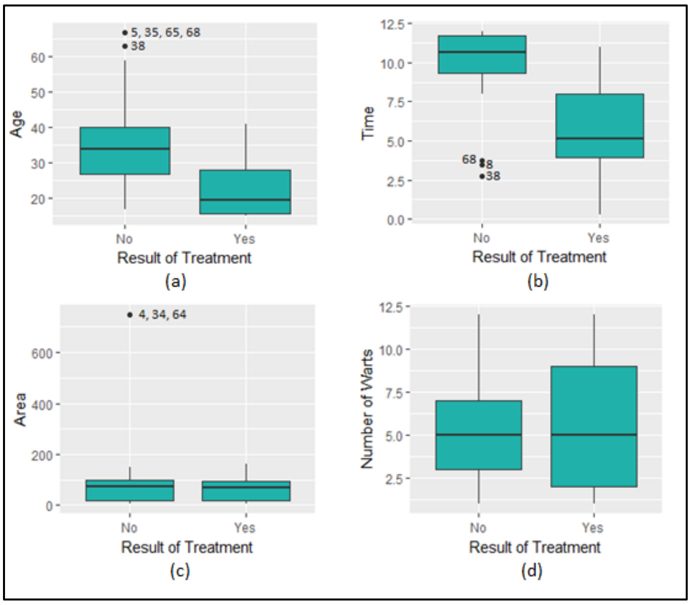

Figure 2. Box-plots. (a) Result of treatment versus age; (b) Result of treatment versus time; (c) Result of treatment versus area; (d) Result of treatment versus number of warts

The box-plot graphs for the age variable indicate that the ages of subjects 38, 5, 35, 65 and 68 were outliers. When the time until initiation of treatment variable was analyzed with a box-plot graphic, subjects 38, 8 and 68 were found to be outliers.

The analyses of area variable contained no outlier values, although the verruca area of subjects 4, 34 and 64 were considered as extreme values. There were no outlier or extreme values in the number of warts variable. When the subjects with outlier and extreme values are investigated, subjects 38 and 68 were found to have outlier values in both the age and time variables.

Figure 3 shows a histogram of the age variable. This graph shows that the success rate of treatment decreases with increasing age. Although verruca may develop at any age, it is rare in infancy and early childhood, its prevalence increases among school-age children, and reaches a peak value between the ages of 12 and 16 years [24]. While one-third of primary school students have verruca, two-thirds of those lesions resolve spontaneously within two years [25]. In their study, Bruggink et al. [26] demonstrated that the rate of treatment success was lower in patients aged 12 years and above when compared to younger patients, and concluded that treatment success decreased with increasing age.

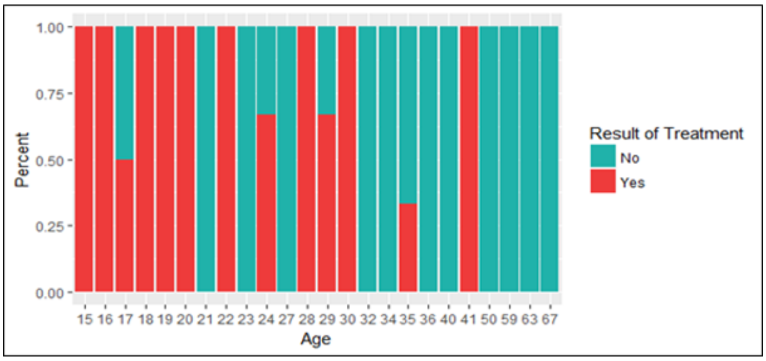

Figure 3. Age versus result of treatment

Figure 4 shows a histogram of the time until the initiation of treatment for verruca (verruca duration) variable. This graph indicates that treatment success decreases with increased time until the initiation of treatment. As verruca are predisposed to spontaneous resolution, the duration of the verruca must be considered while evaluating the efficacy of treatments. In their study that investigated intralesional interferon administration, Varnavides et al. [27] found no significant difference between the treatment and placebo groups regarding treatment response, based on the duration of the verruca. However, several studies in the literature have suggested that the possibility of treatment response increases with the decreasing duration of verruca [28-30].

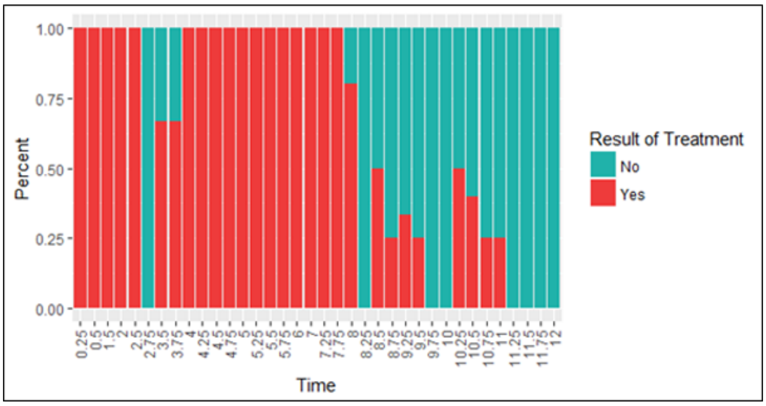

Figure 4. Time versus result of treatment

Figure 5 shows a histogram of the number of warts variable. The number of warts and treatment efficacy appear to be correlated until the number of warts reaches seven, after which, this correlation disappears. A previous study in the literature investigated 254 pediatric patients retrospectively and could identify no relationship between treatment response and the number of warts [31], and this is supported by other studies reporting that the number of warts had no significant effect on the treatment response [29,32].

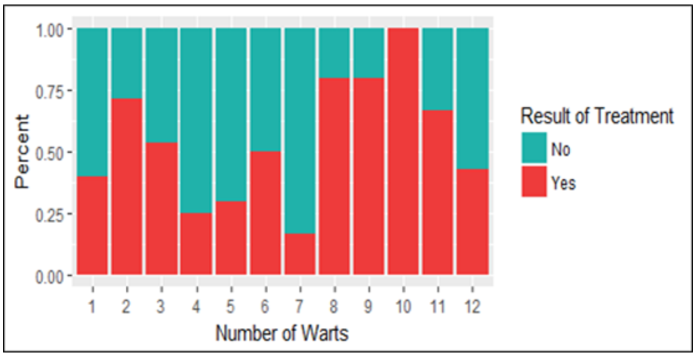

Figure 5. Number of warts versus result of treatment

Figure 6 shows that the results achieved by cryotherapy differ between verruca types. While treatment response is higher in the common type, verruca plantaris is found to be the most resistant to treatment. Previous studies have reported treatment success rates of 33.3–66.6% for verruca plantaris [33,34]. There is very limited information on the relationship between HPV genotypes and patient characteristics. The clinical characteristics, number, prognosis and treatment response of verruca may vary depending on the type of HPV [3], and based on these findings, treatment efficacy can be seen to depend not only on the type of verruca but also factors, such as age and type of HPV [33].

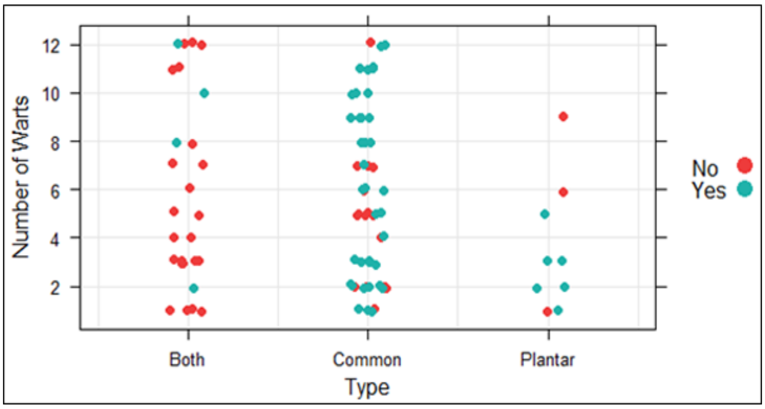

Figure 6. Scatterplot of number of warts versus type of warts

A correlation analysis was carried out to investigate the relationships between variables. A Shapiro-normality test was performed on the numerical variables and showed that they were not normally distributed. Accordingly, a Spearman correlation test was used to analyze the correlations between numerical variables in the dataset. Although no significant correlation was found between the numerical variables, Age variable was found to be also mildly correlated with Time and Area variables.

The results of the data analysis show that the variables Age, Time and Type should definitely be considered in the models that will be developed in the following steps.

4. Results

In the present study, various decision tree methods and multi-layer neural networks were applied to the cryotherapy dataset to analyze the factors that affected verruca treatment. The Weka software was used to implement Unpruned J48 Decision Tree and Pruned J48 Decision Tree methods and IBM SPSS software was used to apply neural networks. As shown in Table 2, the pruning process increased the accuracy of the J48 decision tree but involved only the time and age attributes. In this regard, the decision tree can be considered weak, in that it did not include attributes, such as type, which is particularly important for verruca treatment outcome. In this regard, to obtain a stronger tree structure, SPSS Clementine software was used to apply QUEST Tree, CHAID Tree, C5.0 Tree and C&R Tree (Classification and Regression Tree) methods. 10-fold cross-validation was used for all the methods and the results are summarized in Table 2. Table 2 shows that the highest accuracy is achieved with the C&R Tree method among the decision tree methods. The tree structure obtained by this method (see Figure 7) indicates that the most important factors that affect treatment outcome, in order of effect, are time, age, type of wart, number of warts and area.

Table 2. Decision tree results

Methods	Accuracy (%)
QUEST Tree	0.88
Unpruned J48 Decision Tree	0.88
Pruned J48 Decision Tree	0.93
CHAID Tree	0.93
C 5.0 Tree	0.90
C&R Tree	0.96

Figure 7 presents the decision tree developed using the C&R Tree method and shows that successful treatment response is obtained when the time until initiation of verruca treatment is shorter than 8.125 months, and the patient is aged below 45.45 years. Treatment response is mostly successful when the time until the initiation of treatment is less than 8.125 months, and the patient age is below 16.5 years but is mostly unsuccessful within the same time when the patient is aged above 16.5 years, and the verruca type is both. On the other hand, treatment response is affected by the number of warts and area when the verruca type is Plantar or common. In this case, treatment is generally unsuccessful when the number of warts is fewer than 7.5 and the area is lower than 130, while treatment success increases when the area is greater than 130. In cases where the number of warts is higher than 7.5, treatment is generally unsuccessful when the area is smaller than 20.5 and generally successful when the area is greater than 20.5.

When the number of warts variable is removed from the decision tree developed by the C&R Tree method, no change was seen in the rate of accuracy achieved by the C&R Tree decision tree. This finding suggests that the number of lesions has no significant effect on treatment response.

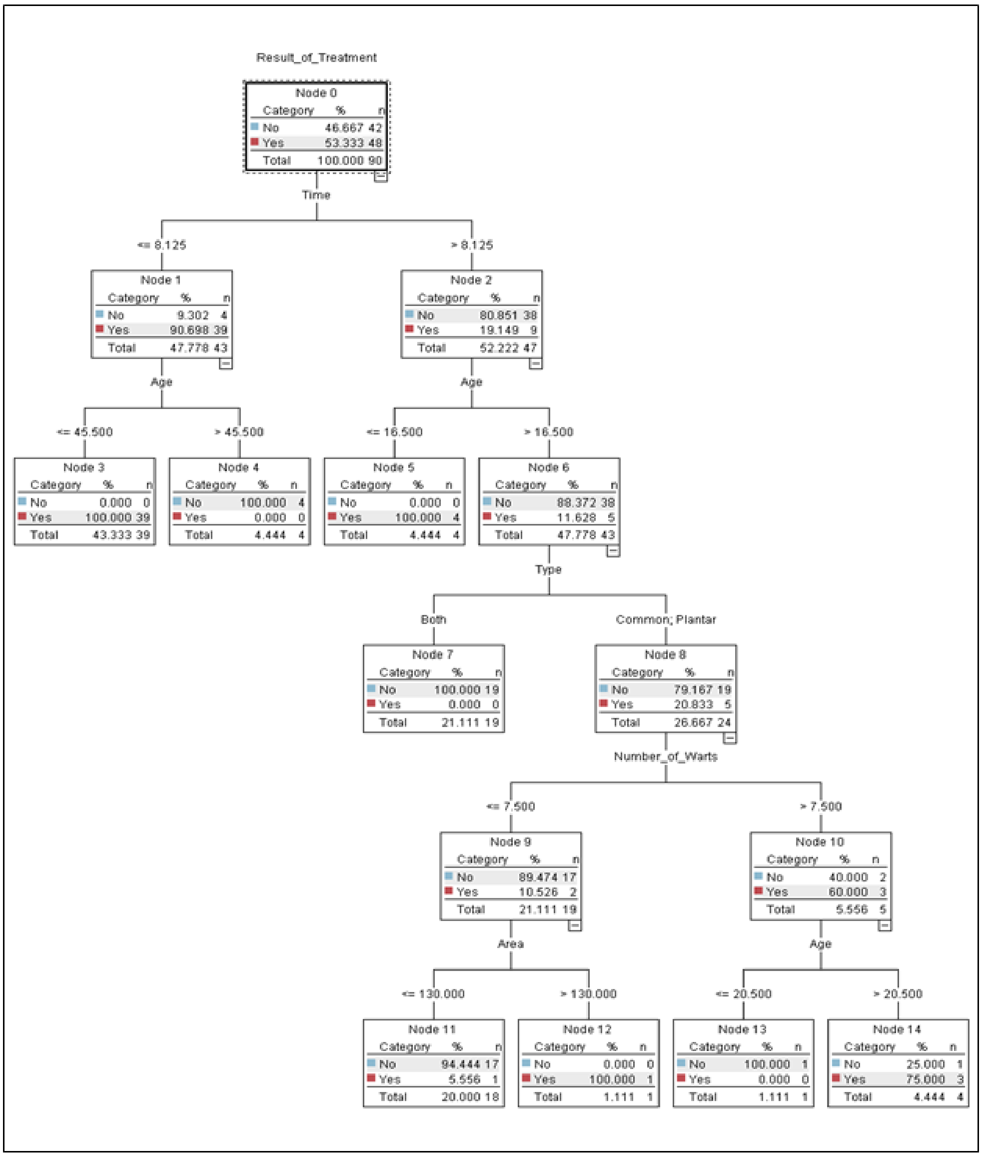

Figure 7. C&R Tree

In medical studies, decision trees are frequently preferred for analyzing the factors affecting the classification and examining the results in detail. On the other hand, closed box algorithms, such as artificial neural networks, have the disadvantage that they cannot be interpreted as much as decision trees [38]. Therefore, just to investigate the predictive performance of artificial neural networks, different artificial neural network architectures were designed and tested in this study. In these architectures, the number of hidden layers, the number of nodes in the hidden layer, the activation function in the hidden layer and the output layer were tested with different alternatives. The results of the best performing experiments are presented in Table 3 and the architecture with the highest correct prediction rate is presented in Figure 8. As can be seen from the results, the artificial neural network architecture, which provides the best predictive performance, performed better than the C&R Tree algorithm with an accuracy rate of 96.2%. In addition, a better estimate was provided by removing the 'Number of Warts' variable from the input variables. This result supports the C&R Tree algorithm, indicating that this variable has no significant effect on the result of treatment.

Table 3. Results of Neural Networks Trials

Inputs	Number of Hidden Layers	Number of Units in Hidden Layer	Hidden Layer(s) Activation Function	Output Layer Activation Function	Accuracy
Age, Sex, Type, Time, Area	2	4 and 3	Hyperbolic tangent	Hyperbolic tangent	83.30%
Age, Sex, Type, Time, Area, Number of Warts	1	3	Hyperbolic tangent	Softmax	83.90%
Age Type, Time, Area	1	3	Sigmoid	Hyperbolic tangent	86.40%
Age Type, Time, Area	2	4 and 2	Hyperbolic tangent	Hyperbolic tangent	93.30%
Age, Sex, Type, Time, Area	2	4 and 3	Hyperbolic tangent	Sigmoid	93.80%
Age, Sex, Type, Time, Area	2	3 and 3	Sigmoid	Sigmoid	95.80%
Age, Sex, Type, Time, Area	2	4 and 3	Sigmoid	Hyperbolic tangent	96.20%

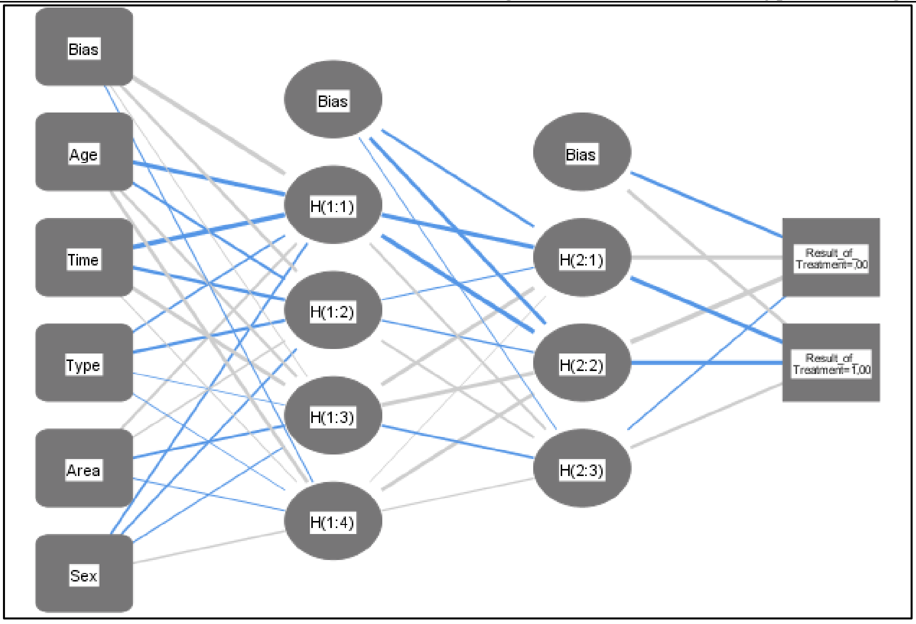

Figure 8. Artificial neural network architecture

5. Discussion

The present study has investigated treatment response to cryotherapy using machine learning algorithms on a cryotherapy dataset of 90 patient records. Decision tree analyses performed in this study showed that the time until initiation of treatment, patient age, verruca type and area were the most important factors that affect response to cryotherapy, which is the most commonly used approach for the treatment of verruca. The results of the data analyses performed on the dataset, based on previous literature and expert opinions during the pre-analysis stage, confirmed the effects of the same factors on treatment success.

The time until initiation of treatment of verruca is one of the most significant factors that affect the success of cryotherapy in verruca treatment, and several studies in the literature have reported higher success rates with shorter lesion durations [25-27]. In line with these findings, the results of this study confirm that the treatment success decreases as the time until initiation of treatment increases. In a previous study, Doğan and Şaşmaz [9] reported that the mean time until initiation of treatment was 15.45±2.34 months in the group that responded well to cryotherapy, while it was 24.28±6.77 months in the non-responder group, although the difference between the two groups was not found to be statistically significant. In their study that aimed to demonstrate the efficacy of cryotherapy in the treatment of verruca vulgaris and plantaris, Erbağcı et al. [35] reported higher treatment success rates in verruca vulgaris patients, while the mean time until initiation of treatment in this patient group (22 months) was higher than in patients with verruca plantaris (15 months).

Verruca can be seen in all age groups, although its prevalence is greater among school-age children [5,23]. Additionally, the outcomes of cryotherapy vary depending on the age of the patient. In their study, Bruggink et al. [25] reported that the rate of treatment success decreases with increasing patient age, and similarly, a regression analysis in the study by Doğan and Şaşmaz [9] indicated a significant decrease in cryotherapy success rates with increasing age, with the mean age of the responder and non-responder groups being 20.10±8.29 and 26.57±10.01 years, respectively (r=0.0761, p=0.008). In the present study, the graphical analyses and results obtained from decision tree algorithms also showed that the rate of treatment success decreased by increasing age, which is consistent with previous studies.

Verruca commonly appears with multiple lesions. Several studies that investigated the effects of the number of lesions on the success of cryotherapy could find no association between these two variables [29,31,32], and this is supported by the findings of the present study. As the number of lesions variable was not normally distributed, a Wilcoxon-Mann-Whitney test was used to investigate the potentially significant differences between the responders and non-responders to cryotherapy. The results of this test with the R software resulted in a p-value of 0.594, meaning that the difference was not statistically significant. Moreover, the rate of accuracy did not change when the number of warts variable was removed from the decision tree developed by the C&R Tree method in this study, suggesting that the number of lesions has no significant effect on treatment response. On the other hand, Erbağcı et al. [35] previously reported a higher cryotherapy success rate in verruca vulgaris patients with a mean number of warts of 5.5, while it was 6.2 in patients with verruca plantaris. In another study, the mean number of warts among patients who responded to therapy was 7.01±0.97, compared to 8.09±3.0 among non-responders, although the difference between the two groups was not statistically significant ($p>0.05$) [9].

The outcomes of cryotherapy differ between types of verruca. Among the several types of verruca, the most treatment-resistant clinical type is known to be verruca plantaris. Alpsoy et al. [36] reported that the best-responders to cryotherapy were verruca plana and verruca filiformis, with a 100% success rate, while in the same study, the lowest success rate was 57.8%, noted in verruca plantaris cases. High success rates were similarly achieved for verruca filiformis and verruca plana cases in another study, while the clinical success rate for verruca plantaris was found to be 56.3% [9]. There have been other studies that reported lower recovery rates in cases of verruca plantaris than in other verruca types [35, 37]. In line with the previous studies, the rate of treatment success was higher for the common-type verrucae in this study, while verruca plantaris was associated with lower treatment success.

While machine learning approaches are widely used in other clinical trials, to the best of our knowledge, there have been no previous studies that used such methods in verrucae. The results of the present study demonstrate that the use of machine learning approaches may support the planning and management of effective treatment of verruca using cryotherapy. On the other hand, it should be noted that the number of patients with plantaris-type verruca was very limited when compared to the other types in the dataset. Moreover, there was no data on the school-age and early-adolescent patient groups, which are associated with the highest prevalence of verruca, which suggests that analyses performed on larger datasets in the future may provide more comprehensive results.

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