The Application of Machine Learning in Predicting Outcome of Cryotherapy and Immunotherapy for Wart Removal

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Background: Warts can be extremely painful conditions that may be associated with localised bleeding and discharge. They are commonly treated by cryotherapy or immunotherapy. However, each of these therapies have discomforting side effects and are not official dermatological guideline that exist that may be used to determine which of these methods would work on an individual patient. Objective: This study aimed at developing a machine learning algorithm that improved the prediction of the outcome of wart removing using cryotherapy and immunotherapy. Methods: Support vector machines, core vector machines, random forest, k-nearest neighbours, multilayer perceptron and binary logistic regression was applied on datasets in to create a model that predicted the outcome of an immunotherapy and cryotherapy treatments based on sex, age, time that has passed since last treatment, number of warts, type, area, diameter and result of treatment. Results: The average accuracy of the immunotherapy prediction was 88.6%±8.0% while the same measure for cryotherapy prediction was 94.6%±4.0%. The most efficient immunotherapy and cryotherapy model had an accuracy of 100%, predicating the correct treatment outcome when applied to all test cases. Conclusion: This study successfully created a machine learning model that improved the prediction ability of the outcome of immunotherapy and cryotherapy for wart removal. This model created a more in-depth guideline for understanding is immunotherapy would work and took a new approach to cryotherapy. (Ann Dermatol 33(4) 345–350, 2021)

Keywords: Artificial intelligence, Cryotherapy, Immunotherapy, Medical informatics, Warts

INTRODUCTION

The human papillomavirus (HPV) forms part of the papillomavirus genus that lies within the Papovaviridae family. Infection with HPV may present in cutaneous warts of various sizes and forms. A wart is characterised as a fleshy, rough, grainy growth that appears most commonly on the hands, fingers or on the soles of the feet. Other types of warts may also appear on the other parts of the body like the face, arms or legs and sometimes grow in the genital or anal area. The two most prevalent types of warts are the common wart (verrucae vulgaris) which typically appear on the hand, and the plantar warts (verrucae plantaris) which mostly presents on the soles of the feet. The United Kingdom and the Netherlands report an annual incidence of cutaneous warts between 4% and 33%, and between 9.1% and 21.7% of visits to the dermatologist are related to warts. Warts are the most common skin infections in children. The annual incidence of anogenital warts among woman in South Africa and a corresponding prevalence of 5.7%. It also has been reported that genital warts are a growing concern in Iran.
Warts can be an extremely painful condition that may be associated with localised bleeding and discharge. The pain associated with warts may result in the hampered ability to use the limb where the wart presents, e.g., a plantar wart may result in altering ones normal posture or gait which can result in muscle and joint pain. Warts are commonly treated by cryotherapy, which consists of freezing off the wart usually using liquid nitrogen\(^9,11\). However the treatment has many side-effects, is painful, and many treatment sessions are required\(^{12,13}\). Immunotherapy is newer alternative, which is based on the activation of the immune system to deal with the virus and suppress its activity. Side effects of immunotherapy include an elevation of temperature, chills, fatigue, diarrhea, headache, nausea, and vomiting (flu-like symptoms)\(^{14}\).

Cryotherapy and immunotherapy do not always work and there are no official dermatological guideline that exist that may be used to determine the efficacy of these methods on an individual patient basis\(^{15,16}\). However, a first ground-breaking recent study used fuzzy logic to determine rules that can help a physician determine if treatment with one of the two therapies would result in a favourable outcome. This is very advantageous in treatment as it will provide some sort of indication to the physician whether this treatment will produce a favourable outcome or if the physician needs to change treatment altogether. This saves resources in a developing country and also ensures the patient does not endure painful procedures for no reason. However, it may be possible to improve the efficiency of the fuzzy logic algorithm. Machine learning techniques have been used in other domains, but not in the domain of predicting immunotherapy and cryotherapy treatment outcomes.

Thus this study aims at developing a machine learning algorithm that improves the prediction of the outcome of wart removing using cryotherapy and immunotherapy.

**MATERIALS AND METHODS**

A total of 160 tuples of publically de-identified data was obtained\(^{12}\). This data is freely available from the public UCI machine learning repository and has been completely dis-associated from any identifiable characteristics of individual patients. Ethics permission was obtained through the Telehealth academic unit at the University of KwaZulu-Natal (BREC/00002203/2020). The dataset consisted of 90 tuples that were associated with patients that underwent cryotherapy and 90 tuples of data associated with patients that underwent immunotherapy. The cryotherapy data consisted of sex, age, time that has passed since last treatment, number of warts, type of wart, area and the result of treatment. The immunotherapy dataset consisted of sex, age, time that has passed since last treatment, number of warts, type of wart, area, diameter and result of treatment. Table 1 describes the input of the machine learning algorithms in more detail. The output was a binary classification either indicating success or failure of the therapy.

**Machine learning**

Machine learning is an artificial intelligence technique that tries to create a mathematical model that maps inputs into outputs. There are two parts to machine learning: training, were one applies the principles of a particular machine learning model on data to create the mathematical mapping function; and the testing component, where one tests the predictive ability of the model on data with known outcomes. The dataset was divided into 50% training and 50% testing split. This means that the data used to test the algorithm was not used to train the algorithm, thus giving more reliable results.

Support vector machines (SVM)\(^{17}\), core vector machines (CVM)\(^{18}\), random forest (RF)\(^{19}\), k-nearest neighbours (k-NN)\(^{20}\), multilayer perceptron (MLP)\(^{21}\) and binary logistic regression (BLR)\(^{22}\) was applied on each of the two datasets in order to perform a classification. SVM is a discriminative classifier that works by separating the input space into various dimensions by finding an optimised hyperplane. CVM uses approximation algorithms as a means to create the model that maps the input and output variables together. RF is an ensemble method based of creating decision trees. k-NN is a non-parametric algorithm based on optimising a representation of distance between the input and output variables. MLP is a type of neural network learning algorithm based on the mechanisms of the synapse in the brain. BLR is a probability based algorithm that bases its output on the odds of an output occurring given the input.

Table 1. Describes the features of the dataset used for the machine learning algorithms.

| Dataset                | Feature     | Value         |
|------------------------|-------------|---------------|
| Cryotherapy/immunotherapy | Sex     | Male          |
|                        |            | Female        |
|                        | Age (yr)   | 15 ~ 67       |
|                        | Time (mo)  | 0 ~ 12        |
|                        | No. of warts (count) | 1 ~ 19    |
|                        | Type of warts | Common     |
|                        |            | Plantar      |
|                        |            | Both         |
|                        | Area (mm\(^2\)) | 4 ~ 750 |
|                        | Result     | Success      |
|                        |            | Failure      |
| Immunotherapy          | Diameter (mm) | 5 ~ 70     |
Table 2. Shows the efficacy of the machine learning algorithms in predicting Immunotherapy outcome

| AI method | Accuracy | Precision | Recall | FPR | FNR | TNR | TPR | F   |
|-----------|----------|-----------|--------|-----|-----|-----|-----|-----|
| SVM       | 79.0     | 100       | 78.9   | 0   | 21.1| 96.1| 98.3| 88.2|
| CVM       | 95.6     | 100       | 94.7   | 0   | 5.3 | 100 | 97.1| 97.3|
| RF        | 100      | 100       | 0      | 0   | 100 | 100 | 100 | 100 |
| k-NN      | 83.0     | 100       | 82.6   | 0   | 17.5| 100 | 98.2| 90.4|
| MLP       | 89.0     | 98.6      | 88.6   | 9.1 | 11.4| 90.9| 95.9| 93.3|
| BLR       | 85.0     | 100       | 84.5   | 0   | 15.5| 100 | 98.1| 91.6|

Values are presented as percentage. AI: artificial intelligence, FPR: false-positive rate, FNR: false-negative rate, TNR: true-negative rate, TPR: true-positive rate, SVM: support vector machines, CVM: core vector machines, RF: random forest, k-NN: k-nearest neighbours, MLP: multilayer perceptron, BLR: binary logistic regression.

Table 3. Shows the efficacy of the machine learning algorithms in predicting cryotherapy outcome

| AI method | Accuracy | Precision | Recall | FPR | FNR | TNR | TPR | F   |
|-----------|----------|-----------|--------|-----|-----|-----|-----|-----|
| SVM       | 92.2     | 87.5      | 97.7   | 12.8| 2.3 | 87.4| 88.3| 92.3|
| CVM       | 97.8     | 97.9      | 97.9   | 2.4 | 2.1 | 97.6| 99.1| 97.9|
| RF        | 100      | 100       | 100    | 0   | 0   | 100 | 100 | 100 |
| k-NN      | 93.3     | 93.8      | 93.8   | 7.1 | 6.3 | 92.9| 93.9| 93.8|
| MLP       | 93.3     | 91.7      | 95.7   | 9.1 | 4.3 | 90.9| 91.9| 93.6|
| BLR       | 91.1     | 87.5      | 95.5   | 13.0| 4.5 | 87.0| 88.1| 91.3|

Values are presented as percentage. AI: artificial intelligence, FPR: false-positive rate, FNR: false-negative rate, TNR: true-negative rate, TPR: true-positive rate, SVM: support vector machines, CVM: core vector machines, RF: random forest, k-NN: k-nearest neighbours, MLP: multilayer perceptron, BLR: binary logistic regression.
Table 4. Shows the average of the efficiency measures obtained for all the models and the Z-score when testing against the models predicting outcomes based purely on chance

| Dataset     | Feature | Accuracy | Precision | Recall | FPR  | FNR  | TNR  | TPR  | F    |
|-------------|---------|----------|-----------|--------|------|------|------|------|------|
| Immunotherapy | Average | 88.6%    | 0.99      | 0.88   | 0.018| 0.12 | 0.98 | 0.99 | 0.99 |
|             | Z-score | 7.403*   | 6.56*     | 8.36*  | −6.53*| −8.36*| 6.53*| 7.42*| 6.57*|
| Cryotherapy | Average | 94.6%    | 0.93      | 0.96   | 0.074| 0.032| 0.93 | 0.93 | 0.93 |
|             | Z-score | 8.56*    | 6.58*     | 8.36*  | −6.53*| −8.36*| 6.53*| 7.42*| 6.58*|

FPR: false-positive rate, FNR: false-negative rate, TNR: true-negative rate, TPR: true-positive rate. *p < 0.0001.

sensitivity, specificity, TNR, TPR, and $F_{\text{measure}}$ were obtained for all the models created. This was coupled with low FPR and FNR which further indicated the efficiency in predicting treatment outcome. The average accuracy of the immunotherapy prediction was $88.6\% \pm 8.0\%$ while the same measure for cryotherapy prediction was $94.6\% \pm 4.0\%$. High average precision and recall values were also obtained by the methods that predicted the outcomes of both the immunotherapy and cryotherapy treatments. The average precision of the immunotherapy prediction was $0.99 \pm 0.01$ while the same measure for cryotherapy prediction was $0.93 \pm 0.05$. The closer the value is to 1, the more effective the model is. These results indicate that the models are correct 99.1% of the time when predicting that immunotherapy will be successful. The results also indicate the models are correct 93% of the time when they predict that cryotherapy will be successful.

The average recall of the immunotherapy prediction was $0.88 \pm 0.08$ while the same measure for cryotherapy prediction was $0.96 \pm 0.02$. The closer the value is to 1, the more effective the model is. These results indicate that the immunotherapy model identified 88% of all the cases that should be classified as successful and that the cryotherapy model identified 86% of all the cases that should be classified as successful.

The low false positive and false negative ratios for both the immunotherapy and cryotherapy models also indicate the efficiency of the models. The results indicate less than 6.3% of the time, the models return incorrect results. Only $12.0\% \pm 8.0\%$ of the time does the models indicate that immunotherapy will not work, when it actually would work; and conversely only $1.2\% \pm 4.0\%$ of the time does the models predict that immunotherapy will work when it would not work. Even lower rates were returned with the cryotherapy models. Only $3.2\% \pm 2.0\%$ of the time does the models predict that cryotherapy will not work, when it actually would have worked; and conversely only $7.4\% \pm 5.0\%$ of the time does the models indicate that cryotherapy will work when it would not have worked.

The high true positive and true negatives rates for all the models indicate that the machine learning techniques correctly predicts when each of the treatments will work and when it would not. All the results obtained indicate the machine learning models created are efficient in predicting the treatment outcomes of immunotherapy and cryotherapy for wart removal.

A chi-squared test comparing the different machining learning models based on accuracy alone resulted in a $p < 0.00001$. An ANOVA test using all the efficiency measures also resulted in a $p < 0.00001$. This indicates that there is a statistical difference in predicting outcome of therapy between the models. The RF model obtained the highest values for all the efficiency measures and is the only model whose value was more than one standard deviation away from the average value for each measure. Thus it is concluded that the RF model outperformed all the other models.

**DISCUSSION**

It is important to compare the results obtained by this study to literature, in order to understand the efficiency of these machine learning models. A recent study showed that when feature selection fuzzy logic technique is applied to this dataset, only three features are important for immunotherapy: time, diameter and type. Age, time, type and area were the important variables when predicating the outcome of cryotherapy. The study reported an average accuracy of $83.33\% \pm 6.02\%$ and $80.00\% \pm 5.23\%$ respectively. At 95% confidence interval, an accuracy that is greater that the upper ranger of the reported fuzzy logic study average accuracy plus 1.96 times standard deviation will prove that the machine learning method outperforms the reported fuzzy learning technique. For immunotherapy the upper range of the fuzzy logic accuracy is $83.33\% + 1.96\% (6.02\%)=95.1\%$ and similarly for cryotherapy the upper range is 90.3%. The results of this study exceeded these upper range values, indicating that the models developed in this study is statistically more accurate than those reported in literature by Khozeimeh et al. Fig. 1 and 2 represent the guideline for assessing the success or failure of immunotherapy and cryotherapy respectively.
Comparison of immunotherapy classification with Khozeimeh et al. fuzzy logic rules

Khozeimeh et al.\(^{12}\) based the success of the immunotherapy treatment on three rules. The first simply states that if the diameter of the wart is less than 7 mm, then the immunotherapy will be successful. When applied to the dataset, this rule results in 37% of cases being classified incorrectly. All these errors were correctly classified when the rules of this study were applied. The model described in Fig. 1 is more complicated than the previously reported rules. It states that if the diameter of the wart is less than 4 mm, then the Immunotherapy will be successful. However, unlike Khozeimeh et al.\(^{12}\) model, if the diameter is greater than 4 mm, other factors affect the outcome of the therapy. If there are less than 5 warts and the area covered by the warts is less than 31.5 mm\(^2\) or the patient is younger than 26.5 years old, then the therapy will be successful. However, older patients with fewer than seven warts lead to therapy failure.

The second rule states that there is a positive treatment response if it is a plantar wart and time elapsed is greater than 6 months. When applied to the dataset it resulted in 7% of cases being misclassified. All these errors were correctly classified when the rules of this study were applied.

This study’s model indicates that if there are more than 5 plantar warts and a combination of common and plantar warts, then the treatment will be successful. Failure is outcome of the therapy, when the number of common warts are greater than 5.

The third rule stated that if the time before treatment was less than 6 months then the treatment will work. However applying this rule, results in 21% of cases being misclassified. All these errors were correctly classified when the rules of this study were applied. This study model did not place the same emphasis on time for immunotherapy outcome. This study also produced a model that predicted both treatment success and failure unlike the Fuzzy logic model that did not include a pathway that may result in failure with regards to immunotherapy.

Comparison of cryotherapy classification with Khozeimeh et al. fuzzy logic rules

Khozeimeh et al.\(^{12}\) based the success of the cryotherapy treatment on a few rules. The first simply states that if the warts is both common and plantar then cryotherapy does not work; however, if is a plantar wart where the time elapsed is greater than 6 months, then the therapy is responsive. However, analysing the data resulted in 15% of cases that are both common and plantar but the therapy works. Similarly, 33% of cases where found where plantar wart with a time elapsed greater than 6 months resulted in non-responsive therapy. All these errors were correctly classified when the rules of this study were applied.

The second rule stated that if the time before treatment was less than 6 months then the treatment will work. However applying this rule, results in 21% of cases being misclassified. All these errors were correctly classified when the rules of this study were applied. The third rule states there is a treatment response if it is a plantar wart and time elapsed is greater than 6 months and when applied it resulted in 7% of cases being misclassified. All
these errors were correctly classified when the rules of this study was applied. The model shown in Fig. 2 shows a very different approach to cryotherapy outcome prediction. Like Khozeimeh et al’s model12, age and time played an important role; but type of wart and time elapsed played no role in this study’s model. This study successfully created a machine learning model that improved the prediction ability of the outcome of immunotherapy and cryotherapy for wart removal. The model correctly classified all the cases that the previously published fuzzy logic model incorrectly classified. This study will be extended by using other machine learning algorithms and performing feature selection and more in-depth data pre-processing. Also, it will be very beneficial to validate the study in a clinical setting.

CONFLICTS OF INTEREST

The author has nothing to disclose.

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DATA SHARING STATEMENT

This data is freely available from the public UCI machine learning repository (https://archive.ics.uci.edu/ml/datasets/Immunotherapy+Dataset).

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