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APPLICATION OF R SOFTWARE TO THE DATA OF THE COMPARATIVE STUDY INTRALESIONAL IMMUNOTHERAPY AND CRYOTHERAPY IN THE TREATMENT OF WARTY LESIONS

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Abstract

For the R software application we have taken two datasets "Immunotherapy" and "Cryotherapy" obtained in comparative study between Intralesional Immunotherapy and Cryotherapy (2) from the database https://achieve.ics.uci.edu/datasets.php. This study was conducted in dermatology clinic "Ghaem Hospital", Mashad, Iran. The study enrolled 180 patients diagnosed with verrucous lesions. The selection of the patients for the application of the treatment method was randomized. The patients were included in two treatment groups in equal number, 90 patients received intralesional immunotherapy treatment with Candida antigen, 90 patients received cryotherapy treatment using liquid nitrogen. In this article the data obtained from this study are analysed as a single dataset by aggregating the two data sets, the study authors analysing them individually. Also the statistical analysis was performed using R software unlike the study authors who performed the analysis using a rule-based fuzzy logic system. The results of the statistical analysis, by evaluating the predicted probabilities, showed that Immunotherapy is more effective than Cryotherpy in treating warty lesions. The values of these probabilities are 0.60 for Cryotherapy treatment and 0.89 for Immunotherapy treatment.
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1 Introduction

Warty lesions are the most common clinical manifestation of human papillomavirus (HPV) infection of the skin and mucous membranes, and are most common on the hands, feet, face and genitals.

[4]Mathematical Subject Classification (2020): {*62-04, 62P10, 62J05*}
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These benign lesions have different clinical forms. Despite the various therapeutic modalities used: topical caustic acid, cryotherapy, electrocautery, surgical removal, laser ablation, intralesional injection of bleomycin, Candida albicans, purified protein derivatives; there is still no single method that can be used as an approved treatment(1). Liquid nitrogen cryotherapy is a favourable and alternative treatment, leading to treatment of up 50%– 70% of lesions after three or four session (1). Intralesional immunotherapy is another current treatment that stimulates the immune sistem to recognise the Candida antigen through the delayed hypersensitivity reaction and subsequently eliminate HPV (1).

The clinical study from which these data were obtained was a comparative analysis of intralesional immunotherapy with candida antigen and cryotherapy with liquid nitrogen. The study included 180 patients with common and plantar warty lesions. The two treatment methods represent two of the most effective therapeutic methods. Cryotherapy is the most widely used treatment method. However the presence of side effect and the numerous treatment sessions require to achive favourable results are not the best option. Immunotherapy is a newer therapeutic method, but it also has the disadvantage found in cryotherapy treatment.

The 180 patients enrolled in the study were divided into two groups. The allocation of patients to the therapeutic variant administred was randomised. The age of the patients ranged from 15 years, the minimum age for inclusion in the study, to 67 years.

	Immunotherapy group	Cryotherapy group
Number of patients	90	90
Age (avarage)	28.6	31.04
Gender: Male	41	47
Female	49	43
Type of injuries: -Verruca vulgaris	39	49
- Plantar warts	30	19
- Both Types	21	22

Table 1: Demographic characteristics of patients in both groups

Within this dataset, the response variable “Result_of_Treatment” is a binomial type 1 representing the positive response to the treatment applied, and 0 representing the negative response to the treatment applied.

The predictor variables are represented by:

- Variable “age”
- Variable “sex” – categorial variable:

1-male
2- female

- Variable “Time” – time before treatment
- Variable “Number of Warts” – number of warts
- Variable “Type” – type of warty lesions: 1 – Verruca vulgaris

2 – Planarian warts
3 – Both types of injuries

- Variable “ Area” – the surface area of warty lesions
- Variable “ Treatment” – type of treatment administered:

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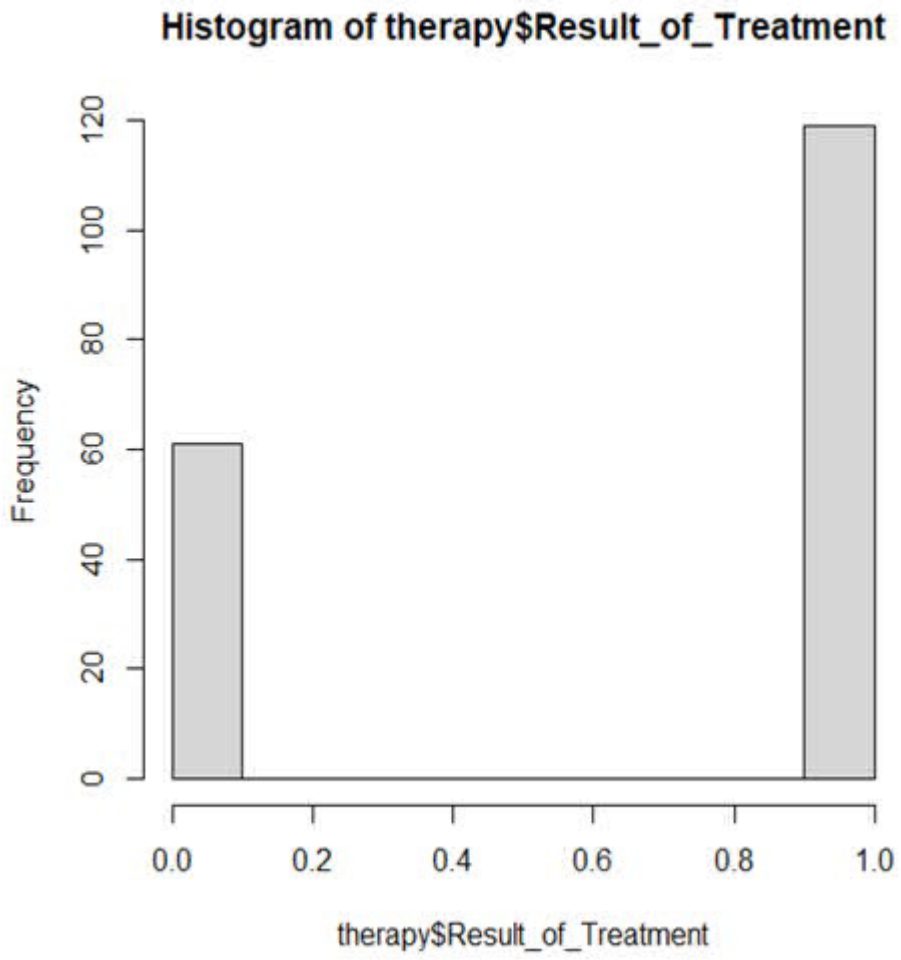


Figure 20: Histogram of the positive/ negative response to treatment

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1 – Immunotherapy
0 – Cryotherapy

2 Methods

2.1 Therapeutic methods

Group A received immunotherapy with intralesional injection of Candida antigen, while group B was treated with liquid nitrogen cryotherapy(1). Patient characteristics were recorded in a questionnaire. Warts were assumed to be in the shape of a circle or ellipse(1). To determine the size of the lesions, the two largest perpendicular radii in each lesion were measured in millimetres, and the area was calculated by multiplying the major and minor radii for each lesion, only the area of the largest lesion was calculated(1). Patients were assessed at the beginning of the study, and the number and size of lesions were also noted at each follow-up visit(1). During follow-up, therapeutic response was considered "positive" if the treated lesion area showed a reduction in the size of the largest lesion >75%(1). A "negative" response was considered when the size reduction was less than 25% of the largest lesion(1). The criteria were applied to both groups. In the case of a partial response (reduction in the size of the largest lesion between 25%- 75%), a negative response was considered(1). Any adverse reactions and their severity were recorded for each patient during the treatment.

Group A

In group A, 0.1 milliliters(ml) of purified Candida 1/1000 antigen solution (Gree USA) was injected intradermally into the flexor side of the left forearm. After 48-72 h, the existence of a response and the size of the skin reaction were assessed. All enrolled patients showed a positive reaction to Candida antigen. The dose of Candida antigen administration for intralesional immunotherapy was determined by the induration diameter after the test dose, as follows: 0.3 ml for an induration diameter of 5-20 mm; 0.2 ml at an induration diameter of 20-40 mm; 0.1 ml for an induration diameter greater than 40 mm. A total of three injections were administrated at 3-week intervals either until the lesions were completely removed or for a maximum of three treatment sessions(1).

Group B

In this group, all patients received cryotherapy once a week until complete elimination of the lesions or for a maximum of 10 sessions. In each session, cryotherapy was done with liquid nitrogen, using cotton probes, until 1-2 mm edge of the normal skin border around the lesion turned white due to frostbite. After thawing, a second cycle was performed in the same way, each session. Any adverse reactions were recorded(1).

2.2 Statistical methods

Model optimization was achived by applying the GLM function (R package "stats")(5). The backward method was used for optimization (3). Following the optimization, the important variables for the prediction of the reaponse variable "Result_of_Treatment" are "age", "Time" and "Treatment". The Wald test, the Nagelkerke R^2 coefficient, the Brier score and Akaike's information criterion were used to evaluate the model obtained (3, 4). The values for Related Odds Ratio were calculated for each of the three important predictor variables.

3 Results

3.1 Structure of the optimal model obtained:

Coefficients:

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Estimate Std. Error z value Pr(>|z|)
(Intercept)
6.48554 1.08357 5.985 2.16e-09 ***
age
-0.07580 0.01802 -4.206 2.60e-05 ***
Time
-0.51240 0.09111 -5.624 1.87e-08 ***
factor(Treatment)1
1.75576 0.45307 3.875 0.000107 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
(Dispersion parameter for binomial family taken to be 1)
Null deviance: 230.51 on 179 degrees of freedom
Residual deviance: 138.22 on 176 degrees of freedom
AIC: 146.22
Logit(π)= ln $(\frac{\pi}{1-\pi})$ = 6.68554 + age* (-0.07580) + Time*(-0.51240) + 1.75576* (Treatment)
> wald.test(b=coef(glm5),Sigma=vcov(glm5),Terms=4)

3.2 Wald test

Chi-squared test:
X2 = 15.0, df = 1, P(> X2) = 0.00011

A test value of 15.0 was obtained χ^2 with a degree of freedom associated with P-value of 0.00011 indication that the overall effect of the variable "Treatment" is significant from statistically.

3.3 Coefficient Nagelkerke

> NagelkerkeR2(glm5)
$N
[1] 180
$R2
[1] 0.5554854
The R^2 Nagelkerke Coefficient assessed the explanatory power of a model(4).
Brier score:
> B<-mean((therapy$pred-therapy$Result_of_Treatment)^2)
> B
[1] 0.1111021
> p<-mean(therapy$Result_of_Treatment)
> p
[1] 0.6611111
> Bmax<-p/(1-p)
> Bmax
[1] 1.95082
> Brier<-1-B/Bmax
> Brier
[1] 0.9430485
The Brier score assesses the predictive power of a model(4).

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3.4 Akaike's Informational Criterion (AIC)

> mysteps<-step(glm5,Result_of_Treatment~age+Time+factor(Treatment),family=
binomial,data=therapy)
Start: AIC=146.22
Result_of_Treatment ~ age + Time + factor(Treatment)
Df Deviance AIC
<none> 138.22 146.22
- factor(Treatment) 1 155.27 161.27
- age 1 158.76 164.76
- Time 1 188.04 194.04

3.5 Odds Ratio

exp(cbind(OR=coef(glm5),confint(glm5)))
[]@ ¿p() * 1.0000@

OR 2.5 % 97.5 %
(Intercept)
655.5905125 95.3649233 6888.5416219
age
0.9270006 0.8930832 0.9589752
Time
0.5990590 0.4932874 0.7068576
factor(Treatment)1
5.7878504 2.4582063 14.6789690

3.6 Predicted probabilities by therapeutic option

> head(newdata1)
age Time Treatment TreatmentP
1 29.82222 7.448611 0 0.6006916
2 29.82222 7.448611 1 0.8969798

4 Conclusions

Applying the Wald Test (R package "aod"), a value of 15.0 was obtained for the χ^2 with a degree of freedom, associated with a P-value of 0.00011 which shows that the overall effect of the variable "Treatment" is statistically significant. The R^2 Nagelkerke Coefficient value is 0.555 (R package "fmsb"), showing the strenght of the model in explaining the response variable. The adjusted Brier score obtained 0.94, shows the predictive power of the model. By applying the step function (R package "lmerTest") it was observed that the value of the deviance and AIC increased in the situation of removing the predictor variables from the obtained optimal model.

Since the confidence intervals for the Odds Ratio (OR) obtained by processing in R did not include the value 1, it can be stated that for an increase of one unit (one year) in the variable "age" the patients' odds will be modified by a factor of 0.92 (decrease); for an increase of one unit (one month) in the variable "Time" the patients' odds will be modified by a factor of 0.599 (decrease). Since the variable "Treatment" is a categorial variable, the reference category being Cryotherapy for a chance ratio=5.78, the chances of a patients treated with Immunotherapy are changed by a factor equal to this ratio (5.78) compare to the chances of the patients treated with Cryotharapy.

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The predicted probabilities obtained, with the variables "age" and "time" held constant (mean), are 0.60 for the Cryotherapy treatment and 0.89 for the Immunotherapy treatment. The interpretation of these results is: a patient aged 29.82 years (mean age) with a time of 7.45 months (mean) before treatment for which the therapeutic option is Cryotherapy has a probability of a positive response to treatment of 0.60; a patient with Immunotherapy treatment has a probability of a positive response of 0.89. For an easier representation of the predicted probablilities according to the type of treatment, age and time prior to treatment administration, the graphical methos (R package "ggplot") (5) was also used.

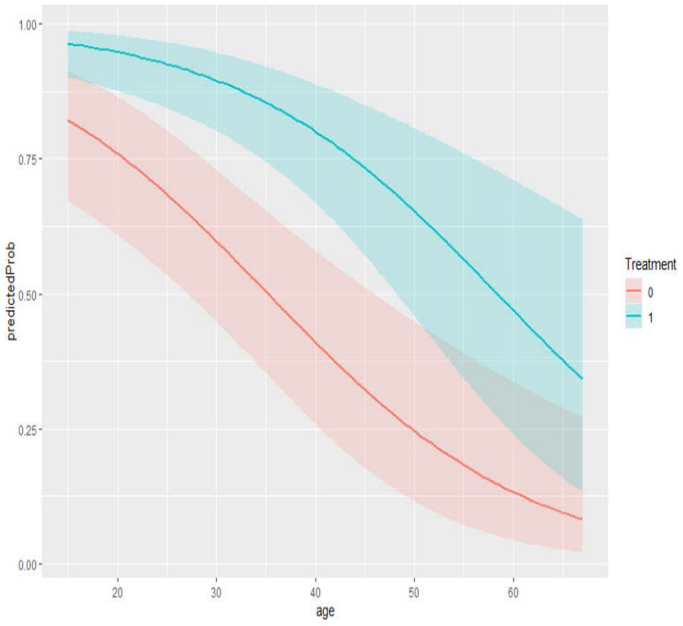


Fig. 2. Predicted probabilities by treatment type and age

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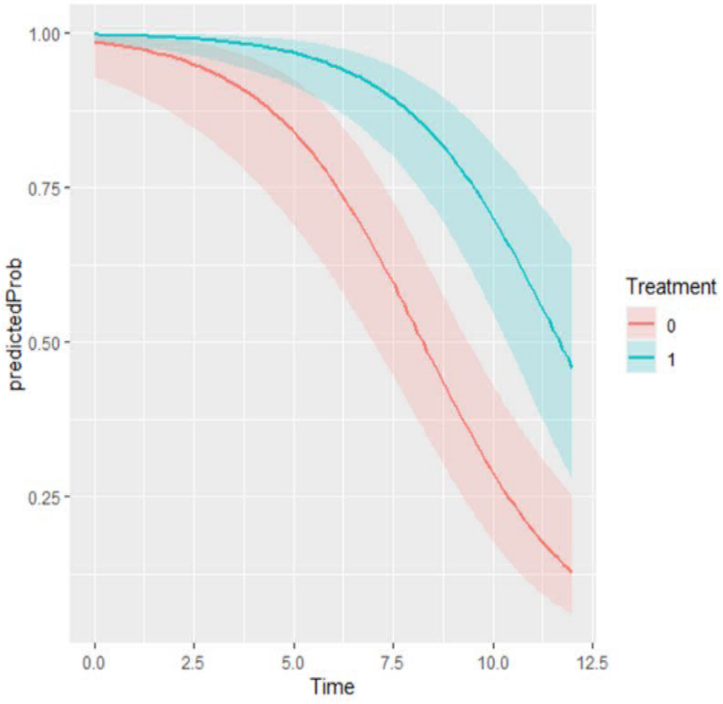


Fig 3. Predicted probabilities by treatment type and time to treatment

Following the statistical analysis, it can be stated that for the dataset presented, age has a negative effect on treatment response for both treatment options: immunotherapy and cryotherapy. Increasing the age of the patients leads to a decrease in the probability of cure. The same influnce is also seen in the length of time prior to the treatment with a negative effect on treatment response, increasing it decreases the probability of cure. In terms of type of treatment, Immunotherapy has been shown to be more effective than Cryotherapy in treating warty lesions.

Khozeimeh F. et al performed statistical analysis of the data using a rule-based fuzzy logic system. They found a better therapeutic effect of Immunotherapy compare to Cryotherapy and the presence of a correlation between age and treatment response, but only in the Cryotherapy group. Patients under 21 years of age showed a better response to cryotherapy treatment. Treatment groups were evaluated individually. There was no mention of a relationship between time prior to treatment and treatment response.

Consulting a dermatology specialist from Timisoara Dermatology Clinic confirmed the results obtained by running the dataset in R.

Increasing age decreases the positive response to treatment. The time between the onset of the symptoms and the administraton of treatment negatively influences the responce to treatment because the lesion becomes deeper and more extensive with the passage of time. Intralesional immunotherapy is more effective than cryotherapy because cryotherapy treatment only removes the surface lesion without treating the human papillomavirus infection.

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