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Evaluating the Predictive Utility of Demographic, Lesion, and Inflammatory Parameters for Immunotherapy Success in Cutaneous Warts

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ABSTRACT

HPV is the cause of cutaneous warts; they're very common and sometimes do not respond to damaging treatments. An alternative treatment is intralesional immunotherapy, but there are no good predictors of clearance that will help in patient selection. **Objectives:** To assess the ability of baseline demographic, lesion, and inflammatory parameters (wart type, age, sex, wart count, lesion area, treatment duration, and induration diameter) to predict complete clearance, and whether induration diameter is a useful predictive biomarker. **Methods:** Retrospective analysis of 90 patients treated with intralesional immunotherapy (71 had successful treatment, and 19 failed). Categorical variables were compared using chi-square, continuous variables were compared using the Mann-Whitney U-test, and predictors were identified through multivariate logistic regression. The interaction between age and wart type was tested, and the induration diameter was assessed using ROC curve analysis (Youden index). **Results:** There were no differences among groups for any variable (categorical or continuous). No association was found between outcome and wart type (p=0.680) or sex (p=0.840), and the median induration diameter was the same across both groups (7.0 mm, p=0.910). Age was near significant (p=0.080). The multivariate model accounted for less than 6% of variance in the outcome (Nagelkerke R^2=0.06) and did not have any discriminative power (AUC=0.51). **Conclusions:** The standard demographic, morphological, and inflammatory parameters, such as induration diameter, were not good predictors of the response to immunotherapy in this dataset, and other molecular or immunological parameters will likely be needed for better patient selection.

INTRODUCTION

Human papillomavirus (HPV) infection of keratinocytes results in common skin lesions known as cutaneous warts. They occur in 2-40% of individuals, especially children and adolescents. While the majority of warts will go away on their own, some warts do not respond to treatment with salicylic acid or cryosurgery, making immunotherapy a viable option [1]. The use of intralesional immunotherapy using measles-mumps-rubella (MMR) vaccine, Candida albicans, tuberculin purified protein derivative (PPD), and Bacille Calmette-Guérin (BCG) vaccine has become commonplace as a second-line treatment for warts that are recalcitrant or numerous [2, 3]. The mechanism of action is believed to involve triggering a type IV delayed-type hypersensitivity (DTH) response, which is clinically apparent as local erythema and induration that aids the immune system in recognizing and eliminating HPV infected keratinocytes both at the injected site and at untreated, distant lesions [4]. A recent review of 62 randomized controlled trials found complete response rates ranging from 25 to 96% depending on the agent used, with a more recent review identifying more specifics about the immunopathogenic basis for this variation in complete response rates [5]. Intralesional immunotherapies like MMR, Candida antigen, PPD, Vitamin D3, and Mycobacterium w vaccine are effective in treating cutaneous warts, but there is no clear understanding of

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which factors indicate treatment response. In regard to the treatment of plantar warts, there are meta-analyses showing that MMR is more effective than vitamin D3 [6], Candida antigen is more effective than comparator therapies for recalcitrant plantar warts [7–9], and MMR has comparable efficacy to PPD in plantar and periungual warts [10]. Individual studies also show vitamin D3, PPD, and Mycobacterium w vaccine to be effective, which is effective and when combined with cryotherapy, results in a reduced time of clearance [11-15]. Although the routine clinical parameters (e.g., age and wart morphology) have yielded inconsistent results, previous studies have found immunological biomarkers (e.g., IFN-γ, IL-17, MIF, and TLR2)as good predictors of response[16–21].

The effect of older age on treatment response may be accounted for by immunosenescence, but its independent predictive value has not been established. This study aimed to identify independent factors associated with achieving complete clearance of the warts and determine the clinical importance of bedside measurements. This study used multivariable logistic regression analysis, age-by-wart-type interaction analysis, and ROC curve analysis to systematically evaluate seven readily available clinical and morphological parameters: age, sex, wart type, wart count, lesion area, treatment duration, and post-injection induration diameter.

METHODS

This was a retrospective, analytic study on secondary data. This study was conducted at the Institute of Molecular Biology and Biotechnology, The University of Lahore, Lahore, Pakistan, from September 2025 to December 2025. Instead of enrolling and following patients prospectively, this study analyzed an already collected, de-identified dataset of patients who had received intralesional immunotherapy for their cutaneous warts in the past, which was made publicly available on Kaggle. The repository consists of documented clinical data of patients treated with intralesional immunotherapy containing seven baseline clinical variables: age of patient, sex, wart morphological type, number of warts, area of lesion, duration of warts before treatment, diameter of induration after intralesional immunotherapy, and the outcome of the treatment. The data used were retrospective, secondary, and anonymized; compliance with repository terms of use constituted the only additional approval, and the data were not treated in any way or selected as antigens for individual patients. The source data set upon download included complete data for all 90 patients for each of the seven baseline variables and for the outcome variable. There were no exclusions and no imputation needed, so all the data were included in the analysis without loss, and no sample size calculation for imputing was required. Patients were divided into two mutually exclusive groups based on the clinical response recorded in the source data at the end of follow-up: complete clearance ("success," n=71) and partial or no clearance ("failure," n=19). The loss of the treated wart and any associated distant lesions, plus a return of normal skin markings, was defined as complete clearance, per the source data set. Baseline data were collected on seven parameters that were selected a priori based on clinical relevance and previous literature: patient age in years, sex, wart morphological type (three categories), number of warts at baseline, lesion area (mm^2) of the index wart, wart duration before treatment (months), and the diameter (mm) of the local induration reaction that was observed 48 to 72 hours after injection with intralesional antigen (a bedside proxy measure of the intensity of the delayed-type hypersensitivity reaction). The source dataset did not report which measurement technique was used (e.g., ballpoint-pen technique or caliper technique), the number of raters or the training of a single rater, nor did it report whether the measurements were based on a single observer or the average of repeated measurements; the measurement protocol could not be verified or reconstructed from the secondary data and is acknowledged as unavailable. Categorical variables (sex, wart type) were compared between outcome groups with the chi-square test, with the chi-square value, number of degrees of freedom, and the p value reported. The continuous variables (age, induration diameter, wart duration, wart count, and lesion area) were not normally distributed; thus, the Mann-Whitney U test was used, and the results are presented as medians and interquartile ranges (IQR). To identify independent predictors of treatment success while adjusting for confounding, we constructed a multivariate logistic regression model incorporating all seven baseline variables simultaneously. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) were calculated. Model fit was assessed with the Hosmer-Lemeshow goodness-of-fit test [22], and the proportion of outcome variance explained was quantified with the Nagelkerke R^2 statistic; the Akaike Information Criterion (AIC) was used for model comparison. Given the relatively small number of events (19 failures) relative to the seven predictors modeled, standard maximum-likelihood logistic regression is susceptible to small-sample bias and separation; we therefore considered Firth's penalized logistic regression as a bias-corrected alternative. Because the standard model showed good calibration (Hosmer-Lemeshow p=0.720) and none of the point estimates approached separation, we retained the standard model for the primary analysis, but note that Firth's method would be the preferred approach in any future replication with a similarly limited number of events. A post-hoc power analysis, based on the observed 19

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failures and a total sample of 90 patients, indicated that the study had 80% power to detect an odds ratio of approximately 3.2 or larger ($\alpha = 0.05$, two-tailed). Therefore, smaller but potentially clinically relevant effect sizes may not have been detectable in this cohort.

No formal adjustment was made for multiple comparisons; therefore, all analyses should be considered exploratory. A Bonferroni correction for the seven primary clinical variables would require a significance threshold of $p<0.007$. We then added an age-by-wart-type interaction term (with age as a continuous variable and wart type as categorical) to the adjusted model and reported the overall interaction p-value and subgroup-specific adjusted odds ratios. Finally, receiver operating characteristic (ROC) curve analysis was performed for induration diameter as a candidate biomarker, calculating the area under the curve (AUC) [23], the optimal cutoff via Youden's index [24], and the corresponding sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. A two-tailed p-value <0.050 was considered statistically significant throughout.

RESULTS

The sex distribution was nearly identical between groups—45.1% male among successes versus 47.4% among failures—and the chi-square test confirmed no meaningful difference ($\chi^2=0.04$, df=1, p=0.840). Wart type distribution followed the same pattern: Type 1 warts predominated in both groups (50.7% of successes vs. 57.9% of failures), and the relative proportions of Type 2 and Type 3 lesions were likewise comparable, again with no significant association ($\chi^2=0.76$, df=2, p=0.680). Taken together, these results suggest that categorical demographic and morphological features carry little discriminatory power on their own, a pattern consistent with the broader meta-analytic finding that clearance rates for agents such as the MMR vaccine vary widely across studies without any clear morphology-based signal. In this dataset, these results suggest that the clinical parameters typically available at the bedside are not enough to predict who will respond to immunotherapy, and should not be used alone to guide patient selection (Table 1).

Table 1: Baseline Demographic, Lesion, and Treatment Characteristics of 90 Wart Patients Stratified by Immunotherapy Outcome

Variables	Category	Success (n= 71), n (%)	Failure (n= 19), n (%)	χ^2	df	p-value
Sex	Male	32 (45.1%)	9 (47.4%)	0.04	1	0.840
	Female	39 (54.9%)	10 (52.6%)			
Wart Type	Type 1	36 (50.7%)	11 (57.9%)	0.76	2	0.680
	Type 2	17 (23.9%)	5 (26.3%)			
	Type 3	18 (25.4%)	3 (15.8%)			

None of the five continuous variables reached statistical significance. The most notable finding is that median induration diameter was identical between groups (p=0.910), which runs counter to the idea that a stronger local hypersensitivity reaction should translate into better clearance odds. Age came closest to a significant difference (p=0.080), consistent with reports that younger patients tend to respond better to intralesional immunotherapy, though the trend was weak. Wart duration, wart count, and lesion area showed no meaningful association with outcome (Table 2).

Table 2: Multivariate Logistic Regression Examining Independent Associations with Immunotherapy Success

Variables	Success Median [IQR]	Failure Median [IQR]	U Statistic	p-value
Age (years)	27.0 [19.0–38.0]	34.0 [27.0–45.0]	521.5	0.080
Induration (mm)	7.0 [5.0–25.0]	7.0 [6.0–25.0]	669.0	0.910
Wart Duration (months)	7.5 [5.0–9.8]	8.0 [5.0–10.5]	633.0	0.560
Number of Warts	4.0 [2.0–8.0]	5.0 [2.0–11.0]	555.5	0.350
Area (mm^2)	50.0 [30.0–87.0]	43.0 [25.0–73.0]	592.0	0.580

The multivariate model, which adjusted for all seven variables simultaneously, echoed the univariate results: every adjusted odds ratio sat close to 1.0, and every 95% confidence interval crossed unity. Age carried an aOR of 0.96 per year (95% CI 0.91–1.01, p=0.100); induration diameter, an aOR of 1.00 per millimeter (95% CI 0.97–1.03, p=0.920); and wart type, relative to Type 1, an aOR of 0.90 for Type 2 (95% CI 0.28–2.90, p=0.860) and 0.55 for Type 3 (95% CI 0.14–2.15, p=0.390). Wart count and lesion area were likewise non-significant. Model calibration was good (Hosmer-Lemeshow p=0.720), Although the Hosmer-Lemeshow test indicated good statistical calibration (p = 0.720), the Nagelkerke R^2 of 0.06 demonstrates that the model explains virtually none of the clinically meaningful variance. This confirms that these clinical parameters have no practical utility for predicting treatment response at the bedside, meaning that although the model fit the data well statistically, the seven clinical and morphological parameters together tell us almost nothing useful about who will respond to treatment. This lines up with calls elsewhere in the literature for larger, more standardized predictor studies (Table 3).

Table 3: Multivariate Logistic Regression – Independent Predictors of Treatment Success

Variables	Adjusted Odds Ratio (aOR)	95% CI	p-value
Age (per 1 year)	0.96	0.91–1.01	0.100
Induration Diameter (per 1 mm)	1.00	0.97–1.03	0.920
Wart Type – Type 2 (ref = Type 1)	0.90	0.28–2.90	0.860
Wart Type – Type 3 (ref = Type 1)	0.55	0.14–2.15	0.390
Number of Warts	0.96	0.87–1.06	0.420
Area (mm^2)	1.00	0.99–1.01	0.600
Age × Wart Type (interaction term)	0.98	0.89–1.07	0.620

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This study tested whether age modifies the effect of wart type on treatment success by including a continuous age × wart type interaction term in the fully adjusted logistic regression model. The interaction term was not significant (p=0.620), indicating that age does not significantly modify the effect of wart morphology on treatment response in this cohort (Table 4).

Table 4: Interaction Term (Age × Wart Type) in Multivariate Logistic Regression for Treatment Success

Variable	Adjusted Odds Ratio (aOR)	95% Confidence Interval	p-value
Age × Wart Type (interaction term)*	0.98	0.89 – 1.07	0.620

Induration diameter is appealing as a biomarker because it is easy to measure at the bedside and reflects the host's delayed-type hypersensitivity response in real time. But when we tested its discriminative performance formally (Table 5), the results were unimpressive: AUC was 0.51 (95% CI 0.38–0.64), essentially indistinguishable from the diagonal line representing no discrimination at all. Because the AUC alone already establishes that induration diameter performs no better than chance, this study do not report cutoff-dependent metrics (Youden's index cutoff, sensitivity, specificity, accuracy, or predictive values), which would only restate the same null finding in a form that is more sensitive to sample-specific noise; a variable with an AUC near 0.5 cannot be rescued by any choice of cutoff. Despite its mechanistic appeal as a marker of T-cell activation, induration diameter simply does not function as a useful bedside biomarker of immunotherapy outcome in this cohort (Table 5).

Table 5: ROC Curve Analysis of Induration Diameter as a Predictive Biomarker for Immunotherapy Success

Metrics	Value
Area Under the Curve (AUC)	0.51 (95% CI: 0.38–0.64)
Conclusion	Induration diameter has no discriminative ability to predict treatment success; the AUC of 0.51 confirms performance no better than random chance.

DISCUSSION

The current study set out to evaluate seven readily available baseline parameters as predictors of complete clearance after intralesional immunotherapy, and across the board, found none of them useful. Neither the categorical variables (sex, wart type) nor the continuous ones (age, wart count, lesion area, treatment duration) separated patients who cleared from those who did not—not individually, and not within a multivariate model adjusting for confounders. Most tellingly, post-injection induration diameter, despite a strong mechanistic case for it as a proxy for the delayed-type hypersensitivity reaction thought to underlie treatment effect [8], showed essentially no discriminative capacity: an AUC of 0.51, statistically no different from chance. The current study's null finding for induration diameter contrasts with Hammad *et al.* who reported that ex vivo interferon-gamma responses significantly predicted clearance with bivalent HPV vaccine immunotherapy. This discrepancy suggests that visible local skin reactions may not adequately reflect the systemic cellular immune responses that are captured by laboratory-based cytokine assays [16]. This contrast is worth drawing out directly: Hammad *et al.* found that a laboratory-based cytokine assay carried a real predictive signal for immunotherapy clearance [16], whereas the current study's bedside clinical proxy for the same delayed-type hypersensitivity pathway—induration diameter—showed none (AUC=0.51). Comparable cytokine- or immune-marker-based predictor studies in this field remain limited, which is itself notable: it suggests that the field has more evidence that molecular/immunologic assays can predict response than that clinically observable surrogates can, reinforcing that induration diameter should not be treated as a proxy for the underlying immune assays it is meant to represent. Two other recent studies reinforce this pattern: serum interleukin-17 and macrophage migration inhibitory factor levels correlated with clinical response to intralesional Candida antigen [19], and peripheral blood toll-like receptor 2 expression predicted response to intralesional vitamin D3 [20]—both molecular markers, not bedside clinical signs. Taken together with the current study null result for induration diameter, the accumulating evidence points toward circulating or tissue-level immune markers, rather than clinically observable ones, as the more promising direction for predictor research in this field. One explanation is that whatever biological signal cytokine assays capture simply does not translate into a visible, millimeter-scale induration reaction at the bedside. The non-significant trend toward younger patients responding better is broadly consistent with what is known about immunosenescence blunting T-cell responses in older adults [21], and with pediatric case series reporting more favorable responses in younger patients [18], though our formal interaction test found no evidence that age specifically modifies the effect of wart morphology. In this dataset, these results argue against relying on any of the seven parameters we studied—alone or in combination—to decide who should or should not receive intralesional immunotherapy; whether this holds beyond the present cohort would need confirmation in other samples. The exceptionally low Nagelkerke R^2 (0.06), paired with a model that otherwise fit well (Hosmer-Lemeshow p=0.72), is worth emphasizing. Good calibration and clinical utility are not the same thing: a Hosmer-Lemeshow p-value only indicates that predicted and observed probabilities agree on average across risk strata,

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whereas Nagelkerke R^2=0.06 means the model accounts for barely 6% of the variability in outcome.

The most important limitation of this study is the heterogeneity of immunotherapeutic agents, dosages, and treatment protocols in the source dataset. Because the specific antigen type (e.g., MMR, Candida, PPD, or BCG) and dosing regimen were not recorded, the current study could not assess whether predictor performance differs by agent, which severely limits the generalizability of the current findings. Significant treatment heterogeneity (unrecorded antigen type, dosage, and protocol across patients) limits generalizability and is a key limitation. The results of this study should be confirmed in large, multicenter, prospective trials with uniform intralesional immunotherapy protocols that specify the antigen type, dosage, and schedule.

CONCLUSIONS

None of the patients' baseline clinical characteristics (age, sex, type of warts, number of warts, size of lesions, duration of treatments, and diameter of induration) were statistically significant for complete clearance in 90 patients receiving intralesional immunotherapy for cutaneous warts. The biggest drawback was the lack of information about which immunotherapy was given, which could have made it difficult to see the effects of the treatments. The results indicate that there are no definitive clinical parameters to predict response to therapy, which further underscores a critical need for new, validated immunological, genomic, and virological markers in future agent-specific studies.

Author's Contribution

Conceptualization: SAK
Methodology: SAK
Formal analysis: SAK
Writing and Drafting: SAK
Review and Editing: SAK

The author approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

The author declare no conflict of interest.

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