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The Predictive Factors of Acne Scarring and Post-Inflammatory Hyperpigmentation: A Retrospective Cohort Study

Awadh Alamri[1–3], Dhaii Alzahrani[1,2], Ghadi Alharbi[1,2], Rami Jan[1,2], Lulu Abdullah Alsubaie[1,2], Amjad Alghamdi[1,2], Amal H Abualola[1,2], Abdulhadi Jfri[1–3]

[1]College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia; [2]King Abdullah International Medical Research Center, Jeddah, Saudi Arabia; [3]Department of Dermatology, King Abdulaziz Medical City, Jeddah, Saudi Arabia

Correspondence: Rami Jan, College of Medicine – Jeddah, King Saud bin Abdulaziz University for Health Sciences, P.O.Box.9515, Jeddah, 21423, Saudi Arabia, Email ramiqj@gmail.com

Introduction: Acne vulgaris, a prevalent dermatological condition, often results in long-term complications such as scarring and hyperpigmentation. While extensive research has focused on treatment modalities, there is a notable gap in understanding the factors contributing to the development of acne scarring and post-inflammatory hyperpigmentation (PIH).

Purpose: This study was conducted to identify the factors contributing to the development of acne scarring and post-inflammatory hyperpigmentation (PIH).

Patients and Methods: This retrospective cohort study, conducted at King Abdulaziz Medical City, Jeddah, Saudi Arabia, analyzed data from patients with acne vulgaris between 2016 and 2023 using the hospital's health information system, BESTCare. Statistical analysis was performed using RStudio (R version 4.3.1). We constructed a multivariable, multinomial logistic regression model to assess the independent predictors of four acne complication groups; no scarring/PIH, scarring alone, PIH alone, and acne scarring with PIH.

Results: Among 417 analyzed participants, 95 participants had acne scarring (22.8%), 93 participants had PIH alone (22.3%), and 151 participants had both acne scarring with PIH (36.2%), and only 78 participants did not develop scarring or PIH (18.7%). Isotretinoin use and papules acne were associated with increased risk of acne complications. While adapalene gel was protective against acne scarring only.

Conclusion: This retrospective study sheds light on factors influencing acne scarring and PIH among Acne Vulgaris patients. Our findings provide valuable insights for tailoring interventions and advancing our understanding of acne vulgaris complications in the future.

Keywords: acne vulgaris, acne scarring, post-inflammatory hyperpigmentation, predictive factors, retrospective cohort study

Introduction

Acne vulgaris is one of the most prevalent inflammatory skin conditions, being the eighth most common disease worldwide in 2010 according to the Global Burden of Disease Study, with a prevalence of 9.38%.[1] Its underlying pathogenesis is multifactorial and encompasses the rise of pubertal hormones, which leads to an increase in sebum production, follicular hyperkeratinization, and an inflammatory reaction in the pilosebaceous glands.[2] The resulting lesion is then classified according to severity into mild, moderate, and severe acne. Acne can also be classified based on the type of lesion, such as comedonal or nodular acne.[2]

Complications can occur during and after the resolution of acne. These include psychosocial effects, scarring, post-inflammatory erythema, and hyperpigmentation. As to the contributing factors of scarring, having severe acne, which occurs in about 20% of patients with acne, was previously considered the main predictor.[3,4] Recently, it is proposed that positive family history of scarring and delay of effective treatment initiation are the two major contributors to acne

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scarring.[4] A systematic review and meta-analysis evaluating the risk factors of acne scars have demonstrated that male gender in addition to both of acne severity and having a positive family history of acne are contributing factors to the development of acne scars.[5] Other risk factors were found in previous studies which include consumption of milk, butter, and relapsing acne.[6,7] Regarding hyperpigmentation, skin color plays a crucial role, with darker skin colors being more affected.[3] Additionally, being a female with severe facial acne, exposure to sunlight with inadequate sunblock, and physical trauma to the lesion with squeezing and scratching contributes to post-acne hyperpigmentation according to a recent study by Al-Qarqaz et al.[8]

A myriad of studies have focused on investigating and comparing the possible treatment options for acne scars and post-inflammatory hyperpigmentation (PIH).[9,10] However, there is a paucity of evidence regarding the contributing factors of both conditions. Consequently, we aim to retrospectively investigate the risk factors of acne scars and hyperpigmentation among Saudi patients. The results of this study will enhance the dermatologists' insight into the possible predictors of acne complications and help prevent and manage the condition more effectively.

Materials and Methods

Study Setting and Design

This is a retrospective cohort study aimed to investigate the risk factors of acne scarring and PIH among patients with acne vulgaris. We included 417 patients who visited the dermatology clinic from 2016 to 2023 at King Abdulaziz Medical City in Jeddah, Saudi Arabia. Inclusion criteria included patients above the age of 18 years old with acne vulgaris and received acne treatments such as topicals, antibiotics, and systemic treatments. Exclusion criteria included patients with other types of acne and patients who lost follow-up or with incomplete medical record documentation. Consecutive sampling was used, and subjects who met the study's inclusion criteria were selected to ensure representative sampling.

Data Collection

The medical charts of all eligible patients were retrieved, and data were collected from the Ministry of National Guard Health Affairs medical record system (BestCare). The abstracted data was collected by a structured data collection sheet that consisted of socio-demographic variables like gender, age, body mass index (BMI), smoking status and history of polycystic ovarian syndrome. The full list of demographic and clinical characteristics is provided in Section A of the appendix. Moreover, clinical variables such as treatment regimen, acne characteristics, and laboratory data were assessed. Details on treatment regimens and their usage are provided in Section B of the appendix, while additional information on acne types and features can be found in Section C. Laboratory data included hemoglobin levels, thyroid function, vitamin D, ferritin, zinc, folate, vitamin B12, baseline lipid profile, and baseline liver enzymes. A copy of the data collection sheet is provided in appendix C.

Ethical Consideration

Ethical approval was received from the Institutional Review Board at King Abdullah International Medical Research Centre, Jeddah, Saudi Arabia (reference number: RYD-24-417,780-11796) to ensure the confidentiality of all patients' data following the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using RStudio (R version 4.3.1). We expressed categorical variables as frequencies and percentages, whereas means and standard deviations (SD) were used to present continuous variables. The differences between study groups were performed using a Pearson's Chi-squared test for categorical variables. The differences in continuous variables were assessed using Kruskal–Wallis rank sum test for the comparisons between four acne complication groups (no scarring or PIH, acne scarring only, PIH only, and acne scarring and PIH). We constructed a multivariable, multinomial logistic regression model to assess the independent predictors of the four acne complication groups. Considering no scarring or PIH as a reference category, we selected the independent variables based on the

significantly associated variables in the bivariate analysis, where each variable should have less than 10% missing records. Results of multinomial logistic regression model were expressed as odds ratios (ORs) and the respective 95% confidence intervals (95% CIs). Statistical significance was considered at $p < 0.05$.

Results

Proportions of Acne Complications

In general, 95 participants (22.8%) reported acne scarring, 93 participants had PIH alone (22.3%), and 151 participants had both acne scarring and PIH (36.2%), and only 78 participants did not develop scarring or PIH (18.7%) (Figure 1).

Demographic Characteristics and Comorbidities Based on the Complications of Acne Lesions

Significant associations were observed between gender and the complications of acne lesions (p=0.007). Females exhibited significantly higher proportions of PIH only (90.3%, N=84) and acne scarring and PIH (80.1%, N=121), compared to 71.6% acne scarring only (N=68) and 73.1% without scarring or PIH (N=57) (Table 1).

Acne Characteristics by the Type of Acne Complications

Comedonal acne was significantly more prevalent in the group with no scarring or PIH (45.5%, N=35), while papules acne showed a higher prevalence in individuals with both acne scarring and PIH (94.0%, N=142) compared to the other groups (p=0.045 and p=0.022, respectively). Nodular acne was significantly more prevalent in the acne scarring and PIH group (20.7%, N=31) compared to the other categories (p=0.005). The average duration of acne was significantly different among the groups (p=0.027), with individuals experiencing both acne scarring and PIH having a longer duration (3.77 ± 2.58 years). Acne recurrence showed significant differences (p=0.003), with individuals experiencing both acne scarring and PIH having a higher recurrence rate (58.7%, N=54) (Table 2).

Treatment Regimen Across Acne Complication Categories

Concerning acne complications, there was a significant difference in the use of antibiotics (p=0.032), with a higher proportion of individuals in the acne scarring and PIH group (51.7%, N=78) having received antibiotics compared to other groups. Isotretinoin exhibited a highly significant association (p<0.001), with the PIH only group having the highest proportion (69.5%, N=66) of individuals currently using isotretinoin compared to other groups. Adapalene gel also demonstrated a significant association (p=0.008), with a higher proportion in the no scarring or PIH group (16.9%, N=13) currently using adapalene gel compared to other groups (Table 3).

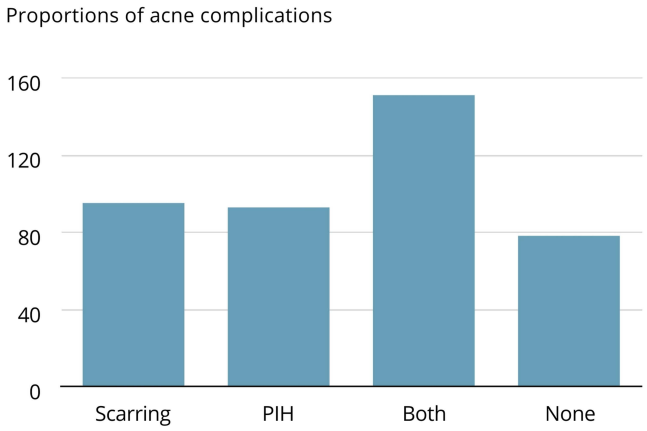

Figure 1 Bar graph showing the proportions of acne complications. The categories include Scarring, Post-inflammatory Hyperpigmentation (PIH), Both, and None. "Both" is the most common, while "None" is the least common".

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Table 1 Demographic Characteristics and Comorbidities Based on the Complications of Acne Lesions

Characteristic	Overall, N=417	No Scarring or PIH N=78	Acne Scarring only N=95	PIH Only N=93	Acne Scarring and PIH N=151	p-Value
Gender						0.007
Male	87 (20.9%)	21 (26.9%)	27 (28.4%)	9 (9.7%)	30 (19.9%)	
Female	330 (79.1%)	57 (73.1%)	68 (71.6%)	84 (90.3%)	121 (80.1%)	
Age	25.58 ± 6.53	24.53 ± 5.99	26.09 ± 6.92	26.04 ± 6.81	25.52 ± 6.38	0.418
Weight	65.34 ± 16.87	65.46 ± 16.66	65.91 ± 19.25	65.28 ± 15.15	64.95 ± 16.54	0.974
BMI	25.31 ± 5.90	25.21 ± 5.83	24.71 ± 4.87	25.95 ± 6.08	25.35 ± 6.42	0.785
Positive Family History of Acne	10 (2.4%)	1 (1.3%)	2 (2.1%)	1 (1.1%)	6 (4.0%)	0.432
PCOS	13 (3.1%)	1 (1.3%)	4 (4.2%)	1 (1.1%)	7 (4.6%)	0.298

Notes: n (%); Mean ± SD. Pearson's Chi-squared test.
Abbreviations: BMI, Body Mass Index; PCOS, Polycystic ovary syndrome.

Table 2 Acne Characteristics by the Type of Acne Complications

Characteristic	Overall, N=417	No Scarring or PIH N=78	Acne Scarring Only N=95	PIH Only N=93	Acne Scarring and PIH N=151	p-Value
Number of Acne						0.093
Single	6 (1.4%)	2 (2.6%)	2 (2.1%)	0 (0.0%)	2 (1.3%)	
Few	105 (25.2%)	16 (20.5%)	23 (24.2%)	34 (37.0%)	32 (21.2%)	
Multiple	305 (73.3%)	60 (76.9%)	70 (73.7%)	58 (63.0%)	117 (77.5%)	
Acne Characteristics						0.407
Inflammatory	145 (35.0%)	29 (38.2%)	31 (33.0%)	38 (40.9%)	47 (31.1%)	
Erythematous	269 (65.0%)	47 (61.8%)	63 (67.0%)	55 (59.1%)	104 (68.9%)	
Acne types						
Comedones	166 (40.1%)	35 (45.5%)	26 (27.7%)	39 (41.9%)	66 (44.0%)	0.045
Papules	369 (88.5%)	63 (80.8%)	82 (86.3%)	82 (88.2%)	142 (94.0%)	0.022
Cyst	23 (5.6%)	7 (9.1%)	7 (7.4%)	1 (1.1%)	8 (5.4%)	0.112
Nodules	64 (15.4%)	9 (11.7%)	19 (20.0%)	5 (5.4%)	31 (20.7%)	0.005
Average duration of acne (years)	3.3 ± 2.4	2.4 ± 2.1	3.1 ± 2.5	3.3 ± 2.3	3.8 ± 2.6	0.027
Acne recurrence	128 (46.7%)	17 (27.9%)	27 (47.4%)	30 (46.9%)	54 (58.7%)	0.003

Notes: n (%); Mean ± SD. Pearson's Chi-squared test; Kruskal–Wallis rank sum test.

Table 3 Treatment Regimen by the Type of Acne Complications

Characteristic	Overall, N=417	No Scarring or PIH N=78	Acne Scarring Only N=95	PIH Only N=93	Acne Scarring and PIH N=151	p-Value
Antibiotics	182 (43.6%)	25 (32.1%)	42 (44.2%)	37 (39.8%)	78 (51.7%)	0.032
Tretinoin	143 (34.4%)	27 (34.6%)	26 (27.4%)	40 (43.0%)	50 (33.3%)	0.157
Azelaic Acid	65 (15.7%)	13 (16.9%)	12 (12.6%)	16 (17.2%)	24 (16.0%)	0.819
Isotretinoin	232 (55.9%)	38 (49.4%)	35 (37.6%)	66 (69.5%)	93 (62.0%)	<0.001
Adapalene gel	43 (10.4%)	13 (16.9%)	5 (5.3%)	15 (16.1%)	10 (6.7%)	0.008
Benzoyl Peroxide	22 (5.3%)	2 (2.6%)	3 (3.2%)	9 (9.7%)	8 (5.3%)	0.136

Note: n (%). Pearson's Chi-squared test.

Laboratory Findings Across Acne Complication Categories

Notably, hemoglobin (Hgb) levels differed significantly among the acne complications groups (p=0.010), with the no scarring or PIH group having a higher mean value (14.84 ± 15.23) compared to acne scarring only (13.43 ± 1.64), PIH

Table 4 Laboratory Data by the Type of Acne Complications

Characteristic	Overall, N=417	No Scarring or PIH N=78	Acne Scarring Only N=95	PIH Only N=93	Acne Scarring and PIH N=151	p-Value
Hgb	13.34 ± 6.78	14.84 ± 15.23	13.43 ± 1.64	12.83 ± 1.48	12.81 ± 1.50	0.010
TSH	2.05 ± 1.74	2.09 ± 2.04	1.99 ± 1.12	2.03 ± 2.03	2.07 ± 1.65	0.594
Free T4	12.99 ± 1.80	13.06 ± 2.21	13.12 ± 1.61	13.05 ± 1.74	12.84 ± 1.74	0.547
LDL	2.80 ± 0.71	2.79 ± 0.80	2.75 ± 0.60	2.81 ± 0.74	2.83 ± 0.72	0.888
HDL	1.34 ± 0.29	1.34 ± 0.27	1.32 ± 0.29	1.38 ± 0.27	1.33 ± 0.30	0.720
Total Cholesterol	4.50 ± 0.80	4.47 ± 0.87	4.48 ± 0.67	4.57 ± 0.83	4.48 ± 0.82	0.856
Triglycerides	0.81 ± 0.38	0.80 ± 0.46	0.83 ± 0.32	0.83 ± 0.36	0.80 ± 0.39	0.394
VIT D 25	41.72 ± 22.47	45.84 ± 20.84	49.77 ± 29.09	38.33 ± 21.34	37.11 ± 17.70	<0.001
Ferritin	39.10 ± 89.42	61.91 ± 174.02	34.02 ± 37.45	36.84 ± 76.11	31.91 ± 41.83	0.133
Zinc	12.95 ± 29.86	9.82 ± 2.53	9.43 ± 1.45	9.54 ± 2.53	18.26 ± 47.88	0.798
Folate	21.07 ± 7.44	25.32 ± 8.58	21.47 ± 6.29	20.59 ± 6.69	18.75 ± 7.39	0.078
VIT B12	260.50 ± 94.68	274.46 ± 105.15	270.59 ± 106.58	246.54 ± 78.70	258.16 ± 93.09	0.660

Note: Mean ± SD. Kruskal–Wallis rank sum test.

only (12.83 ± 1.48), and acne scarring and PIH (12.81 ± 1.50). Finally, vitamin D showed significant differences ($p<0.001$), with higher means among those with no scarring or PIH (45.48 ± 20.84) and acne scarring only (49.77 ± 29.09) compared to PIH only (38.33 ± 21.34) and acne scarring and PIH (37.11 ± 17.70) (Table 4).

Predictors of Acne Scarring and/or PIH

In a multinomial logistic regression analysis assessing predictors of different acne complications, several significant associations were identified, considering no scarring or PIH as a reference category. The application of adapalene gel as a treatment demonstrated a protective effect against acne scarring only (OR = 0.13, 95% CI, 0.02 to 0.67, p = 0.015). Having acne with papules was a significant risk factor for acne scarring and PIH (5.65, 95% CI, 1.83 to 17.5, p = 0.003). The use of isotretinoin was a risk factor identified for PIH only (OR = 0.49, 95% CI, 0.24 to 0.99, p = 0.047). Finally, higher Hgb levels were associated with a decreased risk of acne scarring with PIH (OR = 0.78, 95% CI, 0.66 to 0.93, p = 0.006) (Table 5).

Table 5 Predictors of Acne Scarring and/or PIH Based on a Multinomial Logistic Regression Analysis

Characteristic	Acne Scarring Only			PIH Only			Acne Scarring and PIH		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Acne type (Papules)									
No	Reference	Reference		Reference	Reference		Reference	Reference	
Yes	2.69	0.83, 8.72	0.098	2.51	0.83, 7.64	0.104	5.65	1.83, 17.5	0.003
Acne type (Nodules)									
No	Reference	Reference		Reference	Reference		Reference	Reference	
Yes	1.69	0.61, 4.67	0.311	0.61	0.18, 2.13	0.442	2.31	0.91, 5.90	0.079
Isotretinoin									
No	Reference	Reference		Reference	Reference		Reference	Reference	
Yes	1.91	0.92, 3.98	0.085	0.49	0.24, 0.99	0.047	1.34	0.70, 2.58	0.377
Adapalene gel									
No	Reference	Reference		Reference	Reference		Reference	Reference	
Yes	0.13	0.02, 0.67	0.015	0.71	0.26, 1.90	0.493	0.36	0.13, 1.01	0.053
Lab values (Hgb)	0.98	0.93, 1.03	0.470	0.97	0.90, 1.06	0.546	0.78	0.66, 0.93	0.006

Abbreviations: OR, Odds Ratio; CI, Confidence Interval.

Discussion

Acne vulgaris is one of the most prevalent inflammatory skin conditions. Complications can occur during and after the resolution of acne. These include scarring, post-inflammatory hyperpigmentation (PIH), and erythema. In this study, we aimed to retrospectively investigate the risk factors of acne scarring and hyperpigmentation among Saudi patients. We found significant associations that provide novel insights into the predictors of acne complications, particularly regarding acne scarring and PIH. The most common complications that our participants developed were a combination of both acne scarring and PIH, while most of the remaining developed either scarring or hyperpigmentation alone. It was observed that more females sought treatment for their acne compared to males, which was evident in previous studies as well.[11]

PIH was more common in females. Al-Qarqaz et al reported a similar observation where females were more likely to suffer from PIH.[8] Moreover, acne scarring was considerably more common in male participants. In accordance with our finding, a meta-analysis of 37 studies evaluating the prevalence and risk factors of acne scars showed that male gender was indeed a risk factor for acne scarring.[5]

A significant association between the presence of papules and the development of acne scarring and PIH was found. By focusing on the management of active papules and early effective treatment, clinicians may decrease the risk of developing scarring and hyperpigmentation in patients with acne. Ultimately, this strategy will enhance the aesthetic outcomes and enhance patient satisfaction by reducing the psychological burdens associated with scarring and hyperpigmentation.

Additionally, in our study those with higher rates of recurrence and longer duration of acne were more susceptible to developing acne complications; In contrast, Al-Qarqaz et al denied the correlation between acne duration and PIH.[8]

One of the significant findings of this study is the noteworthy relationship observed between the treatment methods and the occurrence of PIH. However, it is crucial to note that a previous study suggested the opposite and disapproved of the relationship.[12] Specifically, we have found a significant association between isotretinoin and the risk of developing PIH, which may be attributed to the hypersensitivity effect induced by the medication.[13] Therefore, this hypersensitivity response highlights the importance of careful consideration in treatment approaches that include isotretinoin.

Similar to our findings, a case report has emphasized on the importance of considering isotretinoin as a possible underlying cause of inducing hyperpigmentation.[14] In contrast, another report demonstrated a great improvement in PIH in a patient treated with isotretinoin.[15] The relationship between isotretinoin and PIH is not well-understood and further research is needed to investigate the risk of developing PIH after isotretinoin use. Conversely, our analysis suggests that adapalene gel is a protective factor against acne scarring. A study has found that the daily application of adapalene 0.3% gel as a treatment for atrophic acne scars proved positive clinical effectiveness.[16] Another trial that combined Adapalene gel 0.1% with benzoyl peroxide 2.5% showed a similar result.[17] Indeed, it is well-recognized that untreated acneiform lesions can lead to the progression of scarring.[18]

The link between abnormal laboratory results and acne complications was not adequately assessed in the literature. However, we found an association between higher hemoglobin levels and decreased risk of scarring and PIH. This finding highlights the importance of monitoring hemoglobin levels in individuals with acne vulgaris to prevent the occurrence of scarring and PIH related to low levels of hemoglobin. This emphasizes the need in clinical practice for the adaptation of treatment strategies for acne vulgaris patients by assessing their hemoglobin levels before the initiation of therapy and treating the underlying cause of low hemoglobin.

In our cohort, lower means of vitamin D contributed to hyperpigmentation. According to a literature review, lower vitamin D levels correlate with an increased risk of scarring and severity.[19]

In addition, vitamin D is useful in acne management, is comedolytic and antioxidant, and increases the expression of anti-microbial peptides.[20,21] Recent studies also showed that vitamin D deficiency is associated with a higher risk for acne development, and acne severity, yet acne complications were not evaluated.[22,23]

The findings of this research showed numerous notable attributes, rendering it instrumental in elucidating the underlying determinants contributing to the development of acne scarring and PIH during or after the therapeutic interventions. Also, it holds significant potential for increasing our understanding of preventive measures, early detection

strategies, and therapeutic options, therefore, paving the way for more sophisticated diagnostic modalities and treatment methodologies in this medical field.

Limitations

The study has several limitations. First, patients' medical records were obtained from a single dermatology center in Jeddah, Saudi Arabia, which restricts the generalizability of the findings to the broader population. Additionally, the sample size was relatively small, particularly the number of male participants. Some patients were also excluded due to incomplete data or loss to follow-up. Furthermore, because of the retrospective design and the limited data available in the hospital information system, we were unable to assess the relationship between smoking, skin color, family history, and acne complications. Lastly, there was a lack of consensus among the dermatologists and dermatology residents in our institution concerning the classification of acne severity and scarring subtypes as there is no valid scoring system. To address these limitations, a prospective, multi-center cohort study is recommended to better understand the predictive factors for acne scarring and hyperpigmentation.

Conclusion

In general, complications arising from acne, including scarring and hyperpigmentation can develop during or after its resolution. Identifying risk factors for acne complications promptly allows for prevention and management before they arise. Our results provide valuable insights for refining interventions and broadening our understanding of acne vulgaris-related complications in future research.

Disclosure

The authors report no conflicts of interest in this work.

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