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ORIGINAL ARTICLE

The Potential Role of Survivin in the Pathogenesis and Severity of Acne and Post Acne Scars

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ABSTRACT:

Background: Survivin's role in acne vulgaris pathogenesis is implicated, particularly in the fibrogenesis underlying acne scarring. This work aimed to compare the level of serum survivin among acne vulgaris patients versus healthy control subjects and to find out any possible correlation between the serum level of survivin, and the severity of acne vulgaris.

Methods: There were 42 patients in this case control study and 21 healthy controls, all of similar age and gender. There were 21 patients in the acne group who reported acne vulgaris, and 21 patients in the scar group who reported acne scars. Mild, moderate, and severe acne were the three subgroups established by the global acne grading system (GAGS). Using an enzyme-linked immunosorbent assay, the serum levels of survivin were measured in all three groups.

Results: The levels of serum survivin among cases with active acne were significantly higher when compared to the control group (P=0.02). On conducting ROC curve analysis on serum survivin for discriminating between acne and non-acne patients, at cut off point of 5.3, it showed sensitivity (76.19%), specificity (57.14%) and area under curve (AUC) (0.676). Serum survivin was able to discriminate between patients with active acne from patients with acne scar only, with cut off point of 6, it showed sensitivity (76.19%), specificity (42.86%) and AUC (0.594).

Conclusion: This study revealed significantly elevated serum survivin levels among cases with acne vulgaris compared to the healthy controls. These findings support a role for survivin in acne pathogenesis and, more significantly, in the development of post-inflammatory fibrotic scarring.

Keywords: Survivin; Pathogenesis ;Severity ; Post-Acne Scars.

INTRODUCTION

The face, chest, and back are the most common areas affected by acne vulgaris (AV), a chronic inflammatory dermatosis that affects people of all ages, races, and sexes. AV is defined by open, closed comedones as well as inflammatory lesions like pustules, papules, and nodules.[1].

Comedones (including microcomedones), representing primary acne lesions, form through cystic dilation within the pilosebaceous unit (PSU) infundibulum. The majority of inflammatory lesions (papules, pustules, nodules, cysts) arise from these comedones. Acne pathogenesis is multifactorial, involving hyperseborrhea, altered sebum composition, follicular hyperkeratinization, microbial dysbiosis, and inflammatory/immune responses [2].

Acne vulgaris is a globally prevalent inflammatory dermatosis affecting all populations, with peak incidence during adolescence. The significant

clinical and psychosocial burden stems from its visible impact, including scarring and dyspigmentation, which often leads to considerable psychological distress and social impairment [3].

Initially identified as an inhibitor of apoptosis protein (IAP), survivin plays a crucial role in apoptosis regulation. Further research has established its function as a component of the chromosomal passenger complex, essential for mitotic progression [4].

Survivin is implicated in the pathogenesis of acne vulgaris, particularly in the fibrogenesis of acne scarring. Increased survivin expression, correlated with keratinocyte proliferation and inflammation, contributes to acne lesion development [5].

There is a shortage of research that examines the correlation between serum survivin and active acne or post-acne scar. The previous research demonstrated that patients with active acne or post-acne scar had significantly higher serum survivin levels compared to those of age and gender matched control group [5]. So, this study aimed to compare the level of serum survivin among acne vulgaris patients versus healthy control subjects and to find out any possible correlation between the serum level of survivin, and the severity of acne vulgaris.

METHODS

This case-control study (42 patients, 21 age- and sex-matched healthy controls) enrolled participants from the Zagazig University Hospitals Dermatology, Venereology, and Andrology Department outpatient clinic (June 2023-June 2024). The research ethics committee at Zagazig University's Faculty of Medicine gave their stamp of approval after all subjects gave written informed permission. The research followed the guidelines laid down in the Declaration of Helsinki, which is part of the World Medical Association's Code of Ethics for Human Subjects. The Institutional Review Board gave its approval before this study could begin (ZU-IRB#10760-7/5-2023).

Patients

Patients were categorized into three groups: Group I (n=21) comprised patients with acne vulgaris, further stratified into mild, moderate, and severe subgroups using the Global Acne Grading System; Group II (n=21) included patients with acne scarring; and Group III (n=21) consisted of age- and gender-matched healthy controls.

Participants who were aged more than 12 years from both sexes, with mild, moderate, severe acne and post-acne scars cases, Patients with acne scars only were included in group II. Control group (healthy group) had no history of acne or post-acne scars.

Cases with the following characteristics were excluded: Patients who aged less than 12 years, who had autoimmune diseases, patients with inflammatory skin diseases such as psoriasis, individuals who have taken oral isotretinoin during the past six months or who have seen a dermatologist for acne within the past three months. Women who were pregnant or breastfeeding.

A comprehensive assessment was performed on all patients, including a detailed history (onset, duration, course of acne vulgaris, systemic/dermatological history, medications), general physical examination to rule out comorbidities, and dermatological examination to characterize acne lesions (skin type, location, scar type: ice pick, boxcar, rolling). This examination was repeated at each follow-up visit.

The severity of the disease was assed using Global Acne Grading system (GAGS): we used GAGS modification to evaluate the severity of acne. A size-based component was assigned to each of the six parts of the face, chest, and back: forehead, cheeks (bilateral), nose, chin, chest, and upper back.. Lesions were graded (0-4: none, comedones, papules, pustules, nodules respectively). A local score (Factor x Grade) was calculated for each area, and 1–18 indicates mild, 19–30 indicates moderate, 31–38 indicates severe, and >39 indicates very severe based on the global score, which is the sum of the local ratings. [6].

Dermatological examination of post-inflammatory acne scars included an assessment of lesion type and severity. Severity was categorized as follows: mild scarring was defined as mild atrophy or hypertrophy, not readily apparent at a social distance of 50 centimeters or greater and easily concealed with makeup; moderate scarring was characterized by moderate atrophic or hypertrophic scarring, visible at a social distance of 50 centimeters or greater and not easily concealed with makeup; and severe scarring was defined as significant atrophic or hypertrophic scarring, clearly visible at a social distance greater than 50 centimeters and not easily concealed with makeup.

Laboratory investigations involved detection of the survivin level in serum using ELISA: A commercially available enzyme-linked immunosorbent assay (ELISA) kit was utilized for serum survivin quantification. The assay employed a pre-coated microplate with anti-human survivin antibodies. Following the addition of samples, biotinylated anti-human survivin antibodies were

introduced to bind to captured survivin. Next, a biotinylated antibody was bound with a streptavidin-horseradish peroxidase (HRP) conjugate. After washing to remove any unbound conjugate, a substrate solution was added to generate a colorimetric signal that was proportional to the survivin concentration. An acidic solution was used to stop the reaction, and absorbance was measured at 450 nm.

Statistical analysis

A Windows version of IBM SPSS Statistics 23.0 (SPSS Inc., Chicago, IL, USA) was used for data entry, validation, and analysis. Number and percentage were used to represent the qualitative data, whereas mean, median ± SD, and range were used for the quantitative data. We employed Fisher's exact and Chi-square tests to identify correlations among the qualitative variables. Researchers utilize the Mann-Whitney U test and the independent t-test to determine the association between two sets of quantitative variables. To gain a better understanding of the relationship between several sets of quantitative variables, we employed the Kruskal-Wallis test or analysis of variance (ANOVA). The sensitivity and specificity of the quantitative diagnostic measure in distinguishing between the two groups were evaluated through the use of receiver operating characteristic (ROC) curve analysis. If the p-value was less than or equal to 0.05, we considered it statistically significant. If it was larger than 0.05, we considered it non-significant.

RESULTS

Table (1) showed non statistically significant differences ($p > 0.05$) between the studied groups regarding age, sex, comorbidities, medical history, and smoking status. However, a significant difference in employment status was observed ($p = 0.02$), The active acne group had a greater percentage of employed individuals (95.2%) than the acne scar group (76.2%).

The disease duration was shown to differ significantly ($p<0.001$) between the groups in Table (2), with the active acne group having a higher median duration. There was no discernible variation in the severity of acne ($p>0.05$).

Table (3) showed that serum survivin levels differed significantly ($p=0.02$) across the study groups, with significantly higher levels found in patients with active acne than in the control group.

On conducting ROC curve analysis on serum survivin for discriminating between acne and non-acne patients, at cut off point of 5.3, it showed sensitivity (76.19%), specificity (57.14%) and AUC (0.676) (Table 4, Figure 1).

On conducting ROC curve analysis on serum survivin for discriminating between patients with active acne from patients with acne scar only, at cut off point of 6, it shows sensitivity (76.19%), specificity (42.86%) and AUC (0.594) (Table 5, Figure 2).

Table 1: Demographic data, and Past history among the studied groups

Variables	Acne group (n=21)	Acne scar (n=21)	Control (n=21)	P value
Age *(years)* ***Mean ± SD*** ***Range***	20.2 ± 2.1 (17 – 26)	22 ± 4.28 (17 – 33)	23.5 ± 5.63 (17 – 38)	0.16[1]
Sex *(N. %)* **Male** **Female**	 11 (52.4%) 10 (47.6%)	 9 (42.9%) 12 (57.1%)	 8 (38.1%) 13 (61.9%)	0.64[2]
Occupation *(N. %)* **Unemployed** **Employed**	 1 (4.8%) 20 (95.2%)	 5 (23.8%) 16 (76.2%)	 9 (42.9%) 12 (57.1%)	0.02[3]
Smoking status *(N. %)* **Non-smoker** **Smoker**	 21 (100%) 0 (0%)	 20 (95.2%) 1 (4.8%)	 21 (100%) 0 (0%)	1.00[3]

Variables	Acne group (n=21)	Acne scar (n=21)	Control (n=21)	P value
Comorbidities				1.00[1]
Absent	21 (100%)	20 (95.2%)	21 (100%)	
Present	0 (0%)	1 (4.8%)	0 (0%)	
Dermatological disease				1.00[1]
Absent	21 (100%)	20 (95.2%)	21 (100%)	
Present	0 (0%)	1 (4.8%)	0 (0%)	
Drug history				1.00[1]
Absent	21 (100%)	20 (95.2%)	21 (100%)	
Present	0 (0%)	1 (4.8%)	0 (0%)	
Conception history				0.77[1]
Absent	20 (95.2%)	19 (90.5%)	21 (100%)	
Present	1 (4.8%)	2 (9.5%)	0 (0%)	

*[1]Kruskal-Wallis test, [2]Chi-square test, [3]Fisher exact test, Non-significant: P >0.05, Significant: P ≤0.05

Table 2: Disease duration and Degree of Acne among the studied groups

Variables	Acne group (n=21)	Acne scar (n=21)	P value
Disease duration (years)			
Median (IQR)	0.7 (0.6)	2 (1)	<0.001[1]
Range	(0.08 – 3)	(1 – 5)	
Degree of acne *(N. %)*			0.75[2]
Mild	14 (66.7%)	12 (57.1%)	
Moderate	7 (33.3%)	8 (38.1%)	
Severe	0 (0%)	1 (4.8%)	

*[1]Mann-Whitney U test, Non-significant: P >0.05, Significant: P ≤0.05

Table 3: Serum survivin levels among the studied groups

Variables	Acne group (n=21)	Acne scar (n=21)	Control (n=21)	P value
Survivin				P1=0.55
Mean±SD	8.44 ± 5.87	8.22 ± 9.63	5.6 ± 1.94	P2=0.02
Range	(4.4 – 32.2)	(3.4 – 49.5)	(2.7 – 11.3)	P3=0.47

*[1]Kruscal-Wallis test, Non-significant: P >0.05, Significant: P ≤0.05
*P1=comparison between Acne group and Acne scar group
*P2=comparison between Acne group and Control group
*P3=comparison between Acne scar group and control group

Table 4: ROC curve analysis of serum survivin \ to differentiate acne from non-acne patients

Variables	Cut-point	Sensitivity (%)	Specificity (%)	PPV (%)	NPP (%)	AUC (%)
Survivin	5.3	76.19%	57.14%	78.05%	54.55%	0.676

Table 5: ROC curve analysis of serum survivin and IGF-1 to differentiate patients with active acne from acne scar patients

Variables	Cut-point	Sensitivity (%)	Specificity (%)	PPV (%)	NPP (%)	AUC (%)
Survivin	6	76.19%	42.86%	57.14%	64.29%	0.594

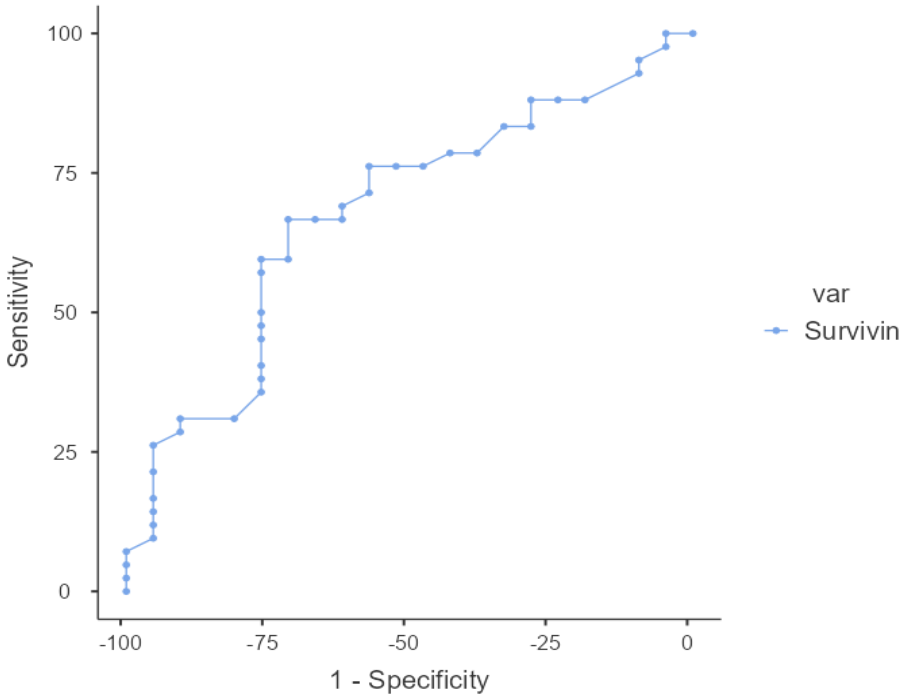

Figure 1: ROC curve analysis of serum survivin in differentiating acne from non-acne patients

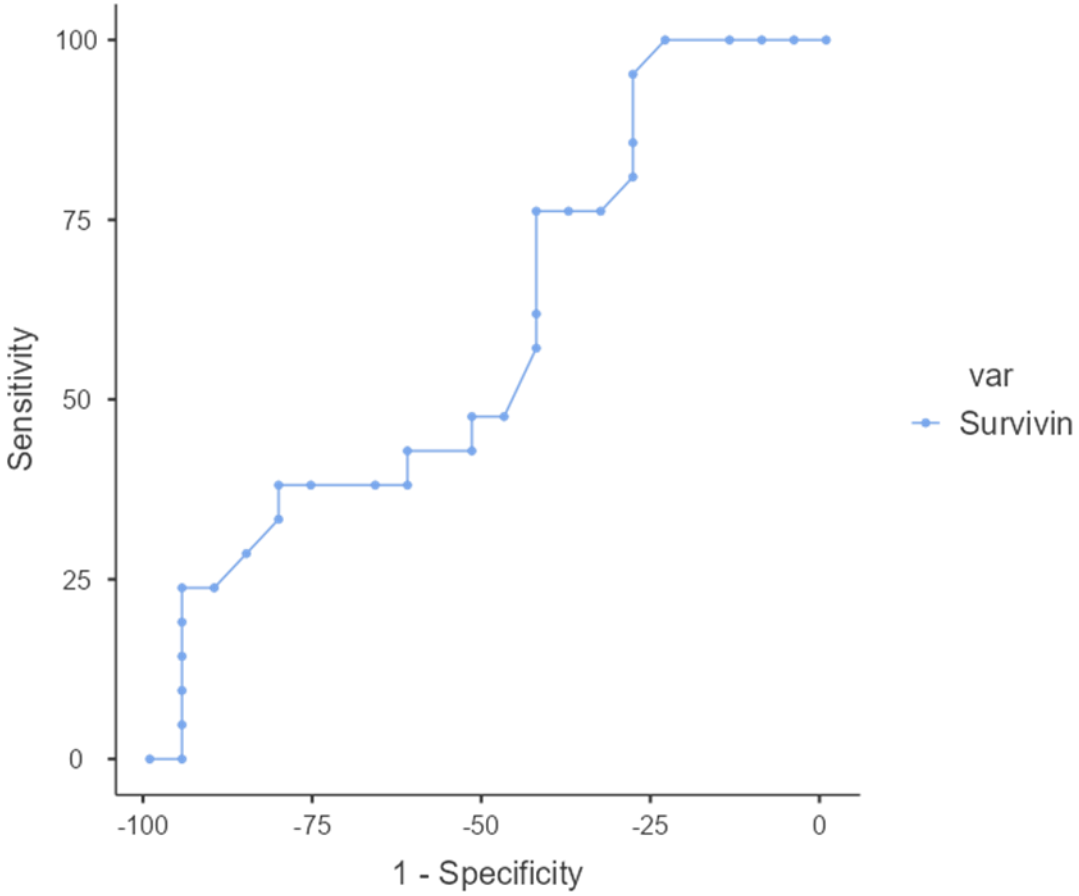

Figure 2 : ROC curve analysis of serum survivin in differentiating patients with active acne from acne scar patients

DISCUSSION

The pathophysiology of acne vulgaris is multifactorial, encompassing a complex interaction of variables such as sebum overproduction, abnormal follicular keratinization, and androgen levels. It is now widely recognized that inflammation plays an important role in all manifestations of acne vulgaris [7].

Acne vulgaris is caused by a variety of variables, including genetics, food, hormones, stress, and environment. According to its intensity, acne may be split into three groups: mild, moderate, and severe. Pustules, papules, nodules, as well as cysts are examples of classifications for both inflammatory and non-inflammatory disorders [8].

Survivin, an inhibitor of apoptosis protein, is encoded by the BIRC5 gene on chromosome 17q25. It is highly expressed in the majority of human malignancies but is scarcely detectable in normal adult tissues such as skin. Overexpression of survivin in tumors is usually linked to a poor prognosis because it inhibits cell death [9,10]. Apoptosis dysregulation and increased sebocyte survival, possibly mediated by survivin, may lead to changes in infundibular keratinocyte differentiation and sebum production, which in turn promotes the development of comedones and acne [11].

Survivin's involvement in the pathogenesis of acne vulgaris, particularly in the development of post-inflammatory scarring, is suggested. This might be associated with the fact that there is a positive correlation between survivin levels in the blood and the PI3K/AKT pathway, which in turn leads to an increase in survivin expression by downregulating nuclear FoxO transcription factors [11].

The present study population comprised three groups: an acne group (mean age 20.2 ± 2.1 years; 52.4% male), an acne scar group (mean age 22 ± 4.28 years; 42.9% male), and a control group (mean age 23.5 ± 5.63 years; 38.1% male). Age, sex, and smoking status were not significantly different between groups. But employment status was different (p=0.02), with a higher percentage of employed individuals in the active acne group (95.2% vs. 76.2% in the acne scar group).

Hussein et al. [12] also studied serum survivin levels in patients with acne and scarring after acne, therefore these results are consistent with their findings. Their study, involved 40 acne patients (20 with active acne, 20 with post-acne scarring) and 20 controls, found non statistically significant differences as regards age and sex across the three groups.

Additionally, our findings are in line with those of El Mokadem et al. [13], who measured survivin levels in acne vulgaris patients and found a correlation between these levels and the severity of the acne and the presence of acne scars. Thirty cases with active acne (average age: 21.53 ± 2.57 years) made up group I in their study, which included 80 participants. Group II included ten cases with acne scars (average age: 23.00 ± 3.43 years), and group III had forty controls (average age: 23.35 ± 3.85 years). When looking at the distribution of age and sex among the three groups, they could not find anything statistically significant.

These findings are consistent with those of El-Sohafy et al. [5], who conducted a comparable study on survivin gene polymorphism and plasma levels in patients presenting with active acne vulgaris and varying degrees of post-acne scarring. Their study, encompassing 60 acne patients (30 with active acne, 30 with post-acne scars) and 30 healthy controls, demonstrated no statistically significant inter-group differences in gender, age, or smoking history.

This study found no statistically significant differences between groups regarding comorbidities, dermatological history, medication use, or contraceptive history. Furthermore, these findings concur with El Mokadem et al. [13], who also reported no statistically significant differences in prior treatment among their study groups.

Results showed that the acne scar group had a considerably longer median illness duration than the acne group, according to the present study, while acne severity did not differ significantly between the groups. This aligns with El-Sohafy et al. [5], but contrasts with El-Tahlawi et al. [14], who found no significant difference in disease duration or severity between acne and post-acne scar groups in their study of 60 participants.

In contrast to El Mokadem et al. [13], who failed to find a statistically significant difference in disease duration between the groups with acne and those with acne scars, this study showed that patients with active acne had significantly higher serum survivin levels than the control group (p=0.02). These results are consistent with those of Hussein et al. [12], who also found that the control group had significantly lower survivin levels (p<0.001) and that the active acne group had significantly higher levels (p=0.008). Moreover, Hussein et al. [12] also found that the control group had significantly lower survivin levels than the active acne group (p<0.001).

In line with previous research, this study's findings show that survivin levels were significantly higher in

the scar group compared to the active acne and control groups ($p<0.001$), and in the active acne group compared to the control group ($p<0.001$). Similarly, Assaf et al. [15] also found that groups with active acne ($p<0.05$) and acne scar ($p<0.001$) had significantly higher serum survivin levels than the control group, with the acne scar group having significantly higher levels than the active acne group ($p<0.01$).

El-Sohafy et al. [5] found similarly elevated serum survivin levels in the acne and acne scar groups compared to controls, and the results are consistent with those of Aksoy et al. [16], who found similarly elevated serum survivin levels in the acne vulgaris group compared to the control group ($p<0.018$).

On conducting ROC curve analysis on serum survivin for discriminating between acne and non-acne patients, at cut off point of 5.3, it showed sensitivity (76.19%), specificity (57.14%) and AUC (0.676). On conducting ROC curve analysis on serum survivin for discriminating between patients with active acne from patients with acne scar only, at cut off point of 6, it shows sensitivity (76.19%), specificity (42.86%) and AUC (0.594)

These results are in line with those of Assaf et al. [15], who used Western blotting to determine that the acne scar group had more survivin expression than the active acne and control groups.

This study's limitations include a relatively small sample size (n=63), potentially affecting the generalizability of the results, and a single-center design, which may have introduced selection bias. Furthermore, the limited number of prior studies investigating survivin levels in acne and post-acne scarring restricted the scope of comparative analysis. Larger, more diverse studies with longer follow-up periods are warranted to validate and extend these findings.

Conclusions

This study revealed significantly elevated serum survivin levels in patients with acne vulgaris compared to healthy controls. These findings support a role for survivin in acne pathogenesis and, more significantly, in the development of post-inflammatory fibrotic scarring.

Conflict of interest statement: The authors declared that there were NO conflicts of Interest.

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