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Serum Level of Survivin in Patients with Psoriasis Vulgaris and Its Relation to Disease Severity

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ABSTRACT

Background: The World Health Organization has identified psoriasis as a serious global health issue. Psoriasis is a persistent, autoimmune skin condition. Survivin is a member of the inhibitor of apoptosis family (IAP) family of molecules that has significant effects on cell survival and proliferation. Survivin, unlike other IAP members, is seldom expressed in healthy adult tissues but is abundantly expressed in the majority of neoplasms. Fetal tissues also have a high level of expression.

Objective: The aim of the current study is to estimate serum level of survivin in psoriatic patients and searching for correlation between its level and disease severity.

Subjects and Methods: This is a case control study was carried out on 45 patients with psoriasis & 45 matched healthy controls. All participants were recruited from those attending the outpatient clinic of Dermatology, Andrology & STDs Department, Mansoura University Hospitals, Mansoura, Egypt.

Results: Non statistically significant difference was found between studied groups as regard occupation, marital status and smoking history. Among all studied cases, 75.6% have gradual disease onset, 40% progressive, median disease duration is 8 years ranging from 1 to 40 years and 13.3% positive family history, 15.6% positive systemic diseases, 15.6% surgical operation, 71.1% have psychological stress, 4.4% positive drug history, 100% topical therapy, 4.4% previous systemic therapy and 26.7% positive previous phototherapy, 100% Skin affection, Presence of trauma, positive Grattage test, 62.2% hair affection and 46.7% nail affection.

Conclusion: Patients with psoriasis have higher levels of survivin. Survivin did not correlate with severity of psoriasis (PASI). Higher survivin could predict psoriasis susceptibility, but not severity of psoriasis.

Keywords: Psoriasis, Serum level of survivin, Inhibitor of apoptosis family.

INTRODUCTION

The World Health Organization has identified the persistent, autoimmune skin condition psoriasis as a significant global health issue [(1)]. An estimated 2-4% of people worldwide are affected [(2)]. Males are twice as likely to be afflicted as females [(3)].

The immune system, psoriasis-associated susceptibility loci, autoantigens, and several environmental variables interact in a complicated way to induce psoriasis [(4)]. Psoriasis has evolved from a purely cutaneous condition to one of the systemic immune-mediated inflammatory disorders, including type 2 diabetes, rheumatoid arthritis, and inflammatory bowel disease [(5)].

Psoriasis causes severe physical and psychological suffering and impairment that often has a negative effect on the quality of life of the patient [(6)].

Psoriasis with abnormalities in the dermal capillary vasculature, a considerable increase in keratinocyte proliferation, and the presence of dermal and epidermal T lymphocytes, monocytes, macrophages, and neutrophils with an uncertain cause is known as psoriasis [(7)].

Numerous immune mediators have been characterised as being increased in the sick skin of these individuals because cytokines play a significant role in the formation and maintenance of psoriatic lesions [(8)].

Additionally, it has been proposed that some pathogenesis may possibly result from deficiencies in apoptosis inhibition brought on by the hyperproliferative state found in psoriasis. Studies have revealed that keratinocytes in psoriatic tissue exhibit high levels of proliferation and are resistant to apoptosis [(9)]. Thus, keratinocyte survival, tissue inflammation, and blood vessel maintenance are associated with activation of cell survival pathways and repression of apoptosis. Survivin promotes the growth of inflammatory cells and is connected to tissue inflammation [(10)].

Survivin is a member of the IAP family of molecules that has significant effects on cell survival and proliferation [(11)].

Survivin is more often expressed in neoplasms than in healthy adult tissues, in contrast to other IAP members [(12)]. Fetal tissues also have a high level of expression [(13)].Increased levels of survivin have been shown in studies to successfully prevent apoptosis[(14)]. Additionally, excessive survivin expression blocks both intrinsic and extrinsic apoptotic pathways[(15)].

It also has an impact on immune system cells, such as T-cell activation, maturation, and dendritic cell activation, in addition to controlling cell division and inhibiting apoptosis [(16)]. With all of its well-known side effects, survival may contribute to the alterations in psoriasis.

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In this study, our aim was to estimate serum level of survivin in patients with psorasis vulgaris.

SUBJECTS AND METHODS

This is a case control study was carried out on 45 patients with psoriasis and 45 matched healthy controls. All participants were recruited from those attending the outpatient clinic of Dermatology, Andrology & STDs Department, Mansoura University Hospitals, Mansoura, Egypt.

Inclusion criteria

- Chronic plaque psoriasis clinical diagnosis (i.e. lasting at least 3 months).
- If they were above 18, recruiters sought out cases and controls.

Exclusion criteria

- Patients who are suffering from another inflammatory dermatological disease or systemic inflammatory disease.
- Patients receiving systemic treatment for psoriasis or phototherapy within two months before enrolling to the study.
- Patients with known malignancy, systemic diseases especially autoimmune disease, chronic renal disease, liver disease, or acute / chronic infection.
- Pregnancy and lactation.

METHODS

1. **All psoriasis patients were subjected to:**
   - **a.** A thorough medical history that includes any systemic disorders, psoriasis in the family history, the length of the condition, any associated arthritis, and nail involvement.
   - **b.** Complete general examination, including; weight, height, body mass index (BMI), any sign of systemic disease, immune disease and inflammatory disease.
   - **c.** A thorough dermatological examination of the skin, hair, nails, oral cavity, and vaginal mucosa to rule out any underlying diseases.
   - **d. Psoriasis Area and Severity Index (PASI) score:**
     Additionally, the patients that were included were divided into three categories based on their PASI scores: mild psoriasis (PASI $\leq$ 10), moderate psoriasis (PASI >10 - <20), and severe psoriasis (PASI $\geq$20). A single score on the PASI scale, which ranges from 0 (no illness) to 72 (maximal disease), combines the evaluation of the area affected and the severity of lesions [(17)].
2. All members of the study were subjected to measurement of serum level of survivin. It was measured using enzyme-linked immunosorbent assay [ELISA: Human surviving (Surv) ELISA Kit Catalogue No. 201-12-8108, China].

Ethical consent:

This study was approved by the Institutional Review Board (IRB) of the Mansoura Faculty of Medicine (MS.22.02.1886). Before enrolling patients in the trial, an informed consent was obtained from them. The privacy of the data was protected with the utmost care. All information was utilised solely for research. The worldwide medical association's code of ethics, the Declaration of Helsinki for Humans, was adhered to throughout the course of this study.

Statistical analysis

Data input, processing, and statistical analysis were performed, using IBM SPSS Corp.'s 2013.. Version 22.0 of IBM SPSS for Windows. IBM Corp., Armonk, New York. Number and percentage were used to describe qualitative data. After confirming normality with the Kolmogrov-Smirnov test, quantitative data were presented using the median (minimum and maximum), mean, and standard deviation for parametric data. Monte Carlo, Chi-Square, and Fischer exact tests were used to compare two or more groups. Two independent groups were compared using a student t-test. Two independent groups were compared using the Mann-Whitney U test.

The strength and direction of a linear link between two ordinal or continuously distributed non-normally is assessed using Spearman's rank-order correlation. Receiver Operating Characteristic (ROC) curve analysis was used to assess a test's diagnostic performance, or its ability to distinguish between instances of disease and cases without disease. Cross-tabulation calculations were used to determine accuracy, PPV, and NPV once sensitivity and specificity were identified from the curve. P value less than 0.05 was regarded as significant.

RESULTS

The present study is case control study that was carried out on 45 matched cases and control groups to estimate the serum level of survivin in psoriatic patients and searching for correlation between its level and disease severity. Table (1) illustrates non statistically significant difference between studied groups as regard age, sex, occupation, marital status and smoking history. Mean age was 44.49 years for cases versus 44.22 years for control group. Of the studied cases ; 53.3% were females, 44.4% housewives,44.4% manual workers, 11.1% employee, 88.9% married and 70.5% non-smokers versus 42.2% were females, 37.8% housewives,44.4% manual workers, 17.8% employee, 82.2% married and 57.8% non-smokers. Also, a statistically significant higher median survivin among cases than control group (123.5 versus 80, respectively).

Table (1): Comparison of sociodemographic characteristics and survivin between studied groups

	Cases group (N=45)	Control group (N=45)	Test of significance
Age/years **Mean±SD**	44.49± 11.74	44.22± 11.61	t=0.108 P=0.914
Sex N(%) **Male** **Female**	 21(46.7) 24(53.3)	 26(57.8) 19(42.2)	 X^2=1.11 P=0.291
Occupation N(%) **Housewife** **Manual worker** **Employee**	 20(44.4) 20(44.4) 5(11.1)	 17(37.8) 20(44.4) 8(17.8)	 X^2=0.936 P=0.626
Marital status N(%) **Single** **Married**	 5(11.1) 40(88.9)	 8(17.8) 37(82.2)	 X^2=0.809 P=0.368
Smoker N(%) **Non-smoker** **Smoker**	 31(70.5) 13(29.5)	 26(57.8) 19(42.2)	 X^2=1.55 P=0.213
Survivin **Median (range)**	123.5 (78.4-170.8)	80 (52.3-103)	Z=7.53 P<0.001*

Median (range): Non-parametric test.

Table (2) illustrates that 75.6% have gradual disease onset, 40% progressive, median disease duration is 8 years ranging from 1 to 40 years and 13.3% positive family history. Also, shows that 15.6% positive systemic diseases, 15.6%surgical operation, 71.1%have psychological stress, 4.4% positive drug history, 100% topical therapy, 4.4% previous systemic therapy and 26.7% positive previous phototherapy. And demonstrates that 100% skin affection, presence of trauma, Grattage test, 62.2% hair affection and 46.7% nail affection.

Table (2): Disease characters, medical history distribution and local examination results among studied cases

	Disease characters	N =45	%
Onset	Acute Gradual	11 34	24.4 75.6
Course	Intermittent Progressive	27 18	0.0 40.0
	Disease duration (years), Median (min-max)	8(1-40)	
Family history	-ve +ve	39 6	86.7 13.3
	Medical history distribution		
Systemic disease	-ve +ve	38 7	84.4 15.6
Surgical operation	-ve +ve	38 7	84.4 15.6
Psychological stress	-Ve +ve	13 32	28.9 71.1
Drug history	-ve +ve	43 2	95.6 4.4
	Topical therapy	45	100.0
Previous systemic therapy	-ve +ve	43 2	95.6 4.4
Previous phototherapy	-ve +ve	33 12	73.3 26.7
	Local examination	N=45	%
	Skin affection Presence of trauma Grattage test Hair affection Nail affection	45 45 45 28 21	100 100 100.0 62.2 46.7

Table (3) shows that median PASI score is 8 ranging from 1.2 to 18.6.

Table (3): PASI score distribution among studied cases.

	Median (range)
PASI score	8.0(1.2-18.6)

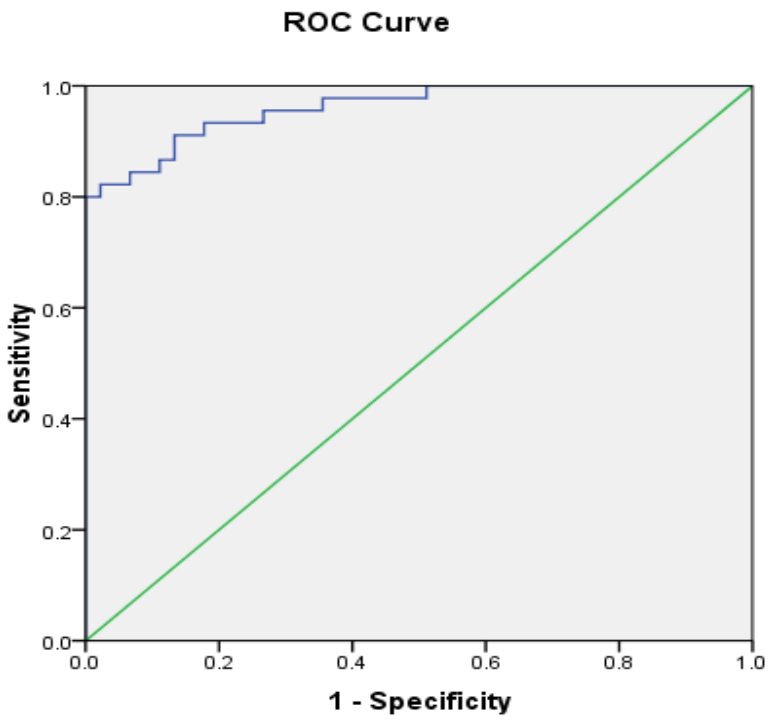

Figure (1): ROC curve showing validity of survivin in differentiating cases from control group

Table (4) shows that area under curve of survivin in differentiating cases from control group is excellent (AUC=0.960) with the best detected cut off point is 99.7 yielding sensitivity 84.4%, specificity 93.3%, positive predictive value and negative predictive values are 92.7% & 85.7%, respectively and total accuracy 88.9%.

Table (4): Validity of survivin in differentiating cases from control group.

	AUC (95% CI)	P value	Cut off point	Sensitivity %	Specificity%	PPV%	NPV%	Accuracy %
Survivin	0.960 (0.926-0.995)	<0.001*	99.7	84.4	93.3	92.7	85.7	88.9

AUC: Area Under curve, PPV: Positive predictive value, NPV: Negative predictive value

Table (5) illustrates non-statistically significant correlation between surviving and age, duration and PASI score among studied cases (p>0.05).

Table (5): Correlation between survivin and age, duration and PASI score among studied cases.

		Survivin
Age/years	R	0.016
	P	0.882
Duration /years	R	-0.115
	P	0.452
PASI	R	0.043
	P	0.778

r: Spearman correlation co-efficient, *statistically significant

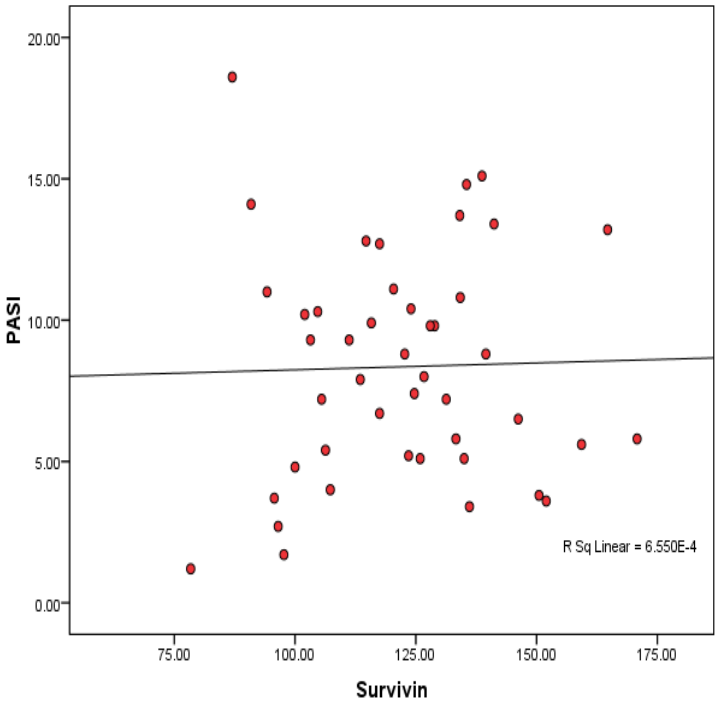

Figure (2): Scatter diagram showing correlation between Survivin and PASI score among studied cases

Table (6) illustrates non statistically significant relation between survivin and disease characters including onset and disease duration and between surviving & family history

Table (6): Relation between Survivin and disease characters among studied cases.

	Survivin, Median (range)	Test of significance
Onset Acute Chronic	126.7(90.9-159.3) 118.95(78.4-170.8)	z=0.475 P=0.634
Course Intermittent Progressive	124.7(78.4-164.7) 123.1(90.9-170.8)	Z=0.162 P=0.871
Family history -ve +ve	123.50(78.4-170.8) 125.85(96.5-150.5)	Z=0.384 P=0.701

Median (range): Non-parametric test.
Z:Mann Whitney U test

Table (7) demonstrates that there is no statistically significant relation between survivin and history of systemic disease, surgical operation, psychological stress, drug history, previous systemic therapy and previous phototherapy (p>0.05).

Table (7): Relation between surviving and present history among studied cases.

	Survivin -Median (range)	Test of significance
Systemic disease -ve +ve	121.55(78.4-170.8) 131.3(94.2-159.3)	Z=1.0 P=0.316
Surgical operation -ve +ve	123.1(78.4-170.8) 124.7(106.3-152)	Z=0.673 P=0.501
Psychological stress -Ve +ve	124.7(78.4-170.8) 121.55 (87.0-152.0)	Z=0.639 P=0.523
Drug history -ve +ve	122.7(78.4-170.8) 138.75(131.3-146.2)	Z=1.32 P=0.186
Previous systemic therapy -ve +ve	124.0(78.4-170.8) 119.1(114.7-123.5)	Z=0.33 P=0.741
Previous phototherapy -ve +ve	124.0(78.4-170.8) 123.1(105.5-164.7)	Z=0.757 P=0.449

Median (range): Non-parametric test. Z:Mann Whitney U test

DISCUSSION

The present study showed that the mean age is 44.49 years for cases versus 44.22 years for control group. Of the studied cases ; 53.3% were females, 44.4% housewives,44.4% manual workers, 11.1% employee, 88.9% married and 70.5% non-smokers versus control group, 42.2% were females, 37.8% housewives,44.4% manual workers, 17.8% employee, 82.2% married and 57.8% non-smokers.

Median disease duration was 8 years ranging from 1 to 40 years, 75.6% had gradual disease onset, 40% had progressive course. There was non-statistically significant difference between studied groups as regard age, sex, occupation, marital status and smoking history, which agreed with a study performed by **Gaber *et al.*** [18] on 37 cases and 25 control revealed that the mean age of psoriatic cases was 42.95± 15 and mean age for control group was 42.88± 12.5, for cases 24 cases were males and 13 were females, from controls 16 were males and 9 were females. The mean±SD psoriasis duration was 13.4±10.21 years.

Although **Kumsa *et al.*** [19] reported that 207 individuals in total were considered for the final analysis, only 122 (58.9%) of them were female. The study's participants had an average age of 37.92± 14.86 years, 124 of them (59.9%) were married and had higher education in 78 of them (37.7%). (diploma

and above). 53 (25.6%) of the total patients were employed, 46 (22.2%) were business owners or self-employed, and 77 (37.2%) had high monthly family incomes. For the treatment of psoriasis, 185 patients (89.4%) got topical corticosteroids, and 12 patients (6.5%) were given two topical steroids with various potencies.

The present study showed regarding family history which is considered one of the risk factors for the development of the disease that 13.3% of their cases had positive family history. While El-**Komy *et al.*** [(20)]**,** the biggest single-center registry investigation of Egyptian psoriasis patients to date, revealed that 17.5% of their psoriatic patients had a favorable family history. Our findings were in agreement with their findings.

The present study revealed regarding the triggering factors of psoriasis that 15.6% of cases had positive systemic diseases, 15.6% had surgical operation, 71.1% had psychological stress, 4.4% had positive drug history, 100% received topical therapy, 4.4% had previous systemic therapy and 26.7% had positive previous phototherapy. 100% of our cases had skin affection, presence of trauma and Grattage test.

Which was in agreement with **Xhaja *et al.*** [(21)] findings that more than 70% of patients said stressful situations make their psoriasis flare up. Patients who underwent stressful situations differed significantly from those who did not. This proved that stress is a trigger for both men and women, and 20% of their patients were taking one or more of the prescribed drugs. 20% of the patients said they experienced recurring infections. Few patients said they had allergies.

The present study showed that 62.2% of their cases had hair affection and 46.7% had nail affection. While**, El-Komy *et al.*** [(20)] revealed the most commonly affected sites with psoriasis were both the lower limbs (75.8%) and upper limbs (70%) while the neck (17%) and soles (16.9%) were the least affected.

The current study showed that the median PASI score was 8, ranging from 1.2 to 18.6, which was in agreement with a study by **Aalemi *et al.*** [(22)]**,** who discovered that the mean PASI score in their study was 13.3 with 7.8 SD.

The present study revealed a statistically significant higher median survivin level among cases than control group (123.5 versus 80, respectively). Which agreed with **Akpinar *et al.*** [(23)]**,** who found that median value of serum survivin level was 84.9 (65.1–125.4) pg/ml in the patient group and 72.5 (60.6–89.3) pg/ml in the control group. Our results also agree with **Nagui *et al.*** [(24)] who reported similar results.

The current study revealed that area under curve of survivin in differentiating cases from control group was excellent (AUC=0.960) with the best detected cut off point is 99.7 yielding sensitivity of 84.4%, specificity of 93.3%, positive predictive value and negative predictive values of 92.7% and 85.7%, respectively and total accuracy of 88.9%.

The present research showed non statistically significant correlation between survivin and age, onset, disease duration, family history and PASI score, history of systemic disease, surgical operation, psychological stress, drug history, previous systemic therapy and previous phototherapy among studied cases, which agreed with **Akpinar *et al.*** [(25)]**,** who revealed that, there was no connection between serum survivin levels and sex, age, illness duration, PASI, arthritis, nail psoriasis, or family history.

In addition to the study by **Nagui *et al.*** [(24)]**,** which demonstrated a link between the PASI and the level of survivin, this wasn't in line with what we found. After exposure to narrow-band ultraviolet B, a substantial drop in survivin levels was seen in this investigation. According to several reports, one of the narrow-band ultraviolet B's effects on psoriatic lesions may result from a decrease in the number of survivin**.** This discrepancy between our results may be attributed to different inclusion criteria for both studies, as well as small sample size of our research.

Although **Wang *et al.*** [(26)] discovered that the patient group's survivin messenger ribonucleic acid (mRNA) expression in psoriatic tissue was much greater than the control group's. As a result, they hypothesised that survivin may contribute to the aetiology of psoriasis.

Serum survivin levels were similarly shown to be considerably higher in active acne vulgaris patients and acne scar groups compared to the healthy control group in **Assaf *et al.*** [(27)] investigation. in comparison to the group with active acne, the serum survivin levels in the acne scar group were noticeably greater.

In a research by **Bokarewa *et al.*** [(28)] it was discovered that patients with rheumatoid arthritis (RA) had greater serum and synovial survivin levels than the control group. A correlation was found between survivin level and participation of erosive joints. Survivin levels have been found to be high even during the preclinical stage, when symptoms are nonexistent. They came to the conclusion that the elevated survivin level may play a key role in the onset and progression of RA in accordance with these findings.

According to **Erlandsson *et al.*** [(29)] who found that patients who initially had arthralgia and later acquired RA had greater serum survivin levels, survivin may serve as a marker for the progression of RA.

The existence of survivin on the outer cell membrane of a wide range of cancer cell types, including both murine and human glioma cells, has been demonstrated by **Fenstermaker *et al.*** [(30)]**.** Moreover, immunogen-derived antibodies to survivin have anticancer effect against mouse GL261 gliomas

in both flank and cerebral tumour models, as well as against B16 melanoma.

CONCLUSION

Patients with psoriasis have higher levels of survivin. Survivin did not correlate with severity of psoriasis (PASI). Higher survivin could predict psoriasis susceptibility, but not severity of psoriasis. Survivin seems to candidate novel inflammatory biomarker in the disease pathogenesis.

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