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Original Research Article

Lnc-HULC, miR-122, and sirtulin-1 as potential diagnostic biomarkers for psoriasis and their association with the development of metabolic syndrome during the disease course

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ABSTRACT

Psoriasis is a persistent inflammatory skin disorder driven by T cells. The disease is characterized by aberrant keratinocytes (KCs) differentiation, epidermal proliferation, and excessive hyperplasia of veins and arteries. The purpose of the study was to identify the levels of circulating *lnc-HULC*, *miR-122*, and Sirtuin 1 (*SIRT-1*) in psoriatic patients, evaluate their possible roles as diagnostic biomarkers, and link their levels with the development of metabolic syndrome during psoriasis progression. This study included 176 participants. The subjects were divided into four groups, with 44 participants in each group. All patients have undergone a complete history taking and clinical examination. Laboratory investigations included Low-density lipoprotein (LDL), High-density lipoprotein (HDL), Triglycerides (TG), Fasting blood sugar (FBS), and cholesterol plasma levels. Serum levels of *miR-122* and *lnc-HULC* were examined by qRT-PCR. Serum levels of *SIRT-1* were examined by ELISA. The serum concentrations of *lnc-HULC* and *miR-122* were significantly higher in psoriatic participants compared to controls. Psoriatic patients' serum concentrations of *SIRT-1* were much lower than those of healthy individuals. There was a negative association between *SIRT-1* concentration and BMI, disease duration, PASI score, LDL, and cholesterol levels. The blood levels of *lnc-HULC*, *miR-122*, and *SIRT-1* in psoriasis patients provide a promising role as diagnostic biomarkers in patients with and without metabolic syndrome.

1. Introduction

Psoriasis is a persistent inflammatory skin ailment driven by T cells and distinguished by aberrant keratinocytes (KCs) differentiation, epidermal proliferation, and excessive hyperplasia of veins and arteries. The incidence of psoriasis varies from 0.09% to 11.43%, based on the report of the World Health Organization (WHO) in 2016 [1]. East African countries have a higher reported prevalence of the disease compared to West African countries [2]. The reported prevalence in Egypt varies from 0.19% to 3% [3]. Psoriasis often manifests on the skin as infiltrative, erythematous, and exfoliative plaques coated with silvery scales. Plaques of psoriasis are most often seen on the hairy scalp, the extensor areas of the elbows and knees, and the sacro-lumbar area. Additionally, nail lesions are characteristic manifestation of psoriasis

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(pitting, oil spots, onycholysis, and splinter hemorrhages) [4]. Psoriasis is characterized by epidermal KCs hyperproliferation, poor KCs differentiation, and decreased KCs apoptosis. The increased capacity of psoriatic KCs to withstand apoptosis may be one of the primary pathogenetic pathways in psoriasis [5]. Throughout psoriasis, local skin lesion irritation is frequently associated with a systemic inflammatory response [6]. Epidemiologic and experimental research findings have demonstrated a linkage between elevated concentrations of cytokines, interleukins, and hormones (adipokine) and metabolic syndrome (MetS), diabetes mellitus (DM), cardiovascular disease (CVD), and obesity, thereby identifying psoriasis as a threat criterion for the progression of systemic illnesses [7].

Epigenetic variables have a key function in the etiology and pathophysiology of psoriasis. Without changing the sequence of DNA, epigenetic processes regulate the expression of genes in response to chemical alterations of histones and DNA that induce new mRNA translation by altering chromatin structure and triggering transcription factors of certain genes [8]. Epigenetic variables may influence the expression of genes at the transcriptional (through histone modification and DNA methylation) and post-transcriptional levels in various ways [via long non-coding RNAs (lncRNA) and microRNAs-(miRNAs)]. Several reports have highlighted the importance of epigenetic mechanisms in inflammatory disorders such as psoriasis [9].

LncRNA, or long non-coding RNA, is defined as any non-coding RNA that is 200 nucleotides or longer and may play a role in pre-transcriptional control. LncRNAs control protein synthesis, transcriptional interference, enhancer activity, regulatory transcription factors, competing for endogenous RNA (ceRNA), variable splicing, and other post-transcriptional regulation [10]. It has been demonstrated that lncRNAs are commonly linked to cancer development and biological functions, including apoptosis, proliferation, and cell differentiation [11]. Multiple differentially expressed lncRNAs (DE lncRNAs) have an essential regulatory function at the gene expression level in patients with psoriasis, according to studies [12].

Across the sequencing and screening of hepatocellular carcinoma (HCC) -specific gene library, it was shown that the highly up-regulated liver cancer (HULC) lncRNA is the gene most significantly up-regulated in HCC [13]. Current studies have shown the significance of *lnc-HULC* in the metastasis and cellular invasion of several human malignancies, including pancreatic, gastric, and liver tumors [14–17]. In addition, *lnc-HULC* has been recognized as a crucial constituent in developing pro-inflammatory processes in endothelial cells during liposaccharide-associated sepsis [18]. A report by Sayad and co-workers found that *lnc-HULC* is down-regulated in male multiple sclerosis (MS) patients relative to healthy people and that its transcript rates are suitable as diagnostic indicators for MS illness [19].

MiR-122, the miRNA targeted by *lnc-HULC*, represents the most prevalent *miRNA* in the liver, accounting for nearly 70% of the overall *miRNA* population [20,21]. It has been shown that it functions as a cancer inhibitor and is significantly suppressed in several malignancies, including non-small lung tumors [22], HCC [23], and bladder tumors [23]. Current reports indicate that *miR-122* levels are considerably elevated in osteoarthritis (OA). In addition, Sirtuin 1 (*SIRT-1*) was recognized as a direct target of *miR-122* since its transcription was controlled by *miR-122* via targeting the 3UTR of the *SIRT-1* gene. *SIRT-1* was dramatically decreased by *miR-122* upregulation, and the *miR-122/SIRT-1* axis may govern the breakdown of the extracellular matrix (ECM) in OA, therefore shedding fresh light on the therapy of OA [24]. Previous studies documented that *lnc-HULC*, *miR-122*, and *SIRT1* have a potential role in the development of metabolic syndrome during different disorders [53–55].

To the best of our knowledge, this is the first report aimed to examine the possibility of using *lnc-HULC*, *miR-122*, and *SIRT-1* as diagnostic biomarkers in psoriasis patients and those with psoriasis who have metabolic disorders by analyzing their serum concentrations. In addition, we investigated the correlations between these biomarkers and the pathogenesis of psoriasis and the occurrence of metabolic syndrome during the disease course.

2. Patients and methods

2.1. Study design and patient selection

This study included 176 participants. They were classified into four groups; psoriatic patients who do not suffer from metabolic syndrome (n = 44), psoriatic patients having metabolic syndrome (n = 44), controls having metabolic syndrome (n = 44), and controls who do not suffer from metabolic syndrome (n = 44). Before enrollment, every one of the patients had to sign an informed permission form. Patients with an autoimmune illness, cancer, other dermatological disorders, a chronic infectious condition, or a newly acquired infection during the previous month were excluded from the study.

2.1.1. Psoriatic patients

The research comprised 88 psoriatic patients. There were 44 patients with psoriasis who were diagnosed as having metabolic syndrome and 44 patients without metabolic syndrome . All patients underwent a complete history taking, clinical examination, assessment of the site of affection (scalp psoriasis with alopecia, nail psoriasis, and vulgaris), and clinical assessment (Extent of disease (%): using the rule of 9 [25], the Dermatology Life Quality Index (DLQI), Body Surface Area for psoriasis (BSA%), and Psoriasis Area and Severity Index (PASI). Any questionnaire-based evaluation was administered in Arabic. Laboratory investigations were included low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), fasting blood sugar (FBS), and cholesterol plasma levels. We excluded any patient with criteria of metabolic syndrome (DM, hypertension, dyslipidemia) from the group of psoriatic patients without metabolic syndrome. According to the age of disease onset, we classified the patients into Type 1 (having its highest prevalence between the ages of eighteen and 39) and Type 2 psoriasis (first appearing after 40). Based on criteria of the International Diabetes Federation [26]. The diagnosis of metabolic syndrome was centered on obesity (body mass index [BMI] $>$ 30 kg/m^2) or a waist circumference above the ethnic threshold and two or more of the following: abnormal lipid metabolism (levels of HDL cholesterol $<$40 mg/dl in males and $<$50 mg/dl in females, triglycerides $\geq$150 mg/dl), diastolic blood pressure $\geq$85 mmHg or systolic blood pressure $\geq$130 mmHg; fasting glucose concentration $\geq$100 mg/dl or previously diagnosed hypertension or type 2 diabetes. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) devised MetS criteria, specifically concerning the waist circumference (WC) cut-off point, settling at $\geq$ 102 cm for males and $\geq$ 88 cm for females regardless of ethnicity [56].

2.1.2. Control group

Eighty-eight healthy subjects served as the comparison group, and none of them had a history of psoriasis, autoimmunity, or skin problems. The controls were classified into forty-four individuals with metabolic syndrome and the same number of individuals without metabolic syndrome.

2.2. Laboratory investigation

All lipid profiles were conducted as part of standard laboratory studies. The relative expression of *miR-122* and *lnc-HULC* was investigated. A vacutainer instrument was used to obtain a blood sample (10 ml) from each patient. Centrifugation at 4000$\times g$ for 10 min separated the serum layer (top) from the packed cells in the obtained blood specimens. Coagulated entire blood was separated into serum, which was frozen at -80° Celsius until it was time to utilize it in the RNA isolation [27] and *SIRT-1* assay.

2.3. RNA extraction

A miRNeasy extraction kit was employed to extract RNA from 100 μL of total serum specimen (Qiagen, Valencia, CA, USA). The reaction mixture was incubated at ambient temperature for 5 min after introducing 500 μL of QIAzol lysis reagent. After incubating at room temperature, the solution was given a 15-s vortex, and then 100 μL of chloroform was introduced after 2–3 min. After that, 15-min centrifugation at 12,000×*g* and 4 °C was performed. Once the aqueous layer was skimmed off the top, it was replaced with 1.5 times its volume of ethanol absolute. The mixture was then centrifuged in 700 μL fractions at 8000×*g* for 15 s at room temperature using an RNeasy Mini spin column in a 2 ml collection tube. Once the mix was thoroughly filtered through each column, 700 μL of buffer RW1 was added, and the columns were centrifuged at 8000×*g* at ambient temperature for 5 min. Afterward, 500 μL of buffer RPE was added to the column, and it was centrifuged at 8000×*g* at ambient temperature for 5 min. The column was then washed with 500 μL of buffer RPE and centrifuged for 2 min at ambient temperature at a speed of 8000×*g*. After transferring the column to a fresh 1.5 mL collection tube, it was centrifuged for 2 min at 8000×*g*. Lastly, 50 μL of RNase-free water was pipetted onto the column, and the RNA was eluted by centrifuging the mixture at 8000×*g* for 1 min. DNase was used to eliminate any lingering DNA from the specimen before reverse transcribing it into cDNA using the DNase Max Kit (Qiagen, Valencia, CA, USA). The concentration of RNA was evaluated by a NanoDrop 2000 spectrophotometer (Thermo Scientific, Waltham, MA, USA), observing its absorbance values at wavelengths of 260 and 280 nm.

2.4. Reverse transcription

Following the manufacturer's recommendations (incubation for 60 min at 37 °C, for 5 min at 95 °C, and then maintenance at 4 °C), 1 μL RNA was reverse transcribed in a final reaction volume of 10 μL using a high-capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, USA).

2.5. Noncoding RNAs expression by real-time quantitative PCR

Quantitative PCR was performed using qPCR primers and a miScript SYBR Green PCR kit (Qiagen) (qPCR). The primers for MiR-122 (Accession no: NR_029667, catalog no: 3416) and housekeeping gene SNORD 68 (catalog no:33712) [28] were supplied by Qiagen, Germany. Gene expression was analyzed using a reference gene. Lnc-HULC (Accession no: NR_004855.2) was analyzed using GAPDH, a commonly used internal control for serum lncRNAs, as an endogenous control, following the manufacturer's instructions [29]. The primer sequences used for Lnc-HULC and GAPDH are:

The primer sequences of lnc-HULC are (forward primer, 5′-TCATGATGGAATTGGAGCCTT-3′, and reverse primer, 5′-CTCTTCCTGGCTTGCAGATTG-3′).

The primer sequences of GAPDH are (forward, 5′-CCCTTCATTGACCTCAACTA-3′ and reverse 5′-TGGAAGATGGTGATGGGATT-3′).

To summarize the methodology for PCR cycling conditions, we carried out the following: 10 min at 95 °C, followed by 40 cycles of 15 s at 95 °C and 60 s at 60 °C. The Rotor Gene Q System (Qiagen) was used to complete the procedure on 20 μL reaction mixture. Quantifying the degree to which target genes are regulated endogenously was accomplished using the cycle threshold (Ct) approach. Ct values for SNORD 68 were subtracted from those for miR-122 to calculate the $^{\Delta}$ Ct of miRNAs. Values for lnc-HULC were subtracted from GAPDH Ct values to get estimates for lncRNA $^{\Delta}$ Ct. When analyzing and quantifying relative gene expression levels, the $^{2-\triangle\triangle}$ Ct technique was used [30].

2.6. Plasma SIRT-1 levels detection

Enzyme-linked immunosorbent assay was utilized to detect plasma levels of SIRT1 (ELISA) (Sun Red Kits, Shanghai, PR China).

2.7. Statistical analysis

Data were gathered, coded to simplify database queries, and double-entered into Microsoft Access before being analyzed using SPSS version 22 on Windows 7 (SPSS Inc., Chicago, IL, USA). Quantitative parametric data were analyzed using arithmetic means as central tendency measurements and standard deviations as measures of dispersion, whilst qualitative data were analyzed using simple descriptive analysis that consisted of numbers and percentages. To evaluate quantitative measurements between two independent groups, the *t*-test was utilized. To evaluate two independent groups, the Mann-Whitney test was utilized. To compare two or more qualitative groups, the Chi-square test was utilized. To evaluate the relationship among variables, the bivariate spearman correlation test was performed. P-values of <0.05 were deemed statistically significant.

3. Results

Our data showed that there were no significant differences in age or sex between the studied groups with a p-value >0.05 (Table 1).

3.1. Different blood levels of miR-122, lnc-HULC, and SIRT-1 in psoriatic patients compared to healthy controls

There were significantly higher levels of both *miR-122* and *lnc-HULC* in addition to significantly lower levels of *SIRT-1* among cases with a p-value <0.001 (Table 2).

3.2. Demographic, clinical characters, and biomarkers levels in different study groups as regards metabolic syndrome

Among the study group with no metabolic syndrome, there was a significantly higher mean of *miR-122*, *lnc-HULC*, LDL, and cholesterol levels and a significantly lower mean of *SIRT-1* among psoriasis cases with a p-value <0.05. In contrast, there was no significant variation with a p-value >0.05 as regards age, BMI, sex, HDL, or TG level (Table 3). There was no significant difference with regard to waist circumference or blood pressure, but a higher mean of FBS among the psoriasis group.

Among the study group with metabolic syndrome, there was a significant higher mean of LDL, HDL, cholesterol, *miR-122*, and *lnc-HULC* levels and lower levels of TG and *SIRT-1* among psoriasis cases with a p-value <0.05. Alternatively, there was no statistically significant variance with a p-value >0.05 as regards age, BMI, and sex (Table 4). There was no significant difference with a p-value >0.05 as regards systolic blood pressure and FBS, but a higher mean of waist circumference and diastolic blood pressure among the psoriasis group.

3.3. Comparisons of demographic, clinical characters, and biomarkers levels in psoriasis cases as regards metabolic syndrome

Among the psoriasis group, there was a significantly higher mean of age, BMI, LDL, cholesterol, PASI score, and DLQI among psoriasis cases

Table 1
Comparisons of demographic characteristics among various research groups.

Variables	Psoriasis (N = 88)		Control (N = 88)		P-value
Age (years)	44.9	12.8	41.6	10.2	0.06
BMI	30.3	5.7	30.09	4.6	0.8
Sex					
Female	49	55.7%	44	50%	0.5
Male	39	44.3%	44	50%	

BMI: body mass index.
*Significant with Chi-square, *t*-test.

Table 2
Comparisons of biomarkers in different study groups.

Variables	Groups				P-value
	Cases (N = 88)		Controls (N = 88)		
	Mean ± SD	Median/ IQR	Mean SD	Median/ IQR	
miR-122	**8.48 ± 12.6**	**3.39/8.1**	**0.94 ± 0.17**	**0.915/ 0.11**	**<0.001***
Lnc-HULC	**3.41 ± 5.4**	**1.38/2.6**	**0.94 ± 0.17**	**0.915/ 0.11**	**<0.001***
SIRT-1	**9.58 ± 1.5**	**9.95/2.3**	**15.75 ± 2.6**	**15.6/4.1**	**<0.001***

miR-122: microRNA-122, lnc-HULC: long noncoding RNA-HULC, SIRT-1: sirtulin-1.
*significant with Mann-Whitney test, *t*-test.

Table 3
Comparisons of demographic, clinical characters, and biomarkers in different study groups without metabolic syndrome.

without metabolic syndrome	Psoriasis (N = 44)		Control (N = 44)		P-value
Age (years)	39.3	12.6	39.4	11.2	0.9
BMI	28.1	5.8	29.5	5.5	0.3
Waist circumference	96.5	16.4	95.7	15.5	0.8
Systolic BP	120.7	12.2	117.9	8.7	0.2
Diastolic BP	78.1	7.4	76.5	5.8	0.3
FBS	87.3	6.3	78.9	13.7	**0.001***
Sex					
Female	25	56.8%	20	45.5%	0.5
Male	19	43.2%	24	54.5%	
Lipid profile					
LDL	100.07	37.4	86.8	51.6	**0.04***
HDL	51.5	18	52.4	12.3	0.8
TG	118.7	35.7	118.5	31.4	0.9
Cholesterol	174.1	43.8	149.6	40	**0.007***
Biomarkers					
miR-122	**5.47**	8	0.92	0.09	**<0.001***
HULC	**2.81**	32	0.925	0.09	**<0.001***
SIRT-1	**10.53**	0.93	17.3	2.11	<0.001*

BMI: body mass index, BP: blood pressure, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, miR-122: microRNA-122, lnc-HULC: long noncoding RNA-HULC, SIRT-1: sirtulin-1.
*Significant with *t*-test.

Table 4
Comparisons of demographic and clinical characters in different study groups with metabolic syndrome.

With metabolic syndrome	Psoriasis (N = 44)		Control (N = 44)		P-value
Age (years)	50.6	10.6	46.7	8.8	0.07
BMI	32.8	4.8	30.7	3.3	0.06
Waist circumference	108.8	13.2	103.6	9.5	**0.03***
Systolic BP	136.4	14.5	132.9	19.8	0.4
Diastolic BP	87.4	14.1	81.8	9.4	**0.03***
FBS	122	45	141.3	68.9	0.1
Sex					
Female	24	54.5%	24	54.5%	1
Male	20	45.5%	20	40.9%	
Lipid profile					
LDL	168.5	45.4	102.9	40.7	**<0.001***
HDL	51.5	18.01	38.6	9.5	**<0.001***
TG	118.7	35.7	204.6	67.8	**<0.001***
Cholesterol	252.8	54.6	200.4	55.4	**<0.001***
Biomarkers					
miR-122	11.5	15.6	0.95	0.22	**<0.001***
HULC	4	6.9	0.95	0.22	**<0.001***
SIRT-1	8.6	1.4	14.2	1.9	**<0.001***

BMI: body mass index, BP: blood pressure, FBS: fasting blood sugar, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, miR-122: microRNA-122, lnc-HULC: long noncoding RNA-HULC, SIRT-1: sirtulin-1.
*Significant with *t*-test, Chi-square, Mann-Whitney.

with metabolic syndrome (p-value <0.05). Furthermore, the metabolic syndrome group had a significant higher percentage of type II and nail affection. Conversely, there was no significant variance with a p-value >0.05 as regards other variables (Table 5). There was a significantly higher mean of waist circumference, systolic, diastolic blood pressure, and FBS among the psoriasis group with metabolic syndrome with a p-value <0.001.

In addition, there were significantly higher levels of *miR-122* and lower levels of *SIRT-1* among cases with metabolic syndrome, with a p-value <0.001. Alternatively, there was no significant difference in *lnc-HULC* level between the two metabolic groups among psoriasis cases (Table 6).

Moreover, there was a significantly lower mean of *miR-122* in cases affected by scalp psoriasis with alopecia, with a p-value of 0.002. Conversely, there was no significant variance with a p-value >0.05 among various patient characteristics as regards the mean of different biomarkers (Table 7).

Our data showed that there was a significant negative correlation with a p-value <0.05 between *miR-122* and patients age, BMI, and waist circumference and a positive correlation with PASI score among cases. There was a significant positive correlation with a p-value <0.05 between *lnc-HULC* and both FBS and BSA score among cases. There was a statistically significant positive correlation between the *lnc-HULC* and both the FBS and BSA scores among the cases, with a p-value <0.05. There was a significant negative correlation with a p-value <0.05 between *SIRT-1* and age, waist circumference, BMI, blood pressure, FBS,

Table 5
Comparisons of demographic and clinical characters in different psoriatic patient groups.

Variables	Psoriasis				P-value
	Without metabolic syndrome (N = 44)		With metabolic syndrome (N = 44)		
Age (years)	39.3	12.5	50.6	10.6	<0.001*
BMI	28.2	5.8	32.4	4.8	<0.001*
Waist circumference	96.6	6.4	108.9	13.2	<0.001*
Systolic BP	120.7	12.2	136.4	14.5	<0.001*
Diastolic BP	78.1	7.4	87.4	14.1	<0.001*
FBS	87.3	6.3	122	45.8	<0.001*
Sex					
Female	25	56.8%	24	54.5%	0.9
Male	19	43.2%	20	45.5%	
Lipid profile					
LDL	100.1	37.4	168.5	45.4	<0.001*
HDL	51.5	18.01	51.5	18.01	1
TG	118.7	35.8	118.8	35.8	1
Cholesterol	174.1	43.7	525.8	54.6	<0.001*
Disease characters					
Duration of illness	86.1	83.9	122.5	123.8	0.09
BSA %	0.078	0.09	0.078	0.09	1
PASI score	4	4.3	12.1	5.1	<0.001*
DLQI	9.6	5.5	14.6	5.5	<0.001*
Type of disease					
Type I	34	77.3%	20	45.5%	0.004*
Type II	10	22.7%	24	54.5%	
Site of disease					
Vulgaris	38	86.4%	40	90.9%	0.7
Nail	12	27.3%	22	50%	0.04*
Scalp	30	68.2%	28	63.6%	0.8
Treatment regimen					
Topical steroid	28	63.6%	28	63.6%	1
MTX	16	34.4%	22	50%	0.3
Acitretin	10	22.7%	4	9.1%	0.1
Topical vit D	12	27.3%	18	40.9%	0.3

BMI: body mass index, BP: blood pressure, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, miR-122: microRNA-122, lnc-HULC: long noncoding RNA-HULC, SIRT-1: sirtulin-1, DLQI: the Dermatology Life Quality Index, BSA%: body surface area for psoriasis, PASI: Psoriasis Area and Severity Index, MTX: methotrexate.
*Significant with Chi-square, Mann-Whitney.

Table 6
Comparisons of biomarkers in different psoriasis groups.

Variables	Psoriasis group				P-value
	Without metabolic syndrome (N = 22)		With metabolic syndrome (N = 22)		
	Mean ± SD	Median/ IQR	Mean SD	Median/ IQR	
miR-122	5.47 ± 8	2.28/6.1	11.50 ± 15.6	5.88/1.89	0.005*
Lnc-HULC	2.81 ± 3.2	1.6/1.8	4 ± 6.9	1.07/3.6	0.2
SIRT-1	10.53 ± 0.93	10.65/1.38	8.6 ± 1.4	8.6/2.6	<0.001*

*Significant with Mann-Whitney, *t*-test.

Table 7
Comparisons of biomarkers in different gender and disease characters among Psoriasis cases.

Variables		*miR-122*	*Lnc-HULC*	*SIRT-1*
		Mean ± SD	Mean ± SD	Mean ± SD
Sex				
Male		8.1 ± 13.7	3.3 ± 6.1	6.56 ± 1.6
Female		8.9 ± 11.4	3.5 ± 4.4	9.6 ± 1.3
p-value		0.9	0.8	0.2
Type of psoriasis				
Type I		10.1 ± 14.8	2.46 ± 3.2	9.5 ± 1.7
Type II		5.8 ± 7.5	4.9 ± 7.5	9.6 ± 1.2
p-value		0.2	0.09	0.9
Site of psoriasis				
Vulgaris	No	5.04 ± 2.8	3.2 ± 3.1	9.3 ± 1.8
	Yes	8.9 ± 13.4	3.4 ± 5.6	9.6 ± 1.5
p-value		0.6	0.5	0.8
Nail	No	8.9 ± 15.1	2.98 ± 4.5	9.8 ± 1.5
	Yes	7.7 ± 7.4	4.1 ± 6.6	9.3 ± 1.6
p-value		0.2	0.5	0.2
Scalp psoriasis With alopecia	No	14.7 ± 18.2	3.1 ± 3.8	9.3 ± 1.8
	Yes	5.3 ± 6.8	3.5 ± 6.1	9.7 ± 1.3
p-value		0.002*	0.7	0.3

*Significant with Mann-Whitney.

disease duration, PASI score, LDL, and cholesterol level among cases. On the other hand, there was no difference between biomarkers and other variables with a p-value >0.05 (Table 8).

3.4. Comparisons of clinical data and biomarkers levels among control groups

This study found that controls with metabolic syndrome had significantly lower median *SIRT-1* levels (p-value <0.001), but there was no difference in *miR-122* or *lnc-HULC* levels (Table 9). In addition, there was a positive correlation with a p-value <0.05 between *miR-122* and HULC levels among controls. There was no significant correlation with a p-value >0.05 between HULC and the study variables among the controls. There was a negative correlation with a p-value <0.05 between SIRT-1 and age, blood pressure, FBS, HDL, TG, and cholesterol levels among controls. On the other hand, there was no difference between biomarkers and other variables with a p-value >0.05 (Table 10).

3.5. Detection of the predictive power of lnc-HULC, miRNA-122, and SIRT-1 in psoriasis

The sensitivity and specificity test for different biomarkers illustrated the significance of the sensitivity and specificity of *miR-122*, *lnc-HULC*, and *SIRT-1* among the non-metabolic group, with a sensitivity of (68.2%, 73.3%, and 100%, respectively) and a specificity of (90.9%, 90.9%, and 100%) respectively (Figs. 1 and 2). Furthermore, among metabolic cases, the sensitivity and specificity of miR-122 were 77.3%,

Table 8
Correlation between biomarkers and study variables among psoriasis cases.

Variables	miR-122	HULC	SIRT-1
	r(p-value)	r(p-value)	r(p-value)
Age	−0.31(0.003*)	0.13(0.2)	−0.26(0.01*)
BMI	−0.22(0.04*)	0.18(0.09)	−0.39(<0.001*)
Waist circumference	−0.27(0.01*)	0.07(0.5)	−0.48(<0.001*)
Systolic BP	0.08(0.5)	−0.08(0.4)	−0.48(<0.001*)
Diastolic BP	−0.06(0.9)	−0.05(0.6)	−0.58(0.001*)
FBS	0.003(0.9)	0.24(0.02*)	−0.30(0.004*)
Disease duration	−0.03(0.8)	−0.03(0.8)	−0.34(0.001*)
BSA%	−0.01(0.9)	0.26(0.01*)	0.13(0.2)
PASI score	0.27(0.01*)	0.04(0.7)	−0.33(0.002*)
DLQI	−0.01(0.9)	0.13(0.2)	−0.13(0.2)
Lipid profile			
LDL	0.13(0.2)	0.08(0.5)	−0.29(0.006*)
HDL	−0.06(0.6)	0.19(0.08)	−0.7(0.5)
TG	−0.005(0.9)	0.16(0.1)	−0.21(0.05)
Cholesterol	0.13(0.2)	0.09(0.4)	−0.28(0.01*)
Biomarkers			
HULC	−0.03(0.8)	–	–
SIRT-1	−0.02(0.8)	0.18(0.09)	–

BMI: body mass index, BP: blood pressure, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, miR-122: microRNA-122, lnc-HULC: long noncoding RNA-HULC, SIRT-1: sirtulin-1, DLQI: the Dermatology Life Quality Index, BSA%: body surface area for psoriasis, PASI: Psoriasis Area and Severity Index,
*Significant with spearman correlation.

Table 9
Comparisons of biomarkers in different control groups.

Variables	Control group				P-value
	Without metabolic syndrome (N = 22)		With metabolic syndrome (N = 22)		
	Mean ± SD	Median/ IQR	Mean SD	Median/ IQR	
miR-122	0.92 ± 0.09	0.91/0.11	0.95 ± 0.22	0.91/0.11	0.9
Lnc-HULC	0.95 ± 0.09	0.92/0.11	0.96 ± 0.22	0.92/0.11	0.9
SIRT-1	17.32 ± 2.1	17.15/3.5	14.18 ± 1.9	14/2.4	0.001*

*Significant with Mann-Whitney.

Table 10
Correlation between biomarkers and study variables among controls.

Variables	miR-122	HULC	SIRT-1
	r(p-value)	r(p-value)	r(p-value)
Age	0.06(0.6)	0.06(0.6)	**−0.24(0.02*)**
BMI	0.09(0.4)	0.09(0.4)	−0.12(0.3)
Waist circumference	0.24(0.02*)	0.24(0.02)	−0.13(0.2)
Systolic BP	0.09(0.4)	0.1(0.4)	**−0.36(0.001*)**
Diastolic BP	0.007(0.9)	0.007(0.9)	**−0.37(0.001*)**
FBS	0.05(0.6)	0.05(0.6)	**−0.23(0.03*)**
Lipid profile			
LDL	0.03(0.8)	0.03(0.8)	−0.13(0.2)
HDL	−0.05(0.7)	−0.05(0.7)	**0.46(0.001*)**
TG	0.001(0.9)	0.001(0.9)	**−0.55(<0.001*)**
Cholesterol	0.19(0.07)	0.19(0.07)	**−0.46(0.001*)**
Biomarkers			
HULC	**0.99(0.001*)**	–	———— ()
SIRT-1	−0.07(0.5)	−0.07(0.5)	–

BMI: body mass index, BP: blood pressure, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, miR-122: microRNA-122, lnc-HULC: long noncoding RNA-HULC, SIRT-1: sirtulin-1.
*Significant with spearman correlation.

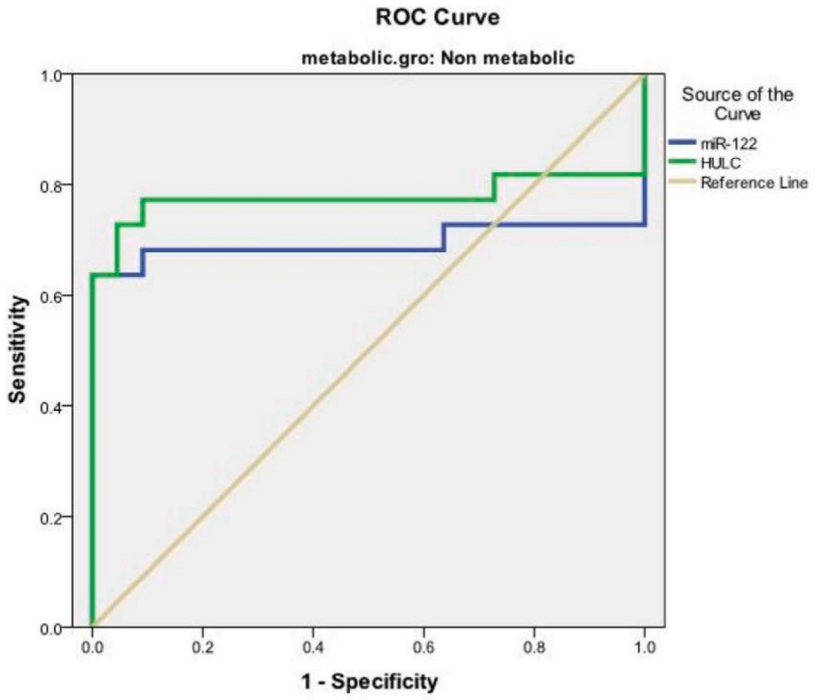

Fig. 1. ROC curve for miR-122 and lnc-HULC in diagnosing psoriasis without metabolic syndrome.

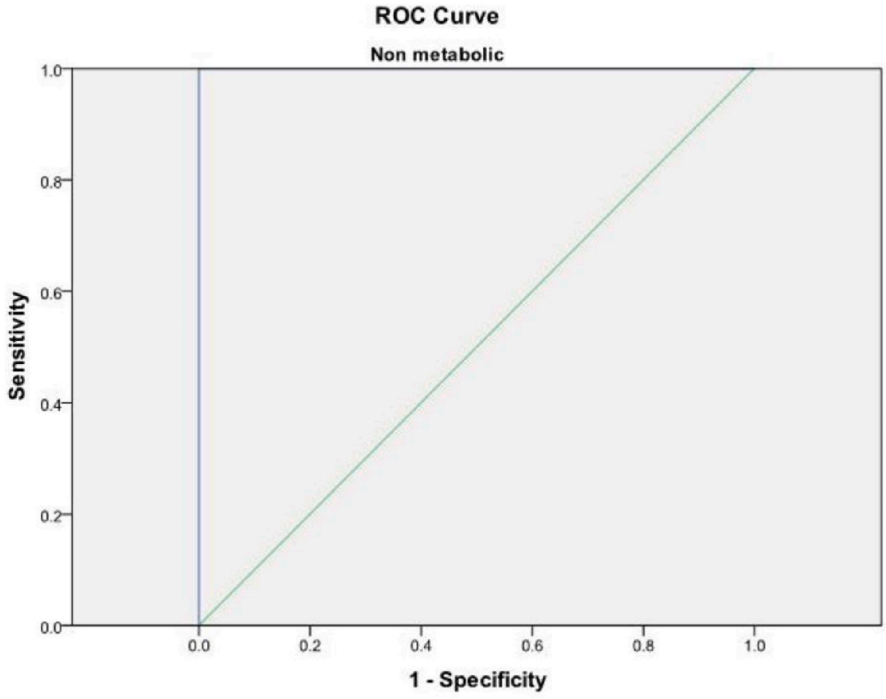

Fig. 2. ROC curve for SIRT-1 in diagnosing psoriasis without metabolic syndrome.

and 100%, respectively. While, the sensitivity and specificity of and SIRT-1 were 90.9% and 95.5%, respectively, with no significance for lnc-HULC (Figs. 3 and 4) (Table 11).

4. Discussion

Psoriasis is a persistent, systemic, immune-mediated illness. The development of this illness is heavily influenced by genetic factors. Lesions on the skin trigger the release of a plethora of inflammatory cytokines [31]. These inflammatory cytokines are secreted into the blood stream in varying concentrations depending on the extent and severity of the lesions [32]. Epigenetic variables have been shown to have a crucial role in the development and progression of psoriasis [33].

To the best of our knowledge, this is the first study to detect *lnc-HULC*, *miR-122*, and *SIRT-1* levels in the serum of psoriatic patients and clarify the possibility of using them as diagnostic biomarkers in psoriasis cases with and without metabolic syndrome. Psoriasis treatment might be affected by the correlation between increased levels of these

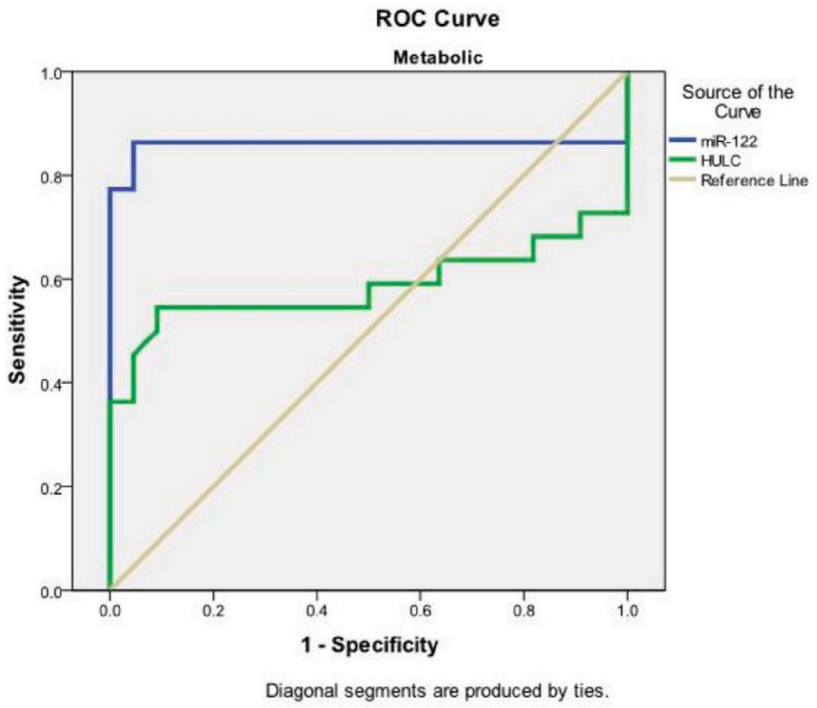

Fig. 3. ROC curve for miR-122 and lnc-HULC in diagnosing psoriasis with metabolic syndrome.

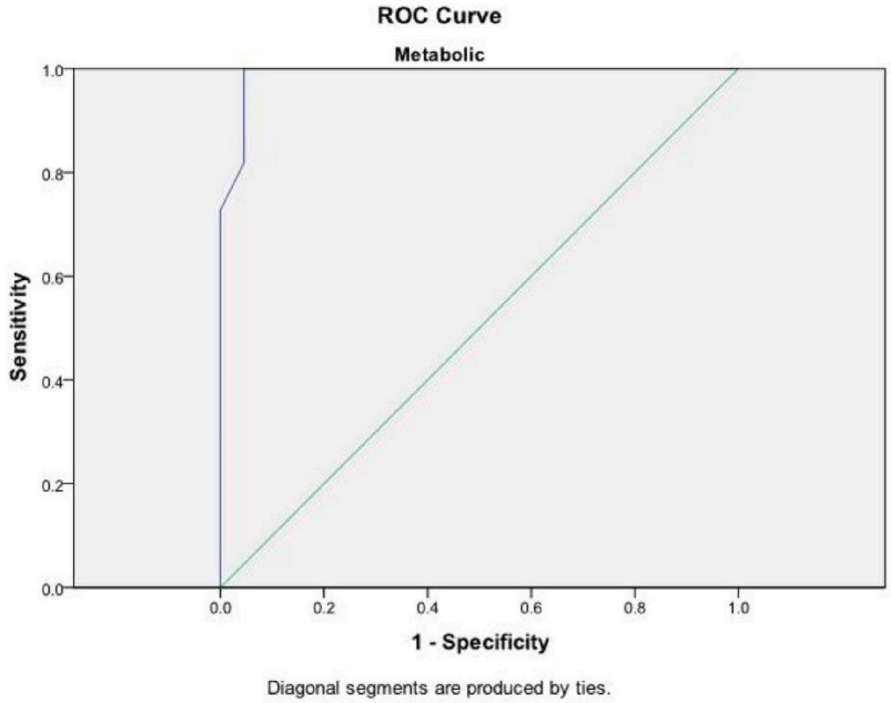

Fig. 4. ROC curve for SIRT-1 in diagnosing psoriasis with metabolic syndrome.

biomarkers and the existence of metabolic syndrome.

Lnc-HULC levels in the blood were substantially higher in psoriatic patients than in controls. Regarding psoriatic groups, we found that *lnc-HULC* was significantly up-regulated in the serum of psoriatic patients with and without metabolic syndrome compared to controls, and there was no significant difference in *lnc-HULC* levels between the two metabolic groups among psoriasis cases. Regarding the ROC curve of *lnc-HULC* in psoriatic patients, *lnc-HULC* can distinguish between psoriatic patients and control subjects with a sensitivity of 73.3% and specificity of 90.9%. It is noteworthy that serum *lnc-HULC* level was related to the severity of disease as it was positively correlated with BSA percentage.

In addition, to the best of our knowledge, this is the first attempt to detect the difference in *lnc-HULC* expression levels between cases of psoriasis and controls. However, some studies investigated the relation between *lnc-HULC* and skin disorders. Besides, Liu and coworkers demonstrated that the lack of the *lnc-HULC* gene accelerates the

Table 11
Sensitivity and specificity of different biomarkers in the diagnosis of psoriasis cases.

Variable	Sensitivity	Specificity	AUC	Cut off point	P-value (CI)
Non-metabolic					
miR-122	68.2%	90.9%	69.4%	1.039	0.002 (0.562–0.826)
Lnc-HULC	73.3%	90.9%	77.7%	1.002	<0.001 (0.659–0.894)
SIRT-1	100%	100%	100%	13.1	<0.001 (1-1)
Metabolic					
miR-122	77.3%	100%	86%	1.943	<0.001 (0.758–0.961)
Lnc-HULC	54.5%	90.9%	58.6%	1.024	0.2 (0.451–0.720)
SIRT-1	90.9%	95.5%	99%	10.45	<0.001 (0–1)

recovery from heat damage by increasing the proliferation and invading ability of human skin fibroblasts (HSFs) and the production of ECM. They found that *lnc-HULC* acts as a molecular sponge and controls miR-663b/toll-like receptor 4 (TLR4) expression to suppress thermally-injured HSF cell proliferation, invasion, and ECM formation [34].

Lnc-HULC was found to be up-regulated in psoriasis cases with metabolic syndrome more than in cases without metabolic syndrome. Depending on the fact that inflammatory cytokine overexpression in psoriasis causes an increased incidence of metabolic syndrome occurrence, *lnc-HULC* overexpression may be a predisposing factor for metabolic syndrome in psoriasis cases, as *lnc-HULC* is positively correlated to inflammatory cytokine levels in multiple diseases such as sepsis [35]. Zhu and coworkers mentioned in their study that blood lipid levels, endothelial cell function, and inflammatory cytokine production are all factors in the pathophysiology of CVD. These processes are regulated by *lnc-HULC* and its target miRNA-128–3p (miR-128–3p). They found that in patients with CVD, upregulation of *lnc-HULC* was related to higher blood lipid levels (TG, LDL-C), inflammatory cytokines (interleukin (IL-1, IL-17A), cell adhesion molecules (VCAM-1), and Gensini score (all $P < 0.05$) [36]. Besides, expression of *lnc-HULC* was higher in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and Guillain-Barré syndrome (GBS) cases compared with controls [37]. *Lnc-HULC* has been shown to regulate immune responses through miR-128–3p/RAC1 axis [38] which regulates a number of inflammatory pathways such as STAT3 and NF-κB [39]. Therefore, the lnc-HULC/miR-128–3p/RAC1 axis might also be involved in the pathogenesis of CIDP and GBS. The relationship between overexpression of *lnc-HULC* and increased inflammatory cytokines may demonstrate its role in the pathogenesis of psoriasis and the occurrence of metabolic syndrome during the course of the disease.

MiR-122 levels in the blood were substantially higher in psoriatic patients than in controls. Regarding patient groups, we found that *miR-122* was significantly up-regulated in the serum of psoriatic patients with and without metabolic syndrome compared to controls. There was a significant difference in *miR-122* levels between the two metabolic groups among psoriasis cases. Regarding the ROC curve in psoriatic patients, *miR-122* can distinguish between psoriatic patients and control subjects with a sensitivity of 68.2% and specificity of 90.9% in psoriasis cases with the non-metabolic syndrome and a sensitivity of 77.3% and specificity of 100% in psoriasis cases with metabolic syndrome. There was a significantly lower mean of *miR-122* in cases affected in the scalp. It is noteworthy that serum *miR-122* levels related to the severity of the disease were positively correlated with the PAS1 score. The previous studies for the detection of the role of *miR-122* in skin diseases are few, but Manfè et al. mentioned that *miR-122*, which was produced in malignant T-cell infiltration and elevated in the advanced stage of mycosis fungoides (MF), lowered the susceptibility to chemotherapy-induced apoptosis via activating Akt and inhibiting p53 [40].

Our study found that in cases of psoriasis with metabolic syndrome, *miR-122* levels were considerably elevated compared to patients without metabolic syndrome. The crucial biomarker *miR-122* may have a molecular function in coupling lipid metabolism and atherosclerosis [41]. *MiR-122* could lower nitric oxide concentrations and promote endothelial deterioration, especially in hypertensive patients [42]. Moreover, *miR-122* inhibits *miR-21*, thereby boosting HMGCR (3-hydroxy-3-methyl glutaryl-co-enzyme A reductase) transposition and transcription and promoting cholesterol production [43]. Furthermore, it has generally been linked to inflammation [44]. Among young people, miR-122 has been linked to increased body fat and insulin resistance, as discovered by Wang et al., [45]. According to Gao et al. patients with hyperlipidemia had higher levels of miR-122 and miR-370, which are related to CVD [46].

MiR-122 was linked to both glucose and insulin regulation. People who were overweight, had type 2 diabetes, or were at risk for developing the disease had much higher levels of this gene [47]. In addition, Long et al. discovered that *miR-122* was elevated in cell lines from an animal model of non-alcoholic fatty liver disease (NAFLD), whereas *SIRT-1* expression was reduced. According to the results of this research, *miR-122* inhibited *SIRT-1* production by directly binding to the 3′-UTR of *SIRT-1*. *MiR-122* knockdown resulted in a reduction in the expression of lipogenic genes and activation of the AMPK signaling pathway, both of which acted to reduce lipid synthesis and TG release in hepatocytes [48]. We can conclude from these studies and from our results that miR-122 may play an important role in the occurrence of metabolic syndrome in psoriasis cases.

We found a lower mean level of *miR-122* in scalp psoriasis with alopecia cases compared to cases afflicted with psoriasis vulgaris or nail psoriasis. The distinction in molecular pathways between psoriasis subtypes has previously been studies. Ahn et al. (2018) performed RNA-seq and flow cytometry on scalp, palmoplantar, and plaque psoriasis tissue samples, and found unique genetic expression profiles for each type. The scalp psoriasis transciptome showed 632 distinct genes. Our finding further validates the difference in genetic and epigenetic profiles of different psoriasis subtypes. Identifying distinct pathways may help in developing treatments that are appropriate for specific psoriasis subtypes and sites [45].

SIRT-1 levels were substantially lower in psoriatic patients than in controls. Regarding patient groups, we found that *SIRT-1* was significantly downregulated in the serum of psoriatic patients with and without metabolic syndrome compared to controls. There was a significant difference in *SIRT-1* levels between the two metabolic groups among psoriasis cases. Regarding the ROC curve in psoriatic patients, *SIRT-1* was able to distinguish between psoriatic patients and control subjects with a sensitivity of 100% and specificity of 100% in psoriasis cases with the non-metabolic syndrome and a sensitivity of 90.9% and specificity of 95.5% in psoriasis cases with the metabolic syndrome. There was a negative correlation between *SIRT-1* and BMI, disease duration, PASI score, LDL, and cholesterol levels.

Becatti et al. discovered that psoriatic fibroblasts had significantly lower levels of *SIRT-1* expression and activity, as well as elevated levels of apoptosis (caspase-3, -8, and -9 activities). When *SIRT1* was turned on, redox equilibrium was restored, mitochondrial activity was revived, and apoptosis disappeared. In addition, they showed that the *SIRT-1* pathway played a crucial role in protecting cells from apoptotic cell death via modulating MAPK. By controlling MAPK signaling, *SIRT1* activation restores mitochondrial functionality and redox equilibrium. *SIRT1* may therefore be recommended as a targeted therapy for psoriasis [49].

We demonstrated the correlation between *SIRT-1* and psoriasis cases with metabolic syndrome, and we found that *SIRT-1* was significantly downregulated in psoriasis cases with metabolic syndrome compared with cases without metabolic syndrome. *SIRT-1* is negatively correlated with LDL, BMI, and plasma cholesterol levels. Taking these points together, we can conclude that *SIRT-1* may play a role in the occurrence of metabolic syndrome in psoriasis.

Systemically overexpressing *SIRT-1* (~ 3-fold) in mice protects them from the physiological damage caused by a high-fat diet (HFD), as previously reported. This protection is achieved through reduced activation of pro-inflammatory cytokines like TNF-α and IL-6, which is achieved through down-modulating NFκB activity [50]. *SIRT-1* has been shown to activate PGC1α, a key cofactor in metabolic rate-driving mitochondrial biogenesis, in a number of separate investigations [51]. Therefore, *SIRT-1* stimulation could be a useful method for avoiding and resolving metabolic syndrome [52].

5. Conclusion

Circulating non-coding RNAs (ncRNAs) are widely present and last in body fluids, making them ideal non-invasive biomarkers. *MiR-122*, the miRNA targeted by *lnc-HULC*, and *SIRT-1* levels in the serum of psoriatic patients provide a promising role as diagnostic biomarkers in psoriatic individuals and may have a role in the pathogenesis of psoriasis and the occurrence of metabolic syndrome during the course of the disease.

Ethics approval and consent to participate

All operations dealing with human subjects/patients were approved by the local ethics committee of Faculty of Medicine, Fayoum University (Ethical code: R293/2022). The consent of all participants was obtained in written form before participating in the trial.

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Availability of data and materials

"The data that support the findings of this study are included in the manuscript".

CRediT authorship contribution statement

Randa Erfan: contributed to the study design, data collection, data analysis, data interpretation, writing of the manuscript. **Olfat G. Shaker:** contributed to the study design, data collection, data analysis, data interpretation, writing of the manuscript. **Mahmoud A.F. Khalil:** contributed to the study design, data collection, data analysis, data interpretation, writing of the manuscript. **Aya M. AlOrbani:** contributed to the study design, data collection, data analysis, data interpretation, writing of the manuscript. **Abeer K. Abu-El-Azayem:** contributed to the study design, data collection, data analysis, data interpretation, writing of the manuscript. **Amira Samy:** contributed to the study design, data collection, data analysis, data interpretation, writing of the manuscript. **Othman M. Zaki:** contributed to the study design, data collection, data analysis, data interpretation, writing of the manuscript. **Haitham Abdelhamid:** contributed to the study design, data collection, data analysis, data interpretation, writing of the manuscript. **Reham Fares:** contributed to the study design, data collection, data analysis, data interpretation, writing of the manuscript. **Asmaa Mohammed:** contributed to the study design, data collection, data analysis, data interpretation, writing of the manuscript, All authors approved the final version of the manuscript, including the authorship list.

Declaration of competing interest

The authors declare no conflict of interest.

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