



Role of Serum Neutrophil Gelatinase-associated Lipocalin in early detection of cardiovascular risk in patients with Vitiligo

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Abstract:

Background: Patients with vitiligo may be more susceptible to cardiovascular disease, atherosclerosis, metabolic syndrome, and other disorders since it is seen as a systemic disorder rather than a skin condition.

Patients and methods: 44 non-segmental vitiligo patients and 41 healthy controls participated in this study. Vitiligo Area Scoring Index (VASI) Score was used in patient evaluation to determine the severity of vitiligo. With vitiligo patients, the Reynolds Risk Score (RRS) was used to assess cardiovascular risk. Serum levels of glycosylated hemoglobin (HbA1c), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), high sensitivity C-reactive protein (hs-CRP), and neutrophil gelatinase-associated lipocalin (NGAL) were measured for each participant using biochemical analyses.

Results: In this study we found that Cases of vitiligo had higher median RRs score (1 (0.2-13.6) than control (0.9 (0.2-3) but this was statistically insignificant. Also, there was significant ($p=0.008$) association between disease status and RRs categories i.e., all control group had low risk of cardiac disease while 80% of vitiligo patients group had low risk, about 13% had medium risk and 7% had high risk. Vitiligo cases had insignificantly ($p = 0.136$) lower median serum NGAL level (246 (104 - 775 ng/ml) compared with control (276 (122 - 783 ng/ml) but this was within normal range of this marker (10ng/ml→3000ng/ml). Non-significant minimal positive correlation between serum NGAL level and RRs score was found ($r=0.086$, $p=0.287$).

Conclusion: Vitiligo patients are more susceptible for cardiovascular diseases and assessment of serum NGAL level had no role in early detection of these disorders.

Keywords: vitiligo, lipocalin, cardiovascular, risk

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Introduction:

Vitiligo is an acquired condition with a fluctuating unpredicted course. Clinically, it is identified by distinct, depigmented or milky-white skin patches and macules that result from the death of melanocytes.⁽¹⁾ Though it can occur at any age, the most frequent age range for it to manifest is between 10 and 30 years old. It is the

most prevalent depigmentation disorder, involving 1% or slightly more of the global population and affecting all races and genders equally.⁽²⁾ Vitiligo was categorized into segmental and non-segmental subtypes.⁽³⁾ Vitiligo may be accompanied by social, mental, and psychiatric problems. Individuals with vitiligo may

experience psychosocial manifestations. ⁽⁴⁾ There are several pathogenic factors, including as abnormalities in the neurological system, defective metabolic pathways, autoimmune reactions, hereditary effects, and deficiencies in melanocyte adhesion. ⁽⁵⁾ Other autoimmune conditions such rheumatoid arthritis, Addison's disease, inflammatory bowel disease, autoimmune thyroid disease, pernicious anemia, and type 1 diabetes mellitus have been linked to vitiligo. ⁽⁶⁾

A subset of vitiligo patients with more severe and chronic disease have been reported to have an increased risk of dyslipidemia, atherosclerosis, and maybe an increase in cardiovascular risk. Vitiligo is an autoimmune disease that causes depigmentation. ^(7, 8)

The most prevalent kind of vitiligo is non-segmental, which is strongly linked to a number of systemic and metabolic disorders, including insulin resistance, lipid abnormalities, metabolic syndrome, and atherosclerotic cardiovascular disease. ^(9, 10)

There are several theories explaining the correlation between vitiligo and atherosclerotic cardiovascular disease in the population, one of which being the increased oxidative stress associated with vitiligo. Reactive oxygen species (ROS) are recognized to be crucial for several aspects of atherosclerosis, including oxidation of low-density lipoprotein (LDL) cholesterol, apoptosis, cell proliferation, and changes in vascular tone. ⁽¹¹⁾

Lipocalin-2, also known as neutrophil gelatinase-associated lipocalin (NGAL), is a little extracellular protein that serves a number of purposes. It is a member of the lipocalin family. First identified as a protein associated to neutrophil gelatinase and extracted from certain neutrophil granules. ⁽¹²⁾ Atherosclerotic plaques and cardiomyocytes have been shown in prior research to express significant levels of NGAL. ⁽¹³⁾ NGAL regulates a variety of cellular reactions in these locations, including apoptosis, differentiation, and proliferation linked to atherosclerosis, vascular remodeling, and vascular function. ^(14, 15) Heart failure has an involvement with NGAL pathogenesis. When heart failure progresses, inflammatory reactions might arise as a result of neutrophil activation and NGAL release. ⁽¹⁶⁾ So, in our study we assessed the serum NGAL level in patients with vitiligo that

may have a role in early detection of cardiovascular risks in those patients.

Patients and Methods:

The Sohag University Faculty of Medicine's Research and Ethical Committees gave the study their approval IBR Registration number: Soh-Med-21-10-20. In every instance, written consent was acquired after full disclosure.

Patients:

This study included 44 patients with non-segmental vitiligo (after fulfillment of the inclusion and exclusion criteria), whom attended Dermatology, Venereology and Andrology department outpatient clinic; Sohag University Hospital as well as 41 healthy controls volunteers between December 2021 and December 2022.

Study design:

Cross-sectional study. Sample size calculation by OpenEpi program, version 3 open source calculator -SSCC. When we assumed that odds ratio be 4 and control number to case number = 1, within an error probability of 0.05 and 80% power on 2- tailed test (type 1 error). 40 cases and 40 controls are needed in the study.

Inclusion criteria:

The vitiligo patients included in this study were both male and female, over the age of 18, and had non-segmental type stable vitiligo (meaning they had no new lesions or changes in the size of the lesions that already existed for at least six months).

Exclusion criteria:

Patients with these criteria were excluded from this study; as patients with segmental vitiligo, Patients with systemic diseases (bleeding disorders, chronic renal diseases, chronic liver diseases, asthma), patients with other dermatological diseases, Patients who were receiving chemotherapy or radiotherapy, Pregnant and lactating women, alcoholics and smokers and those younger than 18 years of age.

Methods:

(A) Clinical evaluation:

(B) The patient evaluation included the following elements:

1- Complete history was taking included:

Personal history: (name, age, sex, address, marital status, occupation and special habits of medical importance), History of present

illness: (onset, course, duration, site, number of vitiliginous areas, previous treatment and did the patient improve with it or not?), Past history :(hypertension, diabetes and other autoimmune disease) and Family history of similar condition.

2- General examination:

included weight (by kg), height (by meter), Body Mass Index will be calculated by dividing body weight (kg) by square height (M²) and Blood pressure both systolic, diastolic Were be assessed.

3- Complete dermatological examination: was done for all participants included Fitzpatrick skin phototype, hair, nail, mucous membrane.

4- Examination of vitiliginous lesion:

Was done for determining the affected anatomical site (face & neck, trunk, upper extremities, hand, lower extremities including groin region & buttocks, feet) and its type (wood's light examination was used for confirmation of the diagnosis).

5- Evaluation of vitiliginous patients: was done to assess severity of the disease by using VASI Score (17).

(B) The Reynolds Risk Score (RRS) was used to assess the cardiovascular risk in vitiligo patients (18). The following factors were used to compute it: total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), history of myocardial infarction, high sensitivity C-Reactive Protein (hs-CRP), HbA1c, and the existence of diabetes. Patients with vitiligo were categorized into low, medium, and high risk subgroups (RRS <5%, \leq 5% RRS <10%, RRS \geq 10%) based on this Score (18).

(C) Biochemical Analyses: All investigations and biochemical analyses done in the laboratory of Sohag University Hospital. 5 ml of blood was collected from patients by venipuncture. Samples were divided into two parts. The first part was 4 ml in plane tube for measurement of serum NGAL, hs-CRP, TC, HDL-C. To calculate RRS, the second part was 1ml in EDTA (Ethylenediaminetetraacetic acid) tube for measurement of HbA1c. The plane tubes were centrifuged and sera were obtained and frozen at -20 c. Serum hs-CRP, HbA1c, TC, HDL-C, were assayed by the

spectrophotometric technology using photometer 5010 apparatus in measurement.

(D) Measurement of NGAL:

Neutrophil gelatinase-associated lipocalin was measured by test kit supplied by Biokits Co. Cat. No E1719Hu/ China. The test kit is an enzyme linked immunosorbent assay (ELISA) for measurement of serum NGAL on the basis of the Biotin double antibody sandwich technology using Stat fax apparatus in measurement. After pre-coating the wells with the NGAL monoclonal antibody, we added NGAL and incubated. Subsequently, biotin-labeled anti-NGAL antibodies were added to combine with streptavidin-HRP and form an immunological complex. Once the enzymes were washed and incubated, we eliminated them. Substrates A and B were added. Then, the acid's impact caused the solution to turn blue and then yellow. There was a positive correlation between the concentration of Human NGAL and the solution hues.

Assay range: 10ng/ml→3000ng/ml.

Sensitivity: 5.01ng/ml.

Statistical analysis

- Using IBM-SPSS/PC/VER 24, the Statistical Package for Social Sciences, the researcher checked, coded, and examined the data that were submitted. Calculations for descriptive statistics included mean, standard deviation, median, range, frequency, and percentage. To compare the variations in frequency distributions between the several groups, the significance test (chi square) was employed. We checked for data normalcy using the Shapiro-Wilk test. Mean differences in continuous variables between groups were tested using the appropriate parametric or non-parametric test as needed. To look at the major determinants of vitiligo disease, multivariate logistic regression analysis was performed (Odds Ratio [OR], 95% Confidence Interval [95% CI], and p-value). When calculating univariate correlations, Pearson's correlation coefficient was used. When a test's p value was less than 0.05, it was deemed significant.
- IBM_SPSS. Statistical Package for Social Science. Ver.24. Standard version. Copyright © SPSS Inc., 2012-2016. NY, USA. 2016.

Results:

In this study, 44 patients with non-segmental vitiligo who visited the Dermatology, Venereology, and Andrology Department's outpatient clinic at Sohag University Hospital between December 2021 and December 2022 were compared to 41 healthy controls.

The socio-demographic data of both groups were demonstrated in **table (1)**. Both groups were age and sex matched.

The clinical characteristics of the studied cases were showed in **table (2)**. All cases had gradual onset and progressive course (n=44). The disease duration ranged from 8 months to 23 years with a mean of 5.7 ± 5.4 and a median of 4 years.

Anthropometric measurements, Total RRs, RRs categories and S.NGAL between vitiligo cases and controls were showed in **table (3)**. Cases and control were matched for the anthropometric measures and blood pressure measurements ($p > 0.05$).

Cases of vitiligo had insignificantly ($p = 0.204$) higher median RRs score (1 (0.2-13.6)) than control (0.9 (0.2-3)). Unlikely, there was significant ($p = 0.008$) association between disease status and RRs categories i.e., all control had low risk of cardiac disease while 80% of cases had low risk, about 13% had medium risk and 7% had high risk.

Notably, vitiligo cases had insignificantly ($p = 0.136$) lower median serum NGAL level (246 (104 - 775 ng/ml)) compared with control (276 (122 - 783 ng/ml)) and this is considered within normal range of serum NGAL marker (10ng/ml→3000ng/ml).

Table (4) showed the data of dermatological examination of the studied cases. Regarding general dermatological examination, nail and MM were free in 100% of cases while only one case (2.2%) had affected hair. Further, the majority of cases (82%) had Fitzpatrick skin phototype IV (n=36) while only 18% had Fitzpatrick skin phototype III.

For the vitiligo lesion examination, two-thirds had hand lesion, 60% had LL/Groin/Buttock, about 53% had upper limb, nearly 49% had feet, almost 47% had head and neck, and about one-third had trunk lesion. Respecting the vitiligo type, most of the cases had vitiligo vulgaris (80%), about 13% had acro-fascial and only 7% had localized (focal) vitiligo. Moreover, the mean total VASI score was 58 ± 0.7 with a median of 4.3 (0.5-21.7).

Table (5) illustrated the difference in serum NGAL level between cardiac risk categories. There was insignificant ($P = 0.558$) difference in the mean s. NGAL level between the risk groups.

(Fig. A) The correlation between s. NGAL level and RRs score, non-significant minimal positive correlation was found ($r = 0.086$, $p = 0.287$).

Table 1: Socio-demographic differences between cases and control:

	Control (n =41)	Case (n=44)	P-value
Age in years	37.56 ± 11.3	41.44 ± 13.8	= 0.156*
Sex			
• Male	17 (41.5%)	22 (48.9%)	= 0.490**
• Female	24 (58.5%)	22 (51.1%)	
Residence			
• Urban	37 (90.2%)	10 (22.2%)	< 0.001**
• Rural	4 (9.8%)	34 (77.8%)	
Occupation			
• Unemployed	1 (2.4%)	22 (51.1%)	< 0.001**
• Employed	40 (97.6%)	22 (48.9%)	
Marital Status			
• Unmarried	4 (9.8%)	9 (20%)	= 0.185**
• Married	37 (90.2%)	35 (80%)	

*T-test was used to compare the mean differences between cases and controls

**Chi-square test was used to compare the proportions among groups

Table 2: Clinical Characteristics of the studied group of vitiligo patients:

Variable	Category	n = 44
Onset	• Gradual	44 (100%)
Course	• Progressive	44 (100%)
Duration	• Mean ± SD	5.65 ± 5.4
	• Median (Range)	4 years (8 months – 23 years)
Lesion Site	• Hands	25 (55.6%)
	• Lower Limb	22 (48.9%)
	• Face	17 (40%)
	• Trunk	15 (33.3%)
	• Arm/Forearm	12 (26.7%)
	• Both	12 (26.7%)
Previous Treatment	• No	8 (17.8%)
	• Topical	23 (53.3%)
	• NB-UVB	1 (2.2%)
	• Both	12 (26.7%)
Improvement	• Yes	23 (51.1%)
Family History	• Positive	9 (20%)
Comorbidity	• DM/HTN/RA	5 (11.1%)

Table 3: Anthropometric measurements, Total RRs, RRs categories and S.NGAL between vitiligo cases and controls:

	Control (n =41)	Case (n=44)	P-value
Weight/kg	74.85 ± 9.8	74.01 ± 11.1	= 0.701*
Height/cm	167.20 ± 5.2	169.13 ± 7.3	= 0.164*
BMI	26.72 ± 3.1	25.81 ± 3.5	= 0.210*
SBP (mmHg)	109.27 ± 8.1	108.44 ± 8.2	= 0.643*
DBP (mmHg)	72.68 ± 5.9	74.67 ± 5.1	= 0.100*
hs-CRP	1.97 ± 0.5	1.26 ± 0.3	= 0.254*
TC	170.02 ± 6.9	163.84 ± 6.1	= 0.502*
HDLC	48.85 ± 2.9	43.36 ± 1.5	= 0.102*
RRs Score			
• Mean ± SD	1.11 ± 0.9	2.28 ± 3.3	= 0.204***
• Median (Range)	0.9 (0.2 – 3)	1 (0.2 – 13.6)	
RRs Categories			
• Low	41 (100%)	36 (82.2%)	
• Medium	0 (0%)	5 (11.1%)	= 0.008**
• High	0 (0%)	3 (6.7%)	
S. NGAL Level			
• Mean ± SD	280.85 ± 108.2	256.51 ± 123.7	= 0.136***
• Median (Range)	276 (122 – 783)	246 (104 – 775)	

P value < 0.05 was significant

*T-test was used to compare the mean differences between cases and controls

**Chi-square test was used to compare the proportions among groups

***Mann Whitney U test was used to compare the median differences between cases and controls

(BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, hs-CRP=high sensitivity C-reactive protein, TC =total cholesterol), HDL-C high-density lipoprotein cholesterol, RRS= Reynolds Risk Score, NGAL= Neutrophil gelatinase-associated lipocalin)

Table 4: Dermatological Examination Results of the studied Cases:

Variable	Category	n = 44
General Free	• Hair	43 (97.8%)
	• Nail	44 (100%)
	• MM	44 (100%)
Fitzpatrick Skin Phototype	• III	8 (17.8%)
	• IV	36 (82.2%)
Vitiligo Lesion Examination	• Head and Neck	20 (46.7%)
	• UL	24 (53.3%)
	• Hand	30 (66.7%)
	• LL/Groin/Buttock	27 (60%)
	• Feet	22 (48.9%)
Type of Vitiligo	• Trunk	14 (31.1%)
	• Vulgaris	36 (80%)
	• Acro-fascial	6 (13.3%)
VASI Score	• Focal	2 (6.7%)
	• Mean ± SD	5.80 ± 0.7
	• Median (Range)	4.3 (0.5 – 21.7)

VASI= Vitiligo Area Scoring Index

Table 5: Correlation between serum NGAL and RRs categories:

RRs Risk Categories	NGAL serum Level (ng/ml)		P-value*	P-value**
	Mean ± SD	Median (Range)		
• Low (I)	250.08 ± 130.2	235 (104 – 775)	= 0.558	I vs II=0.293
• Medium (II)	313.40 ± 99.5	343 (180 – 410)		II vs III=0.432
• High (III)	241.01 ± 50.5	242 (190 - 291)		I vs III=0.904

*One-way ANOVA Test was used to compare the mean difference among cases

*Post-hoc test with Bonferroni correction was used for pairwise comparison

RRs Reynolds Risk Score

RRS= Reynolds Risk Score, NGAL= Neutrophil gelatinase-associated lipocalin

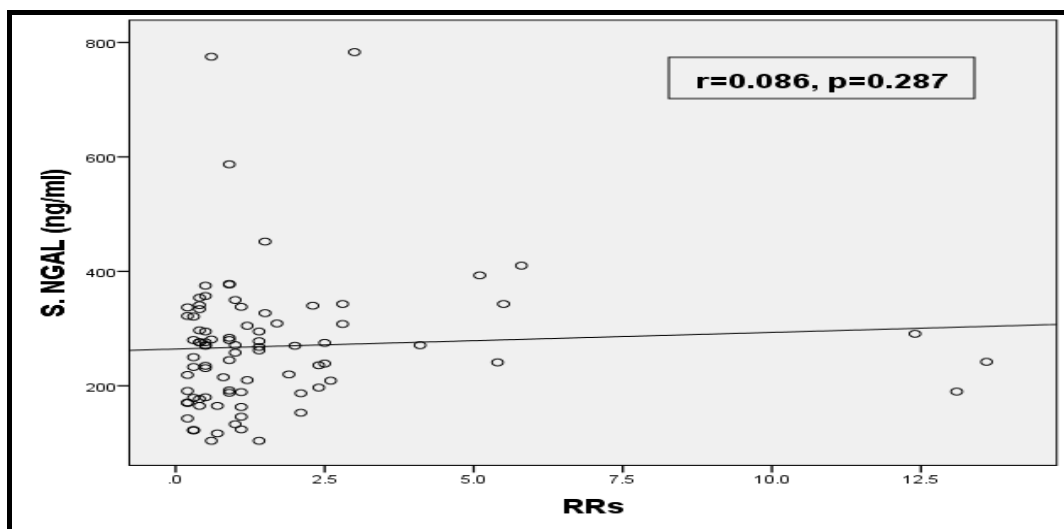


Figure. (A): Correlation between S, NGAL Level and RRs Score.

RRS: Reynolds's Risk score, NGAL: Serum Neutrophil gelatinase-associated lipocalin

Discussion:

Vitiligo is a multifaceted inflammatory skin condition characterized by patchy and hypopigmented skin lesions, as well as the immune system's elimination of epidermal melanocytes.⁽¹⁹⁾

Vitiligo is not a skin condition; rather, it is becoming understood to be a systemic problem associated with an increased risk of metabolic syndrome, atherosclerosis, and cardiovascular disorders.⁽¹⁶⁾

Neutrophil gelatinase-associated lipocalin (NGAL) may be a marker of atherosclerosis, which was supported by a study done by **Elneihoum A et al., (1997)** that conducted on 156 patients with asymptomatic atherosclerosis; he found that NGAL levels in plasma were significantly higher in patients than in healthy controls, being directly linked to diastolic pressure.⁽²⁰⁾ Our present study aimed to assess role of serum NGAL in early detection of cardiovascular risk in patients with vitiligo.

This study included 44 patients with non-segmental vitiligo and 41 healthy control volunteers which were age and sex matched. In our study we found that patients with vitiligo were divided according to RRS (which used to detect cardiovascular risk) into low, medium and high risk groups while all control healthy group was categorized at low risk for cardiovascular problems and this was statistically significant.

Given that non-segmental vitiligo is a systemic skin condition rather than a depigmenting one and that it is strongly linked to a number of systemic and metabolic conditions, including insulin resistance, lipid abnormalities, atherosclerotic cardiovascular disease, and metabolic syndrome, this may help to explain.^(9,10)

These results were consistent with those of **Azzazi et al. (2021)**, who studied 50 patients with non-segmental vitiligo and 50 age- and sex-matched controls. They found that patients with vitiligo may have a higher risk of atherosclerosis and dyslipidemia, which may raise their risk of cardiovascular disease.⁽⁷⁾

Our results were in line with those of **Namazi and colleagues**, who looked for metabolic syndrome criteria in a research including 70 patients with non-segmental vitiligo and 70 age- and gender-matched healthy controls. To evaluate the presence of subclinical atherosclerosis, the

participants' common carotid artery mean intima-media thickness was assessed. Patients with vitiligo, particularly those with more severe and chronic disease, were found to have a higher risk of developing cardiovascular diseases due to the significantly higher frequency of metabolic syndrome and subclinical atherosclerosis in vitiligo patients when compared to controls. Additionally, there was a positive significant correlation found between these two conditions and the severity and duration of vitiligo.⁽⁸⁾

Also, serum NGAL level found to be within normal range in both groups (patients and controls) and its level was not statistically significantly correlated with RRS categories in both groups.

Up till now, no previous study assessed NGAL level in vitiligo patients. Our study was in agreement with the study by **EL-Hadidi et al (2014)** conducted on 30 psoriatic patient and 30 healthy control which

Found that no difference between patients with psoriasis and controls as regarded serum lipocalin-2 levels.⁽²¹⁾

Our research differed from that of **Romani and colleagues (2013)**, who studied 50 psoriatic patients and 50 healthy controls. Their findings showed that lipocalin-2 was higher in patients than in controls, and that the differences in body fat content in psoriatic patients should be attributed to increased lipocalin production. However, it is possible that psoriatic disease acts as an initiator of unknown risk factors that would determine the characteristic fat distribution and adipokine secretion pattern.⁽²²⁾

Based upon the results of our study, vitiligo patients were more susceptible for development of cardiovascular diseases compared to control healthy group and However, the difference in serum levels of NGAL between vitiligo patients and the healthy controls, in this study, was not significant. The limitations of our study such as small sample size and heterogeneity of the experimental group as evident by wide range of variation in disease duration and extension should be avoided in the future researches.

Conclusion:

More accurate methods and investigations are important to be used for regular evaluation and follow up of patients with vitiligo to detect cardiovascular risk that may develop with progression of vitiligo as early as possible.

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