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Research Article

SYSTEMIC INFLAMMATION IN COMORBID METABOLIC SYNDROME AND VITILIGO: A REGRESSION ANALYSIS OF RISK FACTORS!

PAVAN K SINGH[1], KANISHK U KAUSHIK[2], RAHUL BHARGAVA[3]*

[1]Department of Dermatology, LLRM Medical College, Meerut, Uttar Pradesh, India. [2]Department of Ophthalmology, GS Medical College, Pilkhuwa, Uttar Pradesh, India.
*Corresponding author: Rahul Bhargava; Email: brahul2371@gmail.com

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ABSTRACT

Objective: Systemic inflammatory markers are often raised in comorbid metabolic syndrome (MetS) and vitiligo. Why some patients with vitiligo develop MetS while others do not remain to be elucidated. This study aimed to identify independent risk factors for MetS development in vitiligo patients.

Methods: In this prospective study, disease characteristics (disease duration, severity, and subtype) and high-sensitivity C-reactive protein (hs-CRP) were compared between vitiligo patients (n=100) with and without MetS. Multivariate logistic regression of potential risk factors for MetS was done after adjusting for potential confounders (such as waist circumference, basal metabolic rate, serum lipids, blood pressure, and fasting blood sugar). The performance of these parameters (hs-CRP, age, disease duration, and severity) in predicting MetS development was ascertained by the area under the receiver operating characteristic curve (ROC).

Results: Vitiligo patients with MetS had a significantly longer ($p<0.001$) disease duration as compared to those without MetS (56±16 versus 14±12 months). On regression analysis, inflammatory markers (hs-CRP) had significantly higher odds (odds ratio [OR]=5.1) as compared to demographic factors such as gender (OR=3.1) and disease factors such as disease duration (OR=2.4) and disease severity (OR=1.8) of developing MetS. On ROC curve analysis, the performance of these parameters for MetS was hs-CRP>Vitiligo Area Scoring Index score>disease duration >increasing age (Area under the curve=0.952, 0.905, 0.851, and 0.697, respectively). The cutoff value of hs-CRP was 6.42 ug/mL.

Conclusion: Elevated hs-CRP has the highest predictive value for MetS development in vitiligo. Systemic inflammation may be the driving force for MetS development.

Keywords: Metabolic syndrome, Vitiligo, Vitiligo area severity index, Logistic regression.

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INTRODUCTION

In vitiligo, potential factors such as oxidative stress, autoimmune dysfunction, and/or inflammation may lead to the loss of functional melanocytes [1-3]. It affects approximately 1% of the world's population [4]. These depigmented skin patches increase in size and number over time causing undue psychological distress which may be severe enough to impair the quality of life of patients [5].

Metabolic syndrome (MetS) is often a comorbid skin disorder such as vitiligo. CD4+ T-lymphocytes have been found to play a role in the pathogenesis of both these conditions [6]. Cytokines such as tumor necrosis factor alpha, interferon gamma, and interleukins (IL-1, IL-6, IL-10, and IL-17) have been found to be elevated in vitiligo patients [7,8]. Second, high-sensitive C-reactive protein (hs-CRP) has been found to be elevated in patients with vitiligo and MetS. However, it is not currently known whether these cytokines play any critical role in comorbid vitiligo and MetS [9].

Patients with vitiligo often have insulin resistance and a deranged lipid profile [10,11]. Several studies have reported an association between vitiligo and diabetes; a study from the sub-continent observed a higher prevalence of MetS in vitiligo patients [12]. On the contrary, several studies did not find any correlation between metabolic derangements and vitiligo [13,14].

To the best of our knowledge, only a few studies in the literature have evaluated the role of systemic inflammation and independent risk factors for MetS development in patients with vitiligo.

This study aimed to investigate the question, why do some patients with vitiligo develop MetS while others do not? We evaluated serum inflammatory makers and risk factors for developing MetS in vitiligo patients, after adjusting for confounders such as waist circumference, body mass index (BMI), serum triglycerides (TG), high-density lipoprotein (HDL), blood pressure (BP), and fasting blood glucose.

METHODS

Study design

This was a prospective multicenter controlled study carried out at tertiary care teaching hospitals in the sub-continent from June 2022 to June 2023. The institutional ethics committee approved the trial (Letter No.SC/-1/2022/6590). The tenets of the Declaration of Helsinki were followed while obtaining written informed consent from all participating patients.

Study participants

Inclusion criteria

Study participants were selected by non-probability sampling and comprised of patients diagnosed with vitiligo (n=100). To minimize study bias, controls (age-gender matched) were selected from patients visiting the dermatology clinic for minor skin conditions. All study subjects were admitted to the day care of dermatology for medical evaluation.

Exclusion criteria

Patients with a history of alcohol consumption, generalized edema, smoking, or those on systemic corticosteroids or other systemic vitiligo

treatments were excluded. Patients with a history of chronic illness such as neoplastic, collagen, and hematologic disorders were also excluded.

Vitiligo subtypes

The frequency of the subtype of vitiligo and disease duration was noted in each case.

Disease activity

The Vitiligo Area Scoring Index (VASI) score was used for the assessment of disease severity and activation. Furthermore, these patients were divided into 3 groups based on VASI score values (<2, 2.1–6, and >6.1, respectively) [15].

MetS evaluation

Patients with vitiligo and controls were evaluated for MetS; venous blood samples were taken from the subjects after 12 h of fasting and blood glucose (FBS), HDL, cholesterol, low-density lipoprotein cholesterol, total cholesterol, TG, BP measurements, waist circumference, and BMI were measured/recorded. These indices were compared between vitiligo subtypes (segmental and non-segmental vitiligo).

MetS definition

The presence of any three of the following five parameters were consistent with the diagnosis of MetS: Waist circumference ≥102 cm in men and ≥88 cm in women, serum TG ≥150 mg/dL, serum HDL cholesterol <40 mg/dL in men and <50 mg/dL in women, BP ≥130/85 mmHg, and fasting plasma glucose ≥100 mg/dL, respectively. These were in accordance with the 2004 National Cholesterol Education Program Adult Treatment Panel III [16]. However, waist circumference is an essential criterion for MetS as per the International Diabetes Federation [17].

High sensitivity C-reactive protein measurement

Serum hs-CRP levels were measured in vitiligo patients and controls by an ELISA kit (Monobind Inc., Lake Forest, CA92630, USA). A microplate reader was used to quantify CRP levels that measured the amount of light being absorbed at 450 nm. The sensitivity of this kit for CRP measurement was 0.2 μg/mL.

Sample size calculation

The sample size calculation was done using the University of British Columbia, the online sample size calculator. This can be accessed using the link [https://www.stat.ubc.ca/~rollin/stats/ssize/n1.html.] Sample size calculation was based on the principle of "Inference for a mean, comparing means of two independent samples." To calculate the sample size, a pilot study was first done on 10 patients. The mean hs-CRP in vitiligo patients with MetS was 3.2 ug/mL and in vitiligo patients without MetS was 2.4 ug/mL, respectively. The standard deviation was 1.9. Considering 80% power (alpha = 0.05), and a precision error of 5% to detect the difference of 20% or more in hs-CRP, the estimated sample size was calculated to be 90.

Statistics

Statistical analysis was performed using IBM statistical software, SPSS Statistics version 29 (IBM Inc.). The difference between the means of two independent groups on a continuous dependent variable was calculated with an independent sample t-test. The association between two categorical variables was evaluated using Chi-square tests. Significant variables on univariate analysis were entered in the multivariate logistic regression model. The performance of parameters such as hs-CRP, age, disease duration, and VASI score in predicting MetS development was evaluated by area under the receiver operating characteristic curve (ROC) and cutoff values were calculated from coordinate points of the ROC curve.

RESULTS

In this study, 100 patients with vitiligo were compared with 150 age- and gender-matched controls. The mean age of patients in Group 1 (vitiligo) was 35.4±12.4 (range, 20–62 years) and in Group 2 (controls) was 33.3±13.2 (range, 18–60 years), respectively (independent t-test, p=0.202). There were 40 males in Group 1 with a male: female ratio of 0.66:1 and 66 males in Group 2 with a male: female ratio of 0.78:1, respectively.

Table 1 mentions the characteristics of cases and controls. The mean disease duration was 27.6±13.4 (range, 8–48 months). The prevalence of MetS in vitiligo patients was 33% and in controls was 14% (p<0.001).

The waist circumferences in patients with vitiligo ranged from 64 to 116 cm and in controls from 68 to 108 cm, respectively. Vitiligo patients and controls with MetS had a significantly higher (p<0.001) waist circumference (95±12 vs. 83±11 cm and 95±10 vs. 80±8 cm, respectively) as compared to those without MetS.

The TG in patients with vitiligo ranged from 50 to 400 mg/dL and in controls from 70 to 390 mg/dL, respectively. Vitiligo patients and controls with MetS had significantly higher (p<0.001) serum TG (178±88 vs. 134±67 mg/dL and 190±90 vs. 126±52 mg/dL, respectively) as compared to those without MetS.

The HDL in patients with vitiligo ranged from 21 to 98 mg/dL and in controls from 20 to 110 mg/dL, respectively. Vitiligo patients and controls with MetS had a significantly lower (p<0.001) serum HDL (46.7±15 vs. 51±17 mg/dL and 45.6±16 vs. 61±18 mg/dL, respectively) as compared to those without MetS.

The mean systolic BP did not significantly differ between patients with vitiligo and controls. Patients with vitiligo and MetS had higher mean systolic BP as compared to those without MetS (126±20 vs. 122±12 mm Hg) but the difference was not statistically significant (Independent, t-test, p=0.096). The mean systolic BP in controls with MetS was higher than those without MetS (128±18 vs. 120±14 mm Hg) but was not statistically significant (independent, t-test, p=0.078).

Patients with vitiligo and MetS had higher mean diastolic BP as compared to those without MetS (83.4±10 vs. 82.6±8 mm Hg) but the difference was not statistically significant (Independent, t-test, p=0.476). The mean diastolic BP in controls with MetS was higher than those without MetS (86±14 vs. 80±10 mm Hg) but was not statistically significant (independent, t-test, p=0.123).

Impaired glucose tolerance was seen in 21% of patients with vitiligo and 18% of controls. Patients with vitiligo and MetS had significantly higher mean FBS as compared to those without MetS (120±21 vs. 92.6±13 mg/dL). The mean FBS in controls with MetS was significantly higher than those without MetS (124±14 vs. 90±15 mg/dL).

Table 1: Characteristics of cases and controls

Parameter	Group 1 (vitiligo) (n=100)	Group 2 (controls) (n=150)	p-value
Age (years)	35.4±12.4	33.3±13.3	0.202
Gender (n, %)			
Male	40 (40)	66 (44)	0.310*
Female	60 (60)	84 (66)	
Height (m)	1.6±0.1	1.6±0.08	0.066
Weight (kg)	72.3±12.5	62.1±14.2	0.001
BMI (kg/m^2)	26.6±5.2	22.9±5	0.001
Waist circumference (cm)	86.7±12.8	82.9±9.8	0.009
Triglycerides (mg/dL)	148.3±77.3	136.3±63	0.001
HDL (mg/dL)	49.6±16.8	59.3±18.7	0.011
Systolic BP (mm Hg)	124±12	116±14	0.056
Diastolic BP (mm Hg)	84±8.6	78±10	0.076
Fasting blood sugar (mg/dL)	102±21	96±20	0.048
Metabolic syndrome (n, %)	33 (33)	21 (14)	0.001

*Chi-square test. BMI: Body mass index, HDL: High-density lipoprotein, BP: Blood pressure

Vitiligo and MetS

In our study, 88% of patients had non-segmental and 12% had segmental vitiligo. The mean disease duration was significantly higher (independent t-test, p<0.001) in vitiligo patients with MetS as compared to those without MetS (56±16 vs. 14±12 months), respectively.

The overall mean VASI score of the study sample (vitiligo patients with and without MetS) was 3.3±2.4 (range, 1–8). The mean VASI score in vitiligo with MetS was 6.7±1.4 and in vitiligo patients without MetS was 2.1±1.3 (independent t-test, p<0.001).

Characteristics of vitiligo in patients with and without MetS are summarized in Table 2.

Serum levels of Hs-CRP

The mean hs-CRP in vitiligo patients with MetS was 7.9±0.9 and in vitiligo patients without MetS was 5.9±0.5 ug/mL, respectively (independent t-test, p<0.001). The cutoff value of hs-CRP for MetS was 6.42 ug/mL. The area under the curve was significantly higher for hs-CRP (area under the curve [AUC]=0.952) as compared to disease severity and disease duration. The sensitivity of hs-CRP was 86% and specificity was 82% in discriminating vitiligo patients with and without MetS.

Multiple logistic regression models

Multinomial logistic regression ascertained the effects of hs-CRP, age, gender, disease duration, body surface area, disease severity (VASI score), and type of vitiligo on the likelihood that participants have MetS after adjusting for confounders (waist circumference, BMI, TG, HDL, BP, and fasting blood sugar).

Females (Table 3) had 3 times higher odds to develop MetS (odds ratio [OR]=3.1). Disease characteristics such as disease duration (OR=2.4) and higher body surface area (OR=1.8) had higher odds to develop MetS. However, patients with higher hs-CRP had a significantly increased likelihood to develop MetS (OR=5.6).

ROC curve analysis

On the ROC curve (Fig. 1), the performance of these parameters for MetS was hs-CRP>VASI score>disease duration >increasing age (AUC=0.952, 0.905, 0.851, and 0.697, respectively). The cutoff values were 6.4 4.5, 27, and 38 for hs-CRP, VASI, disease duration, and age, respectively. The sensitivity ranged from 64 to 87% and specificity from 70 to 82% (Table 4).

Table 2: Characteristics of vitiligo in metabolic syndrome

Parameter	Metabolic syndrome present (n=33)	Metabolic syndrome absent (n=67)	p-value
Disease duration months	56±16	14±12	<0.001
Vitiligo subtype			
Non-segmental	32 (96.9)	56 (83.6)	0.097
Segmental	1 (3.1)	11 (16.4)	
BSA	14.6±7	6.4±5.8	0.020
Disease severity (VASI score)			
1–2	1 (3)	47 (70.1)	0.001*
2.1–6	18 (54.5)	16 (23.9)	
>6.1	14 (42.4)	4 (6)	

*Chi-square test. VASI: Vitiligo Area Scoring Index

DISCUSSION

The results of this prospective observational study suggest that vitiligo patients have significantly (p<0.001) higher prevalence of MetS (33% vs. 14%) as compared to age and gender-matched controls. Multinomial logistic regression revealed that vitiligo patients with raised inflammatory markers (hs-CRP) had significantly higher odds (OR=5.1) of developing MetS as compared to demographic factors such as gender (OR=3.1), disease factors such as disease duration (OR=2.4), and increased disease severity (OR=1.8), after adjusting for confounders (known determinants of MetS such as BMI, waist circumference, serum lipids, BP, and blood sugar). Inflammatory marker, hs-CRP had the best predictive value in discriminating vitiligo patients with and without MetS.

The prevalence of MetS varies between countries depending on the diagnostic criteria used and geographic factors. In India, a study from Maharashtra state reported a prevalence rate of 24% while a Turkish study reported a prevalence rate of 35% [12,18]. The prevalence of MetS in the United States was 34.7% [19]. The prevalence of MetS in our study was comparable to these reported studies.

Older women (>40 years) have been reported to have a higher prevalence of MetS [20]. In our study, there was a preponderance of females with MetS in both cases and controls (54.5% and 59%, respectively). Second, female gender was an independent risk factor (OR=4.1) for developing MetS in vitiligo patients. However, this observation needs further validation in different age groups and ethnic groups.

The exact cause of MetS in patients with vitiligo is not known. It has been proposed that longstanding inflammation triggers a chain of events

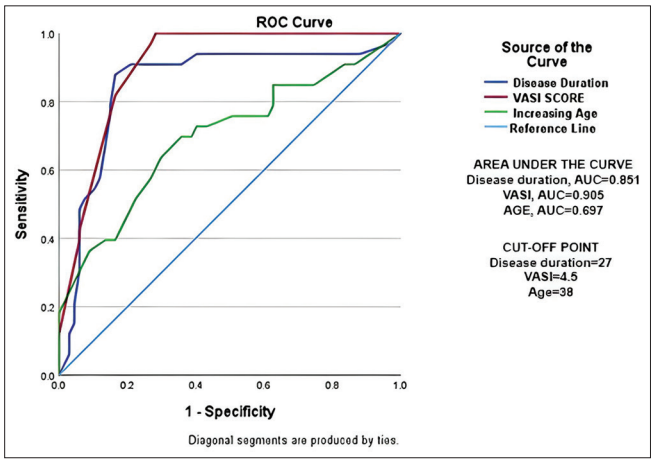

Fig. 1: Receiver operating characteristic curve showing performance of high-sensitivity C-reactive protein, disease duration, Vitiligo area scoring index score and increasing age for metabolic syndrome in Vitiligo patients

Table 3: Multiple logistic regression coefficients

Variable	B (constant)	SE	df	p-value	OR	95%CI	
Hs-CRP	16.42	215.5	1	0.001	5.1	4.62	5.38
Gender	0.24	7.3.44	1	0.076	3.1	3.612	5.422
BSA	−1.19	15.5	1	0.005	2.8	1.4	2.2
Disease duration	2.887	18.3	1	0.001	1.8	4.6	7.4
VASI score	25.9	16.8	1	0.046	2.8	1.4	2.3
Constant	−401.4	346.93	1	0.881	0.000	-	-

OR: Odds ratio, CI: Confidence interval, Hs-CRP: High-sensitivity C-reactive protein, VASI: Vitiligo Area Scoring Index

Table 4: Area under the curve, sensitivity, specificity, and cutoff values of disease duration, VASI score, and age

Parameter	AUC (95% CI)	Sensitivity	Specificity	Cutoff
Hs-CRP	0.952 (0.900–0.988)	88	86	6.42
Disease duration (months)	0.851 (0.761–0.942)	87	84	27
Disease severity	0.905 (0.848–0.961)	82	84	4.5
Age (years)	0.697 (0.581–0.814)	64	70	38

VASI: Vitiligo Area Scoring Index, Hs-CRP: High-sensitivity C-reactive protein, AUC: Area under the curve, CI: Confidence interval

that make vitiligo patients more prone to MetS. Longer the period of inflammation, greater was the likelihood of having MetS [21-23]. This observation also supports our hypothesis that patients having vitiligo for a long period of time have higher odds to develop MetS due to a significantly longer metabolic disturbance secondary to inflammation.

A recently conducted study by Mustafa *et al*. found that inflammatory markers in serum (visceral adipose tissue-derived serine protease inhibitor (vaspin), fatty acid binding protein 4, vascular adhesion protein 1, and chitinase-3-like protein 1) and hs-CRP were significantly raised in vitiligo patients; these markers correlated significantly with MetS components [24]. The latter observation agreed with our study.

A study by Ataş and Gönül observed that independent risk factors for developing MetS in patients with vitiligo were longer disease duration (OR=1.4), a higher percentage of affected (OR=1.2), disease activity (OR=64.4), and segmental vitiligo (OR=215) [25]. Our study agreed with this study and further identified that in addition to these findings, raised hs-CRP had significantly higher odds of developing MetS.

A case–control study by Ibrahim *et al*. highlighted that increasing age was an independent and statistically significant predictor for MetS in patients with vitiligo. In contrast, our study observed that increasing age had lower odds of developing MetS. It is possible that these certain risk factors may vary between geographical regions and ethnic groups [26].

Our findings are consistent with the findings of the studies conducted by Sharma *et al*. and Ataş and Gönül [12-25] However, unlike these studies, we found that vitiligo disease severity was an independent risk factor for the development of MetS. This later finding was substantiated in another study which found that vitiligo severity was associated with MetS [27].

Our study had several limitations and strengths. Selection bias and observation bias cannot be ruled out in a case–control study design. Second, innate inflammatory markers could not be evaluated in this study due to cost constraints. There were a small number of patients in the segmental vitiligo group. Finally, patients need long-term follow-up as disease severity may vary over time. Having said this, a larger control group (n=150) and prospective study design were our strengths. Our study revealed that inflammation plays a significant role in MetS development in vitiligo patients.

CONCLUSION

Inflammatory markers (hs-CRP) had significantly higher odds (OR=5.1) as compared to demographic factors such as gender (OR=3.1) and disease factors such as disease duration (OR=2.4) and disease severity (OR=1.8) of developing MetS after adjusting for confounders.

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AUTHOR CONTRIBUTION

PKS: Data collection, follow-up, literature search, writing the manuscript. KUK: Data collection, literature search, writing the manuscript, editing. RB: Statistical analysis, critical review, discussion, final draft.

CONFLICTS OF INTEREST

None.

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Nil.

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