

Original Article:

Elevated Circulating Interleukin-33 in Vitiligo Diagnostic Potential and Clinical Correlates — A Cross-Sectional Study

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Abstract

Background: Vitiligo is an immune-mediated depigmenting disorder in which oxidative stress, innate immune activation and cytokine dysregulation contribute to melanocyte destruction. As an epithelial alarmin released during cellular stress, interleukin-33 (IL-33) is well positioned to participate in this inflammatory interface, although its circulating profile and diagnostic relevance in vitiligo remain to be established.

Aims: To determine serum IL-33 concentrations in patients with vitiligo and to evaluate their diagnostic potential and clinical correlates.

Methods: This cross-sectional study included 36 patients with clinically and Wood's lamp-confirmed vitiligo and 36 age- and sex-comparable healthy controls. Serum IL-33 was quantified by sandwich enzyme-linked immunosorbent assay. Lesional activity was graded using the Vitiligo Disease Activity (VIDA) score. Between-group differences, clinical correlations and receiver operating characteristic (ROC) performance were evaluated.

Results: Serum IL-33 was significantly higher in patients than controls (median 10.60 [IQR 2.32–22.20] vs 3.03 [2.01–4.44] pg/mL; $p=0.005$). ROC analysis yielded an area under the curve of 0.691 (95% CI 0.563–0.819). At an optimal cut-off of 9.345 pg/mL, sensitivity was 61.1%, specificity 88.9%, positive predictive value 84.6% and overall accuracy 75.0%, with a positive likelihood ratio of 5.50. Serum IL-33 was not significantly associated with sex, age or VIDA grade and showed no meaningful correlation with VIDA score ($p=0.088$; $p=0.611$).

Conclusion: Circulating IL-33 is elevated in vitiligo and demonstrates moderate discriminatory potential, characterised by relatively high specificity but limited sensitivity. Its lack of association with clinical activity suggests greater value as an exploratory disease-associated biomarker than as a marker of current clinical activity.

Keywords: Vitiligo; Interleukin-33; Biomarker; Clinical correlates; ROC curve.

Introduction

Vitiligo is a chronic, immune-mediated depigmenting disorder characterised by the selective loss of functional melanocytes and the appearance of sharply demarcated, chalky-white macules and patches. Beyond visible pigment loss, it imposes a substantial psychological and quality-of-life burden, particularly in populations with darker skin phototypes.^{1,2} A recent systematic review and modelling study estimated the physician-diagnosed

lifetime prevalence at approximately 0.36% globally and 0.52% in South Asia.³ Nationally representative estimates remain limited across the region, and the most recent Bangladeshi report was clinic-based rather than a population-level prevalence study.⁴

Current evidence supports a multifactorial model of vitiligo that integrates genetic susceptibility, melanocyte oxidative stress, innate immune activation and melanocyte-specific adaptive immunity.^{5,6} Oxidative

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Email: drsaifulib@yahoo.com Received: 15th February, 2026; Accepted: 25th April, 2026; Online: 1st July, 2026

Cite this Article:

Khatun H, Asaduzzaman ATM, Khondker L, Azzad MAK, Mohim MNA, Ahmed WD, Talukder S, Zaman F, Bhuyian MSI. Elevated Circulating Interleukin-33 in Vitiligo Diagnostic Potential and Clinical Correlates — A Cross-Sectional Study. Ban Acad Dermatol. 2026; 06 (01): 2-9

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An official publication of Bangladesh Academy of Dermatology (B.A.D.)

stress promotes the release of damage-associated molecular patterns from stressed melanocytes, facilitating dendritic-cell activation and subsequent autoreactive T-cell responses.⁷ The interferon- γ (IFN- γ)/JAK-STAT/CXCL9–CXCL10–CXCR3 axis is central to the recruitment and maintenance of melanocyte-reactive cytotoxic T cells.⁸ Interleukin-33 (IL-33), a member of the IL-1 cytokine family, functions as an alarmin released during cellular injury and therefore represents a biologically plausible link between tissue stress and inflammatory immune activation.

Notwithstanding this strong mechanistic basis, studies evaluating circulating IL-33 in vitiligo have yielded heterogeneous results, leaving its clinical relevance to be fully established. In a study of 104 patients with non-segmental vitiligo and 56 healthy controls, He et al. found virtually identical median IL-33 concentrations between groups, whereas alarmins such as S100B and HMGB1 showed stronger associations.⁹ Broader analyses of circulating cytokine and alarmin profiles have likewise emphasised marked heterogeneity in biomarker expression.^{10,11} Individual case-control studies have linked particular cytokine patterns to vitiligo, although their findings vary.¹² Conversely, serum IL-33 has been reported to be higher in patients with non-segmental vitiligo than in controls,¹³ and IL-33 concentrations have been associated with treatment response.¹⁴ Whether circulating IL-33 is consistently elevated, whether it can discriminate patients from controls, and whether it reflects clinically graded activity therefore remain unresolved. The present study was undertaken to address these questions in a South Asian cohort.

Materials and Methods

This analytical cross-sectional study was conducted in the Department of Dermatology and Venereology, Bangladesh Medical University, Dhaka, from August 2024 to February 2026, with serum IL-33 estimation performed in the Department of Microbiology and Immunology of the same university. Serum IL-33 concentrations were compared between patients with vitiligo and apparently healthy controls, and the discriminatory performance of IL-33 and its associations with demographic and clinical characteristics were assessed.

Patients of either sex and any age attending the dermatology outpatient department with vitiligo formed the case group. Vitiligo was diagnosed clinically by an experienced dermatologist on the basis of acquired, sharply demarcated, chalky-white, non-scaly depigmented macules or patches, and confirmed by characteristic bluish-white accentuation under Wood's lamp. Age- and sex-comparable healthy volu without

vitiligo served as controls. Participants with psoriasis, atopic dermatitis, systemic lupus erythematosus, rheumatoid arthritis, bronchial asthma, autoimmune diabetes mellitus, Graves' disease or inflammatory bowel disease were excluded, as circulating IL-33 may be altered in these conditions, as were those who had received topical, systemic or phototherapy in the preceding month and pregnant or lactating women.

Participants were enrolled by consecutive non-probability sampling until the target was reached, yielding 36 patients with vitiligo and 36 age- and sex-comparable controls (N = 72).

Each participant underwent a structured interview and complete cutaneous examination recorded on a semi-structured case-record form, documenting age, sex, family history of vitiligo, clinical pattern, VIDA grade and associated dermatoses. Clinical distribution was categorised as generalised, focal, acrofacial, mucosal or combined-pattern vitiligo, and participants were grouped as children/adolescents (<18 years) or adults (≥ 18 years). Lesional activity was graded using the Vitiligo Disease Activity (VIDA) score (+4, activity within the preceding ≤ 6 weeks; +3, 6 weeks–3 months; +2, 3–6 months; +1, 6–12 months; 0, stable for ≥ 1 year; –1, stable for ≥ 1 year with spontaneous repigmentation), with VIDA $\geq +1$ defining active disease.

Three millilitres of venous blood were collected aseptically into a plain clot-activator tube, centrifuged at $1000 \times g$ for 15 minutes at 2–8 °C within 30 minutes, and serum stored at –20 °C until analysis. Serum IL-33 was measured by sandwich ELISA (Human IL-33 ELISA Kit, cat. no. E-EL-H2402; Elabscience Biotechnology, Wuhan, China) per the manufacturer's instructions, with optical density read at 450 ± 2 nm (analytical range 15.63–1000 pg/mL; sensitivity 9.38 pg/mL). Values below the lowest calibration standard were extrapolated from the standard curve and retained without censoring.

Data were analysed in IBM SPSS v23.0. Categorical variables are shown as frequencies (%) and continuous variables as mean $\pm$ SD; as serum IL-33 was right-skewed, median (IQR) is also reported. Groups were compared by independent-samples t-test (age), Pearson's χ^2 or Fisher's exact/Fisher–Freeman–Halton tests (categorical), and Mann–Whitney U test (IL-33); IL-33 across VIDA grades was tested by Kruskal–Wallis H, and its correlation with VIDA score by Spearman's ρ . ROC analysis assessed discrimination, with AUC (95% CI) and the optimal cut-off by maximum Youden index; sensitivity, specificity, predictive values, accuracy, likelihood ratios and the diagnostic odds ratio were derived (Clopper–Pearson CIs for proportions, log-based CIs for likelihood ratios, Woolf logit for the diagnostic odds ratio). Predictive values

reflect the sample's 50% pre-test probability given equal enrolment. All tests were two-sided; $p < 0.05$ was significant.

The protocol was approved by the Institutional Review Board of Bangladesh Medical University (Memo no. BSMMU/2024/7121). Written informed consent was obtained from all adult participants and from a parent or legal guardian for those younger than 18 years.

Results

A total of 72 participants were analysed (36 vitiligo patients, 36 controls). The groups were comparable in age (24.42 ± 13.70 vs 28.20 ± 13.40 years; $p = 0.244$), age-group distribution ($p = 0.911$) and sex (male 63.9% vs 58.3%; $p = 0.629$). Patient ages ranged from 4 to 55 years, with 36.1% younger than 18 years (Table I).

Table I. Demographic characteristics of patients with vitiligo and healthy controls (N=72)

Characteristic	Vitiligo (n=36)	Controls (n=36)	p-value
Age, years			
Mean $\pm$ SD	24.42 $\pm$ 13.70	28.20 $\pm$ 13.40	0.244 ^a
Range	4–55	1–53	—
Age group, n (%)			0.911 ^b
≤10	5 (13.9)	4 (11.1)	
11–20	12 (33.3)	9 (25.0)	
21–30	8 (22.2)	9 (25.0)	
31–40	6 (16.7)	6 (16.7)	
41–50	3 (8.3)	6 (16.7)	
51–60	2 (5.6)	2 (5.6)	
Sex, n (%)			0.629 ^c
Male	23 (63.9)	21 (58.3)	
Female	13 (36.1)	15 (41.7)	

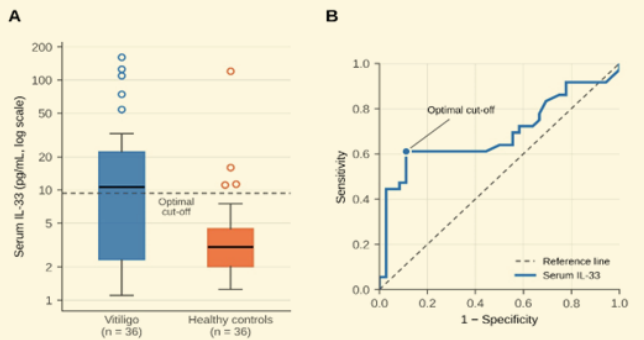
Clinical characteristics. A family history was reported by 8 patients (22.2%). Generalised vitiligo was the commonest pattern (47.2%), followed by combined-pattern (27.8%) and focal disease (22.2%); all combined patterns included mucosal involvement and no segmental cases occurred. Active disease (VIDA $\geq +1$) was present in 31 patients (86.1%), most often VIDA +2 (30.6%) (Table II).

Table II. Clinical characteristics of patients with vitiligo (n=36)

Characteristic	n (%)
Family history of vitiligo	8 (22.2)
Clinical pattern	
Generalised	17 (47.2)
Focal	8 (22.2)
Acrofacial	1 (2.8)
Combined patterns	10 (27.8)
Generalised + mucosal	4 (11.1)
Generalised + acrofacial + mucosal	3 (8.3)
Focal + mucosal	2 (5.6)
Acrofacial + mucosal	1 (2.8)
VIDA score	
–1	1 (2.8)
0	4 (11.1)
+1	6 (16.7)
+2	11 (30.6)
+3	5 (13.9)
+4	9 (25.0)
Active disease (VIDA $\geq +1$)	31 (86.1)
Coexisting dermatosis	
Scabies	4 (11.1)
Seborrhoeic dermatitis	1 (2.8)
None	31 (86.1)

Figure 1. Serum IL-33 in vitiligo patients versus healthy controls.

(A) Box plots of serum IL-33 (log scale); boxes show median and interquartile range, whiskers extend to values within $1.5 \times$ IQR, and open circles denote outliers. The dashed line marks the optimal diagnostic cut-off (9.345 pg/mL); p by Mann–Whitney U test. (B) ROC curve of serum IL-33 discriminating vitiligo patients ($n = 36$) from controls ($n = 36$): AUC 0.691 (95% CI 0.563–0.819; $p = 0.005$). The filled circle marks the optimal cut-off by maximum Youden index (sensitivity 61.1%, specificity 88.9%).



Serum IL-33. Serum IL-33 was markedly right-skewed and significantly higher in patients (median 10.60 pg/mL, IQR 2.32–22.20) than controls (3.03 pg/mL, IQR 2.01–4.44; $p = 0.005$) — approximately 3.5-fold higher — with substantial overlap at lower concentrations (Table III).

Table III. Serum IL-33 concentrations and ROC analysis for discriminating patients with vitiligo from healthy controls

Parameter	Vitiligo (n=36)	Controls (n=36)	p-value
Mean $\pm$ SD, pg/mL	24.03 $\pm$ 36.90	7.16 $\pm$ 19.69	—
Median (IQR), pg/mL	10.60 (2.32–22.20)	3.03 (2.01–4.44)	0.005 ^a
ROC parameter	Estimate	95% CI	p-value
AUC	0.691	0.563–0.819	0.005 ^b
Standard error	0.065	—	—
Optimal cut-off, pg/mL	9.345	—	—
Maximum Youden index	0.50	—	—

Diagnostic discrimination. ROC analysis showed an AUC of 0.691 (95% CI 0.563–0.819; $p = 0.005$). At the exploratory Youden-derived cut-off of 9.345 pg/mL, sensitivity was 61.1% and specificity 88.9%, with PPV 84.6%, NPV 69.6% and accuracy 75.0%; LR+ was 5.50, LR– 0.44 and diagnostic odds ratio 12.57 (95% CI 3.65–43.30) (Tables IV).

Table IV. Cross-classification of serum IL-33 against vitiligo status at the exploratory cut-off (≥ 9.345 pg/mL)

IL-33 result	Vitiligo (n=36)	Controls (n=36)
≥ 9.345 pg/mL	22 (true positive)	4 (false positive)
< 9.345 pg/mL	14 (false negative)	32 (true negative)

Fisher's exact test: $p < 0.001$.

Table V. Diagnostic performance of serum IL-33 at the exploratory cut-off (≥ 9.345 pg/mL)

Diagnostic index	Estimate	95% CI
Sensitivity	61.1% (22/36)	43.5–76.9
Specificity	88.9% (32/36)	73.9–96.9
Positive predictive value ^a	84.6% (22/26)	65.1–95.6
Negative predictive value ^a	69.6% (32/46)	54.2–82.3
Overall accuracy	75.0% (54/72)	63.4–84.5
Positive likelihood ratio	5.50	2.11–14.36
Negative likelihood ratio	0.44	0.29–0.67
Diagnostic odds ratio	12.57	3.65–43.30

IL-33 and clinical features. Serum IL-33 was not associated with sex ($p = 0.365$), age group ($p = 0.897$) or VIDA category ($p = 0.256$), and did not correlate with VIDA score ($p = 0.088$; $p = 0.611$) (Table VI).

Table VI. Serum IL-33 according to demographic and clinical characteristics of patients with vitiligo (n=36)

Characteristic	n (%)	Median IL-33 (pg/mL)	p-value
Sex			0.365 ^a
Male	23 (63.9)	10.10	
Female	13 (36.1)	19.80	
Age			0.897 ^a
<18 years	13 (36.1)	17.40	
≥ 18 years	23 (63.9)	10.40	
VIDA score			0.256 ^b
–1	1 (2.8)	2.20	
0	4 (11.1)	11.70	
+1	6 (16.7)	10.50	
+2	11 (30.6)	19.80	
+3	5 (13.9)	2.30	
+4	9 (25.0)	10.70	
Correlation with VIDA score	—	$\rho = 0.088$	0.611 ^c

Discussion

This study evaluated whether circulating IL-33 differs between patients with vitiligo and healthy individuals and whether it holds diagnostic potential and meaningful clinical correlates as a biomarker. Serum IL-33 was significantly elevated in vitiligo, with a median concentration approximately 3.5-fold greater than that of controls. Nevertheless, its overall discriminatory performance was moderate (AUC 0.691), and the exploratory cut-off of 9.345 pg/mL showed higher specificity (88.9%) than sensitivity (61.1%). IL-33 showed no significant relationship with age, sex, VIDA category or continuous VIDA score.

The elevated IL-33 observed here is biologically plausible within contemporary models of vitiligo pathogenesis, in which oxidative injury to melanocytes activates innate immunity and amplifies melanocyte-specific adaptive responses.¹⁵ The IFN- γ /JAK-STAT/CXCL9–CXCL10–CXCR3 pathway is increasingly recognised as a central inflammatory axis in the disease.¹⁶ Circulating cytokines and chemokines are correspondingly being investigated as biomarkers of activity, prognosis and therapeutic response.¹⁷

Our findings differ from those of He et al., who reported a median IL-33 of 19.0 pg/mL in both patients and controls ($p = 0.818$), with S100B, S100A9, IL-1 α and HMGB1 showing stronger discriminatory properties.⁹ Such inconsistency may reflect differences in population characteristics, vitiligo phenotype, clinical activity, ethnicity, pre-analytical handling or assay platform. In direction of effect, our results align more closely with reports of elevated serum IL-33 in non-segmental vitiligo.¹³

The absence of an association between IL-33 and VIDA is notable because 86.1% of our patients had active disease, suggesting that serum IL-33 does not act as a simple linear

marker of current clinical activity. Stronger activity-related signals have been reported for IFN- γ , CXCL9, CXCL10 and granzyme B.¹⁰ Comprehensive biomarker analyses similarly favour multi-marker models over reliance on a single cytokine.¹⁸ Treatment studies targeting JAK-dependent signalling further show that modulation of inflammatory biomarkers can accompany clinical improvement.^{19,20} Janus kinase inhibitors have accordingly become central to vitiligo management,²¹ a shift reflected in current international recommendations for diagnosis and treatment.^{22,23}

Several limitations warrant emphasis. This small, single-centre, cross-sectional study limits causal inference and generalisability. The absence of segmental cases and a predominance of active disease constrain phenotype-specific comparisons, and the 1:1 case-control design precludes direct extrapolation of PPV and NPV to routine clinical populations. Most importantly, the ROC-derived threshold (9.345 pg/mL) lies below the assay's lowest calibration standard (15.63 pg/mL) and near its analytical sensitivity (9.38 pg/mL); as this value relied on extrapolation, it should be regarded as exploratory rather than clinically validated. Future multicentre studies should use assays validated across the proposed decision range, enrol larger phenotypically diverse cohorts, confirm thresholds externally, and evaluate IL-33 within multi-biomarker panels.

Conclusion

Serum IL-33 was significantly elevated in patients with vitiligo and separated them from healthy controls with high specificity and modest sensitivity, although it did not track VIDA-defined activity. These findings position IL-33 as a promising disease-associated biomarker, best applied as part of a broader diagnostic framework rather than as a standalone diagnostic or activity marker. Larger multicentre longitudinal studies, analytically validated assays, and multi-biomarker models represent the natural next steps toward clinical translation.

Acknowledgement

The authors thank the participants and the staff of the Departments of Dermatology and Venereology and of Microbiology and Immunology, Bangladesh Medical University, Dhaka, for their support.

Conflict of Interest

The authors declare no conflict of interest.

Funding

This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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