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Impacts of Serum Lipocalin-2, Serum Amyloid A, and Calprotectin in Iraqi Patients with Vitiligo

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Abstract

Introduction: Studies on Lipocalin-2, Serum Amyloid A, and Calprotectin have established their relevance to autoimmune and inflammatory conditions, showing their contributions to the etiology and pathogenesis of vitiligo. To determine the serum Lipocalin-2, Serum Amyloid A, and serum Calprotectin levels in patients with vitiligo.

Methods: A case-control study was conducted at the Dermatology Department, Baghdad Teaching Hospital, Baghdad, Iraq (November 2025 – April 2026), enrolling 70 patients with vitiligo and 50 healthy controls. Serum Lipocalin-2 (LCN2), Calprotectin (CAL), and Serum Amyloid A-4 (SAA4) were quantified using BT Laboratory sandwich ELISA kits (Catalog Nos. E1429Hu, E4010Hu, E6165Hu). Statistical analyses included an independent t-test, a one-way ANOVA with Duncan's post hoc test, Spearman's rank correlation, and ROC curve analysis, all performed in IBM SPSS version 27.

Results: Serum Lipocalin-2 was significantly elevated in vitiligo patients compared to controls (718.05 ± 66.844 vs. 434.07 ± 28.805 ng/L; $P<0.001$). Calprotectin was likewise markedly higher in patients (82.88 ± 9.301 vs. 42.51 ± 6.366 ng/mL; $P=0.001$). Serum Amyloid A was also significantly higher in patients than controls (80.62 ± 9.753 vs. 59.45 ± 1.563 ng/L; $P=0.035$). Calprotectin achieved the highest AUC (0.892; 95% CI: 0.831–0.953), with sensitivity of 85.5% and specificity of 84.0%. Lipocalin-2 demonstrated AUC = 0.729, sensitivity 87.0%, specificity 67.0%.

Conclusion: Serum concentrations of Lipocalin-2, Serum Amyloid A, and Calprotectin were higher in patients with vitiligo than in healthy controls. This finding supports the presence of an active inflammatory state in patients with vitiligo. Calprotectin was the strongest inflammatory marker in this study. The three inflammatory markers were positively correlated, indicating they are linked to a common inflammatory pathway in vitiligo.

Keywords: Vitiligo, Lipocalin-2, NGAL, Serum Amyloid A, Calprotectin, Autoimmune skin disease

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Introduction

Vitiligo is a chronic skin condition that results in the loss of skin pigmentation due to the loss of functional melanocytes. It presents as white patches on the skin and mucosal surfaces. Vitiligo is one of the most common skin disorders, affecting 0.5–2% of the world's population. There was no preference for sex or race. This skin condition can occur in individuals of all ages. Vitiligo can have a strong psychosocial impact on people with this condition due to the stigma associated with skin discoloration (1,2). Several factors are known to influence vitiligo, including genetic susceptibility, autoimmune responses, oxidative stress, and environmental triggers (3). Autoimmunity is the primary contributor to melanocyte destruction and is most significant in vitiligo. Numerous studies have shown that the immune system produces inflammatory mediators that destroy melanocytes. This has led to a greater search for inflammatory mediators involved in the development and worsening of vitiligo (3,4). Lipocalin-2 (LCN2) is a multifaceted secreted glycoprotein whose upregulation has emerged as a potential biomarker in various inflammatory, metabolic, infectious, and autoimmune disorders, including vitiligo, due to LCN2's roles in iron metabolism, innate immune response, immune modulation, and stress response of tissues (5). Serum Amyloid A (SAA) is considered a significant acute-phase protein that markedly increases during inflammation and tissue injury. It is mainly produced by the liver and triggered by inflammation-related cytokines such as IL-1β, IL-6, and TNF-α. Studies have hypothesized that SAA is an active player in T-cell migration as well as an inducer of oxidative stress, and since these are the major mechanisms of melanocyte apoptosis, the levels of SAA may be representative of the systemic inflammatory process and disease activity in a patient with vitiligo (6,7). Calprotectin is a heterodimeric protein complex formed by S100A8 and S100A9 calcium-binding proteins, predominantly released by activated neutrophils and monocytes during inflammatory processes. It acts as a damage-associated molecular pattern (DAMP) by binding to TLR4 and RAGE receptors, thereby initiating inflammatory responses. Considerable evidence demonstrates that inflammatory skin disorders, including vitiligo, are marked by the production of inflammatory cytokines, recruitment of leukocytes, and oxidative stress, and calprotectin is now understood to be a central element in the inflammatory

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processes associated with vitiligo (8,9).

Methods

Study Design and Subjects

This case-control study included 120 participants, including 70 patients diagnosed with vitiligo and 50 controls. Patients were recruited from the Dermatology Department, Baghdad Teaching Hospital, Baghdad, Iraq, during the study period from November 2025 to April 2026. The patient group comprised individuals who were clinically diagnosed with vitiligo by a dermatologist. The control group comprised individuals with no personal history of vitiligo or other autoimmune or chronic inflammatory disorders. The control participants were selected to be comparable in age and sex to the patient participants.

Inclusion Criteria

The inclusion criteria included patients who had been clinically diagnosed with vitiligo by a specialist dermatologist, as well as apparently healthy participants of both sexes demonstrating a wide age range who were living in Iraq.

Exclusion Criteria

Participants with other autoimmune diseases and those with acute or chronic inflammatory diseases were also excluded from the study. Patients with any marked liver, kidney, cancer, or other metabolic diseases, pregnant women, and participants who were on immunosuppressive therapy or other therapy were excluded.

Sample Size and Power Analysis

Sample size determination was carried out in G*Power version 3.1.9.7, estimating the sample size based on a t-test for the difference between two independent means. With a moderate effect size (d = 0.5), an alpha error probability of 0.05, and 85% power, the calculated sample size, assuming equal allocation, was 118 participants. The current study comprised 120 participants (70 patients with vitiligo and 50 healthy controls), exceeding the estimated total sample size and thus deemed adequate for statistical analysis.

Sample Collection and Preparation

Venous blood samples were collected from patients with vitiligo and healthy control subjects. The collected blood was allowed to clot at room temperature and then centrifuged to separate the serum. The serum was stored at -20°C until the assay was performed. Following the guidelines in the BT Laboratory ELISA manuals, the samples were thawed completely at room temperature and gently mixed.

ELISA to Determine Immunological Markers

Serum Lipocalin-2 (LCN2), Calprotectin (CAL), and Serum Amyloid A-4 (SAA4) were quantified using BT Laboratory sandwich ELISA kits (Catalog Nos. E1429Hu, E4010Hu, E6165Hu), BT Labs, China. All reagents and protocols were used according to the manufacturer's instructions.

Statistical Analysis

Statistical analysis was carried out using IBM SPSS version 27. Quantitative variables were expressed as mean ± SE, and qualitative variables as numbers and percentages. The independent samples t-test was used to compare vitiligo patients and healthy controls for variables with normal and non-normal distributions, respectively. For non-continuous variables, the Chi-square test, or Fisher's exact test, was used. The relationship of the variables was tested using the Pearson and Spearman correlation tests. For the studied biomarkers, ROC curve analysis was performed to establish their diagnostic value(s), when applicable. A P-value < 0.05 was considered statistically significant.

Results

The demographic characteristics of all participants are presented in Table 1. The study enrolled 70 vitiligo patients, equally distributed between males and 35 females) and 50 healthy controls (24 males and 26 females). The mean age (± SE) was 22.70 ± 1.298 years for patients and 18.96 ± 1.574 years for the controls. The age difference between the two groups was not statistically significant (P = 0.070), confirming that the two groups were broadly comparable.

Serum Lipocalin-2 levels were significantly higher in patients with vitiligo than in healthy controls (mean ± SE: 718.05 ± 66.84 vs. 434.07 ± 28.81 ng/L; median: 561.54 vs. 371.57 ng/L; P < 0.001). Serum Amyloid A was significantly elevated in patients compared to controls (80.62 ± 9.75 vs. 59.45 ± 1.56 ng/L; median: 57.70 vs. 57.63 ng/L; P = 0.035). Serum Calprotectin levels demonstrated the most pronounced elevation among all inflammatory markers, with patients recording markedly higher levels than controls (82.88 ± 9.30 vs. 36.28 ± 1.36 ng/mL; median: 60.63 vs. 32.43 ng/mL; P < 0.001), as illustrated in Table 2.

Sex-based subgroup analysis revealed that serum Lipocalin-2 levels differed significantly among male patients, female patients, male controls, and female controls (672.39 ± 95.38, 763.72 ± 94.42, 395.09 ± 34.62, and 470.05 ± 44.74 ng/L, respectively; P = 0.007). Serum Amyloid A showed significant differences among the studied subgroups (78.39 ± 14.40, 82.86 ± 13.35, 54.53 ± 1.85, and 63.99 ± 2.14 ng/L, respectively; P = 0.019). Serum calprotectin levels also varied significantly among

Table 1. Demographic characteristics of vitiligo patients and healthy controls

Parameter	Male Patients (n = 35)	Female Patients (n = 35)	Male Controls (n = 24)	Female Controls (n = 26)
Age (years)	22.70 ± 1.30	22.69 ± 2.01	18.96 ± 2.43	19.00 ± 1.81
n (%)	35 (50%)	35 (50%)	24 (48%)	26 (52%)

Age: patients 22.70 ± 1.298 vs. controls 18.96 ± 1.574; P = 0.070 (ns). Values are Mean ± SE.

the four groups (74.75 ± 8.94, 91.01 ± 16.35, 33.24 ± 0.53, and 51.06 ± 12.10 ng/mL, respectively; $P = 0.007$), as shown in Table 3.

Table 4 presents a comparison of biochemical markers between male and female patients with vitiligo. No statistically significant differences were detected for Lipocalin-2 (672.39 ± 95.383 vs. 763.72 ± 94.416 ng/L; F = 0.463; $P = 0.499$), Serum Amyloid A (78.39 ± 14.403 vs. 82.86 ± 13.354 ng/L; F = 0.052; $P = 0.820$), or calprotectin (74.75 ± 8.943 vs. 91.01 ± 16.348 ng/mL; F = 0.762; $P = 0.386$) between male and female patients.

Serum concentrations of Lipocalin-2, Calprotectin and Amyloid A were significantly higher in patients with vitiligo than in healthy controls (median: 561.54 vs. 371.57 ng/L; $P < 0.001$; 57.70 vs. 57.63 ng/L; $P = 0.035$; 60.63 vs. 32.43 ng/mL; $P < 0.001$, respectively). Serum Lipocalin-2, Amyloid A, and Calprotectin levels were significantly higher in both male and female patients with vitiligo than in healthy controls (median: 535.0 and 583.0 vs. 371.6 and 371.6 ng/L; $P = 0.007$; 60.7 and 57.1 vs. 55.8 and 64.0 ng/L; $P = 0.019$; 62.4 and 56.0 vs. 32.2 and 35.7 ng/mL; $P < 0.001$), respectively, as illustrated in Figure 1.

As illustrated in Table 5, Spearman's rank correlation analysis within the patient group (n = 70) revealed highly significant positive correlations among the three inflammatory markers: Lipocalin-2 and Calprotectin (r = 0.567; $P < 0.001$), Serum Amyloid A and Calprotectin (r = 0.506; $P < 0.001$), and Lipocalin-2 and Serum Amyloid A (r = 0.360; $P = 0.002$).

As shown in Table 6, the three markers demonstrated statistically significant discriminatory performance in separating patients with vitiligo from healthy controls. Calprotectin achieved the highest AUC (0.892; 95% CI: 0.831–0.953; $P < 0.001$), with an optimal cut-off of ≥ 38.65 ng/mL, yielding a sensitivity of 85.5% and specificity of 84.0%. Lipocalin-2 also demonstrated good and significant discriminatory performance (AUC = 0.729; 95% CI: 0.636–0.822; $P < 0.001$), with a cut-off of ≥ 374.46 ng/L providing a sensitivity of 87.0% and specificity of 67.0%. Although Serum Amyloid A (AUC = 0.498; 95% CI: 0.394–0.602; $P = 0.970$) did not reach statistical significance, the cutoff was ≥ 77.26 ng/L (sensitivity 21.7%; specificity 95.6%), as presented in Table 6 and Figure 2.

Discussion

Vitiligo is a complex, chronic acquired depigmentation disorder driven by the selective autoimmune destruction of epidermal melanocytes. The pathogenesis of vitiligo is increasingly understood as a multifaceted convergence of genetic predisposition, environmental triggers, oxidative stress burden, and severe dysregulation of both innate and adaptive immune signaling pathways (10). The autoreactive destruction of melanocytes is primarily orchestrated by cytotoxic CD8 + T-lymphocytes, which are guided by IFN-γ signaling and critical chemokine gradients, particularly CXCL9 and CXCL10(10,11). However, this adaptive T-cell-mediated cascade does not occur in isolation; it is simultaneously activated and amplified by innate immune cells, including neutrophils and monocytes, which release a constellation of inflammatory mediators. Our current study investigated the serum concentrations of LCN2, Calprotectin, and SAA in patients with vitiligo compared to healthy controls, providing compelling evidence that these innate immune and acute-phase inflammatory markers are significantly elevated in vitiligo and are intricately linked to its pathogenesis.

The initial trigger for vitiligo pathogenesis is increasingly recognized to be oxidative stress in melanocytes. Melanin synthesis, while essential for photoprotection,

Table 2. Biochemical markers between vitiligo patients and healthy controls

Parameter	Patients (n = 70) Mean ± SE	Controls (n = 50) Mean ± SE	t	*P*-value
Lipocalin-2 (ng/L)	718.05 ± 66.844	434.07 ± 28.805	3.902	**< 0.001** ***
Serum Amyloid A (ng/L)	80.62 ± 9.753	59.45 ± 1.563	2.144	0.035 *
Calprotectin (ng/mL)	82.88 ± 9.301	42.51 ± 6.366	3.582	**0.001** **

*** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$. Values are Mean ± SE.

Table 3. One-way ANOVA of inflammatory markers across four sex-dependent subgroups

Parameter	Male Patient (n = 35)	Female Patient (n = 35)	Male Control (n = 24)	Female Control (n = 26)	F	*P*-value
Lipocalin-2 (ng/L)	672.39 ± 95.38^{bc}	763.72 ± 94.42^{c}	395.09 ± 34.62^{a}	470.05 ± 44.74^{ab}	4.244	**0.007****
Amyloid A (ng/L)	78.39 ± 14.40^{b}	82.86 ± 13.35^{b}	54.53 ± 1.85^{a}	63.99 ± 2.14^{a}	2.412	0.019*
Calprotectin (ng/mL)	74.75 ± 8.94^{bc}	91.01 ± 16.35^{c}	33.24 ± 0.53^{a}	51.06 ± 12.10^{ab}	4.268	**0.007****

Different superscript letters indicate significant post-hoc differences (Duncan test). ** $P < 0.01$; * $P < 0.05$. Values are Mean ± SE.

Table 4. Within-patient sex comparison of inflammatory markers between male and female vitiligo patients

Parameter	Male Patients (n = 35) Mean ± SE	Female Patients (n = 35) Mean ± SE	F	*P*-value
Lipocalin-2 (ng/L)	672.39 ± 95.383	763.72 ± 94.416	0.463	0.499 ns
Serum Amyloid A (ng/L)	78.39 ± 14.403	82.86 ± 13.354	0.052	0.820 ns
Calprotectin (ng/mL)	74.75 ± 8.943	91.01 ± 16.348	0.762	0.386 ns

ns = non-significant ($P > 0.05$). Values are Mean ± SE.

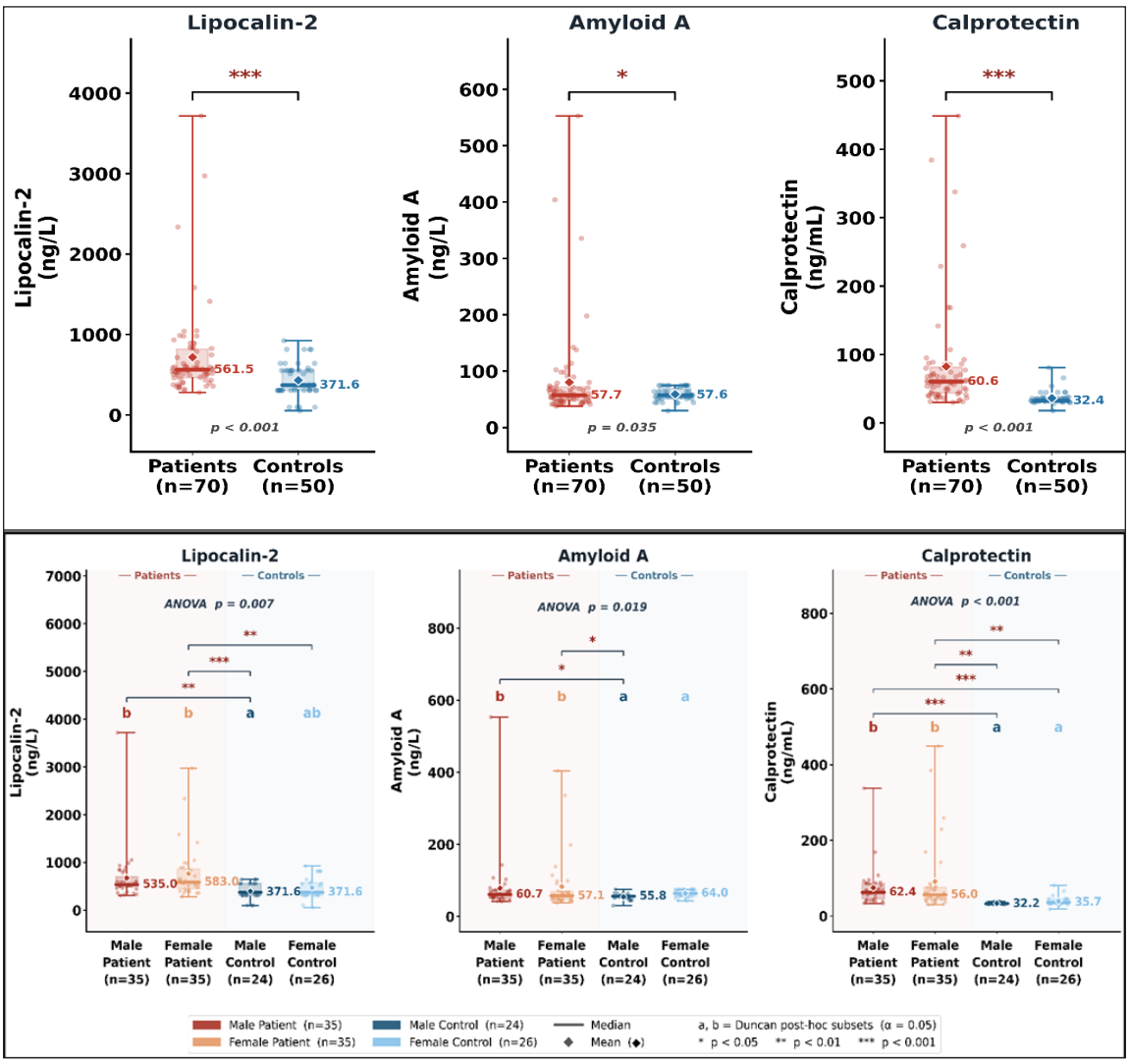

Figure 1. Lipocalin-2, Amyloid A, and Calprotectin median plotting in the studied groups

Table 5. Spearman's rank correlation matrix of inflammatory markers in vitiligo patients

	Lipocalin-2	Serum Amyloid A	Calprotectin
Lipocalin-2	—	r = 0.360, p = 0.002 **	r = 0.567, *P* < 0.001 ***
Serum Amyloid A	r = 0.360, *P* = 0.002 **	—	r = 0.506, *P* < 0.001 ***
Calprotectin	r = 0.567, *P* < 0.001 ***	r = 0.506, p < 0.001 ***	—

*** *P* < 0.001; ** *P* < 0.01. r = Spearman's rank correlation coefficient.

Table 6. ROC curve analysis: diagnostic performance of inflammatory markers for vitiligo

Marker	AUC	SE	95% CI	*P*-value	Cut-off	Sn%	Sp%
Lipocalin-2 (ng/L)	0.729	0.047	0.636 – 0.822	**< 0.001*** **	≥ 374.46 ng/L	87.0%	67.0%
Serum Amyloid A (ng/L)	0.498	0.053	0.394 – 0.602	0.970 ns	≥ 77.26 ng/L	21.7%	95.6%
Calprotectin (ng/mL)	0.892	0.031	0.831 – 0.953	**< 0.001*** **	≥ 38.65 ng/mL	85.5%	84.0%

AUC = Area Under the Curve; SE = Standard Error; CI = Confidence Interval; Sn = Sensitivity; Sp = Specificity. Optimal cut-off at maximum Youden index (J = Sensitivity + Specificity − 1). *** *P* < 0.001; ns = non-significant (*P* > 0.05).

paradoxically generates substantial amounts of reactive oxygen species (ROS) through its biosynthetic pathway (12). Under normal physiological conditions, melanocytes maintain homeostasis through a robust antioxidant defense system comprising catalase, superoxide dismutase (SOD), glutathione peroxidase (GPX), and other antioxidant enzymes. However, in vitiligo patients, this protective mechanism is compromised, leading to ROS accumulation and subsequent melanocyte dysfunction (12). Recent evidence demonstrates that persistent ROS exposure induces endoplasmic reticulum (ER) stress and mitochondrial dysfunction in melanocytes, triggering the release of damage-associated molecular patterns (DAMPs) and melanocyte-specific autoantigens

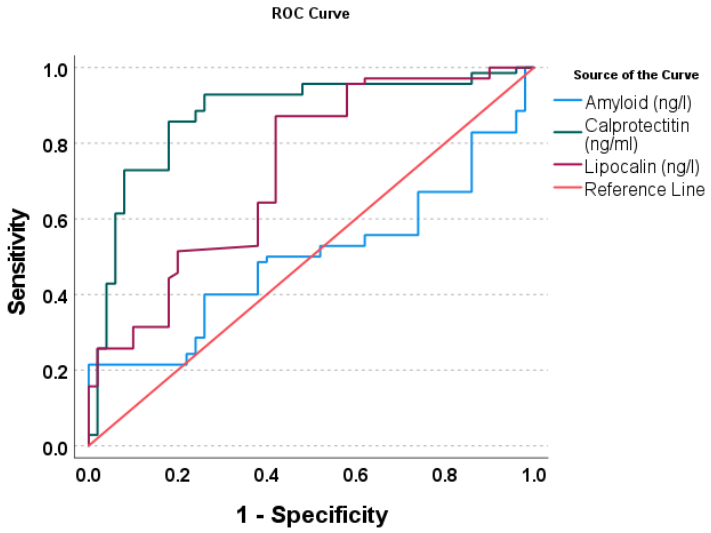

Figure 2. ROC curve analysis of serum biomarkers for vitiligo

(10,12). This oxidative stress-induced activation of innate immunity represents the critical bridge between initial melanocyte damage and the subsequent adaptive immune response that perpetuates disease progression.

The significant elevation of LCN2 observed in our vitiligo cohort (718.05 ± 66.84 ng/L vs. 434.07 ± 28.81 ng/L; $P < 0.001$) aligns with its emerging role as a critical multi-faceted secreted glycoprotein in autoimmune and inflammatory conditions. In the context of vitiligo, the inflammatory environment promotes the release of LCN2 from activated neutrophils and monocytes, which subsequently enhances neutrophil survival and epidermal trafficking(13,14). By sequestering iron-containing siderophores, LCN2 regulates iron availability within the inflammatory microenvironment, creating conditions that favor oxidative stress and immune cell activation. Recent clinical investigations corroborate our findings; for instance, Nassar et al reported significantly elevated LCN2 concentrations in vitiligo patients, proposing that this elevation serves as evidence of systemic neutrophil-mediated inflammatory activity extending beyond the localized cutaneous lesions (15). Their study suggested that LCN2 could serve as a vital marker for early diagnosis and tracking disease pathogenesis, with levels correlating to disease severity (15). Additionally, broader research indicates that elevated LCN2 levels correlate with systemic immune dysregulation, including heightened T-cell activation markers and altered dendritic cell function, which lends biological plausibility to its function as an amplifying systemic inflammatory signal in the vitiligo autoimmune cascade (14,15).

Our analysis revealed a marked elevation of Calprotectin in patients with vitiligo (82.88 ± 9.30 ng/mL vs. 42.51 ± 6.36 ng/mL; $P = 0.001$), which demonstrated the highest diagnostic performance among the evaluated markers (AUC = 0.892; sensitivity 85.5%; specificity 84.0%). Calprotectin specifically binds to Toll-like receptor 4 (TLR4) and the Receptor for Advanced Glycation End-products (RAGE) on immune cells, initiating robust inflammatory signaling pathways that amplify NF-κB-mediated cytokine production (16,17). Our results are strongly supported by recent literature. Atak et al investigated serum calprotectin levels in patients with vitiligo. They found significantly higher levels than in healthy controls, suggesting its active involvement in the disease's etiopathogenesis, independent of specific clinical subtypes (17). The profound elevation of S100A8/A9 complexes suggests that calprotectin-mediated alarmin signaling may precede and potentiate the adaptive T-cell response responsible for melanocyte destruction (10,17). The excellent discriminatory performance of calprotectin observed in our ROC analysis underscores its immense potential as a reliable, non-invasive biomarker for assessing disease activity and monitoring the inflammatory burden in patients with vitiligo. Furthermore, calprotectin's role in recruiting and activating dendritic cells suggests it functions as a critical amplifier of the innate-to-adaptive immune transition.

Our study demonstrated that SAA was significantly higher in patients with vitiligo than in controls (80.62 ± 9.75 ng/L vs. 59.45 ± 1.56 ng/L; $P = 0.035$). SAA is a major acute-phase protein produced primarily by the liver in response to inflammatory cytokines, particularly IL-1β, IL-6, and TNF-α. The significant elevation of SAA in our patient cohort aligns with the modern conceptualization of vitiligo not merely as a localized skin condition, but as a disease characterized by ongoing systemic acute-phase inflammatory activation and metabolic abnormalities (11). Recent comprehensive analyses by Papaccio et al highlighted that vitiligo patients frequently exhibit elevated systemic inflammatory markers (including IL-6 and CXCL10) alongside metabolic disturbances such as increased advanced glycation end-products (AGEs), altered oxidative stress indicators, and dysregulated fatty acid profiles (11). Therefore, SAA participates not only as a passive marker of systemic inflammation but as an active contributor to the self-sustaining inflammatory loop in vitiligo. It is proposed that SAA-mediated innate immune receptor activation may serve as an early amplifying signal that bridges oxidative stress-induced melanocyte damage

with the subsequent destructive adaptive T-cell response (10,11).

Recent evidence highlights the critical role of regulatory T cells (Tregs) in maintaining immune tolerance and preventing the development of vitiligo. A comprehensive 2026 review by Qiu et al. demonstrated that vitiligo patients exhibit reduced Treg frequency in peripheral blood, impaired suppressive capacity, and Th1-like polarization of residual Tregs (18). Furthermore, tissue-resident and antigen-specific Treg subsets are markedly decreased within vitiligo lesions, and the pro-inflammatory microenvironment characterized by elevated LCN2, calprotectin, and SAA further compromises their function (18). This systemic-to-local Treg dysregulation leads to insufficient suppression of autoreactive CD8 + T cells and persistent melanocyte destruction. The elevated inflammatory markers documented in our study likely contribute to this Treg dysfunction through multiple mechanisms, including direct suppression of Treg differentiation and enhanced Th1 polarization of existing Tregs.

A pivotal finding of our study is the highly significant positive correlation among the three inflammatory markers: LCN2, Calprotectin, and Serum Amyloid. This strong co-correlation confirms that these proteins do not fluctuate independently but rather participate in a unified, synchronized inflammatory network. The concurrent elevation of these markers reflects a complex interplay where initial oxidative stress and DAMP release (Calprotectin) trigger innate immune activation, leading to acute-phase responses (SAA) and sustained neutrophil/monocyte activity (LCN2), which collectively create a hostile, pro-inflammatory microenvironment conducive to autoreactive T-cell-mediated melanocyte apoptosis (10). This unified network is further amplified by the dysregulation of regulatory T cells and the failure of local immune tolerance mechanisms (19-22).

Conclusion

The study provides robust evidence that serum concentrations of Lipocalin-2, Calprotectin, and Serum Amyloid A are significantly elevated in patients with vitiligo, reflecting a profound and active systemic inflammatory state. Calprotectin emerged as the strongest diagnostic marker, while Lipocalin-2 also exhibited substantial discriminatory value. The positive correlations among these markers underscore their shared involvement in the intricate inflammatory pathways driving vitiligo pathogenesis. Recognizing vitiligo as a systemic inflammatory disorder rather than a strictly localized cutaneous defect is crucial for understanding disease mechanisms and developing targeted interventions. These findings suggest that Lipocalin-2, Calprotectin, and SAA hold significant promise as non-invasive biomarkers for monitoring inflammatory activity, assessing disease severity, predicting treatment response, and potentially guiding targeted therapeutic interventions to disrupt the innate immune amplification loop and restore regulatory T cell function in vitiligo. Future studies should investigate the longitudinal changes in these markers during disease progression and in response to various therapeutic modalities, and explore their utility in predicting treatment outcomes and identifying patients at risk for severe or rapidly progressive disease.

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Authors' Contribution

Conceptualization: Saja Abed Alnaser, Entedhar Rifaat Sarhat.
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Supervision: Entedhar Rifaat Sarhat.
Validation: Saja Abed Alnaser.
Visualization: Saja Abed Alnaser.
Writing–Original Draft: Saja Abed Alnaser.
Writing–Review & Editing: Saja Abed Alnaser, Entedhar Rifaat Sarhat.

Competing Interests

The authors declare no competing interests, financial or otherwise.

Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available due to participant privacy and confidentiality concerns, but are available from the corresponding author upon reasonable request.

Ethical Approval

Ethical approval for the study was obtained from the relevant institutional ethics committee before the commencement of sample collection. (code MIDTUH13 on 16/4/2026).

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