Original Article

Evaluation of Factors Associated with a History of Skin Cancer in Patients with Actinic Keratosis: AKASI as a Clinical Tool for Risk Stratification

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Abstract

Aim: We aimed to investigate the clinical, demographic, and laboratory factors associated with a personal history of skin cancer in patients with actinic keratosis (AK), incorporating the actinic keratosis area and severity index (AKASI) and systemic inflammatory markers to identify potential risk factors for malignancy.

Materials and Methods: This single-center, cross-sectional study enrolled 110 patients with AK. Participants were categorized as having a histopathologically confirmed personal history of skin cancer (n = 33) or no personal history of skin cancer (n = 77). Demographic data, clinical characteristics, AKASI scores, and systemic inflammatory indices derived from complete blood counts were collected. Between-group comparisons were performed using appropriate statistical tests.

Results: Patients with a history of skin cancer were significantly older (73.6 ± 12.5 vs. 69.0 ± 9.3 years; $P = 0.036$), had longer AK duration (median, 60 vs. 36 months; $P = 0.003$), and had higher total AKASI scores (median, 5.4 vs. 3.9; $P = 0.044$) than those without a history of skin cancer. Right facial AKASI scores were also significantly higher ($P = 0.035$). Receiver operating characteristic analysis identified a total AKASI cut-off of 3.75, with fair discriminatory performance (area under the curve = 0.621, $P = 0.044$). No significant differences were observed in systemic inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR), derived NLR, platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio, mean platelet volume-to-platelet ratio, systemic immune-inflammation index, and systemic inflammation response index, between groups.

Conclusion: Older age, longer disease duration, and greater AK severity, as measured by AKASI, are associated with a personal history of skin cancer among patients with AK, whereas systemic inflammatory indices are not associated. AKASI may be useful for clinical risk stratification and patient surveillance.

Keywords: Actinic keratosis, actinic keratosis area and severity index, skin cancer

Introduction

Actinic keratosis (AK) is one of the most common dermatological diagnoses encountered in daily clinical practice, particularly among older individuals with significant ultraviolet (UV) radiation exposure. Often considered a hallmark of chronic photodamage, AK represents a spectrum of epidermal keratinocyte dysplasia that may regress, remain stable, or progress to invasive squamous cell carcinoma (SCC).[1,2] Epidemiologically, AK affects up to 60% of the adult population in sun-exposed regions, with prevalence increasing

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with age, fair skin phototype, and cumulative sun exposure.[3] The concept of "field cancerization" underscores the idea that AK is not an isolated lesion, but part of a larger area of genetically altered skin at risk of malignant transformation.[4] Consequently, AK serves not only as a precursor to SCC but also as a clinical marker for heightened cutaneous oncologic risk.[5,6]

In daily practice, the burden of AK is often quantified by lesion counting; however, this approach insufficiently captures the extent of field cancerization and severity of individual lesions. To address this, Dirschka et al.[7] proposed the actinic keratosis area and severity index (AKASI), a composite score that incorporates the extent of involvement, lesion distribution, erythema, and thickness across four anatomical regions of the head. Subsequent work confirmed the reproducibility of AKASI and showed that it correlates with physician-based global severity assessments more robustly than total lesion count does.[8] Importantly, higher AKASI scores have been associated with an increased incidence of invasive cutaneous SCC in patients with chronically UV-damaged skin, supporting its use as a quantitative indicator of oncologic risk within the actinic field.[9]

Recent studies have also explored the role of systemic inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) as prognostic factors in cutaneous malignancies, particularly melanoma and non-melanoma skin cancers (NMSC).[10-14] However, data on these markers in the context of AK remain scarce and inconclusive. It remains to be determined whether systemic inflammation contributes meaningfully to the carcinogenic process in early-stage, pre-invasive lesions such as AK.

In this context, our study aimed to investigate the clinical, demographic, and hematologic parameters associated with a personal history of skin cancer among patients diagnosed with AK. By integrating AKASI scoring and systemic inflammatory indices, we sought to evaluate potential predictors of malignancy risk, with the aim of enhancing early identification and clinical management of high-risk individuals.

Materials and Methods

Study Design and Patient Selection

This single-center, cross-sectional study was conducted at the dermatology outpatient clinic of our hospital over a three-month period. Consecutive patients who received a clinical diagnosis of AK were invited to participate during their dermatologic evaluation. Patients who provided written informed consent were enrolled in the study. The exclusion criteria included pediatric patients; individuals with genodermatoses associated with an increased risk of skin cancer (e.g., xeroderma pigmentosum, Gorlin syndrome); individuals with an unclear or unverified history of skin cancer; individuals who did not provide informed consent; and patients with hematological or lymphoproliferative disorders (such as leukemia, lymphoma, or polycythemia vera) that could affect blood count parameters. The study protocol was approved by the Uşak University Non-Interventional Clinical Research Ethics Committee (approval number: 395-395-17, date: 06.06.2024) and was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic information (age and sex), anthropometric measurements [height, weight, and body mass index (BMI)], and smoking status (current, former, or never) were collected for each participant. The presence of systemic immunosuppression, defined as an underlying immunosuppressive condition and/or the use of immunosuppressive medication, was also recorded. The Fitzpatrick skin phototype was determined for all participants. Skin cancer-related clinical data included a personal history of histopathologically confirmed skin cancer [including basal cell carcinoma (BCC), SCC, melanoma, or other skin malignancies] and a family history of skin cancer in first-degree relatives. AK-specific clinical variables included age at AK onset and disease duration (in months), the latter defined as the time elapsed from the patient-reported onset of the first AK lesion to the study enrollment date.

Inflammatory Parameters

Complete blood count (CBC) results were obtained within three months prior to enrollment. Patients without accessible CBC data during this period were excluded from the hematologic analyses. The recorded CBC parameters included white blood cell count (WBC), absolute counts of neutrophils (Neu), lymphocytes (Lym), and monocytes (Mon), hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin (MCH), MCH concentration, red cell distribution width (RDW), platelet count (Plt), mean platelet volume (MPV), plateletcrit, and platelet distribution width. Using these variables, the following systemic inflammatory indices were calculated: (NLR = Neu/Lym), derived NLR [dNLR = Neu/(WBC–Neu)], monocyte-to-lymphocyte ratio (MLR = Mon/Lym), (PLR = Plt/Lym), and MPV-to-platelet ratio (MPR = MPV/Plt). Additionally, more complex composite indices were derived: [SII = (Neu × Plt)/Lym] and systemic inflammation response index [SIRI = (Neu × Mon)/Lym].[11,15]

AKASI Calculation

The clinical severity of AK on the head was assessed using the AKASI. Scoring was performed by the enrolling dermatologist (one of the three study authors) at the time of evaluation. The AKASI system, originally proposed by Dirschka et al.,[7] divides the head into four anatomical regions: the scalp, the forehead, the right facial region, and the left facial region. For each region, four parameters are assessed: percentage of skin area affected, lesion distribution, erythema intensity, and thickness of the most severe lesion. These parameters are graded on predefined ordinal scales. A regional subscore is calculated by multiplying the sum of the component scores by a region-specific coefficient. The total AKASI score is obtained by summing all four regional subscores, yielding a value ranging from 0 (no AK) to 18 (maximum severity).[7-9]

Group Classification

After data collection, patients were categorized into two groups based on their personal history of skin cancer: (i) skin cancer group: patients with histopathologically confirmed skin cancer (current or prior); and (ii) non-skin cancer group: patients without a history of skin cancer. The two groups were compared in terms of demographic and clinical characteristics, AKASI scores, and laboratory parameters, including individual CBC indices and derived inflammatory markers.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). To detect a statistically significant difference between patients with and without a history of skin cancer in the primary outcome (mean total AKASI score) and secondary outcomes (hematologic inflammatory indices), the minimum required sample sizes were estimated as 52 participants for the primary outcome and at least 102 participants for the secondary outcomes, based on a statistical power of 80% and a Type I error rate (α) of 5%. Numerical variables were examined for normality using appropriate graphical methods and tests, and were then summarized as mean ± standard deviation for approximately normally distributed data or as median (interquartile range) for skewed data. Categorical variables were expressed as counts and percentages. Between-group comparisons of continuous variables were performed using independent-samples t-tests or Mann–Whitney U tests, as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off values. A two-sided P-value < 0.05 was considered statistically significant.

Results

A total of 110 patients diagnosed with AK were included in the study. Of these, 33 patients (30%) with a personal history of histopathologically confirmed skin cancer were assigned to the skin cancer group, whereas the remaining 77 patients (70%) comprised the non-skin cancer group. Among patients with skin cancer, 13 had a history of SCC, 22 had a history of BCC (4 of whom had histories of both SCC and BCC), and 2 had a history of melanoma. Table 1 summarizes the demographic, clinical, and laboratory features of patients with AK, along with a comparative analysis between those with and without a history of skin cancer.

The mean age of the entire cohort was 70.4 ± 10.5 years and was significantly higher in the skin cancer group than in the non-skin cancer group (73.6 ± 12.5 vs. 69.0 ± 9.3; $P = 0.036$). There were no statistically significant differences between the groups in terms of sex distribution, height, weight, or BMI ($P > 0.05$ for all). Similarly, no significant differences between the groups were observed in smoking status, Fitzpatrick skin phototype distribution, immunosuppression status, or family history of skin cancer ($P > 0.05$ for all comparisons).

Regarding disease characteristics, the mean age at AK onset was comparable between the groups (66.2 ± 12 vs. 65.3 ± 8.6; $P = 0.689$). However, the duration of AK (months) was significantly longer in the skin cancer group [60 (24–108) vs. 36 (12–60); $P = 0.003$]. In terms of disease severity, the median total AKASI score was significantly higher in patients with a history of skin cancer than in those without [5.4 (3.6–6.3) vs. 3.9 (2.7–5.7), $P = 0.044$]. A significant difference was also noted in the right facial AKASI scores [1.8 (1.5–2.1) vs. 1.5 (1.2–1.8); $P = 0.035$], whereas the other regional scores (scalp, forehead, and left face) were comparable between the groups ($P > 0.05$ for all).

ROC analysis was performed to determine the optimal cut-off value of the total AKASI score for predicting a history of skin cancer. The area under the curve (AUC) was 0.621 (95% confidence interval: 0.512–0.731, $P = 0.044$), indicating fair discriminatory ability. The cut-off point of 3.75 yielded the highest Youden index (J = 0.221), corresponding to a sensitivity of 72.7% and a specificity of 49.4%. Therefore, a total AKASI score ≥ 3.75 may serve as a clinically relevant threshold to stratify patients with a possible history of skin cancer.

Table 1. Comparison of demographic and clinical features, AKASI scores, and inflammatory parameters between patients with and without skin cancer

Variables*	Skin cancer group (n = 33, 30%)	Non-skin cancer group (n = 77, 70%)	Total (n = 110, 100%)	*P*
Age (years)	73.6 ± 12.5	69.0 ± 9.3	70.4 ± 10.5	0.036
Sex Female Male	 17 (51.5%) 16 (48.5%)	 48 (62.3%) 29 (37.7%)	 65 (59.1%) 45 (40.9%)	0.3
Body weight (kg)	70.7 ± 12.4	75.4 ± 14.7	74.0 ± 14.2	0.106
Height (cm)	165 (157–170)	160 (155–170)	160 (155–170)	0.743
BMI (kg/m^2)	26 (23–30)	28.4 (25–31.2)	27.6 (24.7–31.1)	0.092
Smoking status Non-smoker Current smoker Former smoker	 22 (66.7%) 2 (6.1%) 9 (27.3%)	 61 (79.2%) 7 (9.1%) 9 (11.7%)	 83 (75.5%) 9 (8.2%) 18 (16.4%)	0.226
Fitzpatrick skin phototype I II III IV Light-skinned (types I–II) Darker-skinned (types III–IV)	 1 (3%) 20 (60.6%) 12 (36.4%) 0 (0%) 21 (63.6%) 12 (36.4%)	 4 (5.2%) 46 (59.7%) 26 (33.8%) 1 (1.3%) 50 (64.9%) 27 (35.1%)	 5 (4.5%) 66 (60%) 38 (34.5%) 1 (0.9%) 71 (64.5%) 39 (35.5%)	 1
Presence of immunosuppression	1 (3%)	3 (3.9%)	4 (3.6%)	1
Positive family history of skin cancer	2 (6.1%)	10 (13%)	12 (10.9%)	0.505
Skin cancer subtype SCC BCC Melanoma	 13 (39.4%) 22 (66.7%) 2 (6.1%)	 - - -	 13 (11.8%) 22 (20%) 2 (1.8%)	
Age at AK onset (years)	66.2 ± 12	65.3 ± 8.6	65.6 ± 9.7	0.689
Disease (AK) duration (months)	60 (24–108)	36 (12–60)	36 (12–81)	0.003
AKASI score Scalp Forehead Left face Right face Total	 0 (0–0) 1.2 (0–1.8) 1.8 (1.2–2.1) 1.8 (1.5–2.1) 5.4 (3.6–6.3)	 0 (0–0) 1.2 (0–1.5) 1.5 (1.2–1.8) 1.5 (1.2–1.8) 3.9 (2.7–5.7)	 0 (0–0) 1.2 (0–1.8) 1.5 (1.2–2.1) 1.6 (1.2–2.1) 4.3 (3.0–6.2)	 0.709 0.2 0.254 0.035 0.044
Inflammatory parameters NLR dNLR PLR MLR MPR SII SIRI	 2.1 (1.6–3) 1.6 (1.3–2) 111.8 (88.5–152.7) 0.2 (0.2–0.3) 0 (0–0.1) 517.8 (363.3–602) 1 (0.7–1.7)	 2 (1.4–2.6) 1.5 (1.2–1.8) 116.8 (91.6–143.7) 0.2 (0.2–0.3) 0 (0–0.1) 473.3 (342.6–640.2) 0.9 (0.5–1.4)	 2 (1.5–2.7) 1.6 (1.2–1.9) 116.3 (91.2–145.2) 0.2 (0.2–0.3) 0 (0–0.1) 483.7 (348.9–633.5) 1.0 (0.6–1.5)	 0.393 0.389 0.841 0.163 0.9 0.498 0.183

*Data are presented as mean ± SD, median (IQR), or n (%), as appropriate
AK: Actinic keratosis, AKASI: Actinic keratosis area and severity index, BMI: Body mass index, SCC: Squamous cell carcinoma, BCC: Basal cell carcinoma, NLR: Neutrophil-to-lymphocyte ratio, dNLR: Derived neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, MPR: Mean platelet volume-to-platelet count ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, SD: Standard deviation, IQR: Interquartile range

Among the hematologic inflammatory indices, none of the parameters, including NLR, dNLR, PLR, MLR, MPR, SII, and SIRI, showed statistically significant differences between the skin cancer and non-skin cancer groups ($P > 0.05$ for all). These inflammatory indices were also evaluated across skin cancer subtypes (i.e., patients with SCC vs. patients without SCC, patients with BCC vs. patients without BCC, and patients with melanoma vs. patients without melanoma). Similarly, no statistically significant differences were observed between the groups (all $P > 0.05$). In the correlation analysis, neither total nor right facial AKASI scores were significantly associated with systemic inflammatory markers (NLR, PLR, MLR) or composite indices such as SII and SIRI (all $P > 0.05$).

Discussion

In this study, we evaluated the demographic, clinical, and hematological characteristics of patients diagnosed with AK to investigate their associations with a history of skin cancer. Our findings revealed significant differences between patients with and without a history of skin cancer. Patients with a history of skin cancer were older, had longer AK duration, and had higher AKASI scores. These results support the notion that age and cumulative sun exposure are critical factors in the development of skin cancer.[5,6,16] Although hematologic inflammatory parameters were evaluated, no significant differences were observed between groups.

AK is recognized as a precursor to SCC and increasingly viewed as an *in situ* carcinoma because of its potential for malignant transformation. Both AK and SCC exhibit atypical keratinocyte proliferation in the basal and lower spinous layers of the epidermis, with shared molecular alterations such as p53 mutations and UV-signature DNA damage.[17] The annual rate of transformation of AK lesions to SCC ranges from 0.025% to 16%, depending on risk factors.[1] About 60-80% of cutaneous SCCs arise in areas with preexisting AK.[2,18]

Field cancerization highlights that visible AK may reflect broader oncogenic risk in the surrounding skin.[4] AK has been associated with an increased risk of other skin cancers, including BCC and melanoma. In a Swedish cohort study, Guorgis et al.[6] found that AK patients had elevated risks of all major skin cancers, with hazard ratios of 7.7 for SCC, 4.4 for BCC, and 2.7 for melanoma. The highest risk was for SCC, supporting AK as a direct precursor of SCC. In an Australian study, a history of AK was among the top predictors in a melanoma risk model.[19] These findings suggest that AK, especially when severe, predicts SCC risk and indicates photodamage that predisposes to cutaneous malignancies.

Advanced age is a recognized risk factor for cutaneous malignancies due to cumulative UV exposure and age-related decline in immune surveillance.[1] Studies show that longer AK duration and greater extent reflect more severe field cancerization and indicate higher malignant potential.[20,21]

The AKASI has been increasingly utilized to evaluate both the extent and the severity of AK in sun-exposed areas, such as the face and scalp.[7] In our study, patients with a history of skin cancer had significantly higher AKASI scores, suggesting its utility both as a grading tool and as a risk-stratification index for cutaneous malignancies. A multicenter validation study by Pellacani et al.[8] confirmed AKASI's reproducibility and reliability, reporting high intra- and inter-observer consistency (intraclass correlation coefficient > 0.90). They found it superior to total lesion count for assessing disease burden, particularly in cases with confluent erythema and field changes that are common in chronic photodamage. Schmitz et al.[9] showed that AKASI correlates with subclinical field cancerization, with higher scores indicating more extensive keratinocyte dysplasia and UV damage, which are established precursors of SCC and BCC.

Acar and Karaarslan[22] found elevated AKASI scores in patients with previous or current NMSC and proposed a cut-off value of 5.1 to distinguish between patients with and without skin cancer (P = 0.013). Our analysis identified a lower threshold (cut-off = 3.75 for total AKASI) with an AUC of 0.621. These differences may arise from semi-subjective elements in AKASI scoring, such as assessment of erythema and lesion confluence, which can vary between observers despite training. Interobserver variability, differences in clinical experience, and lighting conditions can influence outcomes.[7,8] This necessitates larger studies with standardized protocols to validate thresholds across populations. It should also be noted that these values are calculated based on a history of skin cancer. Prospective studies with long-term follow-up of patients are needed to assess its importance for estimating future risk of skin cancer. Despite these limitations, AKASI remains valuable for evaluating AK severity and field cancerization, potentially enhancing detection strategies and treatment monitoring.

Certain established risk factors, such as systemic immunosuppression and a family history of skin cancer, were not significantly associated with skin cancer in our study population. This divergence may be explained by several factors. Our cohort included a small number of immunosuppressed individuals, limiting statistical power. Previous studies linking immunosuppression to aggressive SCC have often focused on organ transplant recipients or patients with hematologic malignancies, who were underrepresented in our sample.[23] Family history is often underreported in elderly patients, potentially explaining the lack of association.

The role of systemic inflammation in skin cancer development has recently received increased attention. Blood-derived indices have been proposed as biomarkers reflecting tumor-associated immune dysregulation; however, clinical performance varies across studies of melanoma and NMSC, and evidence for precancerous conditions, such as AK, is limited.

In an analysis of United States adults from the National Health and Nutrition Examination Survey, Zhao et al.[11] found that individuals with the highest SII had higher odds of NMSC. Chiu et al.[13] found that higher NLR, PLR, and RDW, and lower lymphocyte-to-monocyte ratio, were associated with worse survival in cutaneous SCC. Maeda et al.[24] showed

that elevated NLR was associated with reduced survival and increased sentinel lymph node positivity. Derebaşınlıoğlu et al.[10] reported higher inflammatory indices in SCC than in BCC and linked higher SII to lymph node metastasis.

Hematologic inflammatory indices from CBC have been linked to melanoma stage and prognosis. In a cohort of 2,721 patients with melanoma, NLR, PLR, and MLR increased with advancing stage, and higher baseline values of these markers were independently associated with poorer melanoma-specific and overall survival.[25] Meta-analyses show that elevated pretreatment NLR is associated with poorer overall and progression-free survival in melanoma.[14,26] For PLR, individual studies suggest prognostic utility, but pooled evidence is inconsistent. One study found PLR independently predicted overall survival,[27] while a meta-analysis showed no significant association with survival outcomes.[28] Composite indices show peripheral blood inflammation indices correlate with advanced cutaneous melanoma,[29] and analyses suggest higher SII associates with increased melanoma odds.[30] However, in advanced melanoma receiving immunotherapy, the pan-immune-inflammation value and SII varied by stage but did not predict response or survival.[31]

The lack of significant associations in our AK cohort may reflect limited statistical power, the presence of many "skin cancer" cases that are prior diagnoses rather than active tumors, and the small number of melanoma cases in our sample, as most supportive data are derived from melanoma cohorts. Cancer-related inflammation varies with tumor stage and condition; different tumors elicit distinct inflammatory responses. AK occurs within a field of cancerization, and localized immune activity may not produce measurable systemic biomarker changes unless invasion or widespread immunosuppression occurs, suggesting the need to study localized and molecular biomarkers for early lesion stratification. Their routine use in AK risk assessment requires larger prospective studies to determine their role in early detection and in predicting progression.

Study Limitations

This study has several limitations. First, the study was a single-center, cross-sectional analysis conducted over a limited period, which limits generalizability and precludes causal inference regarding the associations among AK severity, systemic inflammatory indices, and skin cancer history. AK was diagnosed clinically without histopathological confirmation, potentially introducing diagnostic misclassification. The primary outcome was a personal history of confirmed skin cancer, rather than incident or future cases of cancer; key AK variables (e.g., onset and duration) relied on patient report, thereby introducing recall bias. The statistical power was limited by the modest cohort size (n = 110) and by the small number of patients with prior skin cancer (n = 33), including two cases of melanoma. The inflammatory markers were derived from CBC within three months prior to enrollment and may not reflect inflammation at a time point relevant to carcinogenesis. AK severity was scored by the enrolling dermatologist; despite AKASI's utility, its semi-subjective components may contribute to measurement variability.

Despite its limitations, our study is important, as it is one of the first to evaluate the prognostic relevance of systemic inflammatory indices in AK patients. By incorporating AKASI into the analysis, we found that standardized AK severity scoring for risk stratification.

Conclusion

Collectively, our results suggest that systemic inflammatory indices may have limited practical value for risk assessment in AK, whereas clinical severity measures, such as AKASI, may help identify higher risk patients. Therefore, older patients, those with a longer disease duration, and particularly those with higher AKASI scores may warrant closer surveillance for skin cancer.

Ethics

Ethics Committee Approval: The study protocol was approved by the Uşak University Non-Interventional Clinical Research Ethics Committee (approval number: 395-395-17, date: 06.06.2024) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Patients who provided written informed consent were enrolled in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.E., S.K.Y., N.D.Ö., Concept: E.E., S.K.Y., N.D.Ö., Design: E.E., Data Collection or Processing: E.E., S.K.Y., N.D.Ö., Analysis or Interpretation: E.E., S.K.Y., Literature Search: E.E., Writing: E.E.

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