Dermatology Practical & Conceptual

Comparison of Actinic Keratosis and Severity Index with Physician Global Assessment and Total Lesion Count and the Ability to Predict Skin Cancer

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Key words: actinic keratosis, AKASI, physician global assessment, skin cancer, total lesion count

Citation: Acar A, Karaarslan I. Comparison of actinic keratosis and severity index with physician global assessment and total lesion count and the ability to predict skin cancer. *Dermatol Pract Concept.* 2022;12(1):e2022031. DOI: https://doi.org/10.5826/dpc.1201a31

Accepted: August 14, 2021; **Published:** January 2022

Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Actinic keratosis (AK) is a known indicator for sun damage, and subsequent squamous cell cancer may develop. The actinic keratosis and severity index (AKASI) is a recently developed tool that can evaluate both field cancerization and AK severity.

Objectives: We sought to evaluate if AKASI was a good predictor of cancer in AK patients and to compare AKASI with both the Physician Global Assessment (PGA) and total lesion count (TLC).

Methods: Ninety patients with AK were included in the study. Each patient was examined, and AKs were scored with AKASI, PGA and TLC by 2 dermatologists. The AKASI, PGA and TLC values were compared between patients with skin cancer and patients without skin cancer.

Results: Mean AKASI, PGA, and TLC scores were 4.9, 1.7 and 9 respectively. The patients with skin cancer had higher scores of AKASI, PGA and TLC compared to the patients without skin cancer ($P = 0.022$, $P = 0.014$, $P = 0.005$, respectively). AKASI, PGA and TLC were very strongly correlated with each other ($P < 0.001$). The AKASI threshold value for non-melanoma skin cancer was determined to be 5.1.

Conclusions: AKASI, PGA and TLC may be used in the assessment of the severity of AK in daily practice or studies and may be considered as valuable tools in determining high-risk patients and to choose treatment option. AKASI seems to have an advantage to give a numeric threshold value for skin cancer.

Introduction

Actinic keratoses (AK) are hyperkeratotic lesions on sun-damaged skin characterized by atypical epidermal proliferation of keratinocytes that have a potential for malignant transformation to squamous cell carcinoma (SCC). They are generally asymptomatic, erythematous, or pigmented papules or plaques with scales, located on sun-exposed areas like the face, scalp, ear helices, and dorsum of the hand [1]. Excessive exposure to ultraviolet (UV) radiation is the major cause of AK. Fairer skin types, older age, chronic use of systemic immunosuppressive drugs, and exposure to arsenic have also been described as risk factors [2-4]. In addition to immunosuppressive drugs, other drugs, such as voriconazole, calcium channel blockers, BRAF inhibitors, hedgehog inhibitors, hydroxyurea, and psoralen plus UVA therapy have been linked to a higher risk for AK and SCCs [5-8]. On the other hand, oral retinoids and nicotinamide have been linked to a reduction in the risk of AK and SCC [9].

The estimated risk for an individual AK to transform into SCC has been reported to be 0.075%-0.096% annually [2]. Although most of AKs regress spontaneously or persist without a malignant transformation, the major concern is the difficulty in estimating which lesion might have a higher potential for malignancy. The thickness or hyperkeratosis of an individual AK lesion does not have equal SCC progression risk [10]; thus, treatment is highly recommended for each AK lesion. In recent years, the term field cancerization (FC), which describes an area of severe sun damage with multiple AKs, telangiectasia, wrinkles, dyschromia and elastosis, has been proposed [11] and FC treatment has been recommended for a better management of the patients [3]. The identification of patients with a higher risk for malignant transformation is another important issue to consider when deciding which patients should be included in a closer follow-up program.

There have been some efforts to grade the risk of patients with malignant potential. The Physician Global Assessment (PGA) scale is a subjective assessment tool that allows the physician to evaluate the overall situation of the patient [12]. PGA grades AKs in five categories (0: clear, 1: almost clear, 2: mild, 3: moderate, 4: severe) [12]. The total lesion count (TLC), in which physician counts the clinically evident AK lesions, is another suggested way to evaluate a patient both before and after the therapy [13]. Recently, the actinic keratosis and severity index (AKASI) has been suggested [12]. The AKASI supplies a numerical score on an index and evaluates both the severity of AK and FC (Table 1) [12]. AKASI has also been reported to be useful in monitoring treatment outcomes [10]. In AKASI score, the head is divided into 4 regions: scalp, forehead, left face (cheek, ear, chin, and nose), and right face. The scalp constitutes 40% of the head region, and each of the other areas constitutes 20%. For each of the 4 areas, the percentage of actinic damage is scored 0 to 6. The most prominent AK distribution, erythema, and thickness are assessed from 0-4. The maximum AKASI value is 18. The pivotal study proposed an AKASI score of 2.9 as mild, 5.3 as moderate, 8.3 as severe, 8.7 as very severe [12].

Objectives

In the literature, the data on the association between non-melanoma skin cancer and AKASI, PGA, and TLC is limited [14]. In this study, we sought to evaluate this association and discuss the ability of these methods to predict skin malignancy.

Methods

The study was approved by the local ethics committee (no: 70198063-050.06.04). Patients with AK, who were referred to our dermato-oncology unit within a 6-month period and who signed the informed consent form, were involved in the study. Patients with a history of photosensitivity, non-melanoma skin cancer (NMSC)-prone genodermatoses, and melanoma were excluded.

A detailed anamnesis on accompanying diseases, drug usage, previous history of NMSC, duration of the present lesions, and the Fitzpatrick skin type were recorded. A total-body skin and dermoscopic examination were performed for each patient. The patients were examined by 2 dermatologists at the same time in order to avoid any interobserver variability. The AKASI, PGA and TLC values were noted.

Descriptive statistics of the data were given as mean, standard deviation, median, minimum, maximum, frequency and percentage values. Normality assumption of quantitative data was checked by Shapiro-Wilk test. Independent sample t-test was used for variables with normal distribution, while Mann-Whitney U test and Kruskal-Wallis test (Dunn test for paired comparisons) were used for variables that did not provide the assumption of normality. The correlation of quantitative data with each other was evaluated with Spearman Rho correlation coefficient. Relationships between categorical variables were examined using the Pearson Chi-square test. A receiver operating characteristic (ROC) analysis was used to determine a cutoff point for diagnostic methods. Statistical analysis was performed using IBM SPSS Statistics 25.0 (IBM SPSS Statistics for Windows, Version 25.0, IBM) package program. The significance level was set at 0.05 in all analyses.

Table 1. Definition of Components of Actinic Keratosis Area and Severity Index (AKASI) and How to Calculate AKASI Score*

Evaluation of AKASI [12]		
AKASI Components	**Definitions**	
Solar damage (SD)	Head is divided to 4 areas: scalp (S), forehead (F), right half of the face (R), left half of the face (L). Skin with solar damage for each of the 4 areas is estimated and scored 0-6. 0 (0%), 1(1-9%), 2(10-29%), 3(30-49%), 4(50-69%), 5 (70-89%), 6 (90-100%).	
Distribution of AK (D)	0	No AK
	1	Isolated or scattered AK
	2	Clustered (Small clusters up to 25 cm^2)
	3	Clustered and confluent (AKs are coalescing in a cluster of <25 cm^2)
	4	Confluent (AKs are coalescing and cannot be easily distinguish)
Erythema of AK (E)	0	No erythema
	1	Slight red
	2	Moderate red
	3	Intense red
	4	Very intense red
Thickness of AK (T)	0	No palpable or visible AK
	1	Just palpable AK
	2	Clearly palpable
	3	Thickened
	4	Very thickened
Total AKASI score (0-18)	0.4 x (D+E+T+SD of scalp) + 0.2 x (D+E+T+SD of forehead) + 0.2 x (D+E+T+SD of right face) + 0.2 x (D+E+T+SD of left face)	

*Adapted from the report of Dirschka et al [12].

AK = actinic keratosis; AKASI = actinic keratosis area and severity index.

Results

A total of 90 patients were involved in the study. Fifty-four patients (60%) were males. The age range was 48-87 years (mean age was 69 years and median age was 71). The accompanying diseases were hypertension (43%), diabetes mellitus (27%), coronary arterial disease (CAD) (14%), solid organ malignancy (13%), inflammatory or autoimmune skin diseases (13%), solid organ transplantation (6%) and others (asthma, vertigo, Parkinson disease, migraine, gut, essential thrombocytosis, familial Mediterranean fever, hepatitis B) (10%). Fourteen patients (16%) were receiving calcium channel blockers, 9 patients (10%) were receiving immunosuppressive drugs, and 1 patient was receiving hydroxyurea. The distribution of Fitzpatrick skin type was as follows: 73 patients (81%) had Fitzpatrick skin type II and 17 patients (19%) had type III. The duration of the present AK lesions ranged from 2 months to 30 years. The mean duration was 7 years. Mean AKASI was 4.9, mean PGA was 1.7 and mean TLC was 9.3. Mean AKASI was 6 in male patients and 3 in female patients. The difference between male and female patients was statistically significant ($P < 0.001$). Mean PGA was 2 in male and 1 in female patients. Mean TLC was 11 in male and 7 in female patients. The difference between male and female patients of PGA and TLC was statistically significant ($P < 0.001$, $P = 0.002$).

Fifty-one patients (57%) did not have any current skin cancer or skin cancer history. A total of 39 patients (43%) had a current skin cancer and/or past history of skin cancer. Among them, 28 patients (31.1%) had only previous skin cancer history, 8 patients (8.8%) had only concurrent skin cancer, and 3 patients (3.3%) had both concurrent skin cancer and previous skin cancer history. Nineteen patients (21.1%) had only basal cell carcinoma (BCC) and BCC count was 26. Thirteen patients (14.4%) had only SCC and SCC count was 21. Seven patients (7.7%) had both SCC and BCC, tumor count was 29 (11 for SCC and 18 for BCC). One patient who had both BCC and SCC also had 2 basosquamous cell carcinomas. Total tumor count was 78 (44 for BCC, 32 for SCC, and 2 for basosquamous cell carcinoma). In all but 7 patients all the tumors were located on the face or scalp. In 7 patients, 14 tumors (8 BCCs and 6 SCCs) were located on an extremity or trunk. None of the patients had skin cancer metastasis.

All items were compared between the group with previous or present skin cancer (Group A, n = 39) and the group with no history of skin cancer (Group B, n = 51) (Table 2). The mean age in group A was 70 years (median 73 years), and the mean age in group B was 69 years (median 70 years). The mean age of the patients was higher in the group with skin cancer, but it was not statistically significant (P = 0.261). Mean and median AK duration was longer in the group A (mean 9, median 9) compared to the group B (mean 6, median 5). Having longer AK duration in the group A was statistically significant (P = 0.009). The distribution of demographic features and scores of AKASI, PGA and TLC in the two groups are shown in Table 2. There was no statistically significant relationship between having skin cancer and gender (P = 0.794), or accompanying diseases. However statistically significant relationship was found with not having CAD (P = 0.028). AK duration was significantly related with AKASI, PGA and TLC scores (P = 0.038, P = 0.010, P = 0.016). Mean and median AKASI, PGA score and TLC were higher in group A (mean 6, median 6; mean 2, median 2; and mean 11, and median 11, respectively) compared to group B (mean 4, median 4; mean 2, median 1 and mean: 8, and median 7, respectively) (Table 2). The higher scores of AKASI, PGA and TLC in group A were statistically significant (P = 0.022, P = 0.014, P = 0.005).

Nineteen patients with high risk drugs or diseases for skin cancer had higher AKASI scores and it was statistically significant (P = 0.033). These patients had also higher mean PGA and TLC values, which were not statistically significant (P = 0.077, P = 0.221).

Patients were also grouped as no skin cancer (group I, n = 51 patients), patients with only BCC (group II, n = 19 patients), patients with only SCC (group III, n = 13 patients), and patients with both BCC and SCC (group IV, n = 7 patients). Mean AKASI score, PGA, and TLC were highest in group IV. The ranking of mean values of scores was: group III, II, and I respectively. The increase in the mean values of AKASI, PGA, and TLC from group I to group IV was statistically significant (P = 0.026, P = 0.026, P = 0.038). The total number of skin cancer counts (previous and present) were not related with AKASI, PGA, and TLC (P = 0.064, P = 0.075, P = 0,149).

AKASI, PGA, and TLC were correlated with each other (P < 0.001). Correlation between AKASI and PGA, between AKASI and TLC, and between PGA and TLC were very strong (r = 0.881, r = 0.893, r = 0.849). As a result of ROC analysis, the AKASI threshold value for total NMSC was determined to be 5.1 (P = 0.022, area = 0.642). The AKASI thresholds for SCC and BCC according to ROC analysis were 5.5 (P = 0.056, area = 0.682) and 6.9 (P = 0.926, area = 0.509), respectively. Total NMSC threshold value was statistically significant. However, threshold values for only BCC or only SCC groups were not statistically significant.

Table 2. Comparison Between the Group with Previous or Present Skin Cancer (Group A) and the Group with No History of Skin Cancer (Group B).

	Group A	Group B
Male percent	62%	59%
Mean and median age	70, 73	69, 70
Mean and median AK duration (years)	9, 9	6, 5
Mean and median AKASI	6, 6	4, 4
Mean and median PGA	2, 2	2, 1
Mean and median TLC	11, 11	8, 7

AK = actinic keratosis; AKASI = actinic keratosis area and severity index; PGA = Physician Global Assessment; TLC = total lesion count.

Conclusions

In order to determine the malignant transformation risk in AK, there is a need for scoring the disease extent and overall severity rather than evaluating the individual lesion. PGA and TLC have been used for determining the severity of AK. Recently, in 2017, AKASI was proposed by Dirschka et al [12]. In 2018, Pellacani et al compared AKASI with TLC [13] and found AKASI a reproducible method that can be used in clinical trials as an alternative to TLC. Although no significant difference was found between AKASI and TLC in the interobserver variability, AKASI had a slightly higher intra-class correlation coefficient compared to TLC. They stated that either of the 2 methods could be used [13]. In 2018, Schmitz et al investigated the association between AKASI and keratinocytic tumors [14]. They concluded patients with SCC had a higher AKASI score compared to patients with BCC, Bowen disease or AK solely [14]. Schmitz et al suggested that the AKASI score of 3 is consistent with mild, 5.5 moderate, 8.5 severe, and > 11 very severe AK. Their estimated AKASI score for invasive SCC development was found to be 7, median AKASI scores of 4.8, and 7.1 and PGA 2 and 2.5 in patients with BCC and SCC respectively [14]. Additionally, AKASI was used in studies evaluating AK treatment outcomes [10, 15-18].

In 2017, Dréno et al [19] recommended the actinic keratosis field assessment scale (AK-FAS) to evaluate the severity of AK and sun damage, as AK-FAS evaluates AK area percentage, hyperkeratosis and sun damage. The AK area is graded as I-IV (< 10%, 10%-25%, > 25%-50%, and > 50%) according to percentage of AK covering the face or scalp. Hyperkeratosis and sun damage are assessed as absent or present [19]. In 2019, AKFAS together with AKASI was used in a study of both dermoscopic and reflectance confocal microscopic evaluation of AK before and after imiquimod therapy [15]. We preferred to use AKASI over AK-FAS because AK-FAS does not provide a numerical value as AKASI does.

In the present study, the median AKASI, PGA, and TLC values were found to be significantly higher in patients with NMSC compared with patients without NMSC. These values were highest in the patients who had both BCC and SCC and in the patients who had SCC alone. Additionally, AKASI, PGA, and TLC were well correlated. The AKASI threshold value for NMSC was determined to be 5.1; male patients had significantly higher AKASI, PGA, and TLC scores compared to female patients. The patients with current skin cancer or skin cancer history had significantly longer AK duration, higher AKASI, PGA, and TLC scores compared to patients without skin cancer or history of skin cancer. Patients who had an immunosuppressive condition (drugs, solid organ transplantation, and systemic malignancy) had significantly higher AKASI scores compared to patients without an immunosuppressive condition.

Our study employed AKASI, PGA and TLC to assess the severity of AK and to evaluate the relationship with malignancy risk. We conclude that AKASI, PGA, and TLC may be used in the assessment of the severity of AK in daily practice or studies. Although a longer period is needed for calculation of AKASI, it seems advantageous to have a numerical threshold value for skin cancer. This is the second study that evaluates this threshold value in the literature. To establish a common value, more studies are needed.

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