A multicenter retrospective analysis of the clinical and pathological characteristics of 1188 cases of actinic keratosis in different ultraviolet radiation intensity areas of China

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Abstract
Background: Actinic keratosis (AK) is a precancerous disease, caused by ultraviolet radiation (UV).
Objective: To analyze the clinical and pathological characteristics of AK in four areas with different ultraviolet radiation intensities.
Methods: 1188 diagnosed AK patients, from January 2000 to July 2015, in dermatology department of four hospitals were collected. The UV intensity of hospital located cities from high to low is Kunming, Yinchuan, Shenyang and Nanjing. The information comes from medical records, and the pathological types and Keratinocyte Intraepithelial Neoplasia (KIN) grades were checked by two experienced pathologists.
All information was conducted a retrospective multicenter research.
Results: The patients were mainly middle-aged and elderly female, which was in direct contrast to the majority of men in European. The age of onset in Kunming group was lower than that in Yinchuan Group ($p = 0.013$) and Nanjing Group ($p < 0.01$). The course of disease in Kunming group was significantly shorter than that in Nanjing Group ($p < 0.001$). The lesions were almost located in the exposed area. The proportion of unexposed areas in Shenyang group was significantly higher than that in other groups ($p < 0.001$). There were statistical differences in pathological morphological classification among the four groups. These differences were not affected by age and

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[Correction added on November 8, 2021, after first online publication: Dan Xu, Jian-Fang Sun, Rui-Qun Qi, and Wei Zhang are co-first authors. Also, academic degrees have been updated.]
Actinic keratosis (AK), also known as solar keratosis, is a precancerous disease. This is one of the most common conditions treated by dermatologists in western countries. AKs can potentially progress into squamous cell carcinoma (SCC), with annual rates of transformation ranging from 0.025% to 20%. Studies have shown AK prevalence of 59%–49% in European countries, 4.5%–14% in the USA, and 40%–60% in Australia (Queensland). However, the prevalence of AK in Asian countries was much lower, 0.41% in Japan, 1.38% in Korea and about 0.30%–1.20% in China. With increased number of aging population, and more outdoor activities, the prevalence of AK is increasing, both globally and in China.

AK is caused by ultraviolet radiation (UV), the first sign of severe solar damage of the skin. Reported risk factors for the development of AK include certain phenotypic characteristics, such as red hair, blue-eyes, and fair skin (Fitzpatrick skin phototypes I–III). AK mostly occurs in the elderly people, and it has been reported that the proportion of males in Caucasian population is higher compared with female. But precise data on AK clinical feature was limited in eastern Chinese patients. Because of different genetic background, skin type, lifestyle and accumulated sun exposure, the clinical feature of AK in whole China was unknown.

To understand AK and analyze the related factors affecting AK onset, we collected 1188 cases of the clinical and pathological data of AK patients from four different hospitals. The four hospitals are located in capital of four provinces, from high UV intensity to low, they were Kunming in southwest of China, Yinchuan in northwest of China, Shenyang in northeast of China, and Nanjing in east of China respectively, with different height, greenhouse gas emission intensity (GHG) and so on. The clinical and pathological characteristics of AK were analyzed among four hospitals. We found the patients were mainly middle-aged and elderly female, which was in direct contrast to the majority of men in European. And that the onset age, disease course was lower and shorter of Kunming group compared with other groups, demonstrating that close correlation of UV and AK. The proportion of unexposed lesions and the number of KIN III grade patients in Shenyang group was significantly higher than that in other three groups, demonstrating the industry pollution and other factors also influence the characters of AK.

Conclusion: The Asian patients were mainly female. The clinical characteristics of AK are closely related to UV intensity, and environmental pollution, lifestyle, religious beliefs and other factors are also related.

KEYWORDS
actinic keratosis, clinical characteristics, pathological characteristics, retrospective analysis

INTRODUCTION

This retrospective multicenter study was performed at the departments of dermatology in four hospitals. The hospitals from four provincial capitals included were First Affiliated Hospital of Kunming Medical University (Kunming) in southwestern China, The General Hospital of Ningxia Medical University (Yinchuan) in northwestern China, The First Hospital of China Medical University (Shenyang) in northeastern China, and Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College (Nanjing) in eastern China, according to the UV intensity from high to low. The detailed latitude, altitude, height, UV intensity and GHG depicted in Figure 1. Patients diagnosed as AK between January 2000 and July 2015 by pathological biopsy were included in the study. And found out those tissue sections, two experienced dermatopathologists were employed to conduct a reexamination. Those who met the diagnostic criteria were included, patients who didn’t meet diagnostic criteria or had incomplete data were excluded. The study was approved by the relevant ethics committees of all participating institutions.

MATERIAL AND METHODS

Patients

Basic patient information, including gender, age, time of visit, and clinical information such as lesion location and the course of disease, were collected from the medical records. According to the overall seasonal characteristics of China, February to April were defined as spring, May to July as summer, August to October as autumn, and November to January as winter, the number of visit patients in four seasons was divided.

Clinical data collection

Two experienced dermatopathologists in each institution reviewed the slides, checked the pathological results, and classified the pathological morphology and keratinocytic intraepidermal neoplasia (KIN) grades. The type of AK, according to the histopathological classification, could be divided into the following listed types: hypertrophic, atrophic, acantholytic, pigmented, Bowenoid, lichenoid. According
to the KIN classification, the sections were classified as KIN I, II or III on the basis of the percentage of abnormal cells out of the intraepidermal neoplasia by Roewert-Huber et al.29,30 Grade I confined to the abnormal proliferation of cells, and limited to the lower third of the epidermis; Grade II includes atypical keratinocytes extending to the lower two-thirds of the epidermis; Grade III includes full thickness atypia of the epidermis. Disagreements were resolved by consultation between the two dermatopathologists using a double-headed microscope.

2.4 | Statistical analysis

Statistical analysis was performed using SPSS 19.0 software (IBM Corporation). Normality of distribution was evaluated using the Kolmogorov-Smirnov test. Variables with normal distribution were compared by using ANOVA, and the values were presented as means ± standard deviation. For variables with abnormal distribution, Kruskal-Wallis test was used for comparison, and the values were presented as median (interquartile range), and post-hoc test was used for comparison of data between the groups. Categorical variables were presented as frequencies and were analyzed using chi-square or Fisher’s exact test, as appropriate. Two-sided p-values <0.05 were considered to be statistically significant.

3 | RESULTS

3.1 | Baseline data

A total of 1188 AK patients were included in this study. All the AK patients were classified according to different regions: 579 cases (48.7%) were from Nanjing, 330 cases (27.8%) from Kunming, 196 cases (16.5%) from Shenyang and 83 cases (7.0%) from Yinchuan, respectively. The average age of AK is over 65. The age of patients in Kunming group were younger, with statistical significance compared with that in Yinchuan Group (p = 0.013) and Nanjing Group (p < 0.01). Meanwhile, the patients in the four groups were mostly female, the ratio of female patients was lowest in Yinchuan group, which had significance difference with other three groups (p < 0.001) (Table 1).
The average disease course of AK was more than 1 year, and the time in patient of Kunming group was significantly shorter than that of patients in Nanjing group \((p < 0.001)\), and no significant difference was observed between the other groups. AK lesions in four groups were mainly located at the exposed site, and the proportion of the unexposed site in Shenyang group was significantly higher than that in other groups \((all p < 0.001)\). No significant difference was found between the four groups in the season of patient’s visit, but relatively few patients visited in winter (Table 1).

### 3.2 Pathological characteristics of AK patients

According to the histopathological classification, six kinds of classifications (atrophic, hypertrophic, acantholytic, pigmented, Bowenoid, and lichenoid) showed different distributions among the four region groups \((p < 0.001)\) (Figures 2 and 3). The ratio of atrophic type was highest in Nanjing group patient \((n = 205, 35.4\%)\), while the ratios of hypertrophic type were highest in Kunming, Shenyang and Yinchuan groups, respectively. The pigmented type was only seen in Nanjing group \((n = 30, 5.2\%)\). However, the ratio of acantholytic type \((n = 22, 3.8\%)\) was lowest in Nanjing group (Table 2).

The KIN classification of AK also showed significant differences among the groups of various regions. Compared with the patients from Nanjing, Kunming and Yinchuan, the ratio of Grade III was higher in Shenyang Group \((p < 0.05)\) (Table 2).

### 3.3 The influence of age

Based on this study and other papers from scholars in China\(^{15,18,31}\), the average age of AK patients is about 65 years old, so we defined the age of 65 as the boundary, divided the patients from four regions into two groups, patients under 65 years old (65 years old inclusive) and patients over 65, so as to analyze the influence of age on clinical and pathological characteristics. Same as the general trend, the disease course of patients under 65 years old in Kunming group was significantly shorter than that in Nanjing group \((p = 0.005)\). And the

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**TABLE 1** Comparison of clinical characteristics

|                  | Nanjing \((n = 579)\) | Kunming \((n = 330)\) | Shenyang \((n = 196)\) | Yinchuan \((n = 83)\) | \(p\)  |
|------------------|------------------------|-----------------------|------------------------|-----------------------|-------|
| Ages (years)     | 70 (62–78)             | 67 (56–75)\(^a\)      | 68 (58–76)             | 72 (65–77)\(^b\)     | <0.001|
| Male ratio (n, %)| 189 (32.6)             | 91 (27.6)             | 63 (32.1)              | 38 (45.8)\(^a,b,c\)  | 0.016 |
| Course of disease (month) | 27 (12–36)\(^a\) | 15 (12–36)\(^a\) | 24 (12–36)             | 24 (10–40)            | 0.003 |
| Biopsy season    |                        |                       |                        |                       | <0.001|
| Spring (n, %)    | 163 (28.2)             | 87 (26.4)             | 39 (19.9)              | 17 (20.5)             |       |
| Summer (n, %)    | 211 (36.4)             | 87 (26.4)             | 59 (30.1)              | 24 (28.9)             |       |
| Autumn (n, %)    | 98 (16.9)              | 84 (25.4)             | 71 (36.2)              | 29 (34.9)             |       |
| Winter (n, %)    | 107 (18.5)             | 72 (21.8)             | 27 (13.8)              | 13 (15.7)             |       |
| Exposed-areas (n, %) | 577 (99.7)         | 314 (95.2)\(^a\)     | 169 (86.2)\(^a,b\)    | 80 (96.4)\(^a,c\)    | <0.001|
| Scalp            | 31                     | 6                     | 8                      | 2                     |       |
| Ears             | 17                     | 15                    | 3                      | 3                     |       |
| Hand             | 6                      | 7                     | 4                      | 1                     |       |
| Forehead         | 14                     | 18                    | 4                      | 1                     |       |
| Upper limbs      | 4                      | 5                     | 10                     | 1                     |       |
| Neck             | 5                      | 6                     | 0                      | 0                     |       |
| Cheeks           | 349                    | 147                   | 65                     | 30                    |       |
| Nose             | 47                     | 37                    | 29                     | 20                    |       |
| Jaw              | 5                      | 3                     | 1                      | 3                     |       |
| Temple           | 60                     | 43                    | 30                     | 10                    |       |
| Periorbital      | 39                     | 22                    | 12                     | 9                     |       |
| Lips             | 0                      | 5                     | 3                      | 0                     |       |
| Unexposed-areas (n, %) | 2 (0.3)             | 16 (4.8)\(^a\)       | 27 (13.8)\(^a,b\)     | 3 (3.6)\(^a,c\)      | <0.001|
| Lower limbs      | 1                      | 2                     | 5                      | 1                     |       |
| Trunk            | 1                      | 14                    | 22                     | 2                     |       |

\(^a\)Compared with Nanjing, \(p < 0.05\).

\(^b\)Compared with Kunming, \(p < 0.05\).

\(^c\)Compared with Shenyang, \(p < 0.05\).
proportion of patients with unexposed lesions in the Shenyang group under 65 years old was the highest \( (p < 0.001) \). However, the Kunming and Shenyang groups were both higher than that in Nanjing group in patients over 65 \( (p < 0.001) \) (Table 3).

In terms of histological classification, similar to the general trend, all patients in the Nanjing group were both dominated by atrophic type, while the other three groups were dominated by hypertrophic type, with no obvious differences between different age groups. The KIN classification was basically the same with general trends. All patients in the Nanjing group were mainly KIN I grade \( (p < 0.001) \), which was significantly higher than the other three regions, and the KIN II level of the Nanjing group was the least \( (p < 0.001) \). KIN III grade was the highest in the Shenyang group, significantly higher than the Kunming group, without differences between different age groups \( (p < 0.001) \) (Table 3).

3.4 | The influence of gender

The correlation between AK and gender has a controversial, the Caucasians in the west are predominantly male,\(^8,^9,^17\) while Asian is predominantly female.\(^14,^18\) According to the gender classification, compare the clinical and pathological differences of AK patients between different regions. Same as the general trend, the disease course of female patients in Kunming group was significantly shorter than that in Nanjing group \( (p = 0.007) \). In the Shenyang group, the proportion of unexposed skin lesions in male and female patients was the highest, which both were significantly higher than that in the Nanjing group. The unexposed skin lesions in male patients in the Shenyang group were higher than that in the Kunming group, while the female patients in the Shenyang group were higher than those in the Yinchuan group \( (p < 0.001) \) (Table 4).
and the Kunming group (mean age of 68.9 years in Japanese-Brazilians) was significantly lower than that in the Nanjing group (mean age of 68.76 years in Korea), which was similar to the results of multiple Asian studies. 14,15 The average age in Korea was 68.76 years (men, 70.89 years; women, 65.56 years). While in Caucasians, with the average age of about 65 years old, which was similar to the results of multiple Asian studies. 14,15 The average age in Korea was 68.76 years (men, 70.89 years; women, 65.56 years). In Fourth Military Medical University of China the mean age was 65.6 years old, and in Peking University First Hospital of China was 74.6 years old. The Asian showed a trend, which was in direct contrast to the majority of men in European. 8,9,33,34 Other Asian scholars such as Choi et al. and Han et al. 14,18 obtained similar results. Because the very different trends between Asian and Caucasian, we compared the differences by gender. The results showed that the disease course of female patients in Kunming was significantly shorter than that in Nanjing, and the level of KIN III grade of female patients in the Shenyang group was significantly higher than that in the Nanjing group and the Kunming group (p < 0.001) (Table 4).

### 4 | DISCUSSION

Results of our study revealed that the clinical and pathological characteristics of AK patients in the four regions showed significant differences in age, gender, disease duration, skin lesion location, and histopathological characteristics. First of all, the patients in the four hospitals were all middle-aged and elderly people, with an average age of about 65 years old, which was similar to the results of multiple Asian studies. 14,15 The average age in Korea was 68.76 years (men, 70.89 years; women, 65.56 years). While in Caucasians, with the average age of about 65 years old, which was similar to the results of multiple Asian studies. 14,15 The average age in Korea was 68.76 years (men, 70.89 years; women, 65.56 years). In Fourth Military Medical University of China the mean age was 65.6 years old, and in Peking University First Hospital of China was 74.6 years old. The Asian transmitted to other area also had the similar result, with the mean age of 68.9 of Japanese-Brazilians. 32 While in Caucasians, with the fair skin and lower skin phototypes, the mean age was lower than these Asian. 33 This may due to the skin phototypes and lifestyles.

The Kunming group was the youngest among four groups, meanwhile, the disease course of the Kunming group was significantly shorter than that in the Nanjing group. A comparison by age group also showed that the patients with a significantly shorter course of disease in the Kunming group were under 65 years old. The smaller onset age and shorter duration in the Kunming group was significantly related with strong UV in Yunnan province. Due to different geographical location and climate, the four regional UV intensity is different. In summer, the Nanjing city, Liaoning and Yinchuan area has the strongest UV, the average UV intensity in July is 16 W/m², 30.04 W/m² and 61.2 W/m², while the strongest UV intensity in Yunnan province is 68.54 W/m² in spring and autumn. 19–22 Meanwhile, AK lesions were mainly located at the exposure site, and the number of patients visit doctors in the four regions was relatively small in winter, which was further confirmed the close relationship between AK and UV. 8 However, compared with other groups, the proportion of unexposed lesions in the Shenyang group was significantly higher than that in other groups, especially in patients under the age of 65, suggesting that the occurrence of AK in the Shenyang group was not only related to ultraviolet radiation, but also existed some other important pathogenic factors.

In all the AK patients in the four regions, the majority of women showed a trend, which was in direct contrast to the majority of men in European. 8,9,33,34 Other Asian scholars such as Choi et al. and Han et al. 14,18 obtained similar results. Because the very different trends between Asian and Caucasian, we compared the differences by gender. The results showed that the disease course of female patients in Kunming was significantly shorter than that in Nanjing, and the level of KIN III grade of female patients in the Shenyang group was significantly higher than that in the Nanjing and Kunming groups. However, there was no significant gender difference in the proportion of skin lesions at the exposed sites and the classification of tissue morphology. These results do not fully account for whether Chinese women are more susceptible to AK and has higher type severity.

In our country, the majority of AK patients are women. Whether it is related to the fact that women pay much more attention to facial diseases than men and then have higher rate of medical treatment, the exact results need further analysis of the sex ratio of outpatient patients to draw a conclusion. We observed that although the patient was mostly female, the ratio of female cases in Yinchuan Group were relatively lower compared with other regions. This might be

|                  | Nanjing (n = 579) | Kunming (n = 330) | Shenyang (n = 196) | Yinchuan (n = 83) | p  |
|------------------|-------------------|-------------------|-------------------|------------------|----|
| Bowenoid (%)     | 102 (17.6)        | 23 (7)            | 18 (9.2)          | 9 (10.8)         |    |
| Acantholytic (%) | 22 (3.8)          | 7 (2.1)           | 5 (2.6)           | 1 (1.2)          |    |
| Pigmented (%)    | 30 (5.2)          | 0 (0)             | 0 (0)             | 0 (0)            |    |
| Lichenoid (%)    | 33 (5.7)          | 40 (12.1)         | 16 (8.2)          | 14 (16.9)        |    |
| Atrophic (%)     | 205 (35.4)        | 80 (24.2)         | 15 (7.6)          | 15 (18.1)        |    |
| Hypertrophic (%) | 187 (32.3)        | 180 (54.6)        | 142 (72.4)        | 44 (53)          |    |
| **Histopathological types (n, %)** | **<0.001** |
| **KIN grade (n, %)** | **<0.001** |
| Grade I          | 367 (63.4)        | 141 (42.7)        | 59 (30.1)         | 31 (37.3)        |    |
| Grade II         | 88 (15.2)         | 128 (38.8)        | 71 (36.2)         | 36 (43.4)        |    |
| Grade III        | 124 (21.4)        | 61 (18.5)         | 66 (33.7)         | 16 (19.3)        |    |

*a*Compared with Nanjing, p < 0.05.

*b*Compared with Kunming, p < 0.05.

*c*Compared with Shenyang, p < 0.05.
associated with the religious features of female cases in Yinchuan region. Because Yinchuan region is the Muslim gathering area, local female Muslims wearing long sleeve top and headscarf cover more human body parts, which in turn reduces the exposure to UV radiation.

There was a statistical difference in pathological morphological classification among four groups. The hypertrophic type was dominant in Kunming, Shenyang and Yinchuan, while the atrophic type was dominant in Nanjing group. However, the four groups were mainly hypertrophic type and atrophic type, and the differences in pathomorphological classification were not affected by age and gender. This is similar to the results of some studies.\(^{18,35}\) The pigmented type and acantholytic type are rare, among which the pigmented type was only seen in the Nanjing group, while the acantholytic type in the Nanjing group was the least. It has not been reported whether there are differences in the degree of malignancy between different pathomorphological classifications and whether there are differences in mutant genotypes.\(^{35}\) Roewert-Huber and other scholars referred to the classification pattern of cervical cancer,\(^{29,30}\) they suggested that based on different cell intraepidermal neoplasia (KIN) percentage, AK can be divided into KIN grade I, II, III. It has long been assumed that clinical thickness and histological grade of dysplasia were predictive factors of the aggressive potential of AKs,\(^{30,36,37}\) KIN III is more malignant according to this classification, and it may be more prone to malignant transformation and metastatic invasion. However, the recent literature has challenged these two consolidated assumptions. Clinical thickness

\[\text{TABLE 3 Comparison table of disease course, exposure areas, histopathological types and KIN grade among AK patients at the same age group}\]

|                      | Nanjing (n = 579) | Kunming (n = 330) | Shenyang (n = 196) | Yinchuan (n = 83) | p   |
|----------------------|-------------------|-------------------|-------------------|-------------------|-----|
| Course of disease (month) |                   |                   |                   |                   |     |
| ≤65 ages             | 36 (12–36)        | 15 (12–36)        | 24 (10.5–36)      | 24 (12–36)        | 0.005 |
| >65 ages             | 36 (12–36)        | 15 (12–36)        | 36 (12–36)        | 24 (6–48)         | 0.183 |
| Exposed-areas (n, %) |                   |                   |                   |                   |     |
| ≤65 ages             | 200 (99.5)        | 141 (93.4)        | 60 (75)\(^{a,b}\) | 23 (100)\(^{a}\)  | <0.001 |
| >65 ages             | 377 (99.7)        | 170 (95)\(^{a}\)  | 109 (94)\(^{a}\)  | 57 (95)           | <0.001 |
| Histopathological types (n, %) |                   |                   |                   |                   |     |
| ≤65 ages             |                   |                   |                   |                   | <0.001 |
| Bowenoid            | 37 (18.4)         | 9 (6.0)           | 8 (10.0)          | 2 (8.7)           |
| Acantholytic        | 7 (3.5)           | 2 (1.3)           | 3 (3.8)           | 0 (0)             |
| Pigmented           | 14 (7.0)          | 0 (0)             | 0 (0)             | 0 (0)             |
| Lichenoid           | 9 (4.5)           | 17 (11.3)         | 4 (5.0)           | 3 (13.0)          |
| Atrophic            | 72 (35.8)         | 37 (24.5)         | 6 (7.5)           | 6 (26.1)          |
| Hypertrophic        | 62 (30.8)         | 86 (56.9)         | 59 (73.7)         | 12 (52.2)         |
| >65 ages             |                   |                   |                   |                   | <0.001 |
| Bowenoid            | 65 (17.2)         | 14 (7.8)          | 10 (8.6)          | 7 (11.7)          |
| Acantholytic        | 15 (4.0)          | 5 (2.8)           | 2 (1.7)           | 1 (1.7)           |
| Pigmented           | 16 (4.2)          | 0 (0)             | 0 (0)             | 0 (0)             |
| Lichenoid           | 24 (6.3)          | 23 (12.9)         | 12 (10.3)         | 11 (18.3)         |
| Atrophic            | 133 (33.2)        | 43 (24.0)         | 9 (7.8)           | 9 (15.0)          |
| Hypertrophic        | 125 (33.1)        | 94 (52.5)         | 83 (71.6)         | 32 (53.3)         |
| KIN grade (n, %)    |                   |                   |                   |                   |     |
| ≤65 ages             |                   |                   |                   |                   | <0.001 |
| Grade I             | 127 (63.2)        | 69 (45.7)\(^{a}\) | 23 (28.7)\(^{a}\) | 12 (52.2)         |
| Grade II            | 31 (15.4)         | 55 (36.4)\(^{a}\) | 29 (36.3)\(^{a}\) | 8 (34.8)          |
| Grade III           | 43 (21.4)         | 27 (17.9)         | 28 (35.0)\(^{b}\) | 3 (13.0)          |
| >65 ages             |                   |                   |                   |                   | <0.001 |
| Grade I             | 240 (63.5)        | 72 (40.2)\(^{a}\) | 36 (31.0)\(^{a}\) | 19 (31.6)\(^{a}\) |
| Grade II            | 57 (15.1)         | 73 (40.8)\(^{a}\) | 42 (36.2)\(^{a}\) | 28 (46.7)\(^{a}\) |
| Grade III           | 81 (21.4)         | 34 (19.0)         | 38 (32.8)\(^{b}\) | 13 (21.7)         |

\(^{a}\)Compared with Nanjing, \(p < 0.05\).

\(^{b}\)Compared with Kunming, \(p < 0.05\).

\(^{c}\)Compared with Shenyang, \(p < 0.05\).
cannot predict aggressiveness of AKs, since it does not correlate neither with the grade of dysplasia nor with p53 expression.\textsuperscript{38,39} Likewise, the histopathological grade of dysplasia (AK I–III) is not necessarily correlated to the invasive potential of AKs.\textsuperscript{29,40} So, neither the clinical grade nor the histological grade of dysplasia seems valid predictors of aggressive potential of AKs. On the other hand, the mutational status in AKs appears to predict well the clinical course.\textsuperscript{35,41} Using 77 UV biomarkers, Queen et al.\textsuperscript{41} tried distinguishing between benign and transformation-prone AKs and squamous cell carcinoma, and found the patients with AK had a history of melanoma or nonmelanoma skin cancer in the past, were more prone to progress to squamous cell carcinoma. But Javor et al.\textsuperscript{35} found a significant correlation between p53 staining index and grade of dysplasia, demonstrating that moderate to severe grade of dysplasia may be more aggressive potential.

The number of KIN III patients in the Shenyang group was significantly higher than that in the other three groups, especially female patients, and the number of AK in the unexposed part of the Shenyang group was also significantly higher than that in the other three groups. These results indicated that the occurrence of AK in the Shenyang group was relatively weak in relation to UV exposure, and other relevant factors might be involved. Shenyang is located in the northeast of China, although the UV intensity in July is 30.04 W/m\textsuperscript{2},\textsuperscript{19} which is higher than Nanjing, but there are a lot of heavy industry in Shenyang, which has more chemical carcinogens, may also have an important impact on the occurrence of AK and cause a higher degree of malignancy of AK.

The study also has some limitations to be clarified. This study involved just four clinical centers of various regions of China and
reflected only the clinical features of AK patients visiting the dermatologists in the given settings. Moreover, information about religion and lifestyle of patients were not collected and recorded. In addition, inherent limitations of retrospective studies limit the immediate applicability of these results. Further prospective studies are necessary to clarify whether these factors can be considered to induce disease progression in AK patients.

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CONFLICT OF INTEREST
The authors declare that they have no conflict of interests.

AUTHORS’ CONTRIBUTIONS
DX, RQQ, RXN, LDD and JZ collected information of patients, logged data and checked. DX and RQQ analyzed information and write the paper. JFS, WZ, TYL and SZ reexamined pathological results and classified pathological types and KIN grade. LH and HDC contributed to the study concept and design, and supervised the project. All authors have read and approved the manuscript.

ETHICS APPROVAL
This study was performed following the approval of the Institutional Ethical Committee of First Affiliated Hospital of Kunming Medical University (2020 L-29).

PATIENT CONSENT FOR PUBLICATION
Not applicable.

DATA AVAILABILITY STATEMENT
All data generated or analyzed during this study are included in this published article.

FIGURE 3 The bar charts for different histopathological morphology subtypes of four hospitals

Histopathological classification of AK patients in different regions

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