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Research Article

Clinicopathological Characteristics and Recurrence Risk in Basal Cell Carcinoma Patients: A Cross-Sectional Study at Kariadi General Hospital Semarang, 2012–2023

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Abstract

Background: Basal cell carcinoma (BCC) is responsible for 70–80% of all skin malignancies. Histopathologically, it is classified into two types: high-risk and low-risk. Evidence linking clinicopathological features of BCC to recurrence risk remains limited in Indonesia, particularly in tertiary referral centers such as Kariadi Hospital. ***Objective***: This study aims to assess the clinicopathological features of BCC in relation to other factors influencing recurrence risk in Indonesia. ***Methods***: A retrospective cross-sectional analytic study was conducted using medical records and anatomical pathology examination results of BCC patients diagnosed between January 2012 and December 2023. ***Results***: Among the 405 patients included, 47.4% were classified as having high recurrence risk. Variables analyzed included age, sex, occupation, ulcer size, and tumor location. The risk of recurrence was evaluated according to lesion size, anatomical location, histological subtype, and surgical margins. Ulcer presence showed a significant association with high recurrence risk, with a prevalence ratio (PR)=1.631; 95% CI: 1.337-1.989; $p<0.001$. Other variables, including age, sex, occupation, ulcer size, and tumor location, did not show statistically significant associations with recurrence risk. ***Conclusions***: The fact that an ulcer was present could be considered one of the factors in determining the risk of BCC recurrence.

Keywords: Basal cell carcinoma; Clinical pathology; Recurrence; Risk factor.

الخصائص السريرية المرضية وخطر الانتكاس لدى مرضى سرطان الخلايا القاعدية: دراسة مقطعية في مستشفى كاريادي العام في سيمارانغ، 2012–2023

الخلاصة

الخلفية: سرطان الخلايا القاعدية (BCC) مسؤول عن 70-80٪ من جميع الأورام الخبيثة الجلدية. من الناحية التاريخية، يصنف إلى عالي المخاطر ومنخفض المخاطر. لا تزال الأدلة التي تربط السمات السريرية المرضية لسرطان الخلايا الثانوية بخطر الانتكاس محدودة في إندونيسيا، خاصة في مراكز الإحالة الثالثية مثل مستشفى كاريادي. **الهدف**: تهدف هذه الدراسة إلى تقييم الخصائص السريرية المرضية لسرطان الخلايا القاعدية المرتبط بعوامل أخرى تحدد خطر عودته في إندونيسيا. **الطرائق**: أجريت دراسة تحليلية مقطعية بأثر رجعي باستخدام السجلات الطبية ونتائج الفحوصات التشريحية لمرضى BCC الذين تم تشخيصهم بين يناير 2012 وديسمبر 2023. **النتائج**: من بين 405 مرضى شملوا، تم تصنيف 47.4٪ منهم على أنهم ذوو خطر مرتفع للعودة. شملت المتغيرات التي تم تحليلها العمر، والجنس، والمهنة، وحجم القرحة، وموقع الورم. تم تقييم خطر الانتكاف بناء على حجم الآفات، الموقع التشريحي، النوع النسيجي، وهوامش الجراحة. أظهر وجود القرحة ارتباطا كبيرا بخطر التكرار العالي، بنسبة انتشار 1.631 وفترة ثقة 95٪ ($p<0.001$). لم تظهر متغيرات أخرى، مثل العمر، الجنس، المهنة، حجم القرحة، وموقع الورم، ارتباطات ذات دلالة إحصائية مع خطر الانتكاس. **الاستنتاجات**: يمكن اعتبار وجود قرحة أحد العوامل التي حددت خطر عودة سرطان الخلايا القاعدية (BCC).

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INTRODUCTION

At the global level, basal cell carcinoma (BCC) is known as the most common form of skin cancer, accounting for approximately 70–80% of all skin malignancies [1]. What is more worrying is the fact that the BCC incidence continues to rise, with estimates showing an increase of 1-3% annually across various populations [2]. Frequently affecting Caucasians and individuals with fair skin, it is responsible for about two-thirds of all skin cancer types [3]. In Asia, the skin cancer incidence is around 4%. Studies in China indicate that the BCC incidence rates in Asian women and men were 5.8 and 6.4 (per 100,000), respectively [4]. Similarly, in Indonesia, a study conducted in Jakarta shows that BCC is the most common type of skin cancer at 66.9% prevalence [5]. Environmental factors and occupations are among the risks for BCC. One of the environmental factors that influences the development of BCC is UV radiation [6]. Hence, it is safe to say that geographical conditions play a crucial role in BCC incidence. For instance, Australia and parts of Europe report quite high rates of BCC incidence due to increased sun exposure and a predominantly white population [7]. Regarding sun exposure, Indonesia is a tropical country. It receives high levels of sunlight throughout the year. Many occupations require workers to perform outdoor activities, resulting in prolonged sun exposure, often without adequate protective measures [8]. Using an occupational perspective, a study

revealed that individuals working outdoors, such as farmers and laborers, have a significantly higher BCC incidence rate. As many as 80% of patients working as laborers or farmers developed BCC in their facial area [9]. BCC typically manifests as a pearly and shiny nodule on sun-exposed skin areas, especially the face, neck, and scalp [10]. The lower eyelid is frequently reported as the most common location where BCC appears, with studies showing that over 80% of BCC cases occur in the head and neck [9]. Despite its high incidence rate, BCC is generally associated with a low mortality rate. This outcome is thanks to its indolent nature and the effectiveness of treatment options, including surgical excision and topical therapy [1]. Histopathologically, BCC is classified into two types: high-risk (aggressive) and low-risk (non-aggressive). This risk is assessed based on the size, location, margins, and subtype of the lesion. The malignancy grade of BCC influences its recurrence rate. Factors such as tumor location also play an important role in recurrence rates. BCCs located in high-risk areas, such as the medial canthus of the eyelid, have been associated with higher recurrence rates compared to those in less critical areas [11]. Furthermore, a study carried out in Portugal showed that age influences BCC recurrence. Patients younger than 57 years old had an almost three times higher risk of BCC recurrence [12]. The presence of multiple lesions during treatment also shows a possibility of BCC recurrence. Incomplete excision may increase the risk of BCC recurrence because residual tumor cells at the surgical margins can contribute to local tumor regrowth [13]. The interaction between environmental factors, occupational sun exposure, and demographic characteristics contributes to the widespread BCC incidence and recurrence rates. Eventually, it necessitates continuous research and public health efforts to mitigate its impact. In this study, the researchers aim to further evaluate the clinicopathological characteristics of BCC in relation to other factors that determine the risk of BCC recurrence in Indonesia. It is expected that the results of this study will provide better insights into the epidemiological trends of BCC in Indonesia, support more effective prevention and control efforts for this disease, and provide input for clinicians, especially surgeons, in considering the extent of tumor margin excision.

METHODS

Study design and setting

This cross-sectional study was conducted in October 2024. It used secondary data in the form of medical records and anatomical pathology laboratory notes for BCC patients at General Hospital Kariadi Semarang. The subjects in this study were sampled using consecutive sampling. The data used were patients that had been histopathologically diagnosed with BCC from January 2012 to December 2023. If the data were incomplete and damaged, it was not included in the study sample.

Data collection and outcome measurements

Histopathological diagnosis and subtype classification of basal cell carcinoma were determined in accordance with the WHO Classification of Tumors: Skin Tumors. Recurrence risk was subsequently classified as low-risk or high-risk based on the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Basal Cell Skin Cancer, which incorporate clinical and pathological parameters including tumor location, size, border definition, recurrence status, immunosuppression, prior radiotherapy, histological subtype, and perineural involvement [14,15].

Ethical considerations

The study protocol was approved by the Health Research Ethics Committee of the Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital, Semarang, Indonesia, under approval number 071/EC/KEPK/FK-UNDIP/II/2024.

Data analysis

Data were analyzed using SPSS software version 25. Categorical variables, including sex, occupation, ulcer status, tumor location, and recurrence risk category, were presented as frequencies and percentages. Continuous variables, including age and ulcer size, were first assessed for normality using the Kolmogorov–Smirnov test because the total sample size was more than 50 subjects. Normally distributed continuous variables were presented as mean ± standard deviation, whereas non-normally distributed variables were presented as median and interquartile range. The cut-off values for age and ulcer size were determined using receiver operating characteristic (ROC) curve analysis to evaluate their ability to discriminate between low and high recurrence risk groups. The area under the curve (AUC), sensitivity, and specificity were used to assess the performance of each cut-off value. The selected cut-off values were then used to categorize continuous variables into clinically interpretable groups for further comparative analysis. Associations between categorical clinicopathological variables and high recurrence risk were analyzed using the chi-square test when the expected cell counts were adequate, while Fisher's exact test was used when the expected cell counts were less than five. Prevalence ratios (PRs) with 95% confidence intervals (CIs) were calculated to estimate the magnitude and precision of association between each independent variable and high recurrence risk. Variables were interpreted as statistically significant when the p-value was < 0.05.

RESULTS

A total of 405 patients were included in this study. The mean age of the study population was 62.59 ± 11.96 years. Based on the ROC-derived age cut-off, 223 patients (55.1%) were aged ≥62 years, while 182 patients (44.9%) were aged <62 years. Patients aged

≥62 years were more frequently classified into the low recurrence risk group than the high recurrence risk group, with 121 patients (54.3%) in the low-risk group and 102 patients (45.7%) in the high-risk group. Similarly, among patients aged less than 62 years, 92 patients (50.5%) were classified into the low-risk group and 90 patients (49.5%) into the high-risk group. The association between age category and recurrence risk was not statistically significant (p= 0.457; PR= 1.081; 95% CI: 0.881–1.327). Therefore, age was not identified as a significant factor associated with recurrence risk in this cohort (Table 1).

Table 1: Demographic characteristics of study subjects

Variable Characteristics	Result
Age (year)	62.59±11 96
Sex	
Male	179(44.2)
Female	226(55.8)
Type of Occupation	
Private Sector	46(11.4)
Farmer	116(28.6)
Unemployed	5(1.2)
Trader	37(9.1)
Labored	10(2.5)
Retired	24(5.9)
No information	78(19.8)
Others	4(1.0)

Values are presented as frequency, percentage, and mean±SD.

Clinical characteristics showed that ulceration was present in a subset of patients, and most tumors were located in the central face area. Recurrence risk classification showed that slightly more patients were categorized into the low-risk group than the high-risk group. The clinical characteristics and recurrence risk classification are presented in Table 2.

Table 2: Clinical characteristics of study subjects

Clinical parameter	n(%)
Ulcer	
Positive	150(37)
Negative	255(63)
Location	
Central face	270(66.7)
Non-central face	133(32.8)
No information	2(0.5)
Recurrence risk	
High risk	192(47.4)
Low risk	213(52.6)

ROC curve analysis was performed to explore possible cut-off values for age and ulcer size in relation to high recurrence risk. The ROC-derived cut-off value for age was ≥62 years, with an AUC of 0.469, sensitivity of 53.1%, specificity of 43.2%, and Youden index of -0.037. These findings indicate poor discriminatory ability; therefore, this cut-off was considered exploratory and should not be interpreted as a clinically robust threshold. The ROC-derived cut-off value for ulcer size was ≥ 2.9 cm, with an AUC of 0.534, sensitivity of 66.7%, and specificity of 38.6%, also indicating limited discriminatory ability. Based on these findings, both age and ulcer size cut-off values were used only for descriptive and comparative purposes in this cohort (Table 3).

Table 3: Diagnostic test for age and ulcer size in predicting recurrence

Parameter	Optimal Cut-off	AUC (95%CI)	Sensitivity (%)	Specificity (%)	Youden Index
Age	≥ 62	0.469	53.1	43.2	-0.037
Ulcer Size	≥ 2.9	0.534	66.7	38.6	0.386

In the bivariate analysis, age category was not significantly associated with recurrence risk (p= 0.457; PR= 1.081; 95% CI: 0.881–1.327). Sex was also not significantly associated with recurrence risk (p= 0.126; PR= 1.186; 95% CI: 0.967–1.455). Similarly, occupation showed no statistically significant association with recurrence risk (p= 0.096; PR= 1.217; 95% CI: 0.973–1.563). Tumor location and ulcer size were also not significantly associated with recurrence risk. Non-central face location showed no significant association with recurrence risk (p= 0.113; PR= 1.192; 95% CI: 0.965–1.471), and ulcer size ≥ 2.9 cm was not significantly associated with recurrence risk (p= 0.598; PR= 1.093; 95% CI: 0.833–1.434). The presence of an ulcer was the only variable significantly associated with high recurrence risk (p< 0.001; PR= 1.631; 95% CI: 1.337–1.989), with 94 of 150 patients with ulcers (62.7%) classified into the high recurrence risk group, as presented in Table 4.

DISCUSSION

As the most commonly found non-melanoma skin cancer, especially the aggressive type, BCC has high-risk histopathological characteristics [16]. While it has slow growth and rarely metastasized, its destructive effect on surrounding tissues can lead to high morbidity. Originating from the basal layer of the epidermis, it emerges from non-keratinizing cells as a result of prolonged exposure to ultraviolet (UV) radiation [17]. As one grows older, the duration of UV radiation exposure increases. High UV exposure over a long period can lead to repeated damage to human skin, ultimately triggering mutations in important genes such as PTCH1 and TP53 [18,19]. These mutations are generally associated with BCC development. This aligns with the current study, which found that the majority of BCC patients were 50 years old or older. Additionally, increasing age can trigger structural changes, including epidermal thinning and a decreased number of melanocytes, which can eventually impair the skin's ability to repair UV damage [20]. In regard to recurrence risk, the age limit of 62 years old is not considered a reliable reference for determining the likelihood of BCC recurrence. The relationship analysis and diagnostic test in this study yielded no significant results. This was different from the previous research, which showed that age was one of the risk factors for BCC recurrence (p= 0.005) [21]. Other studies also mentioned that BCC, occurring in young individuals (younger than 35 years old), might have a more aggressive clinical course [22]. It is also reported that sex influences the incidence of BCC.

Table 4: Distribution of demographic and clinical characteristics and BCC recurrence risk in study subjects

Variable	n	Recurrence Risk		*p*-value	PR (95% CI)
		High Risk	Low Risk		
Age					
≥ 62 yrs	223	102(45.7)	121(54.3)	0.457	1.081 (0.881-1.327)
< 62 yrs	182	90(49.5)	92(50.5)		0.932 (0.772-1.124)
Sex					
Male	179	93(52.0)	86(48.0)	0.126	1.186 (0.967-1.455)
Female	226	99(43.8)	127(56.2)		0.855 (0.706-1.035)
Occupation					
Outdoor	254	129(50.8)	125(49.2)	0.096	1.217 (0.973-1563)
Indoor	151	63(41.7)	88(58.3)		0.844 (0.73-1.015)
Location					
Central face	270	120(44.4)	150(55.6)	0.113	0.833 (0.677-1.024)
Non-central face	133	71(53.4)	62(46.6)		1.192 (0.965-1.471)
Ulcer					
Positive	150	94(62.7)	56(37.3)	<0.001	1.631 (1.337-1.989)
Negative	255	98(38.4)	157(61.6)		0.606 (0.482-0.762)
Ulcer size					
≥ 2.9	97	62(63.9)	35(36.1)	0.598	1.093 (0.833-1.434)
< 2.9	53	31(58.5)	22(41.5)		0.869 (0.574-1.316)

Values are presented as frequency and percentage.

A study finds that men have a higher risk of developing BCC as a result of significantly greater UV exposure, especially those who work outdoors [23]. The result was consistent with this study, where it was found that a higher frequency of patients working outdoors showed a higher risk of recurrence, with a recurrence prevalence ratio of >1. However, the statistical analysis showed no significant results between the two. Furthermore, regarding sex, female subjects dominated the population in this study, yet their male counterparts had a higher tendency for recurrence risk, despite the statistically insignificant results. Furthermore, research by Bellenghi *et al*. and Baba *et al*. suggests that the incidence of skin malignancy has been proven to be greater in men than in women, at a 1.5–2:1 prevalence ratio [24,25]. This disparity is because men typically engage in more outdoor activities than women, leading to increased exposure to ultraviolet (UV) radiation, a significant risk factor for skin cancer, including BCC [26]. Additionally, men's skin is more vulnerable to UV damage because of differences in skin thickness and the presence of hair follicles, which can lead to the development of skin tumors [27]. It was possible that the insignificance of this study's results was due to differences in the sample size and the presence of other unanalyzed factors, such as detailed UV exposure duration and a history of personal protection against sunlight, including sunscreen, hats, and clothing types [28]. In addition to age and sex, it is believed that occupational characteristics are also a risk factor for BCC. This study found that outdoor occupations had the highest prevalence of BCC. Farming was the profession with the most prevalence. Comparisons between the present study and previous studies regarding age-related recurrence risk should be interpreted cautiously because different studies used different age cut-off values. The present study used a ROC-derived exploration cutoff of 62 years, whereas some previous studies evaluated younger patients using lower thresholds, such as <50 years or <35 years. This difference may lead to inappropriate direct comparison because patients aged 50–61 years in the present study were categorized into the <62-year group, although they may not be comparable to the younger populations defined in studies using lower age thresholds. The low AUC value in the present study also indicates that the 62-year cut-off had limited discriminatory ability and should not be considered a definitive clinical threshold. Current BCC guidelines emphasize risk stratification based mainly on tumor-related factors, including tumor size, anatomical location, histological subtype, recurrence status, and other high-risk clinical or pathological features, rather than relying solely on age-based thresholds [29,30]. Therefore, the non-significant association between age and recurrence risk in this cohort should be interpreted as a finding specific to the exploratory 62-year cut-off, not as definitive evidence against the role of age in BCC recurrence. The analysis results also showed that outdoor occupations had the highest prevalence of recurrence risk. This had something to do with the duration of UV exposure while performing these occupations. Chronic UV radiation exposure induced the formation of cyclobutane pyrimidine dimers. If nothing was done to mitigate this exposure, it might lead to mutations in important genes such as PTCH1 and TP53 [31]. These gene mutations could cause uncontrolled cell growth and tumorigenesis [32]. The distribution of occupations was analyzed because it provided information on populations that are vulnerable to BCC incidence [33]. Other studies also indicated that occupations requiring high outdoor activity, such as farming, fishing, and construction work, were consistently associated with an increased risk of BCC and recurrence [34]. The presence of an ulcer was found to have a significant relationship with recurrence risk. Patients with ulcers had over 1.5 times higher recurrence risk than those without them. The ulcers found in this study were mostly less than 3 cm in size. A study by Wisdorf revealed that BCC with ulceration had a higher recurrence risk compared to non-ulcerated lesions. This indicated that ulceration could be an indicator of more aggressive tumor behavior or reflect inaccurate incision margins during the excision procedure [35]. This aligns with findings from other studies indicating that ulceration serves as a potential marker for more advanced diseases and poorer prognosis [12]. The presence of an ulcer could

be considered in determining further the likelihood of BCC recurrence risk. However, the cut-off value of 2.9 cm was less suitable, as more detailed consideration was needed to determine the likelihood of BCC recurrence risk. This conclusion was because of the facts, based on the statistical test results, that no significant difference was found and the diagnostic test value was not strong enough. Furthermore, the likelihood of BCC recurrence risk was higher in ulcers located on the non-central face compared to other areas. The reason for this was that the non-central face area exhibited a higher prevalence of comma-shaped and glomerular vascular patterns, which are associated with superficial BCC. This type of vascular pattern was considered to have a higher risk of recurrence and deeper tissue invasion [36]. While the findings of this study were important, it still had its limitations. The study did not analyze other factors that could affect the significance of the research results. These factors included the duration of UV exposure, the duration of the disease, the type of therapy, the response to treatment, and the patient's immune status. Nevertheless, this study has discussed the magnitude of recurrence risk factors that could be helpful in assessing the likelihood of BCC recurrence. The current clinical and pathological parameters commonly used to predict recurrence risk do not consider the presence of an ulcer as one of the predictors. However, this study found that the presence of an ulcer could be a sign of recurrence risk. Therefore, we suggest future research includes the ulcer presence variable as one of the clinicopathological predictive factors for recurrence. The main clinically relevant finding of this study was the significant association between ulcer presence and high recurrence risk. This finding is supported by previous evidence showing that clinical and dermoscopic ulceration is more frequently observed in high-risk BCC and may increase the probability of high-risk tumor classification [37]. From a clinical perspective, ulceration may serve as a simple visible feature that helps clinicians identify patients who require closer assessment, careful treatment planning, and structured follow-up. From a public health and policy perspective, these findings may support local health initiatives that promote early detection of suspicious ulcerated skin lesions, timely referral from primary care to dermatology services, and patient education regarding non-healing or ulcerated lesions. Health promotion programs in populations with high ultraviolet exposure, particularly outdoor workers, may also include education on sun protection, skin self-examination, and early consultation for persistent skin lesions [18,38]. Current guidelines also emphasize patient education, sun protection, self-surveillance, and appropriate referral or follow-up for patients with high-risk BCC [29,30].

Study Limitations

While the findings of this study were important, it still had its limitations. The cross-sectional design limited the ability to assess actual recurrence over time because it is better evaluated through longitudinal follow-up. Several relevant factors were not analyzed, including UV exposure duration, treatment type, surgical margin status, histopathological subtype, immune status, and sun-protection behavior. The age and ulcer size cut-off values were derived from the same dataset, which may limit their generalizability. Future prospective studies are needed to validate these findings and to evaluate recurrence more accurately.

Conclusion

Ulcer presence was significantly associated with high recurrence risk in patients with basal cell carcinoma, while age category, sex, occupation, tumor location, and ulcer size were not significantly associated with recurrence risk. The ROC-derived cut-off values for age and ulcer size showed limited discriminatory ability and should be interpreted cautiously. Further prospective studies are needed to validate ulceration as a potential clinical marker for recurrence risk assessment.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be provided by the corresponding author upon reasonable request.

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