Original Article

Clinical Patterns and Disease Burden of Cutaneous Squamous Cell Carcinoma in a Multiethnic Malaysian Cohort: A Multicentre Study

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Submitted: 26 May 2026
Accepted: 30 Jul 2026
Online: 31 Oct 2026

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To cite this article: Ramasenderan N, Halim AS, Mat Zain MA. Clinical patterns and disease burden of cutaneous squamous cell carcinoma in a multiethnic Malaysian cohort: a multicentre study. *Malays J Med Sci*. 2026;**33(5)**:21–30. https://doi.org/10.21315/mjms-05-2026-364

To link to this article: https://doi.org/10.21315/mjms-05-2026-364

Abstract

Background: **Cutaneous squamous cell carcinoma (CSCC) is an aggressive malignancy with limited epidemiological data available for Asian populations. This study aimed to analyse clinical patterns, risk factors, and disease burden within a multicentre Malaysian cohort.**

Methods: **A retrospective cohort study was conducted across 12 hospitals (nine public and three university-based) between 2013 and 2019, including 229 patients. Univariate and multivariate Cox regression models were employed to identify predictors of recurrence. Disability-adjusted life years (DALY) were calculated to estimate the overall disease burden.**

Results: **The mean patient age was 67 years (SD = 15.14). A male predominance was observed at 69.9%. While Malay patients constituted 52.8% of the cohort, Chinese patients (38.4%) were disproportionately represented relative to national demographics. Advanced presentation was prevalent, with a mean lesion duration of 21.4 months. Significant independent predictors of early recurrence in the multivariate model were tumour thickness (HR = 1.25; 95% CI: 1.03, 1.50) and lymphovascular invasion (HR = 33.68; 95% CI: 2.02, 561.24). The estimated DALY was 5.135 years per patient.**

Conclusion: **In Malaysia, CSCC frequently presents at advanced stages with unique ethnic distributions. High DALY values and aggressive clinicopathological features underscore the urgent need for early detection programmes and tailored management strategies for Asian skin types.**

Keywords: *cutaneous squamous cell carcinoma, Malaysia, disease burden, DALY, ethnicity, recurrence risk*

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Introduction

Cutaneous squamous cell carcinoma (CSCC), a formidable subtype of non-melanoma skin cancer, is characterised by a significant mortality rate attributed to its inherent biological aggressiveness. The pathogenesis of CSCC is primarily driven by cumulative ultraviolet (UV) radiation exposure and a cascade of genetic aberrations that disrupt critical signalling pathways, such as the NF-kB, MAPK, and PI3K/AKT/mTOR pathways, which collectively mediate upregulation of epidermal growth factor receptor expression. Furthermore, genetic alterations in tumour suppressor genes—specifically p53, CDKN2A, and NOTCH—alongside the overexpression of oncogenes such as RAS have been fundamentally implicated in disease progression (1–5).

Accurately identifying individuals at high risk for recurrence and secondary mortality remains a significant clinical challenge. In a comprehensive meta-analysis of 48 studies involving 28,627 patients, Zeng et al. (6) identified several key clinicopathological determinants of local recurrence. The established prognostic indicators of CSCC include poor histological differentiation, perineural invasion, a Breslow thickness exceeding 2 mm, a tumour diameter greater than 20 mm, and anatomical localisation at the temple. The risk of metastasis is further elevated when these factors are present, particularly when the tumour involves the ear, lip, or temple regions. Furthermore, disease-specific death is strongly associated with poorly differentiated tumours, perineural invasion, and a Breslow thickness > 2 mm (5).

The primary driver of CSCC mortality is nodal metastasis, particularly within the head and neck region, which affects approximately 3.5 million individuals annually in the United States (6). Globally, incidence and outcomes exhibit significant geographic variation; while industrialised nations report a higher overall disease burden, they often maintain lower mortality rates due to early intervention. Conversely, in resource-limited settings such as Malaysia, the scarcity of comprehensive epidemiological data and robust cancer registries complicates the evaluation of disease-specific mortality, overall survival, and the clinical utility of sentinel lymph node biopsy (7, 8). National statistics indicate that the mortality rates of patients presenting with advanced-stage CSCC exceed 20% (8). Consequently, CSCC has emerged as a significant health concern in Malaysia, ranking among the top ten cancers impacting quality of life.

Despite its rising prevalence, contemporary research often overlooks Asian populations. This multicentre study aims to address these critical knowledge gaps by characterising the clinical burden and identifying key risk factors for CSCC within a diverse, multiethnic Malaysian cohort.

Methods

Study Design and Population

This multicentre, retrospective cohort study involved patients diagnosed with CSCC confirmed via histopathological evaluation. Clinical and pathological data were retrieved for the period from 1 January 2013 to 31 December 2019, with a minimum follow-up duration of 30 months for surviving patients. Ethical approval was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia, and the respective institutional review boards of the participating university hospitals (approval period: June 2022–June 2024).

Study Setting and Centre Selection

This study incorporated data from nine major public hospitals under the Ministry of Health (Hospital Kuala Lumpur, Hospital Sungai Buloh, Hospital Melaka, Hospital Sultanah Aminah, Hospital Raja Perempuan Zainab II, Hospital Tengku Ampuan Afzan, Hospital Sultanah Nur Zahirah, Hospital Umum Sarawak, and Hospital Queen Elizabeth) and three university teaching hospitals (Hospital Pakar Universiti Sains Malaysia, Hospital Canselor Tuanku Muhriz, and Pusat Perubatan Universiti Malaya). These 12 facilities collectively represent 75% of the nation's tertiary referral centres for skin malignancies.

Data Collection and Variables

Demographic profiles (age, sex, occupation, and smoking status) and clinicopathological characteristics were documented. Clinical variables included anatomical site (e.g., head and neck or limbs) and maximum clinical diameter. Histological features encompassed differentiation grade, lymphovascular invasion (LVI), and perineural invasion (PNI). Lesions were categorised as primary, re-excision, recurrence, or metastasis (nodal, in-transit, or distant).

Inclusion and Exclusion Criteria

A universal sampling method was employed to include all eligible cases within the study period. Exclusion criteria were defined as: i) CSCC involving mucosal, perianal, or genital regions; ii) patients with a history of organ transplantation or those receiving long-term immunosuppressive therapy; iii) patients who underwent primary surgical intervention at non-participating facilities; and iv) cases with incomplete histological or follow-up data.

Sample Size and Statistical Analysis

The sample size was determined on the basis of the reported CSCC incidence of 5.3% by Koh et al. (9). Using Epi Info (version 7, Centers for Disease Control and Prevention, Atlanta, GA, USA), the calculation requirement was 77 subjects; after accounting for a 20% potential data attrition rate, the final target was 94. Our study successfully recruited 229 patients, exceeding the minimum requirement of 101 for robust analysis.

Descriptive statistics (frequency, mean, and standard deviation) characterised the cohort. Risk factors for recurrence were assessed using the Cox proportional hazards model, and assumptions were verified using Schoenfeld residual analysis. Because of the number of recurrence events (n = 34), candidate variables for the multivariate model were pre-selected based on univariate performance and clinical significance to maintain model stability and prevent overfitting.

Results

Patient Demographics and Baseline Characteristics

The cohort comprised 229 patients with a mean age of 67 ± 15.14 years. A male predominance was observed, representing 69.9% (n = 160) of the total participants. Ethnic distribution revealed that the majority were of Malay descent (52.8%, n = 121), followed by Chinese (38.4%, n = 88), with other groups including Indian (3.5%), Iban (3.1%), and Bidayuh (1.3%). Most patients presented with fair skin pigmentation (62.0%). Occupational data revealed that 41.5% were retired and 15.3% were self-employed, with many having outdoor occupations. Smoking was prevalent in 25.3% of the cohort, with an average duration of 33.9 years. Hypertension was the most common comorbidity (50.7%), followed by diabetes mellitus (31.9%) and ischaemic heart disease (9.6%). A familial predisposition to skin malignancies was reported by 0.9% of patients (Table 1).

Clinical and Pathological Presentation

The lesions primarily manifested on previously normal skin (82.5%), whereas 12.2% appeared on chronic wounds. The cheek (13.5%) and the temple (12.7%) were the most common anatomical sites. The mean duration of the lesion prior to presentation was 21.4 months. Clinical suspicion was high, as 56.3% of patients underwent a biopsy before definitive diagnosis, with 51.5% of the total cases already confirmed as cancerous at that stage. Clinically detectable lymph node enlargement at presentation was present in 12.2% of the cohort (Table 2).

Therapeutic Management

Surgical intervention was the primary treatment modality. Wide local excision, achieving a 95% complete excision rate, was standard. Subfascial resection was the most frequent surgical depth, with muscle, subcutaneous, and bone resections occurring at similar rates. Lymph node surgery was performed in approximately 15% of the patients, primarily via selective or radical neck dissection.

Recurrence and Survival Outcomes

CSCC recurrence was observed in 14.8% of the cohort. Among these recurrences, most occurred early, specifically between 1–3 months (3.5%) and 12–18 months (3.5%) post-surgery. The most frequent recurrence patterns involved local skin recurrence (5.7%) and cutaneous satellite lesions (3.1%). Distant and nodal metastases were primarily identified in the sentinel lymph nodes and lungs. The overall mortality rate during the study period was 38.9%, with 21.8% of these deaths directly attributed to disease progression. Notably, 90% of patients experienced relapse within the first two years following primary surgery (Table 3).

Predictors of Recurrence

Univariate Cox regression identified several significant predictors of early recurrence. Hypertension was associated with a reduced risk of relapse (hazard ratio [HR] = 0.65; 95% confidence interval [CI]: 0.42, 0.99; P = 0.049).

Table 1. Demographic characteristics of patients.

Variables	Total (*N* = 229)
Age (years)[a]	67 (15.14)
Gender, *n* (%)	
Male	160 (69.9)
Female	69 (30.1)
Ethnicity, *n* (%)	
Malay	121 (52.8)
Chinese	88 (38.4)
Indian	8 (3.5)
Others	12 (5.3)
Skin pigmentation, *n* (%)	
Fair	142 (62.0)
Dark	36 (15.7)
Occupation, *n* (%)	
Retired	95 (41.5)
Self-employed	35 (15.3)
Employed	14 (6.2)
Unemployed/missing	85 (37.1)

[a] Mean (SD)

Table 2. Disease characteristics at presentation.

Variables	Total (*N* = 229)
Site, *n* (%)	
Normal skin	189 (82.5)
Chronic wound	28 (12.2)
Trauma/scarring	12 (5.2)
Area, *n* (%)	
Cheek	31 (13.5)
Temple	29 (12.7)
Foot/leg	36(15.7)
Head/neck (Others)	71 (31.0)
Tumour duration (months)[a]	21.4 (31.32)

[a] Mean (SD)

Table 3. Disease control and outcomes.

Variables	*n* (%)
Recurrence of tumour (yes)	34 (14.8)
Time to recurrence, months[a]	24 (22.34)
Deceased	89 (38.9)
Progression of disease	50 (21.8)

[a] Mean (SD)

Significant risk factors for early recurrence included split-thickness skin grafts (HR = 1.60; 95% CI: 1.01, 2.52; *P* = 0.044), selective lymph node dissection (HR = 3.68; 95% CI: 1.56, 8.67; *P* = 0.003), cervical lymph node involvement (HR = 12.65; 95% CI: 1.54, 103.88; *P* = 0.018), and Stage 4 tumour-node-metastasis (TNM) staging system (HR = 2.88; 95% CI: 1.24, 6.70; *P* = 0.014). Furthermore, distant metastasis detected on CT scan was associated with a 3.36-fold increase in risk (HR = 3.36; 95% CI: 1.33, 8.52; *P* = 0.011) (Table 4).

Multivariate Cox regression was performed to identify independent prognosticators. The model confirmed that histological tumour thickness was a significant independent predictor, with every 1 mm increase in tumour thickness increasing the risk of recurrence by a factor of 1.25 (HR = 1.25; 95% CI: 1.03, 1.50; *P* = 0.021). LVI was a highly potent predictor and was associated with a 33.68-fold increase in risk (HR = 33.68; 95% CI: 2.02, 561.24; *P* = 0.014). Additionally, compared to Stage 1, patients at Stage 2 (HR = 6.48; 95% CI: 1.16, 36.25; *P* = 0.033) and Stage 3 (HR = 9.00; 95% CI: 1.73, 46.83; *P* = 0.009) demonstrated a significantly higher risk of recurrence. Clark's level of invasion and selective node dissection did not demonstrate statistically significant associations in this model (Table 5).

Disease Burden (DALY) Estimation

The disease burden was quantified using disability-adjusted life years (DALY), calculated as the sum of years of life lost (YLL) and years lived with disability (YLD). With a mean diagnosis age of 67 years, a time to recurrence of 18 months, and a post-recurrence survival of 28 months, the average age at death was estimated to be 70.83 years. The YLL was 3.97 years when the Malaysian life expectancy was 74.8 years (10). A disability weight of 0.5 was selected based on the Global Burden of Disease criteria for symptomatic, disseminated, or incurable skin malignancy. The YLD was calculated to be 1.165 years (survival time of 2.33 years, $P < 0.5$). The resulting total DALY was 5.135 years per patient, reflecting the substantial loss of healthy life years due to premature mortality and the morbidity of recurrent CSCC.

Discussion

Advanced age and chronic cumulative UV radiation exposure are established primary risk factors for the development of CSCC. The mean age of 67 ± 15.14 years in our cohort aligns closely with the findings of Phung et al. (11), affirming that CSCC remains a malignancy

Table 4. Univariate Cox regression analysis for predictors of recurrence.

Variables	HR	95% CI	*P*-value
Hypertension	0.65	0.42, 0.99	0.049
Primary CSCC status	0.14	0.03, 0.62	0.009
Split-thickness skin graft	1.60	1.01, 2.52	0.044
Selective dissection	3.68	1.56, 8.67	0.003
Cervical LN enlargement	12.65	1.54, 103.88	0.018
Stage 4 TNM	2.88	1.24, 6.70	0.014
Submandibular metastases	8.70	1.44, 52.58	0.019
Distant metastasis (CT)	3.36	1.33, 8.52	0.011

CSCC = cutaneous squamous cell carcinoma; HR = hazard ratio; CI = confidence interval; LN = lymph nodes; TNM = tumour-node-metastasis; CT = computed tomography. Cox proportional hazards assumptions were verified using Schoenfeld residual analysis and found to be valid ($P > 0.05$ for all variables).

Table 5. Multivariate Cox regression analysis for predictors of recurrence.

Variables	HR	95% CI	*P*-value
Histological thickness (mm)	1.25	1.03, 1.50	0.021
LVI (yes)	33.68	2.02, 561.24	0.014
Stage 1	1.00	(Ref)	—
Stage 2	6.48	1.16, 36.25	0.033
Stage 3	9.00	1.73, 46.83	0.009
Stage 4	4.75	0.14, 162.60	0.387

HR = hazard ratio; CI = confidence interval; LVI = lymphovascular invasion; Ref = reference group. Cox proportional hazards assumptions were verified using Schoenfeld residual analysis and found to be valid ($P > 0.05$ for all variables).

that predominantly affects elderly individuals. Although males comprised 69.9% of the cohort, the gender difference was not statistically significant. Nevertheless, our findings mirror global trends where a higher frequency of CSCC is reported among men, likely due to increased lifetime occupational or recreational sun exposure (12).

Ethnic Disparity and Photoprotection

While Malays constituted 52.8% of the cohort, the 38.4% prevalence among Chinese patients suggests that CSCC may disproportionately impact the Chinese community relative to national demographics. This disparity is likely explained by the Fitzpatrick skin phototype classification; Malay patients typically possess types IV and V, which offer superior natural photoprotection compared with types III and IV, which are more common among Chinese individuals. Unlike in European populations, where CSCC frequently arises from precursor actinic keratosis (AK), the majority of our patients presented with *de novo* lesions on previously normal skin (13). This finding may be attributed to the protective effects of darker Fitzpatrick skin types against UV-induced mutations. Furthermore, while the traditional multistep carcinogenesis model suggests a linear progression from normal skin to AK and eventually CSCC, our findings align with those of Ra et al. (14), who utilised gene expression analysis to demonstrate that these clinical stages are genetically distinct.

Comorbidities and the Hypertension Paradox

In our cohort, 50.7% of patients had hypertension, which unexpectedly appeared to be a significant protective factor in the univariate relapse analysis (HR = 0.65; 95% CI: 0.42, 0.99) (15). While direct biological links between hypertension and skin malignancy are sparse, some studies suggest that certain antihypertensive medications—such as thiazide diuretics—may increase photosensitivity. However, the reduced hazard observed in this study may reflect a "survivor bias" or the fact that hypertensive patients undergo more frequent medical surveillance, potentially leading to earlier clinical detection of skin changes than in the general population (16–18).

Clinical Presentation and Barriers to Care

Consistent with the findings of Leiter et al. (19), more than two-thirds of lesions were localised to the head and neck, specifically the cheeks and temples. Notably, our patients exhibited a significant delay in seeking medical care (mean = 21.4 months, ranging up to 120 months) compared to those in Western cohorts, who typically seek care within 2 to 24 months. This delay resulted in a high frequency of advanced-stage presentations, including Stage 3 and Stage 4 disease. Such delays likely reflect cultural or behavioural barriers to healthcare access, including cultural taboos regarding surgical interventions. A holistic approach to health literacy is essential to overcome these barriers, especially in underserved regions.

Tumour Biology and Histological Predictors

A notable observation was the presence of large tumours (mean = 40 mm) alongside a disproportionately low prevalence of positive lymph nodes (12.2%). These findings contrast with those observed in Western populations by Navarrete-Dechent et al. (20), where smaller tumours often exhibit earlier locoregional spread. This discrepancy may suggest unique biological behaviour or slower metastatic progression in Asian cohorts.

Multivariate analysis confirmed that LVI and tumour thickness were robust independent predictors of recurrence (and mortality, respectively). The presence of LVI emerged as a remarkably potent independent predictor of recurrence, with a 33.68-fold increase in risk; however, the breadth of the confidence interval is likely due to sparse data in this subgroup (n = 25), necessitating larger prospective studies to refine its precise effect size. Despite their clear prognostic value, these factors are not yet fully integrated into standard TNM staging systems, although our data suggest that they are critical for identifying high-risk individuals.

Surgical Outcomes and Disease Burden

In terms of surgical management, split-thickness skin grafting was associated with relapse according to univariate analysis (HR = 1.60), potentially due to the difficulty in assessing deep margins in massive lesions requiring graft closure. Post-surgical complications occurred in 20% of the patients, primarily due to graft failure or infection, which subsequently delayed adjuvant radiotherapy. While the impact of delayed radiation is not fully understood, combined modality therapy generally showed better outcomes for aggressive diseases, as in papers by Kraus et al. (21) and Eigentler et al. (22). These findings are consistent with those of Marti et al. (23) regarding the advanced management for complex CSCC.

Finally, the calculated DALY of 5.135 years provides a quantifiable measure of the substantial burden that CSCC imposes on the Malaysian healthcare system. A disability weight of 0.5 was utilised based on the Global Burden of Disease criteria for symptomatic, disseminated, or incurable skin malignancy. This high DALY value likely represents an underestimate due to historical underreporting in national registries. Enhancing the quality of national data compilation is paramount to fully understanding and mitigating the clinical and economic impact of CSCC in Malaysia.

Conclusion

This multicentre study provides a comprehensive analysis of CSCC within the Malaysian context, offering critical insights into the risk factors, demographic disparities, and clinical nuances unique to this region. Our findings reveal that the Malaysian population exhibits distinct characteristics in terms of CSCC presentation and disease progression, most notably a significant delay in seeking medical intervention and a disproportionate incidence among the Chinese community.

Despite the prevalence of large, advanced-stage primary lesions, the relatively low frequency of locoregional nodal involvement suggests a unique biological behaviour in Asian cohorts that warrants further genomic investigation. Furthermore, the identification of tumour thickness and LVI as robust independent predictors of recurrence underscores the need for standardised, aggressive surgical protocols across institutions.

By quantifying the disease burden at 5.135 DALYs, this research highlights the substantial public health impact of CSCC, which has historically been underestimated. Ultimately, these findings lay the groundwork for improved clinical management strategies and emphasise the urgent need for enhanced health literacy and robust, population-based cancer registries to mitigate the morbidity and mortality of CSCC in Malaysia.

Acknowledgements

We would like to thank the Hospital Directors of Hospital Pakar Universiti Sains Malaysia, Hospital Canselor Tuanku Muhriz, and Pusat Perubatan Universiti Malaya, as well as the Director-General of Health, Ministry of Health Malaysia, for their permission to publish this article.

We also express our sincere gratitude to our collaborators from the participating centres: Associate Professor Dr. Faezahtul Arbaeyah

(Hospital Pakar Universiti Sains Malaysia); Associate Professor Dr. Farrah Hani Imran and Dr. Khoo Phong Jhiew (Hospital Canselor Tuanku Muhriz); Professor Dr. Alizan Abdul Khalil and Dr. Mohd Ridwan Mirza Asfian (Pusat Perubatan Universiti Malaya); Dr. Nur Aniessa Rahman and Dr. Normala Basiron (Hospital Kuala Lumpur); Dr. Mohd Shahrul Suondoh and Dr. Mun Yoke Chin (Hospital Sultanah Aminah); Dr. Wan Nur Ayusfaiezan Wan Asri, Dr. Mohamad Jeremi Jeffrey, and Dr. Mohd Shakir Bathusha Mohd Hussain (Hospital Sultanah Nur Zahirah); Dr. Muhammad Firdaus Abas and Dr. Fung Chun Hau (Hospital Tengku Ampuan Afzan); Dr. Shawaltul Akhma Harun Nor Rashid and Dr. Syafira Amiera Mohamed Rozlan (Hospital Raja Perempuan Zainab II); Dr. Chooi Lai Kuan and Dr. Nur Laila Syahirah Md Joha (Hospital Sungai Buloh); Dr. Izety Shezlinda Noran and Dr. Maryam Zakiah Mohamed Yusof (Hospital Melaka); Dr. Tie Teck Liang, Dr. Mohamad Sobri Mohamad Saupi, Dr. Aaron Gerarde Paul, and Dr. Zosimo Ken L Jimeno IV (Hospital Queen Elizabeth); and Dr. Muna Fahima Zainuddin and Dr. Daphne Dewi Anak Stephen Kalong (Hospital Umum Sarawak).

Ethics of Study

This study was reviewed and approved by the relevant institutional research ethics committees: the Medical Research and Ethics Committee, Ministry of Health Malaysia via the National Medical Research Register (NMRR ID: 21-1869-61509); the Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/21120832); the Research Ethics Committee of Universiti Kebangsaan Malaysia (JEP-2022-379); and the Medical Research Ethics Committee, Pusat Perubatan Universiti Malaya (MREC ID No.: 2023425-12384).

Conflict of Interest

None.

Funds

None.

Authors' Contributions

Conception and design: NR, ASH, MAMZ
Analysis and interpretation of the data: NR, ASH, MAMZ
Drafting of the article: NR, ASH, MAMZ
Critical revision of the article for important intellectual content: NR, ASH
Final approval of the article: ASH, MAMZ
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