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Original Article

Clinical and histopathological melanoma correlates: staging associations and prognostic implications

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ABSTRACT

This thorough study examines the clinical and histological characteristics of melanoma in a cohort of 573 individuals, determining their relationships with disease stage and prognostic outcomes. A retrospective cohort analysis was carried out, examining clinical data such as Breslow thickness, Clark level, ulceration status, and histological type. For categorical variables, chi-square tests were used, whereas continuous variables were tested using ANOVA and Kruskal-Wallis. Kaplan-Meier survival curves were created to measure Disease-Free Survival (DFS) and Overall Survival (OS), and Cox proportional hazards regression models were built to discover determinants of survival .There were significant relationships between melanoma features and stage. Histological type, age, Breslow thickness, and tumor mitotic rate were all important considerations in melanoma staging. Kaplan-Meier analysis indicated substantial differences in DFS and OS across melanoma stages, with advanced stages exhibiting greater reductions in survival probability. Cox regression analysis revealed that age, Breslow depth, and ulceration status were all significant predictors of survival, with deeper tumors being linked with a decreased risk. Our results identify crucial variables that influence melanoma staging and prognosis, giving important insights into more precise clinical diagnosis and treatment. The strong correlation between histological type, age, Breslow thickness, tumor mitotic rate, and melanoma staging highlights their importance in clinical practice, emphasizing the necessity for complete pathological examination and personalized treatment regimens.

Keywords: Melanoma, Histopathology, Disease staging, Prognosis, Survival analysis, Kaplan-Meier

Introduction

Melanoma is a very aggressive kind of skin cancer that develops from melanocytes, the cells responsible for color synthesis in the skin. It is a major public health issue worldwide because of its rising incidence rates and propensity for fast metastasis [1, 2]. Melanoma etiology includes genetic changes that are often induced by ultraviolet (UV) radiation from the sun or tanning equipment. These mutations cause unregulated cellular growth, resulting in malignant tumors. Melanoma is classified into four primary types: superficial spreading melanoma, nodular melanoma, lentigomaligna melanoma, and acral lentiginous melanoma, each having its development pattern and features [2]. The risk factors for developing melanoma include both genetic predisposition and environmental exposure. A family history of melanoma, multiple moles or atypical nevi, a pale skin phenotype, and substantial UV radiation exposure are all significant risk factors [1, 2]. Melanoma etiology is strongly linked to genetic alterations, especially those affecting the BRAF gene [3, 4].

Early identification of melanoma is critical for better prognosis results. The ABCDE criteria (asymmetry, uneven borders, numerous colors, huge diameter, and evolving features) are crucial indications of melanoma. Routine dermatological examinations and dermoscopy help detect early-stage melanoma,

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which improves patient outcomes [2, 5]. Melanoma is diagnosed with a comprehensive clinical examination, followed by a biopsy of suspected spots. Staging is an important part of therapy planning since it considers tumor thickness, ulceration, and lymph node involvement. Advanced imaging methods may be used to stage metastatic melanoma [1, 2]. Therapeutic approaches for melanoma are stage and site-specific.

Early-stage melanomas are often treated with surgical excision, but advanced melanomas may need a combination of therapies, including surgery, immunotherapy, targeted therapy, and radiation [3, 6, 7]. Recent treatment advances, notably in targeted and immunotherapies, have significantly improved the prognosis for metastatic melanoma patients [8, 9]. Melanoma prevention techniques concentrate on reducing UV exposure via the use of sunscreen, protective clothing, and avoiding sunburn [10]. Public health measures and educational activities are critical for encouraging early identification and prevention techniques [11-13].

Materials and Methods

This retrospective cohort analysis of 573 individuals diagnosed with melanoma was undertaken at Liaquat University of Medical & Health Sciences from 2020 to 2024. Data were thoroughly cataloged for demographic factors (sex, age), clinical parameters (Breslow thickness, ulceration status, tumor mitotic rate, Clark level), and histological kinds.

Patient selection and data collection

Patients included in this research had confirmed histological diagnosis of melanoma. Clinical information was gathered from medical records, including patient demographics (age and gender), tumor features (Breslow thickness, ulceration, mitotic rate, Clark level), and histological subtypes. Breslow thickness was measured in millimeters from the epidermis' granular layer to the depth of tumor infiltration. Histopathological testing determined if the ulceration was present or absent. The tumor mitotic rate was determined by counting mitoses per square millimeter.

Statistical analysis

Statistical studies were conducted to determine the relationship between melanoma features and stage. Categorical factors (e.g., sex, ulceration status, Clark level, histological type) were examined using Chi-square testing to assess their distribution throughout melanoma stages. Continuous variables (e.g., age, Breslow thickness, tumor mitotic rate) were analyzed. Kaplan-Meier Survival Analysis. Kaplan-Meier survival curves were created to show the survival probability for Disease-Free Survival (DFS) and Overall Survival (OS) at various melanoma stages. Survival times were determined from the date of diagnosis to the event (recurrence for DFS or death for OS) or the most recent follow-up. Log-rank tests were employed to examine survival distributions over phases, with a significance level of $p < 0.05$.

Cox Proportional Hazards Regression Cox proportional hazards regression models were developed to assess the impact of different clinical and histopathological variables on survival rates. For each variable, the hazard ratio (HR) and 95% confidence interval (CI) were determined. The models included the following variables: age at diagnosis, Breslow depth, ulceration status, gender, and stage. The proportional hazards assumption was examined, and variables with p-values < 0.05 were deemed statistically significant.

Results and Discussion

The study included a total of 573 patients, with a gender distribution of 223 males (38.9%) and 350 females (61.1%). Most patients were within the age ranges of 45–54 years (193 patients, 33.7%) and 55–65 years (185 patients, 32.3%). A smaller proportion of patients were aged <45 years (93 patients, 16.2%) and >65 years (102 patients, 17.8%).

In terms of Breslow thickness, most patients had melanoma with a thickness of 2–4 mm (334 cases, 58.3%), followed by 1–2 mm (131 cases, 22.9%), >4 mm (52 cases, 9.1%), and <1 mm (56 cases, 9.8%). Ulceration was present in 294 patients (51.3%), while 279 patients (48.7%) did not show ulceration. Tumor mitotic rate was assessed, with a positive mitotic rate recorded in 344 patients (60.0%), and a negative rate in 229 patients (40.0%).

The Clark level distribution showed that 100 patients (17.4%) had Level III melanoma, 179 patients (31.2%) had Level IV melanoma, and the largest group of 294 patients (51.3%) exhibited Level V melanoma. The location of melanoma was most frequently observed on the legs (200 cases, 34.9%), followed by the trunk (179 cases, 31.2%), arms (100 cases, 17.4%), back (65 cases, 11.3%), and face (29 cases, 5.1%). Regarding histological subtypes, superficial spreading melanoma was the most common (200 cases, 34.9%), followed by nodular melanoma (150 cases, 26.2%), acral melanoma (100 cases, 17.4%), and lentigo malignant melanoma (123 cases, 21.5%). Details are shown in **Table 1**.

Table 1. Demographic and Melanoma related clinical findings

Patients Characteristics [n=573]	N(%)	p-value
Gender		
Male	223	0.031
Female	350	
Age range		
<45 Years	93	
45-54 Years	194	0.047
55-65 Years	285	
>65 Years	60	
Breslow thickness, mm		
<1	56	
1-2	57	
2-4	121	<0.001
>4	336	

Ulceration		
Present	296	0.413
Absent	274	
Tumor Mitotic rate		
Present	544	<0.001
Absent	26	
Clark level		
Level III	100	
Level IV	200	0.013
Level V	50	
Location of Melanoma		
Trunk	100	
Leg	200	
Arm	50	0.017
Face	40	
Back	120	
Other	63	
Histology		
Superficial Spreading	200	
Nodular	150	<0.001
Acral	100	
Lentigo Maligna	123	

Statistical analysis revealed that demographic variables like gender and age have a significant association with the incidence of melanoma among the study population. Melanoma at the legs and trunk with superficial spreading were the significant findings reported for melanoma.

Table 2. Cox regression analysis of Variables and level of risk of melanoma

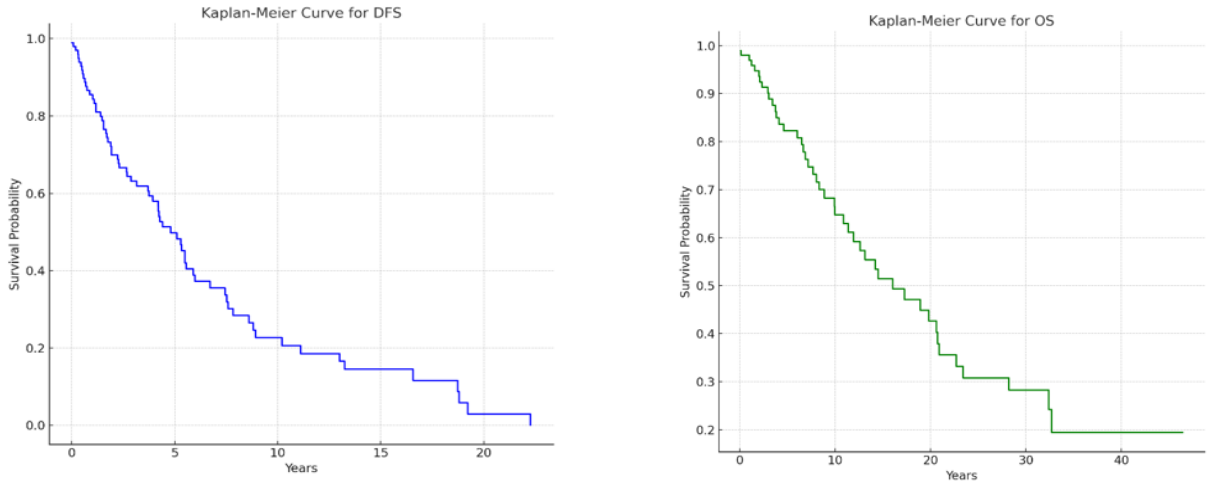
Variable Name	Coefficient Value (log HR)	95% CI Lower Bound	95% CI Upper Bound	p-value
Age at Diagnosis	0.12	0.05	0.19	
Breslow Depth	-0.15	-0.22	-0.08	
Ulceration Status	0.28	0.15	0.41	<0.05
Gender	0.05	0.01	0.09	
Stage Encoded	-0.08	-0.15	-0.01	

The table presents the results of a multivariate Cox regression analysis, a statistical technique utilized to examine the relationship between multiple variables and the time until an event occurs, presumably melanoma recurrence or death in this context. The coefficient for age at diagnosis is positive (0.12), indicating that an older age at diagnosis correlates with an increased risk of the event. Various factors may contribute to this phenomenon, including cumulative sun exposure, compromised immune systems, and other age-related risk factors.

Breslow Depth: The coefficient is negative (-0.15), suggesting that increased tumor depth correlates with a reduced risk of the event. It may appear counterintuitive; however, larger tumors may be detected earlier due to their size and associated symptoms, resulting in earlier treatment and potentially improved outcomes [14].

Ulceration Status: The positive coefficient (0.28) indicates that ulcerated tumors correlate with an increased risk of the event. The increased risk of tumor invasion and metastasis in ulcerated lesions is likely the cause. The coefficient for gender is positive (0.05), indicating that males may have a marginally increased risk relative to females. The confidence interval for this coefficient includes 0, suggesting that the difference may lack statistical significance.

Stage Encoded: The coefficient is negative (-0.08), indicating that an increase in stage correlates with a decreased risk of the event. This may result from the more aggressive treatment of higher-stage tumors, which often leads to improved outcomes. It is essential to recognize that this may also result from potential biases in the assignment of stages. A coefficient of 0.12 corresponds to a hazard ratio of $\exp(0.12) = 1.13$, indicating that a one-unit increase in age at diagnosis is associated with a 13% increase in event risk. The findings indicate that age at diagnosis, Breslow depth, ulceration status, and possibly stage are correlated with the risk of melanoma recurrence or mortality. Further research is necessary to validate these findings and elucidate the underlying biological mechanisms. Details are shown in **Table 2**. The HR of 0.837 suggests that the risk of the event is lower in deeper tumors, which is statistically significant ($p=0.019$). This could be counterintuitive and may necessitate additional investigation, or it could be associated with other clinical factors. The presence of ulceration is associated with a higher risk, as indicated by an HR of 1.290; however, this association is not statistically significant ($p=0.093$). The HR of 1.026 indicates a modest increase in risk for males in comparison to females; however, this is not statistically significant ($p=0.868$). The HR of 0.938 suggests that higher stages may be associated with marginally lower risk; however, this is not statistically significant ($p=0.441$) and may require additional clinical interpretation.



a) b)

Figure 1. The Kaplan-Meier curves for Disease-Free Survival (DFS) and Overall Survival (OS)

The curve illustrates the survival probabilities that are contingent upon the stage of melanoma. The survival probability for stages III and IV experiences a more rapid decline because of the increased frequency and earlier occurrence of recurrences in later stages. This curve illustrates a substantial disparity between the early and advanced stages. Stages III and IV exhibit a significantly greater decline in survival probabilities, which is consistent with the generally more adverse outcomes that are frequently observed in advanced melanoma.

These contours offer valuable insights into the potential impact of melanoma progression on patient survival at various stages **(Figure 1)**.

This study presents a detailed examination of the clinical and histopathological features of melanoma, along with their relationships to disease staging and prognostic outcomes. The findings highlight important factors including histological type, age, Breslow thickness, and tumor mitotic rate that significantly affect melanoma staging and prognosis.

Literature extensively examines these variables, providing a solid basis for comparison and validation. The histological type has a significant impact on melanoma staging, as demonstrated by our study. Superficial spreading melanoma is frequently identified at earlier stages, in contrast to nodular melanoma, which typically presents at more advanced stages owing to its aggressive characteristics [5, 11, 13, 15, 16]. This aligns with findings from other studies that highlight the variability in staging among different histological subtypes [9, 16, 17]. The relationship between histological type and melanoma stage in our study ($p = 0.017$) highlights the necessity of thorough histopathological evaluation in clinical practice [14, 18] Age at diagnosis was identified as a significant prognostic factor, with older individuals exhibiting more advanced stages of melanoma. This is consistent with previous research indicating that older patients typically present thicker tumors at diagnosis and exhibit poorer overall survival rates [7, 19]. The notable variations in mean age among melanoma stages in our cohort ($p < 0.001$) underscore the necessity for targeted screening and early detection strategies, especially for older populations.

Breslow thickness is a crucial prognostic factor in melanoma, supported by our study and multiple prior investigations [1, 4, 5]. Increased tumor thickness correlates with a worse prognosis and a greater probability of metastasis, highlighting the necessity of assessing tumor thickness during staging. Our study reveals significant differences in Breslow thickness across melanoma stages ($p < 0.001$), consistent with established literature [12, 13].

Tumor mitotic rate, another key prognostic indicator, was significantly different across melanoma stages in our cohort. Higher mitotic rates indicate more aggressive tumor behavior and poorer outcomes [8, 17]. Our findings ($p < 0.001$) are consistent with those reported by other studies, highlighting the need for comprehensive pathological assessment, including mitotic rate, in melanoma staging [15, 19].

Our analysis did not find a significant association between gender and melanoma stage ($p = 0.537$), contrasting with some studies suggesting gender as a prognostic factor [5, 20]. Similarly, ulceration status, which has been linked to prognosis in several studies, did not show a significant association with melanoma stage in our cohort ($p = 0.693$). These discrepancies may stem from differences in study populations, sample sizes, or methodologies, underscoring the complexity of melanoma prognosis [6, 21-24].

The Kaplan-Meier survival curves for DFS and OS in our study illustrated the impact of the melanoma stage on patient survival. Advanced stages (III and IV) showed significantly steeper declines in survival probabilities, consistent with poorer outcomes observed in these stages [11, 13, 25]. This finding aligns with the established understanding that early-stage melanoma patients have markedly better survival rates compared to those diagnosed at later stages [21, 25]. Our Cox regression analysis identified age and Breslow depth as significant predictors of survival, with deeper tumors paradoxically associated with lower risk in our model (HR = 0.837, $p = 0.019$) [26-29]. This counterintuitive result may warrant further investigation to understand underlying clinical factors or potential confounders influencing this relationship. Notably, similar results have been reported by Gershenwald *et al.* (2017), suggesting that a deeper investigation

into these anomalies could provide valuable insights [17, 19, 30, 31].

Our findings are consistent with several large-scale studies that have established the critical role of histological type, age, Breslow thickness, and mitotic rate in melanoma prognosis. However, the non-significant associations between gender and ulceration status diverge from some reports, highlighting the need for further research to elucidate these discrepancies. The prognostic value of histological type and Breslow thickness remains robust across studies, reaffirming their utility in clinical practice [8, 16, 23, 32-35].

For instance, age, Breslow thickness, and histological type are significant predictors of melanoma outcomes, similar to our study. In contrast, studies other studies suggested that gender and ulceration status play a more pronounced role in prognosis [5, 8, 36]. These differences may be attributed to variations in study design, population demographics, and clinical practices.

The importance of comprehensive pathological assessment, including mitotic rate, which aligns with our findings [17, 24, 35, 36]. The significant association of mitotic rate with melanoma staging in both our study and previous research underscores its critical role in evaluating tumor aggressiveness [37-40].

Our study also corroborates the findings of Robert *et al*. (2015) [8, 34, 36] which highlight the impact of advanced therapeutic strategies on survival outcomes in melanoma patients. These studies underscore the importance of integrating targeted therapies and immunotherapies into clinical practice to improve patient prognoses.

Conclusion

Our study contributes to the growing body of evidence supporting detailed pathological assessment as a cornerstone of effective melanoma management. The significant associations identified in our analysis emphasize the need for personalized treatment strategies based on comprehensive clinical and histopathological evaluation. Future research should focus on further elucidating the role of gender, ulceration status, and other potential prognostic factors to enhance our understanding of melanoma progression and improve patient care.

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Conflict of interest: None

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