ORIGINAL REPORT

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Immunosuppression Outweighs Clinical AEIOU Heuristics in Predicting Disease Progression of Merkel Cell Carcinoma: A Retrospective Cohort Study

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Merkel cell carcinoma (MCC)is a rare but aggressive cutaneous malignancy with increasing incidence and poor prognosis. Host immune status is a key determinant of MCCmerkel cell carcinoma development and outcome. While the AEIOU criteria are widely used to facilitate clinical recognition, their value for prognostic assessment remains unclear. To evaluate the association between individual AEIOU presentation features and disease progression in patients with merkel cell carcinoma, with particular emphasis on immunosuppression. We performed a retrospective single-centre cohort study including 400 patients diagnosed with merkel cell carcinoma. Disease progression, defined as local recurrence, nodal involvement or distant metastasis, served as the primary endpoint. AEIOU criteria were assessed at diagnosis and analysed using logistic regression. Complete follow-up data were available for 241 patients, of whom 81 (33.6%) experienced disease progression. Patients with progression were significantly older and more frequently male. Among the AEIOU components, immunosuppression was the only criterion significantly associated with disease progression, conferring an increased risk compared with immunocompetent patients (p<0.001). Other AEIOU features showed no consistent prognostic association. **Complete follow-up data were available for 241 patients, of whom 81 (33.6%) experienced disease progression. Patients with progression were significantly older and more frequently male. Among the AEIOU components, immunosuppression was the only criterion significantly associated with disease progression, conferring an increased risk compared with immunocompetent patients (p<0.001). Other AEIOU features showed no consistent prognostic association.**

Key words: merkel cell carcinoma; immunosuppression; disease progression; skin cancer prognosis; risk stratification; clinical predictors.

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SIGNIFICANCE

Merkel cell carcinoma is an aggressive skin cancer in which reliable clinical risk stratification remains challenging. This study demonstrates that immunosuppression is the most relevant clinical predictor of disease progression, outweighing other commonly used presentation features summarized by the AEIOU criteria. By distinguishing immune-driven biological risk from detection-related clinical characteristics, our findings clarify the limited prognostic value of most AEIOU components. These results support an immune-informed approach to surveillance and management of MCCmerkel cell carcinoma and underscore the need for intensified follow-up strategies in immunocompromised patients, while avoiding overtreatment in patients with early detected, visible tumors.

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Merkel cell carcinoma (MCC) is a rare, highly aggressive neuroendocrine skin cancer with rising incidence and high mortality rates (1–3). Its incidence has increased markedly in recent decades, especially among elderly individuals. Prognosis remains poor, with 5 -year survival rates ranging from 30% to 64% depending on stage (2). Epidemiological data show a more than five5-fold rise over the past two2 decades (4, 5). This rise has been attributed to greater diagnostic awareness, an aging global population, and a higher prevalence of immunosuppression, as highlighted in recent epidemiological data (6). The widespread use of immunosuppressive therapies, including biologics and immune checkpoint inhibitors, has reshaped the immunologic landscape in both dermatology and oncology (7, 7–10). Despite advancements in immunotherapy and diagnostic techniques, MCC continues to pose a clinical challenge due to its aggressive behaviour and high metastatic potential.

The typical demographic profile of MCC patients includes advanced age, male sex, fair skin type, and a

history of significant sun exposure (11–13). Importantly, immunosuppression, whether due to underlying diseases such as HIV/AIDS, chronic lymphocytic leukaemia, or iatrogenic causes like organ transplantation, has been identified as a significant risk factor for both the development and the adverse clinical course of MCC (9, 10). Given the often rapid clinical progression and high recurrence rates, early and accurate risk stratification is essential to guide treatment decisions, including the extent of surgical resection, need for sentinel lymph node biopsy, and eligibility for adjuvant immunotherapy.(13–16).

To facilitate early clinical recognition, Heath et al. proposed the “"AEIOU” criteria, an acronym summarizing five5 common clinical features observed at diagnosis: Asymptomatic, Expanding rapidly, Immunosuppressed, Older than 50 years, and occurrence on UV-exposed sites (8). While AEIOU has proven valuable as a diagnostic heuristic, it was not designed to serve as a prognostic model. Nevertheless, its components continue to shape clinical perception of risk and may implicitly influence follow-up intensity and treatment decisions (17). This represents a critical gap, as early identification of high-risk patients could enable more aggressive surveillance and therapeutic strategies. Notably, a comprehensive evaluation of the prognostic relevance of these criteria, particularly regarding disease progression, is lacking (8).

A comparable approach exists for malignant melanoma, where the ABCDE mnemonic (Asymmetry, Border irregularity, Colour variation, Diameter, Evolving) has been successfully implemented to enhance early detection and risk assessment (18). The absence of a similar quantitative framework for MCC represents an unmet clinical need, particularly given the diseases aggressive nature and the potential for early interventions to alter outcomes. As MCC patients are frequently managed in interdisciplinary settings, from dermatologists and surgeons to oncologists and transplant physicians, a validated prognostic model grounded in accessible clinical features could streamline clinical decision-making across specialties. Importantly, several AEIOU features reflect epidemiologic or detection-related factors rather than intrinsic tumor aggressiveness. Features such as UV-exposed location or rapid growth may increase lesion visibility and thereby facilitate earlier diagnosis, whereas immunosuppression directly affects tumor host – immune interactions. Distinguishing between these fundamentally different mechanisms is essential for rational risk stratification in MCC.

The present study therefore aimed to evaluate the association between individual AEIOU components and disease progression in a large retrospective MCC cohort, with a specific focus on metastatic patterns. By contrasting immune-related and visibility-driven clinical features, we sought to clarify which readily available clinical factors meaningfully reflect biological risk and which primarily relate to early detection.

MATERIALS AND METHODS

Study Design and Population

This retrospective cohort study included 400 patients with histologically confirmed MCC, diagnosed and treated at a tertiary dermatology and oncology center between 1986 and 2023 (**Fig. 1**). Patients were identified through institutional cancer registries, and clinical data were extracted from electronic medical records. A minimum follow-up of 6 months was required for inclusion and complete case analysis was performed.

Data Collection

For each patient, detailed clinical and demographic information was collected. Particular attention was paid to the presence or absence of the five5 AEIOU criteria, as defined by Heath et al., at the time of initial diagnosis.(8).

The criterion “Asymptomatic” indicated the absence of pain or subjective complaints at the tumor site, typically discovered incidentally. “Expanding rapidly” described a history of visible tumor growth within weeks, based on patient or physician report. “Immunosuppressed” status encompassed conditions or treatments impairing immune function. “Older than 50 years” was coded dichotomously by age at diagnosis. “UV-exposed site” referred to tumors on chronically sun-exposed areas, face, scalp, neck, or upper extremities.

Primary Outcome Definition

Disease progression was defined as the development of local recurrence, regional lymph node metastases, or distant metastases during follow-up, as confirmed by clinical examination, imaging studies, or histopathology reports. Data completeness and internal consistency were reviewed by two2 independent investigators.

Secondary Outcomes

Further, the AEIOU criteria were evaluated as potential predictors for specific metastatic patterns in MCC. Using logistic regression models, each criterion was assessed for its association with the occurrence of distinct metastasis types. The following secondary outcomes were defined and analyzed accordingly: lymph-node metastases, soft-tissue metastases, cutaneous metastases, and organ metastases.

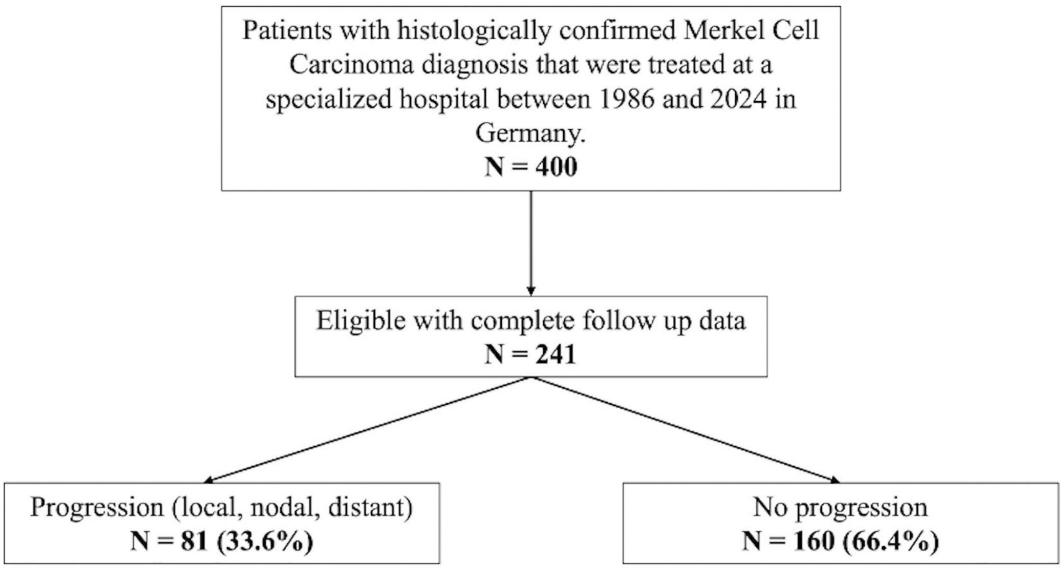

Fig. 1. Patient Flow Chart.

Statistical Analysis

Descriptive statistics were used to summarize baseline demographic and clinical characteristics. Continuous variables were presented as means with standard deviations, and categorical variables as frequencies and percentages. Associations between each AEIOU criterion and disease progression were first examined using univariate logistic regression models, reporting odds ratios (ORs), 95 % confidence intervals (CIs), and p-values. Multivariate models were subsequently constructed, adjusting for age, sex, and tumour localization. A fully adjusted model including all five5 AEIOU criteria was used to assess their independent contributions to disease progression. Interaction effects, particularly between immunosuppression and UV-exposed site, were also explored. Model calibration and fit were evaluated using standard diagnostic tests. Further details on model performance, and sensitivity analyses including multiple imputation lasso regression and inverse-probability-of-treatment-weighting (IPTW) are provided in the Supplement Section II (19–29). All analyses were performed using STATA (Version 16, StataCorp LLC, College Station, TX, USA). A two2-sided p-value<0.05 was considered statistically significant.

RESULTS

A total of 400 patients with histologically confirmed MCC were identified. Of these, 241 patients with complete follow-up data were included in the outcome analysis. During follow-up, 81 patients (33.6%) experienced disease progression, defined as local recurrence, regional lymph node metastasis, or distant metastasis. Patients with disease progression were significantly older (77.8±9.6 vs 73.3±11.8 years; p=0.003) and more frequently male (58.1% vs 42.0 %; p=0.02). Tumour localization differed (p=0.02), with the upper extremity lesions more common in patients without progression, whereas tumors at other anatomical sites were more frequent among progressors. Immunosuppression was more prevalent in patients who developed progression. Treatment patterns varied, with higher rates of metastasis-directed radiotherapy (46.9% vs 11.2 %; p<0.001) and chemotherapy (35.8% vs 3.1 %; p<0.001) among progressors. Hypertension (78.4%), hypercholesterolemia (32.8%), and diabetes (26.6%) were the most common comorbidities; rheumatoid arthritis (p=0.047) and hyperuricemia (p=0.010) were more frequent in the progression group (see **Table I**).

AEIOU as predictors for disease progression

In univariate logistic regression analyses, immunosuppression was the only AEIOU component significantly associated with disease progression, conferring approximately a two2-fold increased risk. (p<0.001). “Asymptomatic” and “UV-exposed site” showed trends (p=0.06). In multivariable analyses adjusting for age, sex, and tumor stage, no AEIOU feature reached significance, though immunosuppression approached it (OR=2.22; p=0.06) (see **Fig. 2**).

AEIOU criteria and metastatic patterns

Lymph-node metastases occurred in 101 patients (41.9%). Although the cumulative AEIOU score was not predictive (p=0.055), tumors on UV-exposed sites showed a significantly lower risk of nodal involvement (OR=0.47; p=0.03). No other individual criterion reached significance, though immunosuppression exhibited a positive trend.

Table I. Demographic and clinical characteristics of the cohort by disease progression

	Cohort N=241	**Without** progression N=160	**With** progression N=81	Pp-value
Age, *years*	74.80±11.30	73.27±11.79	77.80±9.64	0.003
BMI, *kg/m²*	27.58±5.27	27.49±4.69	27.77±6.28	0.71
Sex, *female*	127 (52.70%)	93 (58.1%)	34 (42.0%)	0.02
Tumor Localizations				0.02
Arms	56 (23.24%)	45 (28.1%)	11 (13.6%)	
Legs	29 (12.03%)	19 (11.9%)	10 (12.3%)	
Trunk	13 (5.39%)	7 (4.4%)	6 (7.4%)	
Head & Neck	127 (52.70%)	83 (51.9%)	44 (54.3%)	
Other	16 (6.64%)	6 (3.8%)	10 (12.3%)	
AEIOU Criteria				
Asymptomatic	229 (95.02%)	155 (96.9%)	74 (91.4%)	0.06
Rapid expansion	142 (58.92%)	96 (60.0%)	46 (56.8%)	0.66
Immunosuppressed	37 (15.35%)	15 (9.4%)	22 (27.2%)	<0.001
Age>50 Years	235 (97.51%)	155 (96.9%)	80 (98.8%)	0.37
UV Exposed Areas	105 (43.57%)	63 (39.4%)	42 (51.9%)	0.06
Treatment options				
Lymph-node radiation	77 (31.95%)	51 (31.9%)	26 (32.1%)	0.97
Metastases radiation	56 (23.24%)	18 (11.2%)	38 (46.9%)	<0.001
Chemotherapy	34 (14.11%)	5 (3.1%)	29 (35.8%)	<0.001
Comorbidities				
Rheumatoid Arthritis	16 (6.64%)	7 (4.4%)	9 (11.1%)	0.047
Hyperuricemia	34 (14.11%)	16 (10.0%)	18 (22.2%)	0.010
Hypertension	189 (78.42%)	120 (75.0%)	69 (85.2%)	0.069
Hypercholesterinaemia	79 (32.78%)	54 (33.8%)	25 (30.9%)	0.65
Diabetes	64 (26.56%)	40 (25.0%)	24 (29.6%)	0.44
Smoker	11 (4.56%)	7 (4.4%)	4 (4.9%)	0.84
Thyroid pathologies				0.44
Hypothyroidism	48 (19.92%)	35 (21.9%)	13 (16.0%)	
Hyperthyroidism	1 (0.41%)	0 (0.0%)	1 (1.2%)	
Struma	9 (3.73%)	7 (4.4%)	2 (2.5%)	
S/p. thyroidectomy	5 (2.07%)	3 (1.9%)	2 (2.5%)	

Soft-tissue metastases developed in 64 patients (26.6%). Immunosuppression was strongly associated with soft-tissue metastasis, with more than a three3-fold increased risk (OR=3.55; p=0.004). In contrast, both rapid tumor growth (OR=0.33; p=0.002) and UV-exposed tumor sites (OR=0.33; p=0.001) were associated with significantly lower odds of soft-tissue spread.

Cutaneous metastases were observed in 64 patients (26.6%). Here again, rapidly expanding tumors (OR=0.45; p=0.017) and UV-exposed sites (OR=0.49; p=0.038) were associated with reduced risk. Immunosuppression showed a tendency toward increased risk, although this did not reach statistical significance (OR=1.59; p=0.30).

Visceral metastases occurred in 20 patients (8.3%). None of the AEIOU features significantly predicted the occurrence of organ involvement. While "Asymptomatic" presentation showed a trend toward higher odds (OR=1.73), other factors including rapid growth, UV exposure, and immunosuppression showed no meaningful associations (p>0.5 for all) (see **Fig. 3**).

Sensitivity Analyses

The robustness of our findings was supported by multiple sensitivity analyses. Multiple imputation using chained equations was performed to address missing data among key predictors, thereby reducing potential bias from complete-case analysis, and yielded results consistent with the primary analyses. Similarly, variable selection using LASSO logistic regression with cross-validation confirmed the stability of the identified predictors, including the relevance of specific AEIOU criteria for metastasis risk. In addition,

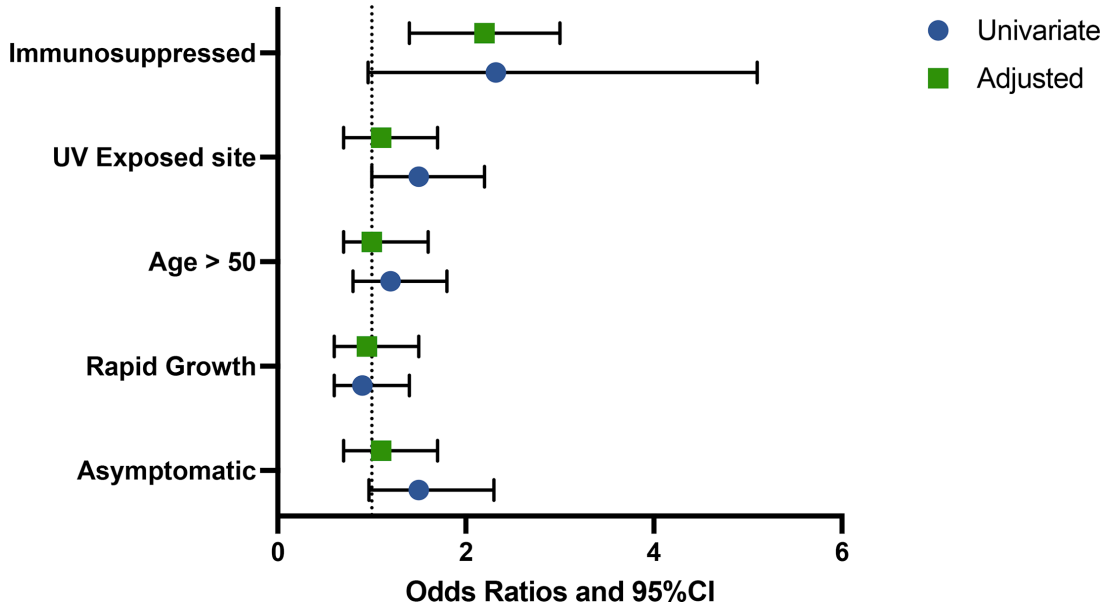

Fig. 2. Forest plot summarizing the effect of the AEIOU features on overall progression.

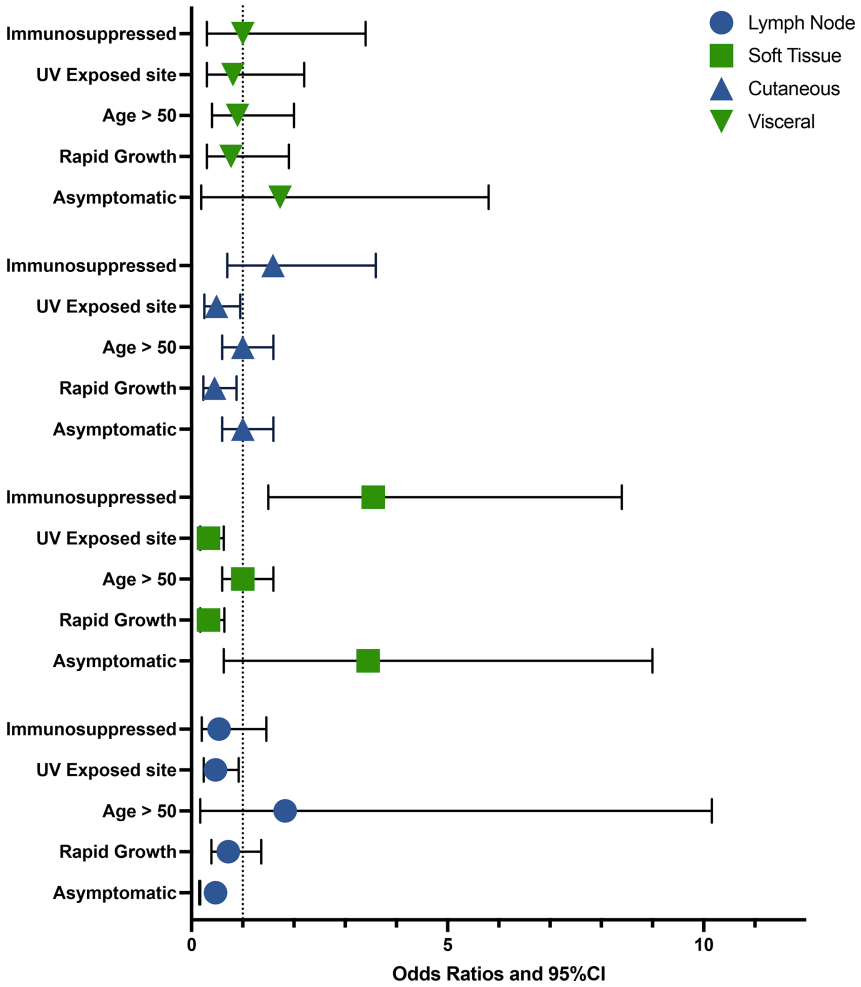

Fig. 3. Forrest Pplot summarizing the AEIOU Ffeatures on specific metastases.

IPTW analyses, applied to estimate the causal effect of immunosuppression while adjusting for potential confounders, produced effect estimates in line with those from the multivariable models, further reinforcing the validity of our conclusions. Full results are provided in the Supplement (Section III).

DISCUSSION

In this retrospective cohort study of patients with MCC, we evaluated whether readily available clinical presentation features, summarized by the AEIOU criteria, are associated with disease progression and metastatic behaviour. Our results demonstrate that immunosuppression is a significant clinical predictor of progression and regional dissemination, whereas most other AEIOU components show limited or inverse prognostic value.

Immunosuppression was the only AEIOU criterion significantly associated with overall disease progression in univariate analysis and was significantly linked to soft-tissue metastases. Although the association attenuated after multivariable adjustment, the effect size remained clinically meaningful.

This finding aligns with extensive prior evidence identifying impaired immune surveillance as a central driver of MCC aggressiveness. Immunosuppressed patients, those with HIV, chronic lymphocytic leukaemia, or organ transplants, have a 5- to 55-fold higher risk of MCC development and poorer survival outcomes (3, 7, 9, 10, 14, 30–32). Our data extend this knowledge by demonstrating that immune status also influences metastatic patterns, particularly regional soft-tissue spread.

The biological plausibility of these findings is supported by current understanding of MCC pathogenesis. Both virus-associated and UV-induced MCC subtypes rely on impaired immune control for tumor progression. In Merkel cell polyomavirus (MCPyV)-positive tumors, reduced T-cell–mediated immunity facilitates viral oncogene-driven growth, whereas UV-induced tumors exhibit high mutational burden and neoantigen load that similarly require immune evasion (33–35). In this context,

immunosuppression emerges as a unifying determinant of disease aggressiveness across etiologic subtypes.

In contrast, several AEIOU components traditionally perceived as markers of aggressive disease were associated with lower metastatic risk. Tumors located on UV-exposed sites and lesions described as rapidly expanding showed reduced odds of nodal, soft-tissue, and cutaneous metastases. These inverse associations likely reflect a "visibility effect"; whereby conspicuous lesions prompt earlier clinical evaluation and surgical management. This interpretation is supported by epidemiologic studies demonstrating poorer outcomes for MCCs arising on sun-protected or anatomically less visible sites (3, 36–38). Mohsin et al. reported no survival difference between head/neck and extremity lesions but found markedly worse outcomes for tumors on sun-protected genital sites, supporting the hypothesis that visibility and timely diagnosis, rather than UV exposure per se, influence prognosis.(38).

Together, these findings highlight a fundamental distinction between clinical recognition features and biological aggressiveness. While AEIOU criteria remain useful for raising diagnostic suspicion, most of their components primarily capture epidemiologic context or detection-related factors rather than intrinsic tumor behaviour. Immunosuppression represents the notable exception, directly modulating tumor-host immune interactions and thereby influencing disease progression.

From a clinical perspective, our results support an immune-informed approach to risk stratification and follow-up. While AEIOU criteria remain useful for diagnostic awareness, they do not provide a reliable framework for prognostic assessment. Although the prognostic relevance of immunosuppression in MCC is well established, the present study adds to the existing evidence by demonstrating its relative importance compared with the other AEIOU features, none of which showed independent associations with disease progression. Immunosuppressed patients may benefit from intensified staging procedures, closer surveillance intervals, and early interdisciplinary management, whereas patients with visible, rapidly detected tumors on UV-exposed sites may be managed more conservatively once adequate staging has been completed.

Strengths and limitations

This study has several strengths, including a relatively large single-center cohort, long observation period, and detailed analysis of distinct metastatic pathways. Nevertheless, limitations must be acknowledged. The retrospective design introduces potential information bias, particularly regarding subjectively documented features such as rapid tumor growth. The monocentric setting may limit generalizability, although the internal consistency of findings and concordance with prior literature support their validity.

Conclusion

In summary, our findings demonstrate that immunosuppression outweighs other common clinical presentation features in predicting disease progression and metastatic spread in MCC. These results underscore the need to distinguish diagnostic heuristics from biologically meaningful risk factors and, while the prognostic role of immune status in MCC is not novel, further support its relative primacy among AEIOU features as a central component of clinical decision-making.

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Data availability statement: The datasets generated and/or analysed during the current study are not publicly available but can be obtained from the corresponding author upon reasonable request.

Ethics committee: Reviewed and approved by institutional review board; Approval #2022-611-f-S.

The authors have no conflicts of interest to declare.

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