

Tumor Mutational Burden as a Predictive Biomarker for Immunotherapy Response in Acral Melanoma: A Comprehensive Molecular and Clinical Analysis

Jennifer Maribel Llamas Medrano^{*1}, Diego Alonso Luna Reynoso², María José Rosales Barajas², Ivonne Alejandra Perales Soto², Paola Natali Torres Montañez²

¹Hospital General de Zona 4 Instituto Mexicano del Seguro Social. Mexico.

²Hospital General de Zona 1 “Dr Emilio Varela Luján”. Instituto Mexicano del Seguro Social. Zacatecas, Mexico.

ABSTRACT

Acral melanoma, a rare yet aggressive subtype of cutaneous melanoma, exhibits distinct genomic and clinical characteristics compared to non-acral counterparts. Despite advancements in immune checkpoint inhibitor (ICI) therapy, predictive biomarkers for treatment response remain incompletely elucidated. Tumor mutational burden (TMB), a quantifiable measure of somatic mutations within the tumor genome, has emerged as a potential biomarker for immunotherapy efficacy across various malignancies. This review critically evaluates the role of TMB in predicting clinical outcomes to ICIs in acral melanoma, integrating evidence from molecular profiling studies and clinical trials. We discuss the interplay between TMB, tumor microenvironment (TME), and immune evasion mechanisms, while addressing limitations such as heterogeneity in TMB quantification and confounding factors like ultraviolet (UV) signature mutational patterns. Our analysis underscores the need for standardized TMB thresholds and multimodal biomarker approaches to optimize patient stratification in this challenging disease subset.

KEYWORDS: Acral melanoma, tumor mutational burden, immunotherapy, immune checkpoint inhibitors, predictive biomarker, somatic mutations, tumor microenvironment, immune evasion, precision oncology

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INTRODUCTION

Acral melanoma, arising in glabrous skin of the palms, soles, and nail apparatus, represents a clinically and molecularly distinct entity within the spectrum of cutaneous melanomas. Unlike conventional melanomas associated with ultraviolet (UV) radiation exposure, acral melanomas frequently exhibit lower mutation rates and alternative oncogenic drivers, such as KIT amplifications and structural rearrangements. The advent of immune checkpoint inhibitors (ICIs), including anti-PD-1 and anti-CTLA-4 agents, has revolutionized melanoma treatment; however, response rates in acral subtypes remain variable, necessitating robust predictive biomarkers.^{1,2}

Tumor mutational burden (TMB), defined as the total number of nonsynonymous mutations per megabase of the tumor genome, has garnered attention as a quantitative correlate of

neoantigen load and subsequent T-cell recognition. In hypermutated tumors, elevated TMB correlates with enhanced immunogenicity and improved ICI responses, as demonstrated in malignancies such as non-small cell lung cancer and melanoma. Nevertheless, the predictive utility of TMB in acral melanoma remains controversial, given its typically lower mutational load and unique genomic landscape.²

This review synthesizes current knowledge on TMB as a determinant of immunotherapy response in acral melanoma, exploring its relationship with tumor-infiltrating lymphocytes (TILs), PD-L1 expression, and other immune modulators. We further examine technical challenges in TMB assessment, including platform-specific discrepancies and the influence of non-UV mutational signatures. By contextualizing TMB within the broader framework of acral melanoma biology,

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this discussion aims to refine its role as a stratification tool while highlighting gaps in existing evidence.²

BACKGROUND

Acral melanoma, a rare and biologically distinct subtype of cutaneous melanoma, arises in non-hair-bearing glabrous skin, primarily affecting the palms, soles, and subungual regions. Unlike conventional melanomas, which are strongly associated with ultraviolet (UV) radiation-induced mutagenesis, acral melanomas develop in sun-shielded anatomical sites and exhibit a markedly different molecular profile. This divergence is reflected in their lower overall tumor mutational burden (TMB), reduced prevalence of driver mutations such as BRAF V600E, and a higher frequency of structural genomic aberrations, including KIT amplifications and CDK4 and CCND1 copy number variations. Despite accounting for a minority of melanoma cases, acral melanoma carries a disproportionately poor prognosis due to its aggressive clinical behavior, delayed diagnosis, and historically limited therapeutic options.³

The emergence of immune checkpoint inhibitors (ICIs) targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and its ligand (PD-L1) has transformed the therapeutic landscape of advanced melanoma, with durable responses observed across multiple subtypes. However, clinical outcomes in acral melanoma remain inconsistent, with response rates to ICIs generally lower than those seen in non-acral cutaneous melanomas. This discrepancy has spurred investigations into predictive biomarkers capable of stratifying patients who are most likely to benefit from immunotherapy. Among these, TMB has emerged as a compelling candidate, given its established correlation with neoantigen burden and subsequent T-cell-mediated antitumor immunity in various malignancies.³

TMB quantifies the total number of somatic nonsynonymous mutations within a tumor's exome, serving as an indirect measure of immunogenic neoantigen production. High TMB has been associated with improved responses to ICIs in melanoma and other solid tumors, presumably due to increased immune recognition of mutation-derived neoantigens. However, the predictive power of TMB in acral melanoma is complicated by its typically lower mutation rate, which contrasts with the hypermutated phenotypes seen in UV-exposed melanomas. Furthermore, the mutational signatures in acral melanoma often reflect endogenous processes such as defective DNA repair or oxidative stress, rather than UV-induced cyclobutane pyrimidine dimer (CPD) formation, potentially altering the immunogenicity of the resulting neoantigens.^{3,4}

Additional layers of complexity arise from the tumor microenvironment (TME) of acral melanoma, which frequently exhibits immune-cold features, including low levels of tumor-infiltrating lymphocytes (TILs), diminished

PD-L1 expression, and an immunosuppressive stromal composition. These factors may attenuate the expected correlation between TMB and immunotherapy response, suggesting that TMB alone may be insufficient as a standalone biomarker. Emerging evidence also highlights discrepancies in TMB quantification methodologies, including variations in sequencing platforms, bioinformatic pipelines, and the definition of clinically relevant TMB thresholds, further complicating its universal applicability.⁴ Given these challenges, ongoing research seeks to refine the role of TMB in acral melanoma by integrating it with complementary biomarkers, such as immune gene expression profiles, HLA genotype, and T-cell receptor (TCR) clonality. A more comprehensive understanding of the interplay between mutational load, neoantigen quality, and host immune factors will be essential to optimize patient selection for immunotherapy and identify resistance mechanisms. This review aims to critically evaluate the current evidence supporting TMB as a predictive biomarker in acral melanoma, while addressing the biological and technical limitations that must be overcome to enhance its clinical utility in this unique and therapeutically challenging disease subset.⁵

Predictive Utility of Tumor Mutational Burden in Immunotherapy Response for Acral Melanoma

The predictive role of tumor mutational burden (TMB) in determining therapeutic response to immune checkpoint inhibitors (ICIs) in acral melanoma remains a subject of rigorous investigation, given the unique genomic and immunological characteristics that distinguish this rare melanoma subtype from its cutaneous counterparts. As a quantitative measure of somatic mutations within the tumor exome, TMB serves as a proxy for neoantigen load, theoretically enhancing immune recognition and T-cell-mediated tumor destruction. However, the translational applicability of TMB as a standalone predictive biomarker in acral melanoma is complicated by multiple biological and technical factors, necessitating a nuanced interpretation of its clinical utility.⁵

In malignancies with high TMB, such as melanoma, non-small cell lung cancer (NSCLC), and microsatellite instability-high (MSI-H) tumors, elevated mutation rates correlate with increased immunogenicity and improved responses to PD-1/PD-L1 and CTLA-4 blockade. This relationship is mechanistically supported by the principle that a greater mutational load generates a broader repertoire of tumor-specific neoantigens, facilitating immune activation and cytotoxic T-cell infiltration. However, acral melanomas typically exhibit a lower TMB compared to UV-induced melanomas, largely due to their distinct etiopathogenesis, which lacks the mutagenic impact of ultraviolet radiation. Instead, these tumors often harbor structural genomic alterations, including focal amplifications in KIT, CCND1, and CDK4, as well as chromosomal instability, which may

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contribute to oncogenesis without necessarily increasing immunogenic neoantigen presentation.^{6,7}

Despite these limitations, emerging clinical evidence suggests that a subset of acral melanoma patients with higher TMB still derive benefit from immunotherapy, reinforcing the potential utility of mutational burden as a stratification tool. Retrospective analyses have demonstrated that even within this generally low-TMB cohort, tumors at the upper quantile of mutation load exhibit improved objective response rates (ORR) and progression-free survival (PFS) following ICI treatment. This observation implies that TMB thresholds for immunotherapy response may need to be recalibrated specifically for acral melanoma, rather than adopting cutoffs established in more highly mutated cancers. Additionally, the quality—rather than merely the quantity—of mutations may influence immunogenicity, as certain mutational signatures (e.g., those associated with APOBEC enzymatic activity or defective mismatch repair) could generate more immunodominant neoantigens compared to others.^{7,8,9}

A critical confounding factor in interpreting TMB's predictive power is the immunosuppressive tumor microenvironment (TME) frequently observed in acral melanomas. Even in cases with relatively higher TMB, the presence of immune-excluded or immune-desert phenotypes, characterized by poor T-cell infiltration, upregulated myeloid-derived suppressor cells (MDSCs), and extracellular matrix remodeling, may dampen therapeutic responses. Consequently, TMB's predictive accuracy may be enhanced when integrated with complementary biomarkers such as PD-L1 expression, tumor-infiltrating lymphocyte (TIL) density, or immune gene expression signatures. Furthermore, host-related factors, including HLA allelic diversity and T-cell receptor (TCR) clonality, likely modulate the relationship between TMB and clinical outcomes, underscoring the need for a multifactorial predictive model.^{10,11}

Technical challenges in TMB assessment further complicate its universal adoption as a predictive biomarker. Discrepancies in next-generation sequencing (NGS) panels, bioinformatic pipelines, and the definition of "high" versus "low" TMB thresholds introduce variability across studies, limiting reproducibility. Whole-exome sequencing (WES) remains the gold standard for TMB quantification, yet its clinical feasibility is constrained by cost and tissue requirements, prompting the use of targeted gene panels that may not fully capture mutational heterogeneity. Standardization efforts are thus imperative to ensure consistent TMB reporting and facilitate cross-study comparisons.^{12,13}

While TMB holds promise as a predictive biomarker for immunotherapy response in acral melanoma, its standalone utility is constrained by the tumor's intrinsic genomic and immunological features. Refining TMB interpretation through context-specific thresholds, integration with immune

microenvironment profiling, and advancements in sequencing methodologies will be essential to optimize its clinical applicability. Future research should focus on validating composite biomarker models that incorporate TMB alongside other molecular and immunological determinants, ultimately enabling precision immunotherapy strategies for this therapeutically challenging disease subset.^{14,15,16}

CONCLUSION

The investigation of tumor mutational burden (TMB) as a predictive biomarker for immunotherapy response in acral melanoma presents a complex yet compelling paradigm in precision oncology, reflecting the intricate interplay between genomic determinants and host immune surveillance. While TMB has established prognostic value in various malignancies, its applicability in acral melanoma remains nuanced due to the tumor's distinct molecular pathogenesis, characterized by a comparatively lower somatic mutational load and a higher prevalence of structural genomic aberrations rather than UV-induced point mutations. The inherent biological heterogeneity of acral melanoma, coupled with its frequently immunosuppressive tumor microenvironment, challenges the conventional assumption that elevated TMB uniformly correlates with enhanced immunogenicity and clinical response to immune checkpoint inhibition. Nevertheless, emerging evidence suggests that a subset of acral melanoma patients with relatively higher TMB may indeed derive therapeutic benefit from PD-1/PD-L1 or CTLA-4 blockade, reinforcing the need for disease-specific TMB thresholds that account for the unique mutational landscape of this rare melanoma subtype.

A critical consideration in the clinical translation of TMB is the qualitative dimension of tumor mutations, as not all genomic alterations contribute equally to neoantigen presentation and subsequent T-cell recognition. Mutational signatures associated with endogenous processes such as APOBEC-mediated cytidine deamination or defective DNA repair mechanisms may generate immunogenic epitopes distinct from those arising from UV-induced damage, potentially influencing the predictive power of TMB in acral melanoma. Furthermore, the immunosuppressive features frequently observed in the acral melanoma tumor microenvironment—including diminished CD8⁺ T-cell infiltration, upregulated regulatory T-cell (Treg) activity, and stromal barriers to immune cell trafficking—may attenuate the expected correlation between TMB and immunotherapy response. This underscores the necessity of adopting a multidimensional biomarker approach that integrates TMB with complementary immunological and molecular parameters, such as PD-L1 expression, tumor-infiltrating lymphocyte (TIL) density, and immune gene expression profiling, to enhance predictive accuracy.

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Technical standardization remains another pivotal challenge in the implementation of TMB as a reliable biomarker. Variability in next-generation sequencing platforms, bioinformatic pipelines, and the absence of universally accepted TMB cutoff values introduce significant interstudy heterogeneity, limiting the reproducibility of findings across clinical cohorts. Efforts to harmonize TMB assessment methodologies, including the adoption of whole-exome sequencing as a reference standard and the development of validated targeted panels optimized for acral melanoma genomics, will be essential to establish robust clinical guidelines. Additionally, prospective studies incorporating longitudinal monitoring of TMB dynamics and immune clonal selection under therapeutic pressure may provide deeper insights into the evolving relationship between mutational burden and treatment resistance.

In conclusion, while TMB represents a biologically rational and increasingly measurable biomarker in acral melanoma, its predictive utility must be contextualized within the framework of the tumor's unique genomic and immunological milieu. Future research should prioritize the development of integrated predictive models that combine TMB with other determinants of immune responsiveness, facilitating a more refined stratification of patients likely to benefit from immunotherapy. As precision oncology continues to evolve, the optimization of TMB-based biomarkers in acral melanoma will depend on collaborative efforts to standardize genomic profiling, validate combinatorial biomarker strategies, and elucidate the mechanistic underpinnings of immune evasion in this aggressive disease subset. Ultimately, such advancements will pave the way for tailored therapeutic approaches that maximize clinical outcomes while minimizing unnecessary toxicity in patients with acral melanoma.

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