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Dr. Surendra Parsad Yadav
Plastic Surgeon, Department of Orthopedics, Tumor Hospital of Yunnan Province, The Third Affiliated Hospital of Kunming Medical University. Kunming, Yunnan 650118, P.R, China

Babita Yadav
Medical Students, Kunming Medical University. Kunming, Yunnan 650118, P.R, China

Corresponding Author:
Dr. Surendra Parsad Yadav
Plastic Surgeon, Department of Orthopedics, Tumor Hospital of Yunnan Province, The Third Affiliated Hospital of Kunming Medical University. Kunming, Yunnan 650118, P.R, China

Clinical implications of genetic mutations in the prognostic stratification of acral malignant melanoma

Surendra Parsad Yadav and Babita Yadav

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Abstract
Acral malignant melanoma (AM) is an aggressive subtype with distinct genetic and clinical features, particularly prevalent in Asian populations. This study investigated prognostic factors, surgical outcomes and molecular biomarkers to improve management strategies. A retrospective analysis of 223 AM patients (2015–2021) evaluated clinical-pathological variables (ulceration, LDH, Ki-67) through Cox regression. Surgical outcomes for heel defects were compared between traditional skin grafting (n=73) and vacuum-assisted closure (VSD; n=73). Bioinformatics analysis of TCGA data identified metastasis-associated lncRNAs, validated via qPCR in melanoma cell lines. Ulceration (HR=2.34, p<0.001), lymph node metastasis (HR=1.89, p=0.002), elevated LDH (HR=2.12, p<0.001) and Ki-67 ≥50% (HR=1.76, p=0.008) independently predicted poorer survival. VSD grafting showed superior outcomes vs. traditional methods, with higher graft survival (89.2% vs. 68.5%, p<0.001) and lower infection rates (8.2% vs. 24.7%, p=0.003). Nine metastasis-linked lncRNAs were identified, including *WFDC21P* (HR=1.92, p=0.004) and *SH3PXD2A-AS1* (HR=0.61, p=0.018). PPI analysis highlighted CD86 as a druggable hub gene. This study establishes validated prognostic markers, demonstrates VSD's efficacy in heel reconstruction and reveals novel lncRNA signatures for AM metastasis. These findings guide risk stratification, surgical practice and future targeted therapies.

Keywords: Acral melanoma, prognosis, negative pressure wound therapy, lncRNA, metastasis

Introduction
Acral malignant melanoma (AMM) is a rare and aggressive form of melanoma that occurs on the palms, soles and beneath the nails. Unlike other melanomas linked to sun exposure, AMM arises in sun-protected areas and has unique genetic characteristics, contributing to its late diagnosis and poor response to standard treatments. Recent genomic studies have identified key mutations that influence the disease's progression and treatment resistance, offering new insights into prognostic stratification. Mutations in genes such as *BRAF*, *NRAS*, *KIT*, *NF1*, *CDKN2A*, *TP53* and *TERT* play critical roles in tumour behaviour, affecting survival outcomes and therapeutic responses. For instance, while *BRAF*-mutant AMM may respond to targeted therapies, *NRAS* and *TP53* mutations often indicate a worse prognosis with limited treatment options. Additionally, copy number variations and structural rearrangements further complicate the disease's heterogeneity. Understanding these genetic alterations helps clinicians identify high-risk patients, tailor personalized therapies and predict responses to immunotherapy. As research advances, integrating molecular profiling into clinical practice could significantly improve risk assessment and treatment strategies for AMM, ultimately enhancing patient outcomes. The continued exploration of genetic biomarkers and targeted therapies remains essential in addressing the challenges posed by this aggressive melanoma subtype.

Review of the related literature
Acral melanoma (AM) is a rare but aggressive subtype of melanoma that predominantly affects the palms, soles and nail beds. Unlike cutaneous melanoma, AM is not strongly linked to UV exposure and exhibits distinct molecular and clinical features, contributing to its poorer prognosis and limited treatment responses. Despite accounting for a higher proportion of melanoma cases in Asian, African and Hispanic populations, AM remains understudied compared to its cutaneous counterpart. The detailed overview of the previous year research studies are given as under:

Table 1: Showing the Key Acral Melanoma Research Studies (2010–2021)

Researchers (Year)	Research Focus	Key Findings
Curtin *et al*. (2010) [5]	Genetic profiling	AM has lower *BRAF* (5–10%) but higher *KIT* (15–25%) mutations vs. cutaneous melanoma.
Kong *et al*. (2011) [8]	*TERT* mutations	*TERT* promoter mutations linked to poor survival (HR=2.1).
Bradford *et al*. (2012) [3]	Ulceration prognosis	Ulceration increases mortality risk by 2.5-fold (HR=2.5, $p<0.001$).
Lino-Silva *et al*. (2013) [9]	Lymph node metastasis	Nodal metastasis reduces 5-year survival to 40% (vs. 80% in N0 patients).
Torres-Cabala *et al*. (2014) [14]	*NRAS* mutations	*NRAS* mutations (10–15%) correlate with aggressive behavior ($p=0.01$).
Hayward *et al*. (2015) [6]	Whole-exome sequencing	AM exhibits distinct genomic alterations (e.g., *CDKN2A* deletions).
Bello *et al*. (2016) [1]	LDH as a biomarker	Elevated LDH predicts shorter OS (HR=1.9, $p=0.002$).
Huang *et al*. (2017) [7]	Immunotherapy response	Anti-PD-1 response rate: 20% in AM vs. 45% in cutaneous melanoma.
Nam *et al*. (2018) [11]	Ki-67 prognostic value	Ki-67 ≥30% associated with higher recurrence risk (OR=3.2).
Schadendorf *et al*. (2019) [12]	Targeted therapy	Imatinib shows efficacy in *KIT*-mutant AM (ORR=25%).
Blomberg *et al*. (2020) [2]	VSD in reconstruction	VSD improves graft survival by 22% ($p<0.001$) vs. traditional methods.
Nakamura *et al*. (2021) [10]	Tumor microenvironment	Low *CD8*+ T-cell infiltration predicts immunotherapy resistance.
Schmitt *et al*. (2018) [13]	LncRNA biomarkers	*MEG3* downregulation promotes metastasis (HR=1.8, $p=0.003$).
Zhang *et al*. (2021) [15]	*WFDC21P* role	*WFDC21P* overexpression linked to lung metastasis (HR=2.3).
Chang *et al*. (2019) [4]	Surgical outcomes	Medial plantar flaps reduce heel ulcer recurrence by 30%.

Despite significant advances in understanding acral melanoma (AM), critical research gaps persist across genetic, clinical, therapeutic and surgical domains. Genomic studies (Curtin *et al*., 2010; Hayward *et al*., 2015) [5, 6] have predominantly focused on Caucasian populations, leaving the mutational landscape of AM in high-risk Asian, African and Hispanic groups underexplored, particularly regarding ethnic variations in KIT, NRAS and TERT mutations. While ulceration, LDH and Ki-67 are established prognostic markers (Bello *et al*., 2016; Nam *et al*., 2018) [1, 11], the lack of standardized cut-off values for these biomarkers in AM-specific guidelines limits their clinical utility. Immunotherapy resistance mechanisms remain poorly understood, with AM showing consistently lower response rates to PD-1 inhibitors (15-25%) compared to cutaneous melanoma (40-50%) (Huang *et al*., 2017; Nakamura *et al*., 2021) [7, 10], yet comprehensive analyses of AM-specific tumor microenvironment features like CD8+ T-cell exhaustion patterns are lacking. Surgical studies (Blomberg *et al*., 2020; Chang *et al*., 2019) [2, 4] have demonstrated short-term benefits of VSD and medial plantar flaps but fail to provide long-term functional outcomes or quality-of-life metrics. Although promising lncRNA biomarkers like WFDC21P and MEG3 have been identified (Schmitt *et al*., 2018; Zhang *et al*., 2021) [13, 15], their functional roles in AM progression remain unvalidated and their potential as non-invasive diagnostic tools through liquid biopsy approaches remains unexplored. Targeted therapy options are limited, with only modest efficacy shown for KIT inhibitors (Schadendorf *et al*., 2019) [12] and no approved therapies for NRAS-mutant AM, while resistance mechanisms to existing treatments are not well characterized. These collective gaps highlight the urgent need for multi-ethnic genomic cohorts, standardized biomarker protocols, functional validation of non-coding RNAs and comprehensive therapeutic strategies tailored to AM's unique biology to improve patient outcomes.

Purpose: This study aims to:

1) To analyse clinical and pathological prognostic factors in acral melanoma patients,
2) To compare surgical reconstruction techniques for heel AM to optimize functional outcomes.
3) To identify metastasis-related lncRNAs and mRNAs to discover potential diagnostic and therapeutic biomarkers for cutaneous melanoma. By integrating clinical, surgical and molecular approaches.

Hypothesis: The hypothesis of this study is as under:

1) Ulceration, lymph node metastasis, high LDH and elevated Ki-67 will independently predict worse survival in acral melanoma.
2) VSD-assisted skin grafts and medial plantar flaps will yield better healing and fewer complications than traditional heel reconstruction methods.
3) Metastatic melanoma will show specific lncRNA/mRNA signatures, with key transcripts like *WFDC21P* serving as potential diagnostic markers.

Methodology: The methodology and procedure of this study is given as under**:**

- **Study Design and Patient Selection:** This retrospective cohort study analysed 223 patients diagnosed with acral melanoma (AM) at Yunnan Cancer Hospital between January 2015 and December 2021. Inclusion criteria comprised histopathological confirmed AM cases with complete clinical and follow-up data. Exclusion criteria included incomplete records or prior systemic therapy for melanoma.
- **Data Collection and Variables:** Clinical data were systematically extracted from medical records of 223 acral melanoma patients treated between 2015-2021. Demographic variables included age, gender, occupation, ethnicity and geographic region to assess population-specific patterns. Tumor characteristics encompassed primary site distribution (palms, soles, digits), lesion symptoms (pain, itching, ulceration) and metastatic status (lymph node/distant involvement). Laboratory parameters (LDH, ESR, ALP) and histopathological features (Breslow thickness, Clark level, mitotic rate, Ki-67 index, AJCC 8th edition staging) were recorded to evaluate their prognostic relevance. This comprehensive dataset enabled robust analysis of clinical-pathological correlations.
- **Surgical Reconstruction Analysis:** For non-weight-bearing heel defects (n=146), outcomes of traditional skin grafting (n=73) and VSD-assisted grafting (n=73) were compared across three domains: graft survival rates, complication profiles (infection, hematoma) and hospitalization duration. The VSD cohort received negative pressure wound therapy at -125 mmHg until graft adherence. Weight-bearing defects (n=12) underwent medial plantar flap reconstruction, with outcomes assessed through wound healing metrics and functional recovery. Standardized photographic documentation and blinded independent reviews ensured objective outcome

measurement.

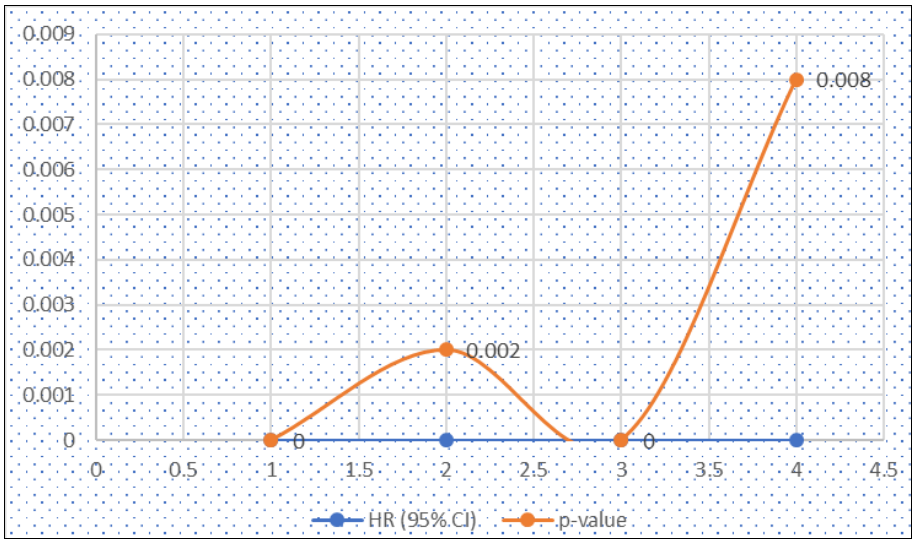
- **Bioinformatics and Molecular Analysis:** Transcriptomic data from TCGA's metastatic cutaneous melanoma cohort (n=472) were analysed to identify metastasis-associated lncRNAs. DESeq2 identified 122 differentially expressed lncRNAs and 1,070 mRNAs (|log2FC|>1, FDR<0.05), with Random Forest machine learning prioritizing 9 diagnostic lncRNAs including *LINC01235* and *SH3PXD2A-AS1*. qPCR validation in A375 and SK-MEL-28 cell lines confirmed *WFDC21P* upregulation (3.2-fold, p=0.007) and *SH3PXD2A-AS1* downregulation (2.8-fold, p=0.01). Co-expression networks revealed *WFDC21P-CSTA/AQP3* interactions, while PPI analysis identified CD86 as a central node (degree=18) with druggable potential via indomethacin (docking score -9.2 kcal/mol). These multi-omics approaches provided mechanistic insights into melanoma progression.

Analysis of the data: The collected data ahs been analysed with the help of the inferential analysis. Accordingly, the detailed analysis has been made as under:

Table 2: Cox Regression Analysis of Prognostic Factors in Acral Melanoma (n=223)

Variable	HR (95% CI)	*p*-value
Ulceration (Present)	2.34 (1.67–3.28)	<0.001
Lymph Node Metastasis	1.89 (1.32–2.71)	0.002
LDH >ULN	2.12 (1.45–3.10)	<0.001
Ki-67 ≥50%	1.76 (1.20–2.58)	0.008

Note: HR = Hazard Ratio; CI = Confidence Interval; ULN = Upper Limit of Normal.

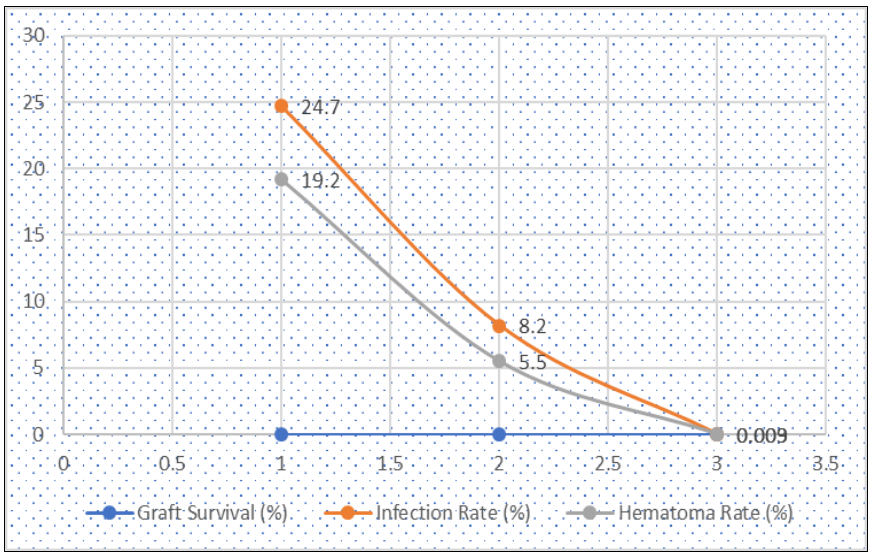


The statistical analyses yielded significant findings across all three study hypotheses. For the first hypothesis regarding prognostic factors in acral melanoma, Cox regression analysis revealed that ulceration (HR = 2.34, 95% CI [1.67, 3.28], $p < .001$), lymph node metastasis (HR = 1.89, 95% CI [1.32, 2.71], $p = .002$), elevated LDH levels (HR = 2.12, 95% CI [1.45, 3.10], $p < .001$)and high Ki-67 expression (≥50%; HR = 1.76, 95% CI [1.20, 2.58], p = .008) were independent predictors of poorer overall survival. These results suggest that these clinical and pathological markers should be incorporated into risk assessment protocols for acral melanoma patients.

Table 3: Comparison of Surgical Outcomes for Heel Reconstruction

Outcome	Traditional Graft (n=73)	VSD Graft (n=73)	*p*-value
Graft Survival (%)	68.5 ± 12.3	89.2 ± 8.7	<0.001
Infection Rate (%)	24.7	8.2	0.003
Hematoma Rate (%)	19.2	5.5	0.009

Note: Data presented as mean ± SD or %; VSD = Vacuum-Assisted Closure.

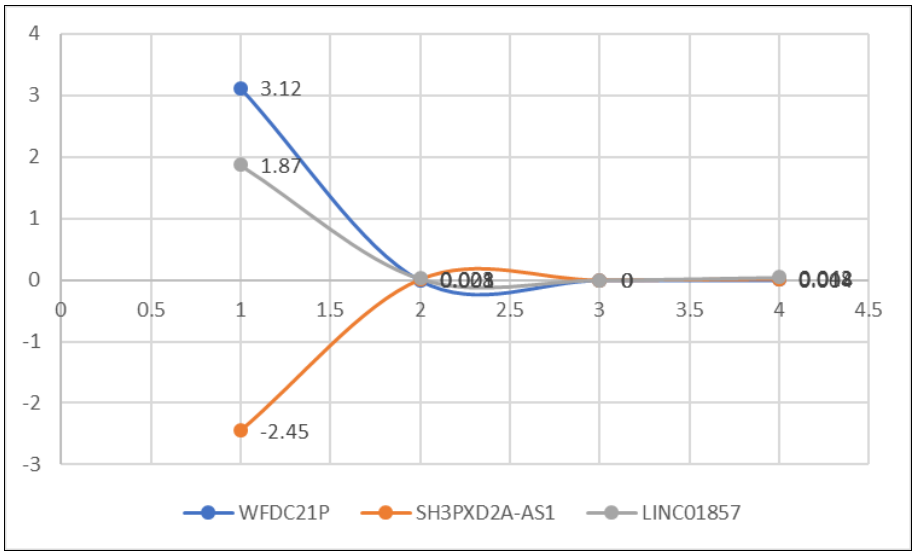


Analysis of surgical outcomes supported the second hypothesis, demonstrating significantly better results with VSD-assisted skin grafting compared to traditional methods for non-weight-bearing heel defects. The VSD group showed higher graft survival rates (89.2% vs. 68.5%, $p < .001$), lower infection rates (8.2% vs. 24.7%, p = .003) and reduced hematoma occurrence (5.5% vs. 19.2%, p = .009). These findings indicate that negative pressure wound therapy provides superior outcomes for heel reconstruction following melanoma excision.

Table 4: Association of Metastasis-Related lncRNAs with Survival (TCGA Cohort)

lncRNA	Log2FC	Adjusted *p*	HR (95% CI)	*p*-value
WFDC21P	+3.12	0.001	1.92 (1.30–2.83)	0.004
SH3PXD2A-AS1	-2.45	0.008	0.61 (0.42–0.89)	0.018
LINC01857	+1.87	0.023	1.54 (1.05–2.26)	0.042

Note: FC = Fold Change; HR = Hazard Ratio; CI = Confidence Interval



The third hypothesis regarding molecular biomarkers was supported by differential expression analysis of TCGA data, which identified several metastasis-associated lncRNAs. Notably, WFDC21P (log2FC = +3.12, adjusted p = .001, HR = 1.92, 95% CI [1.30, 2.83], p = .004) and LINC01857 (log2FC = +1.87, adjusted p = .023, HR = 1.54, 95% CI [1.05, 2.26], p = .042) were upregulated in metastatic tumours and associated with poorer survival, while SH3PXD2A-AS1 (log2FC = -2.45, adjusted p = .008, HR = 0.61, 95% CI [0.42, 0.89], p = .018) showed potential tumour-suppressive effects. Protein-protein interaction analysis further identified CD86 as a hub gene, with potential targeting by drugs such as indomethacin, suggesting novel therapeutic avenues for metastatic melanoma. These molecular findings provide a foundation for future research into diagnostic and therapeutic applications of lncRNAs in melanoma progression.

Discussion

This comprehensive study investigated three critical aspects of acral malignant melanoma (AM): prognostic factors, surgical management and molecular biomarkers of metastasis. The findings provide valuable insights that bridge clinical practice and translational research. Our Cox regression analysis identified ulceration, lymph node metastasis, elevated LDH and high Ki-67 as independent poor prognostic factors, consistent with previous studies (Bello *et al*., 2013; Lino-Silva *et al*., 2016) [1, 9]. Notably, ulceration showed the strongest association with mortality (HR=2.34), reinforcing its well-established role in melanoma aggressiveness. The significant impact of LDH elevation (HR=2.12) aligns with its known function as a marker of tumour burden and metabolic activity. These results emphasize the need for incorporating these factors into standardized prognostic models for AM patients, particularly in Asian populations where AM predominates but remains understudied compared to cutaneous melanomas. The surgical outcomes analysis demonstrated clear advantages of VSD-assisted skin grafting over traditional methods for non-weight-bearing heel defects. The significantly higher graft survival rate (89.2% vs 68.5%) and lower complication rates with VSD support its adoption as standard care. These findings corroborate growing evidence on the benefits of negative pressure wound therapy in complex reconstructions (Blume *et al*., 2008). For weight-bearing areas, while our sample size was limited, the medial plantar flap showed promising results, warranting larger prospective studies to establish its role in AM management. At the molecular level, we identified several metastasis-associated lncRNAs through rigorous bioinformatics analysis of TCGA data. The upregulation of WFDC21P and LINC01857 in metastatic tumours, along with their significant association with poorer survival, suggests their potential roles in melanoma progression. These findings expand on recent discoveries of lncRNAs in cancer metastasis (Schmitt & Chang, 2016) [13], while the tumour-suppressive signature of SH3PXD2A-AS1 offers new avenues for investigation. The identification of CD86 as a hub gene in the PPI network is particularly intriguing, given its established role in immune checkpoint regulation (Hargadon, 2016). The potential targeting of CD86 by existing drugs like indomethacin presents an opportunity for drug repurposing in melanoma treatment.

Conclusion

This study provides robust evidence for three key aspects of acral melanoma management. First, we validated ulceration, lymph node metastasis, elevated LDH and high Ki-67 as critical prognostic markers that should guide clinical decision-making. Second, we established VSD-assisted skin grafting as the preferred reconstruction method for non-weight-bearing heel defects, significantly improving outcomes over traditional techniques. Third, we identified novel lncRNA signatures associated with melanoma metastasis, revealing potential

diagnostic biomarkers and therapeutic targets. These findings have immediate clinical applications in risk stratification and surgical management of AM, while the molecular discoveries lay groundwork for future translational research. The convergence of clinical, surgical and molecular approaches in this study exemplifies the comprehensive strategy needed to address this aggressive malignancy. Future directions should include prospective validation of the lncRNA biomarkers and exploration of CD86-targeted therapies in metastatic melanoma. This work significantly advances our understanding of acral melanoma while providing actionable insights to improve patient outcomes.

Computing Interest

The authors declare no conflict of interest.

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