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Review Article

Prognostic factors in postoperative patients with cutaneous melanoma: a systematic review and meta-analysis

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Abstract: Cutaneous melanoma is a prevalent tumor associated with a poor prognosis. This systematic review and meta-analysis aimed to identify and evaluate prognostic factors for patients with cutaneous melanoma following surgery, thereby providing crucial insights for enhancing patient outcomes. We searched PubMed, Embase, Cochrane Library, CINAHL, and Web of Science for studies on postoperative prognostic factors of cutaneous melanoma up to March 2024. Literature screening, data extraction, and quality assessment were performed, followed by meta-analysis using RevMan 5.3 software. Trial Sequential Analysis (TSA) was conducted with Stata 17 software to verify the robustness of the findings. Eleven studies encompassing 27,352 patients were included. The meta-analysis identified several prognostic factors impacting disease-specific survival post-surgery: age over 50 years (HR=1.05, 95% CI: 1.02-1.08), female gender (HR=0.71, 95% CI: 0.57-0.87), Breslow thickness greater than 2 mm (HR=1.11, 95% CI: 1.06-1.17), presence of ulceration (HR=2.06, 95% CI: 1.63-2.60), and positive sentinel lymph node (HR=3.03, 95% CI: 2.50-3.66). TSA confirmed the adequacy of the sample size. Aggressive treatment strategies are recommended for patients exhibiting these characteristics to improve prognosis and extend 5-year survival rates.

Keywords: Cutaneous melanoma, prognosis, prognostic factors, meta-analysis

Introduction

Melanoma is a malignant tumor that originates from melanocytes and is characterized by its aggressive invasiveness and early metastasis [1]. It primarily affects the skin, which is the most common site, accounting for over 90% of cases, but it can also occur in the eyes and mucous membranes [2]. According to GLOBOCAN 2020, there were 324,635 new cases and 57,043 deaths from cutaneous melanoma in 2020 [3]. Surgical resection is the prevalent treatment; however, the disease is often detected in its advanced stages, leading to a poor prognosis. The median survival is 13.5 months, with a 5-year survival rate of only 16% [4]. There is a notable gap in the systematic evaluation of prognostic factors influencing cutaneous melanoma outcomes post-surgery, despite numerous studies addressing these factors. The available research is scattered and lacks comprehensive statistical analysis [5, 6]. This study collates and systematically assesses the relevant research to provide a robust evidence base for improving clinical management of cutaneous melanoma.

Methods

Search strategy and selection criteria

We conducted a comprehensive literature search for studies on prognostic factors following

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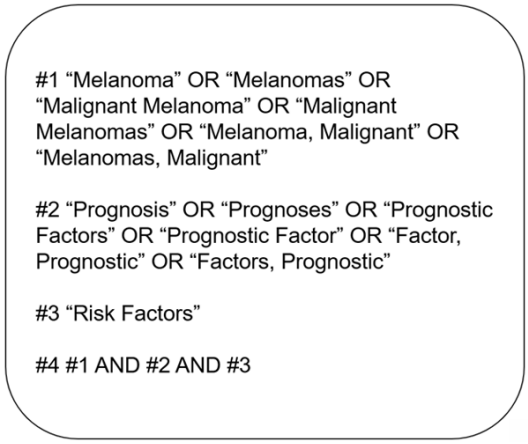

Figure 1. PubMed search strategy.

surgery for cutaneous melanoma using PubMed, Embase, Cochrane Library, CINAHL, and Web of Science. Search terms included “Melanoma”, “Prognosis”, “Risk factors”, and associated free word combinations. We also reviewed the references of selected studies to minimize omissions. **Figure 1** illustrates the specific search strategy employed in PubMed. This study adheres to the PRISMA guidelines (Table S1).

Inclusion criteria: (1) Patients were diagnosed with cutaneous melanoma via histopathological examination and underwent radical resection. (2) Studies (randomized controlled trials, case-control studies, or cohort studies) were published on the postoperative prognostic factors in patients with cutaneous melanoma. (3) Primary outcome focused on disease-specific survival. (4) Studies were published in English from the inception of the database until March 2024. (5) Inclusion of only the most recent and comprehensive reports from the same research unit or for identical patient populations.

Exclusion criteria: (1) Review articles, letters, animal studies, experiential exchanges, case reports, and conference abstracts. (2) Studies with duplication, small sample sizes, low quality, lack of original data, or incorrect statistical methods. (3) Studies lacking detailed follow-up data or where the dropout rate was high. (4) Studies weakly related to the research objectives.

Data extraction

Two researchers independently screened the titles and abstracts to eliminate duplicates, reviews, and case reports according to the predefined inclusion and exclusion criteria. Further eligibility was assessed by full-text review, discarding any studies where data were not extractable or could not be supplemented by contacting the authors. The remaining studies were processed for data extraction collaboratively by the same two researchers and verified by a third researcher. Only factors reported in two or more articles were included in the comprehensive data analysis. Discrepancies were resolved through discussion among the three researchers.

Literature quality assessment

The quality of the selected studies was assessed using the Newcastle-Ottawa Scale (NOS). This scale evaluates three main areas: selection of the study groups (4 items), comparability of the groups (1 item), and the measurement of outcome factors (3 items), with a maximum possible score of 9. The comparability category is weighted with 2 points and each of the other items is weighted with 1 point. Studies scoring above 6 points were considered high-quality and were included in this meta-analysis.

Statistical analysis

The collected data were analyzed using Cochrane’s RevMan 5.3 software. Hazard ratios (HR) and their 95% confidence intervals (95% CI) for all identified prognostic factors were quantitatively synthesized. Combined statistics were subjected to Z-tests for significance testing, with a significance threshold set at $P< 0.05$. Heterogeneity among the studies was evaluated using the Chi-square test and quantified with the I^2 statistic. Due to the presence of heterogeneity, a random-effects model was employed. Factors that could not be quantitatively synthesized were described using descriptive statistics. Publication bias was assessed using a funnel plot; symmetry in the plot indicated no bias, while asymmetry suggested potential bias.

Trial sequential analysis was conducted using Stata 17 software to validate the reliability of the meta-analysis results and to reduce the risk of type I and type II errors, set at 0.05 and 0.20, respectively. This analysis included the calculation of the required information size

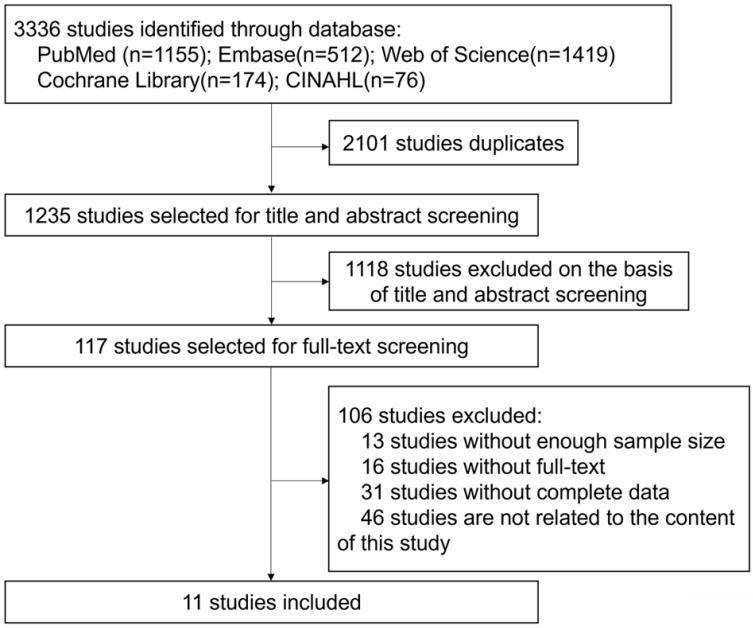

Figure 2. Selection of included studies.

(APIS). The evidence was considered sufficient if the cumulative Z-curve crossed the trial sequential monitoring boundary or reached the APIS. If the Z-curve did not cross these thresholds and the APIS was not met, further studies with larger sample sizes are recommended to substantiate the findings.

Result

Searching results and basic characteristics of studies

A comprehensive database search yielded 3,336 articles, comprising 1,155 from PubMed, 512 from Embase, 174 from Cochrane Library, 76 from CINAHL, and 1,419 from Web of Science. Out of these, 11 studies met the inclusion and exclusion criteria, encompassing a total of 27,352 patients (**Figure 2**) [7-17]. All included studies were retrospective and examined various prognostic factors such as age, sex, primary tumor site, and Breslow thickness. The key characteristics and NOS scores of these studies are detailed in **Table 1**.

Prognostic factors: age >50

Eight studies involving 12,880 patients investigated the impact of age over 50 on prognosis. Substantial heterogeneity was observed among the studies (I^2=80%, P<0.1), with results indicating that older age was associated with poorer prognosis (HR=1.05, 95% CI: 1.02-1.08, P=0.001, **Figure 3**).

Prognostic factors: sex

Four studies, encompassing 18,637 patients, assessed the prognostic impact of being female. The heterogeneity among these studies was moderate (I^2=50%, P>0.1). Findings suggested that females exhibited a better prognosis than males (HR=0.71, 95% CI: 0.57-0.87, P=0.001, **Figure 4**).

Prognostic factors: Breslow thickness >2 mm

Seven studies, involving a total of 5,675 patients, explored the prognostic impact of Breslow thickness greater than 2 mm. Significant heterogeneity was observed in the data (I^2=72%, P<0.1). The analysis revealed that increased Breslow thickness is associated with poorer outcomes (HR=1.11, 95% CI: 1.06-1.17, P< 0.001, **Figure 5**).

Prognostic factors: ulceration

Four studies, with a combined patient count of 4,314, assessed the effect of ulceration on prognosis. The heterogeneity was moderate (I^2=29%, P>0.1), justifying the use of a random-effects model. The findings indicate that ulceration is associated with a poor prognosis following surgery (HR=2.06, 95% CI: 1.63-2.60, P<0.001, **Figure 6**).

Prognostic factors: tumor location on limbs

Four studies reporting on 22,343 patients examined the effect of tumor location on the limbs. There was considerable heterogeneity among the studies (I^2=86%, P<0.1). Results demonstrated that tumor location on limbs does not significantly affect prognosis (HR= 0.76, 95% CI: 0.48-1.20, P=0.24, **Figure 7**).

Prognostic factors: positive sentinel lymph node (SLN)

Four studies, involving 6,528 patients, examined the impact of a positive SLN on prognosis.

Table 1. Basic characteristics of studies

Senior author	Published time	Sample size	Postoperative treatment	Prognostic factors	NOS score
Ribero	2015	2,184	Not given	1, 3, 5, 6, 7, 22, 9	8
Ribero S	2015	350	Immunotherapy	2, 3, 4	7
Madu	2016	250	Adjuvant radiotherapy	1, 3, 13	7
Karakousis	2017	1,518	Not given	1, 4, 7, 26	8
Namikawa	2018	1,898	Not given	1, 5, 6, 11, 15, 16, 17, 22	8
Amaral	2020	245	Not given	1, 3, 21	6
Csányi	2020	176	Not given	1, 2, 3, 4, 6, 18, 19	8
Moncrieff	2020	2,270	No adjuvant systemic therapy	1, 2, 3, 4, 6, 20	8
Ji	2022	13,922	Not given	2, 5, 8, 14	7
Park	2023	200	Not given	2, 3, 18, 27	6
Winge-Main	2023	4339	Not given	1, 2, 5, 8, 10, 11, 12, 23, 24, 25	8

Note: NOS: Newcastle-Ottawa Scale; 1. age; 2. sex; 3. Breslow thickness; 4. Ulceration; 5. tumor location on limbs; 6. positive sentinel lymph node (SLN); 7. tumor location on the trunk; 8. tumor location on head & neck; 9. Nevus count >50; 10. melanoma subtype: other; 11. melanoma subtype: acral; 12. melanoma subtype: nodular; 13. N status =2; 14. T status =1; 15. T status =2; 16. T status =3; 17. T status =4; 18. Clark level; 19. presence of distant metastasis; 20. timing of surgery-late; 21. gene expression profile score; 22. tumor mitotic rate >5/mm^2; 23. TNM II; 24. TNM III; 25. TNM IV; 26. clinical nodal recurrence.

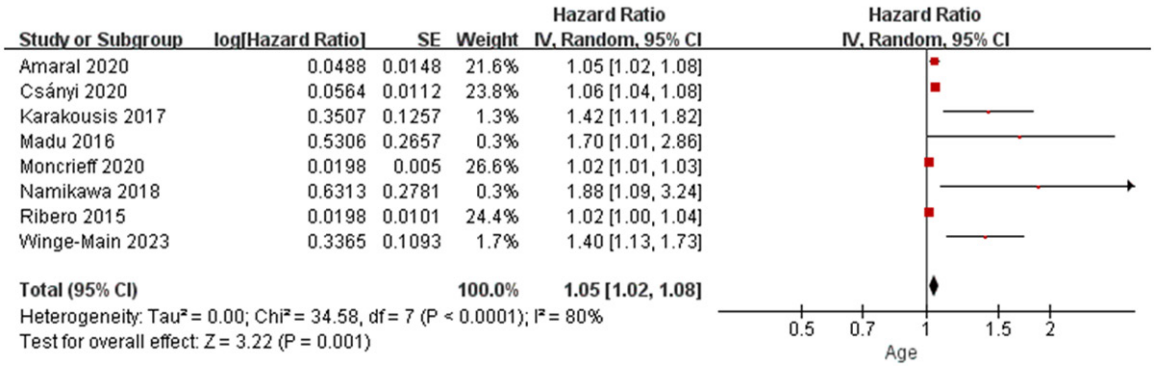

Figure 3. Forest plot of age.

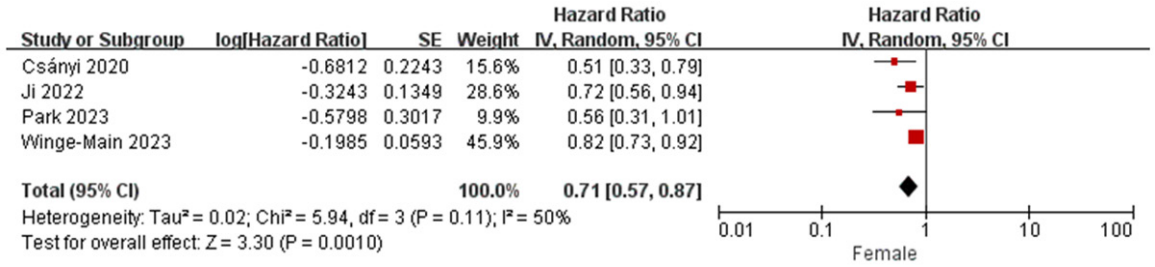

Figure 4. Forest plot of sex.

There was no observed heterogeneity among the studies (I^2=0%, P>0.1). Therefore, a fixed-effects model was employed, revealing a significant association between positive SLN and poor post-surgery prognosis (HR=3.03, 95% CI: 2.50-3.66, P<0.001, **Figure 8**).

Publication bias

A funnel plot was constructed to assess publication bias for the prognostic factors (age, sex, Breslow thickness, ulceration, tumor location on limbs, positive SLN) reported in four or more

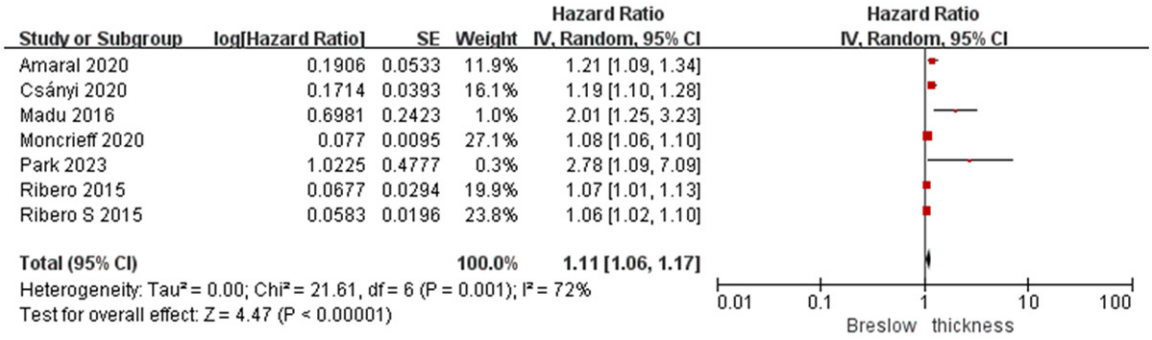

Figure 5. Forest plot of Breslow thickness.

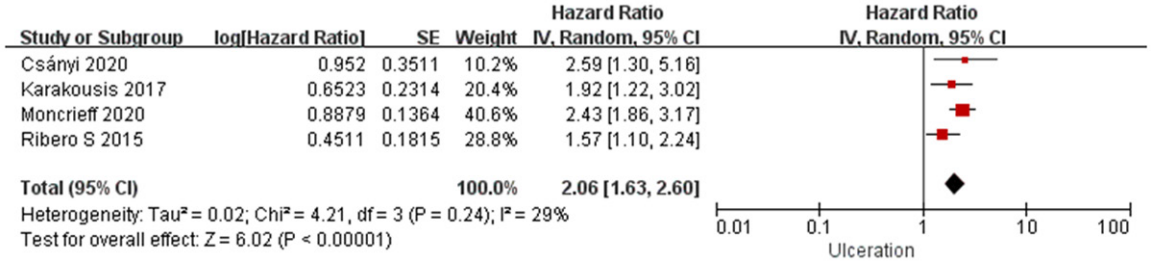

Figure 6. Forest plot of ulceration.

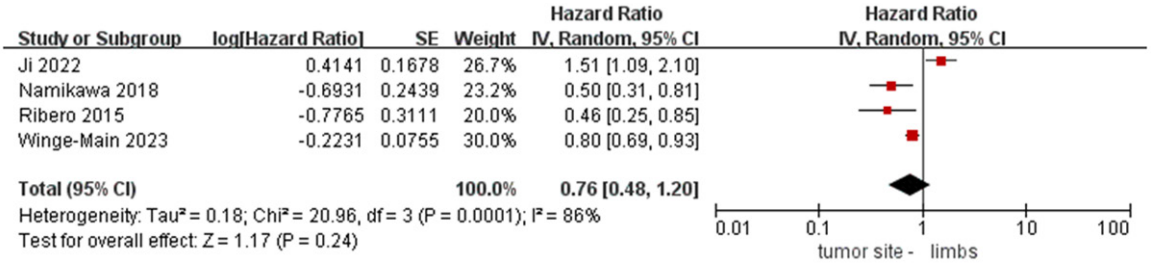

Figure 7. Forest plot of tumor location on limbs.

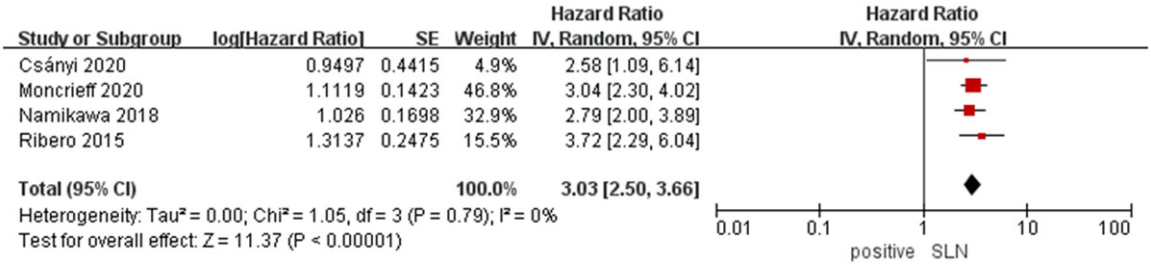

Figure 8. Forest plot of positive sentinel lymph node.

studies. The analysis indicated some level of publication bias (**Figure 9**).

TSA

TSA was conducted to evaluate the robustness of the findings for six prognostic factors. The analysis confirmed that age >50, female sex, Breslow thickness >2 mm, ulceration, and positive SLN significantly influenced the prognosis of patients with cutaneous melanoma post-surgery. In contrast, tumor location on limbs did not impact prognosis. These results demon-

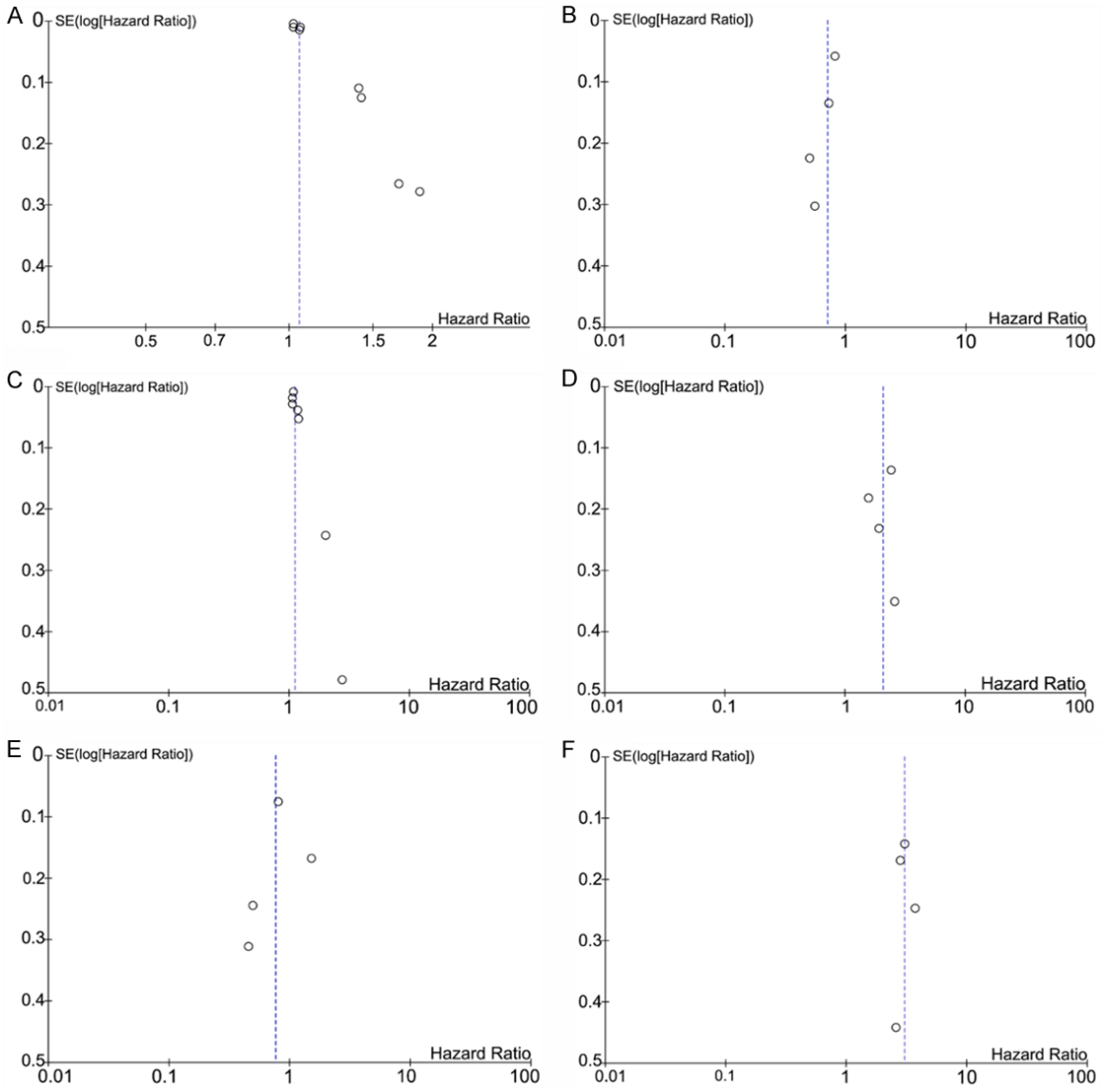

Figure 9. Funnel plot. A. Age; B. Sex; C. Breslow thickness; D. Ulceration; E. Tumor location on limbs; F. Positive sentinel lymph node.

strate the stability of the meta-analysis (**Figure 10**).

Discussion

Cutaneous melanoma is a highly invasive tumor with a high mortality rate, accounting for 90% of skin cancer deaths and ranking as the most prevalent skin malignancy [18-20]. Despite recent advances in chemotherapy, immunotherapy, and targeted therapy, surgery remains the primary treatment option [21, 22]. However, the survival rates post-surgery are still low, underscoring the significant threat this disease poses. Thus, identifying and understanding prognostic factors are crucial for improving management strategies for patients with cutaneous melanoma following surgery.

This meta-analysis identified several key prognostic factors, including gender, age over 50, ulceration, Breslow thickness greater than 2 mm, and positive SLN. Notably, survival rates were higher among female patients, which might be attributed to differences in immune function, mutation burden, and DNA repair capabilities related to oxidative damage between genders. Additionally, behavioral factors such as clothing choices and sunscreen use, which vary by gender, could also play a role

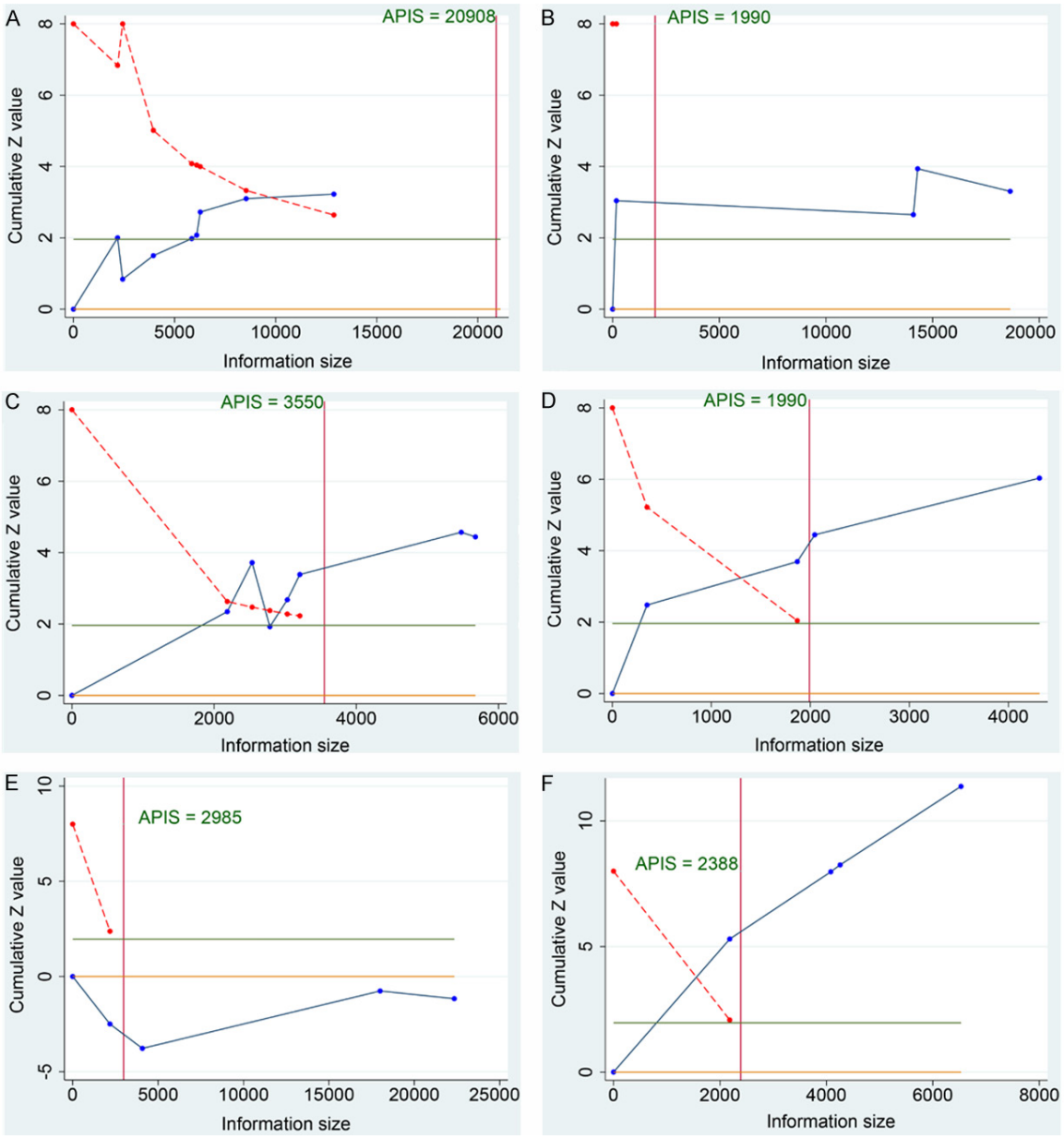

Figure 10. Trial sequential analysis plot. A. Age; B. Sex; C. Breslow thickness; D. Ulceration; E. Tumor location on limbs; F. Positive sentinel lymph node. Note: APIS: a priori information size; blue line: cumulative z-curve; red dotted line: trial sequential monitoring border; red solid line: APIS; green line: traditional boundary line.

[23, 24]. These findings highlight the importance of enhancing public awareness about melanoma risk factors and preventive measures, including the adoption of effective sunscreen practices to mitigate the risk of skin melanoma.

Concerning age, as patients grow older, their physiological functions decline, resulting in decreased disease resistance and compensatory capacity. Elderly patients often exhibit poor tolerance to surgery, radiotherapy, and chemotherapy. Malignant tumors tend to progress more rapidly in this demographic, leading to poorer prognoses. Additionally, age-related reductions in physical strength and energy can diminish self-worth, contributing to pessimistic emotions and reduced physiological functions. These factors may weaken resistance to malignant diseases, potentially shortening survival times in elderly patients [25, 26]. Regular health assessments, medication management,

and pain control are crucial for maintaining the quality of life in these patients.

Ulceration in cutaneous melanoma refers to the absence of a complete epidermis over any part of the primary tumor, accompanied by host responses such as fibrinous and acute inflammatory exudates [27]. Ulceration indicates advanced tumor progression. The observation of perivascular growth of melanoma cells, particularly in the superficial and most severe parts of an ulcerated tumor, is often associated with neutrophil presence. This perivascular growth and neutrophil infiltration may facilitate extravascular migration and metastasis, increasing the likelihood of tumor cells invading the circulation and enhancing the potential for lymph node metastasis and systemic dissemination [28]. Consequently, patients with ulcerated cutaneous melanoma typically face a worse prognosis due to the increased risk of metastasis.

Breslow thickness measures the depth of invasion in cutaneous melanoma and is recognized by the American Joint Committee on Cancer as a primary and potent prognostic factor in its melanoma staging system [29]. Increased tumor thickness correlates with rapid tumor growth, invasive histological features, and a higher likelihood of lymph node and distant metastases. Specifically, lesions thicker than 2 mm are associated with increased lymph node and distant metastases, indicating greater malignancy and poorer prognosis [30, 31].

Approximately a quarter of patients with positive SLNs also show lymphatic vascular invasion, suggesting a higher presence of micrometastases or dormant tumor cells [32]. A study focusing on patients who underwent extensive resection of clinical stage IIB/C primary cutaneous melanoma before starting immunotherapy noted a 30% difference in 5-year disease-specific survival between those with positive and negative SLNs [33]. Thus, positive SLNs are critical prognostic indicators of early lymphatic spread, necessitating stringent monitoring and aggressive treatment to improve outcomes and reduce recurrence risks.

Random errors in cumulative meta-analyses can lead to false positives or negatives. To address this, we employed TSA to validate the reliability of our meta-analysis results. The TSA indicated that the cumulative Z-curve surpassed the required information size or traditional boundaries, confirming adequate sample size for robust analysis.

However, several limitations were noted. Our meta-analysis was retrospective, possibly introducing selection bias. Also, the analysis of some prognostic factors was hampered by insufficient studies and significant heterogeneity. Additionally, variations in researchers' search capabilities and databases may have omitted relevant factors like postoperative treatment, impacting the comprehensiveness of our findings. Further research is necessary to corroborate our results.

Conclusion

Our extensive review of 11 clinical retrospective studies identified key prognostic factors - gender, age, ulceration, Breslow thickness, and positive SLNs - in patients with cutaneous melanoma post-surgery. These findings suggest that patients exhibiting these characteristics should receive aggressive treatment strategies to improve prognosis and 5-year survival rates, thus offering valuable insights for clinical practice.

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Disclosure of conflict of interest

None.

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Table S1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Search strategy and selection criteria
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Search strategy and selection criteria
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Search strategy and selection criteria
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	**Figure 1**
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Search strategy and selection criteria AND Data extraction
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Data extraction
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Data extraction
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Data extraction
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Literature quality assessment
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Statistical analysis
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Statistical analysis
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Statistical analysis
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Statistical analysis
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Statistical analysis AND TAS
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Statistical analysis
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Statistical analysis
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Statistical analysis
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	TAS

RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Searching results and basic characteristics of studies
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	**Figure 2**
Study characteristics	17	Cite each included study and present its characteristics.	**Table 1**
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	**Table 1**
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Result
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Result
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Result
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Result
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Result
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Result
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Result
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	DISCUSSION
	23b	Discuss any limitations of the evidence included in the review.	DISCUSSION
	23c	Discuss any limitations of the review processes used.	DISCUSSION
	23d	Discuss implications of the results for practice, policy, and future research.	DISCUSSION
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Search strategy and selection criteria
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Search strategy and selection criteria
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Search strategy and selection criteria
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgement
Competing interests	26	Declare any competing interests of review authors.	Declaration of Conflict of Interest
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	method

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