Research article

Prognostic model development and clinical correlation of eight key genes in skin cutaneous melanoma

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A R T I C L E   I N F O

A B S T R A C T

Cutaneous melanoma (SKCM) is a challenging and increasingly prevalent cancer with limited effective treatments. In our extensive study of 342 SKCM samples, we developed a prognostic model identifying eight key genes—CASPASE7CLEAVEDD198, FOXO3A, Melanoma gp100, CD171, 1433ZETA, SRC, P21, and CABL—linked to SKCM prognosis. Statistical analysis indicated significant differences in clinical outcomes between low and high-risk groups, corroborated by principal component analysis (PCA). Survival analysis and receiver operating characteristic (ROC) curve analysis confirmed the model's predictive accuracy for SKCM prognosis. Additionally, we observed notable correlations between the expression levels of genes related to prognosis and clinical characteristics. Our research offers crucial insights into SKCM prognosis, suggesting potential diagnostic markers and personalized treatment targets.

1. Introduction

Melanoma which is a highly aggressive tumor originating from melanocyte cells, mainly give the impression on the skin but can also occur in other place such as mucous membranes and internal organs, representing about 3–5 % of all type of tumors [1,2]. Skin cutaneous melanoma (SKCM) is the third most common skin cancer, making up 6.8 %–20 % of cases. It is more prevalent among fair-skinned Caucasians than among Asians and Africans with dark skin [3,4], and some patients present with familial multiple cases [5], however, it is uncommon in children. SKCM can arise from congenital or acquired benign melanocytic nevi, dysplastic nevi, or independently, with its incidence and mortality rates significantly increasing in recent years. Treatment options are limited primarily to early surgical removal [6–9], underscoring the importance of early detection and intervention.

Proteomic research on human organs has greatly enhanced our comprehension of protein function. These studies include the analysis of post-translational modifications, protein expression levels, and protein-protein interactions, offering valuable understandings of disease mechanisms and identifying potential therapeutic targets for disease [10–12]. Identifying novel biomarkers for skin cutaneous melanoma prognosis is crucial for tailored treatment strategies. Proteomic analysis techniques such as mass spectrometry and protein microarrays enable the discovery of dysregulated proteins associated with prognosis, enhancing patient management and therapeutic approaches. Our study aims to leverage proteomic data and clinical information from 352 SKCM samples in the TCGA database to develop a prognostic model for SKCM. Our hypothesis posits that integrating these datasets will allow us to identify prognostic-related genes and construct a reliable model for predicting patient outcomes. Our objectives include screening for

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prognostic-related genes, conducting statistical analyses to compare clinical phenotypes between low and high-risk groups based on the model, and performing various validation analyses such as PCA, survival analysis, independent prognostic analysis, and ROC curve analysis to assess the model's predictive accuracy. Additionally, we will explore the correlation between the expression of prognosis-related genes in the model and different clinical phenotypes in SKCM patients. This research aims to contribute to early diagnosis and tailored treatment strategies for SKCM, ultimately improving patient prognosis and outcomes.

2. Methods and materials

2.1. Methodology for SKCM sample acquisition and data Compilation

Gene expression profiles and patients' clinical information for Cutaneous melanoma (SKCM) samples were outsourced from The Cancer Genome Atlas (TCGA), a leading cancer research database [13]. A total of 352 proteomic samples and 470 clinical data samples were used to prepare the data for subsequent bioinformatics and statistical analyses, and custom Perl scripts were utilized for preprocessing.

2.2. Identification of prognostic-related genes and development of prognostic model

To identify prognostic-related genes and develop a prognostic model for SKCM, univariate Cox regression analysis was first conducted to pinpoint genes significantly associated with overall survival. These identified genes were then refined using least absolute shrinkage and selection operator (LASSO) regression analysis, with cross-validation applied to fine-tune the model and prevent overfitting [14,15]. The final prognostic model was constructed using the selected genes, generating a risk score formula to categorize SKCM patients into high-risk and low-risk groups. Survival differences between these groups were assessed using the R package survminer, and the area under the ROC curve (AUC) was evaluated using the R package timeROC, ensuring statistical significance and visual representation of the results [16,17].

2.3. Evaluation of clinical phenotypes in high- and low-risk groups

Clinical data of all SKCM patients were collected such as age, gender, and tumor stage. These clinical phenotypes were integrated into gene expression profiles related to prognosis profiles, and Chi-square tools were used to define any identify statistical differences between low and high-risk group [18,19].

2.4. Principal component analysis (PCA) of gene expression

To determine whether low and risk groups could be differentiated based on the variance of gene expression related to prognosis, principal Component Analysis (PCA) was performed using the R packages limma and scatterplot3d. PCA helps reduce the complexity of the data by transforming it into principal components that capture the most variation. The results of the PCA were then envisaged to demonstrate the distinctions between the high-risk and low-risk groups, allowing us to see how well these groups separate based on the gene expression profiles [20,21].

2.5. Survival analysis of SKCM prognostic model

We performed survival analyses to compare the low and high risk groups of SKCM patients. Using the R packages survival and survminer, we calculated and analyzed the survival rates for each group. We then plotted survival curves to visually represent the differences in survival between the high-risk and low-risk groups. These curves help us see how the risk categories affect patient outcomes over time, providing clear visual evidence of the prognostic model's effectiveness [22,23].

2.6. Independent prognostic analysis of SKCM prognostic model

Both univariate and multivariate independent prognostic analyses was performed to determine if the risk scores were independent of prognostic factors for SKCM. These analyses assessed whether the risk scores could predict patient outcomes independently of other clinical factors. The results were visualized using forest plots, which clearly showed the impact of the risk scores on survival, while accounting for other variables [24,25].

2.7. ROC curve analysis of SKCM prognostic model

To evaluate the diagnostic accuracy of the SKCM prognostic model, ROC curve analysis was performed in R packages survival, timeROC, and survminer. We calculated the area under the curve (AUC) for survival rates to measure how well the model could predict patient outcomes at these time points. The ROC curves were then visualized, providing a clear representation of the model's performance over different periods [26–28].

2.8. Correlation between prognosis-related genes and clinical phenotypes

The correlation between the gene expression levels related to prognosis and various clinical phenotypes by calculating correlation coefficients and P-values. The findings were visualized using correlation boxplots [29,30].

2.9. Statical analysis

The methods employed in the study included Univariate Cox analysis for gene-survival correlation, LASSO regression with cross-validation for model optimization, Chi-square tests for clinical phenotype differences, and survival analysis using the log-rank test. Independent prognostic analysis was conducted through univariate and multivariate approaches, while ROC curve analysis determined the diagnostic accuracy using AUC values. These statistical tests were chosen for their reliability and relevance in evaluating SKCM prognostic models and clinical phenotypes.
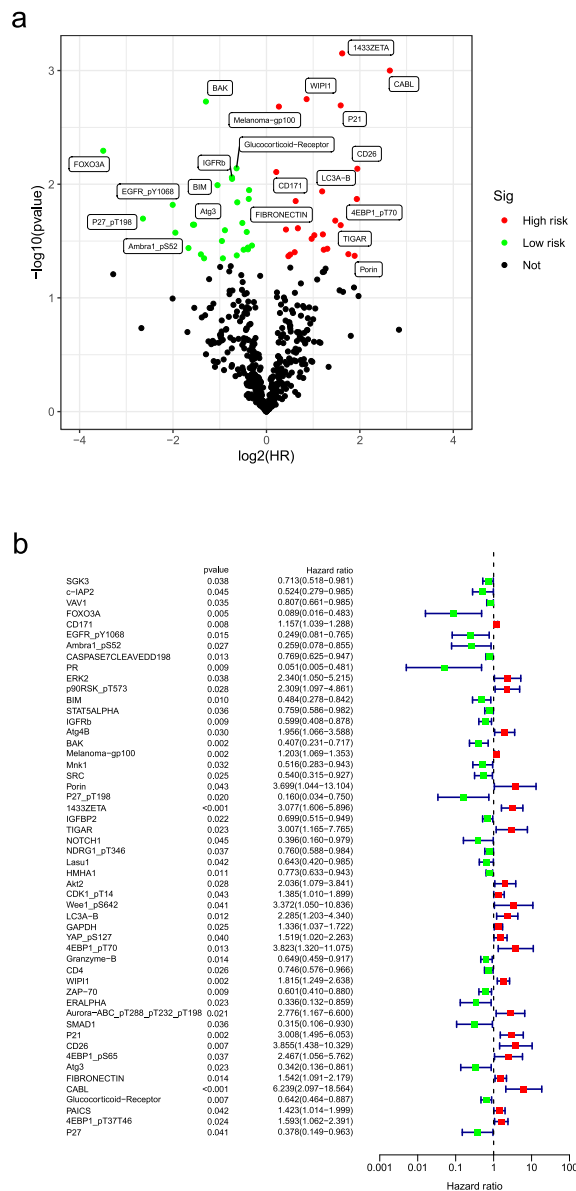

Fig. 1. Differential expression of prognosis-related genes in SKCM. The volcano plot (a) and forest plot (b) of prognosis-related genes expressed in SKCM. Red dots or squares indicate genes with a high hazard ratio (HR) value; Green dots or squares indicate genes with a low HR value; the blue solid line represents 95 % confidence interval. P-value <0.05 and |HR| > 1 were considered statistically significant.

3. Results

3.1. Gene expression and clinical data of SKCM patients

Data from 470 SKCM patients, including survival status, age, survival time, gender, and tumor stage, along with gene expression data for 456 genes, were sourced from the TCGA database. After merging and sorting, 342 SKCM samples were analyzed, resulting in an expression matrix of 456 proteins (see Supplementary Table 1).

3.2. Identification of prognosis-related genes in SKCM patients

Initial analysis focused on genes associated with SKCM prognosis. Cox regression identified 52 prognosis-related genes; 28 were linked to low risk (HR < 1) and 24 to high risk (HR > 1) (Fig. 1a and b). Using LASSO regression and cross-validation, a prognostic model was developed (Fig. 2a and b). This model highlighted eight key prognosis-related genes: CASPASE7CLEAVEDD198, FOXO3A, Melanoma gp100, CD171, SRC, 1433ZETA, P21, and CABL (Table 1). A risk score formula was established as: Risk score = $\beta1 \times X1 + \beta2 \times X2 + \beta3 \times X3 + \ldots + \beta8 \times X8$ (where β represents regression coefficients and X represents prognosis-related proteins). Supplementary Table 2 details risk groupings for the Train group, Test group, and overall patient group.

3.3. Comparison of clinical phenotypes between high- and low-risk SKCM groups

The analysis of clinical phenotypes including age, gender, and tumor stage between high- and low-risk groups in both the Train and Test groups did not reveal statistically significant differences (P > 0.05) (Table 2). This suggests that the grouping of samples into high- and low-risk categories was unbiased concerning these clinical characteristics. In other words, the distribution of age, gender, and tumor stage was similar between the high-risk and low-risk groups, ensuring that any observed differences in prognosis were not confounded by these factors.

3.4. PCA analysis of gene expression in high- and low-risk SKCM groups

Principal Component Analysis (PCA) was employed to assess the differentiation between high- and low-risk SKCM patients based on the expression of prognosis-related genes. While the overall gene expression (Fig. 3a) did not show clear distinctions between the groups, PCA focusing on prognosis-related genes (Fig. 3b) effectively differentiated the high- and low-risk groups. This analysis validates the accuracy of our prognostic model in stratifying SKCM patients based on their risk profiles, emphasizing the relevance of the selected prognosis-related genes in distinguishing between different prognostic groups.

3.5. Survival analysis between high- and low-risk SKCM groups

Overall survival rates were significantly lower in the high-risk group compared to the low-risk group in Train, Test, and overall
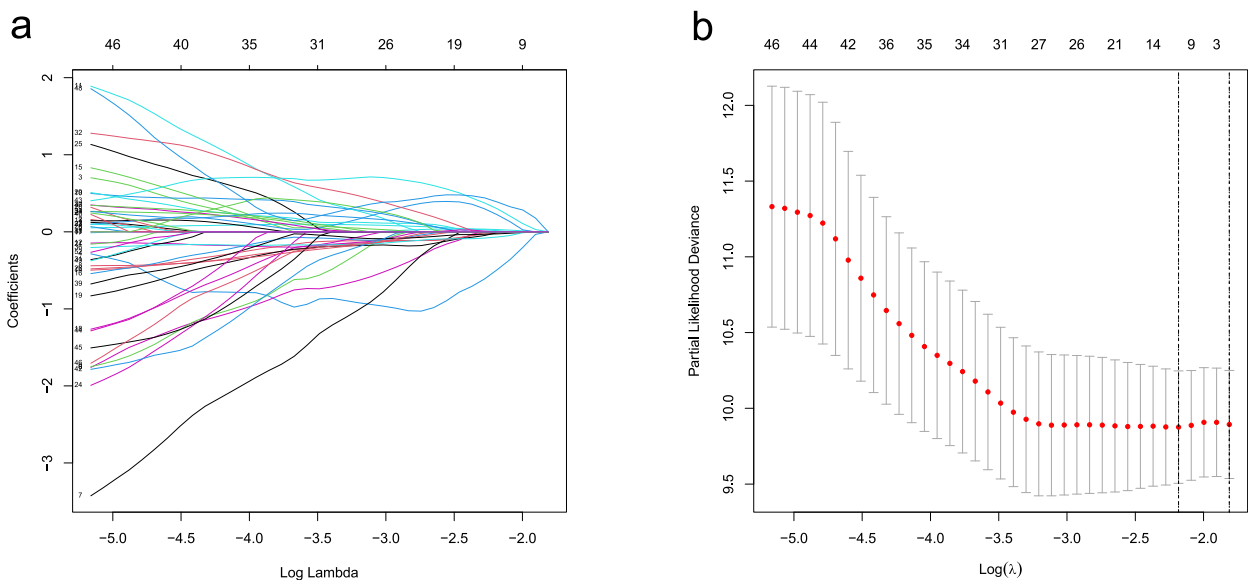

Fig. 2. Construction of prognosis-related model. The model was constructed by selecting the optimal adjustment parameter using the LASSO screening process (a) and cross-validation (b).

Table 1

Eight prognosis-related genes in skin cutaneous melanoma (SKCM).

Genes	coef
FOXO3A	−2.0437871945997200
CD171	0.1426343469432320
CASPASE7CLEAVEDD198	−0.3079263647489130
Melanoma-gp100	0.0909988618740395
SRC	−0.5542081254267140
1433ZETA	0.9183543055850320
P21	1.2411416221872800
CABL	1.3449493224727500

Risk score $= \beta1 \times 1 + \beta2 \times 2 + \beta3 \times 3 + \ldots + \beta8 \times 8$ (β, regression coefficient; X, prognosis-related protein).

Table 2

Statistical differences in clinical phenotypes between high - and low-risk groups.

| Covariates	Variables	Total cases	Test group	Train group	P-value
Age	≤55	152 (44.44 %)	83 (48.54 %)	69 (40.35 %)	**0.1572**
	>55	190 (55.56 %)	88 (51.46 %)	102 (59.65 %)	
Gender	FEMALE	138 (40.35 %)	68 (39.77 %)	70 (40.94 %)	**0.9122**
	MALE	204 (59.65 %)	103 (60.23 %)	101 (59.06 %)	
Stage	Stage I-II	145 (42.4 %)	68 (39.77 %)	77 (45.03 %)	**0.2964**
	Stage III-IV	151 (44.15 %)	81 (47.37 %)	70 (40.94 %)	
	unknown	46 (13.45 %)	22 (12.87 %)	24 (14.04 %)	
T	T1-2	80 (23.39 %)	34 (19.88 %)	46 (26.9 %)	**0.2185**
	T3-4	178 (52.05 %)	92 (53.8 %)	86 (50.29 %)	
	unknown	84 (24.56 %)	45 (26.32 %)	39 (22.81 %)	
M	M0	299 (87.43 %)	153(89.47 %)	146 (85.38 %)	**0.9292**
	M1	21 (6.14 %)	10 (5.85 %)	11 (6.43 %)	
	unknown	22 (6.43 %)	8 (4.68 %)	14 (8.19 %)	
N	N0	158 (46.2 %)	75 (43.86 %)	83 (48.54 %)	**0.2612**
	N1-3	139 (40.64 %)	76 (44.44 %)	63 (36.84 %)	
	unknown	45 (13.16 %)	20 (11.7 %)	25 (14.62 %)	
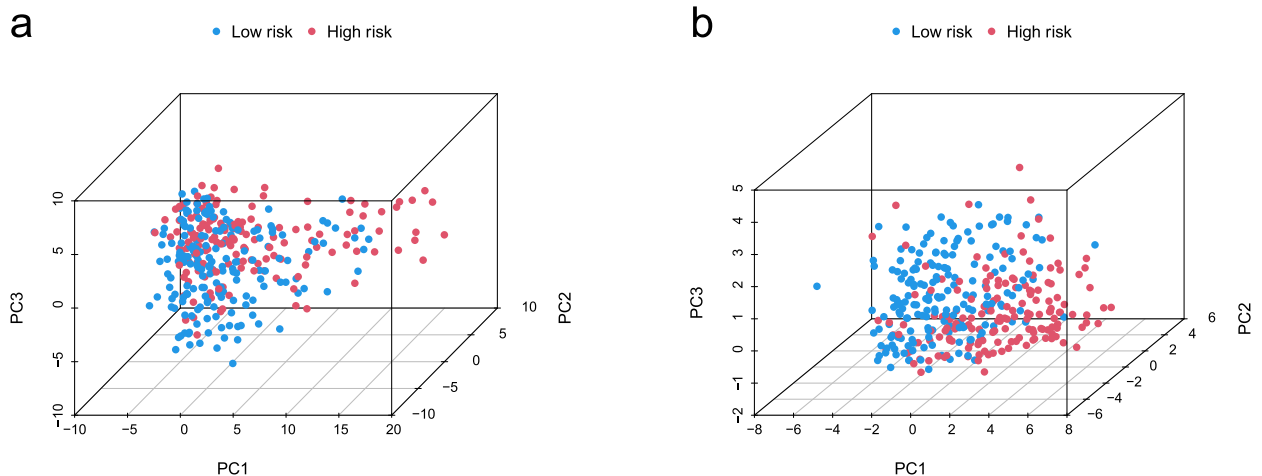
Fig. 3. Scatter plots for principal component analysis based on total genes (a) and prognosis-related genes (b). PC1, principal component 1; PC2, principal component 2; PC3, principal component 3. The red dots represent high-risk patients, and the blue dots represent low-risk patients.

patient groups (P < 0.001, P = 0.004, and P < 0.001, respectively) (Fig. 4a, b, c). Progression-free survival was also notably lower in the high-risk group across all patient groups (P < 0.001) (Fig. 4d).

3.6. Evaluation and validation of the SKCM prognostic model

Independent prognostic analysis and ROC curve analysis confirmed the risk score as an independent prognostic factor for SKCM (Fig. 5a and b). AUC values for predicting 1-year, 3-year, and 5-year survival rates were 0.678, 0.692, and 0.725, respectively (Fig. 5c).
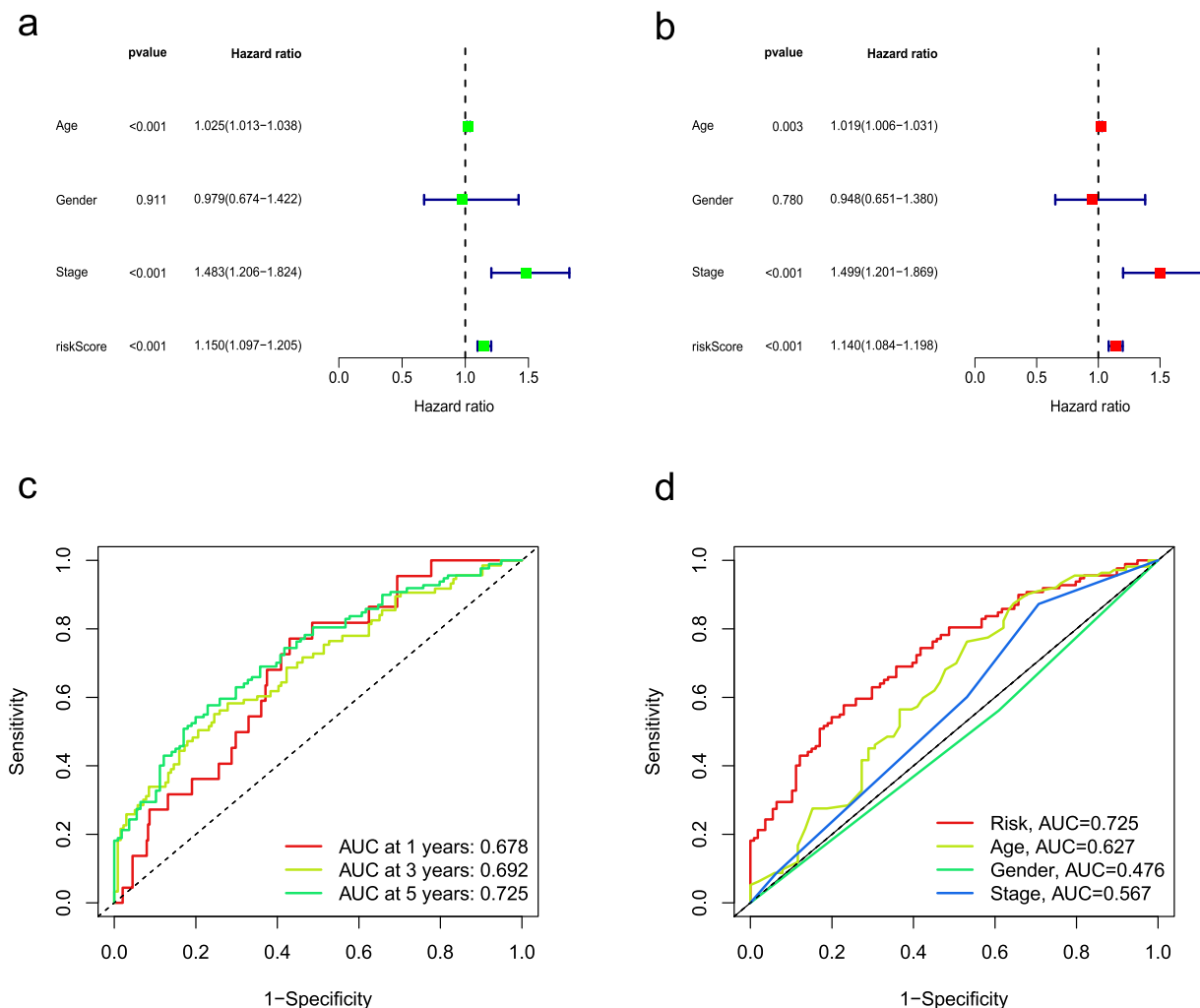
Fig. 4. Survival analysis between high- and low-risk SKCM groups. The overall survival curves of high- (red) and low-risk (blue) patients for Train group (a), Test group (b), and all patient groups (c). The progression-free survival curve of high- (red) and low-risk (blue) patients for all patient groups (d).

Note: The list below the curves showed the number of surviving patients per year.

The model demonstrated higher predictive power for clinical phenotypes than other traits (Fig. 5d), affirming its accuracy in predicting SKCM prognosis.

3.7. Correlation between prognosis-related genes and clinical phenotypes

Correlation analysis revealed significant associations between certain prognosis-related genes and clinical phenotypes such as age, gender, and tumor stage. Genes 1433ZETA (Fig. 6a and b) and CASPASE7CLEAVEDD198 (Fig. 6c and d) correlated significantly with age and tumor stage ($P < 0.05$). CD171 (Fig. 6e), FOXO3A (Fig. 6f and g), and Melanoma-gp100 (Fig. 6h and i) correlated with tumor stage and age ($P < 0.05$), while SRC (Fig. 6j) correlated with gender ($P < 0.05$).

4. Discussion

The characteristics of SKCM remain elusive, with factors such as race, genetics, trauma, and immunity contributing to its complexity [31]. Melanocyte DNA damage is a key pathogenic factor, linked to long-term ultraviolet exposure, genetic background,

Fig. 5. Forest plots of univariate (a) and multivariate (b) logistic analysis of clinical traits in SKCM patients. Green or red square represents HR-value, and blue solid lines represent 95 % confidence intervals. (c, d) ROC curves of the prognostic model. The different colored curves represent different overall survival rates (1, 3, and 5 years) or clinical traits (patient's age, gender, tumor stage, and risk score). AUC: area under the ROC curve.

and factors like friction and trauma that can lead to DNA damage, mutations, or abnormal methylation, culminating in SKCM tumorigenesis [32,33]. Differentially expressed proteins or protein patterns identified through proteomic analysis hold immense potential as prognostic indicators for skin cutaneous melanoma (SKCM). These proteins often reflect crucial biological processes such as cell proliferation, invasion, angiogenesis, and immune evasion, which are integral to SKCM progression and aggressiveness. By assessing the expression levels or patterns of these proteins, clinicians can stratify SKCM patients into different risk categories, allowing for tailored prognostic assessments and treatment strategies. Integrating multiple proteins into signatures or panels further enhances prognostic accuracy, aiding in the development of robust prognostic models. Ultimately, leveraging proteomic analysis for prognostic purposes not only improves risk stratification but also contributes to personalized medicine approaches, optimizing patient outcomes in SKCM management.

Prior studies have highlighted the role of prognosis-related proteins in SKCM development. Dong et al. found that down-regulated gene expression of FOXO3A associates with a good prognosis in SKCM, with the FOXO3A-SIRT6 axis inhibiting cancer cell proliferation [34]. Scortegagna et al. identified PDK3-dependent variations in FOXO3A regulatory genes, impacting SKCM cell proliferation [35]. Similarly, Meier et al. showed that highly expressed CD171 correlates with SKCM progression and metastasis, promoting cell migration and invasion [36]. Fogel et al. associated CD171 immunoreactivity with SKCM progression markers and cell adhesion mechanisms [37]. Additionally, Yin et al. highlighted YWHAZ's crucial role in melanin making and SKCM propagation [38].

In our study, we analyzed data from 342 SKCM samples to construct a prognostic model predicting eight key genes, including
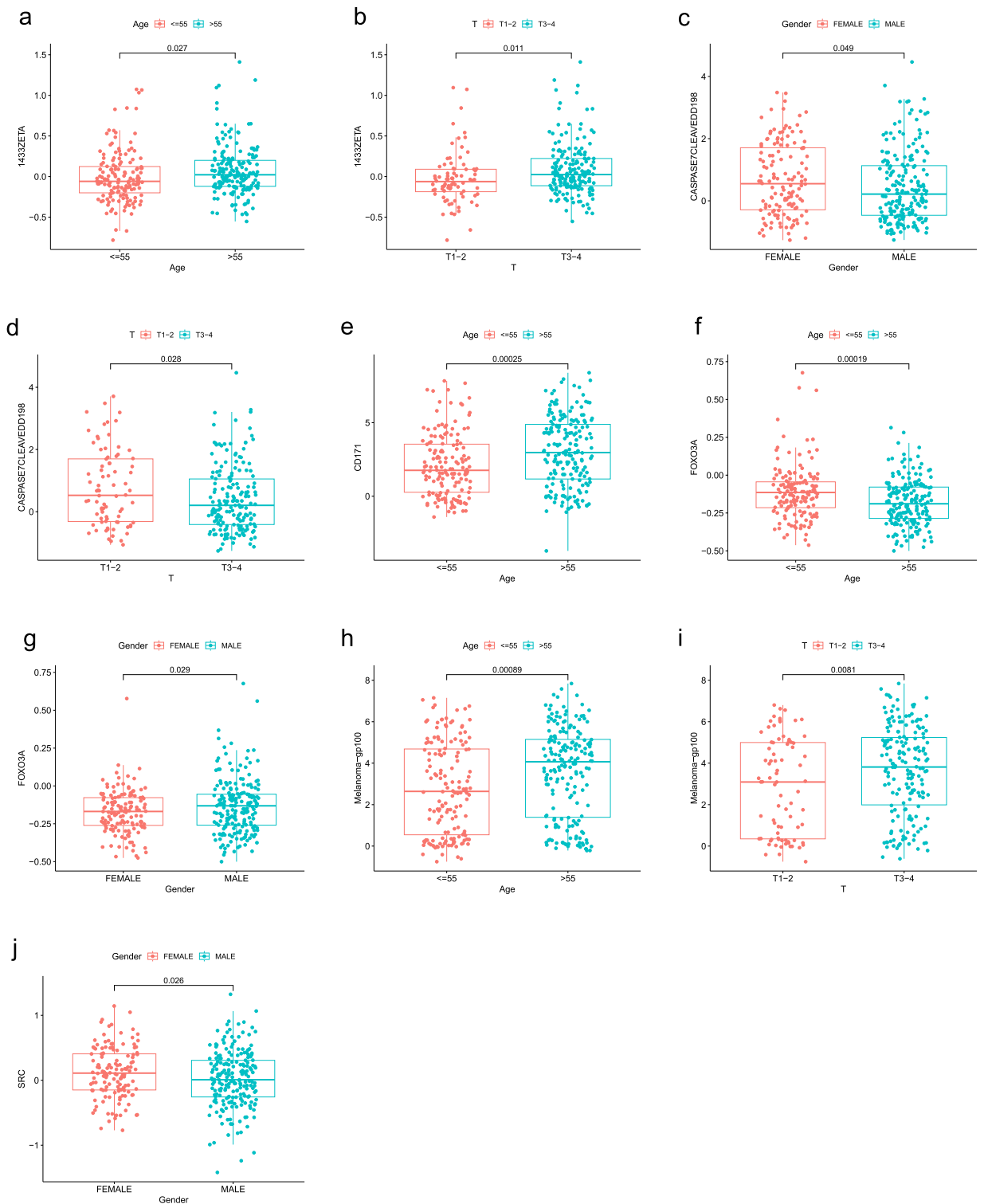
Fig. 6. Correlation analysis indicated that the expression levels of certain prognosis-related genes in the model were significantly associated with specific clinical phenotypes, including patient age the genes 1433ZETA (Fig. 6a and b), and CASPASE7CLEAVEDD198 (Fig. 6 c & d) were significantly correlated with age and tumor stage (P < 0.05). CD171 (Fig. 6e), and FOXO3A. (Fig. 6f and g), and Melanoma-gp100 (Fig. 6h&i) were correlated with tumor stage and age (P < 0.05) (Fig. 6), where as SRC (Fig. 6 j) were correlated with gender (P < 0.05)
Differences were considered statistically significant at P < 0.05.

CASPASE7CLEAVEDD198, FOXO3A, Melanoma gp100, CD171, SRC, 1433ZETA, and P21 (Ref TCGA database). Statistical analyses revealed no significant differences in clinical phenotypes between the Train and Test groups, supporting the model's robustness. PCA analysis validated the model's ability to identify high-risk and low-risk patients based on gene expression profiles. Survival analysis and ROC curve analysis further demonstrated the model's accuracy in predicting SKCM prognosis independently. Additionally, we observed significant correlations between prognosis-related gene expression and clinical phenotypes, aligning with previous studies' findings. However, our study acknowledges limitations such as the lack of subgroup analysis and validation with independent samples, warranting future research in these areas. Overall, our findings contribute to understanding SKCM pathogenesis and hold potential for diagnostic and therapeutic advancements in the field. Recent advancements in proteomic analysis for skin cutaneous melanoma (SKCM) have led to the identification of novel prognostic biomarkers such as MMP9, RAB1A, and ITGB1, offering potential for personalized treatment strategies. Integrating proteomic data with other omics profiles enhances our understanding of SKCM's molecular landscape and aids in patient stratification. These advancements hold promise for early detection of high-risk patients and targeted interventions, ultimately improving patient outcomes in personalized medicine approaches for SKCM management [29–34].

While our study provides valuable insights into SKCM prognosis prediction and the correlation between gene expression and clinical phenotypes, several limitations should be acknowledged. Firstly, our analysis lacked information such as analysis for sub groups based on different pathological types and clinical stages of SKCM patients, which could provide more nuanced insights into prognosis prediction. Secondly, the study primarily relied on TCGA data, and further validation with independent samples would enhance the robustness and generalizability of our findings. Additionally, in vitro and in vivo verification of the identified prognostic genes could provide mechanistic insights into SKCM pathogenesis.

In conclusion, our study identified and screened eight genes with prognostic potential for SKCM, shedding light on their correlation with medical phenotypes such as patient age, gender, and tumor stage. Despite the mentioned limitations, our findings contribute to the development of new diagnostic markers and potential drug targets for SKCM. Future research efforts should focus on addressing these limitations, including conducting subgroup analyses, validating findings with independent samples, and exploring the mechanistic roles of identified prognostic genes in SKCM progression. Overall, this study adds to the growing body of knowledge aimed at understanding and overcoming the challenges associated with SKCM prognosis and treatment.

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Ethics statement

Not required as there was no direct sampling from patients.

Consent for publication

Not required.

Data avaibility statment

The datasets generated and/or analyzed during this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Chaoqun Ma: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ling Xie:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33930.

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