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Integrative Machine Learning Analysis Identifies a Robust Mitoxyperiosis-Related Prognostic Signature in Glioma

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Abstract

Background: Glioma is the most common malignancy of the central nervous system with an extremely poor prognosis. Mitoxyperiosis, a recently defined mode of programmed cell death, has unclear prognostic value and molecular landscape in glioma. **Methods:** We integrated transcriptomic and survival data from the CGGA-657 (training set) and CGGA-313 (validation set) cohorts. Biological interactions among 58 candidate genes were revealed through protein-protein interaction (PPI) network analysis. An integrative machine learning framework comprising 10 algorithms was utilized to identify the optimal prognostic model after exhaustively screening 117 combinations. **Results:** An optimal risk model consisting of 15 genes was identified using StepCox[forward] + Enet[$\alpha = 0.1$]. This model demonstrated excellent predictive accuracy in both training and validation sets (3-year AUC: 0.832 and 0.849, respectively), with Kaplan-Meier curves showing significant prognostic differences between risk groups ($p < 0.001$). Meta-analysis of univariate Cox regression further confirmed the risk score as a robust prognostic marker (combined HR = 4.72). Compared with over 40 established glioma models, our model exhibited superior performance in risk discrimination (HR), predictive consistency (C-index), and diagnostic accuracy (AUC). **Conclusion:** This study developed and validated an integrative machine learning model based on mitoxyperiosis-related genes. The model provides high accuracy and clinical potential for predicting glioma prognosis, offering a novel biomarker for precision medicine.

Keywords

Mitoxyperiosis, Glioma, Machine Learning, Prognostic Signature, Integrative Analysis

1. Introduction

Glioma is the most common malignancy of the central nervous system. Due to its high heterogeneity and invasiveness, patient prognosis remains poor [1]. Despite evolving therapeutic strategies, identifying robust biomarkers for accurate risk assessment remains a core clinical challenge [2].

Recent studies have defined a novel mode of regulated cell death: mitoxyperiosis (mitochondrial oxidative stress-related programmed death), which mediates cell lysis via mitochondrial dysfunction [3] [4]. Mitochondrial oxidative stress plays a key role in glioma metabolic reprogramming, yet the clinical value of mitoxyperiosis-related genes in glioma has not been systematically elucidated [5]. Furthermore, traditional prognostic models often rely on single machine learning algorithms, which frequently lack stability in cross-cohort validation [6].

This study aims to fill this gap. We integrated large-scale transcriptomic data from the CGGA cohorts and revealed the landscape features of candidate genes through protein-protein interaction (PPI) analysis. Subsequently, an integrated machine learning framework was employed to construct and validate an optimal prognostic model after exhaustively evaluating 117 algorithm combinations. Through survival validation, meta-analysis, and performance comparison with over 40 published models, our model demonstrated significant advantages in risk discrimination and predictive accuracy, providing a powerful tool for the precision management of glioma.

2. Materials and Methods

2.1. Data Acquisition and Preprocessing

Transcriptomic and clinical data were obtained from the Chinese Glioma Genome Atlas (CGGA) [7]. The CGGA-657 cohort served as the training set for initial variable selection and model development, while the CGGA-313 cohort was used as the validation set. All expression data were normalized, and samples without survival information were excluded. Both cohorts were analyzed as pan-glioma datasets, encompassing the full clinical spectrum of histological grades and subtypes, to develop a generalized prognostic model rather than one restricted to specific glioma categories. The mitoxyperiosis-related gene set was curated via a two-step approach: first, 13 core "seed genes" (e.g., *BAX*, *BAK1*, *BID*, *MYD88*, and *RICTOR*) essential for mitoxyperiosis execution and regulation were identified based on the defining landmark study. Second, these seeds were expanded into a finalized set of 58 candidate genes by incorporating their high-confidence functional

partners (interaction score > 0.400) from the STRING database.

2.2. Protein-Protein Interaction Network Analysis

To explore the biological architecture and internal associations of the 58 mitoxyperiosis-related genes, we performed network topology analysis using the STRING database (https://string-db.org/) [8]. Based on the density of interactions and functional annotations, the genes were categorized into core biological modules. This analysis allowed for the identification of three distinct functional clusters: 1) apoptosis regulation, 2) innate immunity and inflammation, and 3) endoplasmic reticulum (ER) stress and metabolic homeostasis.

2.3. Data Normalization and Batch Effect Correction

Data Normalization and Batch Effect Correction To ensure the comparability of gene expression profiles across samples, the raw expression data for both the training (CGGA-657) and validation (CGGA-313) cohorts were normalized and stabilized using the $\log_2$ (counts + 1) transformation method. This transformation was applied to minimize the influence of extreme values and variance heterogeneity, making the data more suitable for the subsequent machine learning-based regression algorithms. Furthermore, to address potential systemic biases and technical variations arising from different sequencing platforms, experimental batches, or processing times—specifically between the two independent CGGA cohorts—we applied the ComBat algorithm. This process was implemented via the "sva" package in R. The elimination of batch effects through this integrated preprocessing workflow ensured that the prognostic model development was grounded in a robust and harmonized dataset.

2.4. Integrative Machine Learning Framework

A systematic framework was employed to build prognostic models using the Mime R package (version 0.1.0; https://github.com/l-magnificence/Mime) [9]. This package integrates 10 machine learning algorithms to generate and evaluate 117 model combinations through a cross-combination approach . The algorithms included StepCox (forward, backward, and both modes), Enet, Lasso, Ridge, RSF, GBM, CoxBoost, SuperPC, plsRcox, and survival-SVM.

2.5. Statistical Analysis

All analyses were performed using R software (version 4.3.3). The Mime framework was utilized for model construction and evaluation, which integrates various R packages including survival, glmnet, randomForestSRC, gbm, CoxBoost, superpc, plsRcox, and survivalsvm [9]. Performance was evaluated using timeROC for time-dependent ROC curves [10] and pec for C-index calculation. Survminer and meta packages were utilized for Kaplan-Meier visualization and univariate meta-analysis [11], respectively. All statistical tests were two-sided, with $p < 0.05$ considered statistically significant.

3. Results

3.1. Landscape and Biological Interaction Network of Mitoxyperiosis-Related Genes

To establish a biologically relevant gene set, we first identified 13 core regulatory and executive genes of mitoxyperiosis based on recent landmark research [4]. These include key executioners (BAX, BAK1, BID), upstream signal transducers (MYD88, TNFRSF1A/B, TLR2/4/7/8), and essential regulatory components (RICTOR, RHOA). These "seed genes" were then expanded to a comprehensive set of 58 mitoxyperiosis-related genes through Protein-Protein Interaction (PPI) analysis (interaction score > 0.400). Subsequently, to explore the potential functions and internal associations of these genes in glioma, a detailed PPI network was constructed using the STRING database (**Figure 1**). The analysis revealed that these 58 candidate genes are highly interconnected rather than isolated, showing strong functional correlations and complex physical interactions. Three distinct functional clusters were identified within the network: 1) apoptosis regulation, 2) innate immunity and inflammation modules, and 3) endoplasmic reticulum (ER) stress and metabolic homeostasis modules (**Figure 1**).

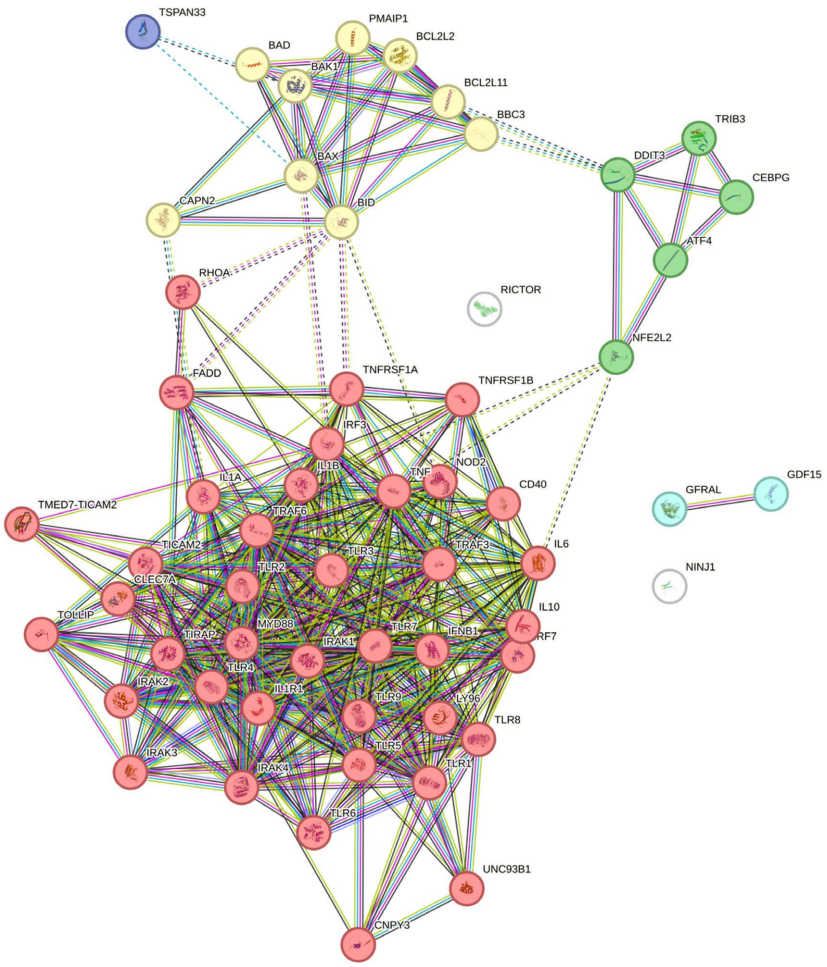

Figure 1. Protein-protein interaction (PPI) analysis of candidate mitoxyperiosis genes.

3.2. Construction of a Mitoxyperiosis-Related Prognostic Model via an Integrative Machine Learning Framework

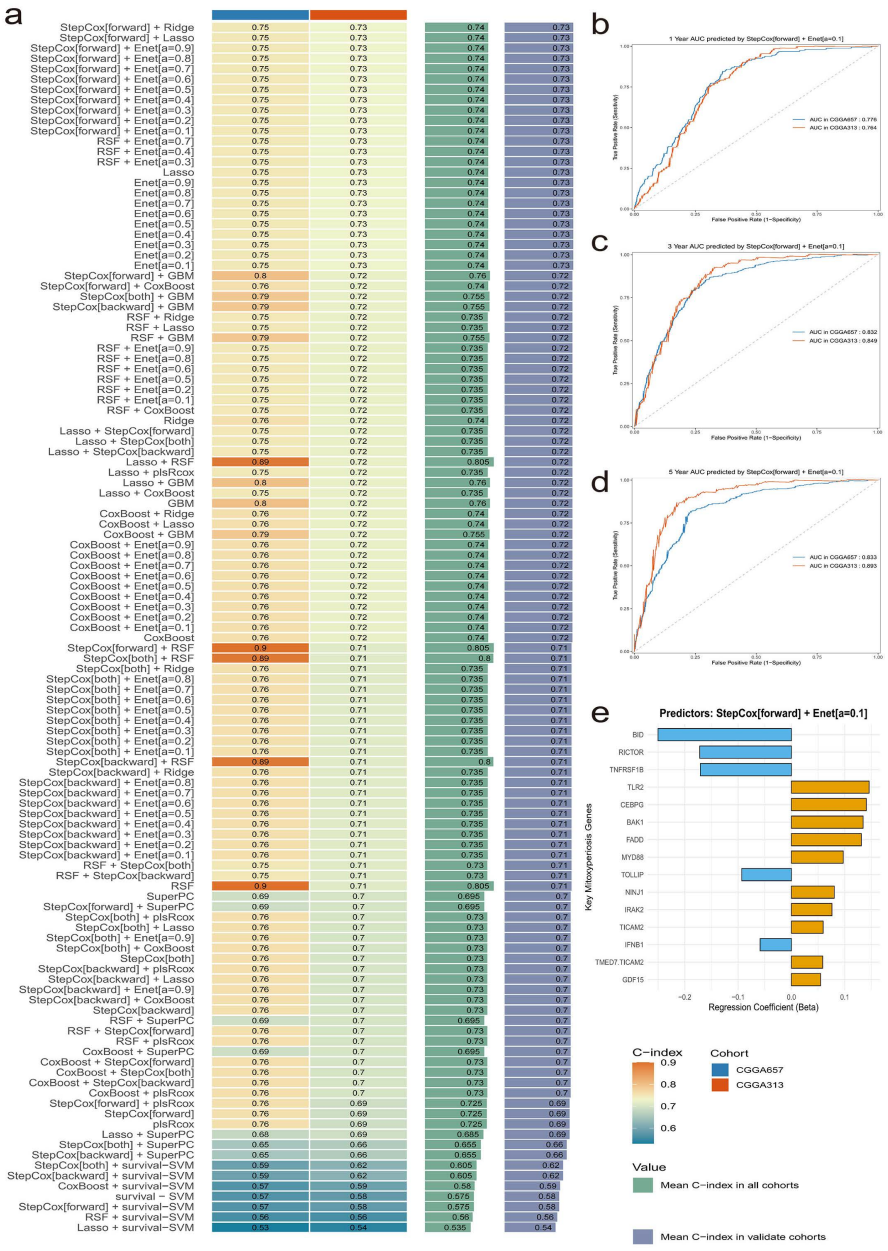

Figure 2. Construction of a mitoxyperiosis-related prognostic model based on an integrative machine learning framework. (a) Performance evaluation heatmap of 117 machine learning model combinations: The C-index performance of all models, generated from 10 base algorithms, is shown for the training set (CGGA-657) and validation set (CGGA-313). (b)-(d) Time-specific predictive performance of the optimal prognostic model: Receiver operating characteristic (ROC) curves illustrate the predictive accuracy of the optimal model at 1-year, 3-year, and 5-year survival nodes. (e) Core characteristic genes and their weights in the optimal prognostic model: Fifteen mitoxyperiosis-related core genes identified by Elastic Net regression and their corresponding regression coefficients (Beta values) are presented.

To develop a robust prognostic model for glioma, an integrative machine learning

framework was employed. This framework combined 10 common variable selection and regression algorithms to generate 117 distinct model combinations. We then evaluated the C-index and area under the receiver operating characteristic curve (AUC) for these models at various survival time points within the CGGA-657 training set and CGGA-313 validation set.

Through cross-comparison of all combinations, StepCox[forward] + Enet[α = 0.1] was identified as the optimal model (**Figure 2(a)**). This model achieved a C-index of approximately 0.75 in the training set and maintained roughly 0.73 in the validation set, demonstrating strong generalizability. It consistently showed high AUC values in survival analyses for 1, 3, and 5 years (**Figure 2(b)-(d)**). Notably, the 3-year AUC reached 0.832 and 0.849 in the training and validation sets, respectively (**Figure 2(c)**), confirming its superior performance in discriminating long-term survival risk. Furthermore, multivariate Cox regression analysis demonstrated that the risk score remained an independent prognostic factor for glioma after adjusting for conventional clinical features, including age, grade, and IDH status (Hazard Ratio [HR] = 1.047, 95% Confidence Interval [CI]: 1.043 - 1.051, $P < 0.001$).

The final model selected 15 representative core genes and determined their respective regression coefficients (Beta values) (**Figure 2(e)**). Analysis of these coefficients indicated that genes such as *BID*, *RICTOR*, and *TNFRSF1B* significantly contributed to the risk score.

3.3. Clinical Validation of the Mitoxyperiosis Risk Score in Glioma

To evaluate the prognostic discriminatory power of the mitoxyperiosis-related model in clinical practice, we calculated risk scores for each patient using the optimal algorithm combination. Patients in the CGGA-657 training set and CGGA-313 validation set were stratified into high- and low-risk groups based on the median risk score. Kaplan-Meier (KM) survival analysis showed that high-risk patients had significantly shorter overall survival than low-risk patients in both cohorts ($p < 0.001$; **Figure 3(a)**, **Figure 3(b)**). In the CGGA-657 cohort, the high-risk group exhibited a substantially increased mortality risk, with a hazard ratio (HR) of 4.37 (95% CI: 3.54 - 5.38). This finding was highly consistent in the independent CGGA-313 validation set (HR = 3.85, 95% CI: 2.89 - 5.14), demonstrating the strong predictive performance of the risk model.

Additionally, to address the limitations of single-cohort studies and verify model robustness, we performed a meta-analysis of univariate Cox regression across both cohorts (**Figure 3(c)**). The results showed a high pooled HR of 4.72 (95% CI: 3.96 - 5.63, $p < 0.001$). These findings confirm the broad generalizability of the mitoxyperiosis risk score across different patient populations and establish it as a robust prognostic marker for glioma.

To further explore the clinical relevance of the risk score in immunotherapy, we quantified its association with critical immune checkpoints. Spearman correlation analysis revealed a significant positive correlation between the risk score

and the expression of *PDCD1* ($r = 0.54$, $P < 0.001$). This quantitative evidence suggests that a higher mitoxyperiosis-related risk score is closely linked to an intensified immunosuppressive tumor microenvironment, potentially identifying patients who may benefit more from immune checkpoint blockade therapies.

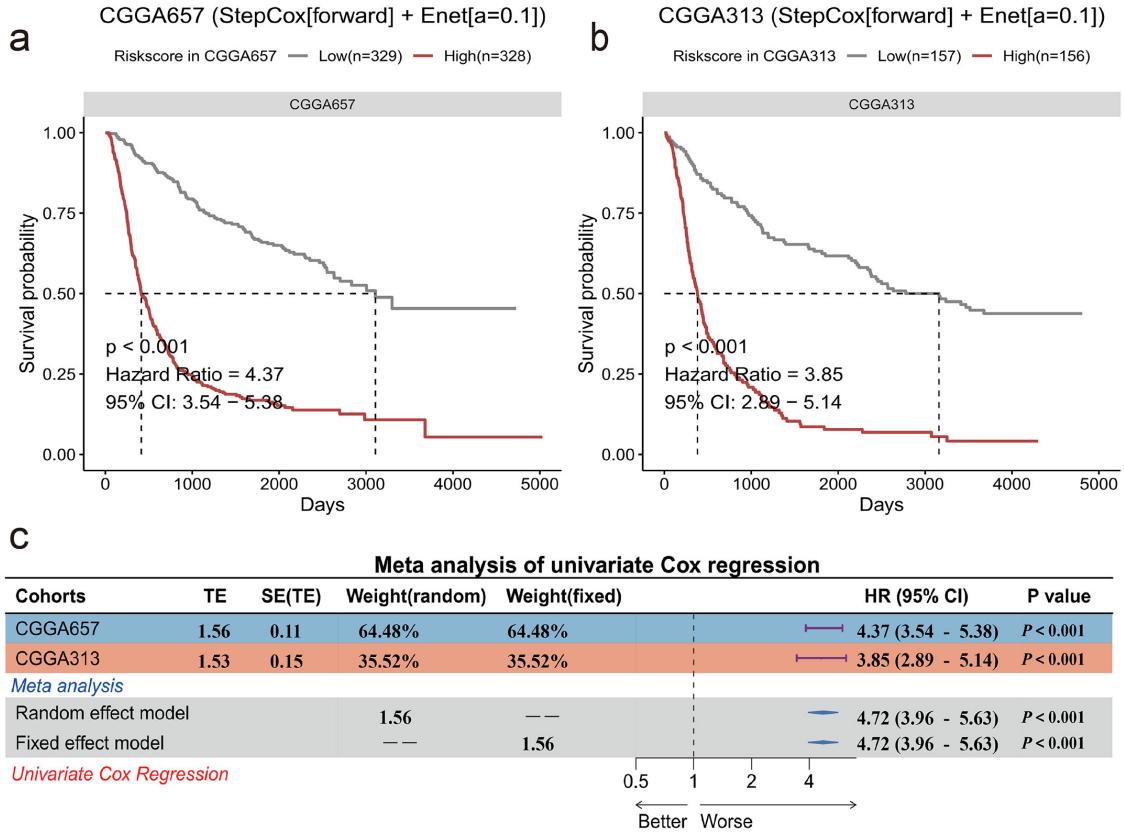

Figure 3. Clinical prognostic value validation of the mitoxyperiosis risk score in glioma. (a) (b) Kaplan-Meier survival curves for the training and validation cohorts: These plots demonstrate prognostic stratification based on risk scores derived from the optimal prognostic model in the CGGA-657 training cohort and the CGGA-313 independent validation cohort. (c) Forest plot of the meta-analysis of univariate Cox regression: This analysis was performed by integrating data from the CGGA-657 and CGGA-313 independent cohorts.

3.4. Comparative Analysis with Published Prognostic Models

To further validate the clinical superiority of the mitoxyperiosis risk score, we performed a multi-dimensional comparison between our model and dozens of established glioma prognostic models published over the past decade, including those for LGG, GBM, and pan-glioma.

First, regarding overall predictive accuracy, our model's C-index ranked among the highest in both the CGGA-657 training set and CGGA-313 validation set, significantly exceeding classic models developed by Zhu *et al.*, Xia *et al.*, and Tan *et al.* (**Figure 4(a)**, **Figure 4(b)**). Second, for short-term predictive efficacy, the mitoxyperiosis model demonstrated excellent diagnostic accuracy, with 1-year AUC values at the top of the comparison list (**Figure 4(c)**, **Figure 4(d)**). Third, in terms of risk discrimination, our model exhibited high Hazard Ratio (HR) values and

significant statistical differences ($p < 0.001$) in both cohorts, outperforming the vast majority of published models (Figure 4(e)).

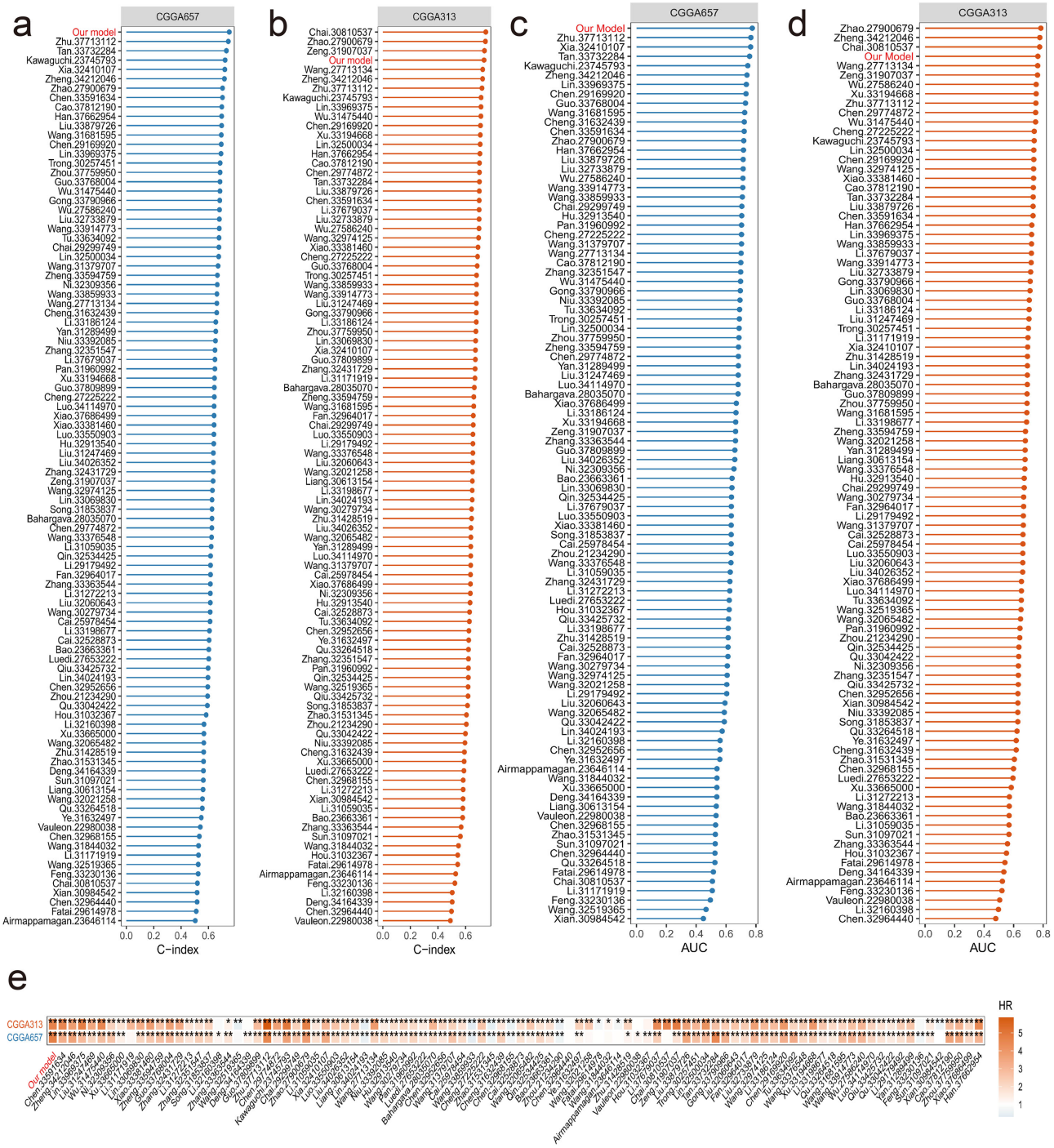

Figure 4. Comparative analysis of the mitoxyperiosis model and other published prognostic models. (a) (b) Ranking comparison of overall predictive accuracy (C-index): These plots illustrate the C-index of our optimal prognostic model compared with over 40 published glioma models in the CGGA-657 and CGGA-313 cohorts. (c) (d) Comparison of 1-year survival predictive accuracy (AUC): The area under the receiver operating characteristic curve (AUC) was used to evaluate the short-term discriminatory power of each model in the CGGA-657 and CGGA-313 cohorts. (e) Heatmap analysis of risk discriminatory power (Hazard Ratio, HR): This panel compares the hazard ratios and statistical significance of various models across the two CGGA cohorts.

4. Discussion

This study systematically developed a glioma prognostic model based on mitoxyperiosis-related genes using an integrative machine learning framework. After evaluating 117 algorithm combinations, the StepCox[forward] + Enet[α = 0.1] combination demonstrated superior and robust predictive performance across multiple independent cohorts. Notably, the 3-year AUC reached 0.849 in the CGGA-313 validation set. Comparative analysis further showed that this model significantly outperformed dozens of established glioma models in terms of risk discrimination, predictive consistency, and diagnostic accuracy. These findings highlight the high clinical value of mitoxyperiosis for prognostic assessment and clinical stratification in glioma5 [4].

Among the core genes, *BID* exhibited the highest positive regression coefficient and was identified as a primary risk factor [12]. As a pro-apoptotic member of the *Bcl*-2 family, *BID* serves as a hub connecting death receptor and mitochondrial pathways [13]. Since mitoxyperiosis is essentially programmed death induced by mitochondrial oxidative stress, *BID*-mediated mitochondrial outer membrane permeabilization (MOMP) may promote glioma malignancy by accelerating reactive oxygen species (ROS) bursts [14]. Another notable gene, *NINJ1*, also acted as a risk factor. As a recently discovered protein mediating plasma membrane rupture, *NINJ1* may remodel the tumor microenvironment and promote compensatory cell proliferation by inducing cell lysis and releasing damage-associated molecular patterns (DAMPs). These results provide a new perspective on the molecular link between mitochondrial dysfunction and glioma progression [15].

Furthermore, this study revealed a close association between mitoxyperiosis and the tumor immune microenvironment (TIME) [16]. The PPI network demonstrated extensive interactions between mitoxyperiosis-related genes and the *TLR* family as well as the *MYD88* signaling pathway [17]. "Inflammatory bursts" triggered by mitochondrial damage might activate innate immune pathways, such as cGAS-STING or *TLR9*, through the release of mtDNA [18]-[20]. Our analysis provided direct evidence for this link, showing a significant positive correlation between the risk score and the immune checkpoint PDCD1 ($r = 0.54$, $p < 0.001$). The robust correlation with PDCD1 confirms that high-risk patients exhibit a distinct immunosuppressive landscape, reinforcing the potential of this model as a biomarker for screening glioma patients who may benefit from immunotherapy [21]. Despite the rigorous machine learning screening and meta-analysis, this study has limitations [22]. This research focused on retrospective transcriptomic analysis. Moreover, as our datasets are derived from the CGGA, further validation in diverse populations, such as the TCGA cohorts, would strengthen the global generalizability of the mitoxyperiosis signature. Future in vitro and in vivo experiments are necessary to explore the molecular mechanisms of *BID* and *NINJ1* in regulating mitoxyperiosis. Additionally, investigating the correlation between risk scores and sensitivity to radiotherapy and chemotherapy will provide stronger evidence for precision medicine in glioma.

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Declaration

These authors contributed equally to this work.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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