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ORIGINAL RESEARCH ARTICLE

Expression patterns and prognostic value of N6-methyladenosine regulators in esophageal cancer

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Abstract

Introduction: Aberrant m6A regulators contribute to esophageal cancer, yet few studies stratify by subtype and compare prognostic models.

Objectives: N6-methyladenosine (m6A) modification broadly regulates cancer progression and prognosis, while its clinical role in esophageal cancer (EC) remains poorly defined.

Methods: Based on The Cancer Genome Atlas data, we analyzed 13 m6A regulators in EC and normal tissues, and constructed a prognostic signature using Cox and least absolute shrinkage and selection operator (LASSO) regression analyses. Model performance was validated using C-index and time-dependent receiver operating characteristic curves and compared with tumor–node–metastasis (TNM) staging and existing models.

Results: Eight m6A regulators (*METTL3, KIAA1429, YTHDC1, HNRNPC, WTAP, RBM15, YTHDF1, YTHDF2*) were significantly upregulated in EC tumors, with *YTHDC1* showing the strongest correlation with *METTL14* (r = 0.55). A four-gene m6A-regulator expression signature was identified using LASSO Cox regression. Both univariate and multivariate Cox analyses revealed that the risk score and TNM stage were independent risk factors. High-risk patients had worse overall survival (OS) across all stages and subtypes. Low-risk stage I–II patients had better OS. Combining the risk score with TNM stage improved prognostic accuracy over TNM stage alone, though differences with the risk score model were not significant. Our risk model was particularly effective at predicting 1-year OS, whereas TNM staging and other signatures were better at predicting 3- and 5-year survival.

Conclusion: We explored the role of m6A in EC and created a four-gene m6A-regulator expression signature risk model that serves as an independent prognostic biomarker, complementing TNM staging to aid in personalized postoperative care for EC patients.

Keywords: Esophageal cancer; Prognostic signature; Survival analysis; N6-methyladenosine modification; N6-methyladenosine-related genes

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1. Introduction

Esophageal cancer (EC) ranks as the eighth most prevalent malignant tumor and the sixth deadliest cancer globally.[1] It mainly includes esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC).[2] ESCC accounts for the majority of EC cases and predominates in East Asia and Africa, while EAC occurs mainly in developed countries. Approximately half of all EC patients have distant metastases, and the prognosis of these patients is poor.[3] Despite recent advances in treatment with the development of targeted therapy, patients with EC have a poor prognosis, with an approximately 15%–25% 5-year survival rate.[4]

N6-methyladenosine (m6A) is the most common and evolutionarily conserved modification of eukaryotic messenger RNAs (mRNAs) in most organisms.[5-7] The m6A modification is a reversible process that involves the coordinated action of adenosine methyltransferases (commonly referred to as "writers"), demethylases ("erasers"), and RNA-binding proteins ("readers"). These molecular entities are responsible for the addition, removal, or recognition of m6A-modified sites, thereby influencing critical biological processes. Writers (Vir-like m6A methyltransferase-associated protein [KIAA1429], methyltransferase-like protein [METTL] 3, METTL14, METTL16, RNA-binding motif protein 15 [RBM15], Wilms tumor 1-associating protein [WTAP], and zinc finger CCCH domain-containing protein 13 [ZC3H13]) form a multisubunit methyltransferase enzyme complex and upregulate the m6A level, while erasers (AlkB homolog 5 [ALKBH5] and fat mass and obesity-associated protein [FTO]) reverse this process. Readers, including YT521-B homology domain-containing protein (YTHDC) 1, YTHDC2, YT521-B homology m6A RNA-binding protein (YTHDF) 1, YTHDF2, YTHDF3, and heterogeneous nuclear ribonucleoprotein (HNRNPC), are responsible for decoding m6A methylation information and converting it into a functional signal. Growing evidence indicates that m6A modification plays a pivotal role in tumorigenesis and metastasis.[5] Therefore, the m6A-regulated genes identified in deadly cancers will provide new therapeutic targets. There have also been a number of studies on the roles of m6A-related genes and m6A RNA methylation regulators, such as *METTL3*, in bladder cancer,[8] breast cancer,[9] and pancreatic cancer.[10] Recent studies have documented the expression patterns and prognostic utility of m6A regulatory gene signatures across multiple malignancies.[11-15] However, relevant clinical evidence specific to EC remains scarce. Although several m6A-based prognostic models have been established for EC to date, these models treat all EC subtypes as a unified cohort without stratifying analyses for EAC and ESCC.[12,13] Notably, ESCC constitutes the predominant pathological subtype of EC in China. Furthermore, the molecular indicators incorporated in the two previously reported predictive models show substantial inconsistency.[12,13] Given these research gaps, we performed rigorous biomarker screening to construct a novel m6A-regulator expression signature model. We then systematically compared its predictive performance with existing published models and validated its subtype-specific prognostic efficacy across distinct EC histological types.

2. Materials and methods

2.1. Public data sources

The RNA sequencing data and sample annotation files from 159 EC patients and 10 normal controls were downloaded from The Cancer Genome Atlas (TCGA) database. We explicitly defined patient exclusion criteria for survival analysis: cases with absent tumor–node–metastasis (TNM) staging data or incomplete prognostic follow-up records were excluded. A total of 22 participants were excluded from clinical cohort analysis, and all irreparable missing clinical information was eliminated rather than imputed.

2.2. Selection of differentially expressed m6A-RNA methylation regulators

The R software (x64 4.0.2, R Foundation for Statistical Computing, Austria) was used to identify differentially expressed genes between EC and normal control samples. An adjusted $p < 0.05$ and an absolute $\log_2$(fold change) > 1 were selected as the cutoff thresholds. Thirteen regulatory factors for m6A RNA methylation, including *KIAA1429*, *METTL3*, *METTL14*, *RBM15*, *WTAP*, *ZC3H13*, *ALKBH5*, *FTO*, *HNRNPC*, *YTHDF1*, *YTHDF2*, *YTHDC1*, and *YTHDC2*, were sourced from the literature.[13-16] To visualize differences, heatmaps were created using the "pheatmap" R package.

2.3. Construction of m6A-based prognostic risk signature and risk stratification model

A univariate Cox analysis was conducted to assess the relationship between m6A RNA methylation regulators and overall survival (OS) in TCGA EC cohort. Prognostically significant m6A RNA methylation regulators with $p < 0.1$ identified via univariate Cox analysis were further incorporated into least absolute shrinkage and selection operator (LASSO) regression modeling to compress redundant variables and avoid model overfitting. Cox-LASSO regression was conducted in R using the "glmnet" and "survival" packages. Survival time was converted from days to years before modeling. The Cox-type LASSO model

was constructed with *family* = "cox" and *maxit* = 1,000 to ensure model convergence. Ten-fold cross-validation via "cv.glmnet" was used to screen the optimal penalty coefficient λ, and "lambda.min" was selected to extract genes with non-zero regression coefficients as prognostic signature genes. According to the LASSO regression model, each patient received a risk score, and EC patients were classified as high- or low-risk based on whether their score exceeded the median. Furthermore, univariate and multivariate analyses were employed to assess if the risk score and clinical features were independent prognostic indicators in EC patients.

2.4. Statistical analysis

Kaplan–Meier (K–M) plots illustrating events (deaths) in relation to clinicopathological characteristics and index levels are shown as hazard ratios (HRs) with 95% confidence intervals (CIs), and the association was assessed using the log-rank test. Survival curves were plotted using the Kaplan–Meier method, and the log-rank tests were conducted to assess OS differences between high-risk and low-risk groups. A calibration plot for 1- and 3-year OS was constructed to examine the performance characteristics of the generated risk score model. The ability of the risk score model and the TNM staging system to predict survival was assessed using Harrell *et al.*[11]'s concordance index (C-index). Bootstrap-based optimism correction with 1,000 resamples was implemented to quantify overfitting bias and calculate the corrected C-index for our four-gene m6A-regulator expression signature model, TNM stage, and Panel 2 signature. The "rms" package was used to construct the TNM stagecombined prognostic nomogram. The "timeROC" package was used to generate time-dependent receiver operating characteristic (ROC) curves for predicting survival at 1, 3, and 5 years, and the corresponding area under the curve (AUC) values were calculated to evaluate the model's discrimination performance. Survival curves for risk subgroups were visualized using the "survminer" package. All figures and data were generated using R. Results with $p < 0.05$ were considered significant.

3. Results

3.1. The expressed N6-methyladenosine RNA methylation regulators in tumor samples and normal control samples

A heatmap was generated to show the expression patterns of m6A RNA methylation regulators in both EC and normal samples. In the plots, red indicates higher expression, while green indicates lower expression (Figure 1A). *METTL3* ($p < 0.001$), *KIAA1429* ($p = 0.01$), *YTHDC1* ($p = 0.01$), *HNRNPC* ($p < 0.001$), *WTAP* ($p = 0.003$), *RBM15* ($p = 0.016$), *YTHDF1* ($p < 0.001$), and *YTHDF2* ($p = 0.003$) were significantly overexpressed in tumor samples compared to normal control samples, while *ZC3H13*, *FTO*, *METTL14*, *ALKBH5*, and *YTHDC2* were not significantly different ($p > 0.05$) between tumor and normal control samples (Figure 1B). A correspondence factor map was constructed to show the correlations among the 13 m6A RNA methylation regulators. Among the regulators of m6A RNA methylation, *YTHDC1* showed the highest correlation with *METTL14*, with a correlation coefficient of 0.55 (Figure 1C).

3.2. Construction of the risk score model

Initially, we assessed the prognostic performance of the 13 m6A RNA methylation regulators using univariate Cox regression analysis before creating the risk score model. Afterward, four factors with p-values < 0.10 in the univariate analysis were considered. (Figure 2B, 2C). The risk score was calculated using **Equation 1**:

$$Risk\ score = 0.027 \times HNRNPC + 0.058 \times WTAP - 0.312 \times METTL14 - 0.059 \times ALKBH5 \quad (1)$$

After the calculation, EC patients were categorized into high-risk and low-risk groups based on a median risk score of 0.565. Figure 2D illustrates the relationships between the risk score and factors such as sex, tumor stage, and tumor status. There was a correlation only between the risk group and status ($p < 0.05$).

3.3. Analysis of clinicopathological features and risk scores using both univariate and multivariate Cox regression

To assess the independence of these variables as risk factors, univariate and multivariate Cox regression analyses were applied to relevant clinicopathological characteristics and risk scores. Lymph node stage, TNM stage, and risk score were associated with poor OS ($p < 0.001$) in the univariate analysis (Figure 3A). According to the multivariate analysis, only the risk score (HR: 2.618, 95% CI: 1.609–4.261; $p < 0.001$) and TNM stage (HR: 2.142, 95% CI: 1.382–3.321; $p < 0.001$) were related to poor OS (Figure 3B).

3.4. Survival analysis of the risk score model

The K-M survival analysis indicated that the high-risk group had a notably shorter OS than the low-risk group ($p < 0.0001$). Patients in the high-risk category exhibited significantly worse OS than those in the low-risk category for stage I–II disease ($p = 0.00026$), stage III–IV disease ($p = 0.047$), EAC ($p = 0.00075$), and ESCC ($p = 0.027$). Stage I–II disease patients in the low-risk group showed improved OS compared to those in other groups (Figure 4B).

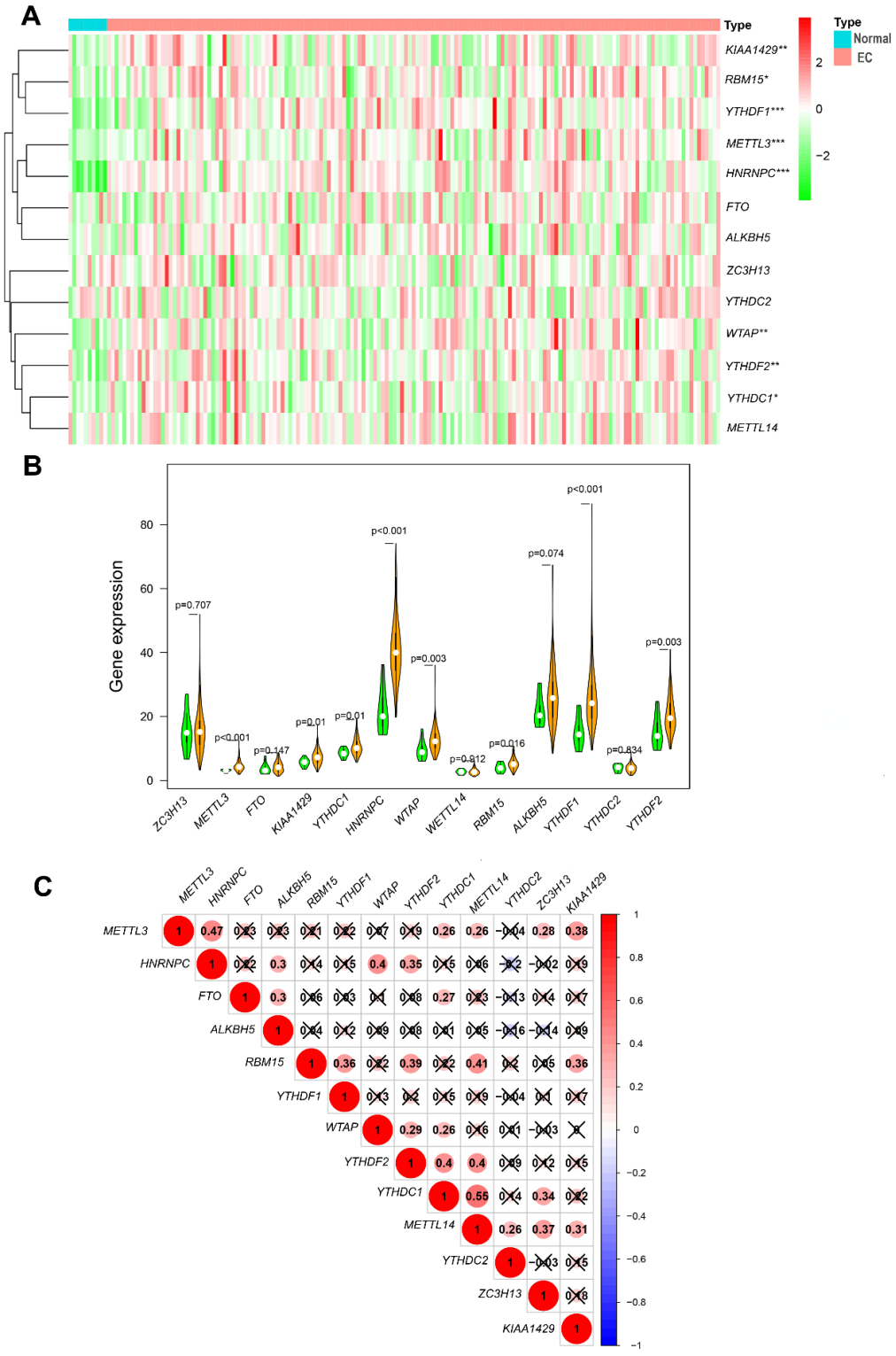

Figure 1. The expression levels of N6-methyladenosine (m6A) RNA methylation regulators between tumor samples and normal control samples in the Cancer Genome Atlas esophageal cancer cohort. (A) The heatmap was used to visualize the expression levels of m6A RNA methylation regulators across clinical samples. (B) Significantly differentially expressed m6A RNA methylation regulators between tumor samples and normal control samples. (C) The Pearson correlation analysis was used to assess correlations among m6A RNA methylation regulators.
Note: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

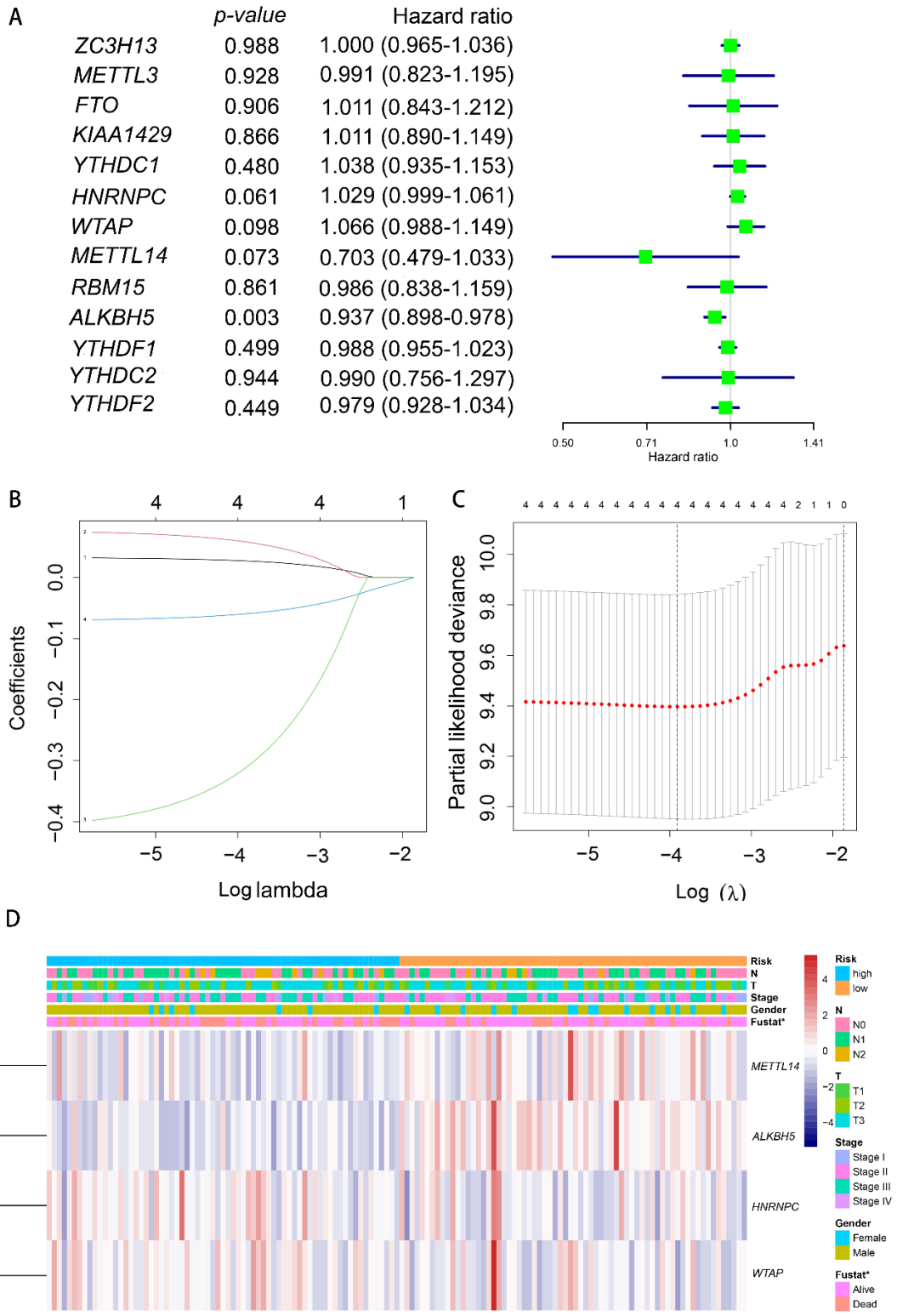

Figure 2. Construction of the prognostic model based on the Cancer Genome Atlas esophageal cancer cohort. (A) Univariate analysis of N6-methyladenosine (m6A) RNA methylation regulators to identify genes that were significantly correlated with overall survival. (B, C) The process of building the least absolute shrinkage and selection operator model with size and coefficients by multivariate Cox regression. (D) Heat map showing expression levels of four m6A RNA methylation-related genes and clinicopathological features in the low- and high-risk groups.

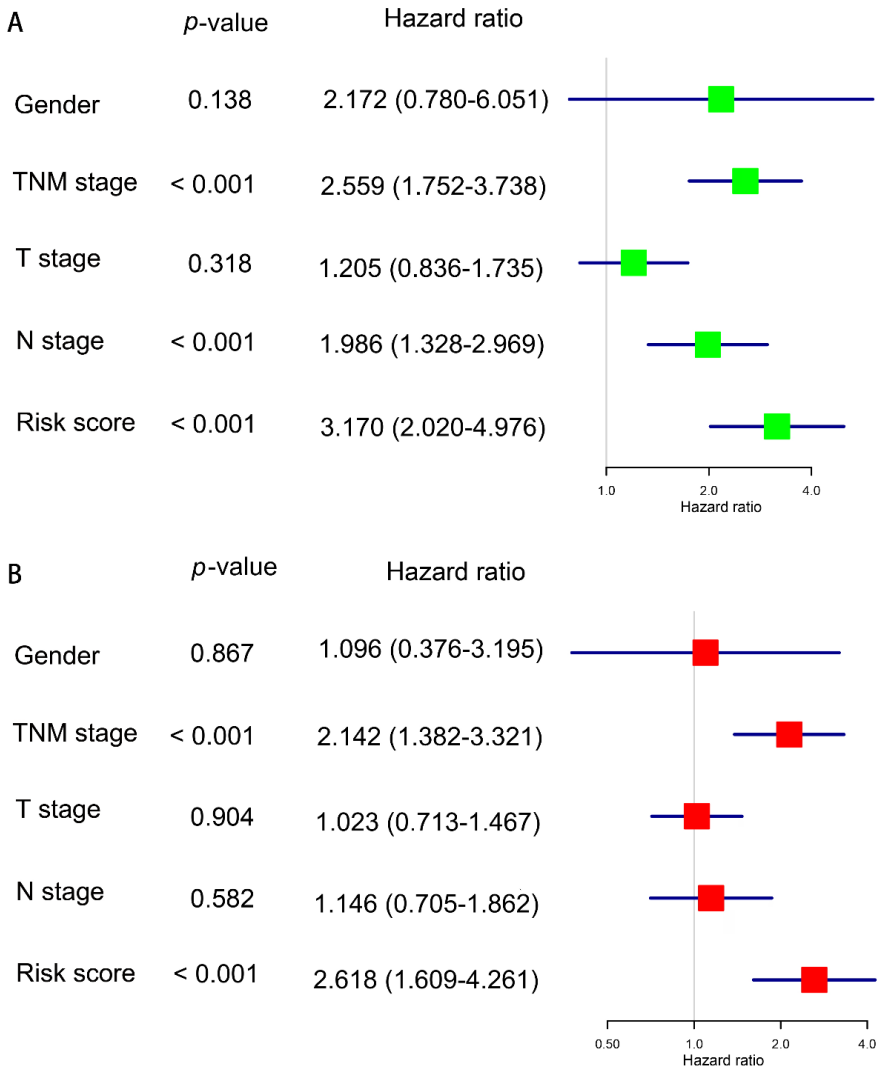

Figure 3. Identification of the independent prognostic factors in the Cancer Genome Atlas esophageal cancer cohort. (A) Univariate analysis of the risk score and clinicopathological parameters for their correlation with overall survival. (B) Multivariate analysis of the risk score and clinicopathological parameters to reveal the independent prognostic factors.
Abbreviations: M: Metastasis; N: Node; T: Tumor.

3.5. The prognostic performance of the risk score model

The calibration curve shows a strong relationship between the risk score model's predictions (four-m6A-regulator expression signatures) and the observed 1-year and 3-year survival probabilities (Figure 5). The C-indexes for the risk score model (four-m6A-regulator expression signature), Panel 2 (*HNRNPC*, *ALKBH5*), TNM stage, and risk score + TNM stage were 0.671, 0.620, 0.666, and 0.707, respectively (Table 1). We further calculated the C-index with bootstrap-based optimism correction (1,000 resamples) to evaluate the internal discriminative ability of each prognostic predictor. The corrected C-index values are also summarized in Table 1. Our model (four-m6A-regulator expression signature) yielded the highest bootstrap-corrected C-index of 0.668, followed by TNM stage (0.664). The Panel 2 signature showed relatively weaker discrimination, with a corrected C-index of 0.607. All predictors exhibited mild overfitting, as reflected by small optimism bias values. Compared to the TNM stage, the risk score + TNM stage had greater prognostic accuracy. Nevertheless, the differences between the risk score + TNM stage group and the risk score model group were not

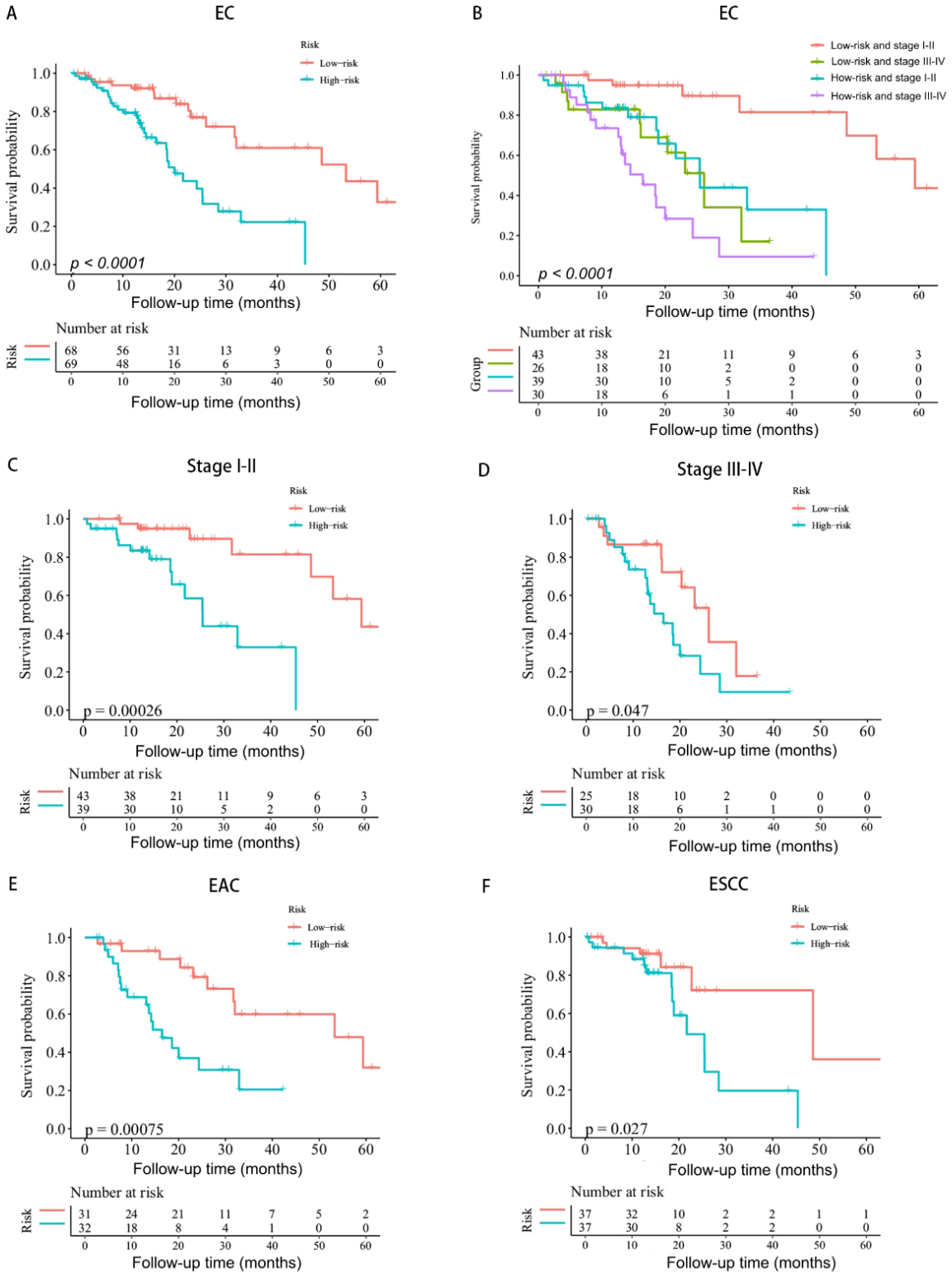

Figure 4. Kaplan–Meier (K–M) analysis between high- and low-risk groups stratified by clinicopathological parameters. (A) K–M survival curve of esophageal cancer (EC) patients in the Cancer Genome Atlas database. (B) The difference in overall survival (OS) stratified by stage and risk group. (C, D) The difference in OS between the high- and low-risk groups stratified by stage. (E, F) The difference in OS between the high- and low-risk group stratified by histopathological types of EC.

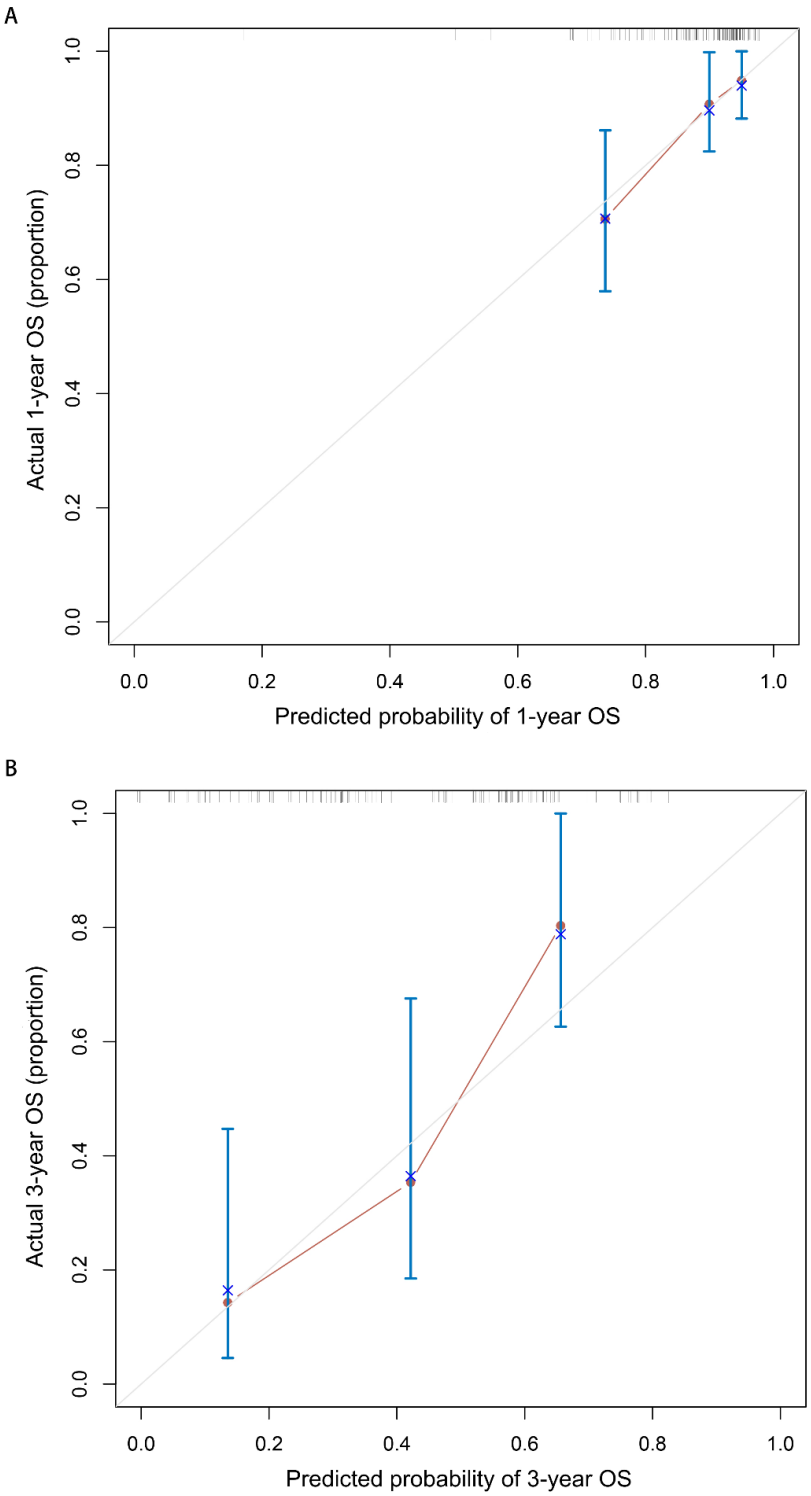

Figure 5. The calibration curves for predicting overall survival (OS) at (A) one year and (B) three years in The Cancer Genome Atlas cohort. Notes: Nomogram model-predicted OS is plotted on the X-axis; actual OS is plotted on the Y-axis. Closer alignment with the diagonal line represents a better estimation.

Table 1. The C-indexes of the risk score, TNM stage, and risk score + TNM stage for the prediction of overall survival in esophageal cancer patients

Factors	C-index (95% CI)		*Corrected C-index*	*Optimism*	*p-value*
Risk score	0.671	(0.581–0.762)	0.668	0.004	
TNM stage	0.666	(0.576–0.757)	0.664	0.002	
Panel 2	0.620	(0.531–0.710)	0.607	0.014	
Risk score +TNM stage	0.707	(0.620–0.795)	0.697	0.010	
Risk score vs. TNM stage					0.923
Panel 2 vs. TNM stage					0.436
Risk score vs. Panel 2					0.047
Risk score + TNM stage vs. Risk score					0.344
Risk score + TNM stage vs. TNM stage					0.005

Notes: The *p*-values were calculated based on a normal approximation using the function *rcorrp.cens* in the *Hmisc* package; Bootstrap optimism correction (1,000 resamples) was used to adjust overfitting bias; Panel 2 = 0.0626 × *HNRNPC* − 0.0246 × *ALKBH5*. Abbreviations: CI: Confidence interval; C-index: Concordance index; TNM: Tumor–node–metastasis.

statistically significant (p = 0.175) (Table 1). We further performed time-dependent ROC analyses to quantitatively compare the predictive accuracy of TNM stage, our four-m6A-regulator expression signature risk score model, and a previously reported signature (Panel 2), for 1-, 3-, and 5-year OS. Our risk score model demonstrated optimal short-term (1-year) prognostic discrimination capacity relative to traditional TNM staging and the published gene signature, while TNM and Panel 2 showed better predictive performance for mid-term (3-year) and long-term (5-year) survival outcomes, respectively (Figure 6).

Subsequently, a prognostic nomogram for OS with scales for TNM stage and risk score was constructed (Figure A1). By assigning points based on their impact on the outcome and summing them, we could obtain a total score for each patient. Then, the patients' survival rates at 1, 2, and 3 years were documented.

4. Discussion

Esophageal carcinogenesis is a progressive and intricate biological process driven by stepwise accumulation of genetic and epigenetic aberrations, which ultimately

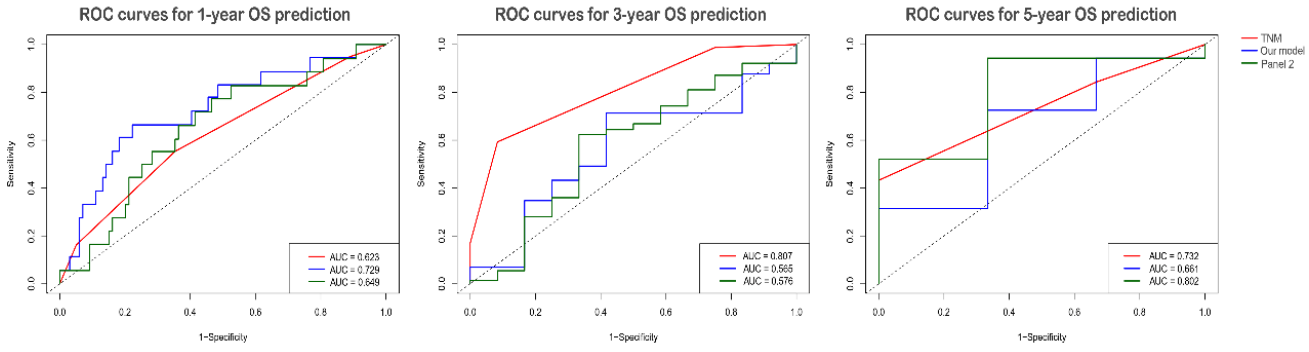

Figure 6. Time-dependent receiver operating characteristic (ROC) curves comparing the predictive performance of the tumor–node–metastasis staging system, our risk score model, and the Panel 2 signature for 1-, 3-, and 5-year overall survival (OS) in esophageal cancer patients.
Notes: Our model: Four-m6A-regulator expression signature risk score model; Panel 2 = 0.0626 × HNRNPC − 0.0246 × ALKBH5.
Abbreviations: AUC: Area under the curve; OS: Overall survival; ROC: Receiver operating characteristic.

trigger uncontrolled proliferation and malignant growth of EC cells. Deciphering the core molecular events underlying EC progression and clarifying their prognostic significance is critical for improving clinical risk stratification. Accumulating evidence has demonstrated that aberrant m6A RNA methylation profoundly modulates tumor initiation and progression across multiple human malignancies.[11-15] Although several prognostic models based on m6A regulators have been developed for EC, existing studies lack systematic evaluations across distinct EC histological subtypes and comparative analyses of predictive signatures.[12,13] In this work, we systematically profiled the expression levels of 13 m6A RNA methylation regulators in EC tissues and paired normal samples. Among these regulators, eight exhibited strikingly different expression between EC patients and healthy controls, consistent with previously published findings and validating the reliability of our analytical workflow. Subsequent correlation network analysis of the 13 m6A-associated genes identified a prominent positive correlation between *YTHDC1* and *METTL14* (correlation coefficient = 0.55). Consistent with previous mechanistic research on oral squamous cell carcinoma and prostate cancer,[17,18] elevated METTL14 levels increase global m6A modification levels in target circRNAs and mRNAs, thereby generating abundant binding sites for *YTHDC1*. Upregulated *YTHDC1*, in turn, stabilizes these m6A-modified transcripts and maintains their nuclear accumulation, forming a coordinated positive-feedback regulatory loop to amplify oncogenic signals. As validated in published studies, *METTL14*-mediated m6A modification is a prerequisite for *YTHDC1* to recognize and bind RNA molecules; their synchronous upregulation jointly accelerates tumor malignant progression, which explains their tight linear correlation in our EC cohort.[12]

Univariate Cox regression analysis revealed that four m6A-regulator genes, including *HNRNPC*, *WTAP*, *METTL14*, and *ALKBH5*, were significantly correlated with OS in EC patients. High expression of *HNRNPC* and *WTAP* clustered in high-risk patients with poor OS, consistent with HR values above 1 that indicate elevated death risk. In contrast, *METTL14* and *ALKBH5* were more abundantly expressed in low-risk long-term survivors, matching HR below 1 and protective prognostic effects. These findings are supported by previous oncological studies. Mechanistically, *WTAP* is overexpressed in acute myeloid leukemia (AML) and functionally sustains AML cell proliferation and survival,[19] and its high expression predicts increased postoperative recurrence risk in bladder cancer.[20] *HNRNPC* has been reported to be a prognostic marker in head and neck squamous cell carcinoma,[21] gastric cancer,[22] and lung adenocarcinoma.[23] In pancreatic and colorectal cancer patients, *METTL14* and *ALKBH5* were notably linked to OS.[24,25] Similar to the results of this study, *METTL14* exhibited low expression in hepatocellular carcinoma,[26] breast adenocarcinoma[27] and glioblastoma.[28] However, to our knowledge, these four m6A RNA methylation genes are not known to be involved in the prognosis of patients with EC. Notably, the aberrant expression and prognostic implications of *HNRNPC* and *ALKBH5* in EC observed in our study are strongly supported by independent experimental evidence. Consistent with our conclusions, previous quantitative reverse transcription polymerase chain reaction (qRT-PCR) and immunohistochemistry (IHC) analyses of esophageal carcinoma clinical specimens verified the dysregulated expression of *HNRNPC* and *ALKBH5* in tumor tissues, and confirmed their significant correlations with patient survival outcomes.[13] A TCGA cohort analysis covering 775 EC patients also demonstrated that high expression of *WTAP*, *HNRNPC*, and *YTHDC2* was significantly correlated with worse outcomes and advanced stage in EC.[29] These m6A regulators showed significant correlations with immune modulators (immunoinhibitors, immunostimulators, MHC molecules) and immune cell infiltration in EC. These associative findings suggest potential contributions of the regulators to EC immune microenvironment remodeling.

Currently, the TNM staging system remains the gold standard for routine EC prognostic evaluation and was identified as an independent prognostic risk factor in our cohort. However, conventional TNM staging relies solely on macroscopic clinicopathological features and fails to incorporate molecular biomarkers, leading to insufficient accuracy for individualized prognostic prediction.[30] Validating and combining additional clinical pathology and molecular biology risk factors to establish an effective prognostic model has become an important research direction. To further investigate the role of m6A RNA methylation regulators in predicting EC patient outcomes, LASSO Cox regression was performed, and a prognostic risk model was built with these four m6A RNA methylation-related genes. The prognostic risk model effectively predicted the clinical outcomes for patients with EC. More importantly, this prognostic risk model was further successfully validated by a calibration curve. Multivariate regression analysis further confirmed that the four-gene m6A signature was an independent prognostic predictor in EC patients. Notably, the combined model integrating risk score and TNM stage yielded a higher C-index than TNM staging alone, achieving superior OS prediction accuracy.

Furthermore, we systematically compared the predictive performance of our four-gene signature with a previously reported two-gene m6A prognostic model for EC using C-index analysis.[12] Our newly constructed signature exhibited a higher C-index, indicating superior prognostic performance and greater clinical applicability than the existing model. Of note, another published two-gene signature (*ALKBH5* and *HNRNPA2B1*) was excluded from comparative analysis due to the lack of available calculation formulas in the original literature.[12]

Kaplan–Meier survival stratification analysis confirmed the stable and robust prognostic performance of our signature across diverse clinical subgroups. Unlike most previously published prognostic signatures for EC that only performed crude subgroup validation limited to the overall EC population, our study conducted comprehensive stratified survival assessments by simultaneously integrating TNM tumor stage with the two dominant pathological subtypes (EAC and ESCC) of EC, thereby enabling more granular and clinically meaningful risk stratification. In the overall EC cohort, high-risk patients exhibited inferior survival ($p < 0.0001$). Joint stratification by risk and TNM stage revealed a graded survival gradient, with high-risk stage III–IV patients having the worst outcomes ($p < 0.0001$). The signature maintained strong predictive power in early (stage I–II) disease ($p = 0.00026$) and retained marginal prognostic discrimination in advanced (stage III–IV) EC ($p = 0.047$), providing prognostic information that is supplementary to tumor staging. Subtype-specific validation confirmed its generalizability across EAC ($p = 0.00075$) and ESCC ($p = 0.027$), two EC subtypes with disparate etiology and treatment profiles. Collectively, this stage- and subtype-independent risk signature may complement routine clinicopathologic factors to improve personalized risk stratification and clinical decision-making for all EC patients.

Time-dependent ROC analyses demonstrated divergent time-specific predictive performance among our risk score, TNM staging, and Panel 2 signature, with each tool dominating discrimination at distinct survival timepoints. Combined use of these prediction systems provides comprehensive multi-temporal prognostic information to refine personalized surveillance for EC patients.

Additionally, we developed a nomogram based on the TNM stage and risk score to help clinicians predict patient outcomes. We also examined the relationships between the prognostic risk model and clinicopathological features in patients with EC. However, we did not observe a correlation between m6A-related gene expression and sex, depth of invasion (T), lymph node metastasis (N), or TNM stage in EC patients.

Despite the promising findings in the present study, several limitations should be acknowledged. First, the relatively small sample size and lack of external independent validation cohorts restrict the generalizability of our prognostic signature. As recommended by standardized reporting guidelines for clinical prediction models, rigorous and transparent reporting is essential to evaluate model reliability; critically, molecular correlations identified from retrospective cohort analyses cannot be equated to clinically validated biomarkers with definitive translational value. The predictive performance and clinical interpretation of molecular signatures are highly context-dependent, and thus cautious translation of retrospective-derived risk models into clinical practice is strictly warranted.[31,32] Currently, our signature should be defined as a hypothesis-generating model pending prospective and independent external validation. Future large-scale multicenter studies with matched clinical tissues and transcriptomic data are required to validate the robustness, stability, and clinical translational value of this four-gene m6A prognostic signature.

5. Conclusion

We developed a four-gene multivariate risk model based on m6A methylation regulators to identify EC patients at high risk of poor survival. This exploratory signature stratified survival outcomes by disease stage and histological subtype and exhibited favorable predictive performance for 1-year survival compared with TNM staging and previously reported models. Independent external validation is needed before clinical application.

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Conflict of interest

None.

Author contributions

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Visualization: Runkun Han, Hao Chen
Writing–original draft: Runkun Han, Hao Chen, Changchun Lai
Writing–review & editing: Xinhua Xu, Xiaobin Wu

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All data were obtained from The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/).

Further disclosure

During the preparation of this work, the authors used Doubao to polish and improve the English expression of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the published article.

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Appendix

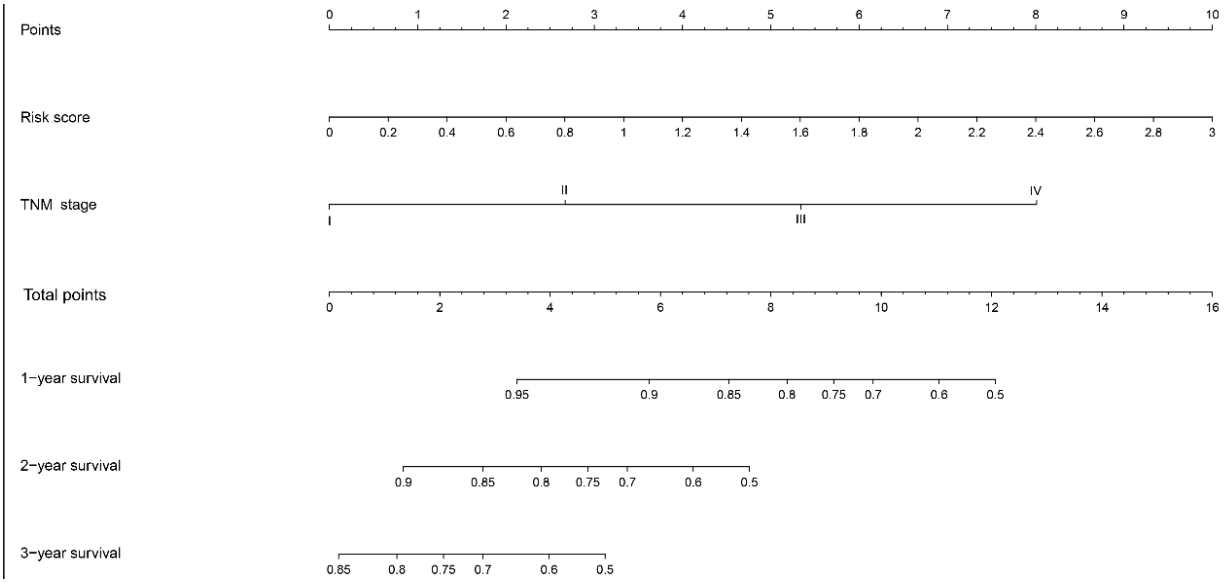

Figure A1. Nomogram model predicting 1-, 2-, and 3- year overall survival in esophageal cancer patients. Clinical interpretation guide: This visual prediction tool integrates the m6A risk score and pathological tumor–node–metastasis (TNM) stage to quantify individual survival risk. For clinical application, clinicians can calculate the total points by summing the points corresponding to the patient's risk score and TNM stage, and the 1-, 2-, and 3-year survival probabilities can be directly matched according to total points.