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META-ANALYSIS

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A novel N7-methylguanosine-associated feature predicts prognosis in gastric cancer

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Abstract

Background Despite substantial advancements in gastric cancer treatment in recent years, our understanding of the disease's pathophysiology and progression processes remains limited, and the prognosis for gastric cancer patients remains poor. This study investigated potential prognostic indicators based on m^7G-associated long non-coding RNA (lncRNA) and its relationship with gastric cancer (STAD).

Methods The researchers used RNA-seq and prognostic data from TCGA, employing Cox regression, co-expression network analysis, and multivariate Cox regression to identify relevant lncRNAs. We compiled four m^7G-related lncRNAs into a single signature.

Results We found it may be used as a prognostic indicator for gastric cancer. The m^7G-related lncRNA profile had an area under the curve of 0.710, significantly more diagnostic than clinicopathological markers. The study also found that the TMB and tumor microenvironment were associated with gastric cancer risk, highlighting their signature's potential utility for personalized treatment and disease monitoring.

Conclusions This study provides a novel signature of m^7G-related lncRNAs that can be used as a prognostic indicator for gastric cancer and may help guide the development of targeted immunotherapy for the condition.

Keywords m^7G methylation, Long non-coding RNA, Prognostic signature, Clinicopathological characteristics, Cox regression

Background

Stomach cancer may not rank among the top 10 malignancies in the USA in terms of incidence or mortality. Still, it does have the second-highest cancer mortality rate worldwide, especially in Northeast Asia and South America [1]. The high incidence and fatality rate of gastric cancer globally make it a significant public health concern, and effective treatment remains an important issue [2]. Advanced gastric cancer often results in tumor invasion and metastasis, significantly reducing the mean survival time [3]. Despite substantial advancements in gastric cancer treatment in recent years, our understanding of the disease's pathophysiology and progression processes remains limited, and the prognosis for gastric cancer patients remains poor [4].

Endoscopic resection is an effective cure for early-stage gastric cancer. At the same time, surgery is the primary treatment for mid to late-stage resectable stomach cancer, and adjuvant or perioperative radiotherapy and chemotherapy are mainly used to treat late-stage gastric cancer [5]. Unfortunately, most diagnoses of stomach cancer are already at an advanced stage, resulting in a low survival rate for patients [6]. RNA post-transcriptional modifications and associated translational control significantly influence tumor oncogenesis. RNA methylation is a reversible post-translational modification that epigenetically affects various biological processes, including RNA splicing, nucleation, stability, and immunogenicity

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[7]. Dysregulation of RNA methylation is required for human malignancies, including stomach cancer [8]. Post-transcriptional modifications profoundly affect cell function and fate, similar to DNA and protein modifications that form the epigenetic code, resulting in the term 'RNA epigenetics' or 'epitranscriptomics' [9]. Due to their tissue-specific expression profiles and genome-wide expression patterns, lncRNAs have potential uses as therapeutic targets and diagnostic indicators [10]. Although several studies have identified connections between lncRNA and RNA methylation in multiplex tumors, few investigations have focused on the relationship between m^7G and lncRNA [11].

This study examined how m^7G-associated lncRNAs predict STAD overall survival (OS). Based on the developmental set, we used four m^7G-associated lncRNAs (m^7G-RNAs) as prognostic markers and verified their predictive ability in the validation set. The detailed flowchart is shown in Fig. 1. Our findings indicate that the predictive signature can predict STAD survival independently.

Materials and methods

Collection clinical and transcriptomic data

To obtain samples of STAD transcriptome RNA sequencing data, we primarily utilized the cancer genome atlas (https://portal.gdc.ancer.gov/) [12] to download relevant data. We excluded patients with poor survival and missing overall survival data, analyzing the remaining patient data to minimize statistical deviation.

Identification of N7-methylguanosine-related lncRNA

This study found a list of 69 N7-methylguanosine genes on the GeneCards website (https://www.genecards.org/) [13]. We analyzed the association of 67 genes associated with necrotizing ptosis with lncRNA expression using Pearson's correlation analysis. All NRlncRNAs (2154) had to meet the requirements of a correlation coefficient (|Pearson R|) > 0.4 and p value < 0.001. We utilized R software V-4.1 and Strawberry Perl V-5.30.0 to screen a synthetic matrix which was then screened (available at https://www.perl.org).

Establishment and validation of N7-methylguanosine associated lncRNAs risk profiles in STADs

We used the "limma" program to investigate the association between genes associated with N7-methylguanosine and lncRNAs. We obtained 795 lncRNAs with higher expression levels related to N7-methylguanosine using correlation coefficients $|r2| > 0.4$ and $p < 0.001$. Before conducting multivariable Cox regression analysis to create N7-methylguanosine-associated predictive RNAs, we

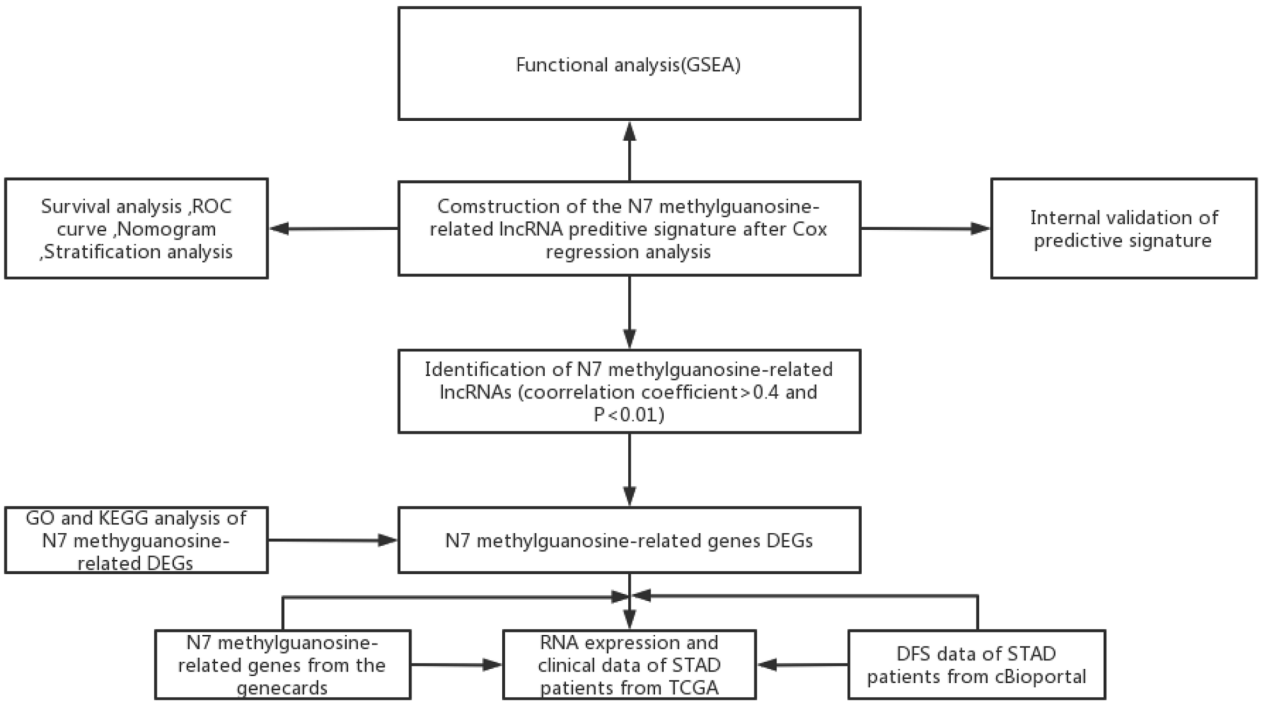

Fig. 1 Our research flowchart. GSEA, genetic enrichment analysis; Kyoto Encyclopedia of Genes and Genomes; STAD, gastric adenocarcinoma; ROC, receiver operating characteristics; single sample genetic enrichment analysis; TCGA, The Cancer Genome Atlas; lncRNA, long non-coding RNA; m^7G, N7-methylguanosine; GO, gene ontology; DFS, disease-free survival; differentially expressed genes DEGs

conducted single-variable Cox regression analysis to collect information about iron-sagging-associated lncRNAs related to STAD patient outcomes.

In conducting multiple Cox regression analyses for lncRNA, we also studied the expression level of lncRNA, where both Expr (I) and Coef (I) represented regression coefficients. Based on the risk score, we classified patients into high-risk and low-risk groups, which served as the main cut-off point. We used the LOG-RANK and Kaplan–Meier methods to investigate the differences in OS between the two groups of gastric cancer patients. We further estimated the risk profiles of established models and clinical features using Chi-square assays. To determine if prognostic indicators were independent prognostic indicators for STAD patients, we conducted single-factor and multifactor regression analyses and presented the results using two forest plots.

To confirm the predictive power of prognostic markers, we used the ROC curve to analyze the time ROC R software package, survival time, and investigators when calculating the area under the ROC curve.

Nomogram and calibration

We developed a nomogram for predicting the overall survival of patients with Stomach adenocarcinoma (STAD) at 1, 2, and 5 years by integrating risk levels and clinical variables such as sex, N, T, and tumor stage using the RMS package. We evaluated the performance of the nomogram by comparing the predicted and actual survival outcomes using a modified Hosmer–Lemeshow test. The results demonstrated good consistency between the predicted and observed survival probabilities, indicating the reliability of the nomogram.

Functional and pathway abundance in risk prognosis signs

The enrichment pathways between the two groups were significantly more frequent when conducting GSEA using GSEA software 4.1.2 (http://www.gsea-msigdb.org/gsea/index.jsp). We considered an FDR of 0.25 and a p value of 0.05 statistically significant thresholds. We utilized the gridExtra, GRID, and ggplot2 R packages to visualize the results.

Functional enrichment analysis of N7-methylguanosine associate 9d lncRNA predictive signaling

Patients with gastric cancer were classified into high-risk and low-risk groups based on their median risk score. We used GSEA 4.1.2 (available at www.broad.mit.edu/gsea/) to identify the enriched pathway genes between these two groups. A statistical significance threshold of FDR 0.25 and a p value 0.05 was applied. Furthermore, we calculated patients' immune pathways and immune cell explicit score using ssGSEA gsa software.

Statistical analysis

All statistical analyses were performed using R software (version 4.1.2). The Wilcoxon method detected differentially expressed genes related to N7-methylguanosine in gastric cancer tissues. Univariate Cox regression was used to examine the association between overall survival and N7-methylguanosine-related DEGs. Furthermore, multivariate Cox analysis was used to screen N7 -methylguanosine-related genes and generate prognostic signatures. We used the log-rank test and Kaplan–Meier method to evaluate overall survival in the two gastric cancer patients. The "GSVA" package was employed for ssGSEA.

Results

Enrichment analysis of m^7G-related genes

Figure 2 represents the genes related to m^7G, amounting to six genes (Fig. 2A). KEGG pathway analysis revealed that the majority of these m^7G-correlated genes were involved in processes such as the p53 signaling pathway, progesterone-mediated oocyte maturation, human immunodeficiency virus type 1 infection, cell cycle, IL-17 signaling pathway, osteoclast differentiation, oocyte meiosis, cellular senescence, viral carcinogenesis, and MAPK signaling pathway (Fig. 2B). Additionally, GO analysis of the biological processes related to these differentially expressed genes (DEGs) showed their involvement in G2/M phase transition in the positive regulation of cell cycle and mitotic cell cycle, purine and ribonucleotide catabolism, positive regulation of fibroblast proliferation, response to metal ions, and inositol metabolism. The DEGs were primarily enriched in the outer kinetochore, chromosomal region, spindle, protein kinase complex, transcription repressor complex, and transferase complex in the cellular component category. The molecular function category showed that the primary components of DEGs were involved in protein connector enzyme join protein kinase activity, DNA transcriptional activity, lapidated dinocarric oxygen activity, R-Smad bond, and cell cycle-dependent serine/cell cycle-dependent transcription factor bond, threonine kinase activity, Na bond transfer activity, RNA polymerase II-specific DNA bonding transfer activity, and CAMP reaction.

Construction of predictive signatures for m^7G-associated lncRNA

After performing univariate regression analysis on the TCGA training set, 870 lncRNAs were associated with m^7G. Lasso analysis was conducted on these lncRNAs and lncRNAs in STAD to prevent overfitting and

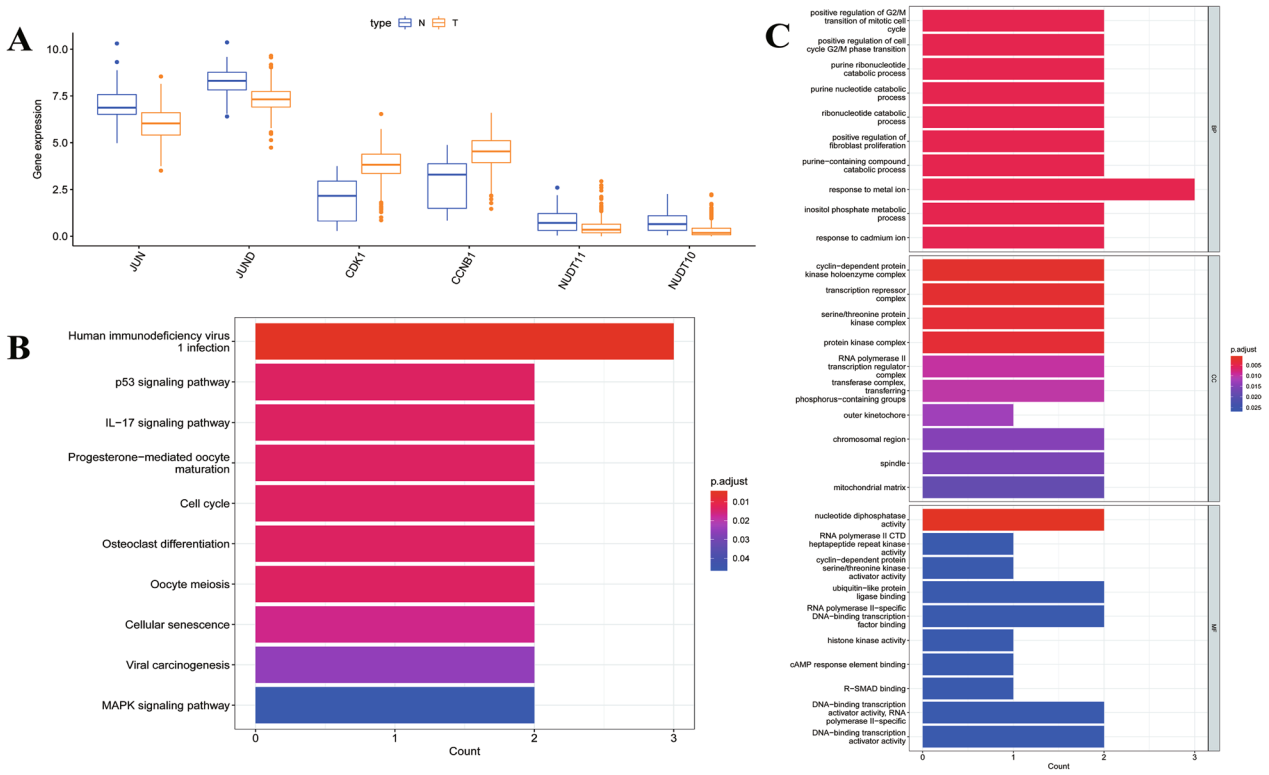

Fig. 2 m^{7}G-associated illnesses in cancer and surrounding tissues: a GO and KEGG investigation. **A** Chart for genetic difference analysis, **B** KEGG study of ailments linked to m^{7}G. **C** GO analysis of conditions related to m^{7}G. Gene ontology, Kyoto Encyclopedia of Genes and Genomes, differentially expressed genes, fold alterations, and KEGG are acronyms for these terms. CC, cellular components; MF, molecular function; BP, biological process

increase the precision and interpretability of prognostic markers. Using multifactorial Cox regression analysis, four lncRNAs (AC005586.1, AL161785.1, AP003392.1, and AC092574.1) were selected to generate four predictive features (Fig. 3A).

Cytoscape and galluvial R tools were utilized to visualize the lncRNAs, and five lncRNA-mRNA pairs with $|r2|>0.4$ and $p<0.001$ were identified (Fig. 3B). There were two m^{7}G-related genes (SRRT, WDR4) co-expressed with AC005586.1, while AC092574.1 was co-expressed with one m^{7}G-related gene (EIF4G1), AL161785.1 was co-expressed with one m^{7}G-related gene (DCP2), and AP003392.1 was co-expressed with one m^{7}G-associated gene (PNP). To calculate the risk score, the expression levels of these lncRNAs were weighted using the coefficients obtained from Cox regression analysis. The formula for the risk score was: risk score = (0.60AL161785.1 expression) + (−0.68AP003392.1 expression) + (−0.57AC005586.1 expression) + (−0.47AC092574.1 expression). Sankey diagrams were then used to visualize the results (Fig. 3C).

Correlation between predicted signs and prognosis in patients with STAD

The study employed an algorithm that learned and categorized patients' risk scores into high-risk and low-risk groups (Fig. 4). The Kaplan–Meier approach was utilized to predict patient outcomes, and the practice period for the low-risk groups was longer than that of high-risk groups, demonstrating its effectiveness. The risk score was a significant predictor of patient mortality, confirmed as an independent prognostic factor for gastric cancer patient OS in COX multifaceted regression analysis. The risk score's AUC was 0.716 (Fig. 4G), higher than clinical variables in predicting STAD patient prognosis. Disparities in N, M, T stages, stage, grade, and fustat were found between high-risk and low-risk groups based on variations in clinicopathological characteristics. The study built a columnar diagram of clinical-pathological factors and the risk score to predict STAD patients' prognosis for 1, 2, 3, and 5 years

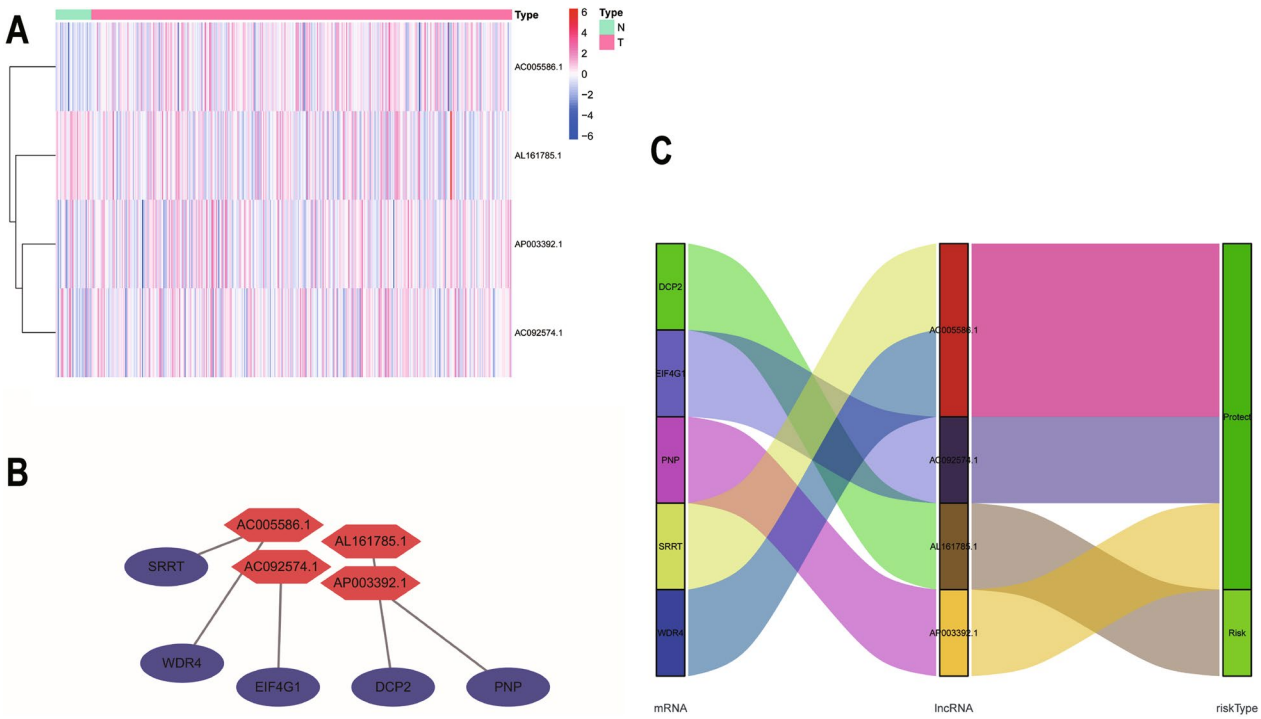

Fig. 3 Study of lncRNAs with prognostic significance in a single variable. **A** After prognosis, the co-expression network of lncRNAs is related to m^7G. **B** m^7G-based prognostic lncRNAs Sankey diagram. **C** Head and neck squamous cell carcinoma; long non-coding RNAs; N, normal; T, tumor

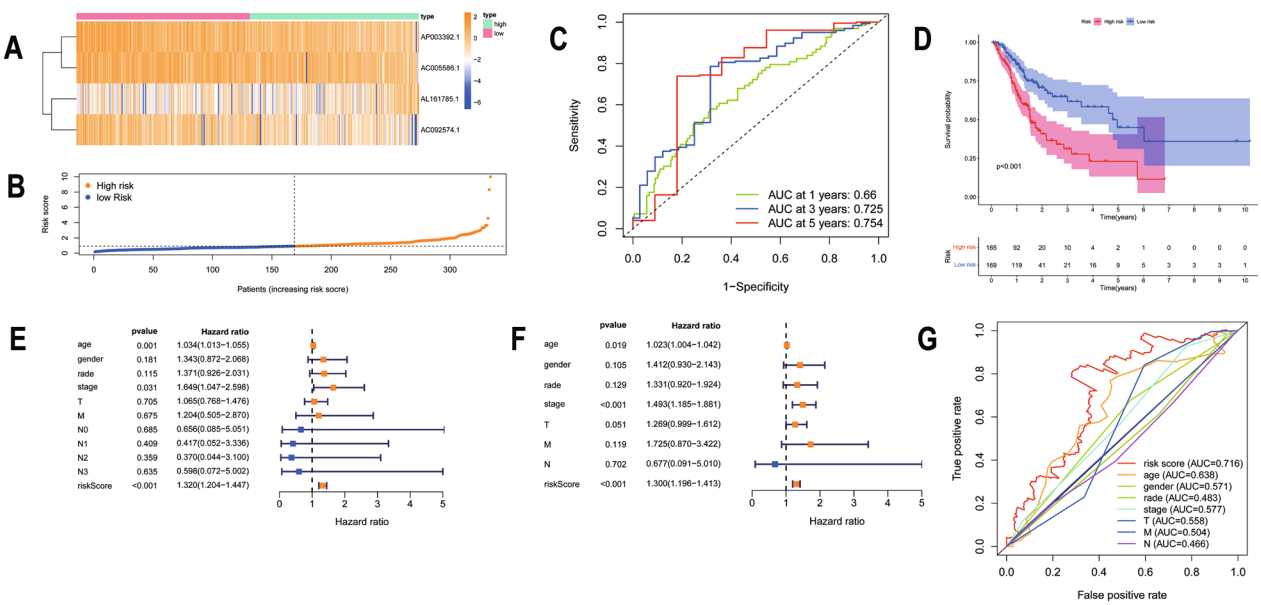

Fig. 4 Heatmap of lncRNA groups with high and low risk. **A** OS rates for STAD patients in the high-risk and low-risk categories, according to a Kaplan–Meier analysis. **B** For predicting signed 1-, 3-, and 5-year survival using ROC curves and AUC. **C** Relationship between STAD patients' prognosis and predicting characteristics. **D** Analyses of univariate Cox regression using a forest plot. **E** Multivariate Cox regression analysis using a forest plot. **F** Risk scores' ROC curves concerning clinicopathological factors. **G** Stomach adenocarcinoma; overall survival; characteristics of the subject work; area under the curve; tumor; and lymph node

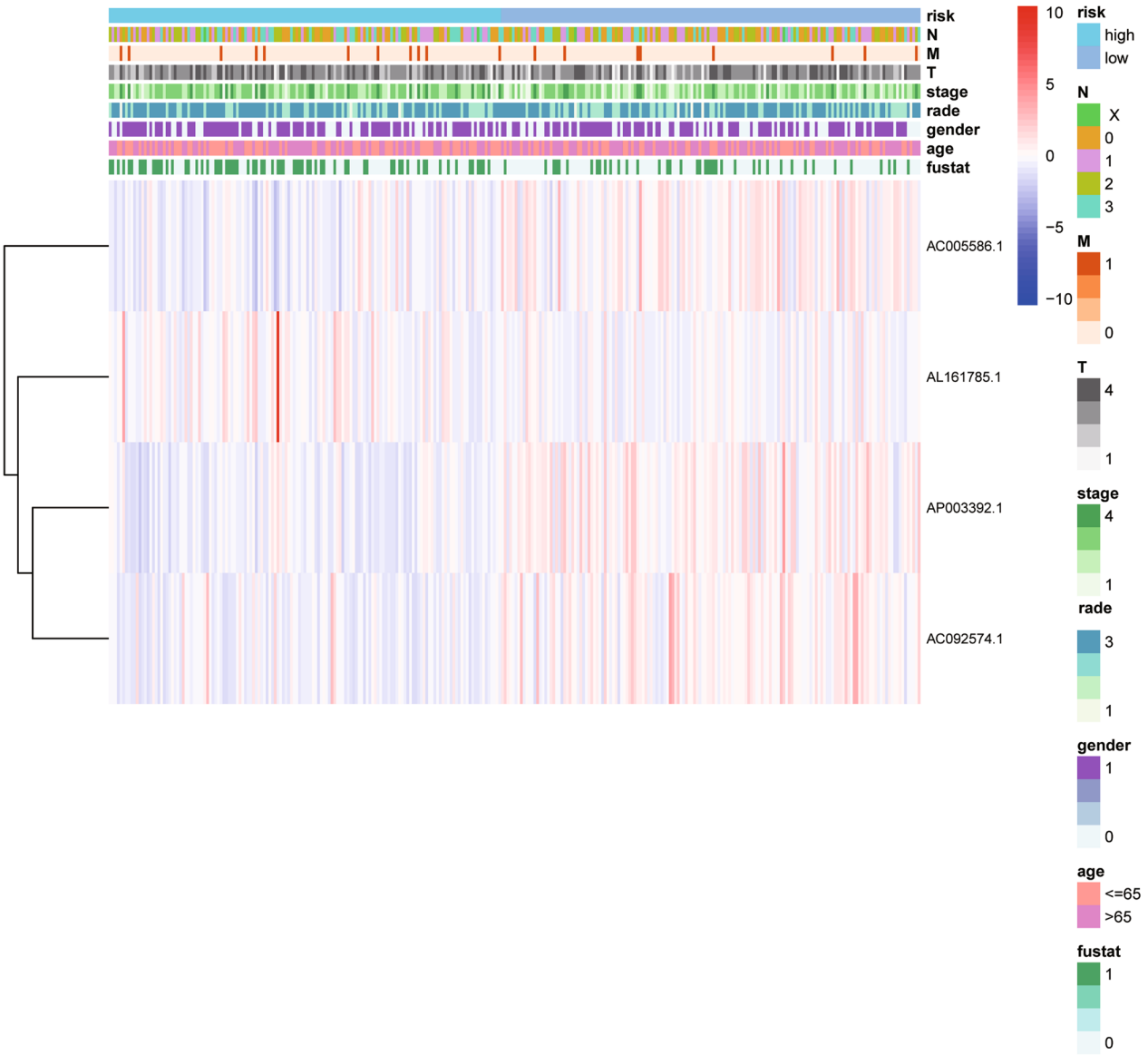

Fig. 5 The heatmap illustrates the distribution of seven m^{7}G-associated clinicopathological factors and prognosis-related lncRNAs in the high-risk and low-risk groups. N, lymphatic metastasis; M, metastasis; T, tumor; lncRNAs, long non-coding RNA

(Fig. 5). The actual OS rate and the expected survival period matched these periods (Fig. 6).

Relationship between different clinicopathological variables predicting the signs and prognosis of patients with STAD

We analyzed the impact of clinicopathological characteristics on the prognosis of gastric cancer patients by examining their OS based on age, gender, division, installment payment, T installation payment, and risk scores. In each category, we found that patients in the high-risk group had a significantly shorter OS than those in the low-risk group (Figs. 7A–U). Our results suggest that the risk score may be an independent prognostic factor in STAD patients, irrespective of other clinicopathological factors.

Internal validation of predictive signatures

The study involved splitting 443 STAD patients into two groups to test the effectiveness of OS prediction features using a comprehensive TCGA dataset. Patients in the high-risk group had lower OS rates following their initial internal surgery than those in the low-risk group, consistent with the entire dataset's findings. The prognosis was worse for the high-risk group

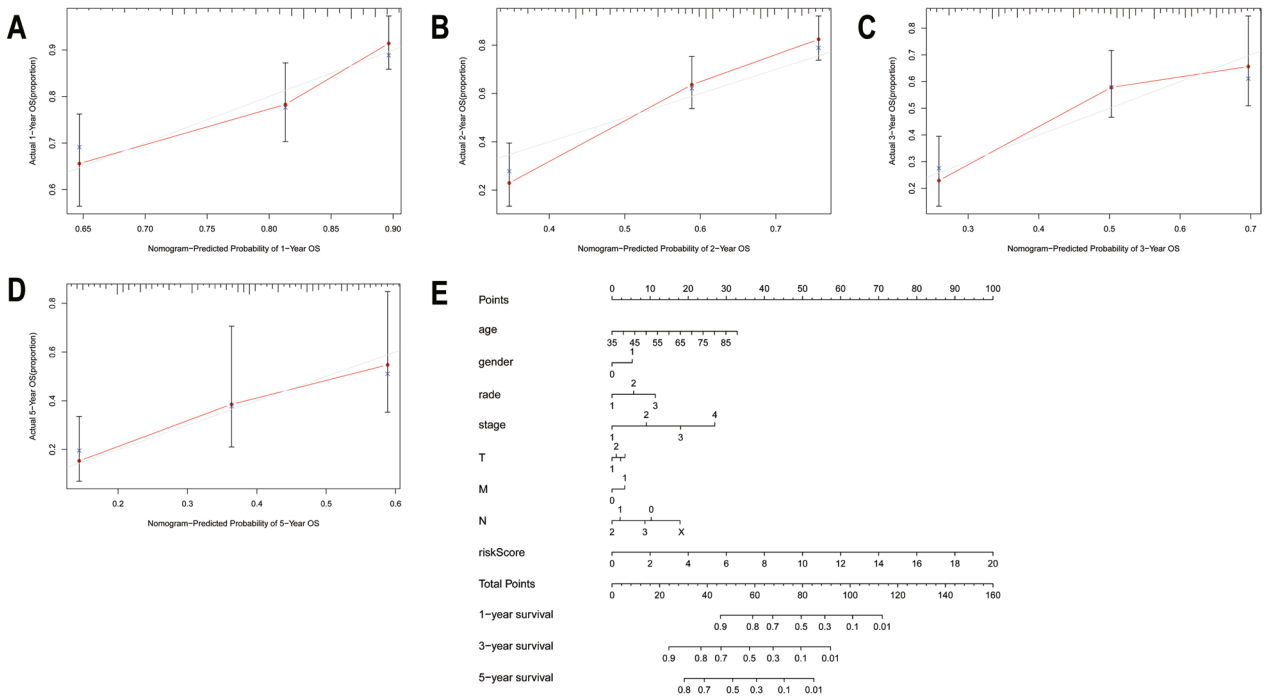

Fig. 6 The agreement between the actual OS rates and the anticipated survival at 1, 2, 3, and 5 years is tested using calibration curves. The nomogram's construction and verification (**A**–**D**). Nomogram used a combination of clinicopathological, pathological, and risk ratings to forecast survival at 1, 3, and 5 years in patients with STAD. (**E**) Head and neck squamous cell cancer; N, lymph nodes; OS, overall survival

than the low-risk group (Figs. 8B, C). Similar results were observed in the second internal queue (Figs. 8E, F). The ROC curve analysis of the two groups showed good predictive accuracy. The AUC of the first internal queue for 1, 3, and 5 years of survival was 0.748, 0.745, and 0.736, respectively (Fig. 8). The AUC of the second internal queue for 1, 3, and 5 years was 0.553, 0.69, and 0.737, respectively (Fig. 8D).

Immune cell infiltration and immune-related pathways

The final results indicate significant differences in B cells, neutrophils, tumor-infiltrating lymphocytes (TILs), antigen-presenting dendritic cells (ADCs), regulatory T cells (TREGs), large cells, plasmacytoid dendritic cells (PDCs), dendritic cells (DCs), TH1 cells, macrophages, and natural killer (NK) cells between high-risk and low-risk groups in patients with gastric cancer (Fig. 9A). Additionally, in the high-risk group, there are elevated levels of APC co-stimulation, T cell co-stimulation, human leukocyte antigens (HLAs), secondary inflammation, APC signal suppression, type II interferon (IFN) response, chemokine receptors (CCRs), T cell co-suppression, type I IFN response, immune checkpoints, and major histocompatibility complexes (MHCs) (Fig. 9B). These results suggest that the immune system of high-risk patients with gastric cancer is less active than that of low-risk patients. Based on the risk model, many patients with gastric cancer may benefit from immune checkpoint inhibitors (Fig. 9C).

Discussion

More than 1 million people are diagnosed with gastric cancer each year, making it one of the most common illnesses and the third leading cause of cancer death [1]. Currently, systemic chemotherapy and surgery are the primary therapeutic options for individuals with stomach cancer. Additionally, targeted therapy, radiation, and immunotherapy are gradually being employed, but the 5-year survival rate for those with stomach cancer remains insufficient [14]. Cancer is the leading cause of mortality worldwide, and stomach cancer continues to have a significant prevalence. The majority of stomach cancers are discovered to be advanced or metastatic due to the absence of effective screening methods and particular symptoms [15]. Chemotherapy-based medications are the mainstay of treatment for this type of gastric cancer. Recently, scholars have shown considerable interest in immunotherapy, and some patients with stomach cancer may find it helpful [16]. Immunotherapy offers advantages over traditional chemotherapy, including long-lasting efficacy, extended survival, low toxicity,

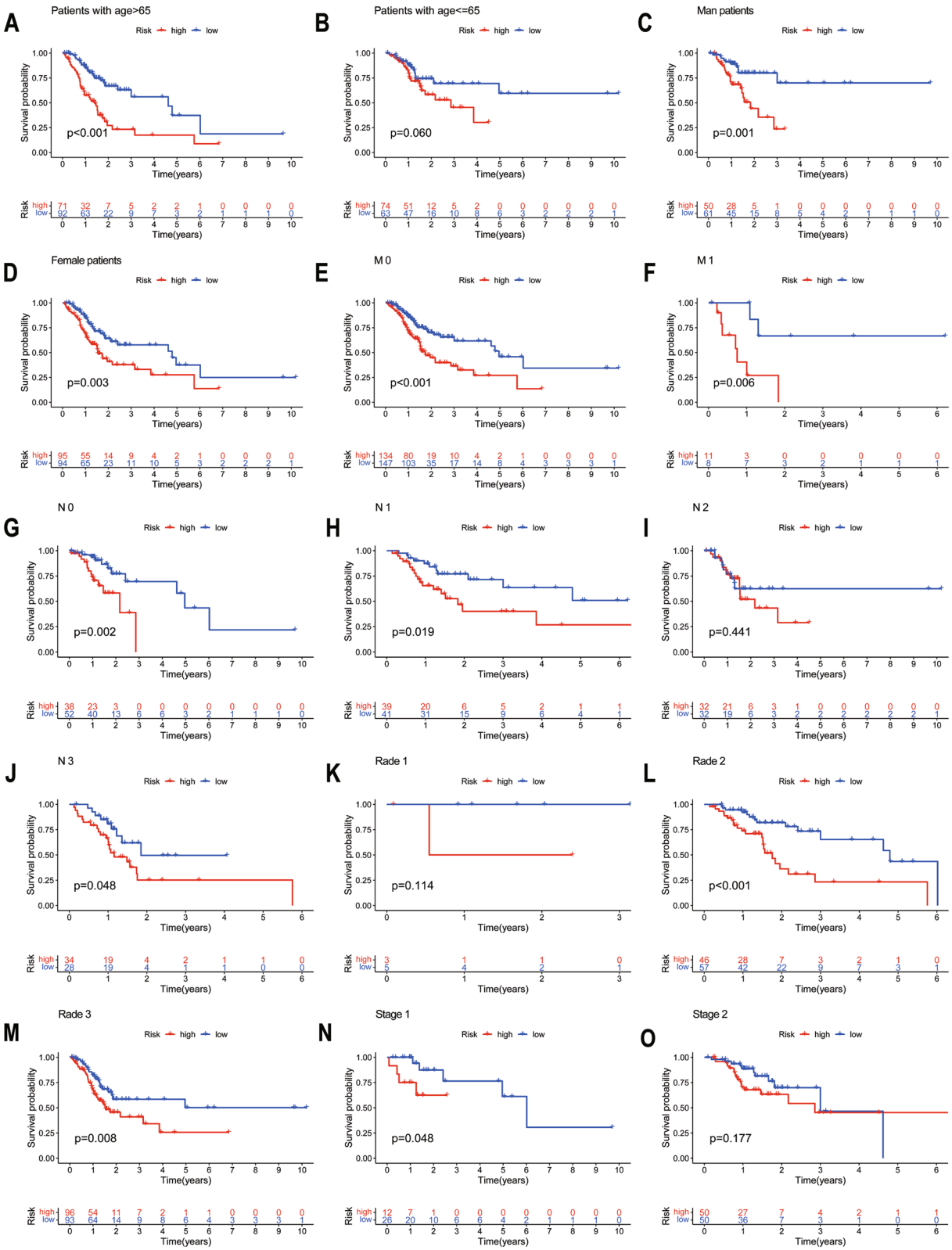

Fig. 7 Various clinicopathological factors were used to categorize the Kaplan–Meier survival curves for patients in the high-risk and low-risk groups. Age (**A**, **B**), sex (**C**, **D**), Rade (**K**–**M**), Stage (**N**–**Q**), Stage (**G**–**J**), N Stage (**E**–**F**), and T Stage (**R**–**U**). N, lymph nodes; T, tumor

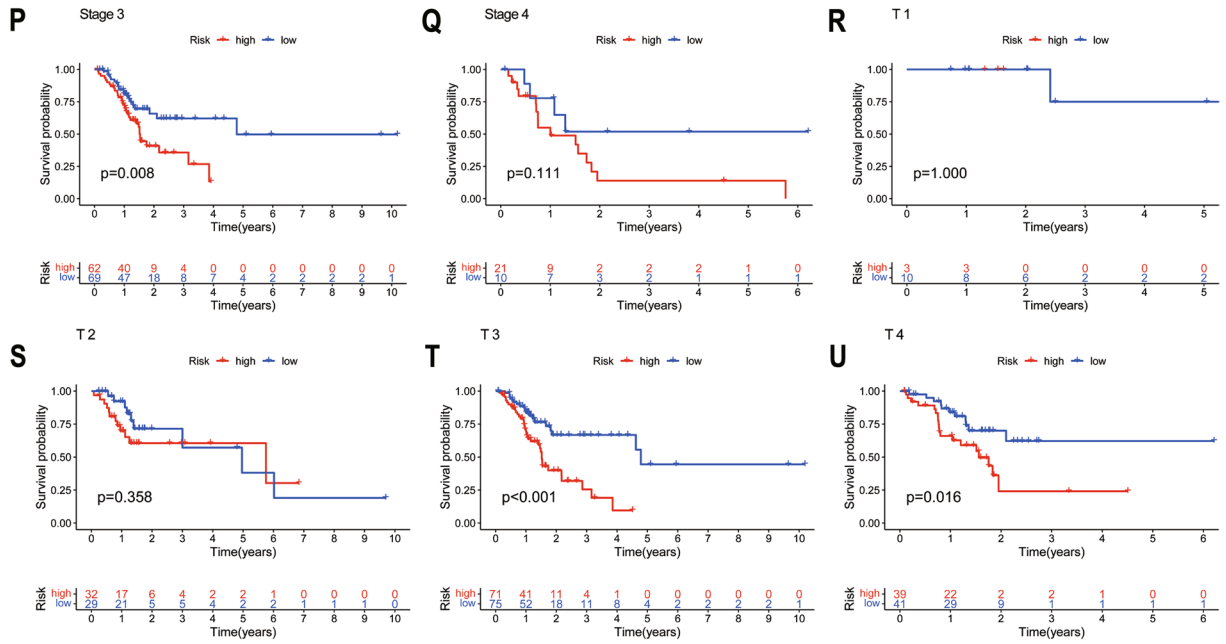

Fig. 7 continued

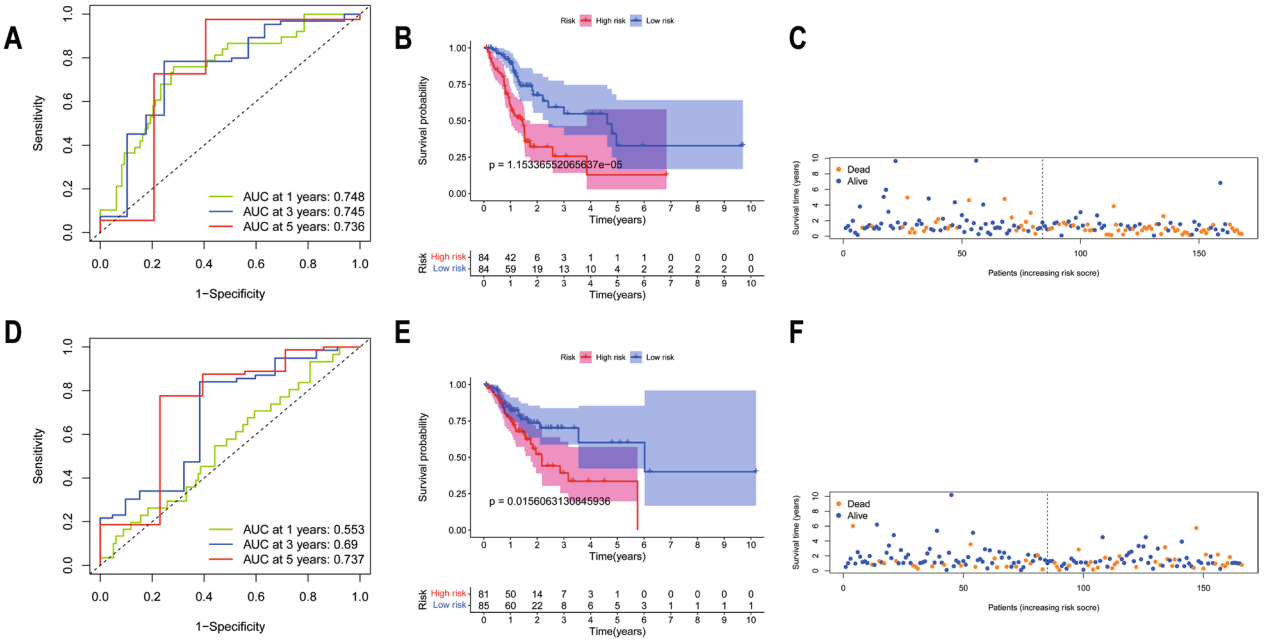

Fig. 8 ROC curves and AUC for the first internal cohort's 1-, 3-, and 5-year survival. **A** Based on the whole TCGA dataset, OS anticipated signatures were internally validated. In the first internal queue, the Kaplan–Meier survival curve. **B** OS scatter plot for the first internal queue. **C** ROC curves and AUC for the second internal cohort's 1-, 3-, and 5-year survival. **D** Two-year internal cohort Kaplan–Meier survival curves. **E** Internal second queue OS scatter plot. **F** TCGA, or the Cancer Genome Atlas, is the area under the curve, overall survival, and roc, or subject working characteristic

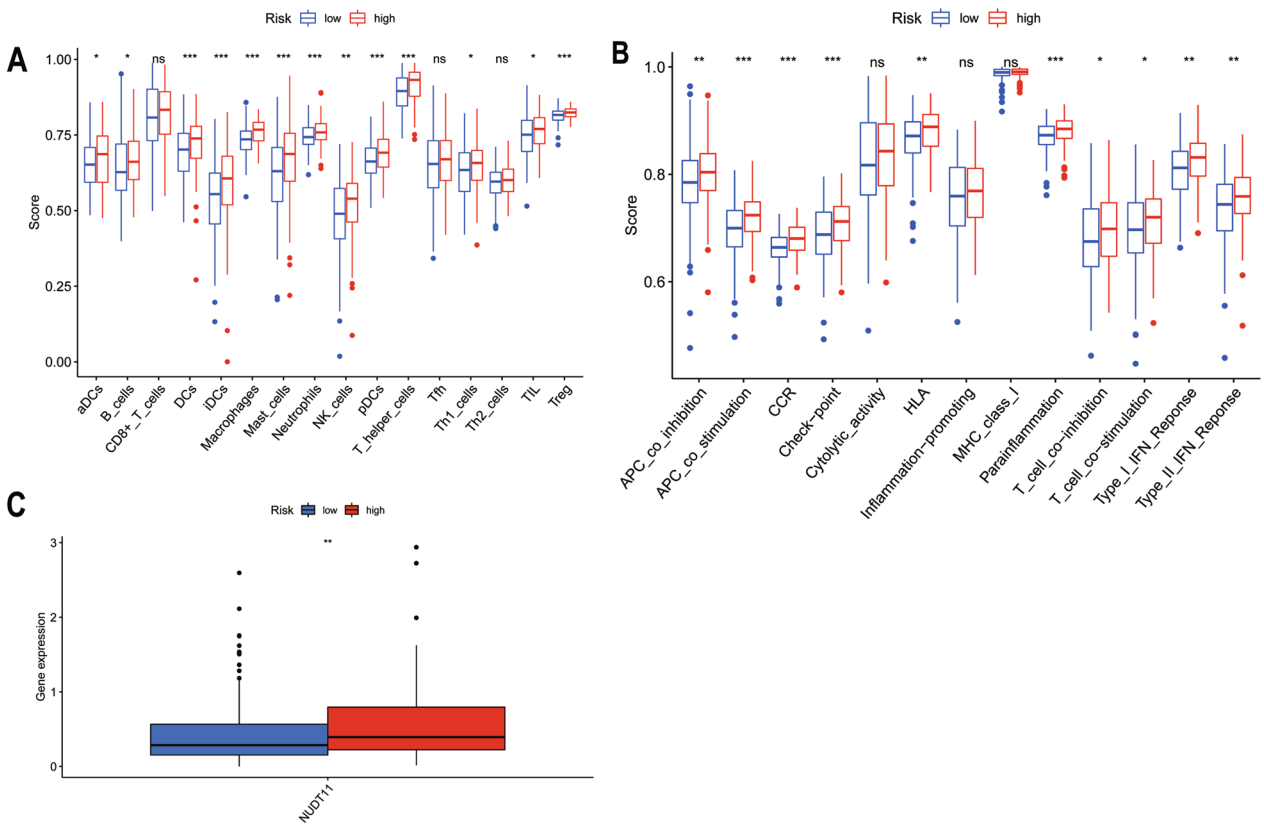

Fig. 9 Scores for immune-related function and infiltration cells in high- and low-risk groups. The ssGSEA algorithm was used to determine the infiltration levels of 16 immune cells in the high- and low-risk groups (Fig. 1A). **B** Correlation between 13 immune-related functions and prognostic factors. Immune checkpoints' varying expression in the risk categories. **C** Single gene set concentration analysis (ssGSEA); ADC stands for activated dendritic cells; IDCs for immature dendritic cells; NK stands for natural killer cells; PDDC for plasmacytoid dendritic cells; Tfh for T follicular helper cells; Th1 for T helper cell type 1; Th2 for T helper cell type 2; TIL for tumor-infiltrating lymphocytes; Treg for T regulatory cells; APC for antigen-presenting cells; CCR for N.S., not significantly expressed; $*p < 0.001$; $**p < 0.01$

and favorable effects on brain metastases. Preclinical antitumor investigations have demonstrated the success of treatments targeting other immune cells. Therefore, immune cell-targeted therapy is emerging as the most effective treatment for gastric cancer [17].

Despite having distinct advantages as biomarkers and potential therapeutic targets, ncRNAs face challenges. For instance, there is still vast unexplored territory in ncRNA research, and the development of next-generation sequencing methods will be necessary to investigate new roles [18]. A growing body of evidence supports the idea that post-transcriptional modifications to RNA and interference with associated translational control play a crucial role in tumorigenesis. In one study, the development of tRNA-derived fragments (tRFs) in stomach cancer is discussed, along with the roles of TRFs in controlling gene expression, such as the inhibition of translation, cell differentiation, proliferation, and the associated signal transduction pathways. This discovery advances research into potential gastric cancer biomarkers and sheds light on the role that alterations in tRNA modifications play in the growth of gastric cancer [19]. While predicting the prognosis of gastric cancer patients by generating lncRNA predictive signals related to m^7G has been documented, forecasting the development and progression of head and neck cancer through a novel NRl-ncRNA-based prognostic signal has not been explored. In the current study, we aimed to create a unique NRl-ncRNA-based prognostic and validate its clinical utility as an immunotherapeutic and predictive factor, guiding clinicians.

Notably, lncRNAs are implicated in the onset and progression of numerous illnesses, including cancer [10]. Recent studies have examined the aberrant lncRNA expression as a diagnostic and prognostic marker [20]. A recent study utilized electronic screening for differentially expressed lncRNAs and confirmation in GC patients and healthy controls to demonstrate a link between specific single nucleotide polymorphisms (SNPs) in lncRNAs and decreased GC risk [21]. Additionally, it was revealed that

the lncRNA expression level in gastric cancer tissue correlated with tumor characteristics such as tumor depth, distant transition, lymph transfer, and clinical installment payment [22, 23].

Little research has been done on the potential therapeutic role of lncRNA linked to m^7G in managing STAD. Therefore, by learning more about lncRNAs, we can understand the role of m^7G and lncRNAs in immunotherapy [24]. lncRNAs have been discovered to be reliable cancer indicators. Therefore, merging patients with m^7G-related lncRNAs can enhance clinical prediction and diagnosis. It has been suggested that alteration of the m^7G gene contributes to the emergence of several illnesses [25]. Numerous biological processes related to tumors involve m^7G methylation, which is intimately linked to tumorigenesis [26].

Infection with human immunodeficiency virus type 1, the p53 and IL-17 signaling pathways, progesterone-mediated oocyte maturation, the cell cycle, osteoclast differentiation, oocyte meiosis, cellular senescence, viral carcinogenesis, and the MAPK signaling pathway were the main areas where DEGs were enriched, according to KEGG analysis. According to one study, exogenous IL-17B and IL-17RB combined facilitated the growth and migration of gastric cancer, and higher IL-17Rb expression was linked to a poor prognosis in this kind of cancer [27]. Additionally, it has been discovered that cellular senescence is accompanied by a second characteristic: the development of functional alterations that permit cells to proliferate uncontrollably. Additionally, due to genetic instability, deadly tumors are better able to spread, move to, and colonize ectopic sites, endure in hostile tissue settings, and avoid immune system response [28]. Various feasible targets have been tested in the clinical treatment of cancer, indicating the feasibility of the MAPK pathway, which has been recognized as the most efficient target. However, stress-activated MAPK pathways, like JNK and p38, have a crucial regulatory function and can change how cancer cells react to chemotherapy and targeted therapies [29].

One of the most common RNA modifications is N7-methylguanosine (m^7G), typically found at the 5′ end and internal sites of eukaryotic mRNAs or inside all species' rRNAs and tRNAs [30]. Methyltransferase-like 1(METTL1), which binds to its equivalent cofactor WD repeat structural domain 4 (WDR4) and places m^7G modifications in tRNA, miRNA, and mRNA, is the most researched m^7G regulator in mammals [31]. Relevant lncRNAs were linked to clinicopathological traits in gastric cancer patients. Most of these parameters (61.70% and 53.19%) were related to invasion and metastasis, respectively. These lncRNAs linked to stomach cancer can be employed as biomarkers for the spread of the disease [32]. In this research, we discovered four lncRNAs linked to m^7G (AC005586.1, AL161785.1, AP003392.1, and AC092574.1).

The latest progress of immune test-inhabitants (ICIS) opens the road to a new era of cancer immunotherapy and represents the turning point for cancer treatment [33]. It is only a matter of time before new methods are created to support the immune control of tumors and the effectiveness of immunotherapy. In the current study, we studied and analyzed immune function, immune cell infiltration, and KEGG pathway enrichment and understood the association between time and m^7G-associated lncRNAs. Compared with the high-risk and the low-risk groups, there were significant differences in Th1 cells, neutrophils, B cells, pDC, T helper cells, mast cells, TIL, Treg, iDC, NK cells, DC, macrophages, and aDC between the two groups. Compared with the low-risk group, the high-risk group had lower levels of APC co-stimulation, T cell co-inhibition, IFN response type, MHC class I, APC co-inhibition, II IFN response CCR, pain-inflammation, HLA, T cell co-stimulation, and checkpoint. The low-risk group showed a higher response type and II IFN response than the high-risk group.

Regarding type II IFN response and response types, the high-risk group was lower than the low-risk group. Immunocheckpoint studies have shown that high-risk groups are relatively more active, and immunocheckpoint inhibitors can be used as a clinical treatment for patients with head and neck cancer. Our work has limitations and uses data from the TCGA database, which is a drawback. It is crucial to determine how to most effectively link the relationship between m^7G-related lncRNAs and STAD for upcoming in vivo or in vitro studies.

Conclusion

This study used clinical data and transcription from the TCGA database to construct four m^7G lncRNA risk models for STAD patients. The risk model demonstrated a favorable prognosis and was identified as an independent prognostic factor for STAD. The study also investigated the impact of the risk models on tumor mutation frequency, the immune microenvironment, and immunotherapy response. The findings suggest that m^7G-related lncRNA risk models could be valuable in predicting prognosis and immunotherapy response in STAD patients. By elucidating the mechanisms of action of M^7G-related lncRNAs, these models offer insights into the immunotherapy of STADs. However, further research is necessary to determine which patients will benefit most from these m^7G-related lncRNAs.

Abbreviations

STAD	Stomach adenocarcinoma
m7G-RNAs	M7G-associated lncRNAs
OS	Overall survival
DEGs	Differentially expressed genes
AUC	Area under curve
SNPs	Single nucleotide polymorphisms
TILs	Tumor-infiltrating lymphocytes
ADCs	Antigen-presenting dendritic cells
TREGs	Regulatory T cells
PDCs	Plasmacytoid dendritic cells
DCs	Dendritic cells
NK	Natural killer
HLAs	Human leukocyte antigens
IFN	Interferon
CCRs	Chemokine receptors
MHCs	Major histocompatibility complexes

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Not applicable.

Author contributions
SXZ involved in designing research plans, feasibility analysis, collated documents, collation and analysis of original results, data analysis, and curating, writing, and editing papers. WBZ involved in data analysis, collated documents, collation and analysis of original results, data analysis and curating, and reviewing papers. CXY and YXT involved in feasibility analysis of research scheme, revising and reviewing papers. All authors agree to be responsible for all aspects of research work and ensure that the accuracy of any part of the paper or the integrity of scientific research issues are investigated and solved. All authors confirm the authenticity of all the raw data, read and approved the final manuscript.

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No.

Availability of data and materials
The data on which the study is based were accessed from a repository and are available for downloading and analyzing date through the following link (https://portal.gdc.ancer.gov/; https://www.genecards.org/; https://www.perl.org; http://www.gsea-msigdb.org/gsea/index.jsp; www.broad.mit.edu/gsea/).

Declarations

Ethical approval and consent to participate
The data were obtained from publicly available websites. This study did not involve human or animal subjects, and thus, no ethical approval was required. The study protocol adhered to the guidelines established by the journal.

Consent for publication
All the authors agreed to submit the manuscript to Current Medical Science. My manuscript does not contain data from any individual person.

Competing interests
All authors disclosed no relevant relationships.

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