Original Article

Development of a novel colon adenocarcinoma m6A-related lncRNA pair prognostic model

Shengmei Liang[#], Xinze Qiu[#], Lulu Cai, Fangyou Wei, Jiean Huang, Shiquan Liu

Department of Gastroenterology, The Second Affiliated Hospital of Guangxi Medical University, Nanning, China

Contributions: (I) Conception and design: S Liang, X Qiu; (II) Administrative support: S Liu, J Huang; (III) Provision of study materials or patients: S Liang, X Qiu; (IV) Collection and assembly of data: S Liang, X Qiu; (V) Data analysis and interpretation: S Liang, X Qiu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Shiquan Liu, MD, PhD. Chief Doctor, Professor, Department of Gastroenterology, The Second Affiliated Hospital of Guangxi Medical University, No. 166 Daxuedong Road, Nanning 530007, China. Email: poempower@163.com.

Background: Colon adenocarcinoma (COAD) is among the most prevalent malignancies. Changes to N6-methyladenosine (m6A), the most common RNA modification, can affect how COAD develops. Furthermore, the involvement of long noncoding RNA (lncRNA) in COAD is significant, and it exhibits a close association with m6A modification. Nevertheless, the prognostic significance of lncRNAs that are related to m6A modification in COAD remains unclear. This study aims to establish a m6A-related lncRNA pair signature and reveal its prognostic value in COAD.

Methods: The current study utilized data from The Cancer Genome Atlas (TCGA) to investigate the predictive significance of m6A-related lncRNA pair signatures in COAD. The identification of m6A-related lncRNAs was conducted through co-expression analysis using the Pearson correlation coefficient. Then, the lncRNA pairs related to prognosis were identified using univariate Cox regression analysis. Receiver operating characteristic (ROC) curves were produced using the least absolute shrinkage and selection operator (LASSO) penalized with Cox analysis to predict overall survival (OS) in order to build a risk score prognostic model. The relationship among the risk scoring model and clinical characteristics, immune-related variables, and medication sensitivity was examined after identifying independent prognostic factors.

Results: Thirty-five of the 319 lncRNA pairings associated with m6A were linked to a pattern that predicted risk ratings. It was verified that the risk score model was a reliable predictor that stood alone from clinicopathological features. Differences between high- and low-risk groups were found in clinicopathological traits, immune-related variables, and medication sensitivity analysis according to correlation analyses.

Conclusions: Based on paired differentially expressed m6A-related lncRNAs, the proposed COAD prognostic model demonstrated potential clinical predictive value.

Keywords: Colon adenocarcinoma (COAD); M6A; lncRNA pairs; The Cancer Genome Atlas (TCGA); prognosis signature

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Introduction

Colorectal cancer (CRC) ranks as the third most prevalent cancer and is responsible for the second highest number of cancer-related fatalities globally (1). CRC consists of two primary types: rectal adenocarcinoma (READ) and colon adenocarcinoma (COAD). The majority of CRC cases are COADs, accounting for 80–90% of all pathological subtypes (2,3). Despite the fact that screening techniques are meant to increase early CRC identification, 25% of patients

are already in an advanced state at the initial diagnosis (4). A higher cancer stage is connected with a higher risk of death in colon cancer, compared to Stage I patient, Stage IV patient has an 8.86 times greater risk of death (5).

Long non-coding RNAs (lncRNAs) are a class of RNA molecules that are longer than 200 nucleotides in length, influence a number of biological functions, including tumor development and immune cell infiltration (6,7). More and more research shows that the dysregulation of lncRNAs is important in many malignancies, including CRC (8-11). For instance, SP1 transcriptionally activates the cancer-causing lncRNA THAP7-AS1 while METTL3-mediated m6A modification stabilizes it post-transcriptionally (9). Through integrin-mediated focal adhesion signaling, the lncRNA ITGB8-AS1 encourages CRC development and migration (11).

However, the mechanisms regulating lncRNA expression are yet unclear. Numerous studies have demonstrated that changes to m6A influence lncRNAs (12,13). The most frequent epigenetic methylation of mRNAs and non-coding RNAs (ncRNAs), N6-methyladenosine (m6A), has a significant effect on RNA translation, splicing, transportation, and stability (14,15). M6A regulators, which are made up of methyltransferases (writers), RNA-binding proteins (readers), and demethylases (erasers), control invertible and dynamic RNA epigenetic modification (16). Writers are made up of METTL3, METTL14, KIAA1429, RBM15, WTAP, and ZC3H13. Readers are made up of the proteins YTHDF1/2/3, YTHDC1/2, IGF2BP1/2/3, HNRNPC, and HNRNPA2B1. Erasers are made composed of ALKBH3, ALKBH5, and FTO to perform demethylation activity (17).

M6A enzymes and lncRNAs are both excellent prognostic and diagnostic biomarkers. In previous studies, m6A-related mRNAs and lncRNAs were found to be useful in predicting the prognosis for multiple cancers (18-20). For instance, Wang *et al.* created a signature to predict the prognosis of gastric cancer (GC) that contained 11 m6A-related lncRNAs with variably elevated levels (21). The area under curve (AUC) for 5-year overall survival (OS) was 0.94, indicating that the lncRNA signature has good predictive accuracy for GC. Additionally, Zhang *et al.* created the m6A-related lncRNA prognostic score (m6A-LRS), which predicted a poor prognosis for bladder cancer patients (22). The receiver operating characteristic (ROC) curves of m6A-LRS for 5-year OS prediction was 0.67, showing that the risk model was effective. LncRNA signature showed promising prognostic potential, but it was not perfect. To lessen batch effects between various testing platforms, specific levels of lncRNAs should be standardized prior to clinical use of the signature. Additionally, by pairing, iterating, and employing a novel modeling approach, Tang *et al.* discovered a ferroptosis-related lncRNA pair predictive signature in pancreatic ductal carcinoma (8).

In the current research, we created a brand-new m6A-related lncRNA pair predictive model for COAD. The model's relationships with clinicopathological traits, immune-related variables, and medication sensitivity analysis were exhibited. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1883/rc).

Highlight box

Key findings

- Our study identified a brand-new N6-methyladenosine (m6A)-related long noncoding ribonucleic acid (lncRNA) pair predictive model for colon adenocarcinoma (COAD).

What is known and what is new?

- The involvement of lncRNA and m6A modification in cancer are significant, they exhibit a close association.
- This is the first study of COAD the m6A-related lncRNA pair prognostic model.

What is the implication, and what should change now?

- Since the data used in this study came from The Cancer Genome Atlas, more research and access to other publicly accessible databases are necessary. Additional experimental confirmation is needed.

Methods

Data collection

Data for the COAD cohort, including mRNA sequencing data, lncRNA sequencing data, and clinical features of patients, were downloaded from the TCGA website (version 13-03-2022) (https://portal.gdc.cancer.gov). Patients with complete survival data in TCGA website were included. The training cohort and validation cohort were attained with a 8:2 ratio based on cases having survival data. Using information from a recent study, we were able to derive the expression matrix for 23 m6A RNA methylation regulators, including writers (METTL3, METTL14, METTL16, WTAP, VIRMA, RBM15, RBM15B, and ZC3H13), erasers (FTO and ALKBH5), and readers (YTHDC1, YTHDC2,

IGF2BP1, IGF2BP2, IGF2BP3, YTHDF1, YTHDF2, YTHDF3, HNRNPC, LRPPRC, HNRNPA2B1, FMR1, and RBMX) (16). Annotation of lncRNAs was acquired from GENCODE (https://www.gencodegenes.org/). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Investigation of m6A-related lncRNAs and matching of m6A-related lncRNAs with differential expression

Pearson correlation was used to determine the lncRNAs linked to m6A from the connection between m6A-related genes and long non-coding RNAs. The absolute value of the correlation coefficient greater than 0.4, and P less than 0.001 was considered statistically significant. $|\log_2 FC|$ more than 1.0 and false discovery rate (FDR) less than 0.05 were selected as significant criteria for differentially expressed m6A-related lncRNAs. After that, based on these differentially expressed m6A-related lncRNAs, we constructed m6A-related lncRNA pairings, as previously described (8). All m6A-related lncRNAs that were differently expressed were paired cyclically and assigned a value based on pairwise comparisons: assuming that lncRNA A and lncRNA B were coupled to form lncRNA pair C, which was assigned a value of 1 if lncRNA A's expression level was higher than lncRNA B's, and a value of 0 otherwise. An lncRNA pair was filtered if it had a 0 or 1 ratio of less than 20% or more than 80% across all samples. Cox regression analysis was used to determine the prognostic importance of m6A-related lncRNA pairs (P<0.01).

Building and evaluating a predictive signature for m6A-related lncRNA pairs

In the training cohort, prognostically correlated m6A-related lncRNA pairings were utilized to build the least absolute shrinkage and selection operator (LASSO) regression model. Then, for these m6A-related lncRNA pairings, we built a risk score model and computed the risk score for each patient as follows: Risk score = coefficient lncRNA $pair^1$ × expression lncRNA $pair^1$ + coefficient lncRNA $pair^2$ × expression lncRNA $pair^2$ + coefficient lncRNA $pair^3$ × expression lncRNA $pair^3$ +……+ coefficient lncRNA $pair^n$ × expression lncRNA $pair^n$. The risk score model was utilized to generate the 1-year ROC curve for predicting OS. Based on the median risk assessments, patients in the training and validation cohorts were separated into high- and low-risk groups. Survival curves were computed using the Kaplan-Meier method. In order to evaluate the stability of this model, a cross test was conducted using the validation cohort. We built the final model using data from the full cohort in order to get an accurate model with a bigger sample size. The ROC curves for 1, 3, and 5 years were calculated. As the ideal cut-off point for classifying various risk categories, the 1-year ROC curve's greatest inflection point was picked. Survival results and risk scores for each patient were anticipated using a risk assessment model of prognosis prediction. Furthermore, univariate and multivariate regression analyses were performed to determine if the model was an independent predictor of OS in COAD patients.

The risk score model's clinical correlation analysis and nomogram creation

The Chi-squared test was used to analyze the associations between the risk score model and conventional clinicopathological parameters, and the results were shown as a heatmap. The Wilcoxon signed-rank test was used to determine the risk score differences between several groups of these clinicopathological traits, and box diagrams were used to illustrate the results. Following are the labels for the P values: ***P<0.001, **P<0.01, and *P<0.05. The risk score model and clinicopathological variables were incorporated in the multivariate logistic model, which was used to produce a nomogram to estimate the survival rate of COAD patients.

Risk score model and immune-related component correlations

The Wilcoxon signed-rank test was used to determine whether there was difference in gene expression between the two risk score groups. To assess the relationships between the risk score and tumor-infiltrating immune cells (TIICs), we used a few widely used algorithms, including XCELL, TIMER, QUANTISEQ, MCPCOUNTER, EPIC, CIBERSORTABS, and CIBERSORT. The statistical significance was set at P<0.05.

Chemosensitivity prediction

Genomics of Drug Sensitivity in Cancer (GDSC) database (https://cancerrxgene.org) can be utilized to do large-scale drug screening. Combining genetic analysis with chemotherapy, medication responses can be systematically discovered. Based on the GDSC database, the half-

Table 1 The clinical characteristics of COAD patients in the TCGA dataset

Variables	Values (N=452)
Age (years)	
<65	169
≥65	283
Gender	
Male	214
Female	238
Stage	
I	76
II	178
III	125
IV	62
NA	11
T	
T0	0
Tis	1
T1	10
T2	77
T3	308
T4	56
N	
N0	269
N1	103
N2	80
M	
M0	334
M1	62
NA	56

COAD, colon adenocarcinoma; TCGA, The Cancer Genome Atlas; NA, not applicable; T, tumor; N, node; M, metastasis.

maximum inhibitory concentration (IC_{50}) of 30 commonly used chemotherapy drugs for gastrointestinal tumors was calculated, and an evaluation of this model's clinical use in the treatment of COAD was conducted. In the above steps, the R package "pRRophetic" was utilized. The Wilcoxon signed-rank test was then used to assess the difference in IC_{50} between the high-risk group and low-risk group. To illustrate the data, box drawings were generated in R using "pRRophetic" and "ggplot2" (23).

Statistical analysis

The HTSeq FPKM and simple nucleotide variation data were extracted and structured using Perl software (version 5.32). The differentially expressed lncRNAs were identified using the Benjamini-Hochberg technique based on the log fold change and FDR. The Kaplan-Meier method was used to evaluate the survival analyses of COAD patients based on the risk score model. The Cox regression model was used for multivariate analysis. The studies were carried out using R software 4.0.5 and Bioconductor packages.

Results

Data characteristics

The current study included 473 COAD and 41 adjacent healthy tissues with expression data. *Table 1* shows the clinical information for the patients (n=452), including age, gender, stage, T status, N status, and M status. Twenty-three m6A-related genes in total were obtained from one earlier article (16). There were 579 lncRNAs identified as m6A-related lncRNAs in total. After that, 243 of them were found to have differently expressed m6A-related lncRNAs (232 of which were upregulated and 11 of which were downregulated), which were displayed using a heatmap (*Figure 1A*) and a volcano plot (*Figure 1B*).

Creation of a predictive model with m6A-related lncRNA pair risk scores

A 0-or-1 matrix of 14,980 m6A-related lncRNA pairs was built for a more objective prognostic evaluation model that did not require normalization of individual expression values. Univariate Cox proportional hazards regression analyses indicated that 318 m6A-related lncRNA pairs were prognostic-associated lncRNA pairs. After performing LASSO regression analysis on the training cohort, a predictive signature containing 26 m6A-related lncRNA pairs was established. The risk score model's AUC for the 1-year survival rate in the training and validation cohort were 0.926 and 0.979, correspondingly (Figure S1A,S1B). In both the training cohort and the validation cohort, survival analyses revealed a substantial difference between the high- and low-risk groups (Figure S1C,S1D). Following that,

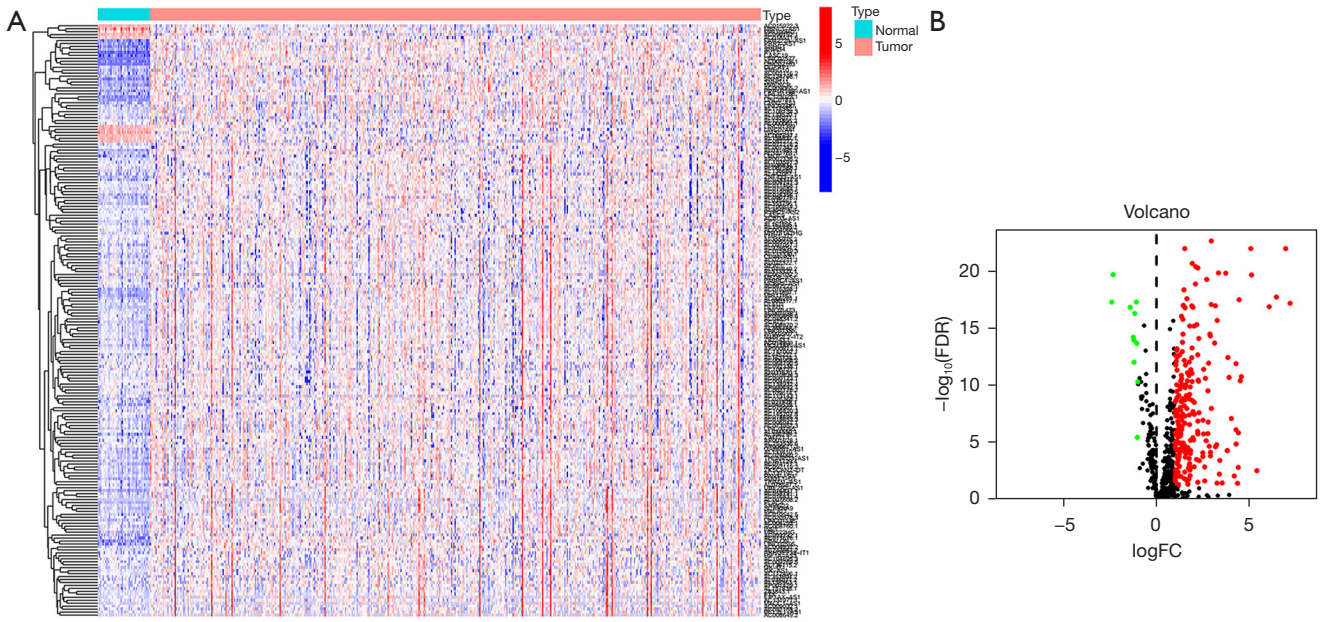

Figure 1 Differentially expressed m6A-related lncRNAs in COAD. (A) Differentially expressed m6A-related lncRNAs in COAD visualized by a heatmap; (B) differentially expressed m6A-related lncRNAs in COAD represented by a volcano plot. Red dots: m6A-related lncRNA is a risk factor for the prognosis of patients with COAD; green dots: m6A-related lncRNA is a protective factor for the prognosis of patients with COAD; black dots: no significant relationship between m6A-related lncRNAs and prognosis of COAD patients. FDR, false discovery rate; FC, fold change; lncRNA, long non-coding RNA; COAD, colon adenocarcinoma; m6A, N6-methyladenosine.

we built a risk score model using data from the complete cohort. A prognostic signature with 35 m6A-related lncRNA pairs was created after LASSO regression analysis (*Figure 2A-2C*). *Table 2* lists the 35 m6A-related pairs along with the appropriate calculation coefficients. LncRNAs sequences were acquired from GENCODE. For the 1-, 3-, and 5-year survival rates, the AUCs were 0.938, 0.933, and 0.930 (*Figure 3A*). Additionally, we determined that the ideal cut-off point on the 1-year ROC curve was the greatest inflection point of 20.296 (*Figure 3B*). Furthermore, the risk score model outperformed standard clinicopathological factors like age, gender, and stage in predicting the OS of COAD patients, according to our findings (*Figure 3C*).

Clinical connection of the prognostic model and prediction evaluation

Using the previously established cut-off point, 344 patients were assigned to the low-risk group and 82 to the high-risk group. According to the risk assessment model for prognosis prediction, there were more deaths as the risk score rose (*Figure 4A,4B*). Analysis of survival data showed that the high-risk group had significantly lower OS than the low-risk group (*Figure 4C*). In the univariate analysis, age (P=0.09), T status, N status, M status, and risk score model were found to be significant risk factors (all P<0.001) (*Figure 4D*). Multivariate analysis supported the risk score model (P<0.001), T status (P<0.001), and M status (P=0.03) as independent predictive variables (*Figure 4E*). Additionally, the risk score model was substantially correlated with the T status, N status, M status, and stage, according to our findings (*Figure 5*). Furthermore, a precise predictive nomogram using the risk score model and typical clinicopathological traits was developed for predicting 1-, 3-, and 5-year OS probabilities. This nomogram could be useful in the clinical assessment of COAD patients (*Figure 6*).

Correlations between the risk score model and immune-related factors

In consideration of the increasing evidence on the correlation between immunological features and survival in malignant tumors, the correlation between risk score model and TIICs was investigated. The results showed that the high-risk group was associated with $CD8^+$ T cells, $CD4^+$ T cells, and macrophage, whereas the low-risk group was associated with neutrophils, B cells, and NK cells (*Figure 7*).

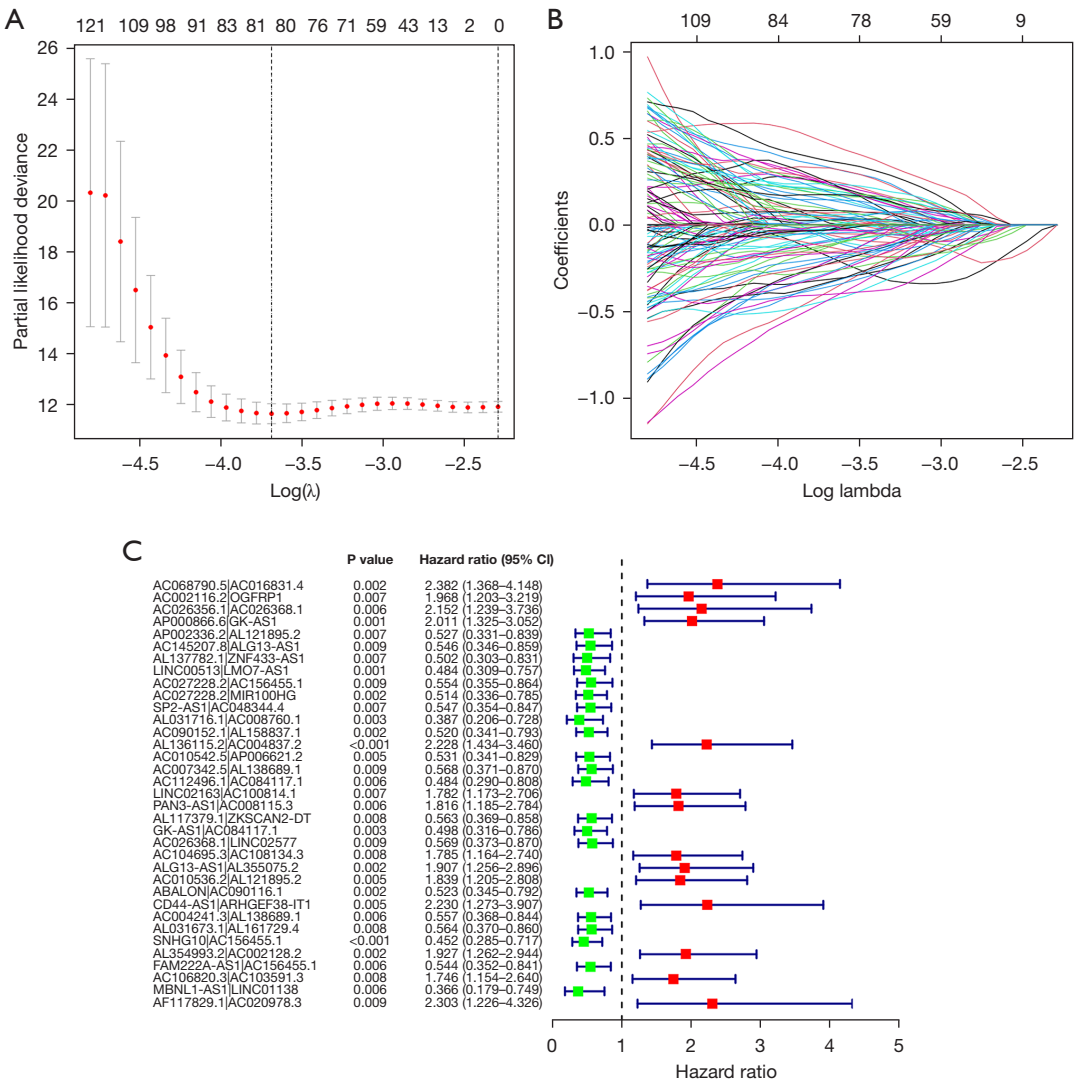

Figure 2 Creation of a prognostic model with m6A-related lncRNA. (A,B) Creation of a prognostic model based on LASSO regression analysis; (C) univariate Cox regression analysis. 95% CI, 95% confidence interval; m6A-related lncRNAs, N6-methyladenosine-related long non-coding RNAs; LASSO, least absolute shrinkage and selection operator.

Correlations between the risk score model and sensitivity to anticancer drugs

In order to determine potential treatment modalities for COAD, the sensitivity to 30 common anticancer drugs between the high- and low-risk groups were compared (*Figure 8A*). According to the findings, patients in high-risk groups had lower IC_{50} values for the Food and Drug Administration (FDA)-approved antitumor medicines rapamycin, lenalidomide, embelin, and dimethyloxallyl glycine (DMOG) (*Figure 8B*). In this context, these drugs have the potential to be applied in the treatment for COAD patients in the high-risk group in the future.

Discussion

m6A is an RNA modification that interacts with mRNAs and lncRNAs, and affects almost all biological functions of tumor cells. For example, METTL14, an m6A writer, is relevant to CRC progression by modulating SOX4 expression (24). Recent study found that LINC00460 improved HMGA1 mRNA stability and protein expression by directly interacting with IGF2BP2 and DHX9 to bind

Table 2 The list of lncRNA pairs and corresponding calculation coefficients

lncRNA pair	Coefficient
AC068790.5|AC016831.4	0.858997115
AC002116.2|OGFRP1	0.742623573
AC026356.1|AC026368.1	0.903499701
AP000866.6|GK-AS1	1.418833278
AP002336.2|AL121895.2	−0.742888613
AC145207.8|ALG13-AS1	−0.607202023
AL137782.1|ZNF433-AS1	−1.564661653
LINC00513|LMO7-AS1	−1.460502637
AC027228.2|AC156455.1	−0.654081795
AC027228.2|MIR100HG	−0.775889553
SP2-AS1|AC048344.4	−0.833135322
AL031716.1|AC008760.1	−0.896116458
AC090152.1|AL158837.1	−0.913222126
AL136115.2|AC004837.2	1.150803418
AC010542.5|AP006621.2	−0.866521051
AC007342.5|AL138689.1	−0.477772369
AC112496.1|AC084117.1	−0.826878942
LINC02163|AC100814.1	0.812451829
PAN3-AS1|AC008115.3	0.737068795
AL117379.1|ZKSCAN2-DT	−1.251469056
GK-AS1|AC084117.1	0.699519969
AC026368.1|LINC02577	−0.876128589
AC104695.3|AC108134.3	0.528219693
ALG13-AS1|AL355075.2	1.055026661
AC010536.2|AL121895.2	0.923678667
ABALON|AC090116.1	−0.728559966
CD44-AS1|ARHGEF38-IT1	1.422617605
AC004241.3|AL138689.1	−0.670518358
AL031673.1|AL161729.4	−1.015071998
SNHG10|AC156455.1	−0.681577301
AL354993.2|AC002128.2	0.453187294
FAM222A-AS1|AC156455.1	−0.529227502
AC106820.3|AC103591.3	1.098883888
MBNL1-AS1|LINC01138	−1.673238208
AF117829.1|AC020978.3	0.62944427

lncRNA, long non-coding RNA.

the 3' untranslated region (UTR) of HMGA1 mRNA. M6A modification of HMGA1 mRNA by METTL3 enhanced HMGA1 expression in CRC (25). Lu and his coworkers revealed that the m6A reader IMP2 worked ZFAS1, and that these two factors work together to induce CRC by boosting mitochondrial energy metabolism (26). It was reported that YTHDF1, an m6A reader, effectively synergizes with cisplatin by inhibiting protein synthesis of GLS1 to induce colon cancer cell death (27). In addition, Zhang *et al.* summarized the mutual regulation mechanism of m6A modification and lncRNA in tumors, further indicating that not only m6A can regulate the level of lncRNA, but also lncRNA can manipulate the level of m6A modification and biological effects by regulating demethylase and methyl-binding protein (28). These investigations showed that m6A is essential for regulating the development and division of colon cancer cells and that it works in synergy with drugs to cause colon cancer cell death. Additionally, researches have showed that m6A-related lncRNA signatures can be utilized to anticipate prognosis, improve risk analysis for survival, and enable tailored treatment in CRC (29-31). Xue *et al.* established a prognostic model of disulfidptosis-associated lncRNA in COAD, and the AUCs of 1-, 3-, and 5-year survival rates were 0.679, 0.703, and 0.744, respectively (32). A study has shown that lncRNAs such as ESRG, LINC00518 and PWRN1 can be used as diagnostic and prognostic biomarkers in COAD (33). Compared with the above prognostic models, our model has better predictive value and we identified a brand-new m6A-related lncRNA pair predictive model for COAD. There are certain practical issues with these models. These forecasting algorithms were developed using the particular expression levels of the discovered lncRNAs. Before applying the measurements in a clinical setting, to remove batch effects between different testing platforms, the measured results must be standardized. We created the brand-new m6A-related lncRNA pair predictive model for COAD. The area under the curve (AUC) for predicting 1-, 3-, and 5-year survival rates demonstrated outstanding predictive accuracy, with values of 0.938, 0.930, and 0.916, respectively. Our prognostic signature, which included 35 m6A-related lncRNA pairs, was verified by Cox regression analysis to be an independent predictive factor. Notably, it was better at predicting the OS for COAD than frequent clinicopathological factors. More crucially, the signature was created by pairing, iteration, and a novel modeling technique; as a result, it may be used more effectively in clinical settings.

The immune microenvironment is crucial in

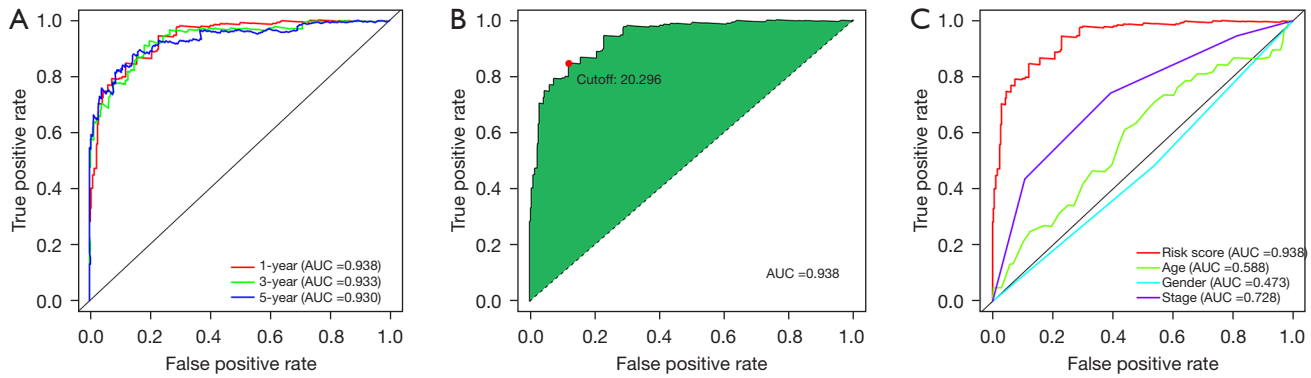

Figure 3 Verification of accuracy and independence. (A) The ROC curves were plotted to predict the 1-, 3-, and 5-year OS rates; (B) the optimal cut-off value was determined by identifying the maximum inflection point on the 1-year ROC curve; (C) the predictive ability of the risk score model was compared with clinicopathological characteristics in predicting the 1-year OS rate. AUC, area under the curve; ROC, receiver operating characteristic; OS, overall survival.

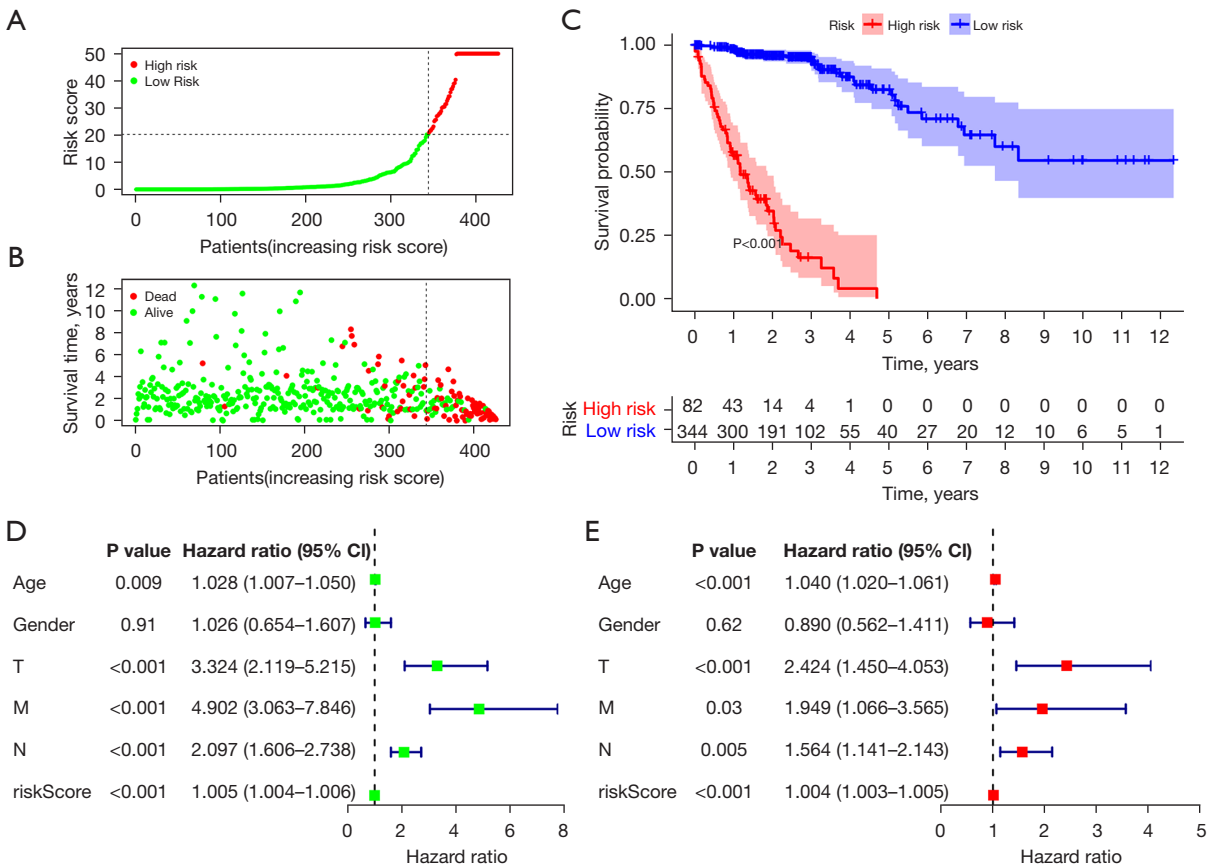

Figure 4 Construction of a novel prognostic risk signature for COAD. (A) Risk scores of each patient; (B) survival outcomes of each patient; (C) survival curves of high-risk group and low-risk group patients; (D) univariate of the risk score model and clinicopathological characteristics; (E) multivariate Cox regression analyses of the risk score model and clinicopathological characteristics. 95% CI, 95% confidence interval; COAD, colon adenocarcinoma.

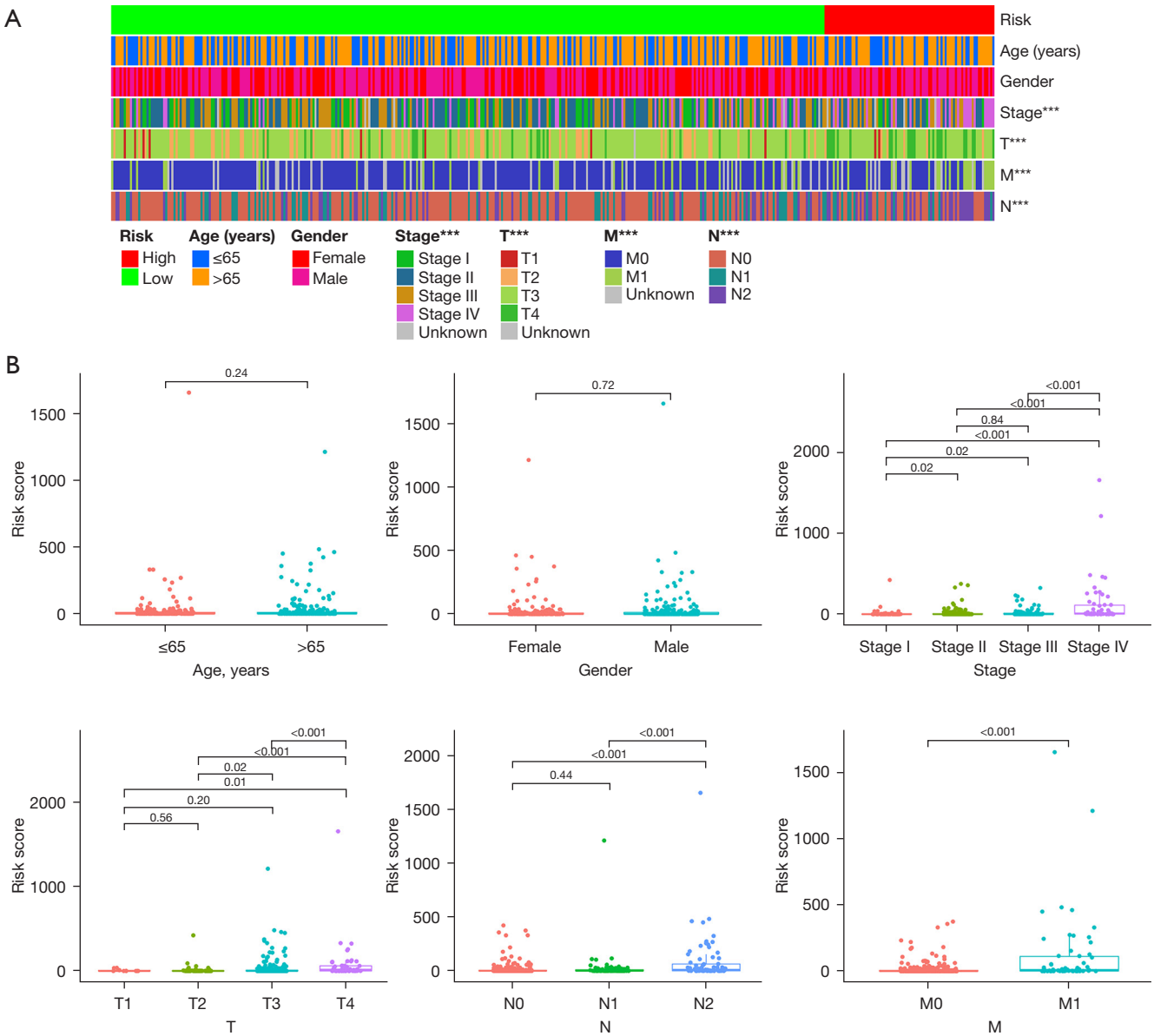

Figure 5 Risk score model and clinicopathological characteristics. (A) The heatmap of correlations between the risk score model and clinicopathological characteristics; (B) the box diagrams of correlations between the risk score model and clinicopathological characteristics. ***, P<0.001.

carcinogenesis. Infiltrating immune cells may work to antagonize tumors or to promote tumors (34,35). Cancer cells have evolved multiple mechanisms to escape immune surveillance, resulting in cancer development (36). In recent years, immunotherapy has been innovated in cancer treatment and has demonstrated remarkable success (37,38). Furthermore, m6A and immunity are intimately related (39). M6A can regulate a wide range of immune cells and has a number of regulatory modes and processes, including influencing T cell development, regulatory T cell status, and dendritic cell maturation (40). A recent study has shown that m6A methylation is a key epigenetic modification in the differentiation of tumor-associated macrophages in CRC, and METTL3 knockdown can promote the invasiveness of CRC by down-regulating miR-146b (41). In this work, we examined the correlation between the risk score model

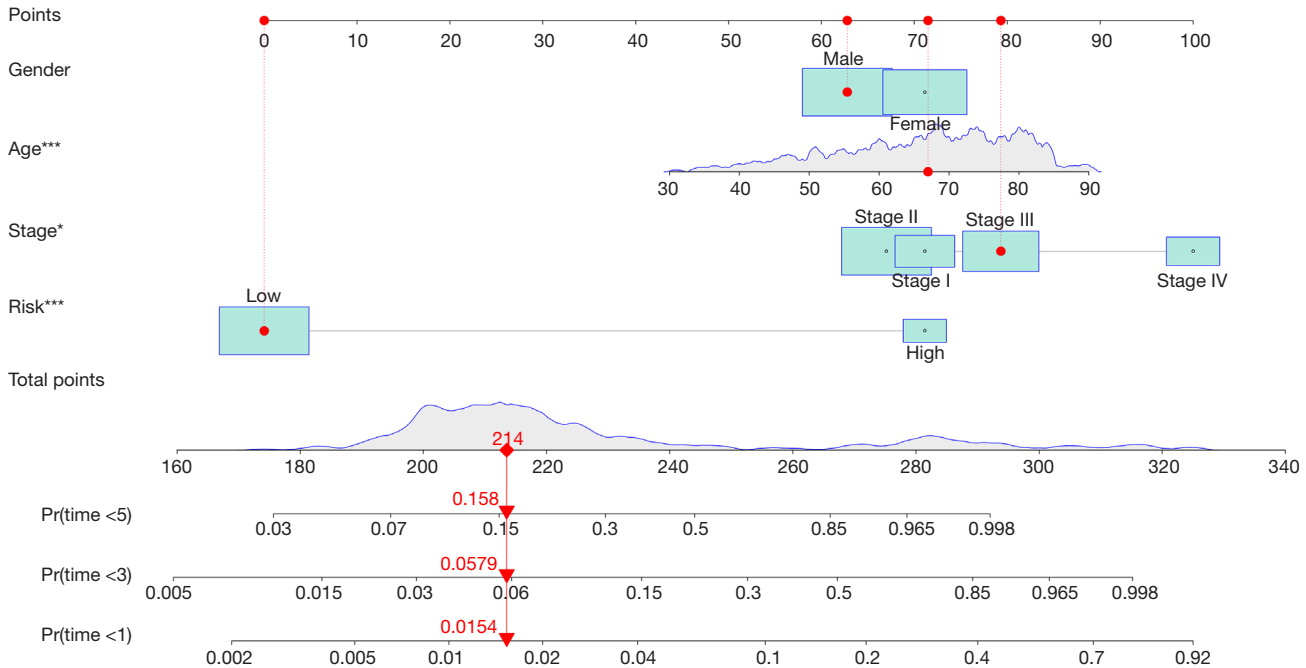

Figure 6 Prognostic nomogram merging the risk score model and clinicopathological characteristics. *, P<0.05; ***, P<0.001.

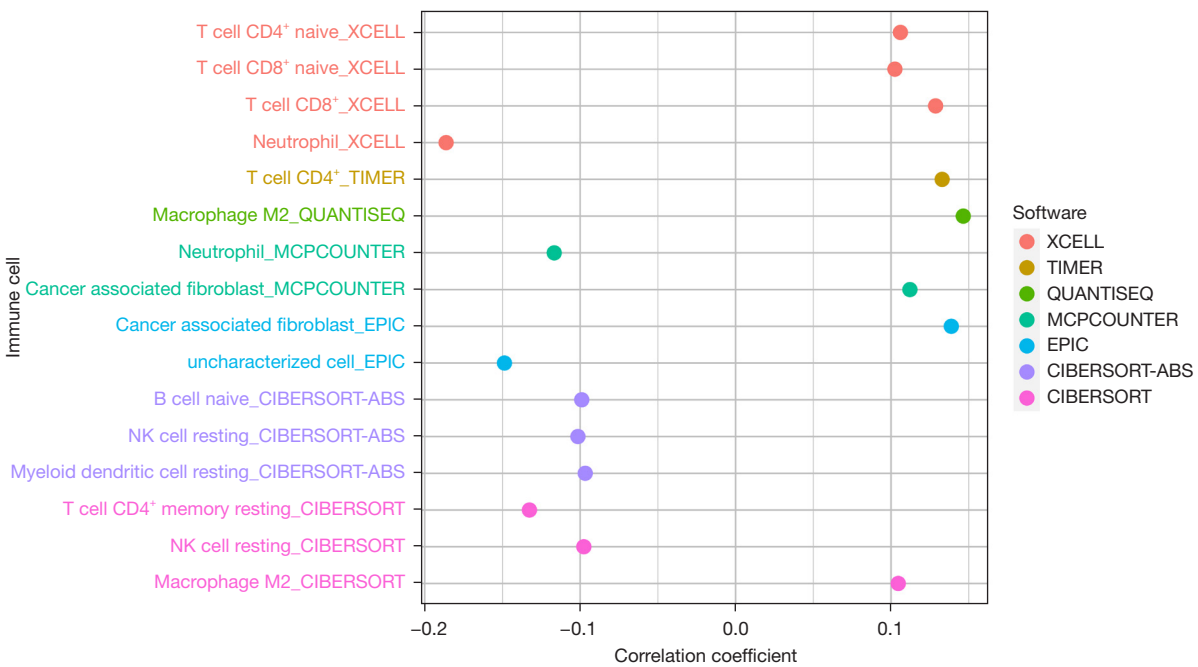

Figure 7 Correlations between the risk score model and tumor-infiltrating immune cells.

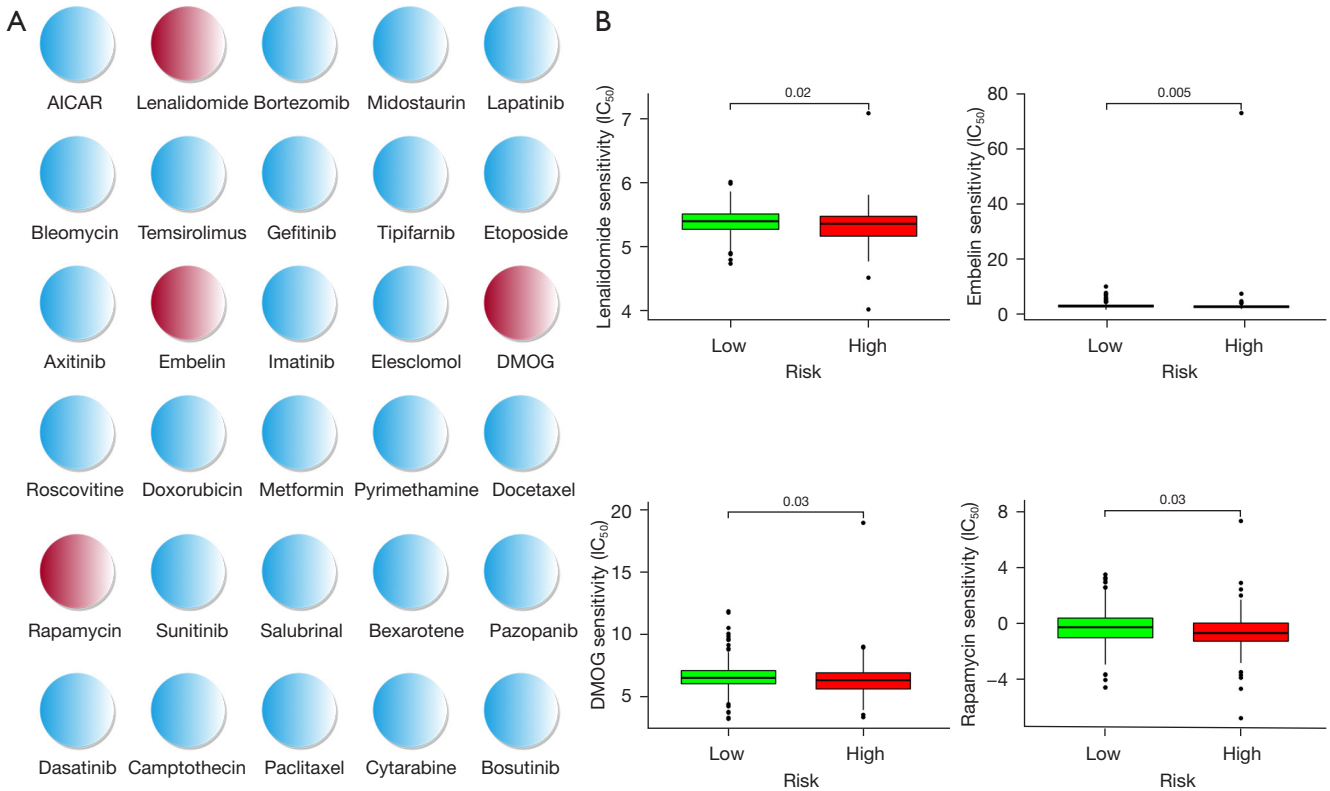

Figure 8 Estimated drug sensitivity in patients with high- and low-risk groups. (A) The sensitivity to 30 common anticancer drugs between the high- and low-risk groups; (B) IC_{50} values for the antitumor medicines rapamycin, lenalidomide, embelin, and DMOG. IC_{50}, half-maximum inhibitory concentration; DMOG, dimethyloxallyl glycine.

and variables related to the immune system. The findings demonstrated that the high-risk group was connected to more TIICs, such as $CD4^+$ T cells, $CD8^+$ T cells, and macrophages, in contrast, the low-risk group exhibited a higher association with TIICs, such as neutrophils, B cells, and NK cells. The discovery that m6A-related lncRNAs were connected to immune cell infiltration in COAD may help us identify new treatment targets. Despite recent advances in tumor immunotherapy, the overall therapeutic impact of COAD is unsatisfactory. Therefore, creating multimode therapy and biointegration targets is required. Further investigation is needed to explore the association between COAD and lncRNAs related to m6A modification.

Typically, patients with high-risk COAD undergo a combination of chemotherapy and surgery as part of their treatment regimen. By utilizing the GDSC database, we found that high-risk individuals demonstrated greater sensitivity to commonly prescribed chemotherapeutic drugs (such as lenalidomide, embelin, DMOG, and rapamycin) compared to low-risk patients. This discovery has the potential to unveil novel treatment possibilities for patients with COAD. Although lenalidomide's anticancer mechanism is still not fully understood, it appears to cause angiogenesis inhibition and immunomodulation (42). In the tumor environment, embelin boosted the infiltration of CD8+ T cells, NK cells, and mature dendritic cells while decreasing the number of regulatory T cells (43). Rapamycin, the first naturally occurring mammalian target of rapamycin (mTOR) inhibitor, prevented the growth of CRC cells that were susceptible to rapamycin (44). Further clinical trials are necessary to assess the effectiveness of these chemotherapeutic drugs in patients with COAD.

There are some limitations in this study. First, additional experimental confirmation is needed as we can only draw inferences from bioinformatics research. Second, more samples should be included in the future.

Conclusions

In conclusion, the m6A-related lncRNA pairs in COAD

were systematically identified and analyzed for the first time in the research. We have identified m6A-related lncRNA pairs that hold prognostic value and have developed a novel risk model that demonstrates excellent predictive ability for prognosis and survival status. The risk score is a new and potential biomarker since it has a strong correlation with the malignant clinicopathological characteristics of COAD. Moreover, our findings offer crucial support for additional research on the role of m6A-related lncRNA pairs in COAD, which may offer fresh perspectives on how to direct an efficient immunotherapy regimen for COAD.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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