Original Article

High expression of RBM15 is associated with better prognosis in esophageal squamous cell carcinoma

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Background: Esophageal squamous cell carcinoma (ESCC) is a highly prevalent and malignant form of esophageal tumor associated with high rates of patient mortality for which there remains a persistent lack of effective targets for therapeutic interventional efforts. This study was developed with the goal of exploring the expression and functional role of RBM15 in ESCC.

Methods: This study was developed with the goal of exploring the expression and functional role of RBM15 in ESCC. To establish the prognostic and therapeutic significance of RBM15 in this cancer, data from the Gene Expression Omnibus (GEO), The Cancer Genome Atlas (TCGA), and UCSC Xena databases were leveraged. Immunohistochemical analyses were used to assess RBM15 expression in postoperative ESCC tumor tissue samples, and the correlations between such expression and patient outcomes were assessed. The effects of RBM15 on ESCC cell proliferative, migratory, and invasive activity were assessed with Cell Counting Kit-8 (CCK8) and Transwell assay approaches. Together, these experiments revealed RBM15 upregulation in ESCC relative to paracancerous tissues, while confirming that it was associated with favorable patient outcomes. RBM15 was also found to suppress ESCC cell proliferation, migration, and invasivity.

Results: We suggest that RBM15 may be a clinically relevant prognostic factor in ESCC such that new therapeutic interventions based on low levels of RBM15 have the potential to be developed for the improved management of ESCC in the future.

Conclusions: The results of the present study provide confirmation that high levels of RBM15 expression are protective and associated with better ESCC patient prognostic outcomes. Pan-cancer analyses performed herein also revealed the correlations between RBM15 expression and prognosis in various cancers.

Keywords: Esophageal squamous cell carcinoma (ESCC); N6-methyladenosine (m6A); RBM15

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Introduction

Esophageal cancer is the seventh most prevalent and sixth deadliest form of cancer in the world (1). While adenocarcinoma is the predominant esophageal cancer subtype in Europe and the Americas, esophageal squamous cell carcinoma (ESCC) is more common in Asian populations (2). Immunotherapeutic regimens have led to a revolution in ESCC patient treatment, but the median patient survival duration remains at under 18 months (3-9). Adding anti-angiogenic treatments has led to the improvement of advanced ESCC patient median survival time such that it holds great promise as a means of overcoming future therapeutic difficulties (10,11). However, reliable prognostic biomarkers are lacking for both anti-angiogenic and immunotherapeutic regimens. There is thus a pressing need to define more effective biomarkers and therapeutic targets in order to guide the more reliable prognostic assessment and management of ESCC.

N6-methyladenosine (m^6A) is the most frequently reported form of internal RNA modification observed in eukaryotic species, serving as a key regulator of the splicing, processing, stability, and translation of RNA (12). The dynamic and reversible m^6A modification of RNA molecules is controlled by methyltransferase complexes (Writers), demethylases (Erasers), and recognition complexes (Readers), with these proteins thus governing both physiological and pathological biological processes (BP) (13). In oncological settings, m^6A can both facilitate and inhibit tumor growth depending on the particular context (14). In ESCC, m^6A methylation has primarily been reported to favor tumor progression (15-19). In prior studies based on data from The Cancer Genome Atlas (TCGA) database, correlations between high levels of m^6A methylation-related protein expression (YTHDF3, RBM15, and KIAA1429) and improved ESCC patient overall survival (OS) were reported. As a member of the m^6A methyltransferase complex, RBM15 is a methylation specific mediator that plays an important role in mRNA_methylation, with the function of binding to m^6A complexes and recruiting them to specific RNA sites (20). Strikingly, high levels of RBM15 expression were found to predict better patient outcomes such that it may be a protective factor in this form of cancer (21). However, the precise mechanisms that link RBM15 to the modulation of ESCC patient outcomes remain uncertain. To resolve this uncertainty, the present study leveraged data from multiple databases [Gene Expression Omnibus (GEO), TCGA and UCSC Xena] in an effort to more fully clarify the prognostic and therapeutic significance of RBM15 in ESCC. Immunohistochemical (IHC) staining was also employed to probe RBM15, YTHDF3, and KIAA1429 protein levels in postoperative tumor tissues from 68 ESCC patients at Daping Hospital with the goal of better validating the relationship linking RBM15 to prognostic outcomes for this type of cancer. Cell-based experiments were then employed to more specifically probe the biological functions that RBM15 plays in ESCC. We present this article in accordance with the MDAR reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-331/rc).

Highlight box

Key findings

- High expression of RBM15 is a protective factor for esophageal squamous cell carcinoma and RBM15 expression influences the prognosis of several malignancies.

What is known and what is new?

- Analysis of the TCGA database identified RBM15 as a protective factor for esophageal squamous cell carcinoma (ESCC).
- RBM15 was validated as a protective factor for ESCC by cellular experiments, clinical samples combined with survival analysis.

What is the implication, and what should change now?

- These findings comprehensively reveal the role of RBM15 in the development of ESCC from different perspectives.
- In future studies, we will endeavour to more comprehensively elucidate the mechanisms by which RBM15 affects the prognosis of ESCC patients, laying the foundation for more effective individualized and precise treatment of this cancer.

Methods

Data collection and processing

Human ESCC GSE67269-GPL571 chip gene expression data comprising 73 ESCC tumor tissue samples and 73 healthy tissue samples were downloaded from the Gene Expression Omnibus (GEO) database. The results were processed with R, converted them into gene expression data for further analyses.

Human ESCC gene expression data from the TCGA-ESCA dataset and corresponding clinical data were downloaded from TCGA database and processed with R.

m^{6}A-related gene expression analyses

To analyze m^{6}A-related gene expression in ESCC and control tissues from the GSE67269-GPL571 dataset, an online tool was used (https://www.home-for-researchers.com/).

Differentially expressed gene (DEG) identification

Median RBM15 expression values were used as a cut-off to separate the 73 ESCC tissue samples into groups with low and high expression levels. DEGs were then identified by comparing these two groups using the "GEO2R" function in the GEO database, arranging the resultant data in a volcano plot.

Functional enrichment analyses

Gene ontology function enrichment analysis is a widely used method that categorizes gene functions into BP, molecular functions (MF), and cellular functions (CC) based on large-scale functional enrichment studies. The DEGs in this study were annotated for Gene ontology function analysis using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) tool (https://david.ncifcrf.gov/). Statistical significance was determined by adjusted P value <0.05. Gene Set Enrichment Analysis (GSEA) is a statistical method that identifies enriched gene sets in gene expression data by analyzing cumulative distribution functions. In this study, GSEA (version 4.3.2) was utilized to analyze the enrichment of gene sets in high and low RBM15 expression groups of GSE67269-GPL571. The gene set 'c1.all.v2023.2.Hs.symbols.gmt' was selected for analysis, and the results were visually represented in a graph.

Predictive analyses of therapeutic responses

Drug response data from the Cancer Genome Project (CGP) database (https://cancer.sanger.ac.uk/cosmic) were leveraged to predict half-maximal inhibitory concentration (IC_{50}) values for particular drugs in different patient samples, utilizing the Oncopredict package to compare the degree of drug response between the low and high expression groups.

Single-gene pan-cancer analyses

Acquisition of pan-cancer expression data

Data from the TCGA and Genotype-Tissue Expression (GTEx) resources were obtained from the UCSC Xena database, which included mRNA sequencing data of RBM15 in various tumor and normal tissues, along with relevant clinical information such as survival status and clinical/pathological stages. Cancers with fewer than 3 samples from a single species were excluded. The R packages 'limma', 'ggplot2', and 'ggpubr' were utilized for comparing RBM15 expression.

Prognostic assessment of pan-cancer

Incomplete survival information and survival status samples were excluded from pan-cancer expression data and clinical information to compile high-quality prognostic expression data. Univariate COX regression models were constructed using the R package 'survival'. The prognostic significance of RBM15 in various cancer types was evaluated based on four clinical endpoints: OS, disease-specific survival (DSS), disease-free interval (DFI), and progression-free interval (PFI). Prognostic factors were evaluated based on criteria including hazard ratio (HR), 95% confidence intervals (CIs), and P values, with statistical significance considered at $P<0.05$.

Human subjects

All patients included in this study were from Daping Hospital. This study included samples with ESCC, as confirmed through postoperative pathological diagnosis, who had undergone radical surgery in the hospital Thoracic Surgery Department between April 2012 and March 2014. All patients did not undergo neoadjuvant therapy according to treatment decisions. Ultimately, this led to the inclusion of 68 adult patients, all of whom had available medical records and underwent postoperative IHC staining analyses of collected tissue samples. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and received approval from the Ethics Committee of the Chinese People's Liberation Army Army Speciality Medical Centre (approval No. 2023-234). The requirement for obtaining informed consent was waived because of the study's retrospective design.

IHC staining

Paraffin-embedded tissue samples were obtained from ESCC patients who had undergone radical esophageal surgery at Daping Hospital (Chongqing, China) in line with appropriate ethical and consenting guidelines as detailed

above. The tissues from these 68 patients were arranged in a tissue microarray for analysis. The obtained sections were successively dehydrated, repaired, incubated with primary and secondary antibodies, subjected to color development, dehydrated, sealed, and imaged with an Eclipse E400 microscope. Primary antibody incubation included three antibodies to RBM15 (proteintech China 10587-1-AP), YTHDF3 (proteintech China 25537-1-AP), KIAA14129 (proteintech China 25712-1-AP). Two senior pathologists graded the resultant samples based on the degree of staining visible by light microscopy as follows: "–" negative staining, "+" yellowish, "++" light brown, and "++++" dark brown.

Vector construction

The RBM15 plasmids (primer1: TACCGGACTCAGATCTCGAGCGCCACCATGAGGACTGCGGGGCGGGACCCTGTG, primer2: GATCCCGGGCCCGCGGTACCGTTAACAGGGTCAGCGCCAAGTTTTCTCTC) and empty vector were obtained from Genechem (Shanghai, China). The lentiviral vector shRNA was designed by Genechem and the shRNA sequence was GCATCAGCTGAACGAGATAGG. Cells were collected for further experiments two days after transfection.

Cell lines, culture conditions, and transfection

Human ECA109 cells were cultured in RPMI (Roswell Park Memorial Institute)-1640 (Pricella, PM150110, China) with 10% fetal bovine serum (FBS, Pricella, 164210-50), and 1% penicillin-streptomycin (Pricella, PB180120), in a 5% CO_2 atmosphere at 37 ℃. Human KYSE150 cells were cultured in RPMI (Roswell Park Memorial Institute)-1640 (Pricella, PM150110, China) with 10% FBS (Pricella, 164210-50), and 1% penicillin-streptomycin (Pricella, PB180120), in a 5% CO_2 atmosphere at 37 ℃.

RBM15 overexpressing ECA109 cells were created through plasmid transfection. The plasmid was introduced into a petri dish containing ECA109 cells using transfection reagents and incubated for 2 days. The overexpression was confirmed through Western blot analysis. Subsequent experiments were conducted following the successful establishment of the RBM15 overexpression cell line. RBM15 knockdown in ECA109 cells and KYSE150 cells were achieved using a lentiviral transfection construct. ECA109/KYSE150 cells were inoculated at a density of 2×10^5 cells/well in six-well plates with RPMI-1640 in 10% FBS. The cells were cultured overnight at 37 ℃ in a 5% CO_2 incubator until the cells reached 30–40% fusion. Subsequent dropwise addition of lentiviral and transfection reagent mixture was performed and incubation was continued for 48 hours, with fluid changes according to cell condition. After 2 days of infection, puromycin was screened for 48 h and western blotting verified the knockdown effect.

Western blotting

Western blotting analysis experiments were conducted using standard kits from BIO-RAD Inc. Cell and protein samples were loaded onto a 4–20% gel for electrophoresis. The isolated proteins were then transferred to polyvinylidene fluoride (PVDF) membranes, followed by incubation with antibodies at a 1:1,000 dilution, washing, and subsequent incubation with horseradish peroxidase (HRP)-conjugated secondary antibodies at a 1:5,000 dilution. Imaging was carried out using the BIO-RAD detection kit.

Cell Counting Kit-8 (CCK8) assay

Cells were added to 96-well plates (5,000/well), and after 24, 48, 72, or 120 h, CCK8 reagent (Bioground, L2545131X, China) was added to each well. Absorbance in each well was then measured with a microplate reader following a further 1.5 h incubation at 37 ℃.

Transwell assays

For migration assays, after preparing 24-well plates with 600 μL of RPMI-1640 containing 10% FBS, 2×10^4 cells were added to the upper chamber in 100 μL of serum-free media for 24 h. Cells that had migrated to the lower chamber were then fixed, stained using crystal violet, and imaged. For invasion assays, the Transwell insert was first coated with pre-cooled substrate (Corning, USA), other steps are the same as migration.

Statistical analysis

SPSS 27.0, R 4.2.2, and GraphPad Prism 9 were used for all data analyses and figure preparation. Categorical data were presented as numbers with corresponding percentages and were compared using Chi-squared tests. The Kaplan-Meier method was used to estimate median progression-free survival (PFS) and OS, with log-rank tests being used to calculate corresponding HRs and 95% CIs. A two-sided

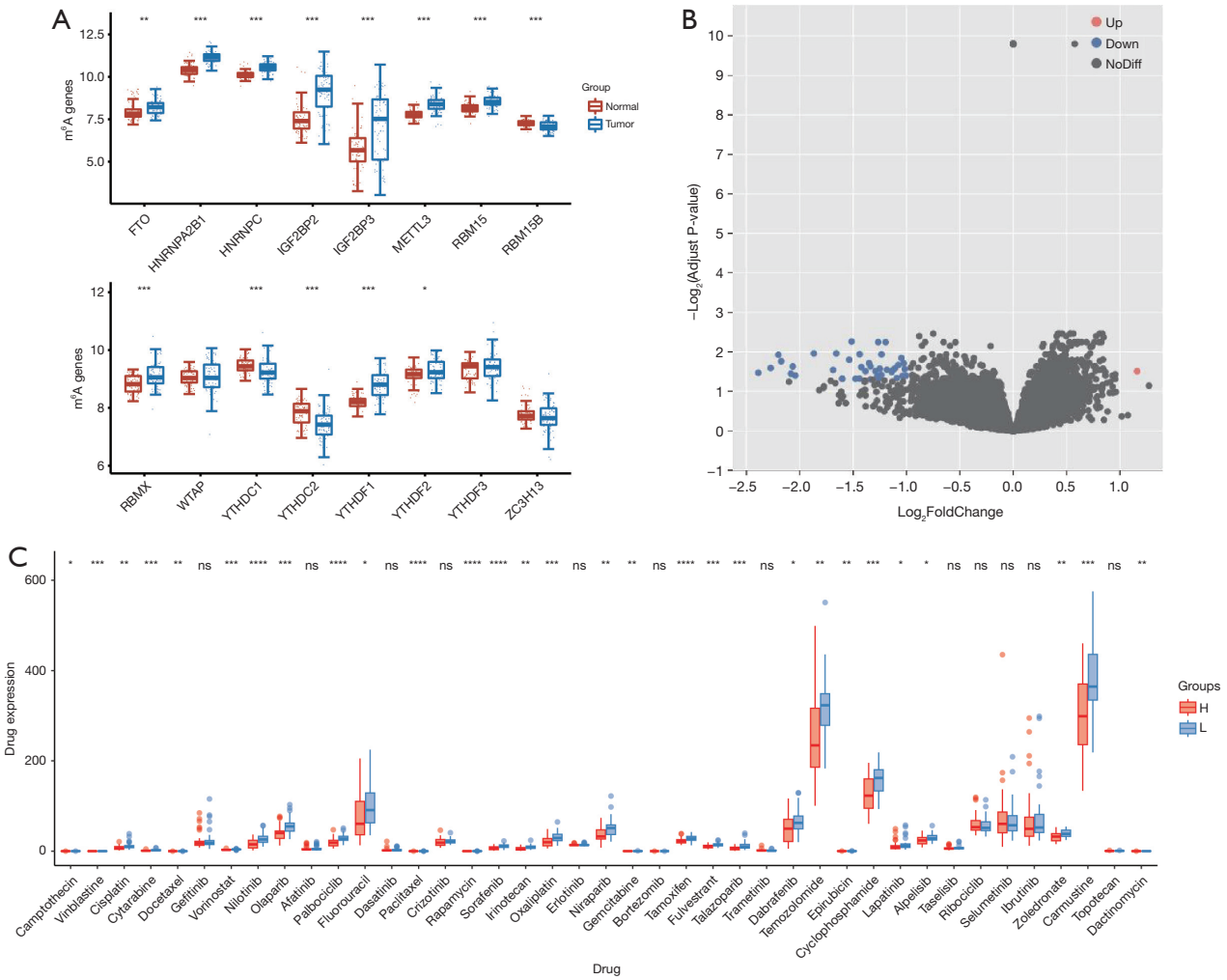

Figure 1 Identification of differential genes and prediction of drug response. (A) Box plots were generated for the 16 m^{6}A methylation-related genes from dataset GSE67269-GPL571 in the GEO database, comparing esophageal squamous carcinoma and normal tissues. (B) The 'GEO2R' function was used to analyze differential gene profiles between high and low RBM15 expression groups, resulting in gene volcano plots. NoDiff represents non difference. (C) A box plot was created to display RBM15 expression levels in relation to commonly used targeted drugs and chemotherapeutic agents. *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001; ns, no significant difference. GEO, Gene Expression Omnibus; H, RBM15 high expression group; L, RBM15 low expression group.

P<0.05 was considered statistically significant. All cellular experiments were repeated at least three times with at least three biological replicates per experiment.

Results

ESCC tumors exhibit m^{6}A-related gene upregulation

Patterns of differential m^{6}A-related gene expression in ESCC relative to normal tissues were initially analyzed using the GSE67269-GPL571 microarray dataset from the GEO database. These analyses led to the finding that 13 of the 16 analyzed m^{6}A-related genes were differentially expressed in ESCC, including 10 and 3 that were respectively upregulated and downregulated when comparing 73 tumors and paracancerous tissues (*Figure 1A*, Figure S1A). Further normalization and ranking of these DEGs revealed that they were primarily m^{6}A Writers and Readers (Figure S1B). Through the integration of the GEO database-derived DEGs with prognostic survival data from the TCGA database, RBM15 was found to be a DEG that

was also significantly associated with the survival of ESCC patients (Figure S1C), and its high expression improves the prognosis of ESCC patients. And according to the research results of the previous team, RBM15 is also one of the influencing factors affecting the prognosis of esophageal squamous carcinoma (21). Based on these data, it appears that the majority of m^{6}A-associated genes are upregulated in ESCC, with RBM15 upregulation making it a promising target for therapeutic intervention in this form of cancer.

RBM15 expression impacts a range of ESCC features

The effects of RBM15 expression on ESCC outcomes were next assessed by using median RBM15 expression to separate tumor samples into those with low and high levels of RBM15 expression. DEGs in the GEO dataset were then identified with the GEO2R function, revealing 42 downregulated genes and 1 upregulated gene (*Figure 1B*). Functional analyses indicated that these genes were primarily related to extracellular environmental features (Figure S1D). In GSEA analyses, RBM15 positively regulates modifications of RNA and protein molecules (Figure S2) and negatively regulates CC including macrophage regulation (Figure S3). Analyses of therapeutic responses indicated that the low-expression group presented with greater sensitivity to common chemotherapeutic and targeted drugs (*Figure 1C*). On the whole, these results suggest that RBM15 serves as an important regulator of many aspects of ESCC tumor development.

RBM15 influences the prognosis of many of cancers

To more fully explore how RBM15 influences the development and activity of various cancers, a single-gene pan-cancer analysis of RBM15 was next conducted. Data from the TCGA and GTEx databases were first leveraged to compare RBM15 expression between tumors and normal tissues from various cancer types, with the results revealing that RBM15 expression varied significantly in CESC, CHOL, COAD, ESCA, HNSC, KICH, KIRP, LIHC, LUAD, LUSC, STAD, THCA, and UCEC (P<0.001) (*Figure 2A*). Analyses of patient OS, PFI, DSS, and DFI in these various cancers revealed that RBM15 was correlated with patient outcomes in THCA, READ, PRAD, LIHC, LGG, KIRP, KIRC, KICH, CHOL, BLCA, and ACC. It was also found that RBM15 was a protective factor for READ, KIRC, CHOL and a risk factor for THCA, PRAD, KIRP (*Figure 2B*).

Clinical validation of the relationships between RBM15 and ESCC patient prognostic outcomes

Next, a retrospective analysis of clinical data from 68 stage I-III ESCC patients was performed (*Table 1*), along with IHC analyses of the expression of RBM15 in paraffin-embedded tissue samples from these patients (*Figure 3*). Strong levels of RBM15 expression were detected in 11 samples (16.2%). Kaplan-Meier survival analyses revealed that patients with and without strong positive RBM15 expression exhibited median disease-free survival (DFS) and DSS of unreached *vs.* 48.53 months (HR, 0.22; 95% CI: 0.10–0.50; P=0.01) and unreached *vs.* 60.5 months (HR, 0.12; 95% CI: 0.05–0.27; P=0.02), respectively (*Figure 3B*,*3C*). In contrast, IHC analyses of YTHDF3 and KIAA1429 failed to reveal any significant differences in prognostic outcomes when comparing ESCC patients with low and high levels of YTHDF3 and KIAA1429 expression (Figure S4A,S4B). Subsequently, we performed univariate and multivariate COX regression analyses of clinical factors and RBM15, KIAA1429, and YTHDF3 in these patients, and the results suggested that T-stage, N-stage, grade, and RBM15 expression were independent prognostic factors for DSS and DFS (*Figure 3D*,*3E*).

RBM15 suppresses the proliferation, migration, and invasivity of ESCC cells

Lastly, an effort to probe the functional roles of RBM15 in ESCC was performed by generating the ECA109-RBM15 (overexpressing RBM15) and ECA109-shRBM15 (knockdown RBM15) cell lines through plasmid and lentiviral transfections. Western blotting was used to confirm successful cell line generation (Figure S4C,S4D). CCK8 assays indicated that overexpressing RBM15 impaired the proliferation of ECA109 cells, whereas knocking it down had the opposite effect (*Figure 4A*,*4B*). We similarly found the same results in another esophageal squamous carcinoma cell line, KYSE150 knockdown of RBM15. That is, knockdown of RBM15 promoted the proliferation of esophageal squamous carcinoma cells (Figure S4E). Similarly, RBM15 knockdown led to improved invasion and migration of ECA109 cells in Transwell assays (*Figure 4C*,*4D*).

Discussion

As a common form of internal RNA modification (13), m^{6}A methylation is closely linked to the pathogenesis of

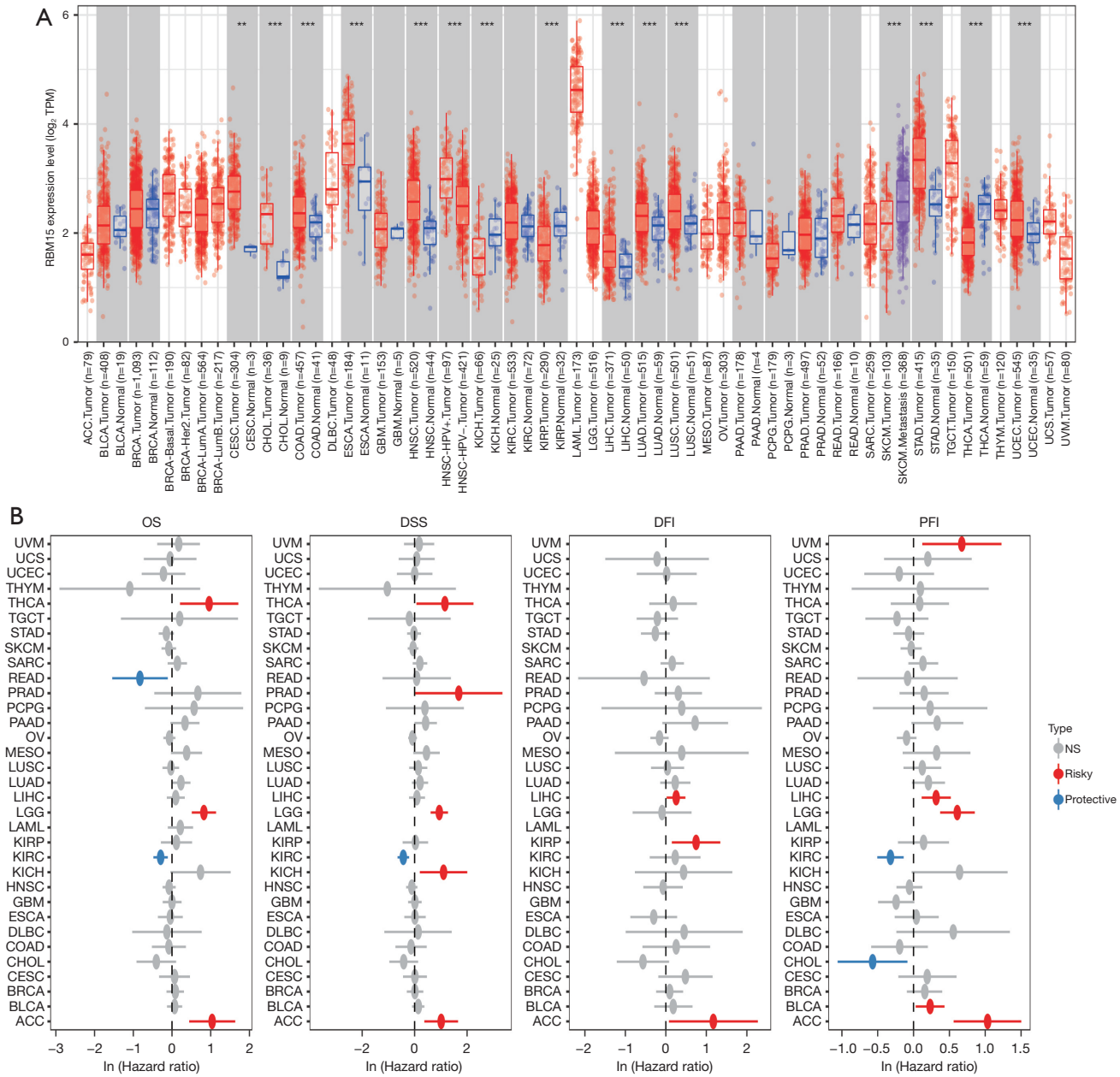

Figure 2 Differential gene analysis and survival prognosis of RBM15 in pan-cancer. (A) A box plot illustrating the variance in expression levels of RBM15 between cancerous and normal tissues across various cancer types, based on a combined analysis of data from the TCGA and GTEx databases. (B) A forest plot depicting the impact of RBM15 on OS, DSS, DFI, and PFI in different cancer types, as assessed through data from the TCGA and GTEx databases. **, P<0.01; ***, P<0.001. NS, no significant difference; TCGA, The Cancer Genome Atlas; GTEx, Genotype-Tissue Expression; TPM, transcripts per million; OS, overall survival; DSS, disease-specific survival; DFI, disease-free interval; PFI, progression-free interval.

Table 1 Baseline characteristic

Characteristic	Subgroups	High RBM15 expression, n	Low RBM15 expression, n	P value
Gender	Female	4	16	0.41
	Male	7	41	
Age (years)	≥60	5	21	0.41
	<60	6	36	
Smoking	Yes	7	37	0.60
	No	4	20	
Body mass index, kg/m^2	≥23	1	20	0.08
	<23	10	37	
Local	Upper	3	13	0.27
	Middle	8	37	
	Lower	0	7	
G	1	1	8	>0.99
	2	7	33	
	3	3	16	
T	1	1	7	0.29
	2	5	10	
	3	4	30	
	4	1	10	
N	0	5	27	0.44
	1	5	17	
	2	1	13	
Pathological stage	0	1	7	0.86
	2	5	21	
	3	5	29	

many malignancies, playing both protumorigenic roles through the enhancement of oncogene expression or the suppression of tumor suppressor genes while also potentially having the opposite effect (22,23). RBM15 is a SPEN (spen family transcriptional repressor gene) protein family member that acts as a m^{6}A methyltransferase (writer) and a crucial mediator of mRNA methylation. By interacting with spliceosome components, RBM15 can bind to RNA transcripts and regulate their splicing, stability, and associated BP (20). RBM15 has recently been linked to the prognoses of several cancers, suggesting that it is associated with the promotion of glycolytic activity and disease progression in osteosarcoma (24). RBM15 has also been linked to head and neck squamous carcinoma (25), hepatocellular carcinoma (26), rectal carcinoma (27), and uterine cervical carcinoma (28) development. Notably, RBM15 has been reported to play a pro-cancer role in many tumor types, yet it was herein found to act as a cancer suppressor in ESCC. To better understand these discrepant results, single-gene pan-cancer analyses were conducted, revealing that RBM15 primarily serves as a prognostic risk factor in most cancer types, whereas it is a protective factor in ESCC and KIRC. We combined the cancer types with significant differences in pan-cancer survival analysis with those with significant differences in pan-cancer expression difference analysis and found that THCA, KICH, KIRP

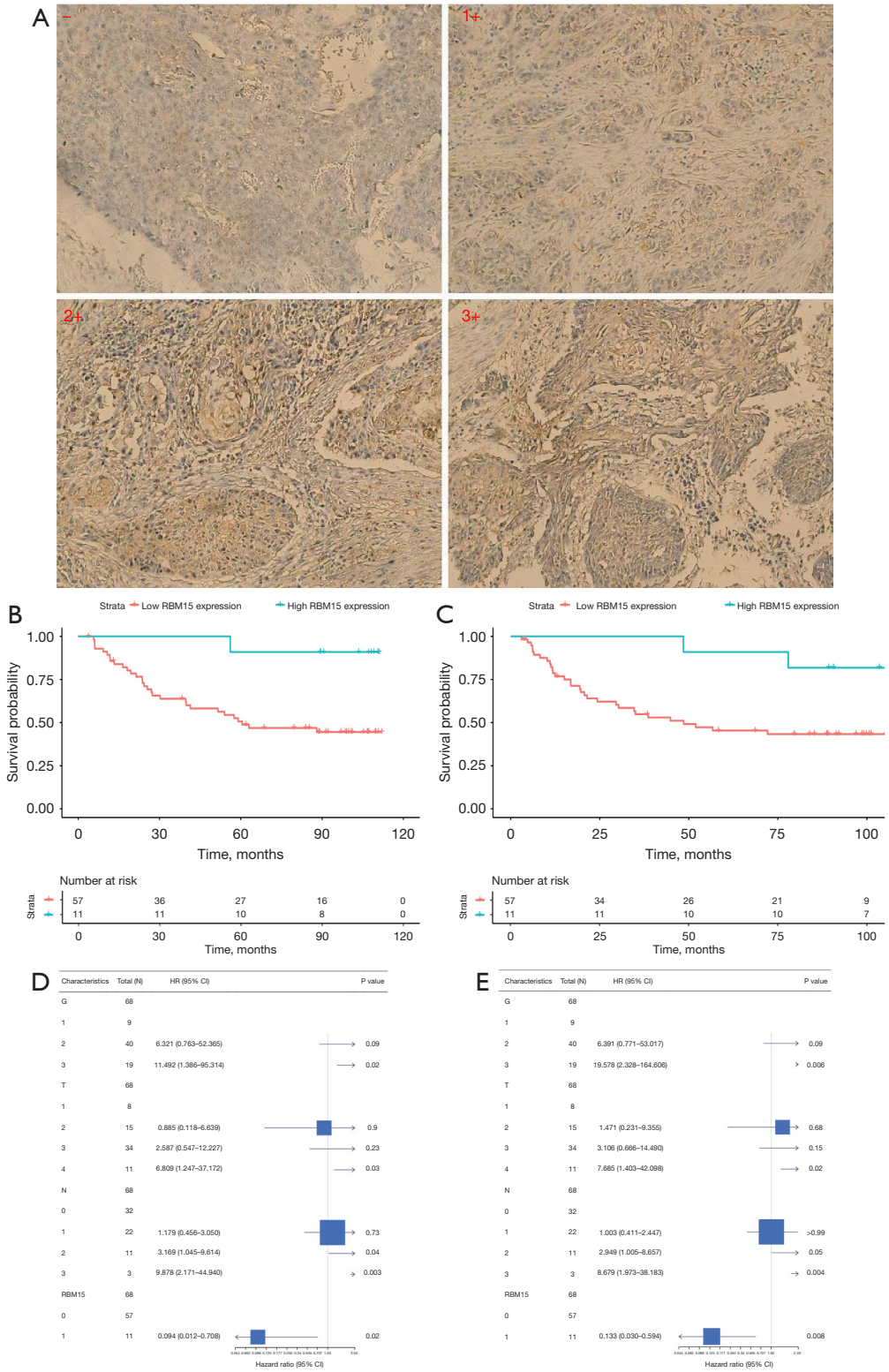

Figure 3 Immunohistochemical of ESCC specimens and survival analysis. (A) Immunohistochemical staining was performed on postoperative specimens of ESCC using RBM15 antibody. The light 10× microscopic images showed negative (–), weakly positive (1+), moderately positive (2+), and strongly positive (3+) expression of RBM15. (B) Kaplan-Meier analyses demonstrates the effect of RBM15 on

DFS in ESCC. (C) Kaplan-Meier analyses demonstrates the effect of RBM15 on DSS in ESCC. (D) Multifactor COX regression analysis of DSS. (E) Multifactor COX regression analysis of DFS. ESCC, esophageal squamous cell carcinoma; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; CI, confidence interval.

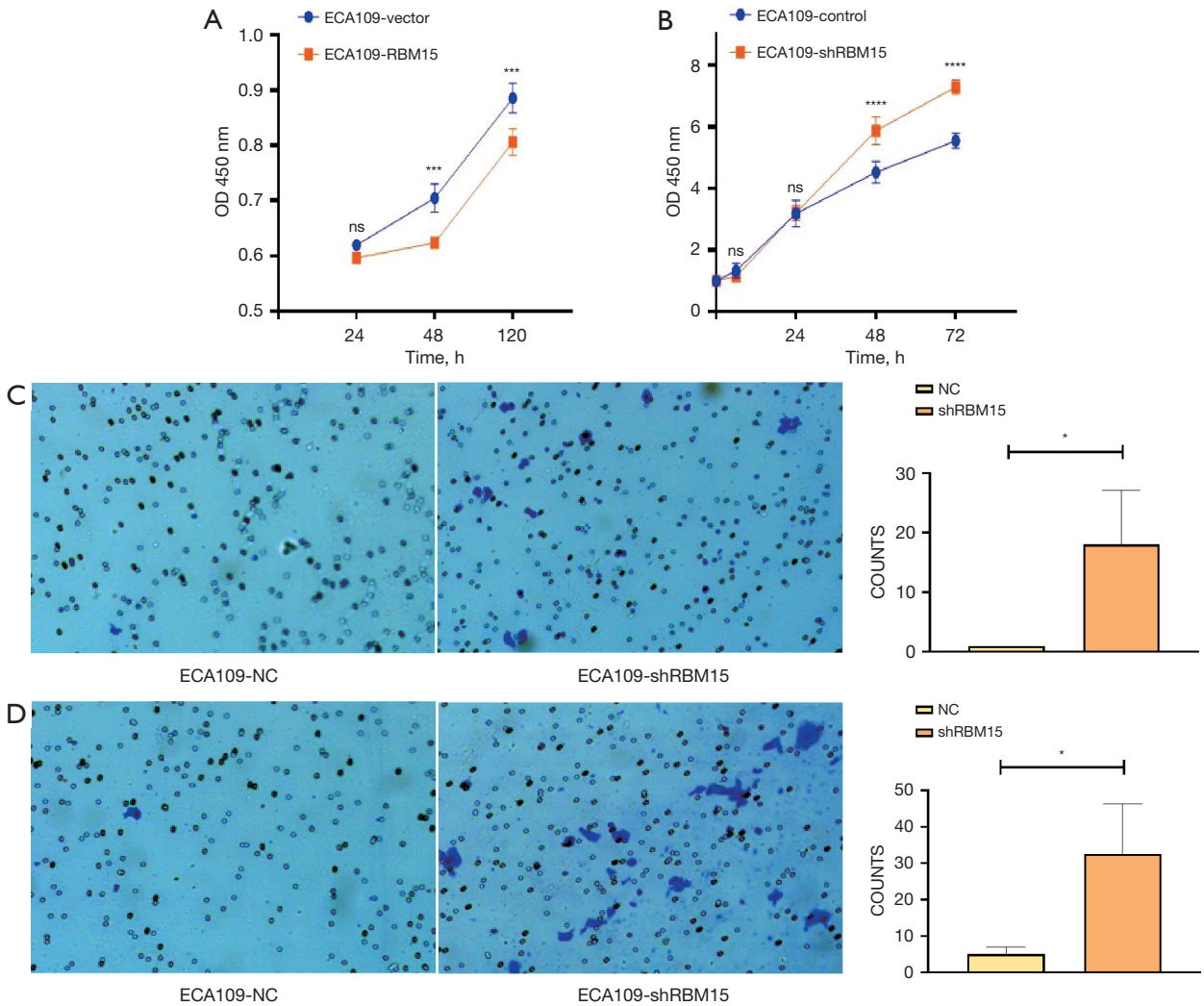

Figure 4 Results of CCK8 and Transwell. (A,B) Cell viability of ECA109 cells after RBM15 overexpression or knockdown in ECA109 cells was measured with CCK8 assay. (C,D) Migration ability and invasion ability of ECA109 cells after RBM15 knockdown in ECA109 cells was measured with Transwell migration assay (C) or Transwell invasion assay (D). The results were visualised by crystal violet staining using a 10× microscope. *, P<0.05; ***, P<0.001; ****, P<0.0001; ns, no significant difference. CCK8, Cell Counting Kit-8; OD, optical density.

were lowly expressed in cancer tissues and RBM15 was a risk factor for their prognosis. CHOL, ESCC had high expression of RBM15 in cancer tissues and RBM15 served as a protective factor for their prognosis. READ, KIRC had higher mean values than normal tissues although there was no statistically significant difference and was a protective factor for their prognosis. The prognostic relevance of RBM15 in various forms of cancer may thus be attributable to its relative expression in tumor tissues as compared to normal tissues, highlighting an important avenue for future exploratory research through preclinical and clinical experiments.

Overall, the present analyses suggested that ESCC patients with low RBM15 expression presented with poorer

prognostic outcomes but greater drug sensitivity, suggesting the potential utility of RBM15 as both a prognostic biomarker and a target for therapeutic treatment in this cancer.

There are a few limitations to this study. For one, while RBM15 was found to shape ESCC cell migratory, proliferative, and invasive activity, the specific mechanisms through which it exerts its protective effects have yet to be established. Furthermore, m^6A methylation modification has a dual effect of inhibiting and promoting cancer in the occurrence and development of cancer (14), which is mainly influenced by two factors: whether the target gene is an oncogene or an inhibiting gene, and whether target mRNA methylation promotes mRNA stability or degradation. The m^6A methylation specific mediator RBM15 mainly promotes cancer in various tumors, but this study found that its effect on ESCC is actually an anti-cancer effect. We will further investigate the specific mechanism in the future. In addition, no drugs that target RBM15 have been produced to date, emphasizing a need for further research probing the specific mechanisms through which this protein shapes ESCC progression, thereby helping better clarify its viability as a target for therapeutic efforts.

Conclusions

The results of the present study provide confirmation that high levels of RBM15 expression are protective and associated with better ESCC patient prognostic outcomes. Pan-cancer analyses performed herein also revealed the correlations between RBM15 expression and prognosis in various cancers. These results thus offer a comprehensive view of the role that RBM15 plays in tumor development from various perspectives. In future studies, efforts will be made to more fully clarify the mechanisms whereby RBM15 can influence ESCC patient prognostic outcomes, laying the groundwork for the more effective individualized precision treatment of this form of cancer.

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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). This study was approved by the institutional review boards at Ethics Committee of the Chinese People's Liberation Army Army Speciality Medical Centre (No. 2023-234). The requirement for obtaining informed consent was waived because of the study's retrospective design.

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