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ORIGINAL ARTICLE

Construction and validation of a prognostic risk model for uterine corpus endometrial carcinoma based on alternative splicing events*

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Abstract

Objective To establish a prognostic risk model for uterine corpus endometrial carcinoma (UCEC) based on alternative splicing (AS) event data from The Cancer Genome Atlas (TCGA) and assess the accuracy of the model.

Methods TCGA and SpliceSeq databases were used to acquire a summary of AS events and clinical data related to UCEC. Bioinformatic analysis was performed to identify differentially expressed AS events in UCEC. Least absolute shrinkage and selection operator (LASSO) regression and multivariate Cox regression analyses were used for constructing a prognostic risk model. Next, using the receiver operating characteristic (ROC) curve, Kaplan-Meier survival analysis, and independent prognostic analysis, we assessed the accuracy of the model. In addition, a splicing network was established based on the association between potential splicing factors and AS events.

Results We downloaded clinical data and AS events of 527 UCEC cases from TCGA and SpliceSeq databases, respectively. We obtained 18,779 survival-associated AS events in UCEC using univariate Cox regression analysis and 487 AS events using LASSO regression analysis. Multivariate Cox regression analysis established a prognostic risk model for UCEC based on the percentage splicing value of 13 AS events. Independent prognostic effect on UCEC risk was then assessed using multivariate and univariate Cox regression analyses ($P < 0.001$). The area under the curve was 0.827. The pathological stage and risk score were independent prognostic factors for UCEC. Herein, we established a regulatory network between alternative endometrial cancer-related splicing events and splicing factors.

Conclusion We constructed a prognostic model of UCEC based on 13 AS events by analyzing datasets from TCGA and SpliceSeq databases with medium accuracy. The pathological stage and risk score were independent prognostic factors in the prognostic risk model.

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Key words: TCGA; SpliceSeq; uterine corpus endometrial carcinoma; alternative splicing event; prognostic model

Uterine corpus endometrial carcinoma (UCEC) is a major malignancy affecting the female reproductive system. UCEC is the second most common cancer of the genital system in China [1]. Given the aging population in China, the incidence and mortality of endometrial cancer are gradually increasing. However, the 5-year survival rate of recurrent/metastatic endometrial cancer is currently 10%–20% [2]. The Cancer Genome Atlas research project (TCGA) aims to classify endometrial cancer into four subtypes by applying high-throughput genome analysis technology and comprehensive analysis: polymerase epsilon (POLE) ultramutated, microsatellite unstable, copy number low/microsatellite stable, and copy number high/'serous-like' [3]. The World Health Organization classification of female genital tumors in 2020 refers to the ProMisE molecular classification. The main obstacle to the application of this method is the need for diverse high-tech cooperation, which is difficult to implement

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and popularize in clinical settings [4]. Therefore, there is an urgent need to identify novel biomarkers to predict the prognosis of endometrial cancer and guide precise treatment.

Alternative splicing (AS) refers to the organization of exons from original gene transcripts (pre-mRNAs) in different ways to generate structurally and functionally distinct mRNA and protein variants. The concept of AS was first derived from the "split gene" discovered by Philip Sharp and Richard Roberts in 1977 [5]. AS and its regulation are crucial for exploring cancer. Simultaneously, the regulation of AS constitutes a hallmark of cancer [6]. More than 8,000 tumor samples from 32 different types of cancers analyzed by Kahles et al. revealed that there exist thousands of AS variants when compared with non-malignant tissues [7]. These splicing variants may provide cancer-specific markers and new antigens, which are potentially critical for cancer treatment. With the development of genome sequencing, growing evidence suggests that AS events are crucial for the prognosis of multiple malignancies [8]. Herein, we constructed a prognostic risk model of endometrial cancer by integrating the AS data in the TCGA SpliceSeq database and clinical data from the TCGA database and verified its efficacy.

Materials and methods

Data collection of alternative splicing events and data processing

We downloaded the transcript profiles (https://portal.gdc.cancer.gov/) from the TCGA data portal of the UCEC cohort on August 22, 2021. In addition, we collected AS event data from TCGA SpliceSeq (https://bioinformatics.mdanderson.org/TCGASpliceSeq/). The percentage splicing (PSI) value, typically used to quantify AS events, was calculated for each AS event. AS events included 35 non-tumor samples and 527 UCEC samples, and mRNA sequencing profiles included 23 non-tumor samples and 552 UCEC samples. Additionally, we downloaded the complete clinical data of 548 UCEC samples (including sex, age, survival status, and overall survival time), as shown in Table 1.

Table 1 Clinical characteristics of uterine corpus endometrial carcinoma

Clinical characteristics	Patients	
	n	%
Age (years)		
≤ 60	181	33
> 60	364	66.4
Unknow	3	0.6
Grade		
G1	99	18.1
G2	122	22.3
G3	316	57.7
High grade	11	1.9
Survival status		
Alive	467	85.2
Dead	81	14.8
Survival time (months)		
< 90	42	7.7
≥ 90	505	92.1
Unknown	1	0.2

Screening for prognostic AS events of UCEC

There are seven types of AS events: mutually exclusive exons (MEs), alternate donor sites (ADs), retained introns (RIs), alternate acceptor sites (AAs), alternate promoters (APs), alternate terminators (ATs), and exon skipping (ES). In total, 28,281 AS events in patients with endometrial cancer are shown in the UpSet plots. The most frequent types of AS events were AT, ES, AT& ES, AP, and ES & AP events (Fig. 1a). The PSI values of AS events in patients with endometrial cancer were supplemented by the Knn function in the R language impute package, subsequently combined with the survival time and survival status of patients. Univariate Cox regression analysis was used to screen for prognostic AS events in endometrial cancer. The screening threshold was set to $P < 0.05$, and the prognostic AS events are shown in UpSet (Fig. 1b), Volcano (Fig. 2a), and Bubble (Fig. 2b–2h).

Establishment of the prognostic model related to AS events of UCEC

Least absolute shrinkage and selection operator (LASSO) regression analysis was used to screen survival-associated AS events of endometrial cancer to construct a prognostic model that prevents overfitting of the model and improves accuracy. Next, the risk score of each UCEC was calculated and divided into high- or low-risk groups based on the median risk score. Subsequently, the screened AS events were analyzed using multivariate Cox regression analysis to construct a prognostic risk model for UCEC. The formula was as follows: Risk score = $\beta_{gene1} \times expr_{gene1} + \beta_{gene2} \times Expr_{gene2} + \cdots + \beta_{genen} \times Expr_{genen}$. A $P < 0.05$ was considered statistically significant, and the PSI value of AS was indicated by $Expr_{genen}$.

Evaluation of prognostic models

To assess the predictive ability of this prognostic model, receiver operating characteristic (ROC) curves and Kaplan–Meier curve survival analysis were performed. In addition, heatmaps, risk scores, and scatter plots of survival-associated AS events were plotted according to the ranking of risk scores. The clinical characteristics of UCEC were analyzed using univariate and multivariate Cox regression analyses ($P < 0.05$).

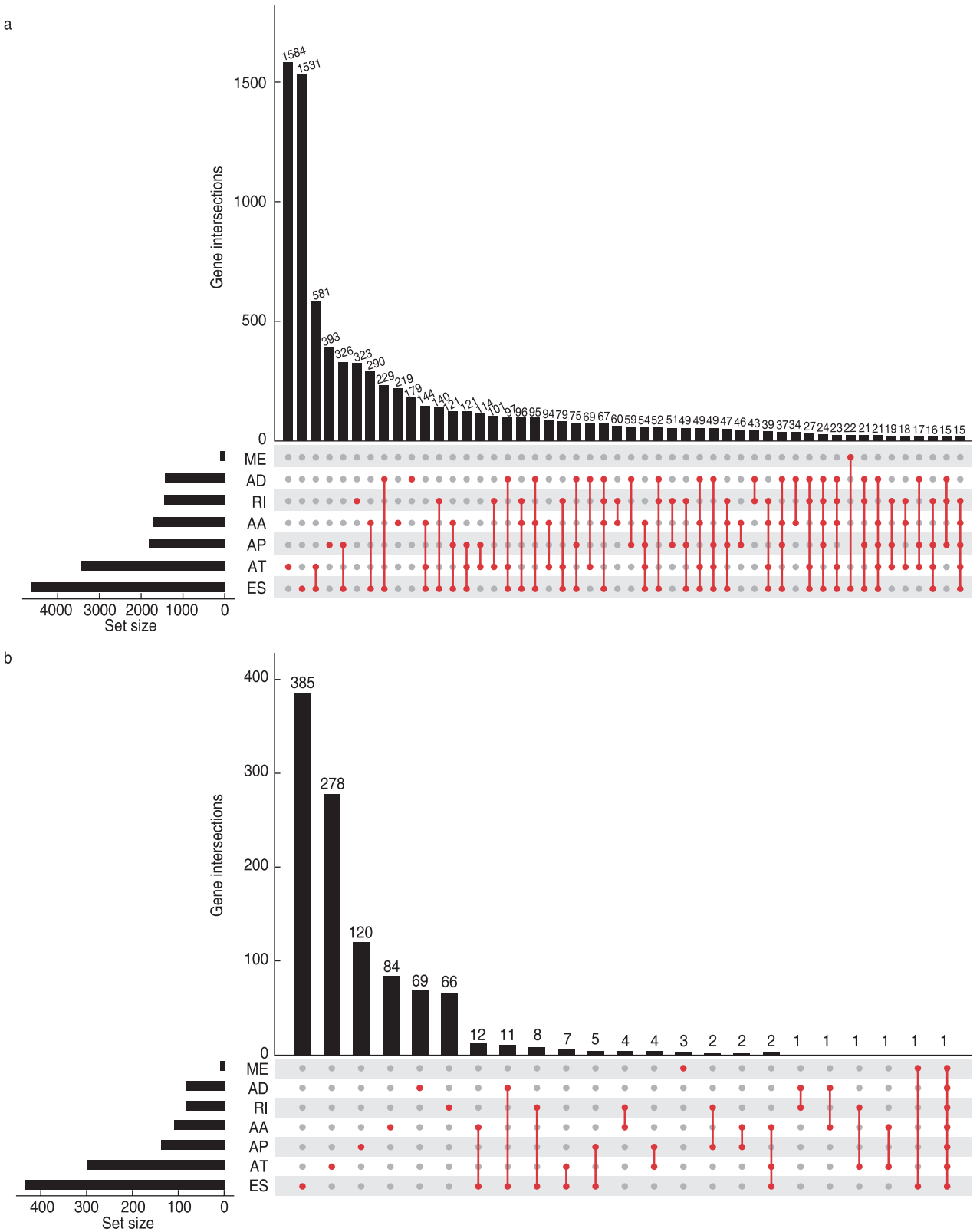

Fig. 1 The UpSet plot shows the distribution of seven types of prognostic AS events in uterine corpus endometrial carcinoma. (a) The distributions of seven different types of AS-related genes in uterine corpus endometrial carcinoma; (b) Distribution of seven AS events that significantly correlate with overall survival. AS, alternative splicing; ME, mutually exclusive exons; AD, alternate donor site; RI, retained intron; AA, alternate acceptor; AP, alternate promoter; AT, alternate terminator; ES, exon skipping

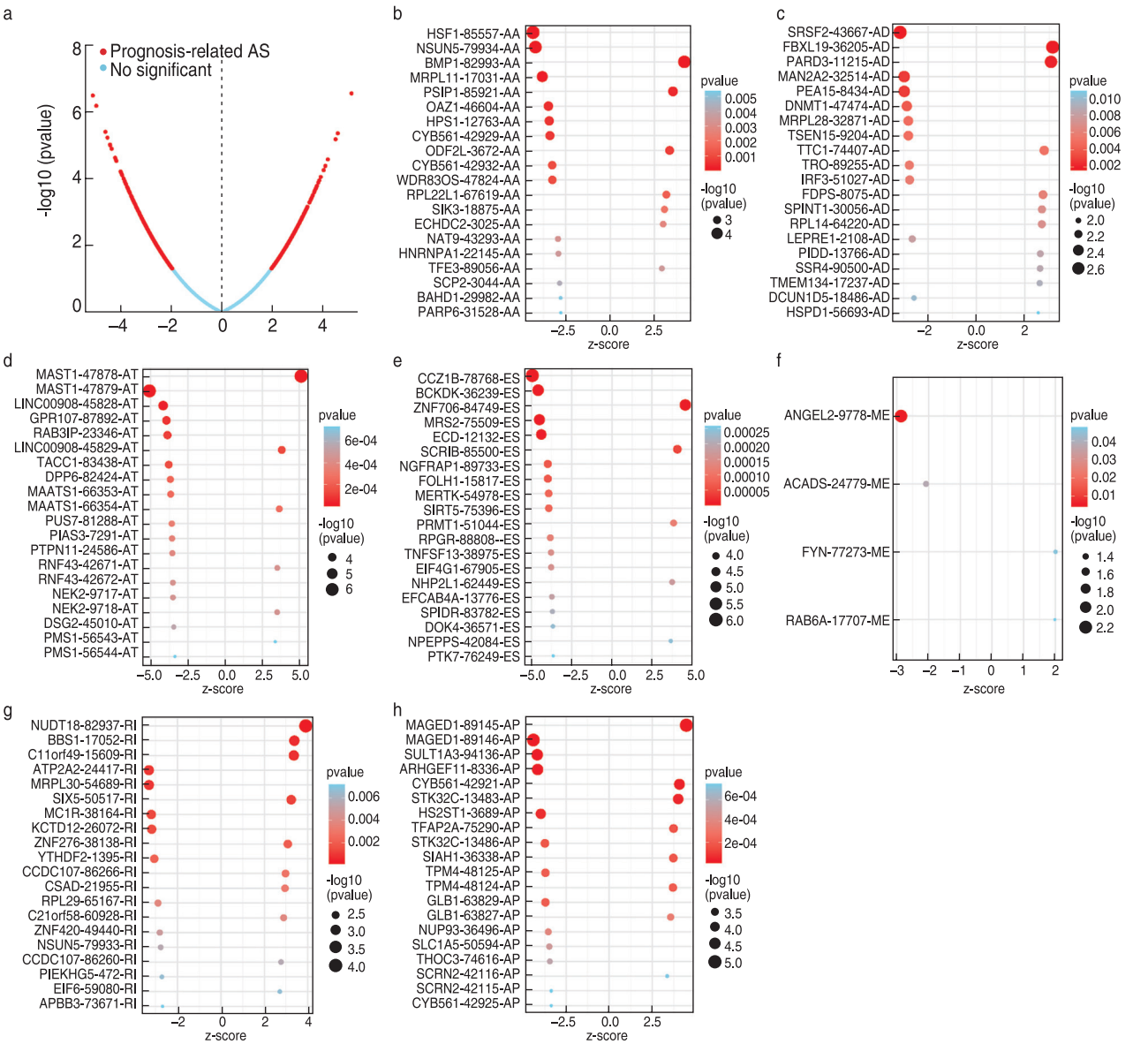

Fig. 2 Prognostic AS events in uterine corpus endometrial carcinoma. (a) Volcano plots of prognostic AS events; (b–h) Forest plots: hazard ratios of the top 20 overall survival-associated AA, AD, AT, ES, ME, RI and AP events. *P* values are indicated by the color scale on the right side. AA, alternate acceptor; AD, alternate donor site; AP, alternate promoter; AS, alternative splicing; AT, alternate terminator; ES, exon skipping; ME, mutually exclusive exons; RI, retained intron

Construction of splicing regulatory network

To better explore the biological processes and pathways of AS-related genes, Cytoscape (version 3.7.2) was used to construct and visualize the regulatory network between survival-related AS events and splicing factors (SFs).

Statistical analysis

Statistical analyses were performed using R version 4.1.1 (R packages: UpSetR, BiocManager, Survival, ggplot, ggplot2, glmnet, Survminer, Survival ROC, estimate, Vioplot, pheatmap, and forestplot). For all analyses, a two-tailed $P < 0.05$ was deemed statistically significant.

Results

Overview of prognostic AS events in UCEC

A total of 2630 prognostic AS events of endometrial cancer were screened using univariate Cox regression analysis ($P < 0.05$), among which ES, AT, AP, AA, and AD events exhibited a higher frequency (Fig. 1b). In addition, prognostic AS events are shown in volcano plots, with the red dots representing prognostic AS (Fig. 2a). Seven types of AS events were most prominently displayed in the forest plots (Fig. 2b–2h). These are indicated by the gene-AS number-AS event type. The size of dots indicates –

log10 (*P* value) using univariate Cox regression analysis, and the color of dots indicates the *P* value (Fig. 1d).

Establishment of a prognostic prediction model for UCEC

On reducing the number of AS events to 18, as indicated by the LASSO regression analysis, the lambda error value of the prognostic model had the minimum error and highest accuracy (Fig. 3a). The coefficients of each PSI value were calculated using the LASSO regression analysis (Table 2).

Evaluation of the prognostic model of UCEC

The overall survival time of the low-risk group was remarkably longer than that of the high-risk group, as determined using the Kaplan–Meier curve analysis (P = 2.148E-11, Fig. 3d). The area under the ROC curve for this score was 0.827 (Fig. 3c). The heatmap, risk score, and scatter plots of prognostic AS events in UCEC indicated that the higher the risk score, the shorter the survival time and greater the number of deaths (Fig. 4a–4c). According to the results of the heatmap, the frequency of 13 AS events, including MAST1|47879|AT, increased the risk score, indicating that all 13 AS events were high-risk AS events (Fig. 4a). Univariate and multivariate Cox regression analyses revealed that the risk score of the prognostic model could be used as a prognostic biomarker (P < 0.001) (Table 3). Tumor grade could be employed as an independent prognostic factor (Table 3).

Network analysis of prognostic AS and SFs

To elucidate the potential mechanism of AS regulation, we constructed a correlation network between the expression level of SFs and the PSI value of prognostic AS events. Two high-risk AS events (red ellipse), four low-risk AS events (green ellipse), and six SFs were identified (purple triangle) (Fig. 5). In our regulatory network, the first four most important nodes were termed central SFs or AS events, including two downregulated AS events (HNRNPA1-22149-ES and TIMM13-46608-AD). Therefore, these key AS factors are involved in the dysregulation of AS in endometrial cancer and further

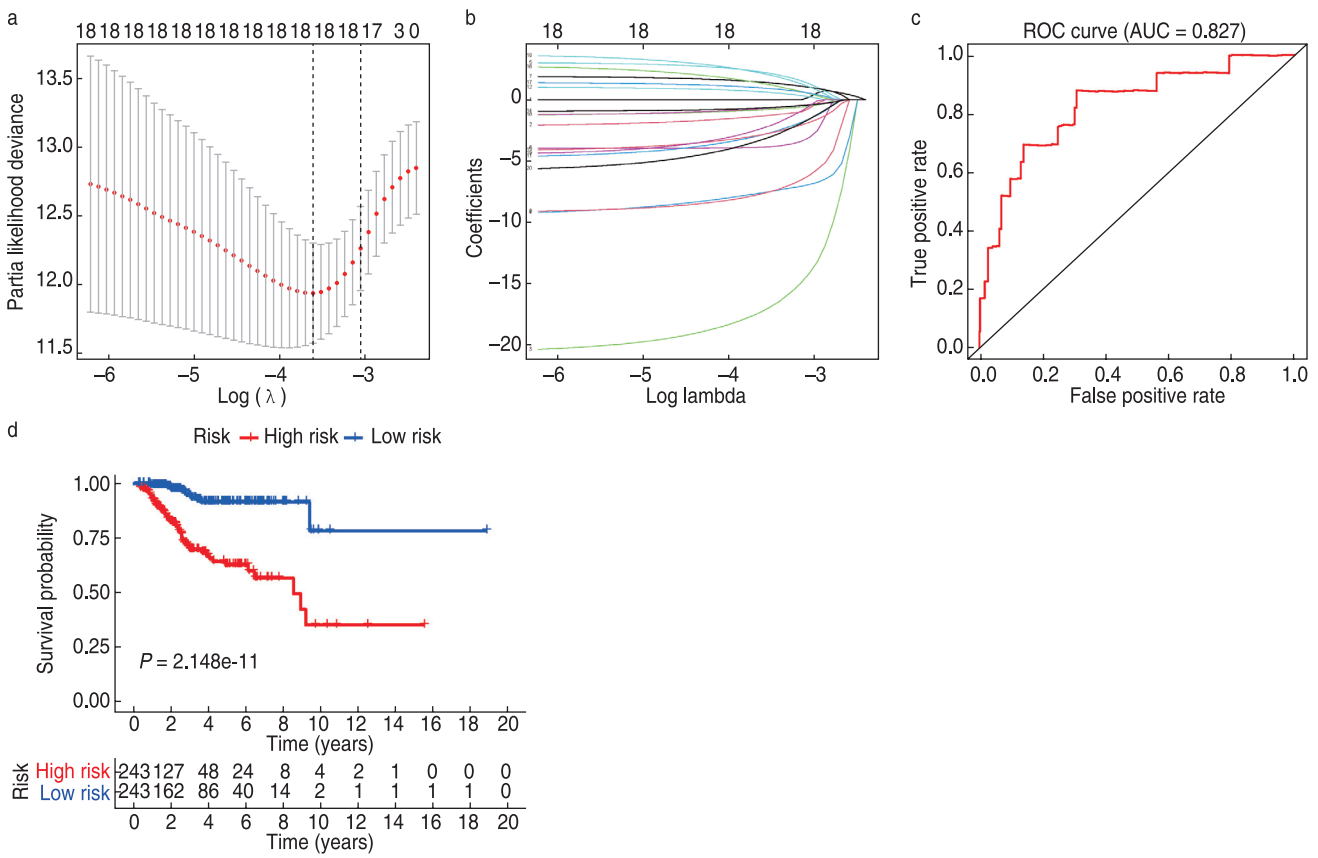

Fig. 3 Confirmation of 13 survival-associated AS event-based prognostic signatures. (a) LASSO coefficient profiles of all AS events; (b) Ten-time cross-validation for tuning parameter selection in the LASSO regression; (c) ROC analysis of risk scores for overall survival prediction. The AUC was calculated for ROC curves, and sensitivity and specificity were calculated to assess score performance; (d) Kaplan–Meier curve of the risk score model based on the characteristic 13 AS events. AS, alternative splicing; AUC, area under the curve; ROC, receiver operating characteristic

Table 2 Survival-associated AS events in uterine corpus endometrial carcinoma identified by multivariate Cox regression analysis

Survival-associated AS events	Coef	HR (95%CI)	*P* value
MAST1|47879|AT	−1.875	0.0153 (0.051–0.464)	0.001
CCZ1B|78768|ES	−21.536	4.43E-10 (2.06E-16–0.001)	0.004
ZNF706|84749|ES	3.660	38.869 (1.155–1307.78)	0.041
MAGED1|89145|AP	2.138	8.483 (0.527–136.567)	0.132
ECD|12132|ES	−15.883	1.27E-07 (1.02E-12–0.016)	0.008
NSUN5|79934|AA	−5.959	0.003 (0.000–0.061)	< 0.001
SULT1A3|94136|AP	−1.460	0.232 (0.050–1.078)	0.062
ARHGEF11|8336|AP	−4.486	0.011 (0.001–0.150)	0.001
CYB561|42921|AP	3.073	21.616 (3.505–133.292)	0.001
SCRIB|85500|ES	1.521	4.579 (0.770–27.235)	0.094
STK32C|13483|AP	4.028	56.151 (6.000–525.480)	< 0.001
NGFRAP1|89733|ES	−7.963	0.0003 (2.31E-07–0.525)	0.033
FOLH1|15817|ES	−5.876	0.003 (0.000–0.037)	8.05E-06

AS, alternative splicing; HR, hazard ratio; coef, coefficient

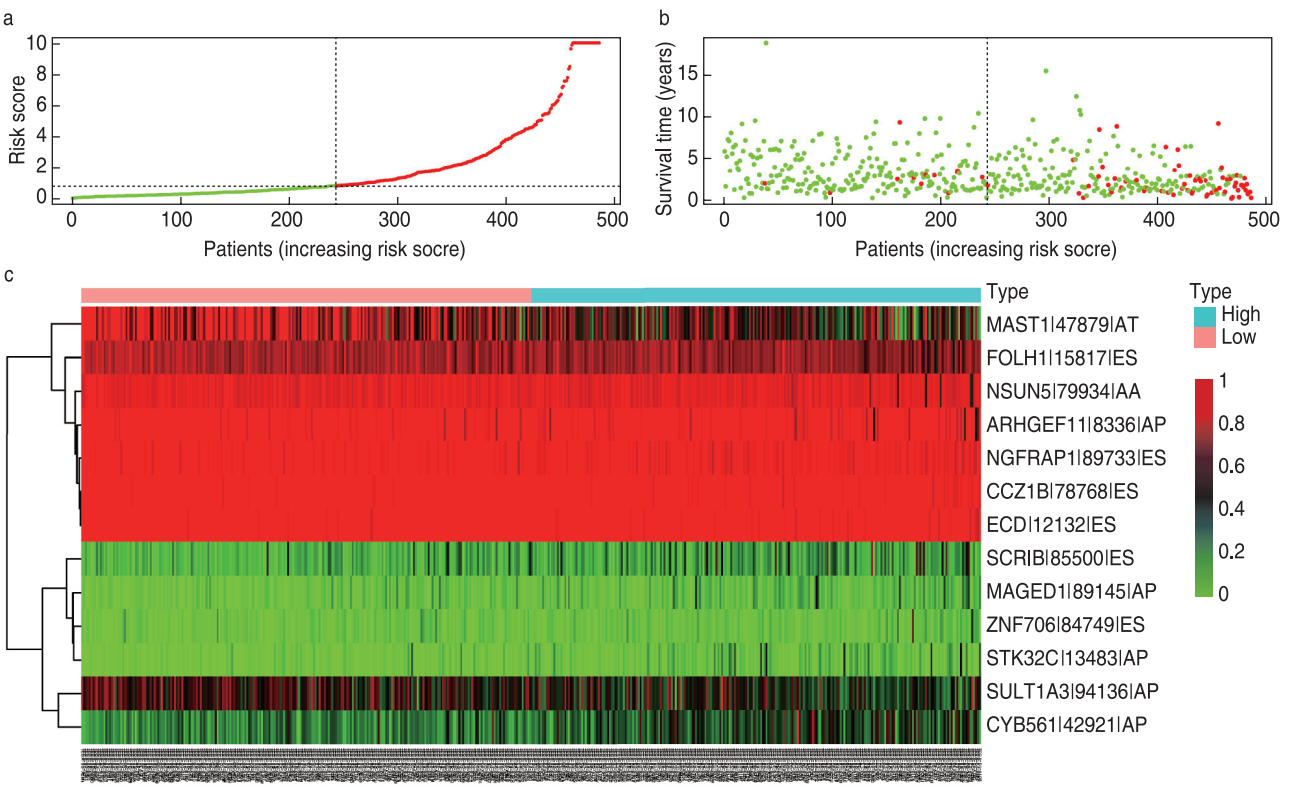

Fig. 4 a–c: Risk score, scatter plots, and heatmap of prognostic AS events in uterine corpus endometrial carcinoma. AS, alternative splicing

mediate cancer occurrence and development.

Discussion

As one of the most common malignant reproductive tumors in females, UCEC has a high incidence worldwide, and the prognosis of patients with advanced disease remains poor [1, 2]. Given the complex molecular mechanisms, such as genomic complexity and epigenetic diversity, endometrial cancer is highly heterogeneous from clinical and molecular perspectives. Moreover, it can be challenging to implement and popularize the prognostic risk model of endometrial cancer predicted by ProMisE and TCGA, owing to technical reasons [3, 4, 9]. Therefore, there is an urgent need to develop a powerful tool for predicting the prognosis of endometrial

Table 3 Univariate and multivariate Cox regression analyses of clinical characteristics in uterine corpus endometrial carcinoma

Clinical characteristic	Univariate Cox regression		Multivariate Cox regression	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age	1.032 (1.008–1.056)	0.008	1.011 (0.987–1.036)	0.364
Grade	2.501 (1.602–3.904)	5.50E-05	2.557 (1.584–4.128)	< 0.001
Risk score	1.070 (1.057–1.083)	1.56E-27	1.071 (1.056–1.086)	3.35E-22

CI, confidence interval; HR, hazard ratio

carcinoma and providing new insights for individualized treatment strategies.

A growing body of research has provided strong evidence indicating the role of AS (post-transcriptional modification process) in the physiological and pathological processes of malignant tumors [8]. Abnormal AS events play an important role in the occurrence and development of endometrial carcinoma [10, 11].

To identify prognostic AS events of UCEC, we obtained 527 AS events of endometrial cancers from TCGA SpliceSeq and clinical data from TCGA database. LASSO Cox regression and univariate/multivariate Cox regression were used for constructing a prognostic risk model based on the 13 AS events. The 13 AS events were MAST1|47879|AT, CCZ1B|78768|ES, ZNF706|84749|ES, MAGED1|89145|AP, ECD|12132|ES, NSUN5|79934|AA and SULT1A3|944. AP, SCRIB|85500|ES, STK32C|13483|AP, NGFRAP1|89733|ES, and FOLH1|15817|ES. Folic acid hydrolase-1 (FOLH1) is a type II transmembrane protein expressed in the lumen of the new vascular system in solid tumors. FOLH1 is widely expressed in the neovascularization of primary and metastatic Merkel cell carcinoma, and the monoclonal antibody J591 can be used for brachytherapy based on the FOLH1 monoclonal antibody in Merkel cell carcinoma [12]. The neurotransmitter N-acetylaspartyl glutamate (NAAG) is a selective endogenous agonist of the metabotropic glutamate receptor 3. Increasing NAAG levels may improve cognition. Glutamate carboxypeptidase II (GCP II) is encoded by the folate hydrolase 1 (*FOLH1*) gene, which regulates synaptic NAAG levels. Increasing the level of NAAG by inhibiting FOLH1/GCPII could improve cognition [13]. In the present study, we found that low expression of FOLH1 was related to poor prognosis in endometrial carcinoma. The B-module protein is a conserved regulator of cell polarity. Originally identified as a tumor suppressor in *Drosophila melanogaster*, the destruction of the Scrib protein can lead to tumorigenesis in mammals and is associated with human cancers (ovarian cancer, gastric cancer, and colorectal cancer) [14–17]. Scrib plays a key role in the establishment of cell polarity during migration [18]. STK32C, a member of the AGC superfamily serine/threonine protein kinase, was found to be highly

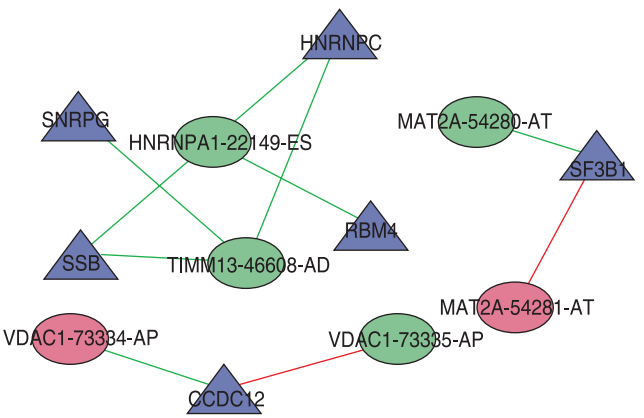

Fig. 5 Gene interaction networks between alternative splicing (AS) factors and prognostic AS events. Purple triangle: spliced factors, green ellipse: low-risk AS events, red ellipse: high-risk AS events, green line: a negative correlation, red line: a positive correlation

expressed in brain tissue. Erlsun et al. have shown that high STK32C protein expression in tumor tissues was significantly related to poor clinicopathological features and short-term recurrence-free survival rate in patients with bladder cancer [19]. STK32C inhibits tumor cell migration, proliferation, and invasion *in vitro* Cytochrome B561 (CYB561) is a conserved transmembrane transport protein with chelating reductase activity that specifically acts on secretory vesicles of neuroendocrine substances (catecholamine and neuropeptide). It is widely expressed in human tissues and promotes the growth and metastasis of castrated neuroendocrine prostate cancer cells. The low expression level of CYB561 mRNA in ovarian cancer has been associated with poor prognosis and may serve as a prognostic biomarker. Zhou *et al.* have reported that CYB561 can be used as a prognostic biomarker for breast cancer [20]. Rho guanine nucleotide exchange factor 11 (ARHGEF11) has been shown to promote tumor metastasis in glioblastoma and ovarian cancer. Du et al. have found that ARHGEF11 can promote the proliferation and metastasis of liver cancer by activating the β-catenin pathway and that ARHGEF11 may be a potential prognostic biomarker of liver cancer [21]. NSUN5 encodes cytosine-5 RNA methyltransferase. Jiang et al. have determined that NSUN5 is a promoter of colorectal

development mediated via cell cycle regulation [22]. Melanoma antigen D1 (MAGED1) is a member of the type II melanoma antibody (MAGE) family. Downregulation of MAGED1 expression has been documented in glioma stem cells and breast cancer cell lines and may play a critical role in cancer and apoptosis. Zeng et al. have reported a correlation between the expression of melanoma antigen D1 in colorectal cancer and prognosis [23]. Microtubule-related serine/threonine kinase 1 (MAST1) is the main driver of cisplatin resistance in human cancer. Mechanistically, cisplatin inhibits the mitogen-activated protein kinase (MAPK) pathway by separating cRaf from MEK1, whereas MAST1 replaces cRaf to reactivate the MAPK pathway in a cRaf-independent manner [24].

According to the prognostic risk model constructed based on AS events of these 13 genes, the AUC of the ROC curve was 0.827, indicating that the model presented medium accuracy. However, this study has some limitations: (1) Data were from a single database, the sample size was relatively small, and a single ethnicity was evaluated. In the future, this needs to be verified in a larger sample population, using multicenter and multi-region populations. (2) The clinical information from the TCGA database is incomplete, and some information, such as tumor stage, was lacking. (3) Currently, few studies are available on the parental genes of AS, and their function in endometrial cancer remains unclear. Additional basic research is needed to further explore the mechanisms underlying these AS events.

In conclusion, we identified 13 AS events based on data from TCGA and TCGA SpliceSeq databases and established a prognostic risk model with moderate predictive accuracy. Furthermore, we identified risk score and tumor grade as independent prognostic factors for UCEC.

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Conflicts of interest
The authors indicated no potential conflicts of interest.

Author contributions
Kai Qin conceived and designed the experiments and revised the manuscript; Yi Cheng, Long Li and Chen Gong analyzed the data; Yi Cheng drafted the manuscript. All authors have read and approved the final manuscript.

Data availability statement
Not applicable.

Ethical approval
Not applicable.

References

1. Xia C, Dong X, Li H, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. Chin Med J (Engl). 2022;135(5):584-590.
2. Morice P, Leary A, Creutzberg C, et al. Endometrial cancer. Lancet. 2016;387(10023):1094-1108.
3. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.
4. Kommoss S, McConechy MK, Kommoss F, et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Ann Oncol. 2018;29(5):1180-1188.
5. Chow LT, Gelinas RE, Broker TR, et al. An amazing sequence arrangement at the 5' ends of adenovirus 2 messenger RNA. Cell. 1977;12(1):1-8.
6. Ladomery M. Aberrant alternative splicing is another hallmark of cancer. Int J Cell Biol. 2013;2013:463786.
7. Jin H, Wang C, Jin G, et al. Regulator of calcineurin 1 gene isoform 4, down-regulated in hepatocellular carcinoma, prevents proliferation, migration, and invasive activity of cancer cells and metastasis of orthotopic tumors by inhibiting nuclear translocation of NFAT1. Gastroenterology. 2017;153(3):799-811.e33.
8. Bessa C, Matos P, Jordan P, et al. Alternative splicing: expanding the landscape of cancer biomarkers and therapeutics. Int J Mol Sci. 2020;21(23):9032.
9. Marín-Jiménez JA, García-Mulero S, Matías-Guiu X, et al. Facts and hopes in immunotherapy of endometrial cancer. Clin Cancer Res. 2022:clincanres.1564.2022.
10. Konno R, Takano T, Sato S, et al. Serum soluble fas level as a prognostic factor in patients with gynecological malignancies. Clin Cancer Res. 2000;6(9):3576-3580.
11. Sun D, Zhang A, Gao B, et al. Identification of alternative splicing-related genes CYB561 and FOLH1 in the tumor-immune microenvironment for endometrial cancer based on TCGA data analysis. Front Genet. 2022;13:770569.
12. Ramirez-Fort MK, Meier-Schiesser B, Lachance K, et al. Folate hydrolase-1 (FOLH1) is a novel target for antibody-based brachytherapy in Merkel cell carcinoma. Skin Health Dis. 2021;1(1):e9.
13. Zink CF, Barker PB, Sawa A, et a. Association of missense mutation in FOLH1 with decreased NAAG levels and impaired working memory circuitry and cognition. Am J Psychiatry. 2020;177(12):1129-1139.
14. Nakajima YI. Scrib module proteins: Control of epithelial architecture and planar spindle orientation. Int J Biochem Cell Biol, 2021. 136: 106001.
15. Shen H, Huang C, Wu J, et al. SCRIB promotes proliferation and metastasis by targeting Hippo/YAP signalling in colorectal cancer. Front Cell Dev Biol. 2021;9:656359.
16. Hussein UK, Ha SH, Ahmed AG, et al. FAM83H and SCRIB stabilize β-catenin and stimulate progression of gastric carcinoma. Aging (Albany NY). 2020;12(12):11812-11834.
17. Hussein UK, Ahmed AG, Choi WK, et al. SCRIB is involved in the progression of ovarian carcinomas in association with the factors linked to epithelial-to-mesenchymal transition and predicts shorter survival of diagnosed patients. Biomolecules. 2021;11(3):405.
18. Osmani N, Vitale N, Borg JP, et al. Scrib controls Cdc42 localization

and activity to promote cell polarization during astrocyte migration. Curr Biol. 2006;16(24):2395-2405.
19. Sun E, Liu K, Zhao K, et al. Serine/threonine kinase 32C is overexpressed in bladder cancer and contributes to tumor progression. Cancer Biol Ther. 2019;20(3):307-320.
20. Zhou X, Shen G, Ren D, et al. Expression and clinical prognostic value of CYB561 in breast cancer. J Cancer Res Clin Oncol. 2022;148(8):1879-1892.
21. Du JP, Zhu ZX, et al. ARHGEF11 promotes proliferation and epithelial-mesenchymal transition of hepatocellular carcinoma through activation of beta-catenin pathway. Aging (Albany NY), 2020. 12(20): 20235-20253.
22. Jiang Z, Li S, Han MJ, et al. High expression of NSUN5 promotes cell proliferation via cell cycle regulation in colorectal cancer. Am J Transl Res. 2020 Jul 15;12(7):3858-3870. Erratum in: Am J Transl Res. 2020 Oct 15;12(10):6976.
23. Zeng ZL, Wu WJ, Yang J, et al. Prognostic relevance of melanoma antigen D1 expression in colorectal carcinoma. J Transl Med. 2012 10:181.
24. Jin L, Chun J, Pan C, et al. MAST1 drives cisplatin resistance in human cancers by rewiring cRaf-Independent MEK activation. Cancer Cell. 2018;34(2):315-330.e7.

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