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MAZ-mediated N6-methyladenosine modification of ZEB1 promotes hepatocellular carcinoma progression by regulating METTL3

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Abstract

Background Hepatocellular carcinoma (HCC) has a hidden onset and high malignancy. Its high metastasis, high recurrence, and short survival time have always been a difficult and hot spot in clinical practice. Our previous study revealed that myc-associated zinc finger protein (MAZ) is highly upregulated in HCC tissues and may promote the proliferation and metastasis of HCC cells by inducing the epithelial-mesenchymal transformation (EMT) process. However, the specific regulatory mechanism by which MAZ functions as an oncogene in HCC has still not been fully elucidated.

Methods Immunohistochemical staining and bioinformatics analyses were conducted to measure the expression of MAZ, key m6A enzymes, and ZEB1 in HCC tissues. RNA sequencing (RNA-seq) of MAZ knockdown HCC cells and human mRNA m6A sequencing (m6A-seq) of HCC tissues were intersected to screen the downstream targets for both MAZ and m6A methylation. The correlations between MAZ and its targets were analyzed by dual-luciferase assays and cell rescue experiments.

Results Here, we report for the first time that MAZ is involved in m6A methylation of HCC by targeting the transcriptional regulation of key m6A enzymes. MAZ expression was significantly correlated with the expression of key m6A enzymes in HCC tissues and cell lines. Moreover, MAZ could bind to the promoters of key m6A enzymes, and multivariate Cox regression analysis suggested that MAZ and METTL3 expression were independent risk factors for the survival of HCC patients. Through RNA-seq and m6A-seq, we screened out EMT regulators ZEB1 and TRIM50 as the downstream targets for both MAZ and m6A methylation. Mechanistically, m6A sites with high confidence in ZEB1 and TRIM50 mRNA were identified by SRAMP, and there were significant relationships between ZEB1 and METTL3 in HCC tissues and cells. A nomogram model was established to better display the combined effect of MAZ, METTL3, and ZEB1 on HCC prognosis.

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Conclusions Our study revealed a promising clinical application of MAZ, METTL3, and ZEB1 in HCC prognosis, further suggesting that MAZ can be used as a potential molecular biomarker for HCC diagnosis and prognosis.

Keywords MAZ, m6A methylation, HCC, EMT, ZEB1

Background

Primary liver cancer is the sixth most common cancer and the third leading cause of cancer death in the world, with nearly 1 million new cases and approximately 830,000 new deaths, of which hepatocellular carcinoma (HCC) accounts for approximately 75-85% [1]. Cohort studies have shown that the prognosis of HCC patients is extremely poor, with relatively low 3-year and 5-year survival rates, which are even lower in patients with advanced HCC [2–4]. HCC has an insidious onset and high degree of malignancy, and most HCC patients are diagnosed and treated in the middle and late stages of disease progression, eventually leading to a poor prognosis [5]. Surgery, radiotherapy and chemotherapy, targeted therapy, and immunotherapy have improved the clinical curative effect, but the high postoperative recurrence and metastasis rates of HCC still need to be solved. Therefore, it is urgent to explore key biomarkers and study the molecular mechanisms involved in the occurrence and development of HCC, which is highly important for the early diagnosis and treatment of HCC patients.

Myc-associated zinc finger protein (MAZ) relies on its carboxyl-terminal six type C2H2 zinc fingers to bind to a GC-rich sequence in the promoter region of target genes [6–8]. MAZ is ubiquitously expressed in most human tissues and has been confirmed to play different regulatory roles in gene transcription. It can transactivate or inhibit some genes, such as the proto-oncogene c-myc [9], ras gene family [10], PDPN [11], VEGF [12], PPARγ1 [13], and eNOS [14]. MAZ also plays a role in the termination of gene transcription, such as p53 [15], the human complement C2 gene [16], ZO-1, occludin, and claudin-5 [17]. Studies have reported that MAZ is abnormally highly expressed in a variety of tumors and is closely related to tumor development because it directly binds to target gene promoters. Our previous study revealed that MAZ is upregulated in HCC tissues, which may promote the proliferation and metastasis of HCC cells by inducing the epithelial-mesenchymal transformation (EMT) process [18], indicating that MAZ can be used as a potential molecular biomarker for the diagnosis and treatment of HCC patients. However, the specific regulatory mechanism by which MAZ functions as an oncogene in HCC has still not been fully elucidated.

Epigenetic modifications have been a research hotspot in the field of cancer in recent years. Abnormal epigenetic regulation plays an important role in the occurrence and development of human malignancies, including HCC. As one of the most common RNA modifications, N6-methyladenine nucleotide (m6A) is involved in stem cell differentiation, embryonic development, adipogenesis, DNA damage repair, and immune homeostasis [19, 20]. Increasing evidence indicates that m6A deregulation is closely related to HCC occurrence and development [21–23]. The m6A modification is a dynamic reversible type of posttranscriptional regulation that is regulated by "writers", "erasers", and "readers" [24]. "Writers", including methyltransferase-like protein 3/14 (METTL3/14), and Wilms tumor-associated protein 1 (WTAP), are responsible for catalyzing the methylation of N6-adenosine on mRNAs. "Erasers" are responsible for the removal of bases with m6A modifications, including fat-mass and obesity-related proteins (FTO) and alkylation repair protein B homolog 5 (ALKBH5). "Readers" are responsible for identifying the bases undergoing m6A modification, thus activating downstream regulatory pathways, including YTH domain proteins, nuclear heterogeneous riboproteins, and eukaryotic initiation factors. The function and mechanism of m6A modification have been studied in various tumors. For example, in gastric cancer, METTL3 promotes the translation of SPHK2 mRNA in an m6A-YTHDF1-dependent manner, and SPHK2 functionally promotes cancer cell proliferation, migration, and invasion by inhibiting the expression of KLF2 [25]. METTL14 overexpression directly targets downstream PERP mRNA through m6A methylation, reducing PERP mRNA and protein levels, and promoting the metastasis of pancreatic cancer [26]. However, the association between MAZ and m6A methylation has not been identified in HCC.

In this study, we first analyzed the correlation between MAZ and key m6A enzymes in HCC cells and tissues, and then performed RNA sequencing to explore the regulatory mechanism by which MAZ participates in m6A modification. Our study reveals the key role of MAZ in HCC progression, and provides novel diagnostic markers and molecular prognostic targets for HCC patients.

Materials and methods

Tissue samples

The paraffin-embedded samples of HCC and adjacent liver tissues from HCC patients were obtained from the Department of Pathology, the Affiliated Hospital of Guilin Medical University. All the patients underwent surgical treatment without preoperative radiotherapy or chemotherapy. The clinicopathological data of the patients were collected from medical records and are shown in Table 1. All patients were followed once every

Table 1 Univariate and multivariate COX regression analysis of overall survival of HCC patients

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
MAZ (High vs. Low)	3.598	1.949–6.632	**0.001**	3.409	1.840–6.316	**0.001**
METTL3 (High & Low)	2.244	1.250–4.026	**0.007**	1.630	0.806–3.295	0.174
METTL14 (High & Low)	0.321	0.176–0.583	**0.001**	0.400	0.150–1.070	0.102
FTO (High & Low)	0.529	0.306–0.915	**0.023**	0.643	0.353–1.172	0.149
ALKBH5 (High & Low)	0.454	0.243–0.847	**0.013**	0.621	0.192–2.005	0.426
Age (≥ 55 & <55 years)	1.080	0.571–2.045	0.812			
Gender (Male & Female)	0.702	0.253–1.946	0.496			
Pathological grade (III+IV & I+II)	1.079	0.511–2.280	0.842			
TNM stage (T3 + T4 & T1 + T2)	1.512	0.602–3.796	0.379			
Tumor size (≥ 5 & <5 cm)	1.903	1.065–3.401	**0.030**	1.900	1.040–3.344	**0.037**
Tumor number (Multiple & Single)	1.743	0.630–4.821	0.285			
Metastasis (Yes & No)	1.241	0.448–3.436	0.677			
Cirrhosis (Yes & No)	1.516	0.898–2.558	0.119			
Hepatitis B infection (Yes & No)	1.511	0.684–3.342	0.308			
Macrovascular invasion (Yes & No)	1.033	0.573–1.864	0.913			
Tumor capsular (No vs. Yes)	1.572	0.887–2.787	0.121			
AFP (≥ 400 & <400 ng/mL)	1.519	0.895–2.579	0.121			
CEA (≥ 3.4 & <3.4 ng/mL)	1.131	0.618–2.069	0.690			
CA-199 (≥ 40 & <40 U/mL)	1.588	0.801–3.148	0.186			
ALB (< 40 & ≥40 g/L)	1.586	0.889–2.830	0.118			
ALT (≥ 40 & <40 U/L)	1.384	0.784–2.445	0.263			
AST (≥ 40 & <40 U/L)	1.321	0.785–2.222	0.295			
GGT (≥ 40 & <40 U/L)	1.764	0.755–4.121	0.190			
ALP (≥ 150 & <150 U/L)	1.188	0.582–2.423	0.636			

Bold value indicates significant

six months by clinic visits or telephone until April 2015, and survival was calculated in months. Overall survival (OS) was calculated from postoperative day 1 to death or the last follow-up. Recurrence-free survival (RFS) was calculated from postoperative day 1 until the onset of recurrence, death, or last follow-up. This study was approved by the Ethics Committee of Guilin Medical University (GLMC2014003), and informed consent was obtained from each patient for all tissue specimens and clinicopathological data.

Cell lines and plasmids

The human liver cell lines L02, HepG2, Hep3B, SK-Hep-1, Huh7, and MHCC-97 H, were obtained and cultured as previously described [27].

Lentiviral plasmids for MAZ and METTL3 knockdown (KD1 and KD2) were synthesized as previously

described [18]. For the luciferase assay, 2,000 bp promoter sequences of ZEB1 (NM_001174096), TRIM50 (NM_178125), METTL14 (NM_020961), METTL3 (NM_019852), ALKBH5 (NM_017758), and FTO (NM_001363900) were incorporated into the GV238 vector. A MAZ overexpressed plasmid was constructed with the CV702 vector. Wild-type ZEB1 sequence was generated and inserted into the GV492 vector. All these plasmids were purchased from Genechem (Shanghai, China).

Total m6A methylation detection

The total m6A methylation of cells was detected via an Epigenase m6A Methylase Activity/Inhibition Assay Kit (Epigentek, Farmingdale, NY, USA) according to the manufacturer's instructions.

Dual-luciferase reporter assay

After plasmid transfection in 293T cells for 48 h, the luciferase activity was measured with the Dual-Luciferase Reporter Assay System (Promega, Madison, WI, USA). The relative firefly luciferase activity was normalized to the Renilla luciferase activity.

Immunohistochemical (IHC) staining

After the paraffin-embedded samples were made into tissue microarrays by OUTDO BIOTECH (Shanghai, China), the IHC staining and scoring processes were conducted according to a previous study [28]. Antibodies against MAZ (ab85725, Abcam, Cambridge, UK), METTL3 (ab195352, Abcam), METTL14 (AMAb91275, Atlas Antibodies, Stockholm, Sweden), FTO (HPA041086, Atlas Antibodies), ALKBH5 (HPA007196, Atlas Antibodies), and ZEB1 (ab181451, Abcam) were used for IHC staining.

RNA transcriptomic sequencing (RNA-seq) and human mRNA&lncRNA epitranscriptomic microarray sequencing (m6A-seq)

Hep3B MAZ-KD1 and Hep3B-NC cells were collected for RNA-seq conducted by Genechem and the differentially expressed genes (DEGs) were analyzed as described in a previous study [28]. QRT-PCR was used to validate the RNA-seq results with corresponding primers shown in Supplementary Table 1.

Six paired HCC and adjacent liver tissues from HCC patients were selected for m6A-seq via Aksomics (Shanghai, China). To compare the two groups (HCC and adjacent liver tissues) for differential m6A modification, the fold change (FC) was set to ≥ 1.5, and the *P*-value was set to ≤ 0.05 for each transcript.

CCK8 assay

A total of 1×10^4 cells in 100 μL of medium were grown in each well of a 96-well plate, with 6 wells for each group. After the addition of CCK8 solution (Beyotime, Shanghai, China) for 2 h, the absorbance of each well was measured at 24, 48, 72, and 96 h.

Transwell invasion and migration assays

Transwell assays were used to detect the invasion and migration ability of HCC cells according to previous methods [29].

In vivo imaging

Twenty BALB/c nude mice (4 weeks old, 18–22 g) were purchased from SJA Laboratory Animal Company (Hunan, China) and fed in SPF Animal Laboratory of School of Public Health, Guilin Medical University. All animal experiments were approved by the Animal Ethics Committee of Guilin Medical University (approval No. GLMC20243166).

After quarantine period, 2×10^7/mL tumor cells were subcutaneously injected into the right anterior axillary region of nude mice, with 200 μL per animal. At day 21 after subcutaneous injection, the in vivo imaging was performed on the animals anesthetized with 0.7% pentobarbital sodium at a volume of 10 μL/g via intraperitoneal injection.

Bioinformatics analysis

The data of HCC patients were downloaded from the Cancer Genome Atlas (TCGA) database. The online tools GEPIA (http://gepia.cancer-pku.cn/detail.php) and starBase (https://Starbase.sysu.edu.cn/) were used to an alyze the expression correlations among MAZ, m6A key enzymes, and ZEB1 in HCC on the basis of TCGA data. The nomogram was created via the rms package for R software.

Statistical analysis

All the data were analyzed via SPSS 28.0 and GraphPad Prism 9 software. Spearman correlation was used to investigate the expression of proteins in HCC tissues detected by IHC. Kaplan-Meier analysis was used to draw survival curves, and the log-rank test was used to compare survival differences between the two groups. Cox proportional hazard regression analysis was used to explore the independent risk factors affecting the outcomes of HCC patients. $P < 0.05$ was considered statistically significant.

Results

MAZ mediates m6A methylation in HCC cells

To explore the potential impact of MAZ on m6A methylation, five HCC cell lines, Hep3B, HepG2, Huh7,

MHCC-97 H, and SK-Hep-1, were first selected to determine the mRNA expression level of MAZ and the total m6A level. As shown in Fig. 1A, MAZ was expressed at higher levels in HCC cells than in L02 cells, especially in Hep3B and Huh7 cells ($P < 0.05$). However, the total m6A level was lower in HCC cells than in L02 cells ($P < 0.05$, Fig. 1B). MAZ expression was subsequently knocked down in Hep3B cells ($P < 0.05$, Fig. 1C), which caused a significant increase in the total m6A level ($P < 0.05$, Fig. 1D), indicating that MAZ inhibits the total m6A level in HCC cells.

Four key enzymes for m6A methylation, METTL3, METTL14, FTO, and ALKBH5, were subsequently chosen for analysis of their correlation with MAZ. Compared with those in negative control cells, the mRNA expression level of METTL3 in MAZ-knockdown Hep3B cells was decreased, whereas the mRNA expression levels of METTL14, FTO, and ALKBH5 were increased (all $P < 0.05$, Fig. 1E). Because MAZ is a transcription factor, we screened the possible binding of MAZ to the promoter sequences of these four key m6A enzymes. After MAZ was overexpressed in 293T cells ($P < 0.05$, Fig. 1F), we found that MAZ could bind to the promoter regions of METTL3, METTL14, FTO, and ALKBH5, with the strongest binding between MAZ and METTL3 promoter (all $P < 0.05$, Fig. 1G). These results show that MAZ plays a role in total m6A methylation by regulating the transcription of key m6A enzymes in HCC cells.

MAZ regulates the expression of key m6A enzymes in HCC tissues

To further clarify the role of MAZ in m6A methylation, we performed IHC staining and bioinformatics analysis to detect the correlation between MAZ and the four key m6A enzymes in HCC tissues. MAZ was significantly correlated with METTL3 ($r = 0.52$), METTL14 ($r = 0.22$), ALKBH5 ($r = 0.39$), and FTO ($r = 0.29$) in the TCGA database (all $P < 0.05$, Fig. 2A). IHC of eighty HCC tissues revealed that MAZ, METTL3, METTL14, FTO, and ALKBH5 were expressed in the cell nucleus and cytoplasm (Fig. 2B), with positive expression in 50 HCC tissues (62.50%), 52 HCC tissues (65.00%), 31 HCC tissues (38.75%), 35 HCC tissues (43.75%), and 23 HCC tissues (28.75%), respectively (Table 2). The eighty HCC tissues were divided into a high MAZ group with positive MAZ expression and a low MAZ group with negative MAZ expression, and the correlations between the four key m6A enzymes and MAZ expression were subsequently analyzed. The rate of high METTL3 expression in the MAZ-high group was 86.00% (43/50), and METTL3 expression was positively correlated with MAZ expression in HCC tissues ($r = 0.568$, $P = 0.001$). However, the high expression rates of METTL14, FTO, and ALKBH5 in the MAZ-high group were 18.00% (9/50), 34.00% (17/50), and 16.00% (8/50), respectively, and the expression of METTL14, FTO, and ALKBH5 in HCC tissues was negatively correlated with MAZ expression ($r = -0.550$, $P = 0.001$; $r = -0.254$, $P = 0.023$; $r = -0.364$, $P = 0.001$; Table 2).

Furthermore, the prognostic significance of MAZ, METTL3, METTL14, FTO, and ALKBH5, was investigated on the basis of the IHC results and clinicopathological features of HCC patients. As shown in Tables 1 and 3, MAZ, METTL3, METTL14, and ALKBH5 expression, were independent risk factors affecting overall survival (OS) and recurrence-free survival (RFS) in HCC patients according to univariate Cox regression analysis (all $P < 0.05$). But FTO was only correlated with OS of HCC patients. However, only MAZ expression was an independent risk factor for both OS and RFS of HCC patients after multivariate analysis (HR = 3.409, 95% CI: 1.840 ~ 6.316, $P = 0.001$; HR = 4.953, 95% CI: 2.362 ~ 10.388, $P = 0.001$). In addition, multivariate Cox regression analysis revealed that tumor size was an independent risk factor for OS (HR = 1.900, 95% CI: 1.040 ~ 3.344, $P = 0.037$), and METTL3 expression (HR = 4.251, 95% CI: 1.289 ~ 14.014, $P = 0.017$) and pathological grade (HR = 5.053, 95% CI: 1.386 ~ 18.414, $P = 0.014$) were independent risk factors for RFS in HCC patients. These results indicate that MAZ and METTL3 are correlated more significantly with HCC prognosis.

As shown in Fig. 2C, the median OS and RFS survival times of HCC patients with high MAZ expression were 14.5 months and 4.3 months, respectively, which were lower than those of HCC patients with low MAZ expression according to the log-rank test (both $P = 0.001$). The median OS and RFS survival times of HCC patients with high METTL3 expression were 16.5 months and 5.1 months, respectively, which were lower than those of HCC patients with low METTL3 expression according to the log-rank test ($P = 0.005$ and $P = 0.006$; Fig. 2D). All these HCC tissue findings verify the above results in HCC cells and support a significant prognostic role of MAZ and METTL3 in HCC patients.

ZEB1 and TRIM50 are key downstream target genes of MAZ via m6A methylation in HCC

To identify the target genes of MAZ in HCC, RNA-seq was performed in MAZ knockdown Hep3B cells. Compared with those in the negative control cells, there were 1,364 DEGs, including 626 downregulated genes and 738 upregulated genes. Six paired HCC and adjacent liver tissues from six HCC patients were selected for m6A-seq, and 474 mRNAs with differentially expressed m6A modifications, including 106 hypermethylated and 368 hypomethylated mRNAs, were identified. After intersecting the RNA-seq data of MAZ and HCC m6A-seq, 19 MAZ downstream genes, including TRIM50, TRIM23,

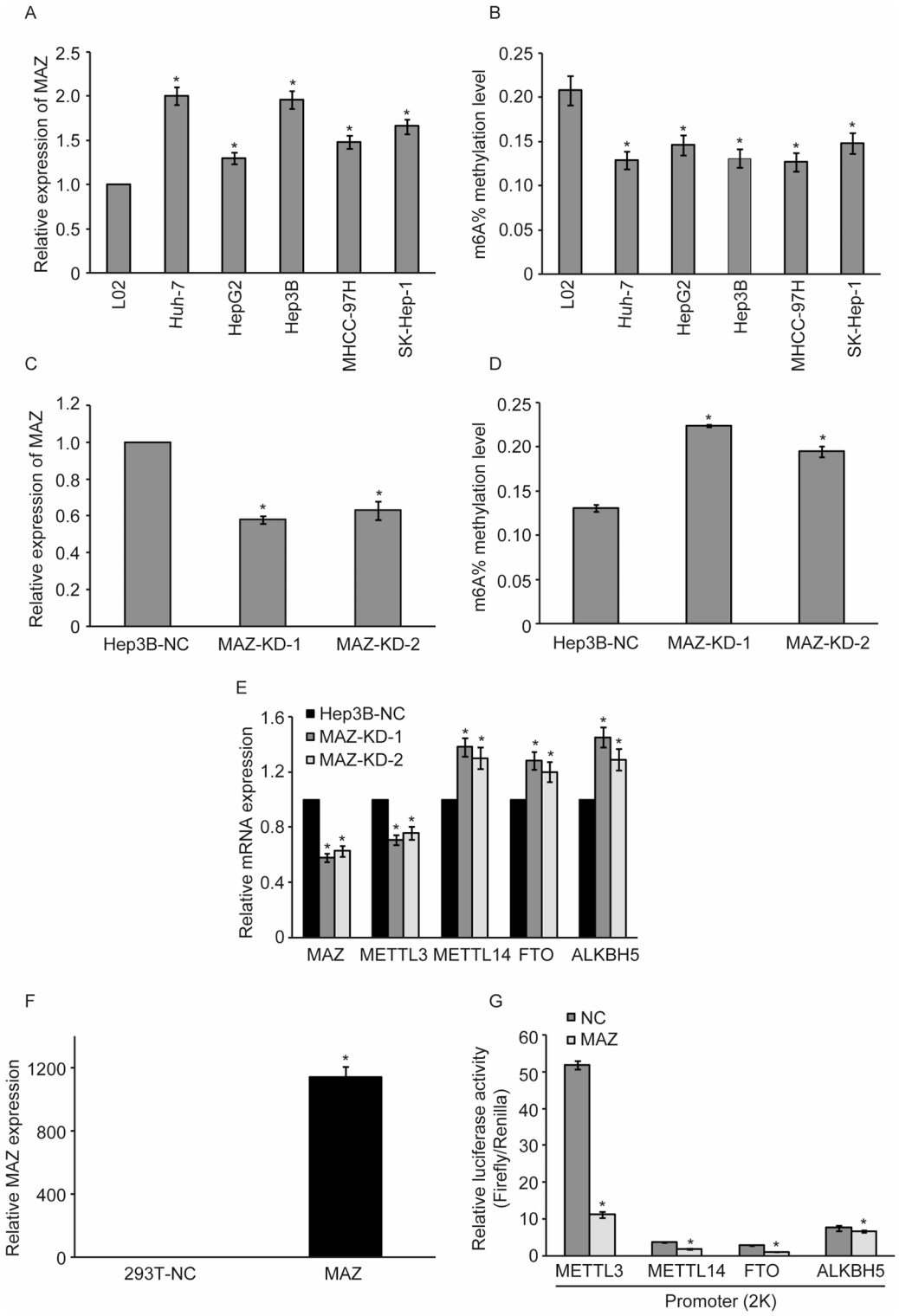

Fig. 1 MAZ regulates m6A methylation in HCC cells. (**A**) MAZ expression in L02 and HCC cells. (**B**) Total m6A methylation in L02 and HCC cells. (**C**) MAZ expression detected by RT-qPCR after MAZ knockdown (MAZ-KD-1 and MAZ-KD-2) in Hep3B cells. (**D**) Total m6A methylation detected after MAZ knockdown (MAZ-KD-1 and MAZ-KD-2) in Hep3B cells. (**E**) Expression of MAZ and m6A key enzymes detected by RT-qPCR after MAZ knockdown (MAZ-KD-1 and MAZ-KD-2) in Hep3B cells. (**F**) MAZ expression detected by RT-qPCR after MAZ overexpressed (MAZ) in 293T cells. (**G**) Binding ability of MAZ to promoter regions of key m6A enzymes detected via a dual-luciferase reporter assay. *, indicates $P<0.05$ compared with L02 cells or negative control (NC) cells

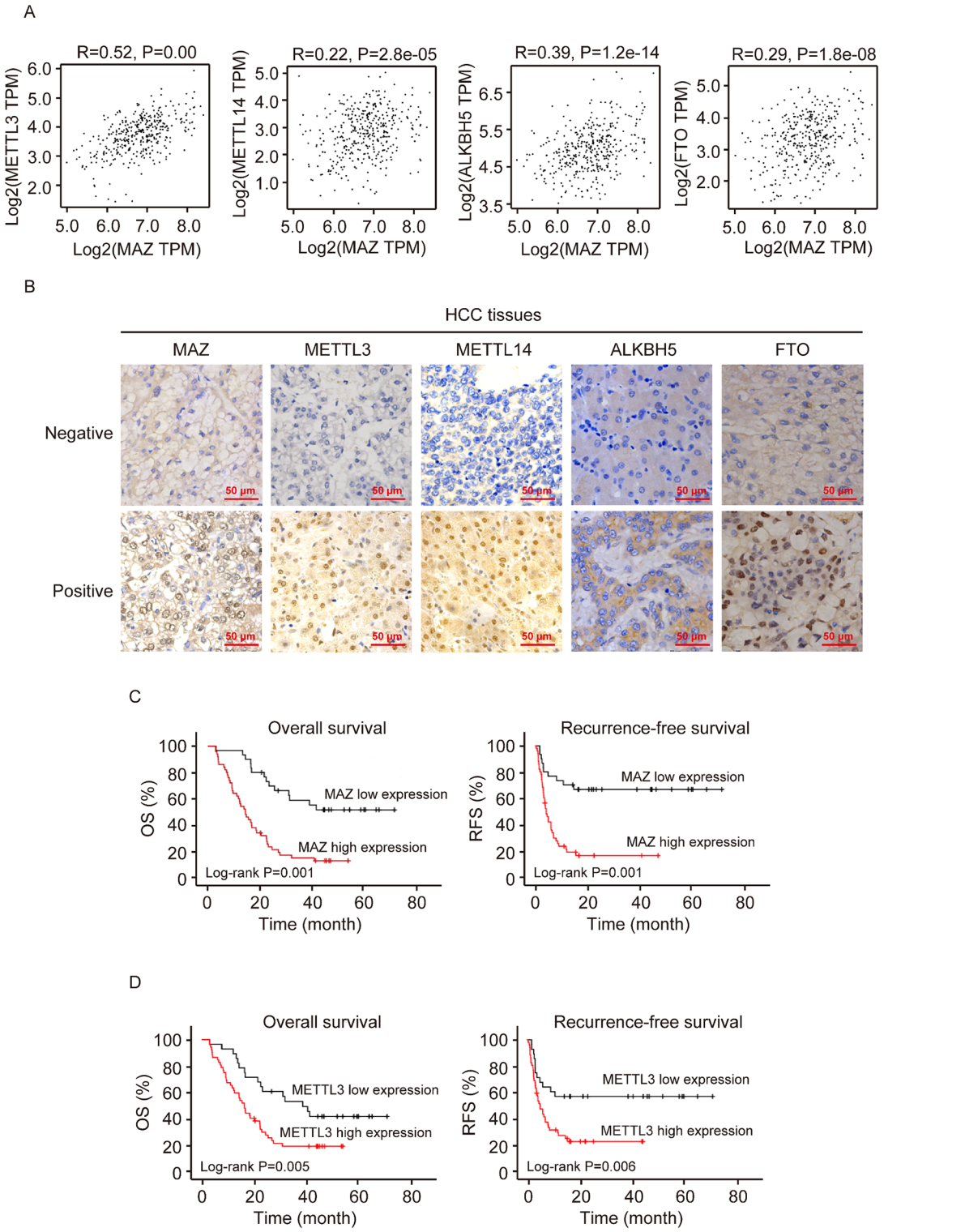

Fig. 2 Correlations between MAZ and key m6A enzymes in HCC tissues. (**A**) MAZ expression is correlated with the expression of METTL3, METTL14, ALKBH5, and FTO in HCC tissues based on TCGA database. (**B**) Positive and negative expression of MAZ, METTL3, METTL14, ALKBH5, and FTO in HCC tissues determined by immunohistochemical analysis. (**C**) Overall survival and recurrence-free survival of HCC patients with low or high MAZ expression. (**D**) Overall survival and recurrence-free survival of HCC patients with low or high METTL3 expression

Table 2 Correlation between MAZ expression and m6A key enzymes in HCC tissues

m6A enzymes	*n*	MAZ expression		χ^2	*r*	*P* value
		High	Low			
METTL3						
High	52	43	9	25.846	0.568	**0.001**
Low	28	7	21			
METTL14						
High	31	9	22	24.188	-0.550	**0.001**
Low	49	41	8			
FTO						
High	35	17	18	5.150	-0.254	**0.023**
Low	45	33	12			
ALKBH5						
High	23	8	15	10.581	-0.364	**0.001**
Low	57	42	15			

Bold value indicates significant

ZNF641, and ZEB1, were identified to have differential m6A modifications in HCC tissues (Fig. 3A). Because our previous study revealed that MAZ regulated HCC cell metastasis by inducing EMT (18), we chose ZEB1 and TRIM50 as the target genes of MAZ because of their key role in EMT.

We verified the RNA-seq results in MAZ knockdown Hep3B cells and found that the knockdown of MAZ caused a significant decrease in ZEB1 expression, but increase in TRIM50 expression (Fig. 3B). The dual-luciferase assay further confirmed that MAZ could bind to the promoter region of ZEB1 and TRIM50 (Fig. 3C). Moreover, both the expression of ZEB1 and TRIM50 was positively associated with MAZ expression in HCC tissues ($r = 0.34$ and 0.16, both $P < 0.01$; Fig. 3D), suggesting that MAZ can regulate the transcription of ZEB1 and TRIM50 in HCC. Next, the SRAMP website was used to predict the m6A methylation sites in the mRNA sequences of ZEB1 and TRIM50. As shown in Fig. 3E, there were eleven high confidence (green site positions) and three very high confidence m6A sites (pink site position) in ZEB1 mRNA sequence, while six high confidence and one very high confidence m6A sites in TRIM50 mRNA sequence, confirming that ZEB1 and TRIM50 mRNA can be methylated by m6A. These results demonstrate that ZEB1 and TRIM50 are potential target genes of MAZ's involvement in HCC m6A methylation.

ZEB1 is correlated with key m6A enzymes in HCC tissues and cells

To further explore m6A methylation possibility of ZEB1 and TRIM50 in HCC, we firstly detected their relationship with METTL3, METTL14, ALKBH5, and FTO in HCC tissues through bioinformatics analysis. ZEB1 was significantly correlated with all the four key m6A enzymes ($r = 0.48$, 0.62, 0.25, and 0.71, all $P < 0.01$; Fig. 4A). However, TRIM50 expression had a correlation only with ALKBH5 expression ($r = 0.11$, $P = 0.035$; Fig. 4B). Subsequently, we confirmed the bioinformatics results in HCC cells. METTL3, ZEB1, and TRIM50 were all up-regulated in HCC cells compared with normal liver L02 cells, especially highly expressed in SK-Hep-1 cells (Fig. 4C and D, and 4E). Then we disturbed METTL3 expression with knockdown plasmids in SK-Hep-1 cells and found that only ZEB1 expression was decreased ($P < 0.05$, Fig. 4F), which was consistent with the tissue results. These analyses indicate that ZEB1 can be regulated by m6A methylation in HCC.

The prognostic significance of MAZ, METTL3, and ZEB1 in HCC patients

We performed rescue experiments to verify if ZEB1 is a key downstream target of MAZ mediated m6A methylation. As shown in Fig. 5A, both MAZ and METTL3 knock-down significantly inhibited Hep3B cell proliferation ($P < 0.05$). However, ZEB1 overexpression increased the cell proliferation after Hep3B cells were knocked-down with MAZ or METTL3 ($P < 0.05$). Moreover, Transwell assays revealed that Hep3B cells with ZEB1 overexpression after MAZ or METTL3 knockdown had greater invasion and migration abilities than did control MAZ or METTL3 knockdown cells ($P < 0.05$, Fig. 5B). These findings suggest that ZEB1 is the key downstream target of MAZ and METTL3. Xenograft models further support that METTL3 and ZEB1 had a crucial role in HCC cell progression (Fig. 5C).

As the significant correlation was found between ZEB1 and METTL3 expression in HCC tissues and cells by bioinformatics and gene knockdown methods, we further measured their expression in another 90 HCC tissues by IHC staining. Supplementary Fig. 1 shows the positive and negative expression of ZEB1 and METTL3 in HCC tissues, and there was a positive relationship between

Table 3 Univariate and multivariate COX regression analysis of recurrence-free survival of HCC patients

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
MAZ (High vs. Low)	4.186	2.073–8.451	**0.001**	4.953	2.362–10.388	**0.001**
METTL3 (High & Low)	2.401	1.253–4.599	**0.008**	4.251	1.289–14.014	**0.017**
METTL14 (High & Low)	0.290	0.148–0.569	**0.001**	0.588	0.195–1.773	0.346
FTO (High & Low)	0.648	0.367–1.145	0.135			
ALKBH5 (High & Low)	0.409	0.198–0.842	**0.015**	0.691	0.214–2.232	0.537
Age (≥ 55 & <55 years)	1.146	0.600-2.191	0.680			
Gender (Male & Female)	1.056	0.329–3.394	0.927			
Pathological grade (III+IV & I+II)	3.665	1.138–11.798	**0.029**	5.053	1.386–18.414	**0.014**
TNM stage (T3 + T4 & T1 + T2)	1.312	0.520–3.311	0.565			
Tumor size (≥ 5 & <5 cm)	2.084	1.109–3.919	**0.023**	1.652	0.830–3.289	0.153
Tumor number (Multiple & Single)	1.308	0.471–3.638	0.606			
Metastasis (Yes & No)	1.257	0.391–4.040	0.702			
Cirrhosis (Yes & No)	1.171	0.676–2.029	0.574			
Hepatitis B infection (Yes & No)	1.802	0.767–4.232	0.176			
Macrovascular invasion (Yes & No)	1.804	0.902–3.609	**0.095**	1.583	0.390–6.422	0.520
Tumor capsular (No vs. Yes)	0.935	0.526–1.662	0.819			
AFP (≥ 400 & <400 ng/mL)	1.010	0.582–1.751	0.973			
CEA (≥ 3.4 & <3.4 ng/mL)	1.236	0.632–2.416	0.536			
CA-199 (≥ 40 & <40 U/mL)	1.756	0.896–3.444	0.101			
ALB (< 40 & ≥40 g/L)	1.693	0.913–3.139	**0.095**	1.416	0.736–2.725	0.297
ALT (≥ 40 & <40 U/L)	1.530	0.813–2.878	0.188			
AST (≥ 40 & <40 U/L)	1.182	0.682–2.048	0.551			
GGT (≥ 40 & <40 U/L)	2.010	0.724–5.585	0.180			
ALP (≥ 150 & <150 U/L)	1.092	0.531–2.246	0.811			

Bold value indicates significant

ZEB1 and METTL3 expression ($r = 0.330$, $P = 0.002$; Table 4), which was consistent with the above results.

To search the potential clinical application of MAZ, METTL3, and ZEB1 in HCC, we analyzed their prognostic significance via online databases. The mRNA expression of MAZ, METTL3, and ZEB1 was greater in HCC tissues than in normal liver tissues from both the starBase and TCGA databases (all $P < 0.05$, Fig. 5D). To better display the combined effect of MAZ, METTL3, and ZEB1 on prognosis, a nomogram model was established on the basis of the mRNA expression of MAZ, METTL3, and ZEB1 in the TCGA database (Fig. 5E). When an HCC patient is aged 60 (point: 0), male (point: 0) at the pathologic stage of T1 (point: 0), N1 (point: 34) and M1 (point: 0), with high MAZ expression (point: 4), high METTL3 expression (point: 28) and high ZEB1 expression (point: 0), the total number of points is 66, and the suspected 1-year survival rate of this HCC patient is approximately

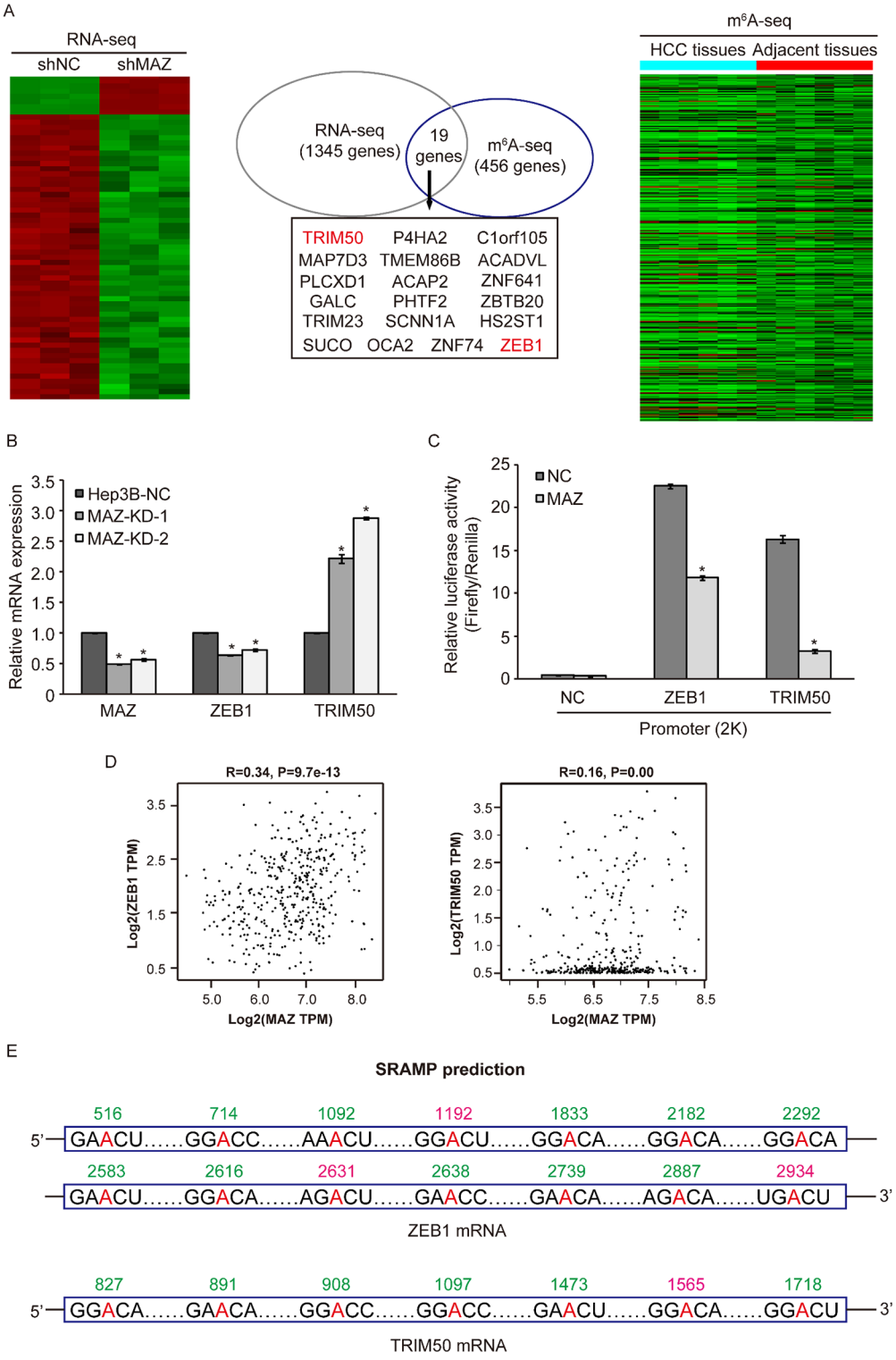

Fig. 3 ZEB1 and TRIM50 expression is regulated by MAZ and m6A methylation in HCC cells. (**A**) Intersection analysis between the RNA-seq data of MAZ-knockdown Hep3B cells and the m6A-seq data of HCC tissues from HCC patients. (**B**) ZEB1 and TRIM50 expression detected by RT-qPCR after MAZ knockdown in Hep3B cells. (**C**) Binding ability of MAZ to ZEB1 and TRIM50 promoter detected by a dual-luciferase reporter assay. (**D**) MAZ expression is correlated with the expression of ZEB1 and TRIM50 in HCC tissues based on TCGA database. (**E**) M6A position in the mRNA region of ZEB1 and TRIM50 as predicted by SRAMP, pink numbers are m6A sites with very high confidence and green numbers with high confidence. *, indicates $P<0.05$ compared with negative control (NC) cells

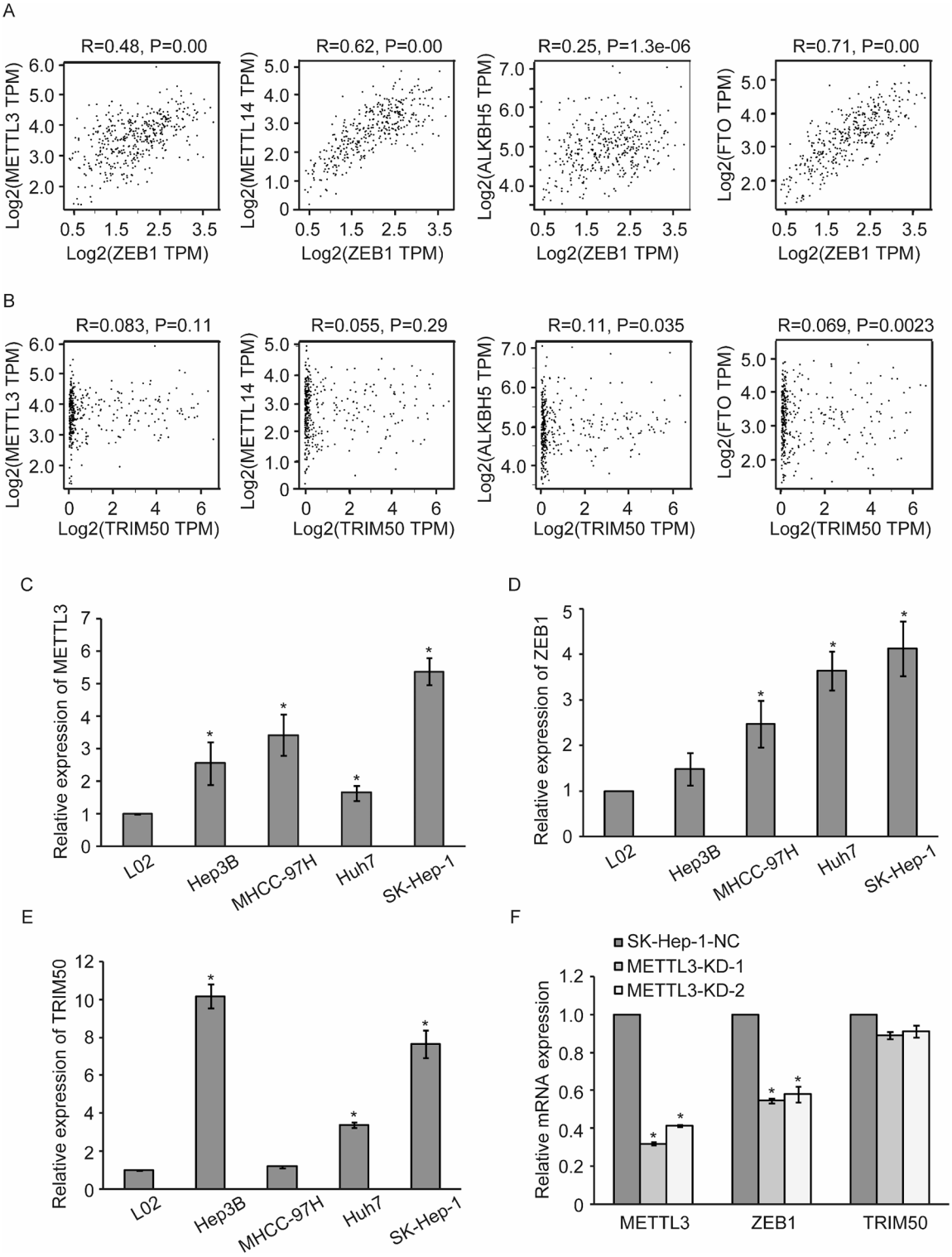

Fig. 4 The correlations of ZEB1/TRIM50 with key m6A enzymes. (**A**) Correlation of ZEB1 expression with key m6A enzymes in HCC tissues based on TCGA database. (**B**) Correlation of TRIM50 expression with key m6A enzymes in HCC tissues based on TCGA database. (**C**) METTL3 expression in L02 and HCC cells. (**D**) ZEB1 expression in L02 and HCC cells. (**E**) TRIM50 expression in L02 and HCC cells. (**F**) The expression of METTL3, ZEB1, and TRIM50 in SK-Hep-1 cells after METTL3 knockdown. *, indicates $P<0.05$ compared with L02 or negative control (NC) cells

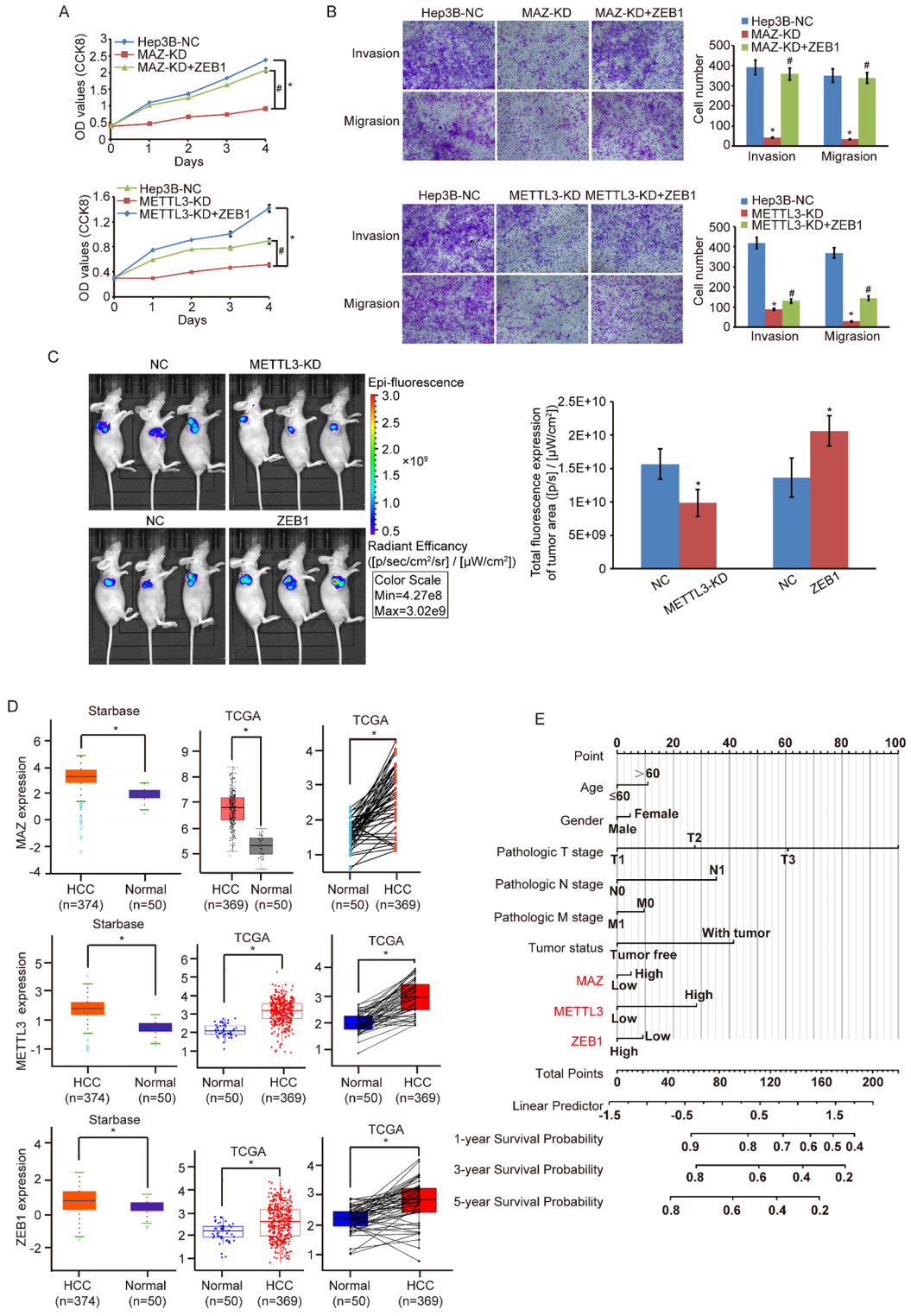

Fig. 5 The expression and prognostic significance of MAZ, METTL3, and ZEB1 in HCC patients. (**A**) Proliferation of Hep3B cells detected by a CCK8 assay after MAZ or METTL3 knock-down and ZEB1 overexpression. *, indicates $P<0.05$ compared with the control (NC) cells, and #, indicates $P<0.05$ compared with the MAZ or METTL3 knock-down (KD) cells. (**B**) Metastasis of Hep3B cells detected by Transwell assay after MAZ or METTL3 knock-down and ZEB1 overexpression. *, indicates $P<0.05$ compared with the control (NC) cells, and #, indicates $P<0.05$ compared with the MAZ or METTL3 knock-down (KD) cells. (**C**) In vivo imaging of nude mice injected Hep3B cells with METTL3 knock-down or ZEB1 overexpression. *, indicates $P<0.05$ compared with the control (NC) cells. (**D**) The expression of MAZ, METTL3, and ZEB1 in HCC tissues in online databases. * indicates $P<0.05$ compared with the normal liver tissues. (**E**) Prognostic nomogram model of MAZ, METTL3, and ZEB1 in HCC patients

Table 4 Correlation between the expression of METTL3 and ZEB1 in HCC tissues

ZEB1 expression	METTL3 expression		χ^2	r	*P* value
	High	Low			
High	39	7	9.791	0.330	**0.002**
Low	24	20			

Bold value indicates significant

88%. The 3-year survival rate is approximately 76%, and the 5-year survival rate is approximately 66%. These online results further support the potential prognosis application of MAZ/METTL3/ZEB1 expression in HCC patients.

Discussion

In this study, we first reported the key role of MAZ in HCC m6A methylation and prognosis via targeting of METTL3 and ZEB1 transcription. MAZ expression was significantly correlated with the expression of the four m6A key enzymes in HCC tissues and cell lines. A dual-luciferase assay verified that MAZ could also bind to the promoter of the four m6A key enzymes, and multivariate Cox regression analysis suggested that MAZ and the four m6A key enzymes expression were independent risk factors for the survival of HCC patients. Mechanistically, m6A methylation of ZEB1 and TRIM50 mRNA was screened out as the critical downstream targets of MAZ by intersection of RNA-seq and m6A-seq. Our study revealed a previously unknown function of MAZ in the regulation of HCC m6A methylation.

As an important transcription factor that is widely expressed in human tissues, MAZ has been reported to be aberrantly highly expressed in multiple malignancies and is considered a potential target for tumor therapy. In breast cancer, MAZ can bind at the start of the tumor-specific promoter pA1 to promote high expression of PPARγ1, which leads to increased cell proliferation and inhibited cell apoptosis [30]. The upregulation of MAZ can activate the RalGEFs/Ral signaling pathway through the transcriptional activation of K-ras, thus further promoting the invasion, migration and bone metastasis of prostate cancer cells [31]. MAZ is highly expressed in clear renal cell carcinoma tissues, and MAZ upregulation promoted renal cancer cell proliferation in vitro [32]. Consistent with our previous study [18], multivariated Cox regression analysis of 80 cases of HCC patients via IHC revealed that MAZ was an independent risk factor affecting OS and RFS in HCC patients, further suggesting that MAZ has significance in the prognosis of HCC patients and may be a potential prognostic biomarker for HCC. Moreover, we found a significant correlation between MAZ expression and key m6A enzymes in HCC tissues from both the IHC and online databases. The total m6A level was increased after MAZ knockdown in HCC cells, and the transcription of key m6A enzymes can be regulated by MAZ through promoter binding, suggesting that MAZ may inhibit m6A methylation through key m6A enzymes, especially METTL3 in HCC.

METTL3 functions in catalyzing m6A methylation by forming a complex with several other m6A writers, and METTL3 is the only catalytic subunit in the complex [33]. METTL3 affects tumor development through multiple processes, including m6A methylation, mRNA stability, and translational regulation. In HCC, METTL3 knockdown significantly inhibited tumorigenicity and lung metastasis in vivo, and reduced the proliferation, migration and colony formation of HCC cells in vitro. Mechanistically, METTL3 degrades SOCS2 mRNA by mediating the m6A modification and promotes HCC progression [34]. Another study revealed that METTL3 is upregulated in HCC and promotes the translation of YAP1 mRNA in an m6A-dependent manner; subsequently, YAP1 activates the Hippo pathway to promote vasculogenic mimicry [35]. In this study, we also revealed that METTL3 was overexpressed in HCC tissues and was correlated with HCC prognosis. Furthermore, a novel pathway of METTL3 in HCC progression was identified, in which METTL3 can be transcriptionally regulated by MAZ and mediate the m6A methylation of ZEB1.

The EMT process is considered to play an important role in the metastasis of tumors, including HCC [36, 37]. ZEB1 and TRIM50 are found deregulated in HCC and associated with HCC metastasis via targeting EMT key factors [38, 39]. In addition to microRNAs, ZEB1 expression can be regulated by various epigenetic modifications. For example, USP51 promotes the deubiquitylation and stabilization of ZEB1 in breast cancer cells [40], PRMT1 activates the transcription of ZEB1 by mediating dimethylation at arginine 3 of histone H4 (H4R3me2) [41], and the DNA methyltransferase inhibitor 5-Aza-2'-deoxycytidine can effectively restore the expression of ZEB1 target genes [42]. TRIM50 also can be modified by HDAC6 to function as an E3 ubiquitin ligase [43]. However, few reports have described the m6A modification of ZEB1 and TRIM50 in tumors. In the present study, the m6A sites with high confidence were identified in ZEB1 and TRIM50 mRNA, and there were significant relationships between ZEB1 and key m6A enzymes in HCC tissues and cells. In addition to the transcriptional regulation of ZEB1 by MAZ, the epigenetic modification of m6A in ZEB1 by METTL3 in HCC provides a new direction for tumor mechanism research.

There are some limitations in this study. As there are numerous m6A regulators, we only elaborated the four key enzymes, METTL3, METTL14, ALKBH5, and FTO in HCC. The relationships between MAZ/ZEB1 and other m6A regulators can be explored in future. In

addition, the correlation and mechanism of MAZ and METTL3 in regulation of ZEB1 need to be further validated from prospective population study.

Conclusions

In conclusion, we revealed a new role of MAZ in m6A methylation and potential clinical application of epitranscriptomic regulation by MAZ, METTL3, and ZEB1 in HCC prognosis. Our findings further support MAZ, METTL3, and ZEB1 as promising biomarkers for HCC diagnosis and prognosis via m6A methylation.

Abbreviations

HCC	Hepatocellular carcinoma
MAZ	Myc-associated zinc finger protein
EMT	Epithelial-mesenchymal transformation
m6A	N6-methyladenine nucleotide
FTO	Fat-mass and obesity-related proteins
ALKBH5	Alkylation repair protein B homolog 5
WTAP	Wilms tumor-associated protein 1
OS	Overall survival
RFS	Recurrence-free survival
IHC	Immunohistochemical
DEGs	Differentially expressed genes
H4R3me2	Dimethylation at arginine 3 of histone H4

Supplementary Information

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Supplementary Material 1

Supplementary Material 2: Positive and negative expression of METTL3 and ZEB1 in HCC tissues determined by immunohistochemical analysis

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Author contributions

DL, XNZ and SKT are involved with the study design. DL, LX, ZNY, RYL, CY, CJZ and SJ are involved in the study conduct. Original draft preparation is collected by DL, LX, ZNY, RYL, CY, CJZ, SJ, XFG and ZBZ. XNZ and SKT drafted and revised the manuscript.

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Data availability

The data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Guilin Medical University (GLMC2014003). Written informed consent was obtained from all the patients involved in the study.

Consent for publication

All authors consented for publication.

Competing interests

There are no competing interests.

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