

# Diagnostic and prognostic values of the mRNA expression of excision repair cross-complementation enzymes in hepatitis B virus-related hepatocellular carcinoma

Lu Yang<sup>1,\*</sup>  
 Ming Xu<sup>2,\*</sup>  
 Chuan-Bao Cui<sup>1</sup>  
 Peng-Hai Wei<sup>1</sup>  
 Shu-Zhi Wu<sup>1</sup>  
 Zuo-Jie Cen<sup>1</sup>  
 Xing-Xing Meng<sup>1</sup>  
 Qiong-Guang Huang<sup>1</sup>  
 Zhi-Chun Xie<sup>1</sup>

<sup>1</sup>Department of Epidemiology, Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, People's Republic of China;

<sup>2</sup>Department of Human Anatomy and Histology and Embryology, Qilu Medical University, Zibo 255213, Shandong Province, People's Republic of China

\*These authors contributed equally to this work

**Background:** The current study aims at using the whole genome expression profile chips for systematically investigating the diagnostic and prognostic values of excision repair cross-complementation (ERCC) genes in hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC).

**Materials and methods:** Whole genome expression profile chips were obtained from the GSE14520. The receiver-operating characteristic (ROC) curve, survival analysis, and nomogram were used to investigate the diagnostic and prognostic values of ERCC genes. Investigation of the potential function of *ERCC8* was carried out by gene set enrichment analysis (GSEA) and genome-wide coexpression analysis.

**Results:** ROC analysis suggests that six ERCC genes (*ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, and *ERCC8*) were dysregulated and may have potential to distinguish between HBV-related HCC tumor and paracancerous tissues (area under the curve of ROC ranged from 0.623 to 0.744). Survival analysis demonstrated that high *ERCC8* expression was associated with a significantly decreased risk of recurrence (adjusted  $P=0.021$ ; HR=0.643; 95% CI=0.442–0.937) and death (adjusted  $P=0.049$ ; HR=0.631; 95% CI=0.399–0.998) in HBV-related HCC. Then, we also developed two nomograms for the HBV-related HCC individualized prognosis predictions. GSEA suggests that the high expression of *ERCC8* may have involvement in the energy metabolism biological processes. As the genome-wide coexpression analysis and functional assessment of *ERCC8* suggest, those coexpressed genes were significantly enriched in multiple biological processes of DNA damage and repair.

**Conclusion:** The present study indicates that six ERCC genes (*ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, and *ERCC8*) were dysregulated between HBV-related HCC tumor and paracancerous tissues and that the mRNA expression of *ERCC8* may serve as a potential biomarker for the HBV-related HCC prognosis.

**Keywords:** HBV, hepatocellular carcinoma, diagnosis, prognosis, ERCC

## Introduction

Liver cancer is one of the most frequent malignant tumors occurring in China; besides, it has emerged as the third leading cause of cancer death in China.<sup>1</sup> According to cancer statistics in China in 2015, liver cancer is most frequently observed in males as well as in rural areas. Moreover, the temporal tendency of incidence rates in liver cancer is decreased.<sup>1</sup> The histological type of most primary liver cancers is hepatocellular carcinoma (HCC).<sup>2</sup> Hepatitis B virus (HBV) infection is identified as a risk factor for HCC, especially in China, where the infection rate of HBV is quite high. HBV is a

Correspondence: Zhi-Chun Xie  
 Department of Epidemiology, Guangxi Medical University, Shuang Yong Road 22#, Nanning 530021, Guangxi Zhuang Autonomous Region, People's Republic of China  
 Tel +86 771 535 8847  
 Email 357154887@qq.com

single-stranded DNA virus, which can be integrated into the host genome, subsequently may activate the cellular proto-oncogenes or suppress growth-regulating genes in cis,<sup>3</sup> and induce chromosomal instability or insertional mutations.<sup>4</sup> HBV-induced DNA damage is one of the potential mechanisms that contribute to the hepatocarcinogenesis of HCC.<sup>5</sup>

The excision repair cross-complementation (ERCC) genes include *ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, *ERCC6*, and *ERCC8*, constituting a set of proteins that are involved in DNA repair. Nucleotide excision repair (NER) is considered as an extensively pivotal excision mechanism, which removes DNA damage caused by various kinds factors, and a key DNA repair pathway in eukaryotic cells, whereas the ERCC genes constitute the key genes in the NER pathway.<sup>6,7</sup> As revealed by the investigations, the genetic variation or mutation of the NER pathway genes is likely to impact the cancer risk by affecting the DNA repair efficacy, and some nonsynonymous coding single-nucleotide polymorphisms or mutations in DNA repair genes or their regulatory sequences induce the phenotypic changes and are involved in cancer development.<sup>8</sup> Previous reports of the ERCC genes, suggesting they were associated with multiple cancer prognoses,<sup>9–12</sup> and polymorphisms of the ERCC genes also have significant association with the HCC development, progression, survival, and cancer susceptibility.<sup>5,13–15</sup> However, the systematic investigation of the diagnostic and prognostic values of the expression level of ERCC genes in HCC continue to be unclear. Therefore, the aim of the present study was to use the whole genome expression data set from the Gene Expression Omnibus (GEO; <https://www.ncbi.nlm.nih.gov/geo/>) public database for the purpose of systematically investigating the diagnostic and prognostic values of ERCC genes in HBV-related HCC.

## Materials and methods

### Data processing

In order to perform the present study, the inclusion criteria of public data set were set as follows: 1) the patients were HBV-related HCC; 2) the information of clinical outcome and features should be available; and 3) the data are the whole genome expression profile data. Through the retrieval of the public database, only the data set of GSE14520 caters to the inclusion criteria. GSE14520 (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE14520>; accessed May 13, 2018), a data set from the GEO public database, was included in the present study. Calculation of the expression profile chip data set of GSE14520 was carried out with the

use of the match probes package in the R platform; subsequent to that, the robust multi-array average (RMA) method in the R affy package was used to obtain probe set expression summaries.<sup>16,17</sup> Details of the experiment protocols and data processing are available at <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSM362992>. Moreover, just the data set of the Affymetrix HT Human Genome U133A Array (platform GPL3921) was included in the current study to avoid the batch effect. These patients having a clearly HBV infection were included in the current study, and those patients without complete prognostic information and other clinical features were excluded. Owing to the fact that the population included in the current study originates from the public databases and the present study does not contain any studies performed by any of the authors with human participants or animals, there is no need for approval by additional ethics committees.

### Expression distribution and survival analysis of ERCC genes

Investigation of the expression distribution of ERCC genes was carried out with the help of the independent samples *t*-test and the Metabolic gEne RAPid Visualizer (MERAV, <http://merav.wi.mit.edu/>, accessed May 13, 2018) online tool.<sup>18</sup> Receiver-operating characteristic (ROC) curves were put to use for the investigation of the potential application values in distinct HBV-related HCC tumors and adjacent normal liver tissues. The Kaplan–Meier method, with a log-rank test, and the univariate and multivariate Cox proportional hazards regression models were employed for the purpose of comparing the prognosis between different groups. Stratified analysis was employed for the assessment of the prognostic values of prognostic ERCC genes in different strata of HBV-related HCCs. Joint effect survival analyses between prognostic ERCC genes and serum alpha-fetoprotein (AFP), which is a recognized prognostic biomarker in HCC, have also been carried out for investigating the combined effect on HCC prognosis prediction. The high- and low-expression groups of the ERCC family genes were cutoff in accordance with the median values.<sup>19–22</sup>

### Nomogram construction

To investigate the individualized prognostic prediction and evaluation system, we also developed a nomogram for the evaluation of the prognostic risk of each patient, which was based on the prognostic clinical indicators and prognostic-related ERCC genes of Cox regression model. Besides that,

evaluation of the nomogram was using the concordance index (c-index). The nomogram was carried out by an *rms* package (<https://CRAN.R-project.org/package=rms>), together with its dependent packages in the R platform, with visualization using *gplots*.<sup>23,24</sup>

## Gene set enrichment analysis (GSEA)

In a bid to figure out the potential mechanism of prognostic-related ERCC genes participating in the HBV-related HCC prognosis, we further performed a GSEA (<http://software.broadinstitute.org/gsea/index.jsp>) to discover the potential biological processes and pathways involved in the different expression levels of ERCC genes.<sup>25,26</sup> The Molecular Signatures Database of GSEA used the c2 (c2.all.v6.1.symbols.gmt) and c5 (c5.all.v6.1.symbols.gmt) reference gene sets.<sup>27</sup> Results with a *P*-value below 0.05 and false discovery rate (FDR) below 0.25 were considered statistically significant.

## Coexpression analysis

To further evaluate the function of *ERCC8* in HBV-related HCC, we further carried out a genome-wide coexpression analysis of *ERCC8* in the HBV-related HCC of the GSE14520 cohort. The Pearson's correlation coefficient was used to evaluate the coexpression genes, and the Database for Annotation, Visualization and Integrated Discovery (DAVID; <https://david.ncifcrf.gov/home.jsp>, accessed May 13, 2018) v6.8<sup>28,29</sup> was used for the purpose of functional assessment.

## Statistical analysis

FDR in the GSEA was used to estimate the probability that the normalized enrichment score represents a false-positive finding, which was calculated with the help of the Benjamini and Hochberg method. A *P*-value <0.05 was regarded as statistically significant. All the statistical analyses were performed using SPSS v20.0 (IBM Corporation, Armonk, NY, USA) and R3.3.1 (<https://www.r-project.org/>).

## Results

### Study population

A total of 212 HBV-related HCC patients were included in the present study, coupled with 204 adjacent normal liver tissue specimens. Both the demographic and clinical features have been presented in Table 1. The clinical features including gender, cirrhosis, Barcelona Clinic Liver Cancer (BCLC) stage, TNM stage, and Cancer of the Liver Italian

Program (CLIP) stage were significantly associated with the recurrence-free survival (RFS) of the HBV-related HCC, whereas the clinical features including cirrhosis, tumor size, BCLC stage, TNM stage, CLIP stage, and serum AFP were significantly correlated with overall survival (OS).

## Expression distribution and survival analysis of ERCC genes

Through the comparison of the expression of ERCC genes in the HBV-related HCC tumor tissues and adjacent normal liver tissues, we observed that *ERCC1*, *ERCC2*, *ERCC3*, and *ERCC8* were significantly upregulated in the HBV-related HCC tumor tissues, whereas *ERCC4* and *ERCC5* were significantly downregulated in the HBV-related HCC tumor tissues (Figure 1). These dysregulated genes are also observable in liver cancer using the MERAV online tool (Figure 2A–G). Thereafter, we performed the investigation of the potential application values of the ERCC genes in distinguishing the HBV-related HCC tumor tissues and adjacent normal liver tissues using the ROC curve. As the ROC analysis suggests, six ERCC genes (*ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, and *ERCC8*) could be a biomarker used to distinguish between HBV-related HCC tumor tissues and the adjacent normal liver tissues; the area under the curve of the ROC was in the range between 0.623 and 0.744 (Figure 3A–G).

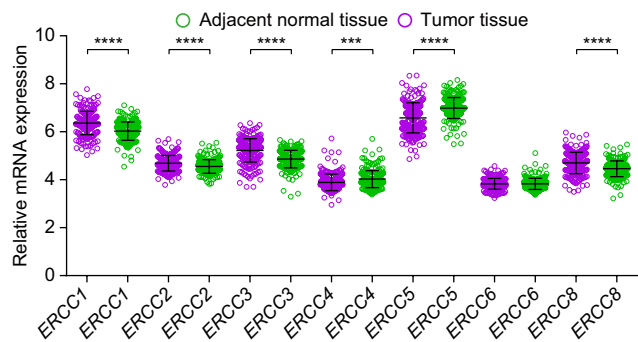
Survival analysis of ERCC family genes has been presented in Figures 4A–G and 5A–G; these findings provide the demonstration that the high *ERCC8* expression significantly reduced the risk of recurrence (adjusted *P*=0.021; HR=0.643; 95% CI=0.442–0.937, Table 2, Figure 4G) and death (adjusted *P*=0.049; HR=0.631; 95% CI=0.399–0.998, Table 2, Figure 5G) in the HBV-related HCC. Stratification analysis was also used to assess the prognostic values of *ERCC8* in the HBV-related HCC. The high expression of *ERCC8* significantly reduced the risk of recurrence in the patients having cirrhosis, serum AFP >300 ng/mL, single nodules, and in the male patients (Table 3), whereas the high expression of *ERCC8* significantly reduced the risk of death in the patients having single nodules, together with the male patients (Table 3). The joint effect survival analysis of *ERCC8* and serum AFP suggests that the patients with high *ERCC8* expression and a serum AFP ≤300 ng/mL (adjusted *P*=0.035; HR=0.583; 95% CI=0.354–0.962, Table 4, Figure 6A) or >300 ng/mL (adjusted *P*=0.004; HR=0.426; 95% CI=0.237–0.768, Table 4, Figure 6A) showed a significantly decreased risk of recurrence in the HBV-related HCC compared with patients having AFP >300

**Table 1** Distribution of HCC patients' characteristics and prognosis analysis

Variables	RFS				OS			
	Events/ total	MRT (months)	HR (95% CI)	Log-rank P	Events/ total	MST (months)	HR (95% CI)	Log-rank P
Age (years)				0.916				0.629
≤60	96/175	46	I		69/175	NA	I	
>60	20/37	48	0.974 (0.602–1.578)		13/37	NA	0.864 (0.478–1.564)	
Gender				0.018				0.148
Male	106/183	40	I		74/183	NA	I	
Female	10/29	NA	0.467 (0.244–0.893)		8/29	NA	0.587 (0.283–1.218)	
Cirrhosis				0.029				0.025
No	5/17		I		2/17	NA	I	
Yes	111/195	38	2.612 (1.066–6.402)		80/195	NA	4.335 (1.065–17.638)	
Tumor size <sup>a</sup>				0.073				0.002
≤5 cm	73/137	51	I		46/137	NA	I	
>5 cm	43/74	28	1.409 (0.966–2.056)		36/74	53	1.975 (1.274–3.060)	
Multinodular				0.381				0.052
Single	90/167	49	I		59/167	NA	I	
Multiple	26/45	28	1.216 (0.785–1.883)		23/45	48	1.607 (0.992–2.604)	
BCLC stage				<0.001				<0.001
0	6/20	NA	I		2/20	NA	I	
A	74/143	51	2.050 (0.892–4.711)		48/143	NA	4.119 (1.001–16.951)	
B	15/22	27	4.019 (1.550–10.421)		12/22	46	8.992 (2.005–40.320)	
C	21/27	9	6.163 (2.477–15.333)		20/27	13	18.993 (4.419–81.632)	
TNM stage				<0.001				<0.001
I	35/89	NA	I		20/89	NA	I	
II	48/76	28	1.995 (1.289–3.088)		32/76	NA	2.214 (1.265–3.873)	
III	33/47	18	3.220 (1.993–5.204)		30/47	18	5.197 (2.930–9.218)	
CLIP stage				0.001				<0.001
0	46/94	57	I		26/94	NA	I	
I	37/71	40	1.197 (0.776–1.846)		25/71	NA	1.414 (0.816–2.449)	
2/3/4/5	33/47	19	2.233 (1.424–3.500)		31/47	27	3.638 (2.153–6.149)	
Serum AFP <sup>b</sup>				0.327				0.047
≤300 ng/mL	62/115	48	I		39/115	NA	I	
>300 ng/mL	54/94	35	1.200 (0.833–1.728)		43/94	NA	1.546 (1.002–2.385)	

**Notes:** <sup>a</sup>Information of tumor size was unavailable in one patient. <sup>b</sup>Information of serum AFP was unavailable in three patients.

**Abbreviations:** AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; HCC, hepatocellular carcinoma; MRT, median recurrence time; MST, median survival time; OS, overall survival; RFS, recurrence-free survival.



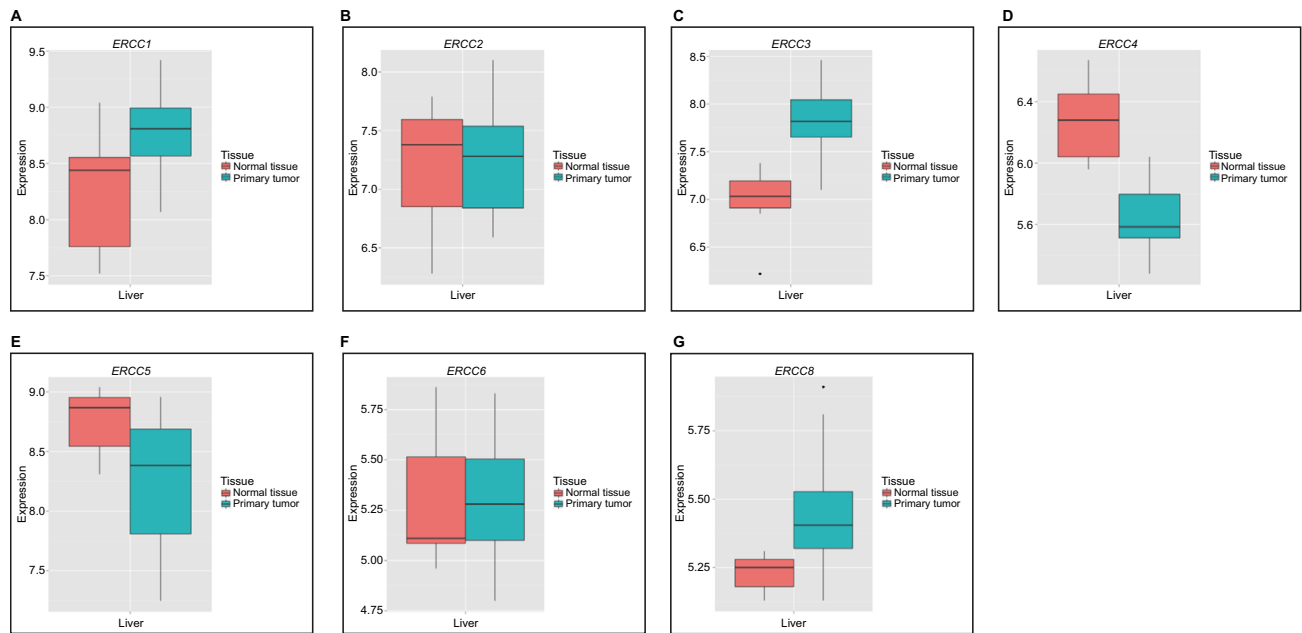
**Figure 1** Gene expression distribution of ERCC genes in GSE14520 HBV-related HCC cohort.

**Notes:** \*\*\* $P < 0.001$ ; \*\*\*\* $P < 0.0001$ .

**Abbreviations:** ERCC, excision repair cross-complementation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

ng/mL and low *ERCC8* expression. In contrast, the patients with high *ERCC8* expression and AFP ≤300 ng/mL showed a significantly reduced risk of death in the HBV-related HCC (adjusted  $P=0.028$ ; HR=0.499; 95% CI=0.268–0.927, Table 4, Figure 6B) compared with patients having AFP >300 ng/mL and low *ERCC8* expression.

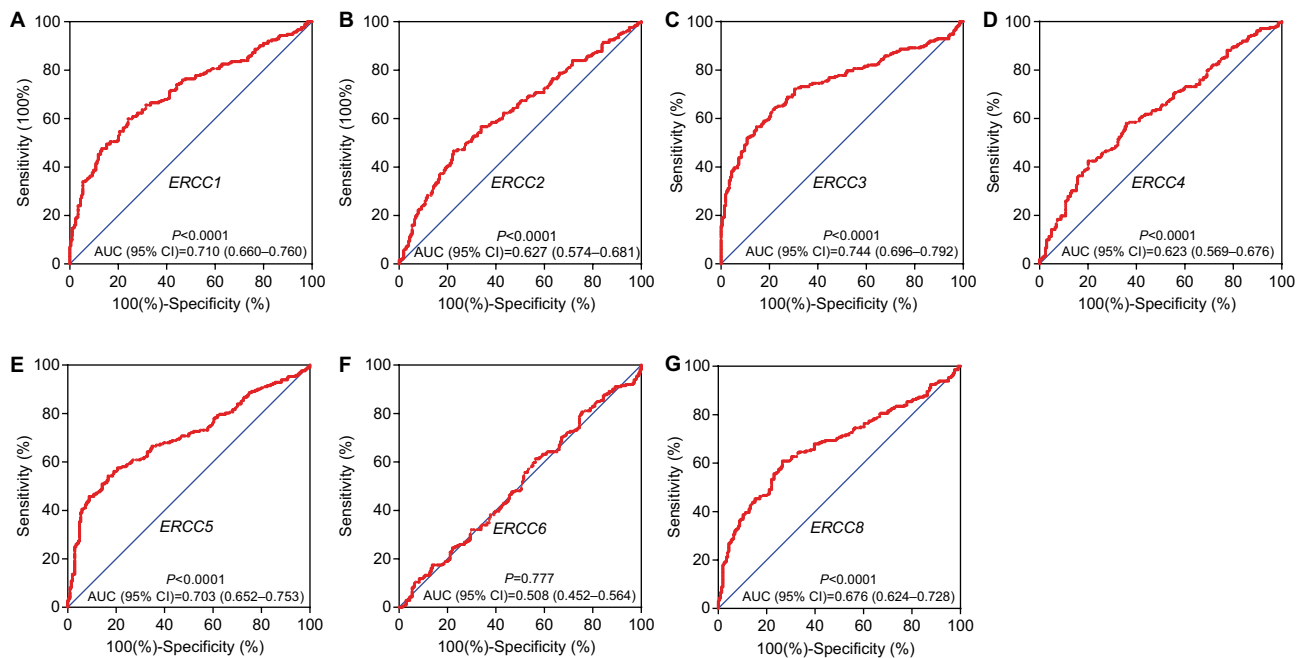
Thereafter, we also performed the verification of these joint effect survival analyses between *ERCC8* and AFP mRNA expression level and demonstrated that the *AFP* mRNA expression also performed well in the HCC prognosis prediction. Patients with high *ERCC8* expression and low (adjusted  $P=0.003$ ; HR=0.443; 95% CI=0.259–0.757, Table 4, Figure 6C) or high (adjusted  $P=0.002$ ; HR=0.418; 95%



**Figure 2** Gene expression distribution of ERCC gene in liver cancer using the MERAV.

**Note:** The order of box plots of ERCC genes were as follows: *ERCC1* (A), *ERCC2* (B), *ERCC3* (C), *ERCC4* (D), *ERCC5* (E), *ERCC6* (F), and *ERCC8* (G).

**Abbreviations:** ERCC, excision repair cross-complementation; MERAV, Metabolic gEne RApid Visualizer.



**Figure 3** ROC curves of ERCC genes in distinguish HBV-related HCC tissue from adjacent normal liver tissue.

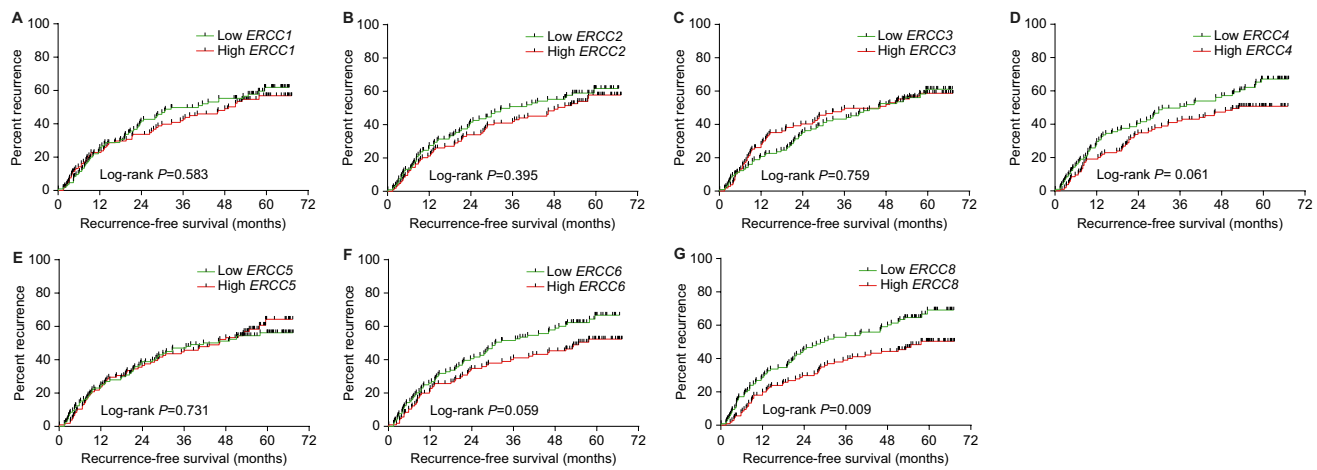
**Note:** The order of ROC curves of ERCC genes were as follows: *ERCC1* (A), *ERCC2* (B), *ERCC3* (C), *ERCC4* (D), *ERCC5* (E), *ERCC6* (F), and *ERCC8* (G).

**Abbreviations:** AUC, area under the curve of ROC; ERCC, excision repair cross-complementation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ROC, receiver-operating characteristic.

CI=0.238–0.734, Table 4, Figure 6C) *AFP* level showed a significantly decreased risk of recurrence in the HBV-related HCC compared with patients who had high *AFP* and low *ERCC8* expression, as well as in patients with low *AFP* and *ERCC8* expression (adjusted  $P=0.004$ ; HR=0.425; 95% CI=0.238–0.757, Table 4, Figure 6C). With respect to OS,

we observed that the patients with high *ERCC8* expression and low *AFP* expression showed a significantly reduced risk of death in the HBV-related HCC (adjusted  $P=0.035$ ; HR=0.487; 95% CI=0.249–0.952, Table 4, Figure 6D) compared with patients who had high *AFP* and low *ERCC8* expression.

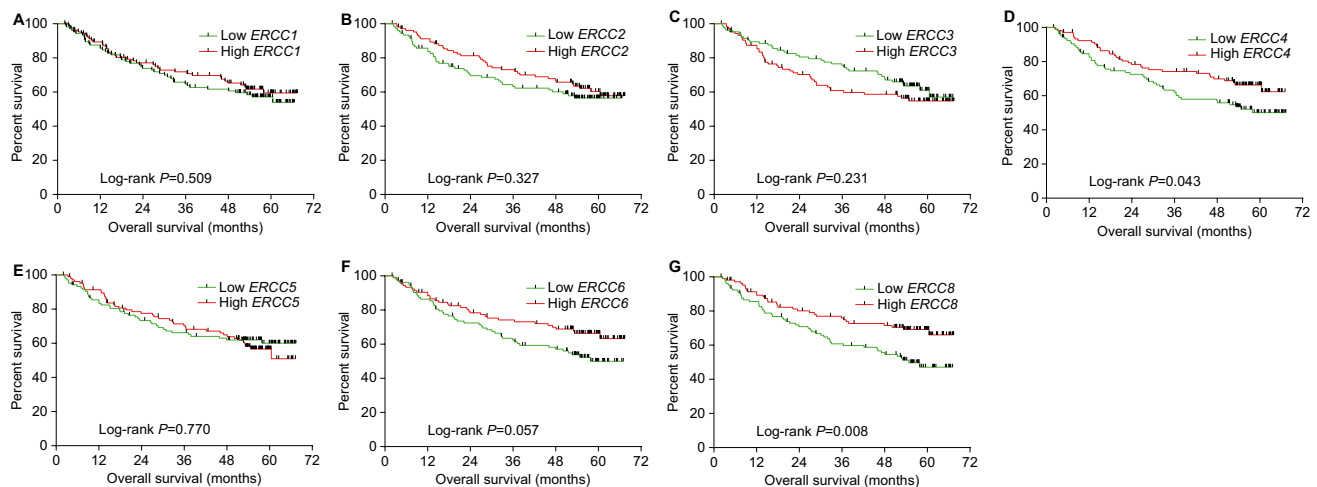




**Figure 4** Kaplan–Meier curves of ERCC genes in HBV-related HCC RFS.

**Note:** The order of Kaplan–Meier curves of ERCC genes were as follows: *ERCC1* (A), *ERCC2* (B), *ERCC3* (C), *ERCC4* (D), *ERCC5* (E), *ERCC6* (F), and *ERCC8* (G).

**Abbreviations:** ERCC, excision repair cross-complementation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; RFS, recurrence-free survival.



**Figure 5** Kaplan–Meier curves of ERCC genes in HBV-related HCC OS.

**Note:** The order of Kaplan–Meier curves of ERCC genes were as follows: *ERCC1* (A), *ERCC2* (B), *ERCC3* (C), *ERCC4* (D), *ERCC5* (E), *ERCC6* (F), and *ERCC8* (G).

**Abbreviations:** ERCC, excision repair cross-complementation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; OS, overall survival.

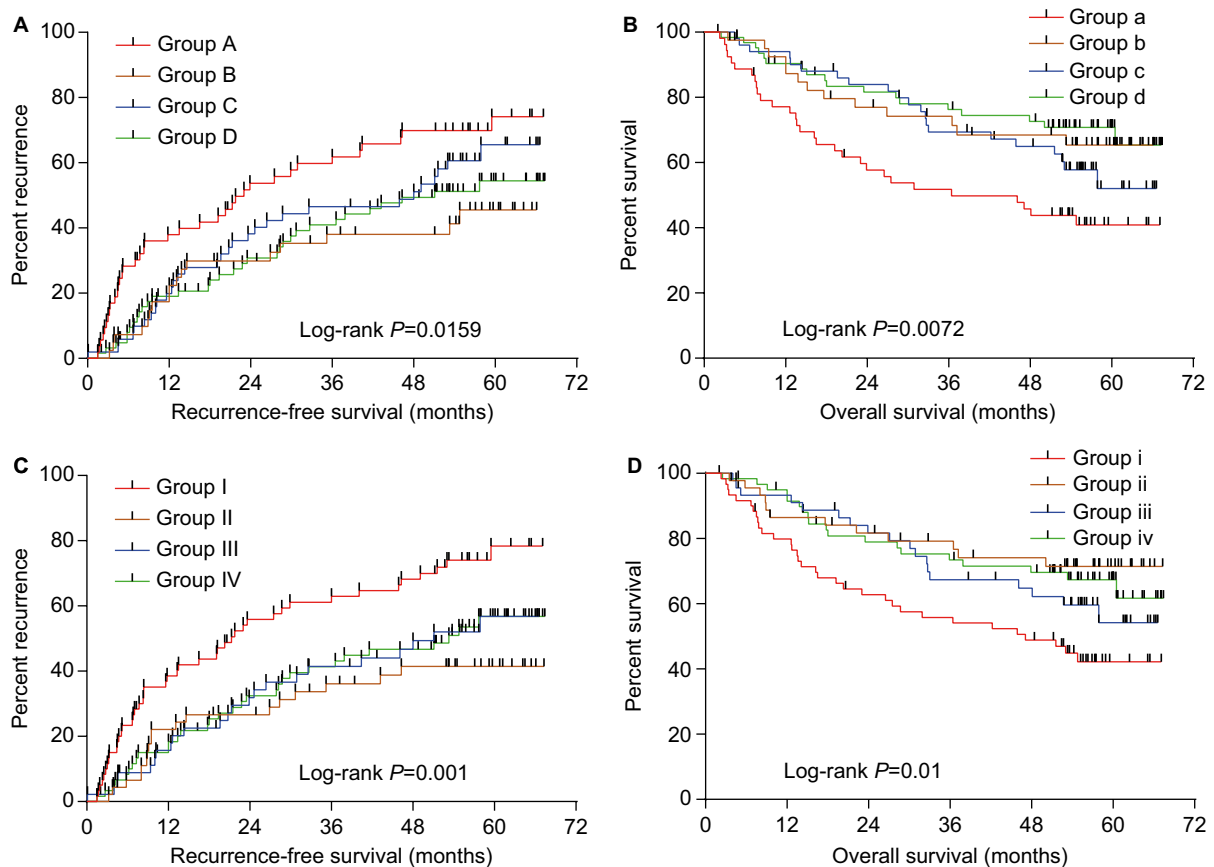
## Nomogram construction

Thereafter, we performed the investigation of the potential application of *ERCC8* mRNA expression in the individualized prognosis prediction. Those clinical features that were significantly correlated to RFS or OS were included in the development of nomogram for RFS and OS, correspondingly. The nomogram of the HBV-related HCC RFS was developed in accordance with the gender, cirrhosis, TMN stage, BCLC stage, CLIP stage, and *ERCC8* expression (c-index [95% CI]=0.68 [0.63–0.74], Figure 7A), whereas the nomogram of HBV-related HCC OS was developed by tumor size, cirrhosis, TMN stage, BCLC stage, CLIP stage, AFP, and *ERCC8* expression (c-index [95% CI]=0.72 [0.66–0.79], Figure 7B). In accordance with the nomogram

for RFS and OS, we observed that the contribution of *ERCC8* expression in the HBV-related HCC prognosis prediction was lower compared with some conventional clinical indicators; however, the expression of *ERCC8* contributed much more than the serum AFP in the nomogram of the HBV-related HCC OS (Figure 7B).

## GSEA of *ERCC8*

Investigation by GSEA using the c2 reference gene set indicates that the high expression of *ERCC8* was significantly enriched in the NF-kappa-B and Wnt signaling pathway, as well as the P53 independent G1-S DNA damage checkpoint, TCA cycle and respiratory electron transport, and oxidative phosphorylation (Figure 8A–F, Table S1). GSEA



**Figure 6** Joint effect survival analysis of *ERCC8* and AFP in HBV-related HCC prognosis.

**Notes:** (A) RFS stratified by *ERCC8* and serum AFP level; (B) OS stratified by *ERCC8* and serum AFP level; (C) RFS stratified by *ERCC8* and AFP mRNA level; and (D) OS stratified by *ERCC8* and serum AFP mRNA level.

**Abbreviations:** AFP, alpha-fetoprotein; ERCC, excision repair cross-complementation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival.

with c5 indicates that the high expression of *ERCC8* was significantly correlated to metabolically related biological processes, for instance, nucleoside triphosphate and cellular amine metabolic processes, and the generation of precursor metabolites and energy (Figure 8G–I, Table S2). In comparison, using the results of the c2 and c5 reference gene set, we observed that the high expression of *ERCC8* may be involved in energy metabolism biological processes, which may have an impact on the prognosis of the HBV-related HCC.

## Genome-wide coexpression analysis and function assessment of *ERCC8*

For the purpose of further exploring the function of *ERCC8* in the HBV-related HCC, a genome-wide coexpression analysis was carried out. With respect to the multiple probes corresponding to one gene, we used the mean values of multiple probes to present the expression values of this gene in a genome-wide coexpression

analysis. A total of 273 genes with |Pearson's correlation coefficient| > 0.4 and  $P < 0.05$  were taken into consideration as coexpressed with *ERCC8* in the HBV-related HCC (Figure 9, Table S3). Thereafter, the functional assessment of the *ERCC8*-coexpressed genes was performed using DAVID v6.8. Gene Ontology (GO) term analysis suggested that *ERCC8* and its coexpressed genes together are significantly enriched in the MAPK cascade, damaged DNA binding, DNA synthesis involved in DNA repair, and DNA damage checkpoints (Figure 10). In contrast, the Kyoto Encyclopedia of Genes and Genomes suggested that *ERCC8* and its coexpressed genes were significantly enriched in the ribosome-signaling pathway (hsa03010,  $P=0.003$ , gene count=8).

## Discussion

Through the review of the literature, we observed that extensive previous studies have focused on the investigation of the association between the ERCC gene polymorphisms and the

**Table 2** Survival analysis of ERCC genes in HBV-related HCC prognosis

Gene expression	Patients (n=212)	MST/MRT (months)	Crude HR (95% CI)	Crude P	Adjusted HR (95% CI)	Adjusted P <sup>a</sup>
<b>RFS</b>		<b>MRT</b>				
<i>ERCC1</i>						
Low	106	40				
High	106	49	0.903 (0.627–1.300)	0.583	1.061 (0.723–1.556)	0.762
<i>ERCC2</i>						
Low	106	35				
High	106	49	0.854 (0.593–1.229)	0.396	0.934 (0.646–1.351)	0.717
<i>ERCC3</i>						
Low	106	46				
High	106	46	1.059 (0.735–1.524)	0.759	1.173 (0.805–1.710)	0.405
<i>ERCC4</i>						
Low	106	36				
High	106	53	0.706 (0.489–1.019)	0.063	0.818 (0.560–1.194)	0.298
<i>ERCC5</i>						
Low	106	41				
High	106	46	1.066 (0.740–1.535)	0.731	0.952 (0.651–1.392)	0.798
<i>ERCC6</i>						
Low	106	30				
High	106	54	0.704 (0.448–1.016)	0.061	0.768 (0.527–1.118)	0.168
<i>ERCC8</i>						
Low	106	30				
High	106	57	0.613 (0.424–0.887)	0.009	0.643 (0.442–0.937)	0.021
<b>OS</b>		<b>MST</b>				
<i>ERCC1</i>						
Low	106	NA				
High	106	NA	0.864 (0.560–1.334)	0.509	1.040 (0.663–1.630)	0.865
<i>ERCC2</i>						
Low	106	NA				
High	106	NA	0.805 (0.522–1.243)	0.328	0.865 (0.558–1.343)	0.518
<i>ERCC3</i>						
Low	106	NA				
High	106	NA	1.303 (0.844–2.012)	0.233	1.511 (0.961–2.375)	0.074
<i>ERCC4</i>						
Low	106	NA				
High	106	NA	0.637 (0.410–0.989)	0.044	0.729 (0.465–1.142)	0.167
<i>ERCC5</i>						
Low	106	NA				
High	106	NA	1.067 (0.691–1.647)	0.77	0.899 (0.572–1.412)	0.643
<i>ERCC6</i>						
Low	106	58				
High	106	NA	0.654 (0.421–1.015)	0.059	0.723 (0.462–1.133)	0.157
<i>ERCC8</i>						
Low	106	54				
High	106	NA	0.549 (0.351–0.858)	0.008	0.631 (0.399–0.998)	0.049

**Note:** <sup>a</sup>Adjustment for age, gender, cirrhosis, tumor size, tumor number, BCLC stage, and serum AFP level.

**Abbreviations:** AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; ERCC, excision repair cross-complementation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MRT, median recurrence time; MST, median survival time; OS, overall survival; RFS, recurrence-free survival.

risk of cancers<sup>30,31</sup> or on the ERCC gene polymorphisms and cancer prognosis.<sup>32,33</sup> Besides that, the ERCC gene polymorphisms have also been reported for having correlation with the prognosis of patients treated with chemotherapy.<sup>34–37</sup> However, there are rare reports of the systematic investigations of the expression of ERCC in cancer diagnosis and prognosis.<sup>9,38,39</sup>

Previous studies substantiated that polymorphisms in *ERCC2* and *ERCC5* confer susceptibility to the acute myeloid leukemia (AML)<sup>40</sup> and that polymorphisms in *ERCC2* and *XPC* were significantly associated with the AML survival.<sup>41</sup> Polymorphisms in *ERCC5* also make contribution toward the susceptibility of lung cancer and squamous cell carcinomas of the oropharynx, larynx, and esophagus;<sup>42</sup> head and



**Table 3** Stratified survival analysis of *ERCC8* in HBV-related HCC prognosis

Variables	Patients (n=218)	Low ERCC8	High ERCC8	RFS		OS	
				Adjusted HR (95% CI)	Adjusted P <sup>a</sup>	Adjusted HR (95% CI)	Adjusted P <sup>a</sup>
Age (years)							
≤60	175	88	87	0.694 (0.456–1.055)	0.087	0.659 (0.396–1.098)	0.11
>60	37	18	19	0.498 (0.172–1.442)	0.199	0.506 (0.133–1.926)	0.318
Gender							
Male	183	91	92	0.664 (0.447–0.984)	0.041	0.647 (0.398–1.053)	0.08
Female	29	15	14	0.099 (0.007–1.319)	0.08	0.140 (0.011–1.844)	0.135
Cirrhosis							
No	17	6	11	1×10 <sup>-6</sup> (1.8×10 <sup>-196</sup> –3.7×10 <sup>e183</sup> )	0.952	4.9×10 <sup>-5</sup> (6.9×10 <sup>e-20</sup> –3.7×10 <sup>e10</sup> )	0.57
Yes	195	100	95	0.673 (0.458–0.988)	0.043	0.676 (0.425–1.075)	0.098
Tumor size <sup>b</sup>							
≤5 cm	137	63	74	0.705 (0.437–1.136)	0.151	0.575 (0.306–1.081)	0.086
>5 cm	74	42	32	0.570 (0.292–1.114)	0.1	0.757 (0.363–1.579)	0.458
Multinodular							
Single	167	81	86	0.618 (0.406–0.939)	0.024	0.524 (0.309–0.888)	0.016
Multiple	45	25	20	0.837 (0.305–2.298)	0.73	1.575 (0.533–4.659)	0.411
BCLC stage							
0	20	9	11	0.592 (0.101–3.457)	0.561	7×10 <sup>-6</sup> (2.64×10 <sup>e-264</sup> –1.7×10 <sup>e245</sup> )	0.968
A	143	65	78	0.755 (0.475–1.199)	0.234	0.684 (0.385–1.216)	0.196
B	22	14	8	0.473 (0.123–1.815)	0.275	1.006 (0.238–4.263)	0.993
C	27	18	9	0.893 (0.291–2.734)	0.842	0.981 (0.312–3.083)	0.973
TNM stage							
I	89	37	52	0.533 (0.266–1.068)	0.076	0.553 (0.223–1.372)	0.201
II	76	39	37	0.807 (0.438–1.488)	0.492	0.987 (0.472–2.064)	0.973
III	47	30	17	1.057 (0.459–2.435)	0.897	1.081 (0.440–2.655)	0.866
CLIP stage							
0	94	40	54	0.827 (0.455–1.503)	0.532	0.735 (0.330–1.639)	0.452
I	71	35	36	0.681 (0.340–1.364)	0.278	0.509 (0.218–1.189)	0.119
2/3/4/5	47	31	16	0.411 (0.159–1.061)	0.066	0.978 (0.391–2.448)	0.962
Serum AFP <sup>c</sup>							
≤300 ng/mL	115	52	63	0.860 (0.516–1.432)	0.562	0.737 (0.386–1.405)	0.354
>300 ng/mL	94	53	41	0.422 (0.232–0.767)	0.005	0.512 (0.259–1.016)	0.055

**Notes:** <sup>a</sup>Adjustment for age, gender, cirrhosis, tumor size, tumor number, BCLC stage, and serum AFP level. <sup>b</sup>Information of tumor size was unavailable in one patient. <sup>c</sup>Information of serum AFP was unavailable in three patients.

**Abbreviations:** AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; ERCC, excision repair cross-complementation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival.

neck,<sup>43</sup> prostate cancer,<sup>44</sup> HCC,<sup>15</sup> and bladder cancer (BC).<sup>31</sup> A study performed by Sakano et al also found that the genetic variants of *ERCC5* contribute to the tumor invasiveness in BC.<sup>45</sup> In addition, the polymorphisms *ERCC2*-rs1799793 and *ERCC5*-rs17655 may also contribute to the recurrence risk of squamous cell carcinoma of the oropharynx.<sup>37</sup>

There have also been reports of the prognostic values of ERCC genetic variants in multiple cancers. An investigation carried out by Liu et al revealed the fact that *ERCC1*-rs11615 is likely to be a useful genetic marker for the prediction of the osteosarcoma prognosis and that the CC genotype is correlated with a better clinical outcome.<sup>46</sup> The work performed by Liu et al indicated that the *XRCC1*-399A/A genotype was

significantly correlated with a better clinical outcome.<sup>47</sup> Previous studies demonstrated that genetic variants of *ERCC2* and *ERCC5* may be the independent prognostic factors in the patients with melanoma<sup>32,48</sup> and osteosarcoma.<sup>49</sup> In addition, polymorphisms of *ERCC5* were also correlated with the response to chemotherapy and the prognosis of osteosarcoma.<sup>50,51</sup> Furthermore, polymorphisms of *ERCC5* have also been reported to have an influence in multiple cancer prognosis, such as lung cancer,<sup>33,47</sup> and colorectal cancer (CRC).<sup>52,53</sup>

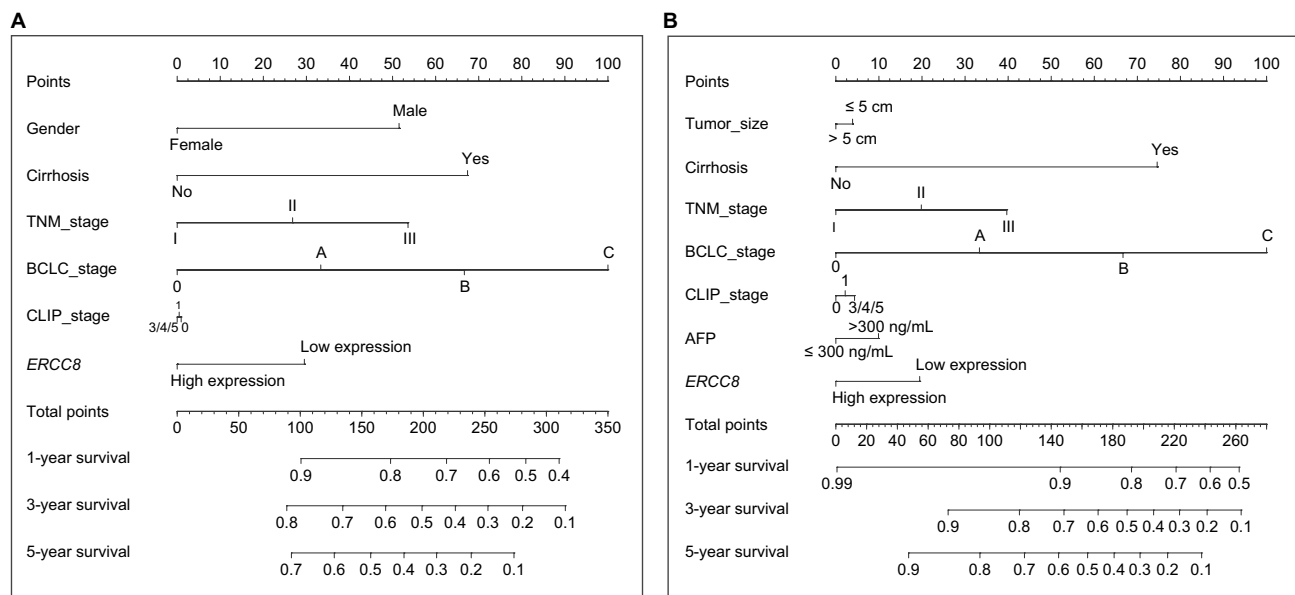
The interindividual differences in the patients treated with chemotherapy mainly affected the efficiency of the DNA damage–repair system in the cells and then affected the clini-

**Table 4** Joint effect survival analysis of ERCC8 and serum AFP in HBV-related HCC prognosis

Group	AFP level <sup>a</sup>	ERCC8 expression	Patients (n=209)	MRT/MST (months)	Crude HR (95% CI)	Crude P	Adjusted HR (95% CI)	Adjusted P <sup>b</sup>
<b>RFS</b>				<b>MRT</b>				
Group A	>300	Low	53	23	1		1	
Group B	>300	High	41	NA	0.448 (0.252–0.795)	0.006	0.426 (0.237–0.768)	0.004
Group C	<300	Low	52	48	0.671 (0.414–1.086)	0.104	0.656 (0.398–1.081)	0.098
Group D	<300	High	63	51	0.546 (0.340–0.877)	0.012	0.583 (0.354–0.962)	0.035
<b>OS</b>				<b>MST</b>				
Group a	>300	Low	53	36	1		1	
Group b	>300	High	41	NA	0.463 (0.242–0.889)	0.021	0.522 (0.268–1.018)	0.057
Group c	<300	Low	52	NA	0.575 (0.329–1.005)	0.052	0.661 (0.369–1.185)	0.165
Group d	<300	High	63	NA	0.401 (0.223–0.719)	0.002	0.499 (0.268–0.927)	0.028
<b>RFS</b>				<b>MRT</b>				
Group I	High	Low	60	21	1		1	
Group II	High	High	46	NA	0.389 (0.224–0.673)	0.001	0.418 (0.238–0.734)	0.002
Group III	Low	Low	46	51	0.519 (0.313–0.859)	0.011	0.425 (0.238–0.757)	0.004
Group IV	Low	High	60	53	0.524 (0.331–0.830)	0.006	0.443 (0.259–0.757)	0.003
<b>OS</b>				<b>MST</b>				
Group i	High	Low	60	47	1		1	
Group ii	High	High	46	NA	0.400 (0.206–0.775)	0.007	0.533 (0.267–1.063)	0.074
Group iii	Low	Low	46	NA	0.602 (0.339–1.069)	0.083	0.612 (0.308–1.215)	0.161
Group iv	Low	High	60	NA	0.478 (0.272–0.841)	0.01	0.487 (0.249–0.952)	0.035

**Notes:** <sup>a</sup>Information of serum AFP was unavailable in three patients. <sup>b</sup>Adjustment for age, gender, cirrhosis, tumor size, tumor number, BCLC stage, and serum AFP level.

**Abbreviations:** AFP, alpha-fetoprotein; ERCC, excision repair cross-complementation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MRT, median recurrence time; MST, median survival time; OS, overall survival; RFS, recurrence-free survival.



**Figure 7** Nomogram for predicting the 1-, 3-, and 5-year event with *ERCC8* expression and clinical indicators.

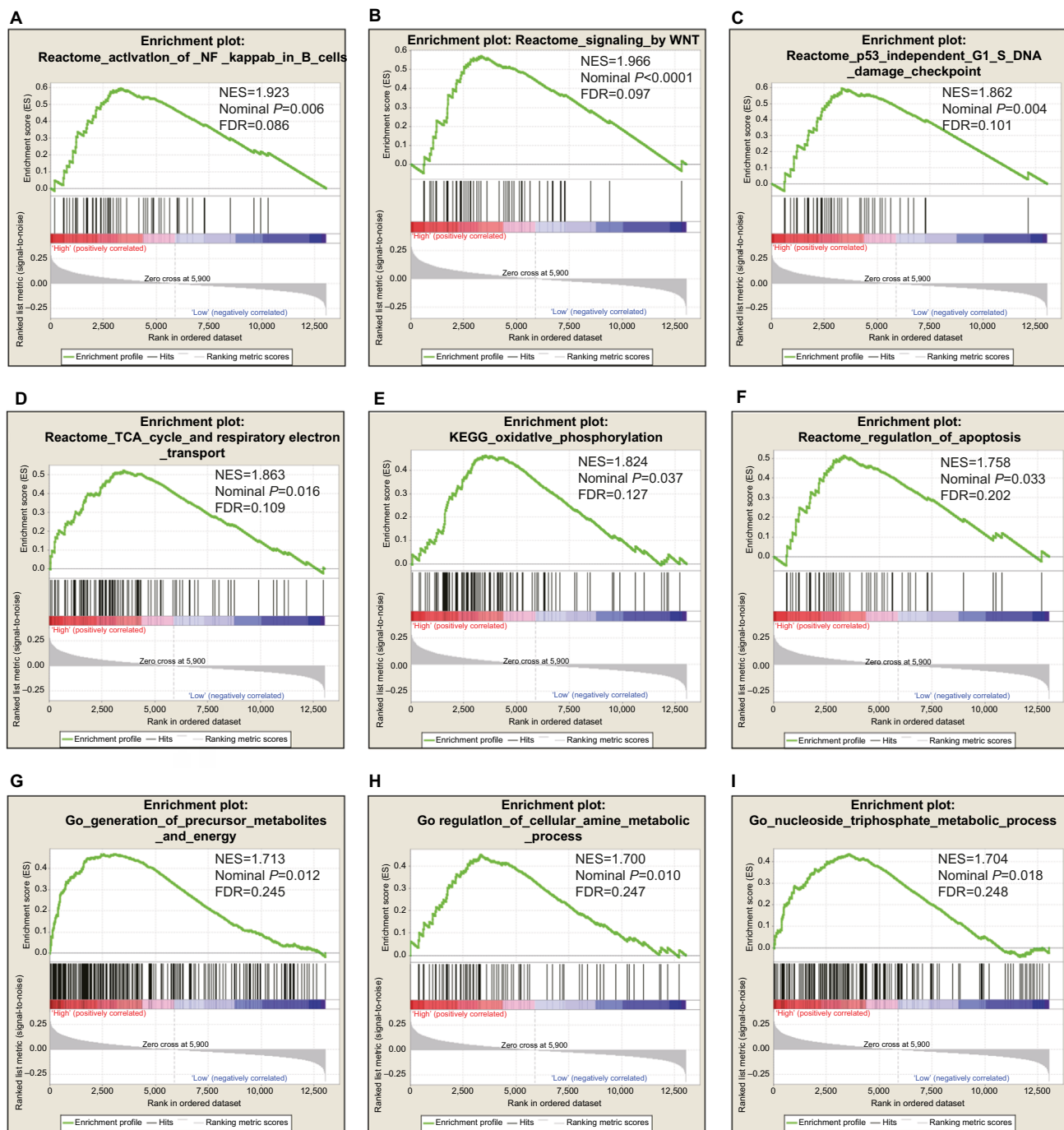
**Notes:** (A) Nomogram for *ERCC8* expression in HBV-related HCC RFS. (B) Nomogram for *ERCC8* expression in HBV-related HCC OS.

**Abbreviations:** AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; ERCC, excision repair cross-complementation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival.

cal outcomes. Extensive studies have demonstrated that the ERCC genes were involved in the responses to chemotherapy and the prognosis of the patients with CRC<sup>36,54–56</sup> as well as advanced non-small cell lung cancer (NSCLC).<sup>57,58</sup> The *ERCC5* polymorphism His46His was reported to be associated with the susceptibility of platinum-based chemotherapy in the advanced NSCLC<sup>35</sup> and significantly affected clinical outcomes.<sup>58</sup> The *ERCC5* promoter polymorphism rs751402 was significantly associated with the chemotherapy response in the advanced NSCLC, and the AA genotype may contribute to increase the effect of chemotherapy response.<sup>59</sup> Hu et al substantiated that the rs2296147 T allele and rs873601 G allele were associated with the better progression-free survival (PFS) and OS in the advanced NSCLC patients undergoing the platinum-based chemotherapy<sup>57</sup>; furthermore, the results of the rs2296147 T allele in OS of the advanced NSCLC patients undergoing platinum-based chemotherapy are also verifiable in another cohort.<sup>60</sup> However, the rs1047768 TT genotype, which showed a significantly shortened median PFS and OS in the advanced NSCLC patients undergoing platinum-based chemotherapy in the study of Zhang et al,<sup>60</sup> is unable to be verified in the cohort collected by Hu et al.<sup>57</sup> With respect to the ERCC genetic variation in CRC response to platinum-based chemotherapy and therapeutic outcomes, multiple studies demonstrated that the *ERCC5* polymorphisms may have an impact on the

susceptibility and therapeutic outcomes to the colorectal cancer patients, who received oxaliplatin chemotherapy.<sup>36,54–56</sup>

By reviewing the above literature, we found that a considerable amount of literature has been published on the genetic variation of ERCC genes in cancer susceptibility, prognosis, and therapeutic outcomes; however, the expression of ERCC genes in cancer diagnostic and prognostic values were rarely mentioned. Several investigations verified the fact that the low expression of ERCC1 was significantly correlated with a better clinical outcome in patients with breast cancer,<sup>38</sup> NSCLC,<sup>61</sup> and ovarian cancer,<sup>9</sup> as well as in advanced NSCLC treated with platinum-based chemotherapy.<sup>10</sup> A systematic investigation of the ERCC genes in the ovarian cancer prognosis was carried out by Zhao et al using the Kaplan–Meier Plotter online tool and revealed that the high expression of *ERCC8* and *ERCC1* had correlations with a poor OS, whereas the high expression of *ERCC4* was associated with a better OS.<sup>9</sup> In our current study, we observed that the high expression of *ERCC8* was significantly correlated with a better RFS and OS in the HBV-related HCC after hepatectomy, and our current study was the first to investigate the potential prognostic application values of *ERCC8* in the HBV-related HCC. Comprehensive survival analysis of stratification analysis and joint effect survival analysis indicates that *ERCC8* may be served as an independent prognostic indicator for the HBV-related HCC; the nomograms indicate that the combination



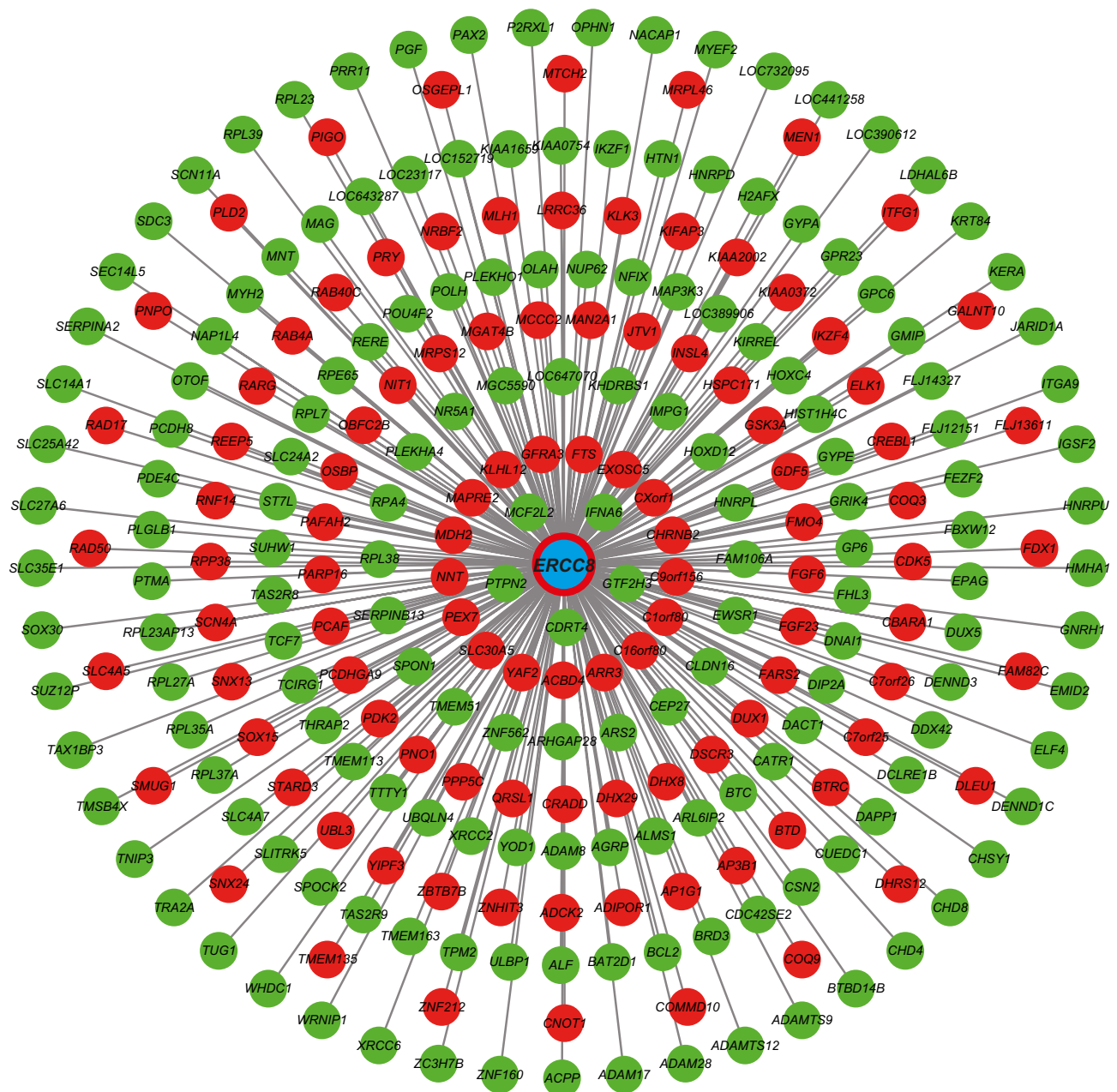
**Figure 8** GSEA results of *ERCC8*.

**Notes:** (A)–(F) GSEA results of c2 reference gene sets for high *ERCC8* expression. (G)–(I) GSEA results of c5 reference gene sets for high *ERCC8* expression.

**Abbreviations:** ERCC, excision repair cross-complementation; GSEA, gene set enrichment analysis; FDR, false discovery rate; ES, Enrichment Score; NES, Normalized Enrichment Score.

of *ERCC8* and traditional prognostic indicators may have an application value in the individualized prognosis prediction. It is worth noting that the results of *ERCC8* obtained in our current study were contradictory to the results of the study carried out by Zhao et al in the ovarian cancer prognosis.<sup>9</sup> The possible causes of the above inconsistency results suggested that the survival analysis in the study by Zhao et al

was derived from the Kaplan–Meier method, which was a univariate survival analysis and that the results obtained from such kinds of statistical methods may be unreliable. However, the key advantage of the results of the current study was assessed by a multivariate Cox proportional hazards regression model, and the statistical method was more reliable than the Kaplan–Meier method in survival analysis. Another pos-



**Figure 9** Coexpression genes of ERCC8 in HBV-related HCC.

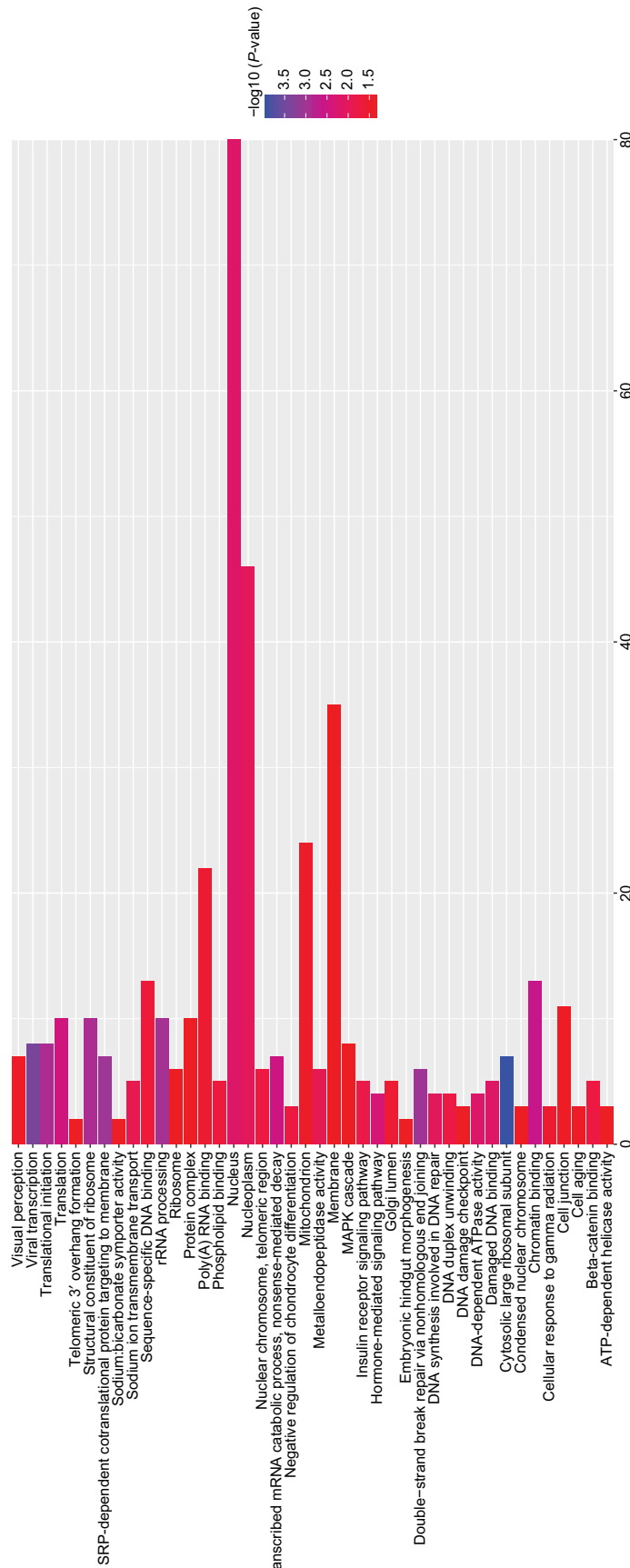
**Notes:** The green nodes represent negative correlation with ERCC8, and the red nodes represent positive correlation with ERCC8.

**Abbreviations:** ERCC, excision repair cross-complementation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

sible reason may be that *ERCC8* plays different roles in both the ovarian cancer and HBV-related HCC. However, these results still require to be further verified in a larger sample, and the hypotheses also need further experimental validation.

The current study has some limitations that need to clarification. First, since the data set is from the public database, the clinical information in the GSE14520 was constrained. Consequently, we are incapable of attaining complete clinical information with which to carry out a comprehensive

prognostic analysis; the incomplete clinical information, such as postoperative treatment, may influence prognosis. Second, the raw values of serum AFP level in GSE14520 were not provided as well, accordingly, we were unable to carry out a joint effect survival analysis in the serum with an AFP cutoff 400 ng/mL, which is a recognized cutoff value. Third, through the retrieval of the public database, only the GSE14520 data set caters to the requirements of the current study. That is why the results of the present study are derived



**Figure 10** GO term enrichments of co-expression genes of ERCC8 in HBV-related HCC. **Abbreviations:** ERCC, excision repair cross-complementation; GO, Gene Ontology; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.



from a single cohort, and additional cohorts to verify the results are needed.

Despite these limitations, our current study is the first to systematically investigate the diagnostic and prognostic values of ERCC genes in the HBV-related HCC. As our findings suggest, the dysregulated ERCC genes may have a potential application in the HBV-related HCC diagnosis and *ERCC8* may be a potential novel indicator for the HBV-related HCC prognosis prediction. We also developed two nomograms for the individualized prognosis prediction and investigated the potential mechanisms and functions of *ERCC8* in the HBV-related HCC using the GSEA and genome-wide coexpression analysis approaches.

## Conclusion

The present study indicates that six ERCC genes (*ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, and *ERCC8*) were dysregulated between the HBV-related HCC tumor and paracancerous tissues, and mRNA expression of *ERCC8* may act as a potential biomarker for the HBV-related HCC prognosis.

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## Disclosure

The authors report no conflicts of interest in this work.

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