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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Si Zhao*; Production Department Director: *Xu Guo*; Editorial Office Director: *Xu Guo*.

**NAME OF JOURNAL**

*World Journal of Clinical Oncology*

**ISSN**

ISSN 2218-4333 (online)

**LAUNCH DATE**

November 10, 2010

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Hiten RH Patel, Stephen Safe, Jian-Hua Mao, Ken H Young

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2218-4333/editorialboard.htm>

**PUBLICATION DATE**

March 24, 2024

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**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

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## Clinical and Translational Research

# Establishment of a prognosis predictive model for liver cancer based on expression of genes involved in the ubiquitin-proteasome pathway

Hua Li, Yi-Po Ma, Hai-Long Wang, Cai-Juan Tian, Yi-Xian Guo, Hong-Bo Zhang, Xiao-Min Liu, Peng-Fei Liu

**Specialty type:** Oncology

**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Rodriguez JC, Spain

**Received:** October 11, 2023

**Peer-review started:** October 11, 2023

**First decision:** December 7, 2023

**Revised:** December 27, 2023

**Accepted:** February 5, 2024

**Article in press:** February 5, 2024

**Published online:** March 24, 2024



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## Abstract

### BACKGROUND

The ubiquitin-proteasome pathway (UPP) has been proven to play important roles in cancer.

### AIM

To investigate the prognostic significance of genes involved in the UPP and develop a predictive model for liver cancer based on the expression of these genes.

### METHODS

In this study, UPP-related E1, E2, E3, deubiquitylating enzyme, and proteasome gene sets were obtained from the Kyoto Encyclopedia of Genes and Genomes (KEGG) database, aiming to screen the prognostic genes using univariate and multivariate regression analysis and develop a prognosis predictive model based

on the Cancer Genome Atlas liver cancer cases.

## RESULTS

Five genes (including autophagy related 10, proteasome 20S subunit alpha 8, proteasome 20S subunit beta 2, ubiquitin specific peptidase 17 like family member 2, and ubiquitin specific peptidase 8) were proven significantly correlated with prognosis and used to develop a prognosis predictive model for liver cancer. Among training, validation, and Gene Expression Omnibus sets, the overall survival differed significantly between the high-risk and low-risk groups. The expression of the five genes was significantly associated with immunocyte infiltration, tumor stage, and postoperative recurrence. A total of 111 differentially expressed genes (DEGs) were identified between the high-risk and low-risk groups and they were enriched in 20 and 5 gene ontology and KEGG pathways. Cell division cycle 20, Kelch repeat and BTB domain containing 11, and DDB1 and CUL4 associated factor 4 like 2 were the DEGs in the E3 gene set that correlated with survival.

## CONCLUSION

We have constructed a prognosis predictive model in patients with liver cancer, which contains five genes that associate with immunocyte infiltration, tumor stage, and postoperative recurrence.

**Key Words:** Liver cancer; Ubiquitin-proteasome pathway; Prognosis prediction; Gene expression; Immune infiltration

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**Core Tip:** This study unveils the crucial role of the ubiquitin-proteasome pathway (UPP) in liver cancer prognosis. Five key genes (autophagy related 10, proteasome 20S subunit alpha 8, proteasome 20S subunit beta 2, ubiquitin specific peptidase 17 like family member 2, and ubiquitin specific peptidase 8) identified from The Cancer Genome Atlas datasets constitute a robust prognostic model, accurately predicting liver cancer outcomes. Immunocyte infiltration analysis highlights associations of these genes with immune cell abundance, while clinical correlations link them to tumor stage and recurrence. Differential gene expression and pathway enrichment elucidate underlying biological processes. E3 analysis identifies specific ligases (cell division cycle 20, Kelch repeat and BTB domain containing 11, and DCAF4L2) with significant expression differences, further emphasizing the integral role of the UPP in liver cancer development and providing valuable insights for precision medicine and prognosis prediction.

**Citation:** Li H, Ma YP, Wang HL, Tian CJ, Guo YX, Zhang HB, Liu XM, Liu PF. Establishment of a prognosis predictive model for liver cancer based on expression of genes involved in the ubiquitin-proteasome pathway. *World J Clin Oncol* 2024; 15(3): 434-446

**URL:** <https://www.wjgnet.com/2218-4333/full/v15/i3/434.htm>

**DOI:** <https://dx.doi.org/10.5306/wjco.v15.i3.434>

## INTRODUCTION

The prevalence of liver cancer has been increasing, with an annual growth rate of up to 2%-3% [1] and survival rate of 18% in 2020 [2]. A total of 336400 new liver cancer cases were detected in China in 2016 [3], and the sharply elevated incidence (18.0 per 100000) of liver cancer caused by sugar-sweetened food must be given extra attention [4].

Hepatitis B/C virus (HBV or HCV) infection, addiction to alcohol, liver cirrhosis, fatty hepatitis, and eating aflatoxin contaminated food are the risk factors for liver cancer [5]. Imaging examinations for liver cancer include ultrasonography, dynamic contrast-enhanced computed tomography (CT), multimodal magnetic resonance imaging, 18F-fluorodeoxyglucose positron emission tomography/CT, and so on. Virtual liver biopsy sampling pipeline for eliminating sampling bias may be the potential diagnostic method to investigate the nature of the lesions and etiology [6]. In recent years, using statistical models combined with machine learning techniques to elevate the diagnostic accuracy of serum biomarkers such as  $\alpha$ -fetoprotein and cell-free DNA or RNA has been widely applied to the early diagnosis of hepatocellular carcinoma [7]. Additionally, surgical resection, transplantation, ablation, chemotherapy, and immunotherapy are common treatment options for liver cancer patients [8]. However, effective surveillance and prediction of the prognosis of liver cancer still face multiple challenges due to the high heterogeneity of this malignancy.

The ubiquitin-proteasome pathway (UPP) is one of the key pathways of protein selective degradation in organisms [9], which is related to cell cycle, proliferation, differentiation, apoptosis, transcription, signal transduction, immune response, stress response, and extracellular effectors [10]. The malfunction of the UPP is linked to various diseases, such as carcinogenesis, infection, autoimmunity, and inflammation. Based on The Cancer Genome Atlas (TCGA) datasets and 961 ubiquitin-proteasome system genes (UPSGs), Liu *et al* [11] found that DDB1 and CUL4 associated factor 13 (DCAF13), cell division cycle 20 (CDC20), and proteasome 20S subunit beta 5 (PSMB5) have excellent performance to predict the survival of liver cancer patients. Zhang *et al* [12] identified a seven-UPSG prognostic signature, of which autophagy related 10 (ATG10) was found to participate in liver cancer development and prognosis through autophagy, immune response, and tumor metastasis. Therefore, proteasome inhibitors, as a class of potential and effective anti-tumor drugs, have attracted a

growing body of attention from researchers. In this study, we examined the correlation of the expression of genes involved in the UPP with the prognosis of liver cancer, to screen out some key genes and construct a prognosis predictive model, in order to provide a new horizon for the role and potential mechanism of the UPP in the development of liver cancer.

## MATERIALS AND METHODS

### **Gene sets and data collection**

The UPP-related gene set included 857 genes from the UPP-related Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways[13], among which 10 was related to E1, 38 related to E2, 651 to E3, 112 to deubiquitylating enzyme (DUB), and 46 to the proteasome.

The expression data of 424 samples related to liver cancer were downloaded from The Cancer Genome Atlas (TCGA) database (<https://portal.gdc.cancer.gov/>). Three recurrent samples, 50 normal tissue samples, and one sample without overall survival (OS) data were deleted and the remaining 370 samples were randomly divided into a training group ( $n = 296$ ) and a validation group ( $n = 74$ ) in a ratio of 4:1. Another validation set (GSE54236) was downloaded from the Gene Expression Omnibus (GEO) database (<http://www.ncbi.nlm.nih.gov/geo/>). This data set included 162 samples, including 81 tumor samples.

### **Construction and validation of a prognosis predictive model**

Univariate and multivariate regression analyses were performed to screen the prognostic genes in the E1, E2, DUB, and proteasome gene sets using the Survival (version 3.2-3) and Glmnet (version 4.0-2) packages in R. The threshold of univariate analysis was  $P < 0.1$ , and stepwise multivariate regression analysis was used to screen genes associated with OS. The risk score of the screened genes was calculated to construct a prognosis predictive model, and the prognostic ability was assessed using the receiver operating characteristic (ROC) curve drawn with Proc (version 1.16.2) package. According to the risk score, the patients were divided into either a high-risk or a low-risk group. The Maxstat (version 0.7-25) package in R was used to calculate the optimal cut-off value. The log-rank method was used to compare the difference in OS between the two groups, and the Survival (version 3.2-3) and Survminer (version 0.4.8) packages in R were used to draw the survival curve. In the validation group, the same method was used to verify the model.

### **Immunocyte infiltration**

The abundance of 40 types of immune cells in each sample was analyzed using GVSA (version 1.32.0). The correlation analysis between the screened genes and immune-related indicators was performed using the Psych (version 2.0.8) and Corrplot (version 0.84) packages in R.

### **Analysis of correlation between clinical parameters and gene expression**

The clinical parameters were compared between the high-risk and the low-risk groups using an independent sample  $t$ -test or two-sample Wilcoxon test, and Spearman correlation analysis was used to determine whether the gene expression and risk scores were statistically related to clinical parameters. The Psych (version 2.0.8) and Corrplot (version 0.84) packages in R were used for plotting. Univariate Cox regression analysis was used to determine the relationship between OS and clinical parameters, as well as the relationship between the gene expression and postoperative recurrence.

### **Identification of differentially expressed genes and enrichment analysis**

The Limma package (version 3.40.2) was used to screen DEGs between the high-risk and low-risk groups, with the threshold set at  $P < 0.05$  and  $|\log_2FC| > 1$ . Then the functional enrichment analysis was carried out using the database for annotation, visualization, and integrated discovery (DAVID, <https://david.ncifcrf.gov/>) to identify the enriched gene ontology (GO) terms and KEGG pathways of the DEGs.

### **Core DEGs in E3 gene set**

As a specific substrate recognition element, E3 plays an important role in the ubiquitin-mediated proteolytic cascade[14]. Because of its specificity, the relationship between the expression of genes in the E3 set and prognostic risk was analyzed separately. Similar to the screening method for DEGs, the Limma package was used to screen the DEGs in the E3 gene set between the high-risk and low-risk groups, and the screening threshold was  $P < 0.05$  and  $|\log_2FC| > 1$ .

### **Statistical analysis**

IBM SPSS Statistics 21 and R (version 3.6.2) were used for statistical analyses. The Shapiro-Wilk test was used for normality test, and the independent sample  $t$  test or the two-sample Wilcoxon test were used to analyze the differences in variables between two groups. The chi-square test or Fisher's test was used for analysis of categorical variables. The log-rank method was used to test the significance of survival data.

**Table 1 Clinical parameters of the whole samples, cases in training group, and those in validation group, *n* (%)**

Parameter	Category	TCGA ( <i>n</i> = 370)	Training group ( <i>n</i> = 296)	Validation group ( <i>n</i> = 74)
Age		59.441 ± 13.517	59.53 ± 13.71	59.081 ± 12.796
<i>P</i> value			0.799	
Gender	Female	121 (32.7)	101 (34.1)	20 (27)
	Male	249 (67.3)	195 (65.9)	54 (73)
<i>P</i> value			0.27	
Height		167.34 ± 10.7	167.32 ± 11.368	167.43 ± 7.622
<i>P</i> value			0.92	
Weight		72.85 ± 19.468	73.05 ± 20.571	72.07 ± 14.478
<i>P</i> value			0.646	
BMI		26.13 ± 8.453	26.25 ± 9.145	25.66 ± 4.909
<i>P</i> value			0.609	
Histological type	FLC	3 (0.8)	2 (0.7)	1 (1.4)
	HCC	360 (97.3)	287 (97)	73 (98.6)
	FLHCC	7 (1.9)	7 (2.4)	0 (0)
<i>P</i> value			0.35	
Stage	I/II	256 (69.2)	209 (69.6)	47 (63.5)
	III/IV	90 (24.4)	69 (23.3)	21 (28.4)
	Not available	24 (6.5)	18 (6.1)	6 (8.1)
<i>P</i> value			0.454	
Grade	G1/G2	232 (62.7)	180 (60.8)	52 (70.3)
	G3/G4	133 (35.9)	112 (37.9)	21 (28.4)
	Not available	5 (1.4)	4 (1.4)	1 (1.4)
<i>P</i> value			0.241	

*P* values refer to statistical results between training and validation groups. BMI: Body mass index; FLC: Fibrolamellar carcinoma; HCC: Hepatocellular carcinoma; FLHCC: Hepatocholeangio carcinoma (mixed).

**Table 2 The five genes significantly correlate with the prognosis of patients with liver cancer**

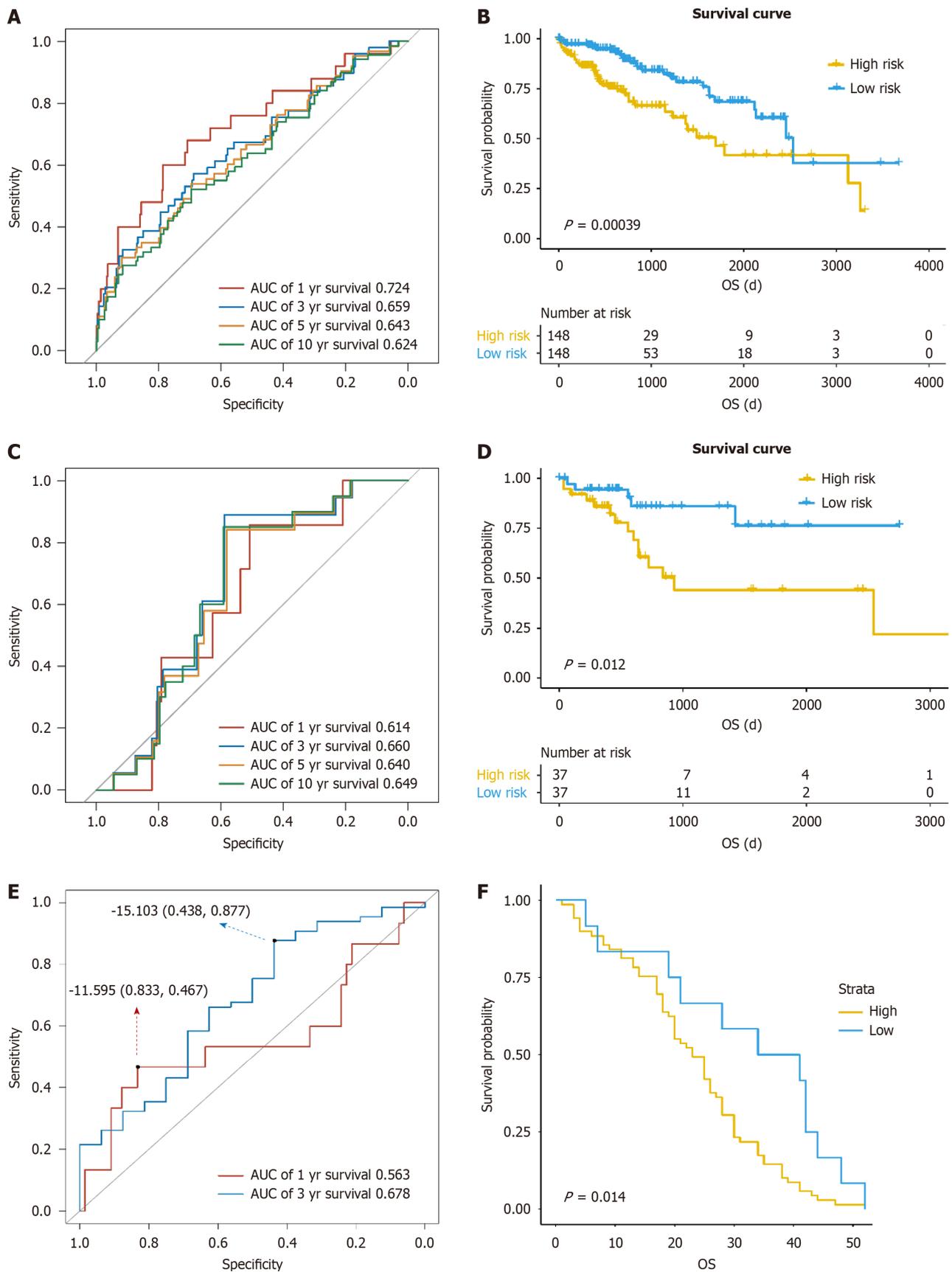
Gene	Gene set	Coef	Hazard ratio	Z	<i>P</i> value
<i>ATG10</i>	Ubiquitin-conjugating enzyme (E2)	0.48387	1.62234	2.364	0.0181
<i>PSMA8</i>	Proteasome	0.20721	1.23024	1.962	0.0497
<i>PSMB2</i>	Proteasome	0.66763	1.94962	2.483	0.013
<i>USP17L2</i>	Deubiquitinating enzyme (DUB)	-2.8057	0.06046	-3.048	0.0023
<i>USP8</i>	Deubiquitinating enzyme (DUB)	-0.46594	0.62755	-1.701	0.0889

*ATG10*: Autophagy related 10; *PSMA8*: Proteasome 20S subunit alpha 8; *PSMB2*: Proteasome 20S subunit beta 2; *USP17L2*: Ubiquitin specific peptidase 17 like family member 2; *USP8*: Ubiquitin specific peptidase 8.

## RESULTS

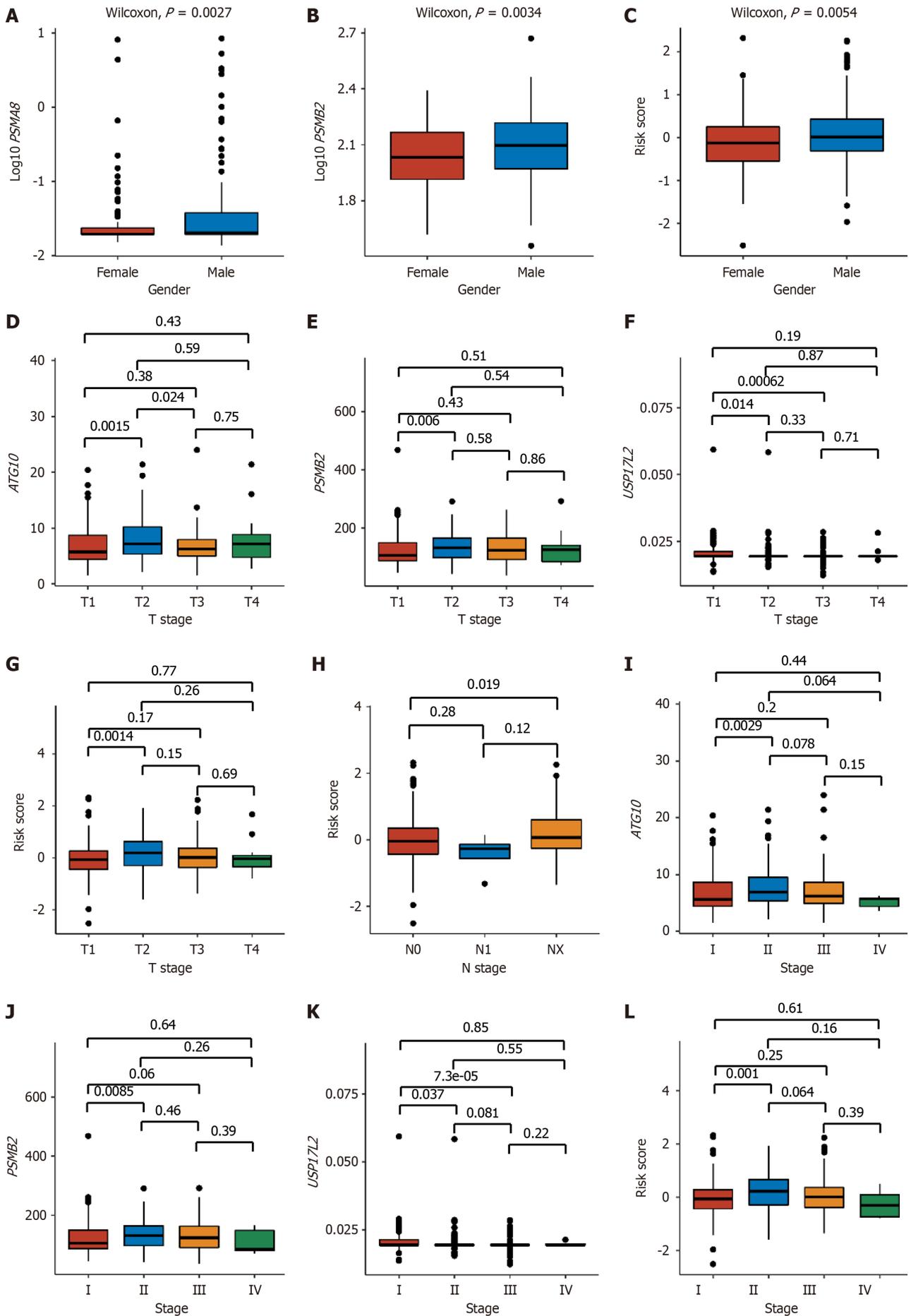
### Construction of a prognosis-predicted model for liver cancer based on five genes

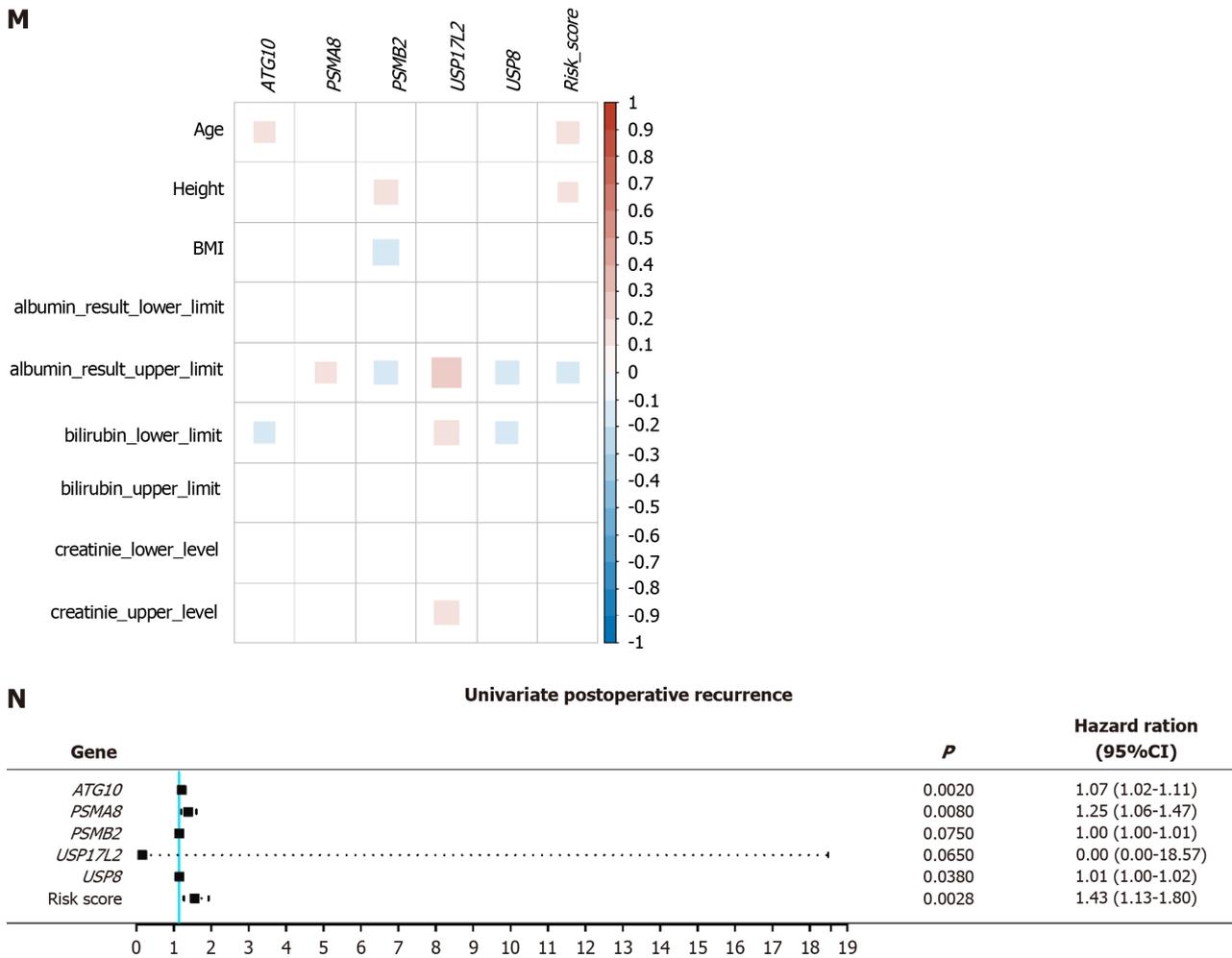
The clinical parameters of the whole samples, cases in the training group, and those in the validation group are listed in Table 1, with *P* value referring to the statistical results between the training group and the validation group. A total of five genes significantly related to prognosis were screened to construct a prognosis predictive model, including *ATG10*,



**Figure 1** Prognosis predictive model for liver cancer. A: Receiver operating characteristic (ROC) curve of the model in training group; B: Survival curve of high- and low-risk patients with liver cancer in training group; C: ROC curve of the model in The Cancer Genome Atlas (TCGA) validation group; D: Survival curve of high- and low-risk patients with liver cancer in TCGA validation group; E: ROC curve of the model in gene expression comprehensive (GEO) validation group; F: Survival curve of high- and low-risk patients with liver cancer in GEO validation group. AUC: Area under the curve; OS: Overall survival.







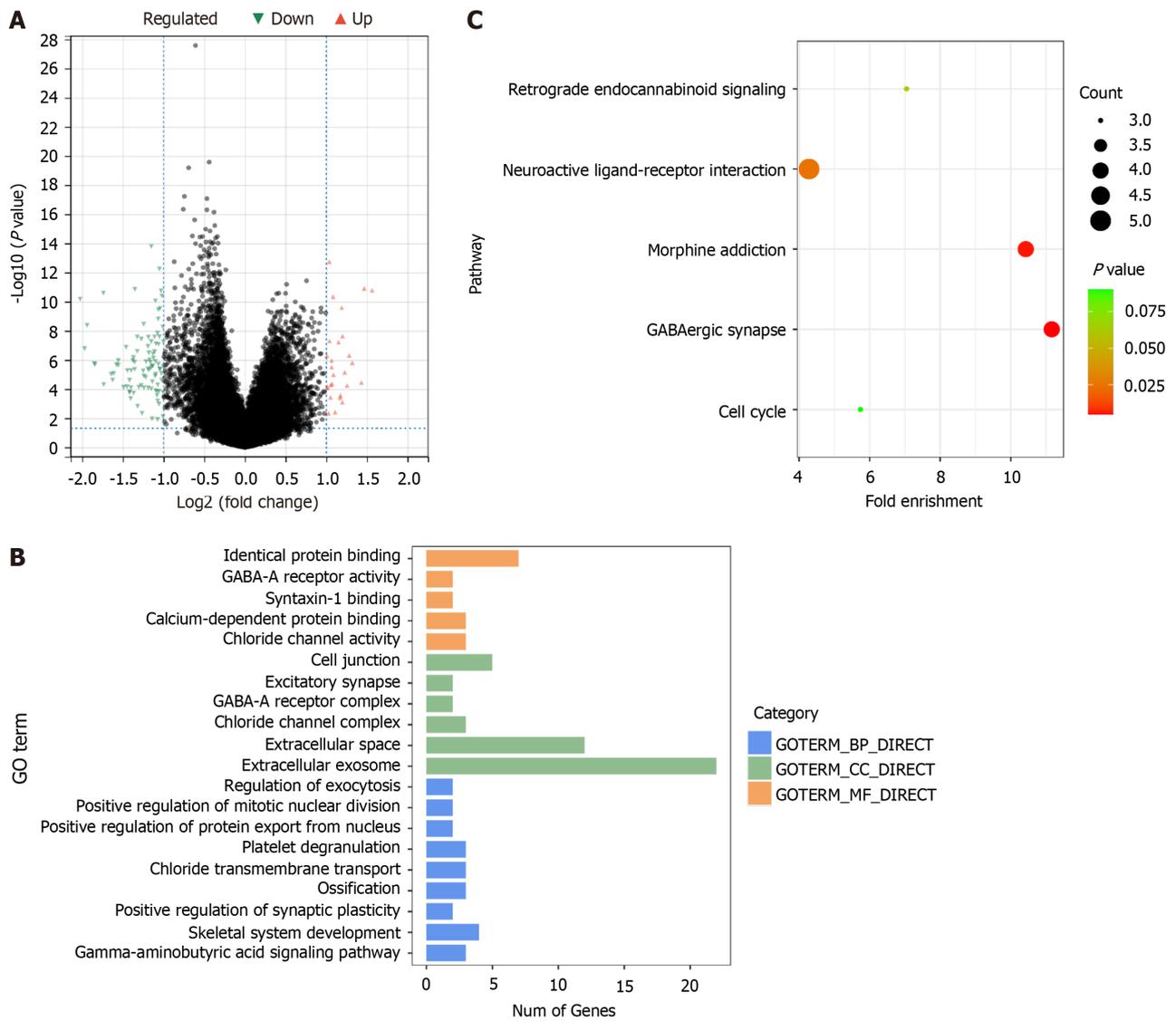
**Figure 3 Correlation of expression levels of ATG10, PSMA8, PSMB2, USP17L2, and USP8 and risk score with clinical parameters.** A-C: Gene expression and risk score between genders; D-G: Gene expression and risk score among T stages; H: Risk score among N stages; I-L: Gene expression and risk score among clinical stages; M: Correlation of gene expression levels and risk score with biochemical indexes; N: Correlation of gene expression levels and risk score with postoperative recurrence in liver cancer, with a hazard ratio (HR) > 1 referring to a positive correlation and HR < 1 referring to a negative correlation. *P* < 0.05 indicated statistical significance. HR: Hazard ratio.

DCAF4L2 and survival, while KBTBD11 displayed a positive correlation with the prognosis of liver cancer (Figure 5).

## DISCUSSION

The key factor to cell survival lies in the balance of protein synthesis and decomposition. The UPP is an ATP-dependent non-lysosomal protein degradation pathway, which is important for the body to regulate the level and function of intracellular proteins, thus efficiently and selectively degrading intracellular proteins. This study showed that the expression of the UPP genes *ATG10*, *PSMA8*, *PSMB2*, *USP17L2*, and *USP8* was significantly correlated with the prognosis of liver cancer. The prognosis model constructed based on these five genes could accurately predict the prognosis of patients (*P* < 0.001 and *P* = 0.012 in training and validation groups, respectively, Figure 1). These genes were statistically correlated with different clinical parameters and immune cell abundance (Figures 2 and 3). The model categorized all patients into either a high-risk group or a low-risk group, and a total of 111 DEGs were screened between the two groups, which were enriched in GO terms related to protein binding, GABA-A receptor, synapse, *etc.*, and KEGG pathways of retrograde endocannabinoid signaling, neuroactive ligand-receptor interaction, morphine addiction, GABAergic synapse, and cell cycle (Figure 4).

Those five genes were found to promote the development of many malignant tumors, including liver cancer[15-22]. Our results showed that the increased expression of *ATG10*, *PSMA8*, and *PSMB2* increased the risk of death (*P* = 0.018, 0.049, and 0.013, respectively), while the increased expression of *USP17L2* and *USP8* decreased the risk of death (*P* = 0.002 and 0.089, respectively). According to previous studies, the overexpression of *ATG10* and *PSMB2* in tumors promoted the invasion or metastasis of tumor cells[16,18], and *USP8* showed the opposite effect[21,22]. Besides, *PSMA8* could affect the progression and prognosis of colorectal cancer due to its strong association with *PSMB2*[23]. Interestingly, higher *PSMA8* expression levels were correlated with good prognoses for breast cancer through epigenetic regulation

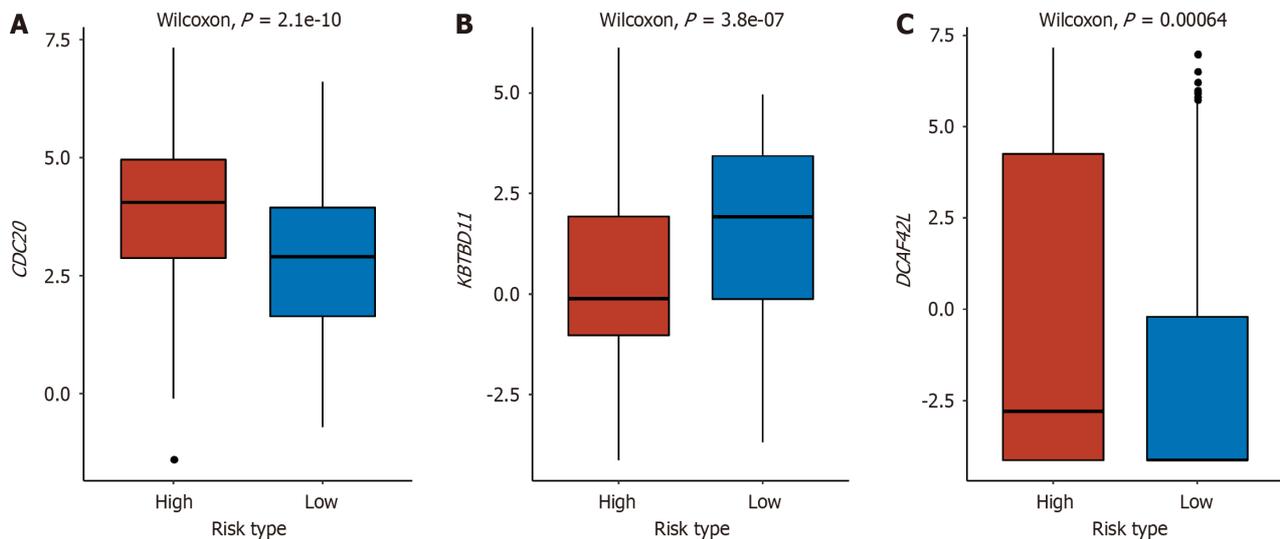


**Figure 4** Enrichment analysis of differentially expressed genes between liver cancer and normal samples. A: Volcano plot of differentially expressed genes (DEGs); B: Gene ontology terms enriched by DEGs; C: Kyoto Encyclopedia of Genes and Genomes pathways enriched by DEGs. GO: Gene ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; DEGs: Differentially expressed genes.

[24]. In our study, it was found that *PSMA8* was positively correlated with the prognosis of patients with liver cancer. On the contrary, *USP17L2* has been found to be overexpressed in a variety of tumors[19,20], which is similar to our results. However, recent studies have found that up-regulation of *USP17L2* causes chemotherapy resistance in colorectal cancer, and knockdown of *USP17L2* could overcome bromodomain and extra-terminal domain inhibitor resistance in prostate cancer cells[25,26]. Hence, the role of *USP17L2* in liver cancer still requires further exploration.

The global immune system functions pose great technical challenges to the research of tumor-immune interaction[27, 28]. Because immune infiltration plays a key role in the development of liver cancer[27], we conducted a thorough correlation analysis to identify the immune cell types associated with the prognosis model. Minor alterations in the distribution of immune cells could potentially exert diverse impacts on the progression of tumors[29]. In this study, myeloid dendritic cells were the immune cell type with a significant difference in abundance only between groups with high and low expression of the *PSMB2* gene, as well as neutrophils and Th17 cells between groups with different expression of the *USP17L2* gene (Figure 2). However, no significant correlation was found between tumor-infiltrating immune cells and gene expression, and it is imperative to conduct additional confirmation and validation in an independent cohort. Furthermore, exploring the connection between the expression levels of some checkpoints and immune infiltration, as well as the tumor microenvironment, will be a hotspot for future research.

Moreover, the expression of one or more of the five genes and the risk score were different among different T, N, and clinical stages (Figure 3). It is widely known that tumor stage is a key prognostic factor for malignant tumors[30]. In addition, all genes except *ATG10* and the risk score were correlated with the upper limit of albumin results (Figure 3). The risk score was not only statistically significant in different stages, but also negatively correlated with the upper limit of albumin results and postoperative recurrence, which proves that the model developed in this study has appreciated value in clinical prediction of recurrence and prognosis.



**Figure 5** Differentially expressed genes in E3 gene set between high- and low-risk groups. A-C: *CDC20* (A), *KBTBD11* (B), and *DCAF4L2* (C) in E3 gene sets were significantly different between high- and low-risk groups.

E3 is the key factor in the UPP, which can specifically recognize different substrates and show high selectivity in protein degradation. Therefore, we analyzed the E3 gene set independently of E1, E2, DUB, and proteasome-related genes. Finally, the expression levels of *CDC20*, *KBTBD11*, and *DCAF4L2* were identified as significantly different between the high-risk and low-risk groups, which were also included in the above 111 DEGs. *CDC20* plays a vital role in chromosome segregation and mitosis[31]. It regulates the stability of phosphorylated mitotic centromere-associated kinesin in metaphase-anaphase transition[32], which may play a role as a cancer protein to promote the development and progression of liver cancer. In the study of Zheng *et al*[33], *CDC20*, proliferating cell nuclear antigen, and minichromosome maintenance complex component 6 synergistically affect the regulation of the cell cycle and may be potential prognostic factors for liver cancer. Shi *et al*[34] found that *CDC20* serves as a crucial factor in the development of hepatocellular carcinoma (HCC) by controlling the prolyl-4-hydroxylase domain 3 protein. By analyzing four expression profiles from the GEO database, it was found that the up-regulation of *CDC20* in HCC tissues indicates poor OS and disease-free survival[35]. Recently, *KBTBD11* was identified as a newly discovered adipogenesis-related gene[36]. In diverse cancer types, such as colorectal cancer, HCC, and head and neck squamous cell carcinoma, the expression of *KBTBD11* was significantly decreased in tumor tissues as compared to normal tissues[37]. This is consistent with our result that patients in the high-risk group had lower *KBTBD11* gene expression levels. *DCAF4L2* is a member of the E3 complex, which is usually used as a mediator of protein-protein interaction and negatively regulates NF- $\kappa$ B signal transduction. Overexpression of *DCAF4L2* has been observed in human colon cancer[38]. In a study of HCC, overexpression of *DCAF4L2* is a common feature of nonalcoholic steatohepatitis-associated HCC and viral hepatitis-associated HCC, which can be used as a candidate therapeutic target for HCC[39]. We also found overexpression of *DCAF4L2* in high-risk patients, which suggested a poor prognosis in patients with liver cancer.

One of the main shortcomings of this study is the lack of clinical cases. All the data were from TCGA and GEO, resulting in the lack of clinical data for some patients, and it was unable to validate the expression of the five genes and comprehensively analyze their correlation with clinical and prognostic indicators. This is a preliminary study, and the results reported are exploratory. We intend to validate these results and the detailed mechanisms in future studies.

## CONCLUSION

In conclusion, we have used gene expression data in TCGA to screen genes involved in the UPP pathway that significantly correlate with the prognosis of liver cancer. Our findings indicate that the UPP plays an important role in the development of liver cancer, which provides new insights into the early prediction of prognosis and precision medicine in liver cancer.

## ARTICLE HIGHLIGHTS

### Research background

The ubiquitin-proteasome pathway (UPP) is crucial for selective protein degradation, and its dysfunction is linked to various diseases, including cancer. Proteasome inhibitors are emerging as potential anti-tumor drugs. This study explored the association between UPP gene expression and liver cancer prognosis, aiming to identify key genes and develop a predictive model. By doing so, the research seeks to offer novel insights into the role and potential mechanisms

of the UPP in liver cancer development, contributing to the ongoing exploration of effective therapeutic strategies for liver cancer.

### Research motivation

Due to the high tumor heterogeneity, effective surveillance and predication of the prognosis of liver cancer still face multiple challenges. This study was performed to analyze the relationship between the expression of genes in the UPP and the prognosis of liver cancer and construct a prognosis predictive model for this malignancy.

### Research objectives

The study aimed to investigate the prognostic significance of genes in the UPP in liver cancer. Using gene expression data from The Cancer Genome Atlas (TCGA) and gene expression comprehensive (GEO) databases, the study identified key genes involved in the UPP, constructed a prognostic predictive model for liver cancer, and explored the associations of the model with immune cell infiltration and clinical parameters, in order to enhance liver cancer prognosis prediction and provide insights into the role and potential mechanisms of the UPP in liver cancer development, contributing valuable information for precision medicine in the context of liver cancer management.

### Research methods

The research employed diverse methodologies, utilizing UPP-related gene sets and patient data from TCGA and GEO databases. A prognostic model was constructed using univariate and multivariate regression analyses, involving five key genes (ATG10, PSMA8, PSMB2, USP17L2, and USP8). The model demonstrated robust predictive abilities for liver cancer prognosis. Immunocyte infiltration analysis and correlation studies with clinical parameters provided additional insights. Differentially expressed genes and enrichment analyses shed light on relevant pathways. The study's comprehensive approach contributes a nuanced understanding of UPP gene implications in liver cancer prognosis.

### Research results

This study investigated the role of the UPP in liver cancer, identifying five key genes (*ATG10*, *PSMA8*, *PSMB2*, *USP17L2*, and *USP8*) associated with prognosis. A predictive model was constructed and validated using TCGA and GEO datasets. The study highlighted differential gene expression between the high- and low-risk groups and enriched relevant pathways. Additionally, differentially expressed genes in the E3 gene set (*CDC20*, *KBTD11*, and *DCAF4L2*) were identified as significant. The findings provide valuable insights into liver cancer prognosis, immunology, and potential therapeutic targets.

### Research conclusions

We have used gene expression data in TCGA to screen genes in the UPP that significantly correlated with the prognosis of liver cancer. Our findings indicate that the UPP plays an important role in the development of liver cancer, which provides new insights into the early prediction of prognosis and precision medicine in liver cancer.

### Research perspectives

This is a preliminary study, and the results reported are exploratory. We intend to validate these results and the detailed mechanisms in future studies.

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## FOOTNOTES

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**Co-first authors:** Hua Li and Yi-Po Ma.

**Co-corresponding authors:** Xiao-Min Liu and Peng-Fei Liu.

**Author contributions:** Liu XM and Liu PF conceptualized and designed the research; Li H and Ma YP collected the data and wrote the manuscript; Wang HL conducted the data mining and prepared the figures; Tian CJ, Guo YX, and Zhang HB conducted the bioinformatics analysis; all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Li H and Ma YP contributed equally to this work and are the co-first authors. Liu XM and Liu PF contributed equally to this study and are the co-corresponding authors. There are two primary reasons behind appointing Li H and Ma YP as co-first authors, and Liu XM and Liu PF as co-corresponding authors. First, our research was conducted through a collaborative effort, and the selection of first and corresponding authors aptly mirrors the distribution of responsibilities and the shared commitment of time and effort needed to carry out the study and produce the resulting paper. This approach ensures effective communication and facilitates the management of post-submission matters, ultimately enhancing the paper's overall quality and reliability. Second, each of these researchers made substantial and equal contributions throughout the entire research process. Designating them as co-first authors or co-corresponding authors not only acknowledges and respects their equivalent input but also highlights the spirit of teamwork and collaboration that characterized this study. In summary, the choice to designate Li H and Ma YP as co-first authors, and Liu XM and Liu PF as co-corresponding authors is appropriate for our manuscript as it accurately reflects our team's collaborative ethos and equal contributions.

**Supported by** the Tianjin Municipal Natural Science Foundation, No. 21JCYBJC01110.

**Institutional review board statement:** TCGA is a public database. The patients involved in the database have obtained ethical approval. Users can download relevant data for free for research and publish relevant articles. Our study was based on open-source data, so there

are no statements on ethics approval and consent.

**Informed consent statement:** Our study is based on open-source data, so there are no statements on informed consent.

**Conflict-of-interest statement:** All authors declare that they have no competing interests to disclose.

**Data sharing statement:** Publicly available datasets were analyzed in this study, and these can be found in the TCGA database (<http://portal.gdc.cancer.gov/>).

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