Research Paper

Complement Factor H is a Novel Biomarker for Diagnosis and Prognosis of Patients with Liver Cancer

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The complement system played critical roles in antimicrobial defense response, immune regulation and immunopathological damage. As an important negative regulator in this system, complement factor H provided selective advantage for tumor cell proliferation to escape immune surveillance, leading to avoid apoptosis. However, the influence of its expression on the pathological process and prognosis of liver cancer were still unclear. In this study, we analyzed the pattern of complement factor H expression in liver cancer in order to clarify its potential application value in the diagnosis and prognosis by bioinformatics analysis of data-set collected from The Cancer Genome Atlas database. By evaluating the clinical diagnostic value of complement factor H, we studied the correlation between complement factor H expression and clinicopathological parameters of liver cancer. Additionally, we found that patients with low complement factor H expression had poor overall survival and relapse-free survival, and confirmed that low complement factor H expression was an independent predictor of poor prognosis through risk regression analysis. Gene-set enrichment analysis identified E2 factor targets, growth 2 phase of mitosis checkpoint, spermatogenesis, mitotic spindle, deoxyribonucleic acid repair and wingless-related integration site/beta-catenin signaling were enriched with low complement factor H expression phenotype. Taking together, these findings suggested that complement factor H may be a useful biomarker for the diagnosis and prognosis of liver cancer.

Key words: Liver cancer, complement factor H, biomarker, complement system, poor prognosis

Liver cancer, a malignant disease with high mortality, often leads to patients with poor prognosis due to high recurrence[1-3]. In recent years, the diagnosis and therapies of liver cancer are significantly improving, including adjuvant radiotherapy, surgical resection, biological therapy and other comprehensive treatments[4]. However, the relapse and metastasis of liver cancer are still steadily increasing[5]. With the research on the treatment of liver cancer, the screening of molecular targets has become a new strategy[6]. Thus, identification, discovery and search for more sensitive and specific new diagnostic and prognostic markers can help patients to make reasonable choices of therapies and to monitor regularly during treatment.

Complement system (also called complement activation pathway), an important component of innate immunity, was widely involved in host antimicrobial defense reactions, immune regulation and immunopathological damage[7-9]. It was able to be activated through three pathways, including classical, lectin and alternative pathway. When C3 convertase cleaved C3 into C3a and C3b, three complement pathways would converge into a final universal pathway and activated C3 leads to the formation of Membrane Attack Complex (MAC) to induce the disintegration of target cells such as tumor cells[10,11]. It had been reported that the complement system stimulated the inflammatory response to isolate microorganisms or toxic-molecules to attack the host

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by attracting neutrophils and macrophages to increase the levels of interferon's and interleukins[12].

Complement Factor H (CFH), produced by urothelial tumor cells and macrophages, gives a selective growth advantage to tumor cells *in vivo*, avoiding apoptosis by escaping host immune surveillance[13,14]. However, CFH played a critical negative feedback role in controlling the alternative pathway of complement activation[15-17]. In addition, CFH prevented cells from being lysed by interfering with the complement cascade[18]. A recent study showed that CFH was able to be a biomarker for progression of cutaneous squamous cell carcinoma[19]. However, few studies had reported the role of CFH expression in clinical diagnosis and prognosis.

In this study, our team focused on the impact of CFH expression on clinical features, diagnosis and prognosis in liver cancer. Based on the clinical dataset of The Cancer Genome Atlas (TCGA), we analyzed the expression pattern of CFH at different stages and revealed its diagnostic value in liver cancer. Further, we suggested that the Overall Survival (OS) and Relapse-Free Survival (RFS) were significantly shortened in patients with low CFH expression. Indeed, its low expression was a risk factor for poor prognosis through Cox analysis. In summary, our findings indicated that CFH might be a useful biomarker for the diagnosis and prognosis of liver cancer in clinical applications.

MATERIALS AND METHODS

Data collection and mining:

We obtained Ribonucleic Acid sequencing (RNAseq) of CFH and clinical information of liver cancer patient from TCGA database by using R software (version 4.0.1) and RNAseq was transformed to RNA-Seq by Expectation Maximization (RSEM) by estimating as log2 (x+1) normalized counts and used for subsequent analysis by selecting R software[20].

Gene-set enrichment analysis:

To explore the distribution of predefined genomes and determine the potential mechanism to influence the effect of CFH expression on the prognosis of Liver Hepatocellular Carcinoma (LIHC) patients, we opted for Gene Set Enrichment Analysis (GSEA) (version 4.0.3). This analysis was performed through the "h.all. v7.2. symbols.gmt" gene set in the molecular signatures database[21]. Gene-sets with a normal p value<0.05 was regarded as significantly enriched.

Statistical analysis:

R software was used for statistical analysis of all data. Data visualization was performed *via* using grammar of graphics (ggplot2) package. The boxplots was used to analyze the expression pattern of CFH. The chi-square test verified the correlation between the expression of CFH and clinicopathological parameters. Receiver Operating Characteristic (ROC) analysis was preformed through pROC package[22]. The ROC curve was used to evaluate the diagnostic value of CFH and the patients were divided into two groups (high and low expression) according to cut-off values[23]. Kaplan-Meier and log-rank tests were used to evaluate the effect of CFH expression on patient's survival. Univariate and multivariate analysis were used to verify the correlation between CFH expression and OS and RFS, $p<0.05$ was expressed as a difference and considered statistically significant.

RESULTS AND DISCUSSION

The clinical dataset of liver cancer patients were obtained from TCGA database. Table 1 lists the patient clinical characteristics, including age, gender, histological type, histologic grade, pathologic stage and Tumor/Nodes/Metastases (T/N/M) classification, as well as radiation therapy, residual tumor and vital status (Table 1). Subsequently, CFH expression analysis (fig. 1) showed that it was significantly higher in healthy tissues than in tumor tissues ($p=1.845\times10^{-7}$). Moreover, we also observed that CFH expression was negatively correlated with histological grades ($p=0.001143$), pathologic stage ($p=4.760\times10^{-9}$), gender ($p=6.550\times10^{-5}$), vital status ($p=0.01352$) and positively correlated with T classification ($p<2.200\times10^{-16}$), indicating that CFH expression was associated with tumor progression.

To evaluate the diagnostic capability of CFH expression, ROC curve was performed. We observed that CFH expression had modest diagnostic value (Area Under the Curve (AUC)=0.727; fig. 2) and it can also distinguish non-cancerous tissues from stage I disease (AUC=0.644), stage II disease (AUC=0.774), stage III disease (AUC=0.851) and stage IV (AUC=0.790). Additionally, we also observed that the low expression of CFH was related to the patient's clinical characteristics (Table 2), including gender ($p=0.002$), histologic grade ($p=0.025$), pathologic stage ($p=0.0001$), T classification ($p=0.0001$), RFS ($p=0.014$) and worse survival ($p=0.0001$).

TABLE 1: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF TCGA-LIHC COHORT

Parameters	Variables	Numbers (%)
Age	NA	1 (0)
	≥55	256 (67.90)
	<55	120 (32.10)
Gender	Male	255 (67.64)
	Female	122 (32.36)
Histological type	Fibrolamellar carcinoma	3 (0.8)
	HCC	367 (97.35)
	Hepatocholangiocarcinoma (mixed)	7 (1.86)
Histologic grade	NA	5 (1.33)
	G1	55 (14.59)
	G2	180 (47.75)
	G3	124 (32.89)
	G4	13 (3.45)
Pathologic stage	NA	22 (5.84)
	I	175 (46.42)
	II	88 (23.34)
	III	86 (22.81)
	IV	6 (1.59)
M classification	M0	272 (72.15)
	M1	4 (1.06)
	MX	101 (26.79)
N classification	NA	1 (0)
	N0	257 (68.17)
	N1	4 (1.06)
	NX	115 (30.50)
T classification	NA	2 (0.53)
	T1	185 (49.07)
	T2	95 (25.20)
	T3	81 (21.48)
	T4	14 (3.71)
Radiation therapy	NA	30 (7.96)
	NO	338 (89.66)
	Yes	9 (2.39)
Residual tumor	NA	7 (1.86)
	R0	330 (87.53)
	R1	17 (4.51)
	R2	1 (0)
	RX	22 (5.84)
RFS	NA	33 (8.75)
	No	233 (61.80)
	Yes	111 (29.44)
Vital status	Dead	191 (50.66)
	Survival	286 (75.86)
CFH	NA	6 (1.59)
	High	157 (41.64)
	Low	214 (56.77)

Note: NA: Not available

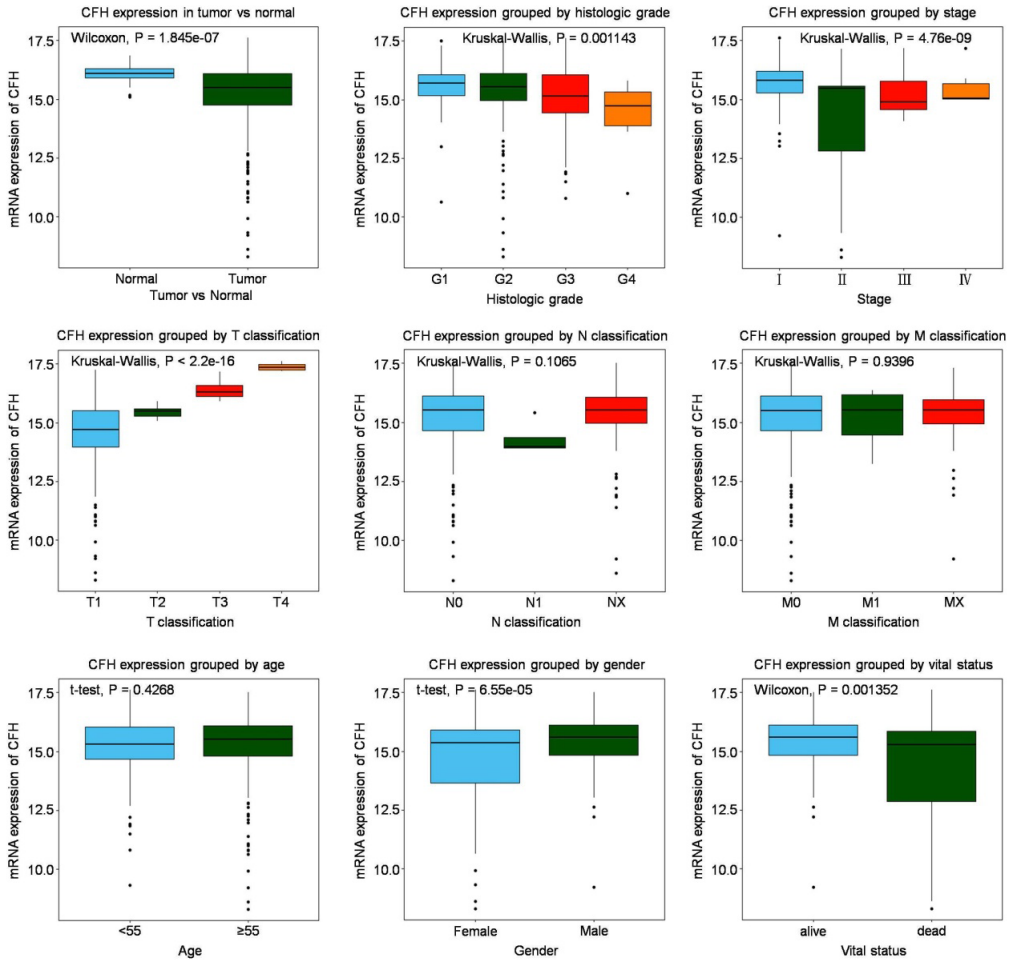

Fig. 1: Expression of CFH in liver cancer. Expression of CFH between tumor and normal tissue was compared. The expression of CFH was compared according to different age, gender, histologic grade, histological type, T/N/M classification, as well as radiation therapy, residual tumor, sample type, stage and vital status

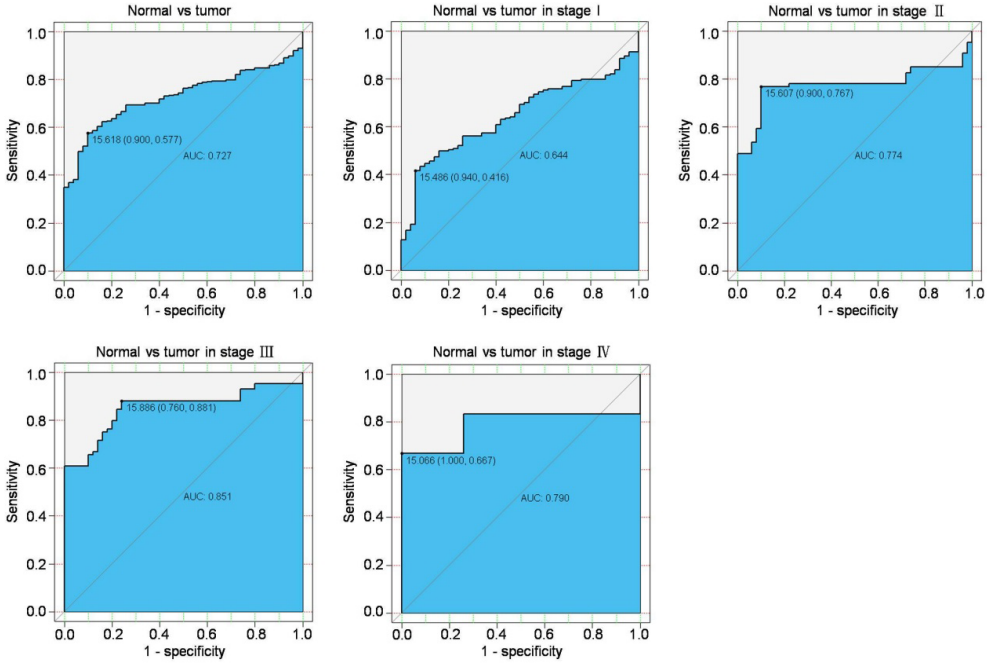

Fig. 2: Diagnosis value of CFH expression in liver cancer. The ROC curves of CFH expression in cancerous *vs.* normal liver tissues was generated. Cancerous *vs.* normal liver tissues was analyzed in different stages of liver cancer

TABLE 2: CORRELATION BETWEEN THE EXPRESSIONS OF CFH AND THE CLINIC PATHOLOGIC CHARACTERISTICS IN LIVER CANCER

Parameters	Variables	Numbers	CFH				χ2	p-value
			High	Probability (%)	Low	Probability (%)		
Age	≥55	256	117	72.22	139	64.95	2.242	0.134
	<55	120	45	27.78	75	35.05		
Gender	Male	255	124	76.07	131	61.21	9.333	0.002
	Female	122	39	23.93	83	38.79		
Histological type	Fibrolamellar carcinoma	3	1	0.61	2	0.93	2.57	0.277
	HCC	367	161	98.77	206	96.26		
	Hepatocholangiocarcinoma (mixed)	7	1	0.61	6	2.81		
Histologic grade	G1	55	29	18.01	26	12.32	9.383	0.025
	G2	180	86	53.42	94	44.55		
	G3	124	43	26.71	81	38.89		
	G4	13	3	1.86	10	4.74		
Pathologic stage	I	175	98	64.05	77	38.12	25.61	0.001
	II	88	22	14.38	66	32.67		
	III	86	31	20.26	55	27.23		
	IV	6	2	1.31	4	1.98		
M classification	M0	272	120	73.62	152	71.03	0.448	0.799
	M1	4	2	1.23	2	0.93		
	MX	101	41	25.15	60	28.04		
N classification	N0	257	114	69.94	143	67.14	3.193	0.203
	N1	4	0	0	4	1.88		
	NX	115	49	30.06	66	30.99		
T classification	T1	185	44	27.33	141	65.89	23.66	0.001
	T2	95	22	13.66	73	34.11		
	T3	81	81	50.31	0	0		
	T4	14	14	8.7	0	0		
Radiation therapy	NO	338	170	96.59	168	98.25	0.816	0.366
	Yes	9	6	3.41	3	1.75		
Residual tumor	R0	330	140	86.96	190	90.91	6.985	0.072
	R1	17	12	7.45	5	2.39		
	R2	1	1	0.62	0	0		
	RX	22	8	4.97	14	6.7		
RFS	No	233	108	75	125	62.5	5.985	0.014
	Yes	111	36	25	75	37.5		
Vital status	Dead	191	25	15.34	66	30.84	12.15	0.001
	Survival	286	138	84.66	148	69.16		

We had previously shown that CFH expression was associated with poor survival. To assess the effect of CFH expression on patient survival, we constructed Kaplan-Meier curves. We found that patients with low expression of CFH had lower OS levels (p=0.00072) and subgroups analysis also showed that low CFH expression decreased the OS in liver cancer cases of histologic grade, G1: Well differentiated (low grade)/ G2: Moderately differentiated (intermediate grade), G3: Poorly differentiated (high grade)/G4: Undifferentiated (high grade), stage I/II, T1, N0, N1/NX, M0 and M1/MX (fig. 3). Moreover, patients with low CFH expression had poor RFS (p=0.0062) and subgroups analysis also showed that low CFH expression decreased the RFS in liver cancer cases of histologic grade G1/G2, stage I/II, T1, N1/NX and M1/MX (fig. 4).

Low CFH expression is an independent risk factor for prognostic among patients with liver cancer. We selected potential variables that were significant in univariate analysis to conduct multivariable Cox analysis to assess the prognostic significance of CFH expression (Table 3 and Table 4). We found that low CFH is an independent risk factor for poor OS (Hazard Ratio (HR)=2.190, 95 % Confidence Interval (CI): 1.19-4.02, p=0.011 and RFS (HR=1.892, 95 % CI:1.21-2.37, p=0.038).

Identifying the activation of signaling pathways would facilitate a better understanding of molecular interactions, reactions and relationships, as well as disease process. To determine the signaling pathways activated in LIHC, we used GSEA to analyze the high and low CFH expression datasets. The results showed that E2 Factor (E2F) targets, Growth 2 phase of Mitosis (G2M) checkpoint, spermatogenesis, mitotic spindle, Deoxyribonucleic Acid (DNA) repair and Wingless-related integration site (Wnt)/beta (β)-catenin signaling were enriched to the low CFH expression phenotype (Table 5 and fig. 5).

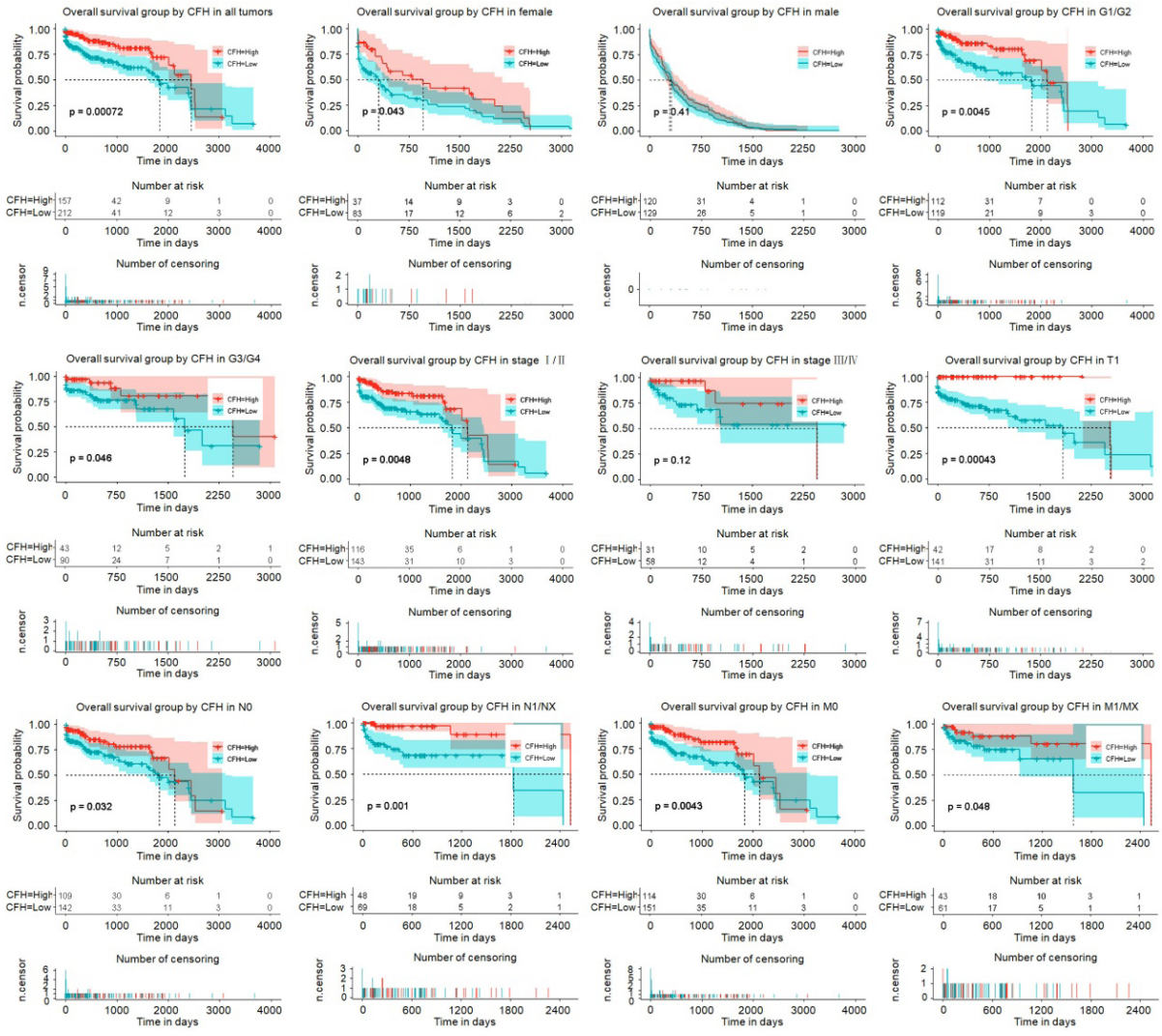

Fig. 3: The effect of CFH expression on OS in liver cancer, Kaplan-Meier curves of CFH expression in all patients and Kaplan-Meier curves of CFH expression in subgroup

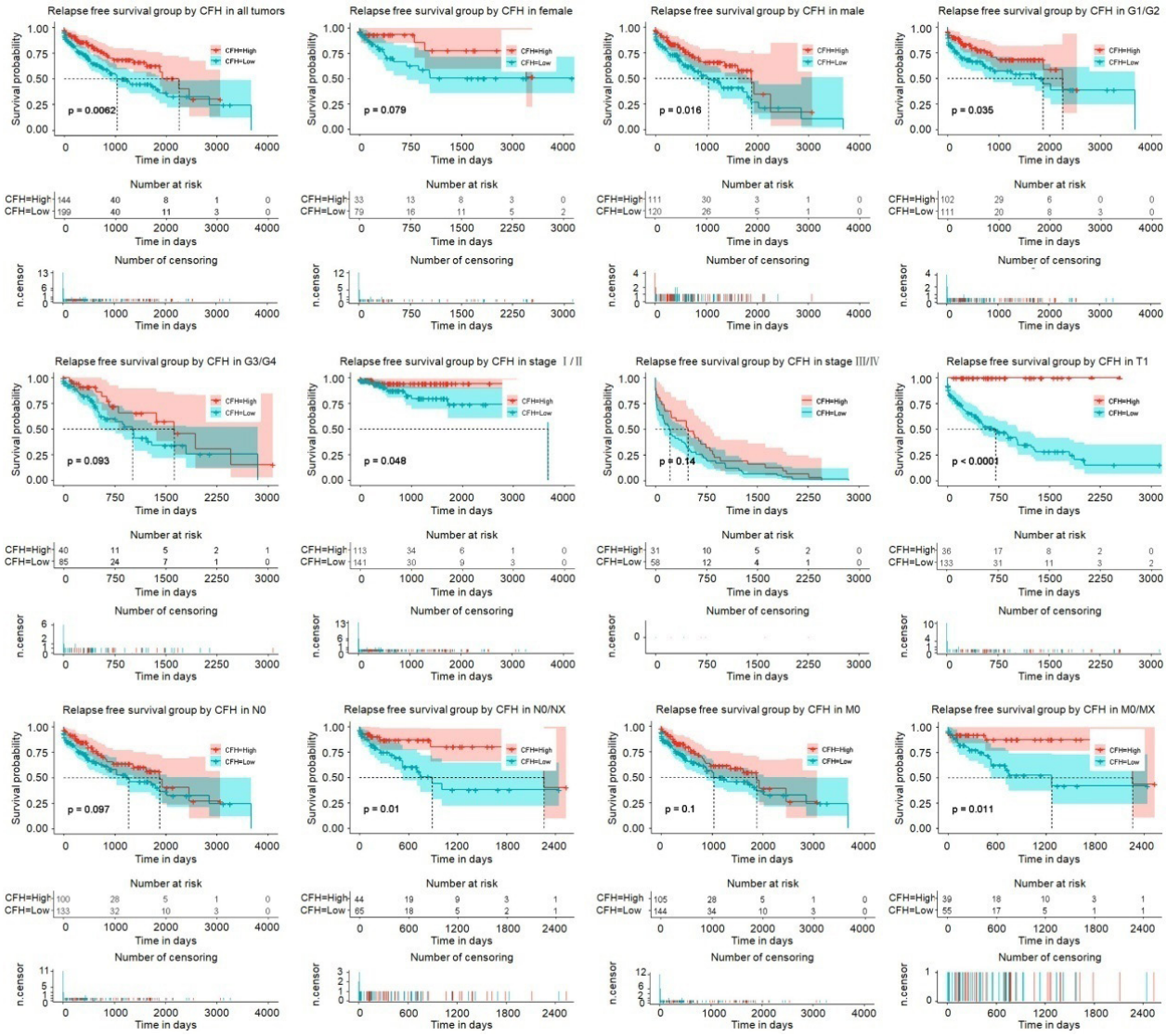

Fig. 4: The effect of CFH expression on RFS in liver cancer, Kaplan-Meier curves of CFH expression in all patients and Kaplan-Meier curves of CFH expression in subgroup

TABLE 3: UNIVARIATE AND MULTIVARIATE ANALYSIS OF OS IN PATIENTS WITH LIVER CANCER

	Univariate analysis			Multivariate analysis		
	HR	CI95	p value	HR	CI95	p value
Age	0.881	0.57-1.37	0.572			
Gender	0.998	0.80-1.24	0.994			
Histological type	0.500	0.12-2.07	0.340			
Histologic grade	0.957	0.72-1.27	0.759			
Pathologic stage	1.758	1.40-2.20	0.001	1.736	1.37-2.20	0.001
M classification	0.962	0.75-1.24	0.764			
N classification	0.93	0.72-1.19	0.555			
T classification	1.286	1.00-1.65	0.050	1.090	0.77-1.55	0.632
Radiation therapy	1.706	0.63-4.60	0.997			
Residual tumor	0.993	0.86-1.15	0.994			
CFH	2.210	1.38-3.54	0.001	2.190	1.19-4.02	0.011

TABLE 4: UNIVARIATE AND MULTIVARIATE ANALYSIS OF RFS IN PATIENTS WITH LIVER CANCER

	Univariate analysis			Multivariate analysis		
	HR	CI95	p value	HR	CI95	p value
Age	0.900	0.61-1.34	0.600			
Gender	1.599	1.02-2.51	0.042	2.134	1.34-3.41	0.001
Histological type	1.725	0.47-6.34	0.411			
Histologic grade	1.240	0.97-1.58	0.086			
Pathologic stage	4.373	3.44-5.56	0.000	5.014	3.75-6.70	0.001
M classification	0.874	0.69-1.10	0.252			
N classification	0.924	0.74-1.15	0.477			
T classification	1.357	1.08-1.71	0.009	1.630	1.07-2.49	0.023
Radiation therapy	3.036	0.80-13.7	0.099			
Residual tumor	0.902	0.67-1.21	0.486			
CFH	1.737	1.16-2.59	0.007	1.892	1.21-2.37	0.038

TABLE 5: GENE SET ENRICHMENT ANALYSIS IN LOW CFH EXPRESSION PHENOTYPE AMONG LIVER CANCER

Name	ES	NES	NOM p-value
Hallmark_E2F_targets	0.64	1.85	0.008
Hallmark_G2M_checkpoint	0.62	1.84	0.014
Hallmark_spermatogenesis	0.39	1.58	0.017
Hallmark_ mitotic_spindle	0.50	1.70	0.024
Hallmark_ DNA_repair	0.43	1.64	0.035
Hallmark_Wnt_beta_catenin_ signaling	0.48	1.56	0.039

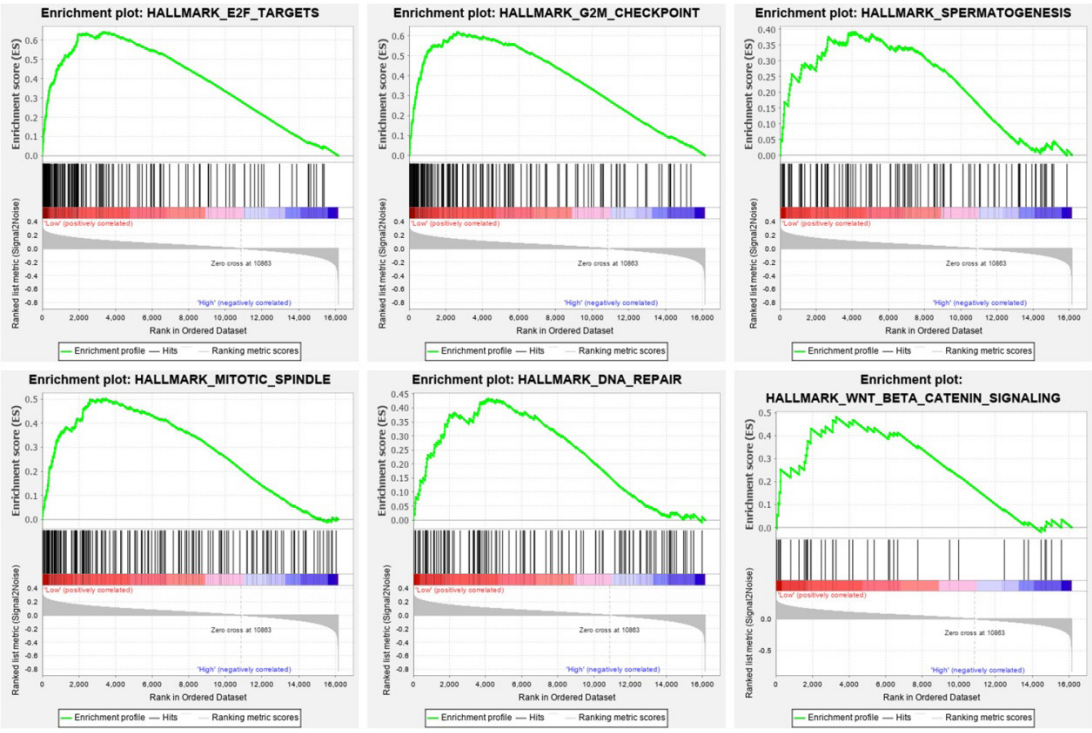

Fig. 5: Gene-set enrichment plots. GSEA results showing differential enrichment of genes related to mitotic spindle, PI3K/Akt/mTOR signaling, notch signaling, apoptosis, G2M checkpoint and Wnt/β-catenin signaling in LIHC cases with low CFH expression

In the past decades, with the deepening understanding of clinical research on liver cancer, many therapies have been developed, including surgical resection, adjuvant chemotherapy, radiotherapy and biological comprehensive therapy[2]. At the same time, researchers had also made great efforts to search and identify therapeutic targets and prognostic markers of liver cancer. However, patients often have poor prognosis due to tumor invasion, local recurrence and distant organ metastasis[24]. This brings not only serious challenges for patients to choose treatment methods, but also huge problems for clinicians to predict patient outcomes[25]. Therefore, it is still extremely important to find useful biomarkers for liver cancer diagnosis and prognosis.

In this study, we revealed that CFH was down-regulated in liver cancer and found that low CFH expression was relevant to histological grades, pathologic stage, T classification, patient's gender and survival status. The ROC curve showed that CFH expression had excellent clinical diagnostic value. Through the survival curve, we observed that patients with low CFH expression had a worse OS and RFS. Univariate and multivariate Cox regression analysis confirmed that CFH is an independent predictor of poor prognosis in patients with liver cancer.

As an important negative regulator in the alternative pathway, CFH played a critical role in the activation of the alternative pathway, target cell binding and amplification[18,26-28]. It has been reported that CFH was considered to be a functional role for tumor cells to escape from complement-mediated cytotoxicity, including lung cancer[29], ovarian cancer[30], bladder cancer[31] and glioblastoma[32]. Recent studies have shown that CFH controls the stemness of liver cancer cells *via* Liver Suppressor Factor 1 (LSF-1) and CFH-deficient mice had spontaneous liver tumors due to T cell infiltration and neutropenia[33,34]. This means that CFH down-regulated, plays an important role in the development of liver tumors. Consistent with our findings, CFH was down-regulated in liver cancer and the expression of CFH gradually increased with the worsening of T classification (fig. 1). Interestingly, patients with low CFH expression can hardly survive to T3 and T4 (Table 2), suggesting that CFH was related to liver cancer progression. Thus, we speculate that liver cancer cells protect themselves from complement-mediated cell killing by affecting CFH, but the mechanism needs further study.

CFH also had other functions which might play important roles in tumor progression and tumorigenesis. Previous studies had shown that CFH combined C3b by competing with complement factor-B to inhibit the activity of C3 convertase[35]. Additionally, it regulated cells adhesion by binding to cell surface receptors (Cluster of Differentiation (CD) 11b (CD11b)/CD18) to promote their proliferation, including some endothelial cells and tumor cells[36]. The over-expression of Complement Factor H-Related protein 3 (CFHR3) promoted apoptosis of Hepatocellular Carcinoma (HCC) cells by inhibiting the Phosphoinositide 3-Kinase (PI3K)/protein kinase B (Akt)/mammalian Target of Rapamycin (mTOR) signaling pathway[37], which indicated that CFH was extremely important for the occurrence and progression of liver cancer. In fact, our results indicate that CFH expression is related to liver cancer progression and malignant tumors and the implicit mechanism may be linked to E2F targets, G2M checkpoint, spermatogenesis, mitotic spindle, DNA repair and Wnt/β-catenin signaling as GSEA identified.

Considering the association with immune response and anti-tumor therapy, obviously, that tumor cells were regulated by many new antigens that might be recognized by the immune system[38]. It had been reported that CFH was a barrier to monoclonal antibody therapy in ovarian cancer, because it protected tumor cells from being attacked by the immune system[39]. Additionally, it promoted the progression of skin squamous cell carcinoma by regulating immune surveillance, which indicated that it could be used as indicator of the disease's progression and possible therapeutic targets[40]. Recently, abnormal CFH expression (mutation or deletion) has been associated with poor prognosis of many tumors, including gallbladder cancer[41] and lung adenocarcinoma[42]. In this study, our findings revealed that low CFH expression reduced OS and RFS in patients with liver cancer. Furthermore, we also found that it impacted patients OS at G1/G2, stage I/II, T1, N0, N1/NX, M0, M1/MX stage and RFS at G1/G2, stage I/II, T1, N1/NX and M1/MX stages. These indicated that CFH expression was specific in predicting the prognosis of patients, which was conducive to accurate clinical treatment of patients.

To our knowledge, this is the first report of the effect of CFH expression on the clinical features and poor prognostic of patients with liver cancer. We revealed that it has good clinical diagnostic value in patients with liver cancer and is a risk factor of poor prognosis. However, we need to further determine specific mechanisms between low CFH expression and poor prognosis in the future, so as to provide patients with more treatment options and supervision strategies.

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Author's contributions:

Chaoxiang Lv and Qiqi Zhang contributed equally to this work.

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Conflict of interests:

The authors declared that there were no conflicts of interest.

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