Hepatobiliary & Pancreatic Diseases International 18 (2019) 242–248

Contents lists available at ScienceDirect

Hepatobiliary & Pancreatic Diseases International

journal homepage: www.elsevier.com/locate/hbpd

Original Article/Liver

Expression of IL-26 predicts prognosis of patients with hepatocellular carcinoma after surgical resection

Zhi-Feng Xi, Seogsong Jeong, Chen-Chen Wang, Hong-Jie Li, Han Guo, Jie Cai, Jia-Xin Li, Xiao-Ni Kong, Ying Tong, Qiang Xia*

Department of Liver Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China

ARTICLE INFO

Article history:
Received 11 October 2018
Accepted 14 March 2019
Available online 27 March 2019

Keywords:
Interleukin 26
Hepatocellular carcinoma
Surgical resection
Prognostic factors

ABSTRACT

Background: There is no data regarding prognostic impact of interleukin (IL)-26 on outcomes of patients with hepatocellular carcinoma (HCC). The present study aimed to evaluate the prognostic impact of IL-26 on HCC patients undergoing liver resection.

Methods: From 2003 to 2008, 122 patients with HCC who received surgical curative resection were enrolled. Patients were stratified into IL-26-upper and -lower groups according to the median expression level from immunohistochemical staining of resected specimens. Prognostic impact of IL-26 was estimated using Kaplan–Meier curves. Univariate and multivariate analyses were performed to evaluate time-dependent prognostic impact and independency of IL-26. Demographic and clinical factors that were associated with IL-26 were comprehensively identified.

Results: Prognosis of the patients with high level of IL-26 revealed to be significantly unfavorable in both cumulative recurrence-free survival ($P < 0.001$) and overall survival ($P = 0.002$). Upper expression of IL-26 (HR: 1.643; 95% CI: 1.021 to 2.644; $P = 0.041$) and microvascular invasion (HR: 3.303; 95% CI: 1.255 to 8.696; $P = 0.016$) were identified as significant independent prognostic factors for overall survival in the multivariable analysis.

Conclusions: IL-26 is a novel prognostic factor for HCC after resection. Evaluation of IL-26 expression may be potentially valuable in clinical therapy when planning individualized follow-up schedule and evaluating candidates for prophylactic adjuvant treatment to prevent recurrence.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer that frequently appears in cirrhotic livers [1,2]. Surveillance by biannual ultrasound is recommended for patients with cirrhosis for diagnosis at early stage [3]. For resectable cases with preserved liver function, radical resection of the tumor is the standard of care, whereas liver transplantation is the only curative surgical modality for unresectable tumors or cases with underlying chronic liver diseases, such as severe cirrhosis [4,5]. However, due to shortage of organs and rapid progression of HCC, it is not eligible for all patients [6]. Thus, strict evaluation of candidates who may mostly benefit has become one of the most important procedures [7].

Outcomes after surgery remain dismal due to frequent recurrence. Numerous staging systems were developed to predict a subset of patients under high probability of recurrence due to insufficient accuracy and discrimination of preexisting staging models, such as TNM stage and Barcelona Clinic Liver Cancer Classification (BCLC), which are built on the basis of clinicopathological characteristics [8,9]. However, even the predictive tools built based on large-scale cohorts failed to achieve generalized use in prediction of prognosis because of the limited sensitivity of prognostic factors [10]. Therefore, there is an unmet need to identify prognostic biomarkers with high priority of precision to reduce population bias and increase accuracy. In addition, combination of biomarkers and clinicopathological characteristics may be the only way to achieve ideal predictive accuracy. However, due to limited specified biomarkers with high priority and cost efficacy, this ideal approach remains hard to apply in real-world.

Herein, we explored prognostic impact of interleukin (IL)−26 in a single center-based Chinese population with HCC undergoing resection. Prognostic significance of IL-26 is estimated and

* Corresponding author.
E-mail address: xiaqiang@medmail.com.cn (Q. Xia).

https://doi.org/10.1016/j.hbpd.2019.03.006

clinicopathological factors associated with expression of IL-26 were comprehensively identified.

Methods

Patients

Patients with pathological confirmation of HCC who received hepatic resection at Renji Hospital, School of Medicine, Shanghai Jiao Tong University between March 2003 and July 2008 were screened. Inclusion criteria of the present study include: (1) resectable tumor; (2) hepatic resection as first treatment; (3) single type of tumor excluding combined multiple type of tumors, such as HCC with cholangiocarcinoma; (4) patients with full records of demographic and clinicopathological data, and the Eastern Cooperative Oncology Group (ECOG) score of 0 to 1. Written informed consent was obtained from participants before surgery. This study was approved by the local Ethics Committee of Renji Hospital.

Data collection

The hospital-based HCC database was analyzed. Demographic data were collected at the time of diagnosis. Status of viral hepatitis was confirmed using serological examinations. Liver function results including total bilirubin, direct bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST), and tumor markers including alpha fetoprotein (AFP) and carcinoembryonic antigen (CEA), were presented with preoperative results that were tested within one week before surgery. Presence of cirrhosis, tumor size, nodule number, vascular invasion, and nodal metastasis were evaluated by pathological examinations. Immunohistochemistry of liver specimens for IL-26 was performed and analyzed using the imagescope standard procedure (Image-pro Plus version 6.0), which was used in the description of IL expression.

Immunohistochemistry

Immunohistochemical analysis was performed as described previously [11]. Briefly, paraffin-embedded liver tissues were cut into 5-μm-thick sections. First, the sections were rehydrated and the antigen unmasking procedure was carried out, then incubated with primary antibody against IL-26 (R&D Systems Inc. Minneapolis, USA; 1:100) for 12 h at 4 °C, followed by peroxidase-conjugated secondary antibody. Sections were evaluated by a pathologist without knowing clinical data of patients. As shown in Fig. 1, positive expression of IL-26 was mainly found in hepatocytes and the extent of IL-26 expression varied significantly among the HCC patients. Evaluation of IL-26 levels was performed using the imagescope standard procedure. All patients were stratified into the upper and lower groups according to the median immunohistochemical score of IL-26 from resected specimens for clinical analyses.

Follow-up

The primary endpoint of the study was overall survival (OS, time from surgery to death by any cause). Patients were suggested to make active visits one month after the surgery, then once every 3 months for the first year and twice per year thereafter. Main outcomes of interest were time to recurrence, location of recurrence, and survival. Follow-up investigation was performed using telephone inquiry for those without active visits. Follow-up for patients was performed with a median of 53.0 months [interquartile range (IQR): 40.2 to 65.9 months].

Statistical analysis

Data were presented as median (IQR) for the description of central tendency and distribution. Univariate and multivariate analysis was performed using dichotomous covariates by Cox proportional hazard regression model, which were presented with HR and 95% CI. Between-group analysis was performed using Chi-square test. Survival curves were generated and evaluated using Kaplan–Meier method. All statistical analyses were performed using SPSS version 20.0 (Chicago, IL). A P value of <0.05 was considered statistically significant.

Results

Patient characteristics

The median age was 48 years old (IQR: 41 to 55 years) with a 13.1% of female distribution (Table 1). Viral hepatitis B infection was present in most cases (93.4%), whereas none of the patients were found to have hepatitis C virus infection. The median expression of IL-26 was 0.206 (IQR: 0.164 to 0.262). Serum levels of total bilirubin, direct bilirubin, albumin, ALT, AST, and CEA were within normal range in majority of patients, whereas AFP (median 1000 μg/L) was elevated in more than half of the patients. Approximately three fourth of patients presented with large tumors (>5 cm) with predominance of single nodule cases (94.3%). Ascites and cirrhosis were positive in 31 (25.4%) and 76 (62.3%) patients. Macro- and microvascular invasion was found in 58 (47.5%) and 97 (79.5%) patients, whereas there were only 3 (2.5%) patients with nodal metastasis. According to the TNM stage, 63 (51.6%) patients were of stage III or IV. In addition, BCLC stage was 0 to A

Table 1
Baseline demographic and clinical characteristics.

Characteristics	Patients ($n=122$)
Age (yr)	48 (41–55)
Female (*n*,%)	16 (13.1%)
Viral hepatitis (*n*,%)	
Hepatitis B virus	
Hepatitis B surface antigen	114 (93.4%)
Hepatitis B surface antibody	11 (9.0%)
Hepatitis B core antibody	114 (93.4%)
Hepatitis B e antigen	14 (11.5%)
Hepatitis B e antibody	66 (54.1%)
Hepatitis B virus DNA (>10^3 copies)	21 (17.2%)
Hepatitis C virus	0
IL-26 expression[a]	0.206 (0.164–0.262)
Total bilirubin (μmol/L)	14.5 (11.4–17.6)
Direct bilirubin (μmol/L)	5.3 (4.0–6.9)
Albumin (g/L)	41.2 (38.2–43.9)
Alanine aminotransferase (U/L)	48.0 (33.1–66.1)
Aspartate aminotransferase (U/L)	49.0 (40.6–70.2)
Alpha fetoprotein (μg/L)	>1000 (85.6–>1000)
Carcinoembryonic antigen (ng/mL)	1.7 (1.1–2.7)
Tumor size (cm)	8.0 (5.0–11.0)
Multinodular (*n*,%)	7 (5.7%)
Ascites (*n*,%)	31 (25.4%)
Cirrhosis (*n*,%)	76 (62.3%)
Macrovascular invasion (*n*,%)	58 (47.5%)
Microvascular invasion (*n*,%)	97 (79.5%)
Lymph node metastasis (*n*,%)	3 (2.5%)
TNM stage (*n*,%)	
I-II	59 (48.4%)
III-IV	63 (51.6%)
BCLC stage (*n*,%)	
0-A	11 (9.0%)
B	52 (42.6%)
C	59 (48.4%)

Data are median (IQR) unless indicated otherwise. a: IL-26 was analyzed using the imagescope standard procedure. BCLC: Barcelona Clinic Liver Cancer.

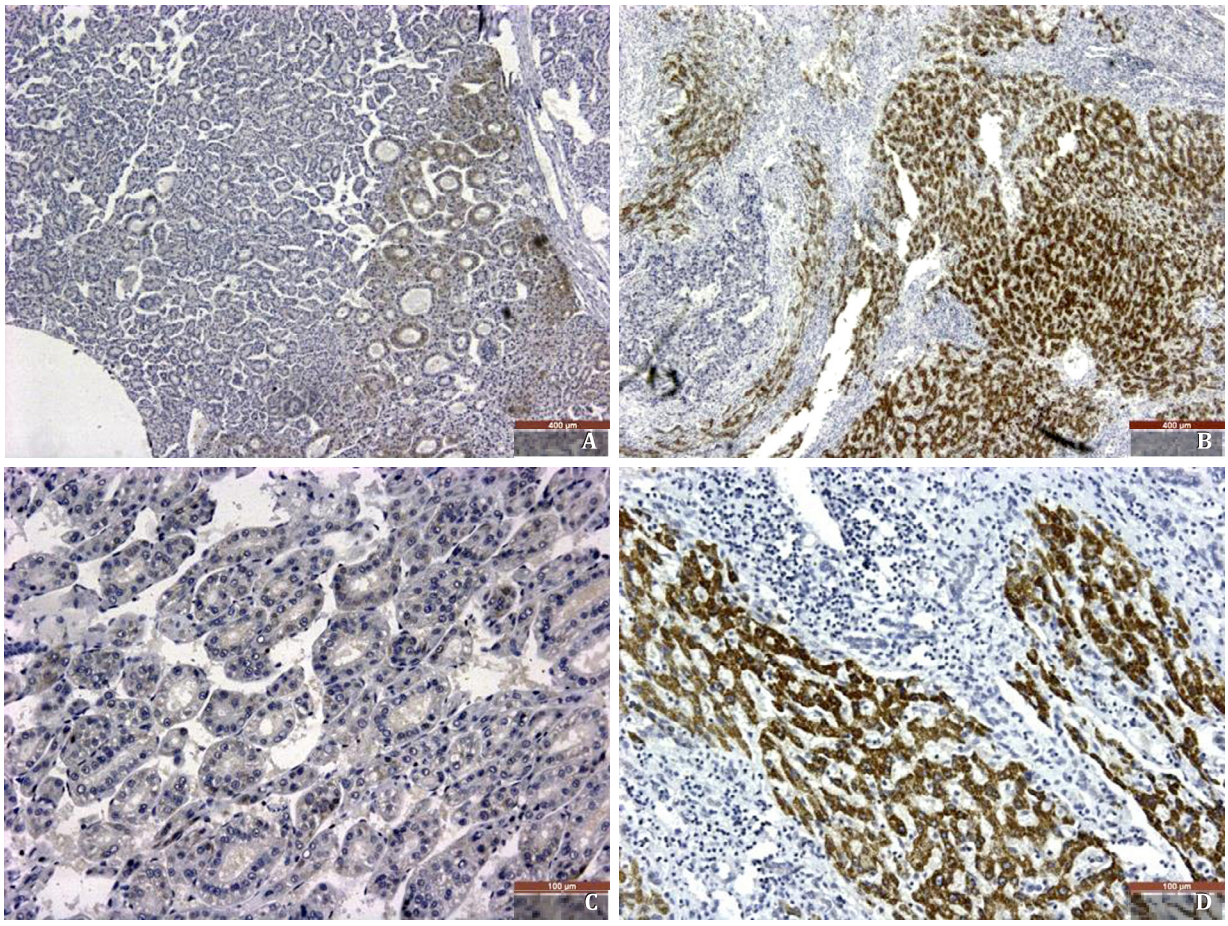

Fig. 1. Immunohistochemistry staining of IL-26 in patients with HCC. As shown above, expression of IL-26 is mainly distributed in hepatocytes. **A:** Lower expression of IL-26 (original magnification × 50). **B:** Upper expression of IL-26 (original magnification × 50). **C:** Lower expression of IL-26 (original magnification × 200). **D:** Upper expression (original magnification × 200).

in 11 (9.0%), B in 52 (42.6%), and C in 59 (48.4%) patients, respectively.

Prognostic factors of all HCC patients with liver resection

IL-26 expression, AFP >50 μg/L, tumor size >5 cm, macrovascular invasion, and microvascular invasion revealed significance for both cumulative recurrence-free survival (RFS) and OS in the univariate analysis, then were enrolled into the multivariate analysis. Upper expression of IL-26 (HR: 1.667; 95% CI: 1.076 to 2.582; $P=0.022$), tumor size >5 cm (HR: 1.096; 95% CI: 1.034 to 1.162; $P=0.002$), and microvascular invasion (HR: 2.696; 95% CI: 1.322 to 5.497; $P=0.006$) remained statistically significant in the multivariate analysis for the RFS. As for the OS, upper IL-26 expression (HR: 1.643; 95% CI: 1.021 to 2.644; $P=0.041$) and microvascular invasion (HR: 3.303; 95% CI: 1.255 to 8.696; $P=0.016$) were found to be significant independent prognostic factors for HCC patients after liver resection (Table 2).

Prognostic impact of IL-26

The patients were divided into the upper and lower groups according to the median expression level of IL-26 for between-group evaluation of prognosis. In the RFS, the patients in the upper group demonstrated significantly worse outcomes (HR: 2.007; 95% CI: 1.393 to 3.220; $P<0.001$; Fig. 2A) compared with the lower group. Similar results were detected in the OS with HR of 1.999 (95% CI: 1.290 to 3.196; $P=0.002$; Fig. 2B). Important to note is that the slope of the survival curves in the OS was relatively similar between 12th to 60th month after surgical resection. However, the mortality was significantly high within 12 months after surgery ($P<0.001$).

Factors associated with expression of IL-2

All demographic and clinical characteristics were compared according to the expression of IL-26 to identify impact of IL-26 on clinicopathological characteristics in HCC patients (Table 3). Tumor size >5 cm ($P=0.040$), microvascular invasion ($P=0.014$), and TNM stage of III-IV ($P=0.046$) were significantly more common in the upper group compared to the lower group. Furthermore, slight differences were found in ALT elevation (49.2% vs. 34.4%; $P=0.099$), AFP >50 μg/L (82.0% vs. 68.9%; $P=0.093$), and macrovascular invasion (55.7% vs. 39.3%; $P=0.070$) with all higher proportions in the IL-26-upper group. In addition, 12 (19.7%) and 9 (14.8%) patients in the upper and lower groups had elevated HBV DNA copies ($>10^3$), respectively. These factors still have potential to be significant when evaluated in larger sample size.

Prognostic impact of IL-26 in subgroups of patients with tumor size >5 cm, microvascular invasion, and TNM stage of III-IV

Since distributions of tumor size >5 cm, microvascular invasion, and TNM stage III-IV were significantly different between the

Table 2
Univariate and multivariate analyses of covariates that affected survival outcomes.

Covariates	Recurrence-free survival			Overall survival		
	Univariate	Multivariate		Univariate	Multivariate	
	P value	HR (95% CI)	*P* value	*P* value	HR (95% CI)	*P* value
IL-26 expression[a]	**<0.001**	1.667 (1.076–2.582)	**0.022**	**0.003**	1.643 (1.021–2.644)	**0.041**
AFP >50 μg/L	**0.025**	1.020 (0.596–1.745)	0.942	**0.023**	1.267 (0.692–2.320)	0.444
Tumor size >5 cm	**<0.001**	1.096 (1.034–1.162)	**0.002**	**0.001**	1.504 (0.753–3.006)	0.248
Macro VI	**<0.001**	1.512 (0.944–2.421)	0.086	**<0.001**	1.222 (0.551–2.713)	0.622
Micro VI	**<0.001**	2.696 (1.322–5.497)	**0.006**	**<0.001**	3.303 (1.255–8.696)	**0.016**

HR: hazard ratio; 95% CI: 95% confidence interval; AFP: alpha fetoprotein; VI: vascular invasion. a: the upper half of the patients with relatively high levels of IL-26.

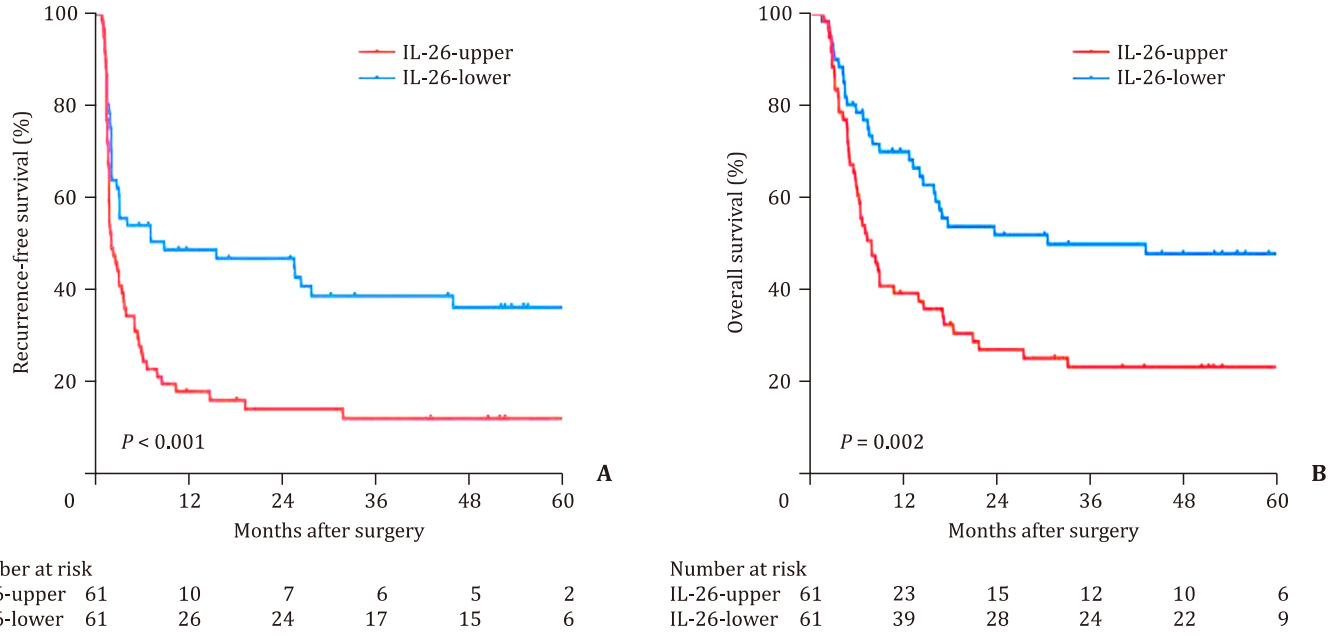

Fig. 2. Kaplan–Meier estimation of survival outcomes in HCC patients according to the expression of IL-26. **A:** Recurrence-free survival of patients with upper and lower levels of IL-26. **B:** Overall survival of patients with upper and lower levels of IL-26.

Table 3
Between-group analysis of demographic and clinical characteristics according to IL-26 expression.

Characteristics	Upper group ($n=61$)	Lower group ($n=61$)	*P* value
Age (yr)	46 (39–56)	49 (43–53)	0.171
Female	10 (16.4%)	6 (9.8%)	0.283
HBV infection[a]	59 (96.7%)	55 (90.2%)	0.143
HBV DNA >10^3 copies	12 (19.7%)	9 (14.8%)	0.472
Total bilirubin ≥21 μmol/L	8 (13.1%)	11 (18.0%)	0.454
Direct bilirubin >5.1 μmol/L	30 (49.2%)	31 (50.8%)	0.856
Albumin <35 g/L	3 (4.9%)	3 (4.9%)	1.000
ALT elevation[b]	30 (49.2%)	21 (34.4%)	0.099
AST elevation[c]	46 (75.4%)	44 (72.1%)	0.681
AFP >50 μg/L	50 (82.0%)	42 (68.9%)	0.093
CEA >2.5 ng/mL	13 (21.3%)	17 (27.9%)	0.322
Tumor size >5 cm	50 (82.0%)	40 (65.6%)	**0.040**
Multinodular	3 (4.9%)	4 (6.6%)	0.697
Ascites	19 (31.1%)	12 (19.7%)	0.145
Cirrhosis	38 (62.3%)	38 (62.3%)	1.000
Macrovascular invasion	34 (55.7%)	24 (39.3%)	0.070
Microvascular invasion	54 (88.5%)	43 (70.5%)	**0.014**
Lymph node metastasis	1 (1.6%)	2 (3.3%)	0.559
TNM stage III-IV	37 (60.7%)	26 (42.6%)	**0.046**
BCLC stage B-C	58 (95.1%)	53 (86.9%)	0.114

Data are number (%) unless indicated otherwise. a: hepatitis B surface antigen-positive patients. b: >52 U/L and >34 U/L were indicative values for male and female patients, respectively. c: >40 U/L and >34 U/L were indicative values for male and female patients, respectively. HBV: hepatitis B virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AFP: alpha fetoprotein; CEA: carcinoembryonic antigen; BCLC: Barcelona Clinic Liver Cancer.

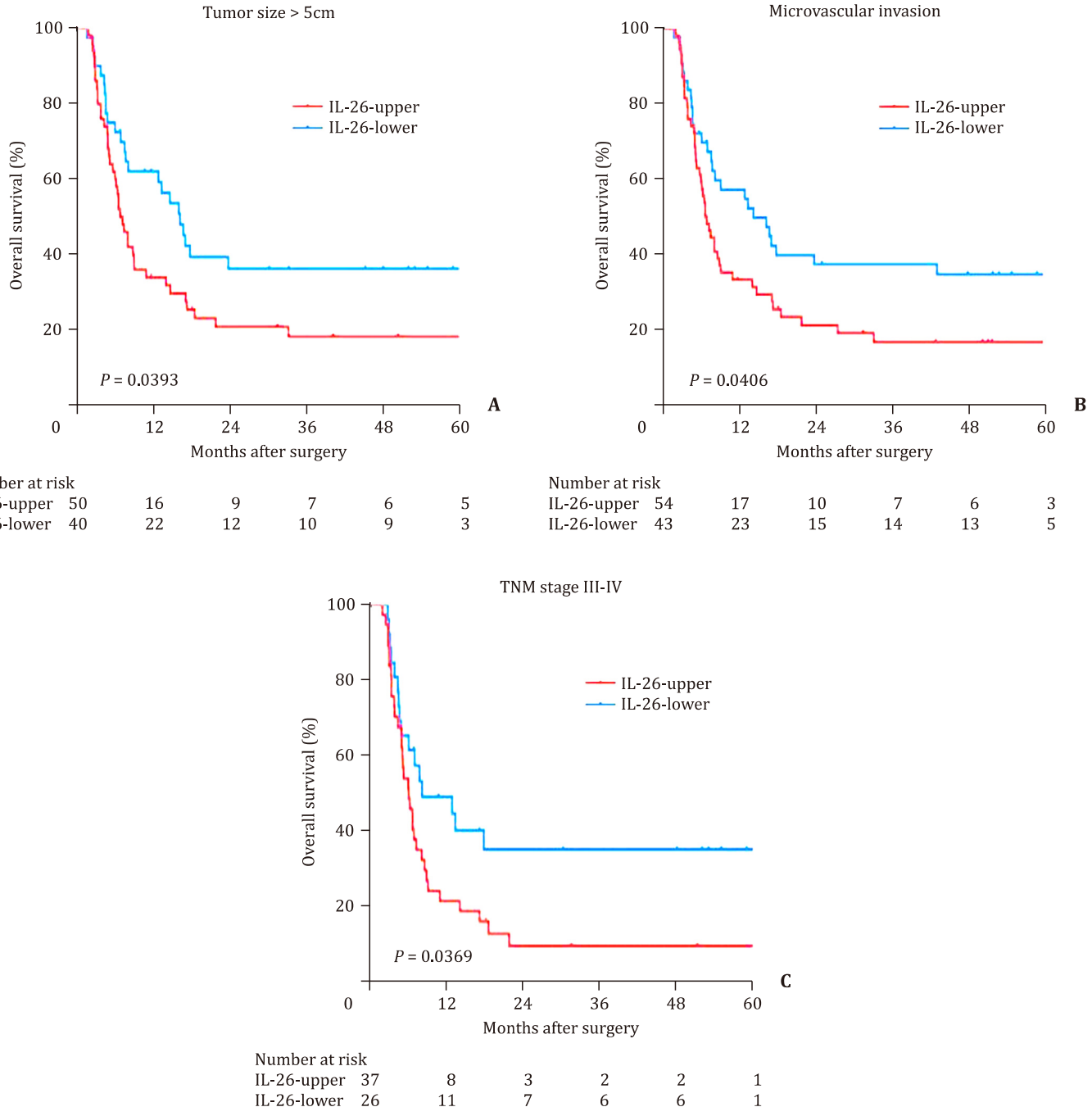

Fig. 3. Kaplan–Meier estimation of overall survival in patients with tumor size >5 cm, microvascular invasion, and TNM stage III-IV. **A:** Overall survival of patients with tumor size >5 cm between IL-26-upper and -lower groups. **B:** Overall survival of patients with microvascular invasion between IL-26-upper and -lower groups. **C:** Overall survival of patients with TNM stage III-IV between IL-26-upper and -lower groups.

IL-26-upper and -lower groups, we have explored prognostic impact of IL-26 in patients with tumor size >5 cm, microvascular invasion, and TNM stage III-IV, respectively. In patients with tumor size >5 cm ($n=90$), upper expression of IL-26 was found to be a significant factor indicating unfavorable OS with an HR of 1.686 (95% CI: 1.030 to 2.744; $P=0.0393$; Fig. 3A). Among the patients with microvascular invasion ($n=97$; HR: 1.634; 95% CI: 1.026 to 2.601; $P=0.0406$; Fig. 3B) and TNM stage III-IV ($n=63$; HR: 1.857; 95% CI: 1.044 to 3.205; $P=0.0369$; Fig. 3C), IL-26 also revealed to be a significant unfavorable prognostic factor. These results suggest that IL-26 still serves as an independent prognostic factor in subgroups of patients with tumor size >5 cm, microvascular invasion, and TNM stage of III-IV.

Discussion

For HCC patients, radical surgical resection of the tumor is the standard of care for resectable cases [12]. However, on account of the distinctive characteristics of the tumor, including rapid progression and aggressiveness, recurrence still remains common [13]. One of the most effective strategies to improve survival outcomes of recurrent HCC is early detection [14,15]. To date, a number of

clinicopathological characteristics and biomarkers were found to be significantly associated with prognosis of HCC patients [16,17]. However, identification of prognostic factors is far from being sufficient that none of the previous predictive tool, as well as typical staging systems, could be generally applied in the real-world. In the present study, we identified IL-26 as an unfavorable prognostic factor that significantly reduces survival of HCC patients after surgical resection. The underlying mechanisms may include progression of the tumor indicated by significantly larger proportion of patients with large tumor (>5 cm), promotion of vascular invasion, and advanced TNM stage. Future basic investigations are required to validate our results.

The expression of IL-26 is attributed to T cells, especially Th17 cells [18]. Recent advances revealed that IL-26 is emerging as a potential player in host defense and could be a pathogenic factor in chronic inflammatory diseases [19]. Along with interactions between nervous system and HCC, association between immunology and HCC has emerged as a major concern in further understanding of characteristic of HCC and development of new potential therapies [20,21]. However, there is no data regarding prognostic impact of IL-26 in HCC patients after surgical resection. In the present study, we have stratified the patients into two independent groups according to the immunohistochemistry expression of IL-26, and found that IL-26 is an important prognostic factor that is significantly associated with recurrence of the tumor and reduced OS. Therefore, we explored clinical factors that are associated with expression of IL-26 and found that the high expression is directly proportional to elevation of AFP, larger tumor size, microvascular invasion, macrovascular invasion, and advanced TNM stages.

Regarding preoperative usability and convenience, application of serum IL-26 as a biomarker may be better than immunohistochemical IL-26 expression in tissue. Previously, Miot et al. [22] found that IL-26 is significantly elevated in chronic viral hepatitis-infected patients. Our preliminary results also indicated that serum IL-26 is significantly affected by presence of hepatitis and/or cirrhosis, which led us to assess expression of IL-26 within the tumor only using immunohistochemistry. However, serologic approach may be superior to pathologic approach in terms of preoperative applicability and generalization in HCCs without hepatitis and cirrhosis. Future clinical studies are required to confirm our hypothesis.

To date, number of staging systems predictive to survival outcomes were developed with practical intent [23,24]. Most of them were consisted of clinical covariates, such as AFP, vascular invasion, tumor size and cirrhosis. However, the accuracy, which is presented by calculating the C-index, was insufficient for general use (the predictive value is 0.75 for overall survival and 0.70 for disease free survival) [25]. In our point of view, it may be on accounts of limited identification of prognostic biomarkers. Involvement of IL-26 may elevate predictive accuracy and discrimination of staging systems and prediction models.

Although our study contains initial findings, there are several underlying limitations that need to be considered. First, limited number of patients may be a weakness. Second, no further external validation could be performed. Further validation studies are warranted in the future. Finally, no biological investigations were performed to support the results. Regardless the above limitations, the present study is the first to evaluate prognostic impact of IL-26 in HCC patients.

In conclusion, IL-26 is a novel prognostic factor for HCC patients after surgical resection. Application of IL-26 to a conventional prediction models, including AFP, tumor size, macrovascular invasion, and microvascular invasion may significantly increase performance accuracy and discrimination. In a clinical setting, IL-26-high HCC patients were found to have large-sized tumor (>5 cm), microvascular invasion, and TNM stage III-IV. However, IL-26 still could serve as a significant unfavorable prognostic factor in the above subgroups. Therefore, IL-26 is an independent prognostic factor indicating unfavorable prognosis in HCC patients with liver resection.

Contributors

KXN, TY and XQ proposed the study. XZF and JS performed the research and wrote the first draft. WCC and LHJ performed the immunohistochemistry. LJX collected the data. GH and CJ analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. XZF and JS contributed equally to this article. XQ is the guarantor.

Funding

This work was supported by grants from the National Natural Science Foundation of China (81670562, 81670598 and 81472243), the Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support (20171911), and the National Key R&D Program for Precision Medicine (2017YFC908101).

Ethical approval

This study was approved by the Ethics Committee of Renji Hospital, Shanghai Jiao Tong University School of Medicine.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

[1] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301–1314.
[2] Fujiwara N, Friedman SL, Goossens N, Hoshida Y. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. J Hepatol 2018;68:526–549.
[3] Ayuso C, Rimola J, Vilana R, Burrel M, Darnell A, García-Criado Á, et al. Diagnosis and staging of hepatocellular carcinoma (HCC): current guidelines. Eur J Radiol 2018;101:72–81.
[4] Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol 2018;15:599–616.
[5] Menahem B, Lubrano J, Duvoux C, Mulliri A, Alves A, Costentin C, et al. Liver transplantation versus liver resection for hepatocellular carcinoma in intention to treat: an attempt to perform an ideal meta-analysis. Liver Transpl 2017;23:836–844.
[6] Rich NE, Parikh ND, Singal AG. Hepatocellular carcinoma and liver transplantation: changing patterns and practices. Curr Treat Options Gastroenterol 2017;15:296–304.
[7] Rudnick SR, Russo MW. Liver transplantation beyond or downstaging within the Milan criteria for hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol 2018;12:265–275.
[8] Hu L, Xue F, Li Y, Shao M, Sun Y, Wei G. A long-term follow-up and comprehensive observation of risk and prognosis factors of recurrence and survival after resection of hepatocellular carcinoma. Cell Biochem Biophys 2014;69:421–431.
[9] Hsu CY, Liu PH, Ho SY, Hsia CY, Kudaravalli P, Lee YH, et al. Using nomogram of the Barcelona clinic liver cancer system for treatment selection in patients with stage C hepatocellular carcinoma. BMC Cancer 2018;18:289.
[10] Chen ZH, Hong YF, Chen X, Chen J, Lin Q, Lin J, et al. Comparison of five staging systems in predicting the survival rate of patients with hepatocellular carcinoma undergoing trans-arterial chemoembolization therapy. Oncol Lett 2018;15:855–862.
[11] Sha M, Jeong S, Chen XS, Tong Y, Cao J, Sun HY, et al. Expression of VEGFR-3 in intrahepatic cholangiocarcinoma correlates with unfavorable prognosis through lymphangiogenesis. Int J Biol Sci 2018;14:1333–1342.
[12] Fan ST. Hepatocellular carcinoma–resection or transplant. Nat Rev Gastroenterol Hepatol. 2012 Dec;9(12):732–737.
[13] Gingold JA, Zhu D, Lee DF, Kaseb A, Chen J. Genomic profiling and metabolic homeostasis in primary liver cancers. Trends Mol Med 2018;24:395–411.
[14] Fu J, Wang H. Precision diagnosis and treatment of liver cancer in China. Cancer Lett 2018;412:283–288.

[15] Mehta AS, Lau DT, Wang M, Islam A, Nasir B, Javaid A, et al. Application of the Doylestown algorithm for the early detection of hepatocellular carcinoma. PLoS One 2018;13:e0203149.
[16] Bao H, Su H. Long noncoding RNAs act as novel biomarkers for hepatocellular carcinoma: progress and prospects. Biomed Res Int 2017;2017:6049480.
[17] Selçuk H. Prognostic factors and staging systems in hepatocellular carcinoma. Exp Clin Transp 2017;15:45–49.
[18] Fujii M, Nishida A, Imaeda H, Ohno M, Nishino K, Sakai S, et al. Expression of Interleukin-26 is upregulated in inflammatory bowel disease. World J Gastroenterol 2017;23:5519–5529.
[19] Tengvall S, Che KF, Lindén A. Interleukin-26: an emerging player in host defense and inflammation. J Innate Immun 2016;8:15–22.
[20] Jeong S, Zheng B, Wang H, Xia Q, Chen L. Nervous system and primary liver cancer. Biochim Biophys Acta Rev Cancer 2018;1869:286–292.
[21] Ringelhan M, Pfister D, O'Connor T, Pikarsky E, Heikenwalder M. The immunology of hepatocellular carcinoma. Nat Immunol 2018;19:222–232.
[22] Miot C, Beaumont E, Duluc D, Le Guillou-Guillemette H, Preisser L, Garo E, et al. IL-26 is overexpressed in chronically HCV-infected patients and enhances TRAIL-mediated cytotoxicity and interferon production by human NK cells. Gut 2015;64:1466–1475.
[23] Huang JL, Fu YP, Jing CY, Yi Y, Sun J, Gan W, et al. A novel and validated prognostic nomogram based on liver fibrosis and tumor burden for patients with hepatocellular carcinoma after curative resection. J Surg Oncol 2018;117:625–633.
[24] Kim Y, Park HC, Yoon SM, Kim TH, Lee J, Choi J, et al. Prognostic group stratification and nomogram for predicting overall survival in patients who received radiotherapy for abdominal lymph node metastasis from hepatocellular carcinoma: a multi-institutional retrospective study (KROG 15-02). Oncotarget 2017;8:94450–94461.
[25] Zhang W, Tan Y, Shen S, Jiang L, Yan L, Yang J, et al. Prognostic nomogram for hepatocellular carcinoma in adolescent and young adult patients after hepatectomy. Oncotarget 2017;8:106393–106404.