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ORIGINAL ARTICLE

Increased expression of interleukin-8 is an independent indicator of poor prognosis in clear-cell renal cell carcinoma

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Abstract On the basis of aberrant interleukin-8 (IL-8) expression, a crucial angiogenesis factor and potential therapeutic target, in clear-cell renal cell carcinoma (ccRCC), this study aims to assess the prognostic significance of IL-8 in ccRCC. This retrospective study enrolled 271 patients who underwent nephrectomy for ccRCC in a single institution. The associations of IL-8 expression with clinical and pathological features were assessed using chi-squared tests. The impact on cancer-specific survival (CSS) and relapse-free survival (RFS) was analyzed using univariable and multivariable Cox regression models. The area under the receiver operating characteristic (ROC) curve (AUC) was used as an index of prognostic performance. Intratumoral IL-8 was found to be significantly elevated in ccRCC tissues compared with peritumor tissue and be predominately localized in the cytoplasm. Moreover, high IL-8 expression was positively correlated with Fuhrman grade ($P<0.001$). Multivariate Cox regression analysis identified IL-8 as an independent adverse prognostic factor of CSS ($P<0.001$) and RFS ($P<0.001$), which could be incorporated into the traditional TNM staging system to improve the prognostic value for CSS and RFS in ccRCC patients. The predictive accuracy of traditional TNM stage model was significantly improved when IL-8 expression was added. Increased expression of IL-8 is a potential independent adverse prognostic biomarker for CSS and RFS in patients with ccRCC after nephrectomy.

Keywords Clear-cell renal cell carcinoma · Interleukin-8 · Prognostic biomarker · Cancer-specific survival · Relapse-free survival

Introduction

Clear-cell renal cell carcinoma (ccRCC) is the most common subtype of kidney cancer [1]. ccRCC patients (20~30 %) have incurable advanced disease with limited therapeutic options at diagnosis; none of the cytotoxic drugs demonstrated any reproducible efficacy, so new treatment approaches such as targeted therapy are urgently required [2]. The aggressive nature of ccRCC has been shown to be related to numerous abnormalities in growth factors and their receptors, which confers a tremendous growth advantage to a variety of malignant cells [3]. There is strong evidence showing that intratumoral genetic and epigenetic heterogeneity plays a significant role in ccRCC prognostic and the development of therapeutic resistance [4, 5]. Apparently, further investigation is warranted to elucidate the potential mechanism of intratumoral genetic and epigenetic heterogeneity to improve the prognosis and provide novel therapeutic targets for ccRCC patients.

The CXC chemokine interleukin-8 (IL-8 or CXCL8), which was originally known as neutrophil chemotactic and inflammatory factor, has also shown to be a potent promoter of angiogenesis [6, 7]. IL-8 is produced by cells with toll-like receptor (e.g., macrophages) exposed in the innate immune

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response [8]. IL-8 has a series of physiological responses in target cells; it activates neutrophils inducing, intracellular Ca^{2+} increasing, chemotaxis, exocytosis, and the respiratory burst [9]. Moreover, both monomer and homodimer forms of IL-8 have been reported to induce multiple intracellular signaling downstream of two G protein-coupled receptors (CXCR1 and CXCR2) [10] that impinge on gene expression, modulate the cellular proteome, and affect the organization of the cell cytoskeleton [11]. Overexpression of IL-8 has been verified in cancer cells. The secretion of IL-8 from cancer cells may function as a key regulatory factor in tumor microenvironment, owing to the expression of CXCR1 and CXCR2 on cancer cells, endothelial cells, infiltrating neutrophils, and tumor-associated macrophages [11–15].

Previous studies have shown that IL-8 not only contributes to tumor angiogenesis, but also plays a role in tumor proliferation. König and colleges found for the first time that IL-8 was significantly upregulated in malignant cells unlike in normal renal tubule cells [16]. Mestas et al. clarified that CXCL8/CXCR2 biological axis in kidney cancer played an important role in the process of angiogenesis and tumor formation [17]. Moreover, higher microvessel density was found in sunitinib-resistant tumors, coinciding with increased secretion of IL-8 [7]. Renaud Grepin et al. showed that in two kinds of IL-8 receptor CXCR1 and CXCR2 abnormally expressed in ccRCC tumor cells, their inhibitor SB225002 could effectively inhibit tumor cell proliferation and promote apoptosis [18]. Kidney cancer cells could be induced to secrete IL-8 by

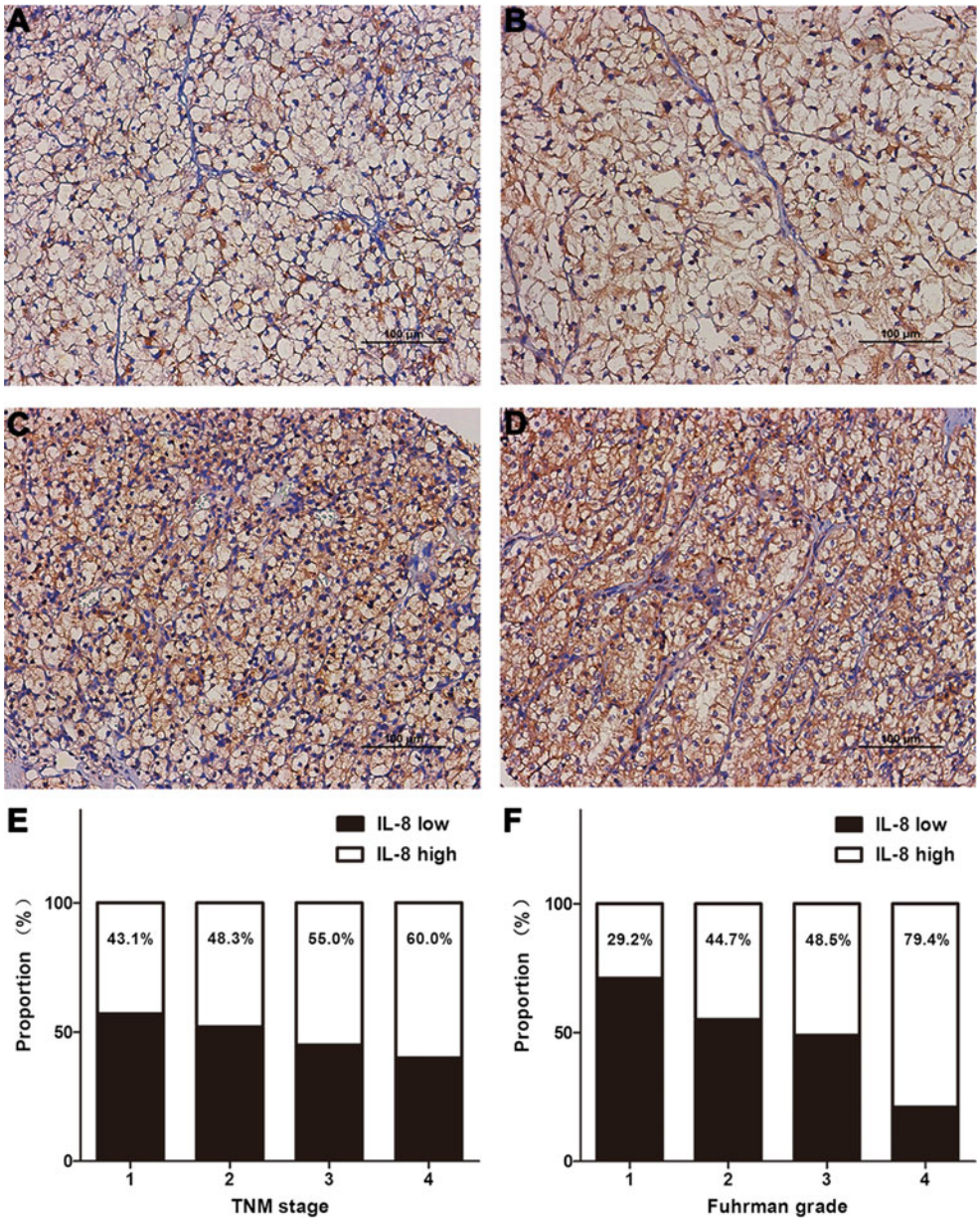

Fig. 1 IL-8 expression in tumor tissues from ccRCC patients. **a**–**d** Representative microphotographs of tumor tissues with intratumoral IL-8 expression in TNM stage I (**a**), TNM stage II (**b**), TNM stage III (**c**), and TNM stage IV (**d**). **c**, **d** The percentage of patients with low or high intratumoral IL-8 intensity according to TNM stage (**e**) and Fuhrman grade (**f**). Original magnificent (×200)

induction of IL-17 from tumor-reactive T cells, which confirmed that RCC cells can be used as a source of the IL-8 in tumor microenvironment [19]. Despite the high expression and secretion of IL-8 in ccRCC, the clinical significance of IL-8 overexpression, underlying molecular mechanism and its correlation with ccRCC progression, remains largely unknown and needs to be further verified.

In this study, we analyzed the expression of IL-8 by immunohistochemical analysis in ccRCC samples and their associations with clinicopathologic characteristics and clinical outcomes. IL-8 overexpression can be used as an independent prognostic factor and incorporated with traditional TNM staging system to improve predictive accuracy of well-established TNM staging system in ccRCC patients.

Materials and methods

Patients

A total of 271 patients with localized ccRCC who received radical or partial nephrectomy at Zhongshan hospital, Fudan University (Shanghai, China) between 2001 and 2004 were enrolled in this study. The study was approved by the research medical ethics committee of Fudan University, and informed consent was obtained from each patient. Patients who received preoperative neoadjuvant or postoperative adjuvant therapy were excluded. Clinicopathological variables including age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), tumor size, TNM stage, Fuhrman grade, and necrosis were collected. Patients were reassigned according to 2010 AJCC TNM classification. Survival status of each patient was updated in October 2013. Cancer-specific survival (CSS) was calculated from the date of surgery to date of death from RCC. Recurrence-free survival (RFS) was calculated from the date of curative surgery to date of recurrence. Median follow-up period was 92 months (range, 12–120) and 80 months (range, 30–118).

Immunohistochemistry

Tissue microarrays were constructed as previously described[11]. Primary anti-IL-8 antibody (ab18672; dilution 1:200; Abcam, Cambridge, MA, USA) was applied for immunohistochemistry (IHC) staining according to the procedure as previously described[12]. The staining intensity of each specimen was assessed by two pathologists blinded to the outcome information. A semi-quantitative H-score that ranged from 0 to 300 was calculated for each specimen by multiplying the distribution areas (0–100 %) at each staining intensity level by the intensities (0, below the level of detection; 1, weak staining; 2, moderate staining; 3, strong staining) [13]. We selected the optimum cutoff score (140) for the expression of IL-8 using X-tile software version 3.6.1 (Yale University School of Medicine, New Haven, CT, USA) based on the association with the patients' CSS.

Table 1 Correlation between IL-8 expression and clinical characteristics of patient with clear cell renal cell carcinoma

Variable	*n*=271				
	No.	%	Low (*n*=143)	High (*n*=128)	*P*
Mean age, years [a]			55.8±11.2	57.3±13.2	0.209
Gender					0.386
Male	190	70.1	97	93	
Female	81	29.9	46	35	
ECOG-PS					0.155
0	222	81.9	122	100	
≥1	49	18.1	21	28	
Mean tumor size, cm[a]			4.1±2.1	5.5±3.1	0.088
T stage					0.077
1a	98	36.2	59	39	
1b	75	27.7	40	35	
2a	25	9.2	13	12	
2b	7	2.6	3	4	
3	60	22.1	26	34	
4	6	2.2	2	4	
N stage					0.670
N0	266	98.2	141	125	
N1	5	1.8	2	3	
M stage					0.395
M0	258	95.2	138	120	
M1	13	4.8	5	8	
TNM stage					0.302
I	167	61.6	95	72	
II	29	10.7	15	14	
III	60	22.2	27	33	
IV	15	5.5	6	9	
Fuhrman grade					<0.001
1	48	17.7	34	14	
2	123	45.4	68	55	
3	66	24.4	34	32	
4	34	12.5	7	27	
Necrosis					0.063
Absent	207	76.4	116	91	
Present	64	23.6	27	37	

ECOG-PS Eastern Cooperative Oncology Group performance status, *UISS* UCLA Integrated Staging System, *SSIGN* stage, size, grade, and necrosis

[a] The results of continuous variables are presented as mean±SD (standard deviation)

Statistical analysis

Analysis was performed with SPSS for windows (version 21.0; SPSS Inc., Chicago, IL), Medcalc for windows (version 12.7.0.0; MedCalc Software, Mariakerke, Belgium), and Stata for windows (version 12.0; Stata software, College Station, TX). Pearson χ^2 test or Fisher's exact test was used to compare qualitative variables. Survival curves were calculated by Kaplan-Meier method and compared by log-rank test. Numbers at risk were calculated at the beginning of each time period. Univariate and multivariate Cox proportional-hazard models were used to evaluate the hazard ratios of prognostic factors. Receiver operating characteristic (ROC) curve analysis was used to determine the predictive value of the parameters. All P values were two-sided, and differences were considered statistically significant at values of $P<0.05$.

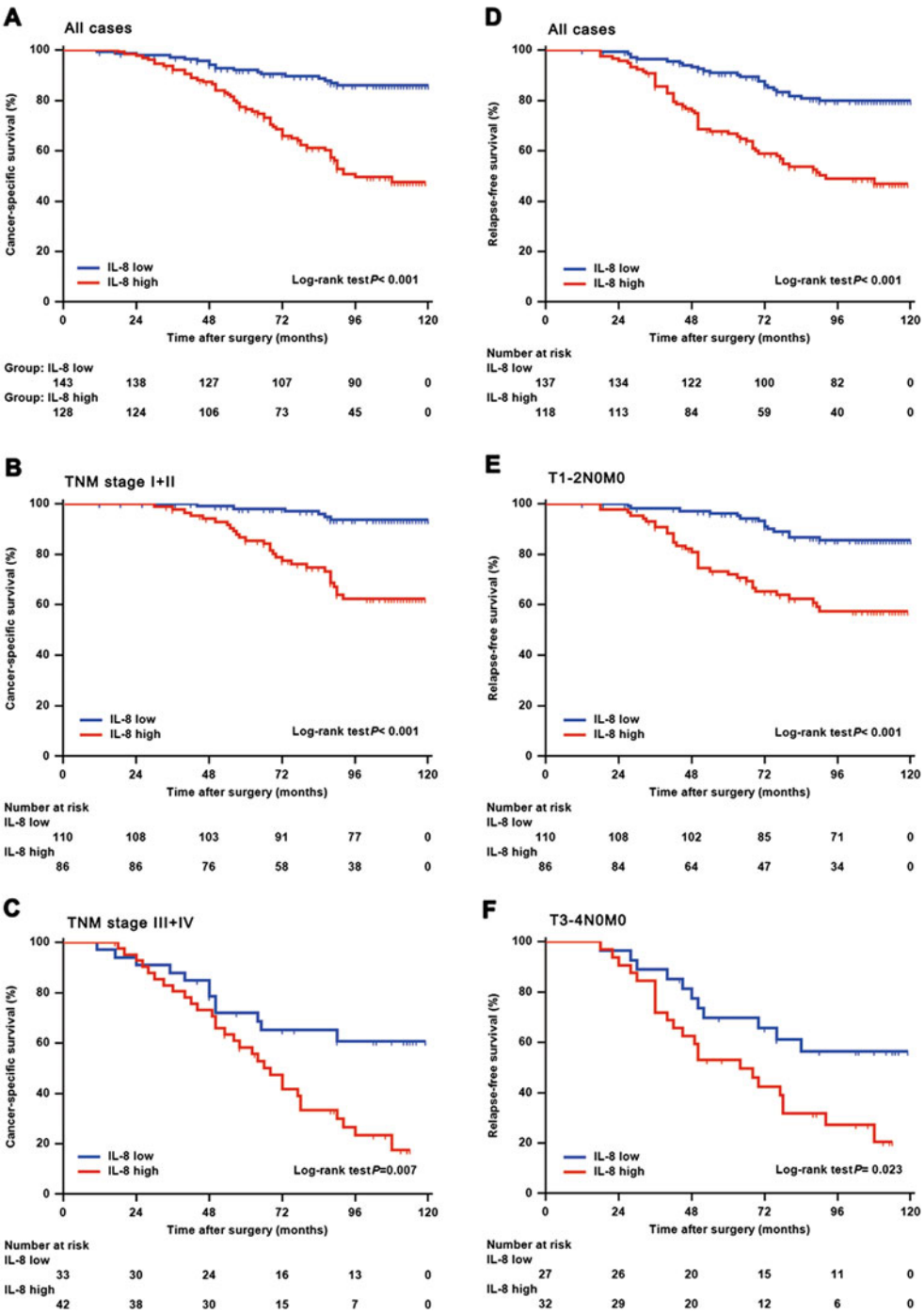

Fig. 2 Kaplan-Meier analysis of CSS and RFS according to IL-8 expression in ccRCC patients. **a**–**c** Kaplan-Meier analysis of CSS according to IL-8 expression in ccRCC patients (**a**, all ccRCC patients for CSS, $n=271$, $P<0.001$; **b**, TNM stage I+II ccRCC patients for CSS, $n=196$, $P<0.001$; **c**, TNM stage III+IV ccRCC patients for CSS, $n=75$, $P=0.007$). **d**–**f** Kaplan-Meier analysis of RFS according to IL-8 expression in ccRCC patients (**a**, all ccRCC patients for RFS, $n=255$, $P<0.001$; **b**, pathological T1-2N0MO ccRCC patients for RFS, $n=196$, $P<0.001$; **c**, pathological T3-4N0MO ccRCC patients for RFS, $n=59$, $P=0.023$). P value was calculated by Log-rank test

Results

Immunohistochemical findings

IL-8 expression was determined in 271 matched surgical specimens from primary ccRCC patients by IHC staining, and the correlations between IL-8 expression and clinical and pathological characteristics were analyzed. As shown in Fig. 1a–d, the expression of IL-8 is mainly located in the cell cytoplasm and membrane of tumor area and showed variable intensity. In addition, the percentage of patient with high IL-8 expression increased accompanied with disease progression (Fig. 1e, f), even though the association did not reach statistical significance between IL-8 expression and TNM stage. A total of 128 (47.2 %) patients were scored as high IL-8 expression. Moreover, IL-8 expression was significantly associated with Fuhrman grade (Table 1, $P<0.001$). Taken together, these results indicated that IL-8 expression might correlate with ccRCC progression.

Correlations between IL-8 expression with clinical outcomes

To assess the prognostic significance of IL-8 expression in patients with ccRCC, we applied Kaplan-Meier survival analysis to compare the CSS and RFS according to IL-8 expression. The patients with high IL-8 expression had significantly shorter CSS (Fig. 2a, $P<0.001$) and RFS (Fig. 2d, $P<0.001$) compared with those with low IL-8 expression. When stratified by TNM stage, IL-8 expression could still separate patients with different prognosis. As shown in Fig. 2b, c, IL-8 expression shows prognostic significance with CSS in both TNM stage I+II ($P<0.0001$, Fig. 2b) and TNM stage III+IV ($P=0.007$, Fig. 2c). Similarly for RFS, in both T1-2N0M0 and T3-4N0M0, IL-8 low expression had a greater survival benefit compared with high expression ($P<0.001$ and $P=0.023$, respectively, Fig. 2e, f). These results indicated that elevated IL-8 expression was a biomarker for unfavorable prognosis in ccRCC patients.

IL-8 expression is an independent prognostic factor

To identify the prognostic significance of clinicopathological factors for CSS and RFS, univariate Cox analysis showed that clinicopathologic factors statistically significantly associated with short CSS and RFS (Table 2) were ECOG-PS (≥1), tumor size, TNM stage(III+IV) for CSS and T stage (3+4) for RFS, Fuhrman grade (3+4), necrosis (yes), and IL-8 expression (high). No association with CSS and RFS was observed for age or gender. Cox multivariate regression analysis showed

Table 2 Univariate and multivariate Cox regression analysis for cancer-specific survival and relapse-free survival

Variable	Univariate		Multivariate	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*
Cancer-specific survival				
Age (years)[a]	1.020(1.000–1.040)	0.048		
Gender (female vs male)	1.137(0.688–1.880)	0.616		
ECOG-PS (≥1 vs 0)	3.570(2.244–5.678)	<0.001	1.877(1.132–3.111)	0.015
Tumor size (cm)[a]	1.197(1.118–1.281)	<0.001	1.065(0.978–1.160)	0.146
TNM stage (III+IV vs I+ II)	4.726(2.999–7.447)	<0.001	3.525(2.195–5.660)	<0.001
Fuhrman grade (3+4 vs 1+2)	2.829(1.793–4.464)	<0.001	2.053(1.281–3.291)	0.003
Necrosis (yes vs no)	2.463(1.548–3.917)	<0.001	1.561(0.964–2.528)	0.070
IL-8 (high vs low)	4.413(2.596–7.501)	<0.001	2.924(1.676–5.100)	<0.001
Relapse-free survival[b]				
Age (years)[a]	1.013(0.994–1.032)	0.192		
Gender (female vs male)	0.744(0.472–1.172)	0.202		
ECOG-PS (≥ 1 vs 0)	2.597(1.600–4.216)	<0.001	2.070(1.312–3.266)	0.002
Tumor size (cm)[a]	1.170(1.093–1.253)	<0.001	1.089(1.011–1.173)	0.025
T stage (3+4 vs 1+2)	2.985(1.980–4.501)	<0.001	2.225(1.453–3.407)	< 0.001
Fuhrman grade (3+4 vs 1+2)	2.696(1.739–4.178)	<0.001	2.309(1.516–3.519)	< 0.001
Necrosis (yes vs no)	1.945(1.218–3.105)	0.005	1.270(0.811–1.989)	0.296
IL-8 (high vs low)	3.329(2.074–5.344)	<0.001	2.060(1.304–3.255)	0.002

HR hazard ratio, *95 % CI* 95 % confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group performance status

[a] Factors were treated as continuous variables

[b] For relapse-free survival, patients with metastasis were excluded, $n=255$

that ECOG-PS, TNM stage (CSS) and T stage (RFS), Fuhrman grade, and IL-8 expression were all significantly associated with short CSS and RFS. Conclusively, intratumoral IL-8 expression may be a novel independent prognostic factor for ccRCC patients.

Extension of the TNM stage with IL-8 expression

To generate a more sensitive predictive model for outcomes of patients with ccRCC, we combined IL-8 expression with TNM stage to create a prognostic model. ROC analysis was used to compare the prognostic capability. The combination of IL-8 expression and TNM stage (AUC 0.807) showed a better prognostic value with CSS compared with TNM stage (AUC 0.714, $P<0.001$) or IL-8 expression (AUC 0.702, $P<0.001$) alone (Fig. 3a). Similarly, TNM stage combined with IL-8 expression (AUC 0.754) also revealed an improved predictive accuracy compared with TNM stage (AUC 0.673, $P<0.001$) or IL-8 expression (AUC 0.668, $P=0.003$) alone for RFS (Fig. 3b). Therefore, these results demonstrated that combination of IL-8 and TNM stage could generate a better prognostic model for ccRCC patients.

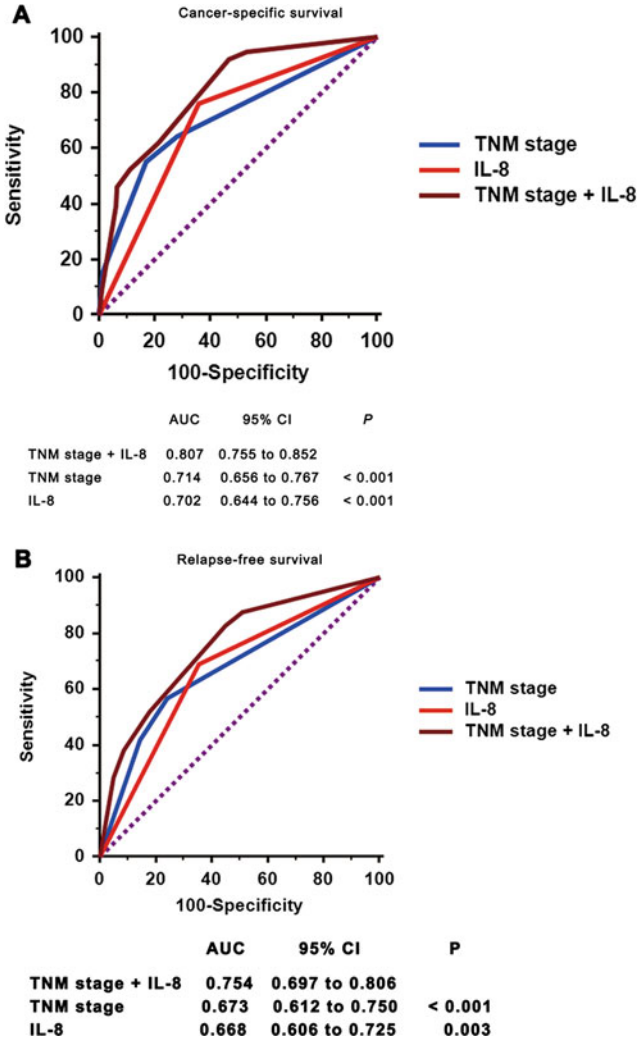

Fig. 3 ROC analysis for the predictive value of IL-8 expression for CSS and RFS in ccRCC patients. Receiver operating characteristic analysis of the sensitivity and specificity for the predictive value for CSS (**a**) and RFS (**b**) of combined TNM stage and IL-8 stratification model, TNM stage model, IL-8 model. *P* value <0.05 was considered statistically significant

Discussion

Our study confirmed the biological and prognostic significance of IL-8 in ccRCC and provided evidence for its use to stratify patients with different prognoses after surgical resection. To our knowledge, this study was the first to demonstrate the association between IL-8 expression and a greater risk of mortality and recurrence in ccRCC patients following surgery. Furthermore, the incorporation of IL-8 into the TNM staging system led to a more accurate risk classification after surgery.

IL-8, also known as CXCL8, is a proinflammatory CXC chemokine involved in the promotion of neutrophil chemotaxis and degranulation. It exerts its biological effect by binding to two cell surface, G-protein-coupled receptors (CXCR1 and CXCR2), activating the multiple intracellular signaling pathways. Elevated expression of IL-8 and its receptors has been observed in endothelial cells, neutrophils, tumor-associated macrophages, and cancer cells. Generated by autocrine/paracrine, IL-8 signaling pathway has been proven to play critical roles in tumor proliferation [20, 21], migration [22], invasion [23], and anti-apoptosis [24] in cancer cell lines. While in xenograft or orthotopic models, IL-8 was shown to promote angiogenesis, tumorigenicity, and metastatic potential in many series of solid tumors [25–27].

Consistent with a previously published data, IL-8 was overexpressed in RCC [16]. Here, we further investigated the prognostic significance of IL-8 expression in 271 ccRCC patients. We found that high IL-8 expression was more likely to be seen in ccRCC patients with and advanced TNM stage and high Fuhrman grade. Previous studies indicated the IL-8 overexpression contributes to tumor progression, angiogenesis, and metastasis in RCC [16, 17, 28]. A recent study demonstrated that an increased secretion of IL-8 is associated with a sunitinib resistance in human ccRCC [7], suggesting that IL-8 has a critical role in tumor progression and drug resistance. Strategies to inhibit IL-8 signaling may sensitize hypoxic tumor cells to conventional treatments.

Angiogenesis is indispensable for the growth of solid tumors, and the metastatic potential of primary tumors is highly correlated with the degree of tumor-associated angiogenesis. We speculate that optimal use of IL-8 neutralizing antibodies might prevent tumor growth and metastasis. There is evidence that blocking IL-8 signaling with neutralizing antibodies can inhibit the angiogenesis, proliferation, invasion, and metastasis of tumor cells in melanoma and bladder cancer [25, 27].

The major limitations of this study are the retrospective design in nature and the relatively small size of the cohort. A

multicenter, prospective study is warranted to validate these results in a larger cohort in the future. The expression of IL-8 is subjectively analyzed. Furthermore, the IL-8/CXCR1/CXCR2 axis is a key component implicated in tumor development among CXC chemokine family; the clinical and prognostic implications of IL-8/CXCR1/CXCR2 axis in patients with ccRCC remain to be evaluated.

Conclusions

Our present study demonstrated that IL-8 expression is an unfavorable independent prognostic factor for CSS and RFS in ccRCC patients. The prognostic capability of TNM staging system was significantly improved when the IL-8 expression was incorporated. Inhibiting the effects of IL-8 signaling may be a potential therapeutic intervention for ccRCC.

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Conflicts of interest None

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