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ORIGINAL RESEARCH

Changes in Serum Interleukin-8 Levels Predict Response to Immune Checkpoint Inhibitors Immunotherapy in Unresectable Hepatocellular Carcinoma Patients

Jiao Zhang[1,2], Yi Yin[3,4], Jiliang Tang[5], Yingrong Zhang[1,2], Yanan Tian[1,2], Fengkai Sun[1,2,6]

[1]Department of Gastroenterology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, People's Republic of China; [2]Department of Gastroenterology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, People's Republic of China; [3]Department of Paediatrics, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, People's Republic of China; [4]Department of Paediatrics, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, People's Republic of China; [5]Emergency Department, Rizhao Central Hospital, Rizhao, People's Republic of China; [6]College of Acupuncture and Massage, Shandong University of Traditional Chinese Medicine, Jinan, People's Republic of China

Correspondence: Fengkai Sun, Department of Gastroenterology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jingwu Road 324#, Jinan, 250021, People's Republic of China, Tel +86-531-68776902, Fax +86-531-68776072, Email sunfengkai2016@126.com; sunfengkai@sdfmu.edu.cn

Background: Effective biomarkers are needed to predict the efficacy of immune checkpoint inhibitors (ICIs) therapy in hepatocellular carcinoma (HCC). We evaluated the early changes in serum interleukin-8 (IL-8) levels as a biomarker of response to ICIs in patients with unresectable HCC.

Methods: Eighty patients who received ICIs therapy alone or in combination with other treatments for unresectable HCC were included. Serum was collected at baseline and 2–4 weeks after the first dose. Serum IL-8 levels were measured using by ELISA.

Results: In the progressive disease (PD) group, serum IL-8 levels increased significantly before the second dose of ICIs therapy compared with baseline levels ($P < 0.001$). Early changes in serum IL-8 levels were significantly associated with the response to ICIs therapy ($P < 0.001$). A cutoff value of 8.1% increase over the baseline most effectively predicted the response to ICIs. Increases in serum IL-8 levels > 8.1% indicated the uselessness of ICIs immunotherapy in patients with unresectable HCC. Patients with increases in serum IL-8 levels > 8.1% had significantly shorter overall survival (OS) and progression-free survival (PFS) than those with increases in serum IL-8 levels ≤ 8.1% ($P < 0.001$). Increases in serum IL-8 levels > 8.1% were independent prognosticators of worse OS ($P = 0.003$) and PFS ($P < 0.001$).

Conclusion: Early changes in serum IL-8 levels, measured only 2–4 weeks after starting therapy, could predict the response to ICIs therapy, as well as OS and PFS of patients with unresectable HCC. Increases in serum IL-8 levels > 8.1% indicated the uselessness of ICIs immunotherapy and predicted worse OS and PFS.

Keywords: interleukin-8, immune checkpoint inhibitor, response, serum biomarker, hepatocellular carcinoma

Introduction

As the major primary tumor in the liver, hepatocellular carcinoma (HCC) ranks sixth as most frequently diagnosed cancer and fourth as most common cause of cancer-related deaths worldwide.[1] Curative therapy remains limited to a small subset of patients because approximately 80% of patients with HCC are already at an advanced stage at the time of diagnosis.[2] In recent years, the landscape of systemic therapy for advanced HCC has changed dramatically with the emergence of immune checkpoint inhibitors (ICIs). The objective response rate (ORR) of patients who receive anti-PD-1 therapy as monotherapy for advanced HCC has been reported to be 15–20%.[3,4] Recently, a combination of atezolizumab, an anti-PD-L1 mAb, and bevacizumab, an anti-vascular endothelial growth factor mAb, has been approved as the first-line treatment for unresectable HCC, considering that the combination outperformed sorafenib in terms of survival and

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response.[5,6] Although the clinical progress of ICIs for HCC has been accelerating, only some patients benefit from immunotherapy. Besides, about 25% of patients develop grade 3–4 immune-related adverse events.[7] Therefore, exploring biomarkers that predict the clinical response to immunotherapy can potentially improve patient selection, maximize clinical benefits, and avoid unnecessary toxicity. Studies to identify possible predictive biomarkers for immunotherapy in HCC have recently begun.[7]

Interleukin-8 (IL-8), a member of the CXC chemokine family, is secreted by the tumor and stromal cells in various tumor types. It is reported that IL-8 enhances tumor cell growth and metastasis through multiple mechanisms.[8] We previously demonstrated that IL-8 is highly expressed in HCC and promotes the invasion of HCC cells through the activation of the PI3K/Akt pathway.[9] In addition, IL-8 overexpression is associated with vascular invasion, intrahepatic metastasis, advanced tumor stage, and early tumor recurrence and can predict the adverse clinical prognosis of patients with HCC.[10,11] In a small cohort of patients with melanoma and non-small cell lung cancer, elevated serum IL-8 levels were associated with a reduced response to PD-1 blockade.[12] Recently, high levels of IL-8 in the plasma, peripheral blood mononuclear cells, and tumors were reported to be closely related to the decreased efficacy of atezolizumab (anti-PD-L1 mAb) in three randomized trials representing 1445 patients with metastatic urothelial carcinoma and metastatic renal cell carcinoma.[13] Here, we investigated the association between serum IL-8 levels and clinical performance of patients with unresectable HCC during ICIs therapy, either as monotherapy or in combination with other treatments.

Materials and Methods

Patients and Study Design

From November 2018 to June 2023, 80 patients who received ICIs therapy for unresectable HCC at Shandong Provincial Hospital Affiliated to Shandong First Medical University were included in this study. The diagnosis of HCC was confirmed through pathological examination or laboratory and radiological assessments according to the guidelines of the American Association for the Study of Liver Diseases.[14] The study protocol was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Medical Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University (JNKJ: NO. 2020–3001). Informed consent was obtained from all patients.

Peripheral blood samples were collected via venipuncture within seven days before the first dose of ICIs therapy and at the time of the second dose (2–4 weeks). Serum was obtained by centrifugation and stored deep frozen. Serum levels of IL-8 were measured using R&D Human IL-8 Valukine ELISA Kit.

Assessment of Treatment Response

Response to immunotherapy was evaluated radiographically and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria for HCC.[15] The objective response rate (ORR) was defined as the proportion of patients who achieved CR or PR as their best overall response, based on the mRECIST criteria. Disease control rate (DCR) was defined as the proportion of patients who achieved CR, PR, or SD as their best overall response based on the mRECIST criteria. Patients were divided into a progressive disease (PD) group or a non-progressive disease (non-PD) group, including CR/PR/SD, based on their initial response to immunotherapy.

Statistical Analysis

The chi-square test was used to analyze categorical data. Wilcoxon tests were used to compare changes in serum IL-8 levels during treatment between the PD and non-PD groups. Nonparametric Mann–Whitney *U*-tests were used to assess the strength of the association between serum IL-8 levels and clinical response. In the survival analysis, overall survival (OS) was defined as the time from the date of the first dose of immunotherapy until death or last follow-up. Progression-free survival (PFS) was calculated as the time from the date of the first dose of immunotherapy until disease progression, death, or the last follow-up, whichever occurred first. Differences in OS and PFS were compared using the Kaplan-Meier method and Log rank test. Variables associated with OS and PFS were determined using univariate and multivariate Cox

regression analysis, respectively. The ability of changes in serum IL-8 levels to predict response was estimated using receiver operating characteristic (ROC) curves, and optimal cut-off points were set under the Youden index with maximal sensitivity and best specificity to predict response. Differences were considered statistically significant at two-tailed p-values < 0.05. Statistical analyses were performed using SPSS version 26.0.

Results

Patient Characteristics and Response to Immunotherapy

Eighty patients who received immunotherapy for unresectable HCC were included in this study. The median age of this cohort was 57 years (range, 31–76 years old). Most patients were male (88.75%, 71/80), and the leading etiology of HCC was hepatitis B (90%, 72/80). The Child-Pugh grade was A in 88.75% (71/80) of the patients and B in 11.25% (9/80). Macrovascular invasion and extrahepatic metastases were observed in 42.5% (34/80) and 60% (48/80) of the patients, respectively, and 75% (60/80) of the patients had advanced-stage HCC according to Barcelona Clinic Liver Cancer (BCLC) staging.

Among all patients, 1.25% (1/80) received ICIs as monotherapy, 1.25% (1/80) received ICIs plus transarterial chemoembolization (TACE), 57.5% (46/80) received ICIs plus targeted drugs, and 40% (32/80) received ICIs combined with targeted drugs and locoregional treatments including radiofrequency ablation, TACE, or hepatic arterial infusion chemotherapy. Among the 80 enrolled HCC patients, 5% (4/80) achieved CR. PR and SD were identified in 17.5% (14/80) and 35% (28/80) of patients, respectively, with an ORR of 22.5% and a DCR of 57.5%. During follow-up, all adverse events were manageable and no toxicity-related deaths occurred.

Comparison Between the Patients with or Without Disease Control

All patients were divided into a progressive disease group (PD, n = 34) or a non-progressive disease group (non-PD, n = 46), including CR/PR/SD, based on the initial response to immunotherapy. Based on the treatment responses, a comparative study between the non-PD and PD groups was conducted, and the results are summarized in Table 1. A higher proportion of patients with advanced BCLC stage and extrahepatic metastasis was observed in the PD group

Table 1 Baseline Characteristics Between the Patients with or Without Disease Control Under Immunotherapy

Characteristics	CR+PR+SD (n = 46)	PD (n = 34)	*P* value
Age (years old)			0.070
≥50	40	24	
<50	6	10	
Sex			0.629
Male	42	29	
Female	4	5	
HBV infection			0.497
Yes	40	32	
No	6	2	
Baseline AFP level (ng/mL)			0.208
≥400	14	15	
<400	32	19	
Baseline PIVKA-II level (mAU/mL)			0.091
≥400	21	22	
<400	25	12	
Child-Pugh grade			1.000
A	41	30	
B	5	4	

(*Continued*)

Table 1 (Continued).

Characteristics	CR+PR+SD (n = 46)	PD (n = 34)	*P* value
BCLC stage			0.019
B	16	4	
C	30	30	
Macrovascular invasion			0.104
Present	16	18	
Absent	30	16	
Extrahepatic metastasis			0.034
Present	23	25	
Absent	23	9	

than in the non-PD group (52.9% vs 34.8% and 73.5% vs 50%; $P < 0.05$, respectively). There were no differences in age, sex, hepatitis B virus (HBV) infection, baseline alpha-fetoprotein (AFP), protein induced by vitamin K absence or antagonist II (PIVKA-II) levels, Child-Pugh grade, or macrovascular invasion between the two groups.

Changes in Serum IL-8 Levels of the PD Group and Non-PD Group

We assessed the serum IL-8 levels in 80 patients with unresectable HCC before the first dose of ICIs therapy and at the time of the second dose. In the PD group, median serum IL-8 levels increased significantly before the second dose of ICIs therapy, when compared with baseline levels [before 2nd dose: 16.4 pg/mL (Q1-Q3: 8.6–23.3) vs before 1st dose: 14.4 pg/mL (Q1-Q3: 6.9–21.3); $P < 0.001$]. However, the changes in serum IL-8 levels were not significant in the non-PD group [before 2nd dose: 11.4 pg/mL (Q1-Q3: 7.5–22.1) vs before 1st dose: 13.5 pg/mL (Q1-Q3: 7.3–23.7); $P = 0.21$] (Figure 1).

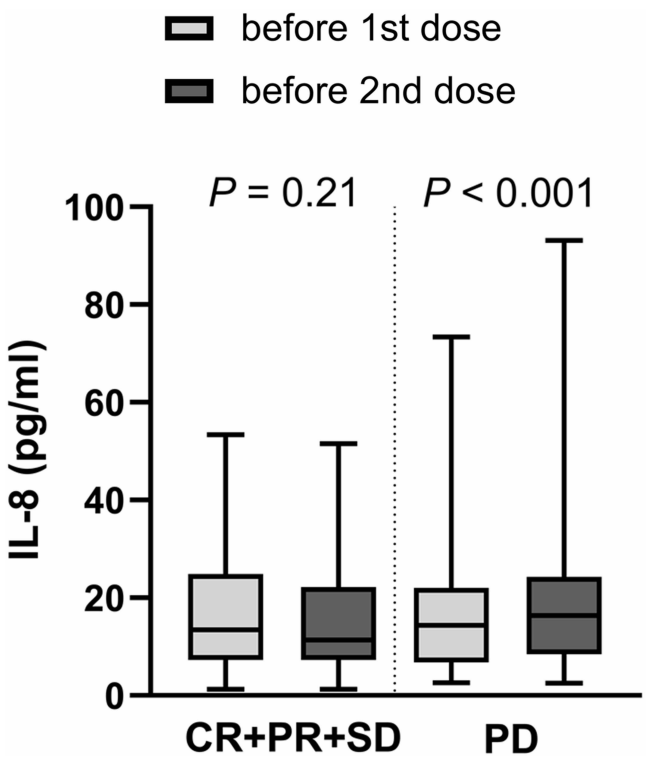

Figure 1 Changes in serum IL-8 levels reflect tumor response in unresectable HCC patients during treatment with ICIs. Eighty unresectable HCC patients were treated with ICIs and serum IL-8 levels were assessed before the first dose and before the second dose of ICIs. In the progressive disease (PD) group, median serum IL-8 levels increased significantly before the second dose of ICIs therapy, when compared with baseline levels ($P < 0.001$). However, the changes in serum IL-8 levels were not significant in the nonprogressive disease (CR+PR+SD) group ($P = 0.21$). Boxes indicate the 25th and 75th percentiles; whisker display the range; the bars at the end of axis mean the minimum and maximum values; and horizontal lines in each box represent the median.

Value of Changes in Serum IL-8 Levels in Predicting Response to Immunotherapy in HCC Patients

Owing to the observed association between serum IL-8 levels and therapeutic response, we hypothesized that early changes in serum IL-8 levels might serve as early predictors of treatment response to ICIs therapy. Therefore, we compared the percentage of changes in serum IL-8 levels between the PD and non-PD groups, and ROC curves were generated to assess the ability of changes in serum IL-8 levels to predict therapeutic responses.

Early changes in serum IL-8 levels were significantly associated with response to ICIs therapy [median change (%): non-PD −2.0% (Q1-Q3: - 8.2% to 7.0%) vs PD 15.9% (Q1-Q3: 3.4%-24.1%); P <0.001], with an area under the curve (AUC) in the ROC function of 0.815 (95% CI 0.717–0.912, P <0.001) (Figure 2A and B). Using the ROC curve to determine the change in serum IL-8 levels to predict response, we chose a > 8.1% increase over baseline as the cut-off point that combined maximal sensitivity (70.6%) with the best specificity (87.0%).

Prognostic Role of Changes in Serum IL-8 Levels in OS and PFS

Kaplan-Meier curves indicated that overall survival was significantly shorter in ICI-treated HCC patients with increases in serum IL-8 levels > 8.1% than in those with increases in serum IL-8 levels ≤ 8.1% (median OS: 11.5 months vs 22 months; P < 0.001) (Figure 3A). After adjusting for other clinicopathological variables, including age, sex, HBV infection, baseline AFP and PIVKA-II levels, Child-Pugh grade, BCLC stage, and macrovascular invasion, increases in serum IL-8 levels > 8.1% and extrahepatic metastasis remained independent risk factors for worse OS (P = 0.003 and 0.041, respectively) (Table 2).

Similarly, the PFS of patients with HCC with increases in serum IL-8 levels > 8.1% was significantly shorter than that of those with increases in serum IL-8 levels ≤ 8.1% (median OS: 4 months vs 11 months; P < 0.001) (Figure 3B). After multivariate Cox regression analyses, only increases in serum IL-8 levels > 8.1% remained an independent predictor of shorter PFS (P < 0.001). Age, sex, HBV infection, baseline AFP and PIVKA-II levels, Child-Pugh grade, BCLC stage, macrovascular invasion, and extrahepatic metastasis were not significantly correlated with PFS (Table 3).

Discussion

The use of ICIs has led to substantial progress in the development of systemic therapies for patients with unresectable HCC. Specifically, the use of ICIs alone and in combination with other treatment modalities has proven to be an effective strategy for patients with advanced HCC.[16,17] However, there are clinical challenges in identifying patients who would benefit from ICIs therapy. To date, there are no effective biomarkers to predict the efficacy of ICIs therapy in patients with advanced HCC. Although biomarkers such as PD-L1 and tumor mutational burden (TMB) have been used for

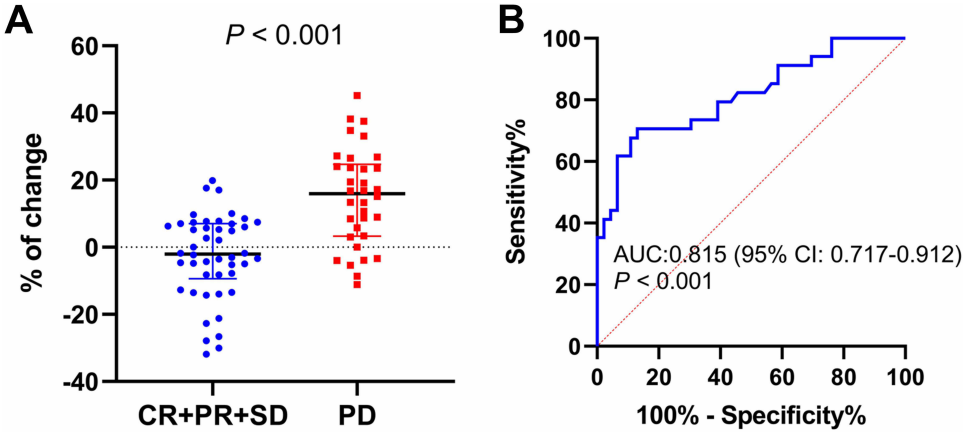

Figure 2 Early changes in serum IL-8 levels are associated with response in unresectable HCC patients treated with ICIs. (**A**) Percentages of changes in serum IL-8 levels in the progressive disease (PD) group are significantly higher compared to the nonprogressive disease (CR+PR+SD) group (P < 0.001). (**B**) ROC curves for the correlation of early changes in serum IL-8 levels with response to ICIs treatment in unresectable HCC patients. The cut-off point of > 8.1% increase in serum IL-8 levels is designated.

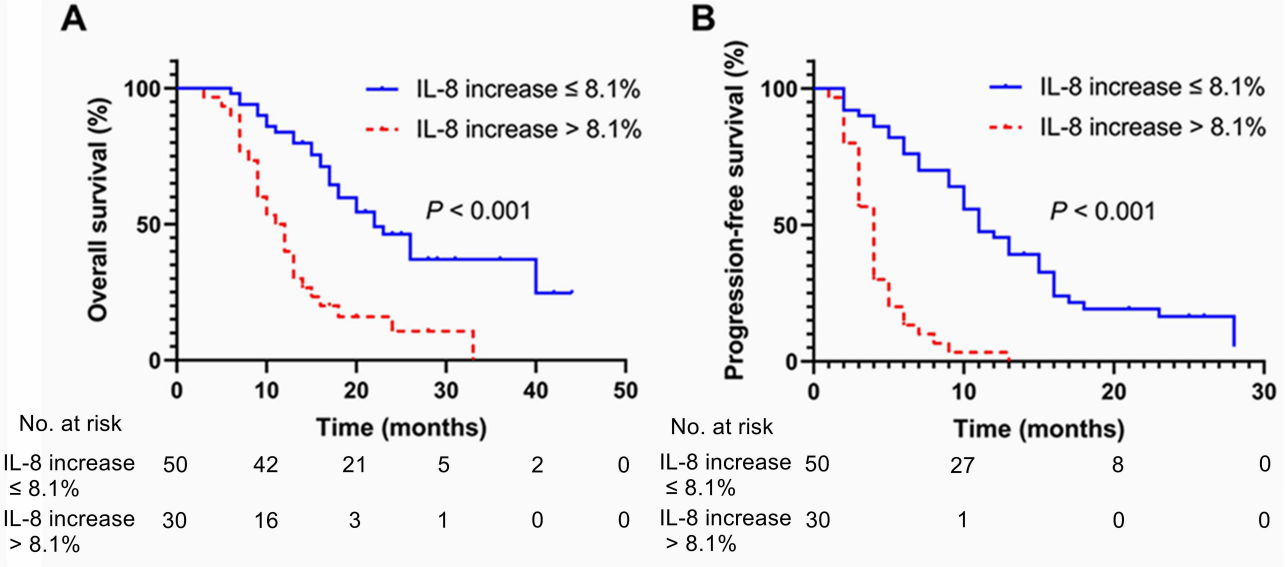

Figure 3 Changes in serum IL-8 levels are associated with overall survival and progression-free survival in unresectable HCC patients treated with ICIs. Kaplan-Meier curves indicate that overall survival (**A**) and progression-free survival (**B**) was significantly shorter in ICIs-treated HCC patients with increases in serum IL-8 levels > 8.1% compared to those with increases in serum IL-8 levels ≤ 8.1% ($P < 0.001$, respectively).

response prediction to ICIs therapy in several cancer types, their utility is limited in HCC, necessitating the exploration of additional effective biomarkers.[18,19] Early identification of responders and non-responders to ICIs treatment could help avoid unnecessarily prolonged therapy, thus reducing associated toxicities and costs.

In recent years, the tumor inflammatory microenvironment has attracted considerable attention as a crucial factor affecting both the sensitivity of tumor cells to immunotherapy and patient prognosis. IL-8, an important angiogenic chemokine expressed in various types of cancer, not only effectively promotes the recruitment of various immunosuppressive cells into the tumor microenvironment but also exerts direct oncogenic effects, such as promoting tumor cell proliferation, angiogenesis, and facilitating invasion and metastasis.[20–22] We previously demonstrated that IL-8 is highly expressed in HCC and promotes the invasion of HCC cells through the activation of the PI3K/Akt pathway.[9] Moreover, it has been reported that serum IL-8 level is a significant and independent prognostic factor for survival in HCC, and changes in plasma IL-8 levels during the first few days could predict the response to sorafenib therapy in patients with HCC.[23,24] Recent clinical studies evaluating IL-8 levels in patients receiving ICIs agents have deduced that myeloid tumor infiltration driven by IL-8 contributes to resistance to ICIs therapy, and patients with low IL-8 levels after

Table 2 Univariate and Multivariate Analyses for Overall Survival (OS)

Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (≥50 vs <50)	0.374	0.203–0.688	0.002	0.610	0.316–1.179	0.141
Sex (Male vs Female)	0.824	0.370–1.835	0.635			
HBV infection (Yes vs No)	1.136	0.451–2.857	0.787			
Baseline AFP (≥400 vs <400)	1.252	0.719–2.181	0.427			
Baseline PIVKA-II (≥400 vs <400)	1.334	0.776–2.295	0.297			
Child-Pugh (A vs B)	0.814	0.367–1.807	0.614			
BCLC stage (B vs C)	0.671	0.362–1.243	0.204			
Macrovascular invasion (Yes vs No)	1.426	0.814–2.498	0.215			
Extrahepatic metastasis (Yes vs No)	2.488	1.381–4.480	0.002	1.900	1.028–3.510	0.041
Serum IL-8 increase (>8.1% vs ≤8.1%	3.349	1.929–5.814	<0.001	2.513	1.380–4.579	0.003

Table 3 Univariate and Multivariate Analyses for Progression-Free Survival (PFS)

Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (≥50 vs <50)	0.419	0.234–0.750	0.003	0.622	0.339–1.142	0.126
Sex (Male vs Female)	0.815	0.390–1.703	0.586			
HBV infection (Yes vs No)	1.128	0.515–2.467	0.764			
Baseline AFP (≥400 vs <400)	1.080	0.665–1.755	0.754			
Baseline PIVKA-II (≥400 vs <400)	1.044	0.651–1.675	0.857			
Child-Pugh (A vs B)	1.370	0.627–2.995	0.430			
BCLC stage (B vs C)	0.838	0.499–1.407	0.503			
Macrovascular invasion (Yes vs No)	1.476	0.917–2.377	0.109			
Extrahepatic metastasis (Yes vs No)	1.285	0.802–2.061	0.297			
Serum IL-8 increase (>8.1% vs ≤8.1%	5.396	3.048–9.553	<0.001	4.962	2.746–8.967	<0.001

immunotherapy exhibit improved OS, PFS, and ORR compared to those with high IL-8 levels in several types of solid tumors such as melanoma, urothelial carcinoma, renal cell carcinoma, and non-small cell lung cancer.[12,13,25–27]

In this study, we discovered that serum IL-8 levels in patients with HCC increased significantly before the second dose of ICIs therapy when compared with baseline levels in the PD group. Moreover, we demonstrated that early changes in serum IL-8 levels, measured only 2–4 weeks after starting therapy (before imaging evaluation), could predict the response to ICIs therapy, as well as OS and PFS of unresectable HCC patients. Increases in serum IL-8 levels > 8.1% indicated the uselessness of ICIs immunotherapy and predicted worse OS and PFS in patients with unresectable HCC. These results are consistent with the fact that serum/plasma IL-8 levels can accurately reflect the tumor burden of patients following antitumor therapy and are negatively correlated with the clinical outcome of ICIs treatment.[13,25,28,29] Therefore, these early biochemical changes detected in the peripheral blood could reflect changes in tumor burden in the first few weeks of ICIs therapy before the radiological evaluation is conclusive.[12] Thus, IL-8 may be a serum biomarker for predicting the clinical benefits of ICIs in patients with unresectable HCC. Interestingly, a recent study using an IL-8-humanized mouse strain demonstrated that IL-8-producing CD4+ T cells orchestrate myeloid-derived suppressor cell infiltration and angiogenesis, resulting in enhanced tumor growth but reduced ICIs efficacy. Moreover, they found anti-PD-1 administration alone could partially alleviate CD8+ T cell exhaustion while augmenting systemic IL-8 expression and the consequential myeloid derived suppressor cell infiltration, which in turn attenuated ICIs efficacy.[30] Systemic elevation of IL-8 by anti-PD-1 treatment might be caused by therapeutic stress, a similar phenomenon found during chemotherapy.[31] Various stimuli such as chemotherapy, hypoxia, and inflammatory signals have been shown to upregulate IL-8 expression.[31–34] A recent study reveals that Interferon-α induces differentiation of cancer stem cells and immunosuppression in HCC by upregulating IL-8 secretion.[34] Several studies have found that HBV can directly induce the production of IL-8.[35,36] These potential factors may contribute to the increased level of IL-8 during ICIs therapy. Interestingly, recent data indicate that neutralizing IL-8 treatment enhances the efficacy of immune checkpoint inhibitors in glioma and hepatocellular carcinoma,[30,37] providing additional support for our discovery that early increases in serum IL-8 levels predict unfavorable response and poor prognosis in unresectable HCC patients receiving ICIs therapy.

This study has some limitations. First, this was a single-center, retrospective study that enrolled patients with unresectable HCC who received ICIs immunotherapy. This study enrolled relatively few patients because they received various ICI-based combination treatments. However, this cohort may better represent the real-world population with unresectable HCC. Second, the sample size of the study was small. Due to the limited sample size, we are unsure if there were any differences of ICIs therapy management (the drug differences, combination or monotherapy, etc) which contributed to increased or decreased level of IL-8. In a recent systematic review and meta-analysis of existing clinical studies, subgroup analysis was conducted to investigate the impact of various factors, including drug types, on the association between IL-8 and prognosis of patients treated with ICIs. The authors found that despite the diversity of ICIs and their distinct targets, the predictive value of IL-8 for various ICIs in solid tumors remains generally consistent.[27] We speculate that the drug differences in ICIs therapy management may not have an impact on the increase or decrease of IL-8

levels. However, a previous study reported that during the first few days after sorafenib therapy in patients with unresectable HCC, plasma IL-8 levels changed, which could predict the response to sorafenib therapy, indicating that targeted drug therapy may affect the IL-8 levels.[24] We speculate that combination or monotherapy may lead to an increase or decrease of IL-8 levels. However, our findings and above speculations required validations in larger groups. Further assessment of the cutoff value for changes in serum IL-8 levels in a larger cohort of HCC patients receiving ICIs treatment is needed.

Conclusions

Despite the pilot nature of our study, we revealed that early changes in serum IL-8 levels, measured before responses were evaluated by radiologic imaging, correlated with subsequent clinical responses in patients with unresectable HCC during ICI treatment. We also found that early changes in serum IL-8 levels during ICIs therapy correlated with OS and PFS in patients with unresectable HCC. Increases in serum IL-8 levels > 8.1% indicated the uselessness of ICIs immunotherapy in patients with unresectable HCC. These data suggest that serum IL-8 levels can be used to monitor and predict the clinical benefits of ICIs immunotherapy in patients with unresectable HCC.

Abbreviations

HCC, Hepatocellular carcinoma; ICI, Immune checkpoint inhibitor; PD-1, Programmed death-1; PD-L1, Programmed death-ligand 1; ORR, Objective response rate; IL-8, Interleukin-8; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; mRECIST, Modified Response Evaluation Criteria in Solid Tumors; DCR, Disease control rate; OS, Overall survival; PFS, Progression-free survival; ROC, Receiver operation characteristics; BCLC, Barcelona Clinic Liver Cancer; TACE, Transarterial chemoembolization; HBV, Hepatitis B virus; AFP, Alpha-fetoprotein; PIVKA-II, Protein induced by vitamin K absence or antagonist II; AUC, Area under curve; TMB, Tumor mutational burden.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Informed Consent

The study protocol was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Medical Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University (JNKJ:NO. 2020-3001). Informed consent was obtained from all patients.

Consent for Publication

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest related to this work.

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