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Status of inflammation in relation to health related quality of life in hepatocellular carcinoma patients

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Abstract

Purpose Both Inflammation and health-related quality of life (HRQoL) are independent prognosticators in HCC patients. We hypothesized that inflammation can cause impairment in HRQoL and investigated the correlation between inflammatory status and HRQoL in HCC patients.

Methods Clinical, laboratory and HRQoL (using EORTC QLQ-C30, QLQ-HCC18, C30 and HCC18 index-scores) data were prospectively collected from HCC patients at diagnosis. Correlation analyses were performed between HRQoL and inflammation-based markers including C-reactive protein (CRP), CRP/albumin ratio (CRP/alb), Glasgow Prognostic Score (GPS), Inflammation-Based Index (IBI) and Prognostic Index (PI).

Results Among 445 HCC patients, higher inflammatory states were significantly correlated with worse HRQoL. For CRP and CRP/alb ratio, the HRQoL factors with higher correlations included C30 and HCC18 index-scores, certain QLQ-C30 domains and items ('physical functioning', 'role functioning', 'fatigue', 'pain', 'appetite loss') and QLQ-HCC18 items ('fatigue', 'body image', 'nutrition' and 'abdominal swelling'), where the Pearson's correlation coefficients were up to 0.416. Multivariate analyses indicated that worse HRQoL factors were significantly correlated with worse scores in GPS, IBI and PI.

Conclusion In HCC patients, inflammatory status correlates with HRQoL at presentation. In particular, relatively stronger correlations with CRP-based markers have been observed in HRQoL scales that assess constitutional symptoms (QLQ-C30 'physical functioning', 'role functioning', 'fatigue', 'appetite loss' and QLQ-HCC18 'fatigue' and 'nutrition') and tumor burden (QLQ-C30 'pain' and QLQ-HCC18 'abdominal swelling' and 'body image'). Future studies are warranted to evaluate whether intervention that reduces inflammation could improve HRQoL in HCC patients.

Keywords EORTC QLQ-C30 · QLQ-HCC18 · Index score · Liver cancer · C-reactive protein (CRP)

Abbreviations

CI	Confidence intervals
CRP	C-reactive protein
CRP/alb ratio	C-reactive protein-to-albumin ratio
EORTC	European Organization for Research and Treatment of Cancer
GPS	Glasgow prognostic score
HCC	Hepatocellular carcinoma
IBI	Inflammation-based index
OR	Odds ratio
OS	Overall survival
PI	Prognostic index
HRQoL	Health related quality of life
r	Pearson's correlation coefficient
SD	Standard deviations

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Introduction

Hepatocellular carcinoma (HCC) carries high morbidity and mortality. It is the 5th commonest cancer and the 2nd leading cause of cancer death in the world [1]. When treatment options were limited in early days, the prognosis of HCC patients was poor with median overall survival (OS) of 2–4 months, albeit a wide range in reported survival ranging from 0.1 to 65 months [2–5]. In order to better predict survival, a number of staging systems have been developed and various factors have been identified to be prognostic in HCC. Two novel factors of note are inflammatory markers [6] and health-related quality of life (HRQoL) [7–11].

The inflammatory process is actively involved in HCC pathogenesis and progression, while at the same time, immunosuppressive environment has been illustrated in HCC [12]. Tumor-promoting inflammatory cells and microenvironment could enable immune evasion of cancer cells, promote tumor proliferation, invasiveness and angiogenesis [13]. Inflammatory tumor microenvironment has been associated with more aggressive disease [14], and patients with such tumors have been reported to have more advanced stage of HCC, poorer liver function and survival [15].

C-reactive protein (CRP) is an acute phase reactant of hepatic origin; it is produced in response to inflammation and is circulated in plasma. Plasma CRP level could reflect the degree of systemic inflammatory response [16]. Moreover, various CRP-based inflammation scoring systems have been developed, namely the CRP-to-albumin (CRP/alb) ratio, Glasgow Prognostic Score (GPS), Inflammation-Based Index (IBI) and Prognostic index (PI); higher CRP/alb ratio, GPS, IBI or PI indicates higher inflammatory response. Apart from indicating the level of inflammation in individual patients, they have been shown to be significant independent prognostic factors for survival in HCC patients, where high CRP, CRP/alb ratio, GPS, IBI and PI were associated with poor survival [17–24].

HRQoL has also been demonstrated to be an independent prognostic factor for survival in patients with early as well as advanced stage HCC [7–10]. Supplementing HRQoL data to various staging systems has been demonstrated to further enhance their prognostication powers [8, 9, 25]. In our recent report of a prospective cohort of HCC patients, the prognostic significance of HRQoL at diagnosis was independent of liver function and tumor stage. Both the general HRQoL instrument for cancer (the European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30) [26] and the liver cancer-specific HRQoL instrument (the EORTC QLQ-HCC18) [27] were used in the study. In addition, our proposed C30 and HCC18 index-scores were, respectively, shown to be good representatives of the overall domains and items in the EORTC QLQ-C30 and QLQ-HCC18. They were also found to be stronger prognostic factors than the individual domains and items in the original EORTC instruments [10]. Index scoring is user friendly; it enables routine clinical use of complicated HRQoL data by transforming them into two meaningful single scores.

Inflammation in HCC may cause HRQoL impairment in HCC patients. It has been postulated that cancer could cause inflammatory response, and this could attribute to malignant cachexia [28]. Plasma CRP level and various CRP-based markers are measurable biological variables that reflect inflammatory status of individual cancer patient [16]. Inflammatory response could lead to systemic symptoms that include anorexia, poor oral intake, weight loss, protein-energy malnutrition and fatigue [29, 30]. These constitutional symptoms contribute to cancer cachexia which is frequently associated with a decline in a patient's functional status, emotional performance and social functioning [31]. All these could have negative effects on their health perceptions. HRQoL of HCC patients could be impaired as a result. Therefore, we hypothesized that CRP and related markers in HCC patients may be correlated with their HRQoL. In this study, the objectives were to investigate the correlations between HRQoL variables and CRP-based inflammation markers in HCC patients.

Methods

Patients

This study was approved by the regional ethics committee (the Joint Clinical Research Ethics Committee of Chinese University of Hong Kong and New Territories East Cluster of Hospital Authority). From 1st Jan 2007 to 31st Dec 2011, newly diagnosed HCC patients who attended the Joint Hepatoma Clinic of the Prince of Wales Hospital in Hong Kong were invited to participate in the study. Patients were eligible if they had a diagnosis of HCC (either by histology, typical findings from radiological and biochemical tests, or typical findings from two radiological modalities), had no prior treatment for HCC, had adequate blood sample for inflammatory marker studies and were able to read and comprehend Chinese. Patients were excluded if they had history of other malignancies, cognitive impairment or hepatic encephalopathy. Informed consents were obtained from all participants. Upon entering the study, patients were given the Chinese versions of the EORTC QLQ-C30 [26] and QLQ-HCC18 [27] questionnaires to complete in the clinic. They were allowed as much time as they needed to fill in the

questionnaires, which were subsequently collected by the research assistant or research nurse.

HRQoL assessment and index-scores calculation

The EORTC QLQ-C30 [32] is a general cancer HRQoL assessment tool that contains 30 questions covering five functional domains ('physical functioning', 'role functioning', 'cognitive functioning', 'emotional functioning' and 'social functioning'), three symptom domains ('fatigue', 'pain', 'nausea and vomiting') and a global QOL domain. Five items assess common symptoms of cancer ('dyspnea', 'appetite loss', 'sleep disturbance', 'constipation' and 'diarrhea') and 1 item assesses financial problem. Items and domains are transformed to scores ranging from 0 to 100. A higher score for a functional or global QOL domain reflects a better functional level or global QOL, while a lower score for a symptom/problem scale reflects less symptoms/problem (better HRQoL) [26]. The Chinese version of the EORTC QLQ-C30 has been extensively evaluated and psychometrically validated in cancer patients [33–39]. The EORTC QLQ-HCC18 [40] encompasses 18 questions covering six domains ('fatigue', 'body image', 'jaundice', 'nutrition', 'pain' and 'fever') and 2 scales ('abdominal swelling' and 'sex life'). All scales are transformed to scores ranging from 0 to 100. A lower score reflects less symptom or problem (better HRQoL) [27]. The Chinese version of the EORTC QLQ-HCC18 has also been validated psychometrically for use in HCC patients [41]. C30 and HCC18 index-scores were calculated as previously published (see Table 1) [10].

Inflammatory markers, clinical factors and follow-up

Laboratory tests were done on the same day of study entrance and included measurements for cell counts, CRP and albumin levels. CRP/alb ratio was calculated by dividing CRP level (in mg/L) by albumin level (in g/L); a higher CRP/alb ratio reflects higher inflammatory status. GPS, IBI and PI were scored according to published literature (Table 2) [18, 19, 21]. A higher GPS, IBI or PI indicates a higher inflammatory status.

Table 2 Scoring systems for inflammation-based markers used in the study

	Score 0	Score 1
Albumin (g/L)	≥ 35	< 35
C-reactive protein (mg/L)	≤ 10	> 10
Glasgow prognostic score	Sum of the above 2 scores	
Albumin (g/L)	≥ 35	< 35
C-reactive protein (mg/dL)	< 10	≥ 10
Inflammation-based index	Sum of the above 2 scores	
White cell count ($\times 10^9$/L)	≤ 11	> 11
C-reactive protein (mg/L)	≤ 10	> 10
Prognostic index	Sum of the above 2 scores	

Statistical analyses

Patient characteristics were assessed by standard descriptive analyses. Correlation between continuous inflammatory markers and continuous HRQoL factors was analyzed using Pearson's correlation analysis. The following inflammatory scoring systems were dichotomized for correlative analysis: GPS 0 versus 1–2, IBI 0 versus 1–2, PI 0 versus 1–2. To investigate the correlations between continuous HRQoL factors and dichotomized inflammatory markers (GPS, IBI and PI), logistic regressions were performed. To adjust for clinical factors, HRQoL variables with p value < 0.0001 in univariate logistic regressions together with baseline clinical variables, including age, gender, performance status, liver function biochemistry, alpha-feto protein level, presence of cirrhosis, etiology of cirrhosis, tumor stage and treatment received, were forwarded to multivariate logistic regressions. For all logistic regression analyses, odds ratio (OR) and 95% confidence intervals (95% CI) were calculated using GPS 0, IBI 0 and PI 0 as the reference groups. The statistical analyses were performed using statistical software (SAS version 9.3; SAS institute, Cary, NC, USA). A p value of < 0.05 was regarded as statistically significant.

Sample size calculation and handling of missing data

To calculate the target sample size with enough power to investigate the correlations between HRQoL and

Table 1 C30 and HCC18 index scores used in the study

C30 index score	∑ [(100-'Physical functioning'), (100-'Role functioning'), (100-'Emotional functioning'), (100-'Cognitive functioning'), (100-'Social functioning'), (100-'global QOL'), scores of 'Fatigue', 'Nausea and vomiting', 'Pain', 'Dyspnoea', 'Insomnia', 'Appetite loss', 'Constipation', 'Diarrhea', 'Financial Diffculty'] ÷ 15
	Range of C30 index score: 0-100; a lower score represents a less severe symptom/problem
HCC18 index score	∑(scores of 'Fatigue', 'Body Image', 'Jaundice', 'Nutrition', 'Pain', 'Fever', 'Sex life', 'Abdominal distension') ÷ 8
	Range of HCC18 index score: 0–100; a lower score represents a less severe symptom/problem

inflammatory markers, we assumed Pearson's correlation coefficients between HRQoL variables and inflammatory markers to be at least 0.3. With two sided alpha-level of 0.05 and power of 0.9, the target sample size was 133 patients [42]. Since all questions in the QLQ-C30 and QLQ-HCC18 have to be completed in order to obtain C30 and HCC18 index-scores for an individual patient, complete-case analysis would be preferred in the study in order to obtain accurate index-scores. In order to minimize the impact of complete-case analysis, a larger sample size that consisted of three times the target patient number (> 399 patients) was the final target.

Results

Patient characteristics

490 patients consented to the study; 445 (91%) had complete HRQoL data and completed all study procedures. There was no significant difference in HRQoL data between all consented patients and patients with complete data (see Table 3). Therefore, complete-case analysis was adopted for handling of missing data to preserve the integrity of the index-scores. Four hundred and forty-five patients were eligible for analysis (see Fig. 1 for the

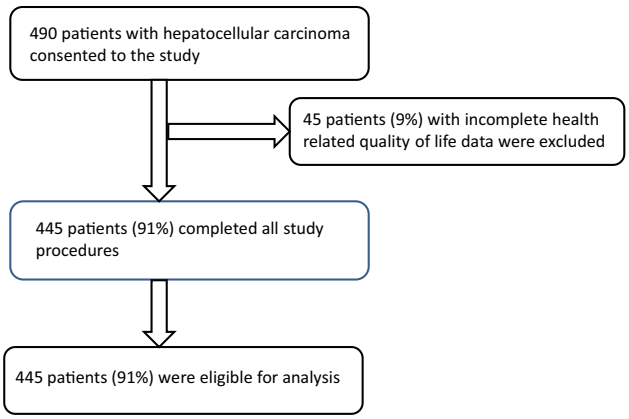

Fig. 1 Flow diagram of number of patients at each stage of the study

Table 3 Comparison of health related quality of life data between all consented patients and patients with complete data

	All consented patients (n = 490)		Patients with complete data (n = 445)		Missing	p Value
	Mean	± SD	Mean	± SD		
EORTC QLQ-C30						
Physical functioning	72.06	24.17	72.28	23.96	0	0.8910
Role functioning	74.59	32.71	75.06	32.18	2	0.8267
Emotional Functioning	70.37	25.33	70.45	25.52	1	0.9621
Social functioning	76.65	24.90	77.08	24.59	2	0.7900
Cognitive function	68.00	30.30	68.58	30.28	4	0.7710
Global quality of life	52.92	26.33	52.53	26.38	2	0.8205
Fatigue	42.90	30.02	42.56	29.81	1	0.8623
Nausea/vomiting	11.56	21.87	11.01	21.28	0	0.6956
Pain	32.31	31.57	32.10	31.55	0	0.9169
Dyspnoea	29.98	31.28	29.74	31.27	3	0.9063
Insomnia	41.33	35.84	40.90	35.87	2	0.8561
Appetite loss	31.83	35.69	31.84	35.62	3	0.9974
Constipation	17.01	27.07	16.63	26.72	0	0.8303
Diarrhea	16.43	27.04	16.10	26.52	3	0.8545
Financial difficulties	51.06	37.38	51.16	37.26	1	0.9659
EORTC QLQ-HCC18						
Fatigue	34.96	26.11	34.77	25.79	1	0.9116
Body Image	25.47	23.20	25.24	22.78	9	0.8821
Jaundice	23.80	22.73	23.48	22.23	2	0.8274
Nutrition	26.97	21.62	26.88	21.40	0	0.9497
Pain	23.98	25.77	23.26	24.44	2	0.6636
Fever	7.29	16.07	6.37	14.48	3	0.3568
Sex life	29.39	35.20	28.31	34.40	8	0.6381
Abdominal swelling	32.58	34.91	32.66	35.12	5	0.9716

EORTC European Organization for Research and Treatment of Cancer, *SD* standard deviation

Table 4 Baseline clinical and laboratory characteristics of the HCC patients

Factors	No. (%)	Median (range)
Age (years)	445	60 (18–88)
Gender		
Male	395 (88.8)	
Female	50 (11.2)	
ECOG performance status		
0	137 (30.8)	
1	283 (63.6)	
2	18 (4.0)	
3	7 (1.6)	
Baseline biochemistry		
Bilirubilin (umol/L, range)		19 (3–548)
Albumin (g/L)		37 (8–53)
ALT (iu/L)		57 (12–564)
Prothrombin time (s)		12.3 (8.9–32.9)
AFP (ng/mL)		239 (1–3637000)
Hepatitis B (%)	361 (81.1)	
Hepatitis C (%)	29 (6.5)	
Cirrhosis (%)	260 (58.4)	
Ascites	111 (24.9)	
Vascular involvement	144 (32.4)	
Tumor number (single: multiple)	165: 280	
Child–pugh class		
A	303 (68.1)	
B	125 (28.1)	
C	17 (3.8)	
AJCC stage		
I	17 (3.8)	
II	112 (23.1)	
III	57 (12.9)	
IV	259 (58.2)	
Okuda stage		
I	203 (45.6)	
II	202 (45.4)	
III	40 (9.0)	
CUPI		
Low risk	224 (50.3)	
Medium risk	164 (36.9)	
High risk	57 (12.8)	
CLIP score		
0	57 (12.8)	
1	86 (19.3)	
2	105 (23.6)	
3	96 (21.6)	
4	64 (14.4)	
5	34 (7.6)	
6	3 (0.7)	
BCLC stage		
A	64 (14.4)	
B	107 (24.0)	
C	251 (56.4)	
D	23 (5.2)	
C-reactive protein (mg/L)		11.13 (0.05–17.62)
C-reactive protein/albumin ratio		0.30 (0.001–0.87)
Glasgow prognostic score		
0	163 (36.6)	
1	172 (38.7)	
2	110 (24.7)	
Inflammation-based index		
0	163 (36.6)	
1	171 (38.7)	
2	111 (24.7)	
Prognostic index		
0	194 (43.6)	
1	220 (48.4)	
2	31 (7.0)	
First line treatment		
Surgical intervention	51 (11.5)	
Percutaneous RFA/ethanol injection	28 (6.3)	
LEM/TACE/TAE	110 (24.7)	
Systemtic therapy	85 (19.1)	
Best supportive care	171 (38.4)	

AFP α-fetoprotein, *ALT* alanine transaminase, *AJCC* American Joint Committee on Cancer, *BCLC* Barcelona clinic liver cancer, *CI* confidence interval, *CLIP* the Cancer of the Liver Italian Program, *CUPI* the Chines University Prognostic Index, *ECOG* Eastern Cooperative Oncology Group, *LEM* transarterial lipiodol ethanol mixture, *TACE* transarterial chemoembolisation, *TAE* transarterial embolisation, *RFA* radiofrequency ablation

flow diagram of the study). Tables 4 and 5 illustrate the baseline clinical characteristics, CRP-based markers and HRQoL scores of these patients. The median age at diagnosis was 60. 89% were male. 94% of patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 58% had cirrhosis, 81% had hepatitis B, while 6% had hepatitis C infection. 14% were Barcelona Clinic Liver Cancer (BCLC) stage A, 24% were stage B, 56% were stage C, and 5% were stage D. Regarding first line treatment, 51 patients (12%) received surgical intervention, 28 (6%) had percutaneous radiofrequency ablation or ethanol injection, 110 (25%) had trans-arterial therapy, 85 (19%) had systemic therapy, and 171 (38%) could only receive best supportive care. The mean C30 index-score was 30.4 (± 19.5), and the mean HCC18 index-score was 25.1 (± 17.1) (where index-score of '0' means the best HRQoL and '100' means the worst HRQoL).

Table 5 Pearson's correlation analysis between health related quality of life and inflammation-based markers

	Mean	SD	C-reactive protein		C-reactive protein/Albumin ratio	
			Pearson's r	*p*-Value	Pearson's r	*p*-Value
EORTC QLQ-C30						
Physical functioning	72.28	23.96	−0.349	<0.0001	−0.416	<0.0001
Role functioning	75.06	32.18	−0.347	<0.0001	−0.390	<0.0001
Emotional functioning	70.45	25.52	−0.074	0.1205	−0.076	0.1104
Social functioning	77.08	24.59	−0.103	0.0301	−0.130	0.0059
Cognitive function	68.58	30.28	−0.258	<0.0001	−0.277	<0.0001
Global quality of life	52.53	26.38	−0.279	<0.0001	−0.323	<0.0001
Fatigue	42.56	29.81	0.334	<0.0001	0.367	<0.0001
Nausea/vomiting	11.01	21.28	0.252	<0.0001	0.244	<0.0001
Pain	32.10	31.55	0.345	<0.0001	0.300	<0.0001
Dyspnoea	29.74	31.27	0.184	<0.0001	0.224	<0.0001
Insomnia	40.90	35.87	0.156	0.001	0.177	0.0002
Appetite loss	31.84	35.62	0.376	<0.0001	0.358	<0.0001
Constipation	16.63	26.72	0.067	0.1565	0.059	0.2111
Diarrhea	16.10	26.52	0.105	0.0266	0.129	0.0063
Financial difficulties	51.16	37.26	0.188	<0.0001	0.189	<0.0001
C30 index score	30.40	19.45	0.348	<0.0001	0.371	<0.0001
EORTC QLQ− HCC18						
Fatigue	34.77	25.79	0.329	<0.0001	0.371	<0.0001
Body Image	25.24	22.78	0.323	<0.0001	0.359	<0.0001
Jaundice	23.48	22.23	0.043	0.3692	0.090	0.0567
Nutrition	26.88	21.40	0.313	<0.0001	0.315	<0.0001
Pain	23.26	24.44	0.232	<0.0001	0.213	<0.0001
Fever	6.37	14.48	0.144	0.0024	0.158	0.0008
Sex life	28.31	34.40	0.133	0.0048	0.120	0.0112
Abdominal swelling	32.66	35.12	0.300	<0.0001	0.361	<0.0001
HCC18 index score	25.12	17.08	0.339	<0.0001	0.372	<0.0001

EORTC European Organization for Research and Treatment of Cancer, *SD* standard deviation

Correlation between health-related quality of life and C-reactive protein

The mean CRP level was 9.6 mg/L, with standard deviations (SD) ± 5.5. CRP level was significantly correlated with HRQoL (see Table 5). In Pearson correlation analysis, CRP had significant positive correlations with C30 index-score, HCC18 index-score, a number of domains and items in QLQ-C30 ('fatigue', 'nausea and vomiting', 'pain', 'dyspnea', 'insomnia', 'appetite loss', 'diarrhea', 'financial difficulty') and QLQ-HCC18 ('fatigue', 'body image', 'nutrition', 'pain', 'fever', 'sex life' and 'abdominal swelling') ($p < 0.03$ for all the above correlations). Moreover, CRP had significant negative correlations with QLQ-C30 'physical functioning', 'role functioning', 'cognitive functioning', 'social functioning' and 'global QOL' ($p < 0.05$). In other words, higher CRP levels (higher inflammatory state) were associated with worse HRQoL. Among the strongest correlations were those with C30 index-score ($r = 0.348$, $p < 0.0001$), HCC18 index-score ($r = 0.339$, $p < 0.0001$), QLQ-C30 'appetite loss' ($r = 0.376$, $p < 0.0001$), QLQ-C30 'physical functioning' ($r = -0.349$, $p < 0.0001$), QLQ-C30 'role functioning' ($r = -0.347$, $p < 0.0001$), QLQ-C30 'pain' ($r = 0.345$, $p < 0.0001$), QLQ-C30 'fatigue' ($r = 0.334$, $p < 0.0001$), QLQ-HCC18 'fatigue' ($r = 0.329$, $p < 0.0001$), QLQ-HCC18 'body image' ($r = 0.323$, $p < 0.0001$), QLQ-HCC18 'nutrition' ($r = 0.313$, $p < 0.0001$), QLQ-HCC18 'abdominal swelling' ($r = 0.300$, $p < 0.0001$).

Correlation between health-related quality of life and C-reactive protein per albumin ratio

The mean CRP/alb ratio was 0.28 (SD ± 0.18). There were significant correlations between HRQoL variables and CRP/alb ratio (Table 5). In Pearson correlation analysis, CRP/alb ratio had significant positive correlations with C30 index-score, HCC18 index-score, a number of QLQ-C30 domains/items (including 'fatigue', 'nausea

and vomiting', 'pain', 'dyspnea', 'insomnia', 'appetite loss', 'diarrhea', 'financial difficulty') and QLQ-HCC18 domains/items (including 'fatigue', 'body image', 'nutrition', 'pain', 'fever', 'sex life' and 'abdominal swelling') ($p < 0.03$ for all the above correlations). Furthermore, CRP/alb ratio had significant negative correlations with QLQ-C30 'physical functioning', 'role functioning', 'cognitive functioning', 'social functioning' and 'global QOL' ($p < 0.01$). That is to say, higher CRP/alb ratio (higher inflammatory state) was associated with worse HRQoL. Among the strongest correlations were those with QLQ-C30 'physical functioning' ($r = -0.416$, $p < 0.0001$), 'role functioning' ($r = -0.390$, $p < 0.0001$), 'global QOL' ($r = -0.323$, $p < 0.0001$), 'fatigue' ($r = 0.367$, $p < 0.0001$); 'pain' ($r = 0.300$, $p < 0.0001$), 'appetite loss' ($r = 0.358$, $p < 0.0001$), QLQ-HCC18 'fatigue' ($r = 0.371$, $p < 0.0001$), 'nutrition' ($r = 0.315$, $p < 0.0001$), 'abdominal swelling' ($r = 0.361$, $p < 0.0001$), as well as C30 index-score ($r = 0.371$, $p < 0.0001$) and HCC18 index-score ($r = 0.372$, $p < 0.0001$).

Correlation between health-related quality of life and Glasgow prognostic score

Two hundred and eighty-two patients (63%) had GPS 1–2, 163 (37%) had GPS 0. There were significant correlations between GPS and HRQoL variables in univariate logistic regressions (see Table 6). Patients with worse C30 index-score, HCC18 index-score, as well as worse HRQoL scores in a number of QLQ-C30 domains/items (including 'physical functioning', 'role functioning', 'social functioning', 'global QOL', 'fatigue', 'nausea and vomiting', 'pain' and 'appetite loss') and QLQ-HCC18 domains/items (including 'fatigue', 'body image', 'nutrition' and 'abdominal swelling') were more likely to have higher inflammatory scores (1–2) in GPS ($p < 0.0001$). Table 7 shows the multivariate logistic

Table 6 Univariate logistic regressions of health related quality of life variables for Glasgow Prognostic score 1–2, Inflammation Based Index 1–2 and Prognostic index 1-2

	Glasgow prognistic score 1-2			Inflammation based index 1-2			Prognostic index 1-2		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
EORTC QLQ-C30									
Physical functioning	0.966	0.956–0.977	< 0.0001	0.966	0.956–0.977	< 0.0001	0.972	0.963–0.981	< 0.0001
Role functioning	0.974	0.966–0.982	< 0.0001	0.974	0.966–0.982	< 0.0001	0.977	0.970–0.984	< 0.0001
Emotional functioning	0.997	0.990–1.005	0.4596	0.997	0.990–1.005	0.4596	0.993	0.985–1.000	0.0622
Cognitive functioning	0.990	0.982–0.999	0.0236	0.990	0.982–0.999	0.0236	0.992	0.985–1.000	0.0545
Social functioning	0.984	0.977–0.991	< 0.0001	0.984	0.977–0.991	< 0.0001	0.981	0.974–0.988	< 0.0001
Global quality of life	0.982	0.974–0.990	< 0.0001	0.982	0.974–0.990	< 0.0001	0.980	0.973–0.988	< 0.0001
Fatigue	1.025	1.017–1.032	< 0.0001	1.025	1.017–1.032	< 0.0001	1.022	1.014–1.029	< 0.0001
Nausea/vomiting	1.027	1.014–1.041	< 0.0001	1.027	1.014–1.041	< 0.0001	1.031	1.018–1.044	< 0.0001
Pain	1.018	1.011–1.025	< 0.0001	1.018	1.011–1.025	< 0.0001	1.024	1.017–1.031	< 0.0001
Dyspnoea	1.011	1.004–1.018	0.0011	1.011	1.004–1.018	0.0011	1.010	1.004–1.016	0.0017
Insomnia	1.007	1.001–1.012	0.0178	1.007	1.001–1.012	0.0178	1.008	1.003–1.013	0.0035
Appetite loss	1.020	1.013–1.027	< 0.0001	1.020	1.013–1.027	< 0.0001	1.023	1.017–1.030	< 0.0001
Constipation	1.005	0.997–1.012	0.2062	1.005	0.997–1.012	0.2062	1.005	0.998–1.012	0.1609
Diarrhea	1.009	1.001–1.017	0.0216	1.009	1.001–1.017	0.0216	1.008	1.001–1.015	0.0344
Financial difficulty	1.008	1.003–1.013	0.0028	1.008	1.003–1.013	0.0028	1.011	1.006–1.017	< 0.0001
C30 index-score	1.037	1.024–1.050	< 0.0001	1.037	1.024–1.050	< 0.0001	1.040	1.028–1.052	< 0.0001
EORTC QLQ-HCC18									
Fatigue	1.025	1.016–1.035	< 0.0001	1.025	1.016–1.035	< 0.0001	1.027	1.018–1.035	< 0.0001
Body Image	1.030	1.019–1.040	< 0.0001	1.030	1.019–1.040	< 0.0001	1.030	1.020–1.040	< 0.0001
Jaundice	1.008	0.999–1.018	0.0699	1.008	0.999–1.018	0.0699	1.003	0.994–1.011	0.5495
Nutrition	1.029	1.017–1.040	< 0.0001	1.029	1.017–1.040	< 0.0001	1.034	1.023–1.045	< 0.0001
Pain	1.014	1.006–1.023	0.0013	1.014	1.006–1.023	0.0013	1.018	1.009–1.027	< 0.0001
Fever	1.022	1.005–1.040	0.0105	1.022	1.005–1.040	0.0105	1.013	0.998–1.027	0.0810
Sex life	1.006	1.000–1.012	0.0416	1.006	1.000–1.012	0.0416	1.006	1.000–1.012	0.0354
Abdominal swelling	1.019	1.012–1.026	< 0.0001	1.019	1.012–1.026	< 0.0001	1.019	1.013–1.025	< 0.0001
HCC18 index–score	1.042	1.028–1.057	< 0.0001	1.042	1.028–1.057	< 0.0001	1.042	1.028–1.056	< 0.0001

CI Confidence intervals, *EORTC* European Organization for Research and Treatment of Cancer, *OR* odds ratio

Table 7 Multivariate logistic regressions of clinical and health related quality of life variables for Glasgow Prognostic Score 1–2, Inflammation Based Index 1–2 and Prognostic Index 1–2

	Glasgow prognistic score 1–2			Inflammation based index 1–2			Prognostic index 1–2		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
C30 Physical functioning	0.978	0.967–0.989	0.0001	0.978	0.967–0.989	0.0001	–	–	–
C30 Pain	–	–	–	–	–	–	1.017	1.009–1.025	< 0.0001
Treatment type	3.202	1.726–5.944	0.0002	3.202	1.726–5.944	0.0002	3.796	1.812–7.535	0.0001
Bilirubin level	1.023	1.007–1.039	0.0045	1.023	1.007–1.039	0.0045	–	–	–
CUPI	2.514	1.611–3.923	< 0.0001	2.514	1.611–3.923	< 0.0001	2.823	1.884–4.230	< 0.0001
Alpha-feto protein level	–	–	–	–	–	–	1.083	1.014–1.158	0.0181

CI Confidence intervals, *CUPI* the Chinese University Prognostic Index, *C30* European Organization for Research and Treatment of Cancer QLQ-C30, *OR* Odds ratio

regressions of baseline clinical variables and HRQoL variables for worse scores (1–2) in GPS. After adjusting for age, gender, performance status, liver function biochemistry, alpha-feto protein level, presence of cirrhosis, etiology of cirrhosis, tumor stage and treatment received, QLQ-C30 'Physical Functioning' remained significantly correlated with GPS (OR 0.978 [95% CI 0.976–0.989], $p = 0.0001$).

Correlation between health-related quality of life and inflammation-based index

63% of patients had IBI 1–2, the rest had IBI 0. There were significant correlations between IBI and HRQoL variables in univariate logistic regressions (see Table 6). Patients with worse C30 index-score, HCC18 index-score, as well as worse HRQoL scores in a number of Q-C30 domains/items (including 'physical functioning', 'role functioning', 'social functioning', 'global QOL', 'fatigue', 'nausea and vomiting', 'pain', 'appetite loss') and QLQ-HCC18 domains/items ('fatigue', 'body image', 'nutrition' and 'abdominal swelling') were more likely to have higher inflammatory scores (1–2) in IBI ($p < 0.0001$). After adjusting for baseline clinical variables, QLQ-C30 'Physical Functioning' was significantly correlated with IBI (OR 0.978 [95% CI 0.967–0.989], $p = 0.0001$) (Table 7).

Correlation between health-related quality of life and prognostic index

One hundred and ninety-four patients (44%) had PI 0, while 251 (56%) had PI 1–2. There were significant correlations between PI and HRQoL variables in univariate logistic regressions (see Table 6). Patients with worse C30 index-score, HCC18 index-score, as well as worse HRQoL scores in some of the QLQ-C30 domains/items ('physical functioning', 'role functioning', 'social functioning', 'global QOL', 'fatigue', 'nausea and vomiting', 'pain', 'appetite loss' and 'financial difficulty') and QLQ-HCC18 domains/items ('fatigue', 'body image', 'nutrition', 'pain' and 'abdominal swelling') were more likely to have higher inflammatory scores (1–2) in PI ($p < 0.0001$). After adjusting for baseline clinical variables, QLQ-C30 'Pain' was significantly correlated with PI (OR 1.017 [95% CI 1.009–1.012], $p < 0.0001$) (Table 7).

Discussion

In this study, the correlations between HRQoL and CRP-based inflammatory markers among HCC patients were investigated. C30 and HCC18 index-scores, as well as the majority of domain/item scores in EORTC QLQ-C30 and QLQ-HCC18 were significantly correlated with the CRP-based inflammation markers that were evaluated, namely CRP, CRP/alb ratio, GPS, IBI and PI. After adjusting for a series of important baseline clinical factors, HRQoL variables were still significantly correlated with these markers. This suggests that inflammatory status of individual patient may affect his/her HRQoL.

Pearson's correlation analysis allows assessment of the strength of correlations between HRQoL factors and inflammation-based markers with continuous scoring (CRP and CRP/alb ratio). Majority of these correlations were mild. However, certain HRQoL scales were consistently shown to have relatively stronger correlations with CRP and CRP/alb ratio. These included QLQ-C30 'physical functioning', 'role functioning', 'fatigue', 'pain' and 'appetite loss', QLQ-HCC18 'fatigue', 'body image', 'nutrition' and 'abdominal swelling', as well as the C30 and HCC18 index-scores. Based on logistic regression analyses with categorical CRP-based markers, these HRQoL factors also had stronger odds ratios than other factors.

In other words, certain HRQoL scales were relatively more correlated with inflammation. These HRQoL scales include QLQ-C30 'physical functioning', 'role functioning', 'fatigue', 'appetite loss', QLQ-HCC18 'fatigue' and

'nutrition'. The QLQ-C30 'physical functioning' assessment originates from questions 1–5 of the QLQ-C30 questionnaire which address troubles in strenuous activities, walking, dressing, bathing and any need for staying in bed during the day. QLQ-C30 'role functioning' is assessed by questions six and seven which measure limitation in daily activities, leisure time activities and work. QLQ-C30 'fatigue' is assessed by questions 10, 12 and 18 which evaluate tiredness, weakness and any need for more rest. QLQ-C30 'appetite loss' is assessed by question 13 which looks for any lack of appetite. Questions 45-47 in the QLQ-HCC18 questionnaire assess QLQ-HCC18 'fatigue' in terms of decline in energy, difficulty finishing things and need for sleep at daytime. Whereas QLQ-HCC18 'nutrition' is based on questions 31, 32, 42–44 which gauge symptoms on thirst, altered taste, malnourishment, early satiety and weight loss. In summary, these questions assess patients for loss of appetite, malnutrition, weight loss, tiredness, staying in bed/chair as well as difficulties in daily activities, exertion or work. When these clinical features are considered collectively, they signify malignancy-related constitutional symptoms. The correlations between inflammation and the described HRQoL scales support our hypothesis that inflammatory response in HCC patients could lead to constitutional symptoms [29, 30], which in turn could lead to functional and HRQoL impairments [31].

Other HRQoL scales that had relatively higher correlation with inflammation were QLQ-C30 'pain', QLQ-HCC18 'abdominal swelling' and 'body image'. QLQ-C30 'pain' scale originates from questions 9 and 19 of the QLQ-C30 questionnaire, which examine pain and pain-related hindrance in daily activities, whereas QLQ-HCC18 'abdominal swelling' derives from question 34 of the QLQ-HCC18 questionnaire and questions any presence of abdominal swelling, while QLQ-HCC18 'body image' is based on questions 33 and 35 which evaluate muscle wasting and any concern over the appearance of the abdomen. In summary, these questions assess patients for pain and abdominal swelling. Pain in HCC patients is commonly due to hepatomegaly; whereas abdominal distension can either be caused by gross hepatomegaly or severe ascites; the mechanisms for the latter could be multifactorial and include portal vein thrombosis, hypoalbuminemia resulting from chronic liver disease, tumor compression on stomach causing early satiety thereby impairing oral intake and leads to malnutrition, or liver failure due to tumor invasion of normal liver parenchyma. In other words, these questions indirectly assess liver tumor burden. Patients with larger liver tumor burden are more likely to have pain, abdominal swelling and have impaired HRQoL [27]; at the same time, it has also been reported that they are also more likely to have higher inflammatory environment [12, 15].

In our previous report, C30 and HCC18 index-scores were the HRQoL factors with the strongest prognostic significance on survival, a finding possibly explained by their representativeness of the overall HRQoL instruments [10]. In the current analysis, these two HRQoL index-scores were shown to have significant correlations with all the CRP-based inflammation markers analyzed; their corresponding correlation coefficients were among the strongest when compared to the majority of HRQOL domain/item scores within the HRQoL instruments. This further demonstrates the representative power of these two index-scores. Instead of handling a constellation of separate domain/item scores in the conventional manner, these two single index-scores allow complex HRQoL data to be interpreted and used in daily clinical practice.

With the demonstration that systemic inflammation could substantially influence HRQoL in an adverse manner, means of reducing inflammation may in turn improve HRQoL. Isolated randomized studies in other malignancies have suggested that exercise program or anti-inflammatory medication may improve patients' HRQoL and lower their CRP levels [43, 44]. The observations from the current study prompt for clinical trials to assess whether intervention directed against inflammation may ameliorate the HRQoL impairment in HCC patients.

Although 9% of the recruited patients did not complete the study questionnaires, the recruitment of more than thrice the initial target sample size enabled complete case analysis to be conducted and minimized the associated bias. However, there remain a number of study limitations. One of the limitations is the lack of longitudinal follow-up assessments of HRQoL and inflammation-based markers. It would be of interest to analyze whether changes in CRP-based markers correlate with changes in HRQoL in HCC patients. In addition, since this study was conducted in Chinese HCC patients in whom the majority suffered from hepatitis B infection with chronic liver disease, it is unknown whether the current study findings are generalizable to patients of other cultures, ethnicities or geographic regions where hepatitis C and alcoholism are more prevalent. Thus validation studies in other populations of HCC patients are warranted.

Conclusion

In HCC patients, CRP-based inflammation markers (CRP, CRP/alb ratio, GPS, IBI and PI) correlate with baseline HRQoL assessment using EORTC QLQ-C30, QLQ-HCC18, C30 and HCC18 index-scores. In particular, relatively stronger correlations with CRP-based markers have been observed in HRQoL scales that assess constitutional symptoms (QLQ-C30 'physical functioning', 'role functioning', 'fatigue', 'appetite loss' and QLQ-HCC18 'fatigue' and 'nutrition') and tumor burden (QLQ-C30 'pain' and QLQ-HCC18 'abdominal swelling' and 'body image'). Future

studies are warranted to evaluate whether intervention for controlling inflammation could improve HRQoL in HCC patients.

Author contributions LL and WY contributed to this paper with conception and design of the study. LL, WY, EPH, SLC, JK, KFL, CMC, JH, NLST and SY contributed to acquisition of data. FM, LL and WY contributed to data analysis and interpretation of data. All authors contributed to drafting and critical revision and editing, and final approval of the manuscript.

Data availability Upon request the database could be made available at the discretion of owners of the database.

Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

Ethical approval This study was approved by the regional ethics committee (the Joint Clinical Research Ethics Committee of Chinese University of Hong Kong and New Territories East Cluster of Hospital Authority). The study was performed in accordance with the Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study.

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